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Vonoprazan and Proton Pump Inhibitors in *Helicobacter pylori* Eradication Therapy: A Systematic Review

(Vonoprazan dan Perencat Pam Proton dalam Terapi Eradikasi *Helicobacter pylori*: Suatu Ulasan Sistematik)

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ABSTRACT

This systematic review sought to summarise data on the efficacy of vonoprazan, a novel potassium-competitive acid blocker, as compared with a proton pump inhibitor (PPI)-based regimen for first-line treatment of Helicobacter pylori *eradication. A systematic literature search of MEDLINE, EMBASE, and the Cochrane Library using the primary keywords 'vonoprazan', 'takecab', 'TAK-438', 'potassium', 'competitive', 'potassium-competitive',* 'Helicobacter'*, and* 'pylori' *was performed. Studies were included if they evaluated the eradication rate between vonoprazan-based and PPI-triple therapies. Overall, 15 studies were included in this review (three randomised controlled trials (RCTs), 12 non-RCTs). Both the included RCTs and non-RCTs showed a statistically significant superiority of vonoprazan-based therapy to PPI-based therapy as esomeprazole. Only 11 of the included studies were deemed as having good quality. In two RCTs, vonoprazan-based therapy showed a statistically significant superiority over PPI-based therapy with* H. pylori *eradication rates in excess of 90% (p-value < 0.001). Meanwhile, observational studies demonstrated first-line therapy eradication rates ranging between 85.0 and 95.5% in the vonoprazan-based group versus between 66.8 and 86.7% in the PPI-based group with statistical significance. In conclusion, vonoprazan-based triple therapy provided superior efficacy in* H. pylori *eradication versus PPI-based triple therapy. Vonoprazan shows a promising ability as a potent and long-acting, acid-reducing agent, with some potential advantages over traditional PPIs, particularly in the treatment of* H. pylori *infection. As a relatively new agent, whether vonoprazan is appropriate and safe for long-term or life-long use remains to be determined in the near future.*

Keywords: Eradication; Helicobacter pylori*; potassium-competitive acid blocker; proton-pump inhibitor; triple therapy; vonoprazan*

ABSTRAK

Kajian ulasan sistematik ini meringkaskan data berkenaan keberkesanan Vonoprazan iaitu penghalang asid potassium-kompetatif novel berbanding regimen penghalang pam proton (PPI) sebagai rawatan barisan pertama eradikasi Helicobacter pylori*. Kajian perpustakaan di MEDLINE, EMBASE dan Cochrane Library mengunakan kata kunci 'vonoprazan', 'takecab', 'TAK-438', 'potassium', 'competitive', 'potassium-competitive',* 'Helicobacter'*, dan* 'pylori' *telah dilakukan. Kajian dipilih seandainya terdapat bandingan kadar eradikasi antara vonoprazan-based dan PPI-tiga serangkai. Secara keseluruhan, sebanyak 15 kajian telah diterima-pakai dalam kajian ini (tiga kajian kawalan rawak (RCT), 12 bukan-RCT). Kedua-dua RCT dan bukan-RCT menunjukkan keberkesanan rawatan secara signifikan dengan vonoprazan berbanding PPI seperti esomeprazole. Hanya 11 kajian diterima-pakai kerana mempunyai kualiti kajian yang bagus. Dalam dua kajian RCT, terapi berasaskan vonoprazan menunjukkan kesan signifikan secara statistik berbanding PPI untuk kadar eradikasi* H. pylori *sebanyak 90% (p < 0.001). Manakala, kajian pengamatan menunjukkan kadar eradikasi antara 85.0 dan 95.5% pada kumpulah vonoprazan berbanding 66.8 dan 86.7% pada kumpulan PPI dengan signifikan. Sebagai kesimpulan, terapi berasakan vonoprazan memberikan keberkesanan unggul dalam pembasmian* H. pylori *berbanding terapi berasaskan PPI. Vonoprazan menunjukkan keupayaan yang memberangsangkan sebagai agen pengurangan asid yang poten dan berjangkamasa tindak panjang, dengan beberapa kelebihan yang berpotensi berbanding PPI, terutamanya dalam rawatan jangkitan* H. pylori*. Sebagai agen yang agak baru, sama ada vonoprazan sesuai dan selamat untuk jangka panjang atau penggunaan sepanjang hayat masih perlu ditentukan dalam masa akan datang.*

