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VONOPRAZAN-BASED THERAPY HAS LOWER FAILURE RATE IN ERADICATING HELICOBACTER PYLORI COMPARED TO PROTON PUMP INHIBITORS-BASED THERAPY: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Introduction: *Helicobacter pylori infection is worldwide health problems and well known as causative agent of gastric ulcer and gastric cancer. Main therapy of Helicobacter pylori infection is still Proton-pump inhibitor based therapy. However, previous studies using Vonoprazan-based therapy showed promising results. This study aims to compare the success rate and failure rate of Vonoprazan-based therapy with the Proton-pump inhibitor based therapy in eradicating Helicobacter pylori infection.*

Method: *Comprehensive searching was done in online databases of Pubmed, EMBASE, and the Cochrane Library. Randomized controlled trials comparing eradication rate between Vonoprazan and first generation Proton Pump Inhibitor with Clarithromycin-sensitive Helicobacter pylori was included in this studies, while other study designs were excluded. Analysis of the studies was performed using Revman 5.3 (fixed effects model based heterogeneity test) to provide pooled risk ratio (RR) with 95% confidence intervals (CI).*

Result: *Five Randomized controlled trials met inclusion criteria with total of 2753 patients. Vonoprazan-based therapy has higher eradication rate (pooled RR=1.11, 95% CI 1.07-1.16, p<0.00001) and lower failure rate (pooled RR=0.43, 95% confidence intervals 0.34-0.55, p<0.00001) compared with Proton-pump inhibitor based therapy.*

Conclusion: *Vonoprazan-based therapy lower failure rate in eradicating Helicobacter pylori infection than Proton-pump inhibitor based therapy.*

Keywords: *vonoprazan, potassium inhibitor, proton-pump Inhibitor, Helicobacter pylori*

Introduction

Helicobacter pylori is unique bacterium which can live and infect human stomach. *H. pylori* infection may cause chronic gastritis, gastric ulcer, and gastric cancer. *H. pylori* infection is one of common health problems in all countries. Based on systematic review and meta-analysis done by [*Hooi JKY et al., 2017*], *H. pylori* infection is highest in Africa (79.1%), while Asia is the third with prevalence of 54.7%. *H. pylori* infection prevalence in Indonesia is about 22.1% in 2015 [*Syam AF et al., 2015*]. Its prevalence is predicted increase as the evidence of antimicrobial resistance in *H. pylori* eradication using Proton-pump inhibitor (PPI) based therapy.

H. pylori infection eradication regiment is mainly using PPI-based therapy. The first line therapy is combining PPI, Amoxicillin, and Clarithromycin, but the eradication rate decreases until 60-70% because of emergence of Clarithromycin-resistant *H. pylori* [*Hirata Y et al., 2016*]. The second line of *H. pylori* eradication is using combina-

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tion of PPI, Amoxicillin, and Metronidazole and this combination can eradicate up to 90% of *H.pylori* infection [*Nishizawa T et al., 2009*]. Unfortunately, Metronidazole combination therapy does not only has higher eradication rate, but also has higher resistance rate than Clarithromycin in Asia, especially in South East Asia. [*Miftahussurur M, Yamaoka Y, 2015*] study showed that the Metronidazole resistance rate in South East Asia is about 36-100%, while Clarithromycin resistance rate is only about 0.0-27.8%. Increasing PPI dosage in the therapy also does not improve the outcome of treatment [*Graham DY Dore M, 2018*].

Novel drug, Vonoprazan Fumarate, first generation of Potassium-Competitive Acid Blockers (P-CAB), nowadays has been used as combination therapy in *H. pylori* eradication since introduced first at February 2015 in Japan [*Echizen H, 2016*]. Vonoprazan has been proposed as the first line combination therapy and replaced the role of PPI. Retrospective study by [*Saito Y et al., 2019*] confirmed that replacing PPI with Vonoprazan results in significant higher eradication rate than using PPI-based therapy. Another study also found that Vonoprazan has more potentials and longer duration of action compared to PPI [*Oshima T, Miwa H, 2018*]. Based on the reasons, we did meta-analysis of Randomized controlled trials (RCT) studies to compare the *H. pylori* both success and failure eradication rates using Vonoprazan-based and PPI-based triple therapies.

