





Review

Expectations for the Dual Therapy with Vonoprazan and Amoxicillin for the Eradication of *H. pylori*

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Abstract: Vonoprazan (VPZ) inhibits gastric acid secretion more potently than proton pump inhibitors. Recently, attention has been focused on the dual therapy with VPZ and amoxicillin (AMOX) for the eradication of *H. pylori*. The dual VPZ/AMOX therapy attains the sufficient eradication rate with lowering the risk of adverse events in comparison with the triple therapy and quadruple therapy. Therefore, the dual VPZ/AMOX therapy is considered a useful eradication regimen for *H. pylori* infection.

Keywords: *H. pylori*; dual therapy; vonoprazan (VPZ); amoxicillin (AMOX); clarithromycin (CAM)



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1. Introduction

One of the first-line eradication regimens for *H. pylori* has long been a triple therapy with proton pump inhibitor (PPI), amoxicillin (AMOX), and clarithromycin (CAM). However, with the recent increase in CAM-resistant strains of *H. pylori*, the eradication rates of PPI/AMOX/CAM therapy have been declining [1], which is a global problem. The reported incidences of CAM-resistance strains of *H. pylori* are approximately 25–32% [2–4]. In addition, since the effects of PPIs are influenced by the genetic polymorphism of CYP2C19, which is the main metabolic enzyme of PPIs, it has been pointed out that the eradication rates in the CYP2C19 extensive metabolizers are lower in comparison with other metabolizers [5,6]. In order to recover the eradication rates of the first-line eradication therapy, bismuth or non-bismuth quadruple therapies are being used, which are recommended especially in areas with high CAM-resistance rates [7]. Although the eradication rates of quadruple therapy are high, multiple drugs must be taken and the frequency of side effects is high.

There have been some reports of dual therapy with PPIs and AMOX as listed in Table 1 [5,8–25]. Originally, eradication therapy for *H. pylori* started with classical triple therapy followed by the dual therapy. However, the eradication rates of the dual therapy have varied as shown in Table 1. After the triple therapy for 1 week was developed [14], the dual therapy with PPI and AMOX was no longer the main therapy for *H. pylori* infection.

Vonoprazan (VPZ) has been clinically available since 2015. VPZ inhibits gastric acid secretion more potently than PPIs [26]. The eradication rate of the triple therapy with VPZ 20 mg bid, CAM 200 mg bid, and AMOX 750 mg bid was reported 92.6%, which was significantly higher than that of the triple therapy with lansoprazole 30 mg and the same doses of CAM and AMOX [27]. Interestingly, in this report, the eradication rate by the triple therapy with VPZ, CAM, and AMOX in patients infected with CAM-resistant strains

of *H. pylori* was 82.0%, suggesting that the dual therapy with VPZ and AMOX for 1 week can attain the eradication rate higher than 80.0%. Then, the attention has recently been focused on the dual therapy with VPZ and AMOX.

Table 1. Lists of reports of dual therapy with PPI and AMOX.

Author	Year	Dosing Scheme of AMOX	Dosing Scheme of PPI	Duration	n	Eradication Rate (%) (ITT)
Furuta [8]	2001	500 mg qid	RPZ 10 mg qid	14 days	17	100.0%
Tai [9]	2019	750 mg qid	EPZ 40 mg tid	14 days	120	91.7%
Shirai [10]	2007	500 mg qid	RPZ 10 mg qid	14 days	66	90.9%
Bayerdorffer [11]	1995	750 mg tid	OPZ 40 mg tid	14 days	139	90.6%
Furuta [12]	2010	500 mg qid	RPZ 10 mg qid	14 days	49	87.8%
Miehlke [13]	2003	750 mg qid	OPZ 40 mg qid	14 days	38	83.8%
Furuta [5]	2001	500 mg tid	RPZ 10 mg bid	14 days	97	81.4%
Schwartz [14]	1998	1000 mg tid	LPZ 30 mg tid	14 days	51	77%
Miehlke [15]	2006	1000 mg tid	OPZ 40 mg tid	14 days	72	70%
Miyoshi [16]	2001	500 mg tid	OPZ 20 mg bid	14 days	98	66.3%
Nishizawa [17]	2012	500 mg qid	RPZ 10 mg qid	14 days	46	63.0%
Moiyoshi [16]	2001	500 mg tid	RPZ 10 mg tid	14 days	101	62.4%
Isomoto [18]	2003	1000 mg bid	RPZ 20 mg bid	14 days	63	59%
Wong [19]	2000	1000 mg bid	LPZ 30 mg bid	14 days	75	57%
Attumi [20]	2014	1000 mg bid	Dexlansoprazole 120 mg bid	14 days	13	53.8%
Schwartz [14]	1998	1000 mg tid	LPZ 30 mg bid	14 days	49	53%
Koizumi [21]	1998	500 mg tid	OPZ 20 mg qd	14 days	25	52%
Furuta [22]	1998	500 mg qid	OPZ 20 mg qd	14 days	62	50%
Bell [23]	1995	500 mg tid	OPZ 40 mg qd	14 days	60	46%
Cottrill [24]	1997	1000 mg bid	OPZ 40 mg qd	14 days	85	44%
Kagaya [25]	2000	750 mg bid	LPZ 30 mg qd	14 days	24	43%