Kata kunci: Helicobacter pylori*; pembasmian; penyekat asid kompetitif kalium; perencat pam proton; terapi tiga kali ganda; vonoprazan*

Introduction

Peptic ulcer is among the most serious and common gastrointestinal diseases in the world. It is the most predominant gastrointestinal disease (Adinortey et al. 2013), with a worldwide prevalence of about 40% in the developed countries and 80% in the developing countries. One of the most common causes of peptic ulcers is *Helicobacter pylori* infection. Chronic infection with *H. pylori* is the most frequent chronic bacterial infection worldwide and causes chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer (Pereira & Medeiros 2014). Finding an effective treatment for *H. pylori* infection has consistently remained a very challenging goal. The first-line regimen to treat *H. pylori* infection currently is triple therapy, consisting of a combination of two standard antibiotics [amoxicillin and clarithromycin (CAM) or metronidazole] plus a proton pump inhibitor (PPI) (Chey et al. 2017). Conventional PPIs are used as the first-line therapy to treat acid-related diseases worldwide. However, they have several limitations, including slow onset of action, limited by cytochrome P450 polymorphisms, unsatisfactory effects at night, and instability in acidic conditions (Oshima & Miwa 2018). Therefore, a more effective strategy is needed for treating this infection.

Being approved in 2015, vonoprazan is a novel potassium-competitive acid blocker (P-CAB) and an addition to a new class of gastric acid-suppressive agents. Vonoprazan was developed to show a rapid, long-lasting, and reversible inhibition of the gastric hydrogen potassium ATPase, the proton pump of the stomach. As such, vonoprazan has been reported to have strong and long-lasting effects (Graham & Dore 2018) and was shown to be more potent than PPI, but the current research on its efficacy against *H. pylori* infection is still lacking. A randomized, double-blind study indicated that vonoprazan (P-CAB)-based treatment was more effective in both first- and second-line *H. pylori* eradication therapy as compared with treatment with lansoprazole, with 16.7% of the findings were in favour of vonoprazan, thus confirming the noninferiority of this medication (Murakami et al. 2016). Importantly, though, most vonoprazan studies have been reported in Japanese populations, however current relative potency PPI data are more established in Western populations (Graham & Tansel 2018). It is also still unclear as to the recommended of vonoprazan-containing *H. pylori* therapies in terms of drugs, doses, or duration.

This systematic review focuses on literature from the year 2010 until the present. Studies describing the clinical effectiveness and safety of vonoprazan-based *H. pylori* eradication therapy in which its effectiveness in comparison to the conventional PPI-based therapy in clinical practice were included. The summation of the efficacy of vonoprazan-based triple therapy including the doses and duration will be discussed with the intention to provide a clearer picture for the use of vonoprazan in the treatment of *H. pylori* infection in a clinical setting.

Methods

Search strategy and study selection

The criteria for considering studies for this review was determined in line with the Population Intervention Comparison Outcome Study (PICOS) design (Methley et al. 2014) framework. Inclusion criteria were as follows: Clinical studies comparing the efficacy of vonoprazan to that of PPI as a first- or second-line regimen for the eradication of *H. pylori* infection in adult participants; therapy administered as part of triple therapy; reported eradication rates; and human study. Animal studies, abstract-only publications, and unpublished studies were excluded.

The MEDLINE, EMBASE, and Cochrane Library electronic databases were searched for potential articles published between 2010 and the third week of February 2019. The following keywords were used: (vonoprazan OR TAK-438 OR Takecab OR P-CAB OR potassium-competitive acid blocker) AND (proton pump inhibitor OR PPI) AND (*Helicobacter pylori* OR *H. pylori*) and MeSH/Emtree terms. The results were not restricted by language. The last search was performed on 21 February 2019.

Titles and abstracts of all retrieved articles were evaluated independently by two reviewers (NMF and NCR) against the inclusion and exclusion criteria. Articles that did not meet the eligibility criteria were excluded based on either the study design, participants, or outcomes. Any disagreement was discussed and resolved by consensus. Full-text versions of the relevant articles were acquired for detailed assessment.