Materials and Methods

Searching Strategy: We did comprehensive searching in online databases of Pubmed Central, EMBASE, and the Cochrane Library, looked for all relevant published studies until 11 March 2019. The keyword strings used were ("Vonoprazan" or "TAK-438" or "Potassium Inhibitor") and "*Helicobacter pylori*".

Study Selection: The first step in selecting studies was screening the titles and abstracts of the search results to exclude irrelevant studies. After finishing the first screening, we continued to screening the full-text of all selected studies matched to our criteria. The inclusion criteria were all Randomized Controlled Trial (RCT) studies assessing eradication of patients with *Helicobacter pylori* infection received Vonoprazan-based therapy compared to patients treated with the PPI-based therapy. Animal and *in vitro* studies were excluded. We used the Newcastle-Ottawa Scale to assess the articles quality for studies.

Data Extraction: We extracted data about first author, study year, study design, eradication regiments, eradication criteria, and eradication rate per protocol, then compared the eradication rate between patients received Vonoprazan-Clarithromycin-Amoxicillin and patients received PPI-Clarithromycin-Amoxicillin whose clarithromycin-sensitive *Helicobacter pylori* infection.

Statistical Analysis: We performed analysis and reporting according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The software used for conducting statistical procedures were Review Manager 5.3 (version 5.3.5; Cochrane Collaboration, Denmark) to assess the pooled risk ratios (RRs) with 95% Confidence Interval (CI) using fixed effects model.

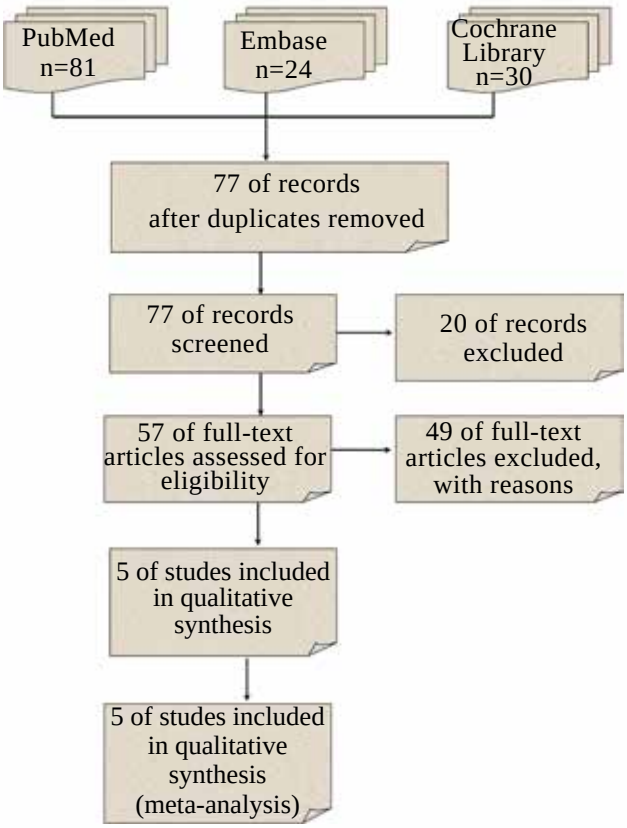


Figure 1: *Study Flow Diagram*

RESULTS

Study Selection and Characteristics:

The flow diagram of this study is showed in Figure 1. The searches through the online databases using the terms resulted total of 135 studies. After 58 duplicates were removed, 77 studies were done for the title and abstract screening. Finally, after assessing the 57 remaining full-text studies, we finally selected 5 RCT studies to be analyzed in this meta-analysis. (Fig. 1)

The 5 studies characteristics are summarized in table 1. All RCT studies were performed in Japan and published in 2016-2017. All included studies consists of 2159 patients treated with Vonoprazan-based therapy and 594 patients treated with PPI-based therapy.