Abbreviations: PPI = proton pump inhibitor, EPZ = esomeprazole, LPZ = lansoprazole, OPZ = omeprazole, RPZ = rabeprazole, qd = once daily, bid = twice daily, tid = three times daily, qid = four times daily.

2. Gastric Acid Secretion Required for the Dual Therapy with Amoxicillin

AMOX exerts its antibacterial action by binding to penicillin-binding protein (PBP) and inhibiting the synthesis of bacterial cell wall. According to a report examining the relationship between PBP expression in *H. pylori* and pH, *H. pylori* does not proliferate and PBP expression is low at around pH 3.0 [28]. However, at pH 7.4, *H. pylori* proliferates vigorously and the expression of PBP also increases, indicating that the number of targets of AMOX increases, and it is thought that AMOX becomes more effective. In addition, inhibition of gastric acid secretion leads to stabilization of antibacterial drugs in the stomach and increases their concentration in gastric juice [29], which greatly contributes to the success of eradication.

There is a report examining the relationship among the success or failure of eradication by triple therapy, CAM-resistance of *H. pylori* and intragastric pH [30]. When the mean 24-h intragastric pH is less than 4.5 and when the percent time for intragastric pH < 4.0 is longer than 40%, eradication will fail even if *H. pylori* strain is sensitive to CAM (Figure 1 blue area). In contrast, when the mean 24-h intragastric pH exceeds 5, CAM-susceptible bacteria can be successfully eradicated (Figure 1 yellow area). Interestingly, if the mean 24-h intragastric pH in the stomach is higher than 6.5 and the percent time for intragastric pH < 4.0 is 5% or less (pink part in Figure 1), in other words, if the pH 4 holding time ratio (pH 4 HTR) is 95% or more and if the mean 24 h intragastric pH is no less than 6.5, CAM-resistant strains can be eradicated. Therefore, it is suggested that eradication of *H. pylori* can be attained by a single antibiotic, such as AMOX, when the intragastric pH is strictly controlled to be neutral.