Study quality assessment

The methodological risk of bias for randomized controlled trials (RCTs) was assessed and reported in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1.0) (Higgins & Green 2011), which recommends categorical reporting of the following elements: Random sequence generation; allocation sequence concealment; blinding of participants and personnel; blinding of outcome assessment; completeness of outcomes data; selective outcomes reporting; and other sources of bias (e.g. source of funding). Each domain was judged as being of high, low, or unclear risk of bias as set out in the criteria provided by the handbook. Studies were deemed as having the highest risk of bias if they scored 'high' or 'unclear risk of bias' for the: sequence generation, or allocation concealment, or blinding of participants and personnel, or blinding of outcomes assessment domains based on the growing empirical evidence that these factors are particularly important sources of bias (Egger et al. 2003; Higgins & Green 2011).

The quality of nonrandomized studies or observational studies was assessed in accordance with the Newcastle-Ottawa Scale (NOS) (Stang 2010). The NOS scale uses the total number of stars to assess the quality of a study, with the maximum number of stars being nine. The following domains were evaluated: Selection of participants and representativeness of the cohort; comparability of subjects in different groups according to factors adjusted for; and assessment of outcomes. Studies scoring seven to nine stars were considered as high quality, whereas studies scoring five to six stars were considered as average quality. Separately, a study was considered to be of poor quality if it scored zero stars in any of the three domains.

DATA EXTRACTION

Data from the selected studies were extracted independently by two reviewers using a customised data extraction form. Any discrepancies in data extraction were resolved by discussion between the reviewers. Discrepancies were also resolved between the reviewers with the assistance of an arbiter when necessary. The following information was extracted from the eligible studies: Study details (e.g. name of the first author, year of publication, article title, and sample size); dosage of vonoprazan and PPI therapy; duration of therapy; and eradication rate (per protocol (PP) where applicable). Only PP data were considered in this study unless otherwise stated. Sue et al. (2017a) investigated the efficacy of treatment in CAM-susceptible and CAM-resistant patients. However, only data on CAM-susceptible patients were considered in this review, due to the availability of data for comparison with PPI. Likewise, only the empirical therapy data were considered from the study by Tanabe et al. (2018).

The reporting of this systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Liberati et al. 2009).