Comparison of Efficacy on Eradicaton Therapy:

The patients received PPI-based therapy was divided in three groups, first group was patients received first generation PPI (Lansoprazole and

TABLE 1

Study Characteristics Included in Meta-Analysis

First Author	Year of Study	Study Design	Eradication Confirmatory Test	Eradication Regiments	Eradication Rate
Murakami K	2016	RCT	^{13}C UBT	Vonoprazan 20 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	323/329 (98.2%)
				Lansoprazole 30 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	318/321 (99.1%)
Maruyama M	2017	RCT	^{13}C UBT	Vonoprazan 20 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	67/70 (95.8%)
				Lansoprazole 20 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	8/9 (88.9%)
				Rabeprazole 20 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	37/54 (68.5%)
Sue S.	2017	RCT	^{13}C UBT	Vonoprazan 20 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	48/54 (88.9%)
				Lansoprazole 30 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	31/34 (91.2%)
				Rabeprazole/Esomeprazole 20 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	8/8 (100.0%)
Takimoto M.	2017	RCT	^{13}C UBT	Vonoprazan 20 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	6/18 (33.3%)
				Lansoprazole 30 *mg*, Amoxicillin 750 *mg*, Clarithromycin 400 *mg*	2/18 (11.1%)
Ozaki H.	2018	RCT	^{13}C UBT	Vonoprazan 40 *mg*, Amoxicillin 1500 *mg*, Clarithromycin 400 *mg*	1534/1688 (90.9%)
				Rabeprazole/Esomeprazole 20 *mg*, Amoxicillin 1500 *mg*, Clarithromycin 400 *mg*	107/147 (72.8%)

NOTES: RCT - Randomized Controlled Trials, ^{13}C UBT - ^{13}C Urea Breathe Test

Pantoprazole), the second was patients received second generation PPI (Esomeprazole and Rabeprazole), and the last group was the patients received PPI regardless of the generation. We compared the success eradication rate and the failure eradication rate for each groups with the Vonoprazan groups.

Comparison of Efficacy Between Vonoprazan and First Generation of PPI

Based on meta-analysis for the first group, Table 2 and Table 3 shows no statistical and clinical significance for both success eradication rate (pooled RR = 1.01, 95% CI 0.98-1.04, p=0.41) and failure eradication rate (pooled RR=0.84, 95% CI 0.57-1.25, p=0.39). However, although not significant, Vonoprazan has lower failure rate in eradicating *H. pylori* than the first generation of PPI with pooled failure rate respectively 5.73% and 6.75% (table 2, table 3).

Comparison of Efficacy Between Vonoprazan and Second Generation of PPI

Pooled success eradication rates between patients received Vonoprazan-based and PPI-based therapies are 91.1% and 72.7%, while pooled failure eradication rates between patients received Vonoprazan-based therapy and PPI-based therapies are 8.9% and 27.3%. Vonoprazan has higher success eradication rate (pooled RR = 1.25, 95% CI 1.15-1.37, p<0.00001) and lower failure eradication rate (pooled RR = 0.31, 95% CI 0.23-0.42, p<0.00001) compared with the second generation of PPI. Both comparisons are also statistically and clinically significant. (table 3, table 4)

Comparison of Efficacy Between Vonoprazan and All Generations of PPI

After combining all RCT studies, we did meta-analysis to compare success eradication rate and failure eradication rate between patients received Vonoprazan and those who received PPI. Pooled success eradication rates between Vonoprazan-based and PPI-based therapies are 91.6% and 86.0%, while pooled failure eradication rates between Vonoprazan-based and PPI-based therapies are 8.4% and 14.0%. Vonoprazan is statistically significant in eradicating *H.pylori* (pooled RR = 1.11, 95% CI 1.07-1.16, p<0.00001). However, Vonoprazan-based therapy has lower failure therapy than PPI-based therapy and the result is both statistically and clinically significant (pooled RR = 0.43, 95% CI 0.34-0.55, p<0.00001). (table 6, table 7)

Discussion

Vonoprazan has been proposed as the first line combination therapy in eradicating *H. pylori*. In this meta-analysis, the eradication using Vonoprazan-based therapy has pooled RR of 1.11, 95% CI 1.07-1.16, p<0.00001. Although this study has statistical significance in eradicating *H. pylori*, the pooled RR value is not clinically significant. However, we did meta-analysis compare the failure eradication rate between Vonoprazan-based therapy and PPI-based therapy and the result showed that Vonoprazan-based therapy is both statistical an clinically significant in lowering failure eradication rate compared to PPI-based therapy (pooled RR = 0.43, 95% CI 0.34-0.55, p<0.00001).