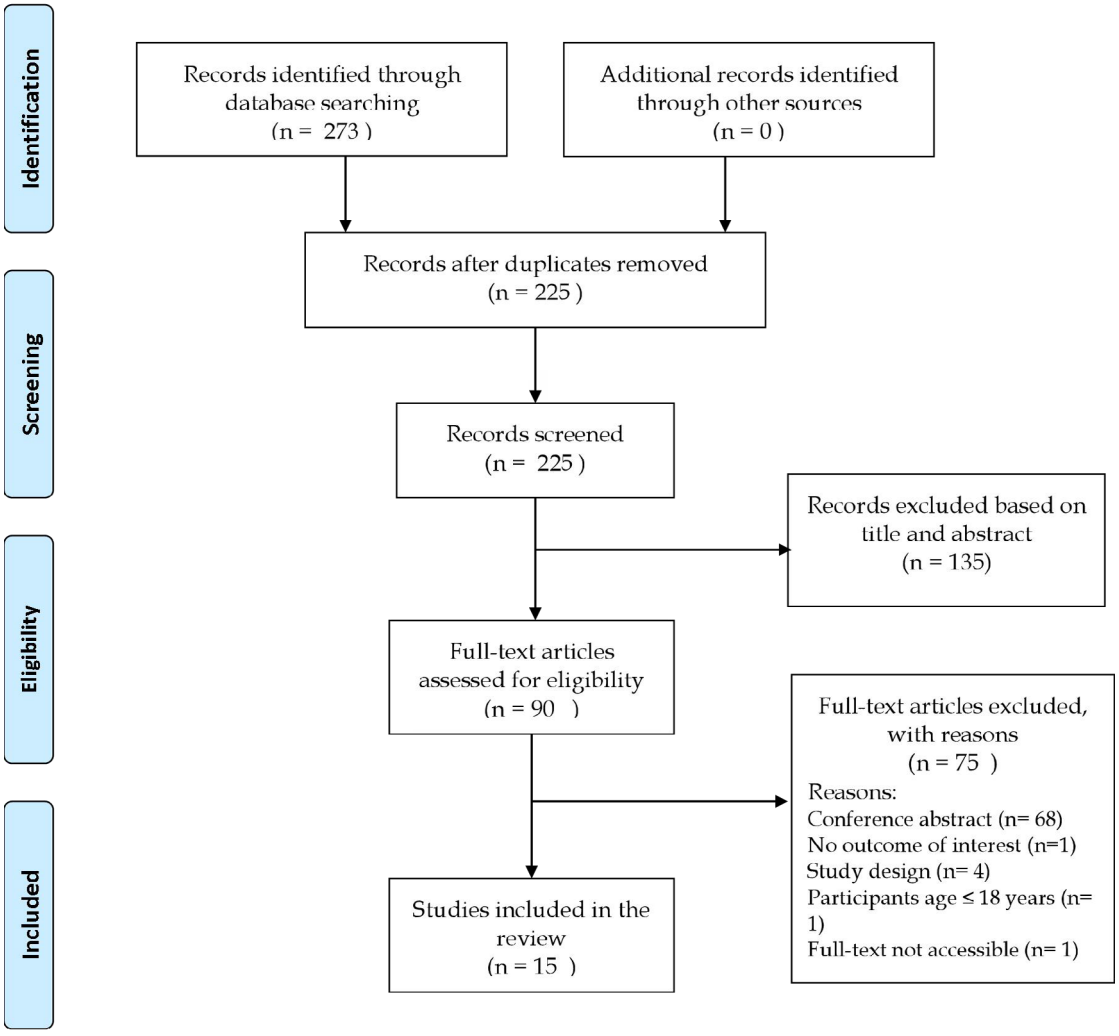

FIGURE 1. Flow of study selection

Results

Study selection and characteristics of the included studies

The details of the search strategy and the literature identified are summarized in Figure 1. The search from the electronic databases using the defined keywords yielded 273 citations. Following the exclusion of duplicates, the titles and abstracts of 225 articles were screened for eligibility. One hundred thirty-five records were excluded based on the type of publication (editorial, review, case reports), study design (single-arm study), study population (negative *H. pylori*, children), and study outcome. Finally, 15 studies were selected for inclusion in this review: three RCTs (Maruyama et al. 2017; Murakami et al. 2016; Sue et al. 2017b); one non-RCT; and 11 observational studies, which included both retrospective and prospective cohort studies (Kajihara et al. 2017; Matsumoto et al. 2016; Mori et al. 2018; Nishizawa et al. 2017; Ono et al. 2017; Saito et al. 2019; Shinozaki et al. 2016; Suzuki et al. 2016; Tanabe et al. 2018; Yamada et al. 2016).

The characteristics of the included studies are summarised in Table 1. All of the studies were published between 2016 and 2019 in Japan. The mean age of participants across all studies was 51.9 years. The proportions of male and female participants were fairly equal across all studies except in one study. In a retrospective study of 88 patients with allergy to penicillin, Ono et al. (2017) has reported a highly disproportionate distribution of male and female participants with a ratio of 2:1. Altogether, 3,715 patients received vonoprazan-based eradication therapy, whilst 7,381 patients received PPI-based eradication therapy. The majority of studies used rabeprazole, lansoprazole, or esomeprazole at standard dose in the PPI-based treatment arm. In most studies, the duration of first-line *H. pylori* eradication therapy was seven days with a regimen composed of amoxicillin and CAM. In one study enrolling participants with allergy to penicillin (Ono et al. 2017), metronidazole and sitafloxacin were used as alternatives for first- and second-line therapies, respectively. Of the 15 studies, only seven provided data on second-line eradication rate comparisons.

Study quality

The risk of bias in one (Murakami et al. 2016) RCT was considered good, whereas the remaining two studies were deemed as being average (Sue et al. 2017b) or poor (Maruyama et al. 2017) quality. Of the 12 non-randomized studies, 10 were judged as being of good quality according to the NOS criteria, with the scoring ranging between seven and nine stars. The study conducted by Ono et al. (2017) scored seven stars, whereas the study by Tanabe et al. (2018) attained zero stars under the comparability domain and hence was considered to be of poor quality.