Vonoprazan has higher eradication rate of 92.6% compared to Lansoprazole-based combination since used in phase III trial of Vonoprazan as first line therapy [*Murakami K et al., 2016*]. Previous meta-analysis combining both RCT and non RCT studies also favor Vonoprazan-based therapy than PPI-based therapy [*Dong S et al., 2017*] did meta-analysis included both RCT and non RCT studies then concluded that Vonoprazan-based is more superior than PPI-based therapy in eradicating *H. pylori* infection (pooled RR=2.44, 95% CI 1.99-2.99, p<0.00001) while meta-analysis done by [*Jung YS et al., 2017*] also showed that Vonoprazan is more favorable than PPI in eradicating *H. pylori* infection (pooled RR=1.19, 95% CI 1.14 – 1.24, p<0.00001).

The superiority of Vonoprazan in eradicating *H. pylori* can be explained through pharmacological approach. Vonoprazan is H^+/K^+-ATPase competitive inhibitor acts by binding of potassium ions on the receptor. Vonoprazan has more potential and longer duration of action as anti-secretory effect on H^+/K^+-ATPase [*Mori H, Suzuki H, 2019*]. Un-

TABLE 2.

Forest Plot of Comparison of Success Eradication Rate Between Vonoprazan and First Generation PPI

Study or Subgroup	Vonoprezan Events	Vonoprezan Total	First Generation Events	First Generation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maruyama M 2017	67	70	8	9	3.8%	1.08 [0.85, 1.36]
Murakami K 2016	323	329	318	321	85.9%	0.99 [0.97, 1.01]
Sue S. 2017	48	54	31	37	9.8%	1.06 [0.89, 1.26]
Takimoto M. 2017	6	18	2	18	0.5%	3.00 [0.70, 12.93]
Total (95% CI)		**471**		**385**	**100%**	**1.01 [0.98, 1.04]**
Total events	444		359			
Heterogeneity: Chi2 = 7.73, df = 3 (p=0.05), I^2 =61%						
Test for overal effect: z = 0.82 (p = 0.41)						

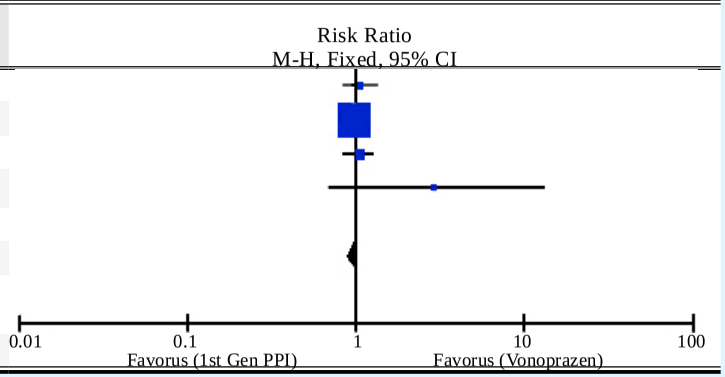


TABLE 3.

Forest Plot of Comparison of Failure Eradication Rate Between Vonoprazan and First Generation PPI.