Efficacy of vonoprazan-based therapy

In two RCTs (Maruyama et al. 2017), first-line vonoprazan-based therapy showed a statistically significant superiority over PPI-based therapy with *H. pylori* eradication rates greater than 90%. In a single-centre, single-blind RCT enrolling 141 patients with *H. pylori*-positive chronic gastritis, Maruyama et al. (2017) reported an PP eradication rate of 95.7% in the vonoprazan treatment group versus 71.4% in the PPI treatment group. Likewise, a randomized double-blinded, multicentre study conducted among 650 patients with a history of peptic ulcer noted PP an eradication rate of 92.6% in the vonoprazan treatment group versus 75.9% in the PPI treatment group. Conversely, one RCT showed no significant difference between the two treatment approaches. In a small multicenter, open-label randomized study enrolling treatment-naïve *H. pylori*-positive patients, Sue et al. (2017b) indicated eradication rates of 88.9 and 86.7% in the vonoprazan and PPI treatment groups, respectively. Alternatively, Kajihara et al. (2017) reported a significant superiority of vonoprazan versus PPI in a retrospective analysis of 209 patients with similar characteristics. It is important to note that the study only used rabeprazole as a comparator.

Similar to the RCTs, the observational studies demonstrated that first-line triple therapy with vonoprazan is significantly superior to the conventional PPI-based triple therapy. One of the earlier studies investigated the effect of vonoprazan versus PPI triple therapy in 2,507 patients, who were further divided into two groups: 2,055 receiving first-line eradication therapy and 452 receiving second-line eradication therapy (Yamada et al. 2016). The authors reported an PP eradication rate of 90.3% in the vonoprazan-based treatment group versus 76.4% in the PPI-based treatment group. However, there was no statistical significance between those receiving vonoprazan-based and PPI-based therapies in the second-line eradication cohort (96.7 and 92.8%, respectively). In another study, Shinozaki et al. (2016) retrospectively reviewed the medical records of 573 patients receiving *H. pylori* eradication therapy and reported that, overall, the treatment using vonoprazan-based therapy is significantly superior to the PPI-based regimen (85 versus 74%, respectively). It is also noteworthy that the subgroup analysis demonstrated that the esomeprazole-based regimen has a similarly high PP eradication rate as the vonoprazan-based regimen (87 and 85%, respectively). The two studies compared vonoprazan-based regimen to an esomeprazole-based regimen. In a retrospective, open-label, single-centre study enrolling 874 patients, Tsujimae et al. (2017) reported an eradication rate of 86.3 versus 79.9% in the vonoprazan- and esomeprazole-based groups, respectively. Elsewhere, a comparable outcome was reported by Saito et al. (2019) in 793 patients in a similarly designed study (88.4% for vonoprazan, 69.5%

for esomeprazole). Furthermore, a higher eradication rate was observed in a study comparing vonoprazan-based and lansoprazole-based therapies. Mori et al. (2018) reported PP eradication rates of 91.0% in the vonoprazan-based treatment group versus 84.7% in the lansoprazole-based treatment group from a retrospective analysis of 580 subjects.

Additionally, Suzuki et al. (2016) investigated both conventional analysis and propensity score-matching in a cohort of 661 patients. The findings showed a PP eradication rate of 91.5% in the vonoprazan-based group versus 77.9% in the PPI-based group in the former and 91.2 versus 71.7%, respectively, with the latter approach. Eradication rates ranging between 85.0 and 95.5% in the vonoprazan-based group versus 66.8 and 86.7% in the PPI-based group were noted with statistical significance.

Meanwhile, Nishizawa et al. (2017) presented eradication rates of 89.4 and 66.8% in the vonoprazan-based and PPI-based regimens, respectively, in a cohort of 3,261 patients with positive *H. pylori* findings. This study also found that the efficacy of vonoprazan was fairly equal among those who are younger or older than 50 years. In a population with allergy to penicillin, Ono et al. (2017) used metronidazole instead of amoxicillin in the first-line treatment regimen and reported a significantly higher eradication rate with the vonoprazan-based treatment compared with the PPI-based therapy (92.3 and 55.6%). Alternatively, use of sitafloxacin together with metronidazole in the second-line regimen attained a 100% eradication rate in both treatment groups. Nevertheless, the *H. pylori* second-line regimen that compared vonoprazan with PPI did not reveal significant differences in the remaining studies (Nishizawa et al. 2017; Mori et al. 2017; Saito et al. 2019; Tsujimae et al 2017; Yamada et al. 2016).

TABLE 1. Characteristics of included studies

Author	Study design	Sample size (V/P)	Dosage of VPZ/PPI	Eradication rates	
Maruyama et al. (2017)	RCT	70/63	VPZ: 20 mg bd PPI: RPZ 10 mg bd/ LPZ 30 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	95.7%*** 71.4%
Murakami et al. (2016)[a]	RCT	329/321	VPZ: 20 mg bd PPI: LPZ 30 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	92.6%*** 75.9%
Sue et al. (2017b)	RCT	54/45	VPZ: 20 mg bd PPI :RPZ 10 mg bd/ LPZ 30 mg bd/ ESO 20 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	88.9% 86.7%
Sue et al. (2017a)	NRCT	823/748	VPZ: 20 mg bd PPI: LPZ 30 mg bd/ RPZ 10 mg bd/ OPZ 20 mg bd/ ESO 20mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM VPZ-AMX-MTZ PPI-AMX-MTZ	86.4%** 79.4% 82.4% 82.1%
Kajihara et al. (2017)	Observational	110/98	VPZ: 20 mg bd PPI: RPZ 10 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	95.5%* 86.7%
Matsumoto et al. (2016)	Observational	125/290	VPZ: 20 mg bd PPI: RPZ 10 mg/ bd/ LPZ 30 mg bd/ ESO 20 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	89.6%** 73.1%

Mori et al. (2018)	Observational	275/249	VPZ: 20 mg bd PPI: LPZ 30 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM VPZ-AMX-MTZ PPI-AMX-MTZ	91.0%* 84.7% 87.0% 87.9%
Nishizawa et al. (2017)	Observational	246/1532	VPZ: 20 mg bd PPI: RPZ 10 mg bd/ LPZ 30 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM VPZ-AMX-MTZ PPI-AMX-MTZ	89.4%*** 66.8% 96.8% 90.5%
Ono et al. (2017)	Observational	31/57	VPZ: 20 mg bd PPI: RPZ 10 mg bd/ LPZ 30 mg bd for 7 days	VPZ-CAM-MTZ PPI-CAM-MTZ VPZ-STX-MTZ VPZ-STX-MTZ	92.3%** 55.6% 100.0% 100.0%
Saito et al. (2019)	Observational	259/272	VPZ: 20 mg bd PPI: ESO 40 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM VPZ-AMX-MTZ PPI-AMX-MTZ	88.4%*** 69.5% 90.7% 90.4%
Shinozaki et al. (2016)	Observational	114/435	VPZ: 20 mg bd PPI: RPZ 10 mg bd/ LPZ 30 mg bd/ ESO 20 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	85.0%** 74.0%
Suzuki (2016)	Observational	181/480	VPZ: 20 mg bd PPI: RPZ 20 mg bd/ LPZ 30 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	91.5%*** 77.9%
Tanabe et al.(2018)	Observational	341/717	VPZ: 20 mg bd PPI: RPZ 10 mg bd/ LPZ 30 mg bd/ ESO 20 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM	97.4%*** 86.3%
Tsujimae et al. (2017)	Observational	439/427	VPZ: 20 mg bd PPI: ESO 20 mg bd for 7 days	VPZ-AMX-CAM PPI-AMX-CAM VPZ-AMX-MTZ PPI-AMX-MTZ	86.3%* 79.9% 91.9% 88.2%
Yamada et al. (2016)	Observational	318/1647	VPZ: 20 mg bd PPI: RPZ 20 mg bd/ LPZ 60 mg bd/ ESO 40 mg bd for 7 days	VPZ-AMX-MTZ PPI-AMX-MTZ VPZ-AMX-MTZ PPI-AMX-MTZ	90.3%*** 76.4% 96.7% 92.8%

DISCUSSION

The standard treatment of *H. pylori* infection involves the use of an acid suppressant, which elevates intragastric pH in combination with at least two antibiotics for seven to 14 days. *H. pylori* will enter the growth phase from a stationary phase at an intragastric pH above 5 (Sachs et al 1996; Sugimoto et al 2007), at which point it becomes susceptible to antibiotics, which targets actively dividing bacterial cells to work. Although the conventional PPIs such as lansoprazole or rabeprazole have been used to suppress gastric acid secretion, the recent *H. pylori* eradication rates resulted from those PPIs have decreased due to an increase in antibiotic-resistant *H. pylori* strains. Increasing the dosage of PPIs and changing antibiotics have been attempted to increase the eradication rate. However, this approach has several limitations related to PPIs, including the slow onset of action, cytochrome P450 polymorphisms, unsatisfactory effects at night, and instability in acidic conditions (Oshima & Miwa 2018).