Study or Subgroup	Vonoprezan Events	Vonoprezan Total	First Generation Events	First Generation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maruyama M. 2017	3	70	1	9	6.3%	0.39 [0.04, 3.32]
Murakami K. 2016	6	329	3	321	10.9%	1.95 [0.49, 7.74]
Sue S. 2017	6	54	6	37	25.5%	0.69 [0.24, 1.96]
Takimoto M. 2017	12	18	16	18	57.3%	0.75 [0.52, 1.08]
Total (95% CI)		**471**		**385**	**100.0%**	**0.84 [0.57, 1.25]**
Total events	27		26			
Heterogeneity: Chi2 = 2.46, df = 3 (p = 0.48), I^2 =0%						
Test for overal effect: z = 0.85 (p = 0.39)						

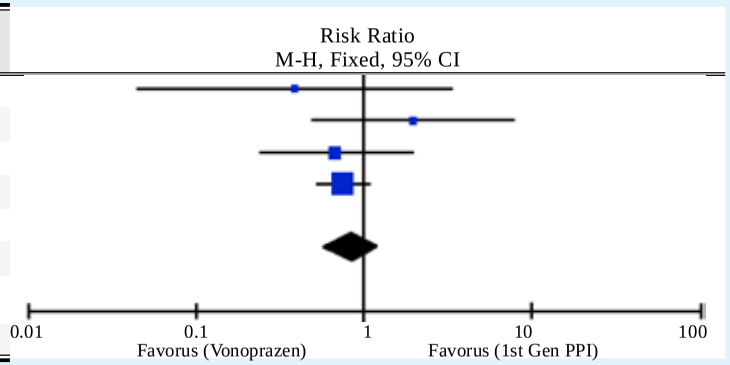


Table 4.

Forest Plot of Comparison of Success Eradication Rate Between Vonoprazan and Second Generation PPI

Study or Subgroup	Vonoprezan Events	Vonoprezan Total	First Generation Events	First Generation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maruyama M. 2017	67	70	37	54	16.5%	1.40 [1.16, 1.68]
Ozaki H. 2018	1534	1688	107	147	77.7%	1.25 [1.13, 1.38]
Sue S. 2017	48	54	8	8	5.8%	0.93 [0.78, 1.12]
Total (95% CI)		**1812**		**209**	**100%**	**1.25 [1.15, 1.37]**
Total events	1649		152			
Heterogeneity: Chi2 = 11.01, df = 2 (p=0.004), I^2 = 82%						
Test for overal effect: z = 5.26 (p < 0.00001)						

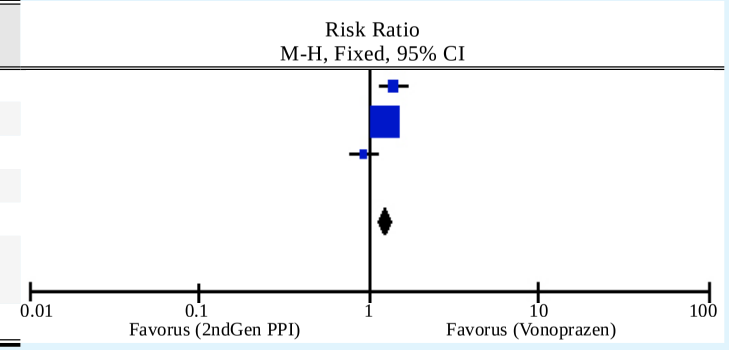


TABLE 5.

Forest Plot of Comparison of Failure Eradication Rate Between Vonoprazan and Second Generation PPI

Study or Subgroup	Vonoprezan Events	Vonoprezan Total	First Generation Events	First Generation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maruyama M 2017	3	70	17	54	20.5%	0.14 [0.04, 0.44]
Ozaki H. 2016	154	1688	40	147	78.6%	0.34 [0.25, 0.45]
Sue S. 2017	5	54	0	8	0.9%	2.13 [0.13, 34.59]
Total (95% CI)		**1812**		**209**	**100%**	**0.31 [0.23, 0.42]**
Total events	163		57			
Heterogeneity: Chi2 = 3.96, df = 2 (p = 0.14), I^2 =50%						
Test for overal effect: z = 7.57 (p <0.00001)						

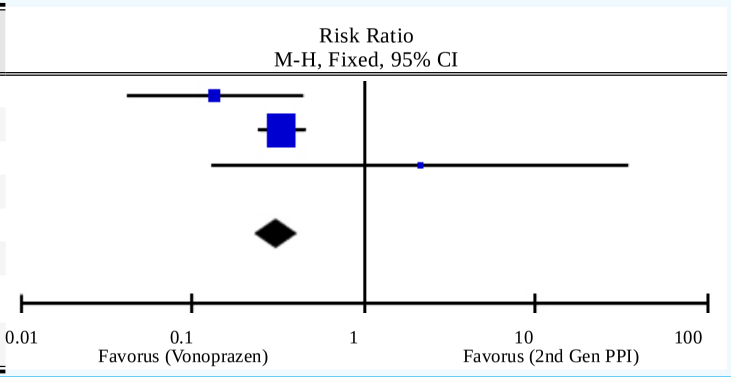


TABLE 6.

Forest Plot of Comparison of Success Eradication Rate Between Vonoprazan and PPI

Study or Subgroup	Vonoprezan Events	Vonoprezan Total	First Generation Events	First Generation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maruyama M. 2017	67	70	45	63	7.8%	1.34 [,]
Murakami K. 2016	323	329	318	321	%52.7	0.99 [,]
Ozaki H. 2018	1534	1688	107	147	32.2	1.25 [1.13, 1.38]
Sue S. 2017	48	54	39	45	%7.0	1.03 [0.88, 1.19]
Takimoto M. 2017	6	18	2	18	%0.3	3.00 [0.70, 12.93]
Total (95% CI)		**2159**		**594**	**100%**	**1.11 [1.07, 1.16]**
Total events	1978		511			
Heterogeneity: Chi2 = 163.16, df = 4 (p <0.00001), I2 = 98%						
Test for overal effect: z = 5.11 (p < 0.00001)						

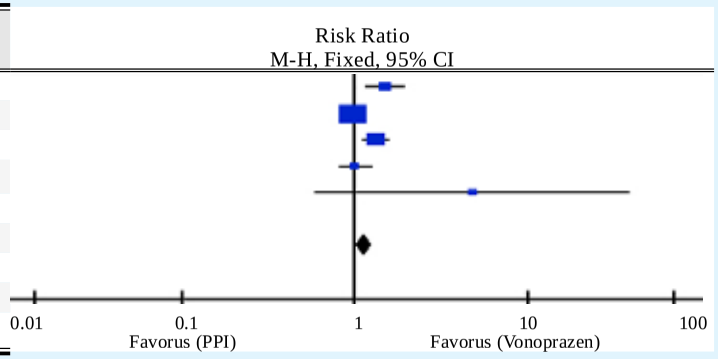
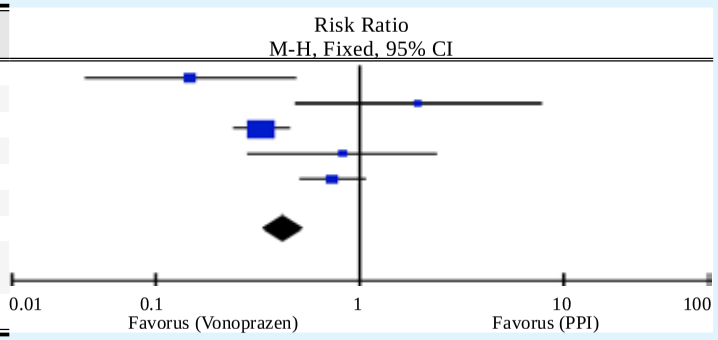


TABLE 7.

Forest Plot of Comparison of Failure Eradication Rate Between Vonoprazan and PPI.