As an alternative, the development of a newer agent, vonoprazan, which can strongly suppress acid secretion, has been an attractive option for increasing the eradication

rate. The ability of vonoprazan to achieve an intragastric pH greater than 5 and possibly higher than 6 makes it an useful adjuvant for *H. pylori* eradication therapy and able to achieve a high curing rate in combination with amoxicillin plus an antisecretory agent as a dual therapy (Graham & Dore 2018). Given these clinical findings, vonoprazan-based therapy could serve as an appropriate treatment option for *H. pylori* infection. Previously published meta-analyses involving both RCTs and non-RCTs consistently suggested a significantly higher eradication rate for vonoprazan compared with the PPI triple therapy (Dong et al. 2018; Jung et al. 2017; Li et al. 2018). Vonoprazan has several advantages over conventional PPIs, including rapid onset of action, long duration of acid suppression, fewer interindividual variations in terms of acid suppression, and minimum dietary influence on its action (Sugano 2018).

Based on two published RCTs that are included in this study, the eradication rate of vonoprazan based on the PP analysis was above 90%, which is considered highly efficacious and strongly recommended based on the current guidelines. In comparison with the PPI-based therapy, overall, a significantly higher eradication rate for vonoprazan was observed (Maruyama et al. 2017; Murakami et al. 2016; Sue et al. 2018). This superiority of vonoprazan could be due to the better enhancement of antibiotic therapy which is more stable, faster, and with a longer acid reduction capability compared with the PPI (Maruyama et al. 2017; Murakami et al. 2016; Sue et al. 2018). It could therefore be suggested that vonoprazan could be used as an alternative to PPI as the first-line therapy, especially in areas where the use of PPIs falls below an acceptable level. One of the limitations of the currently available research is the lack of data involving a prolonged duration of treatment, which is 14 days, since the recommended *H. pylori* first-line eradication regimen in Japan is seven days of triple therapy (Satoh et al. 2016), which is not recommended in most of the current consensuses elsewhere. A longer duration of treatment with vonoprazan is proven to be more effective based on the Maastricht V. Florence consensus report (Malfertheiner et al. 2012), which stated that the eradication rate can be improved by 5% when the duration of triple therapy is increased from seven to 14 days.

Out of the 15 published studies included in this systematic review, 12 were non-RCTs or observational in nature. Based on these studies; it can be concluded that vonoprazan-based triple therapy is superior to PPI-based triple therapy based on the PP analyses for the treatment of CAM-susceptible *H. pylori* infection (Kajihara et al. 2017; Matsumoto et al. 2016; Mori et al. 2018; Nishizawa et al 2017; Saito et al. 2019; Sue et al. 2017a; Suzuki et al. 2016; Tanabe et al. 2018; Tsujimae et al. 2017; Yamada et al. 2016). This could be due to the highly effective acid-reducing properties of vonoprazan. Sakurai et al. (2016) showed that vonoprazan suppressed acid secretion more rapidly and persistently than the two PPIs esomeprazole and rabeprazole. This was observed from the first day of administration, where the mean pH following the vonoprazan administration was above 5 but dropped to 4 after 24 h of holding time, which greatly exceeded that of the PPIs (Sakurai et al. 2016). However, when CAM is substituted by metronidazole, the eradication rate of vonoprazan-based triple therapy was comparable but noninferior when compared with the PPI-based triple therapy in most studies (Mori et al. 2018; Nishizawa et al. 2017; Ono et al. 2017; Saito et al. 2019; Sue et al. 2017a; Tsujimae et al. 2017; Yamada et al. 2016).

Importantly, although this systematic review demonstrated the benefits of vonoprazan-based triple therapy over PPI-based therapy, it does have several limitations. Most of the included studies are observational studies. The retrospective nature of these studies is a potential cause of heterogeneity across the included studies due to the risk of bias associated with the study design. The PPI subclass (lansoprazole, rabeprazole, esomeprazole) and doses varied in the included studies; for example, the dose of esomeprazole varied from 20 to 60 mg. The relative efficacy of vonoprazan-based triple therapy compared with the PPI-based triple therapy may differ according to the PPI subclass and dose. Shinozaki et al. (2016) showed that the eradication rate of H. *pylori* using vonoprazan was significantly higher than that with lansoprazole and rabeprazole in both intention-to-treat and PP analyses, but showed a similar rate with esomeprazole.