Study or Subgroup	Vonoprezan Events	Vonoprezan Total	First Generation Events	First Generation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maruyama M 2017	3	70	18	63	16.0%	0.15 [0.05, 0.49]
Murakami K. 2016	6	329	3	321	2.6%	1.95 [0.49, 7.74]
Ozaki H. 2018	154	1688	40	147	62.3%	0.34 [0.25, 0.45]
Sue S. 2017	6	54	6	45	5.5%	0.83 [0.29, 2.41]
Takimoto M. 2017	12	18	16	18	13.5%	0.75 [0.52, 1.08]
Total (95% CI)		**2159**		**594**	**100.0%**	**0.43 [0.34, 0.55]**
Total events	181		83			
Heterogeneity: Chi2 = 20.673, df = 4 (p = 0.0004), I^2 = 81%						
Test for overal effect: z = 6.92 (p < 0.00001)						



like PPI, Vonoprazan is not a prodrug that requires acid activation and also more stable in acidic environment than PPI, thus Vonoprazan suppress gastric acid secretion longer than PPI [*Tsujimae M et al., 2016*]. Previous studies also reported that Vonoprazan shows more superior acid inhibition effect than PPI. Therefore, Vonoprazan has more beneficial pharmacologic effects than PPI.

Vonoprazan nowadays has been a treatment option in according to the newest Japanese guideline for *H. pylori* infection management. The guideline stated that the 7-day triple therapy of Vonoprazan 20 mg bid, Clarithromycin 200 or 400 mg bid, and Amoxicillin 750 mg bid has higher *H. pylori* eradication rate than PPI-based therapy, which is about 92.6% [*Kato M et al., 2019*]. Besides, [*Mori H, Suzuki H, 2019*] also proposed Vonoprazan as the long-term therapy of both PPI-resistant non-erosive and erosive reflux esophagitis. However, early phase trials studies showed complications followed previous P-CAB therapy. In the early P-CAB invention, previous P-CAB is imidazole-pyridine derivate causes more hepatotoxicity than Vonoprazan, which is pyrole derivate [*Mori H, Suzuki H, 2019*]. Stronger acid inhibition of Vonoprazan results in increase of gastrin serum. Preclinical studies also showed that long-term Vonoprazan therapy in rodents caused hyperplasia of neuroendocrine cells and malignancy due to hypergastrinemia, nevertheless it was still an uncertainty whether the evidence can be extrapolated to the human [*Echizen H, 2016*]. Another adverse events caused by chronic strong acid inhibition by Vonoprazan or PPI are intestinal bacterial overgrowth, *Clostridium difficile*-associated diarrhea, pneumonia, spontaneous bacterial peritonitis, iron deficiency anemia, vitamin B12 deficiency, hypomagnesium, osteoporosis, bone fracture, hyperplasia of gastric neuroendocrine cells, and gastric neuroendocrine tumor [*Mori H, Suzuki H, 2019, Sugano K, 2018*]. The exact effects and complications for long-term use of Vonoprazan is still under examination and hopefully can also be used for long-term management for gastroesophageal reflux disease and erosive gastritis.

The efficacy of both Vonoprazan and PPI is also affected by individual varieties such as age, gender, race, and P450 cytochrome polymorphisms. This study does not regard the individual varieties due to lack of data. The polymorphism may cause different pharmacological effect because of different outcome of the drug metabolism. People who have CYP2C19 Extensive Metabolizers (EM) polymorphism have lower efficacy of PPI because of its extended metabolism. Unlike PPI, Vonoprazan is mainly metabolized by CYP3A4/5 and partially by CYP2C19, CYP2B6, and CYP2D6 [*Graham DY Dore MP, 2018*]. Echizen H stated that the inhibition of Vonoprazan to the cythocromes also inhibits the extended metabolism of other drugs such as Clarithromycin. Another study limitation is the published RCT studies were only done in Japan [*Echizen H, 2016*]. We did not found any published RCT studies done outside Japan until March 2019. Vonoprazan is expected to have beneficial effect to the Western population whose high prevalence of CYP2C19 EM [*Sugimoto M, Yamaoka Y, 2018*]. Thus, we need conduct RCT using Vonoprazan outside Japan and consider the individual variabilities especially the cytochrome polymorphisms.

CONCLUSION

Vonoprazan-based therapy has lower failure rate in eradicating *Helicobacter pylori* infection than PPI-based therapy. However, further research about roles of Potassium-Competitive Acid Blockers (P-CAB) in eradicating *H. pylori* is needed, especially clinical studies of Vonoprazan in countries outside Japan.

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