Most studies suggested that the vonoprazan-based triple therapy looks more prominent in terms of the eradication rate for CAM-resistant strains (Li et al. 2018). Although this is true, the eradication rates were not as high as in the susceptible strains (Jung et al. 2018). Based on these findings, the vonoprazan-based triple therapy still cannot be determined as the ultimate therapy for CAM-resistant strains. Interestingly, a prior meta-analysis has reported that the vonoprazan-triple therapy is still superior compared with PPI-triple therapy in both CAM-susceptible and CAM-resistant strains based on a subgroup analysis (Jung et al. 2017), although many other studies have shown no advantages (Mori et al. 2018; Saito et al. 2019; Sue at al. 2017a; Tsujimae et al. 2017). Future studies on this subject with larger sample sizes could provide a better understanding of the possible greater benefit of vonoprazan-based therapy versus PPI for CAM-resistant strains.

The cost-effectiveness of vonoprazan-based therapy compared with the standard PPI would also determine the acceptance and usage of this agent globally. Currently, in Japan, a vonoprazan-based triple therapy costs about USD$51, while a PPI-based triple therapy (rabeprazole, amoxicillin, and CAM) costs

about USD$39 (17). Despite the slightly higher cost of the former, it is overall more cost-effective than the PPI-based triple therapy due to its higher eradication rate, which reduces the needs for second- or third-line treatment (Kajihara et al. 2017).

While vonoprazan might be effective in *H. pylori* eradication therapy, adverse effects are still possible with this new drug. When comparing the safety profiles of vonoprazan and PPIs used for *H. pylori* eradication, there was no significant difference in the incidence of adverse effects (Murakami et al. 2016; Sakurai et al. 2017; Sue et al. 2017a). Notably, vonoprazan caused a wider variety but relatively milder adverse effects as compared with PPIs. The reported adverse effects include diarrhoea, skin eruption, dysgeusia, nausea and vomiting, abdominal pain, appetite loss, and general fatigue (Maruyama et al. 2017; Mori et al. 2018; Sakurai et al. 2017). These adverse effects were only observed in a very small number of patients composing less than 2% of (Murakami et al. 2016) and, overall, there were no serious drug-related, treatment-emergent adverse events reported during the clinical trials on vonoprazan (Sugano et al. 2018). However, with any relatively newer agent, vonoprazan-associated adverse effects need to be closely monitored for and reported for future reference.

Currently, there are only two published systematic reviews on vonoprazan therapy. Li et al. (2018) reviewed primarily the effects of vonoprazan in the treatment of clarithromycin-resistant strains instead of as the first line therapy (Jung et al. 2017), on the other hand, reviewed publications from the years 2011 to 2016; there were at least 7 new publications on vonoprazan published, which was included in this review. Based on these two systematic reviews, it was concluded that vonoprazan is superior to conventional PPI-based therapy for the eradication of clarithromycin-resistant *H. pylori* strains and as the first-line therapy against *H. pylori* infection.

However, one main limitation to consider is all included studies were performed in Japan; thus, the results are not generally applicable to populations in the other regions. Further studies should be conducted in a multitude of regions in order to reach a definitive global conclusion. This review only considered the conventional first-line triple therapy and the second-line step therapy. Since the eradication rate of the vonoprazan-based triple therapy was insufficient in the context of CAM-resistant *H. pylori*, alternative vonoprazan-based regimens including third-line therapy, concomitant therapy, and hybrid therapy should be studied as well. This review also only focused on the *H. pylori* eradication in adults due to limited data on children; thus, the findings is not generally applicable to the other age groups.

Despite these limitations, our systematic review provides a better understanding of the benefits of vonoprazan-based triple therapy as compared to the conventional therapy. In view of a low level of evidence in most of the studies, more high-quality RCTs are warranted in the near future to support the currently available evidence. Up until now, the vonoprazan-based triple therapy has been proven to possess superior efficacy to that of the PPI-based triple therapy as the first-line treatment of *H. pylori* infection.

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