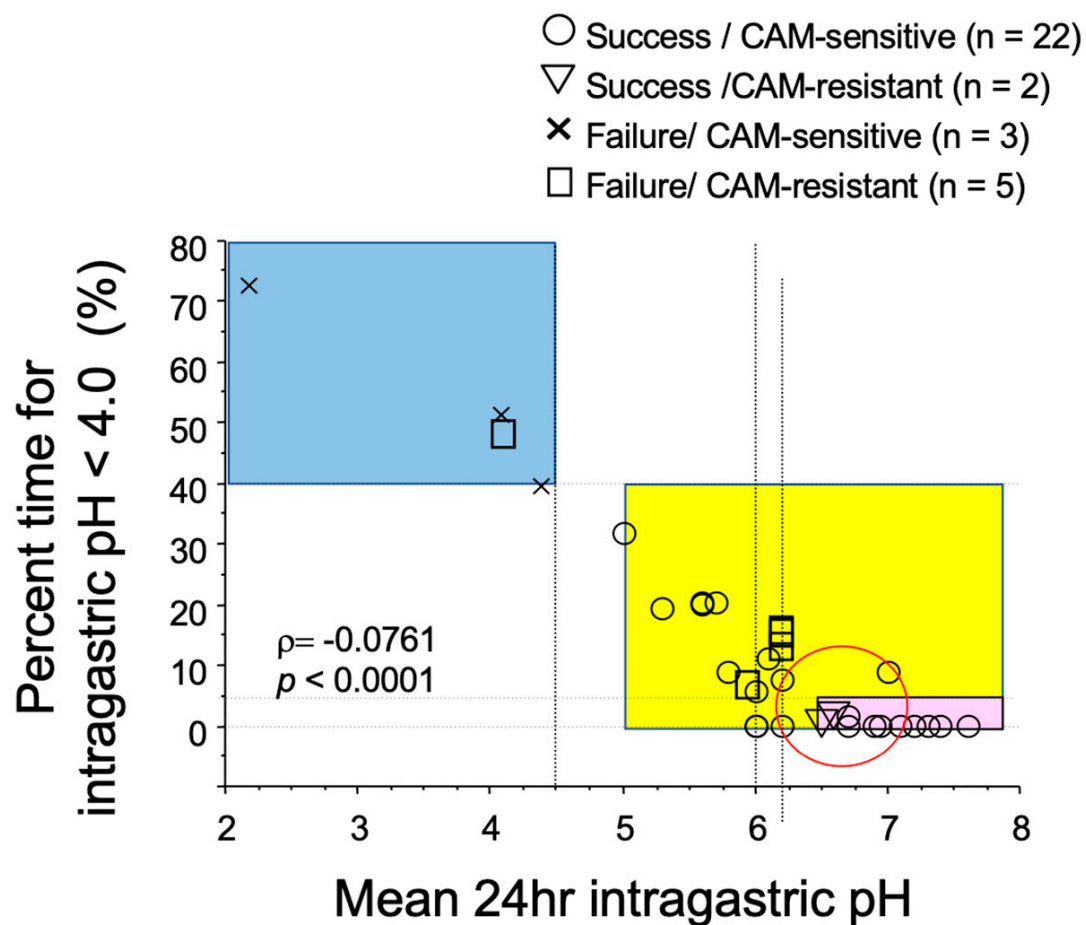


Figure 1. Relationship of success or failure of eradication of *H. pylori* by the triple therapy with PPI, amoxicillin, and clarithromycin (CAM) with CAM-resistance, 24 h intragastric pH, and percent time for intragastric pH < 4.0. When the mean intragastric pH is less than 4.5 and the percent time for intragastric pH < 4.0 was longer than 40% (blue area), eradication of *H. pylori* fails in patients infected with not only CAM-resistant strains (□) but also CAM-sensitive strains (×) of *H. pylori*. When 24 h intragastric pH is higher than 5.0 (yellow area), eradication of *H. pylori* succeeds for CAM-sensitive strains (○) of *H. pylori*. When the mean intragastric pH is no less than 6.5 and the percent time for intragastric pH < 4.0 is less than 5% (pink area), eradication of *H. pylori* succeeds in patients infected with CAM-resistant strains (▽) as well as CAM-sensitive strains (○) of *H. pylori*. Modified [30].

The relationship between dosing schemes of PPI and eradication rates of the dual therapies with PPI and AMOX listed in Table 1 is plotted in Figure 2. As the dosing frequency of PPI increases, the eradication rates increase. Because the acid inhibitory effect of PPI is enhanced by the divided dosing [31], the eradication rates with dual therapy with PPI and AMOX increase with the grade of acid inhibition.

Kagami et al. [32] compared the acid inhibitory effects of VPZ and EPZ and found that 95% of pH 4 HTR could be achieved by VPZ 20 mg once daily and that 100.0% of pH 4 HTR and 6.8 of the mean 24 h intragastric pH could be attained by VPZ 20 mg twice daily, but not EPZ (Figure 3). Moreover, the acid inhibitory action of VPZ was not influenced by CYP2C19 polymorphism, meaning that the gastric acid inhibition required for eradication of the *H. pylori* by the dual therapy with AMOX can be achieved by VPZ 20 mg twice a day irrespective of CYP2C19 polymorphism.

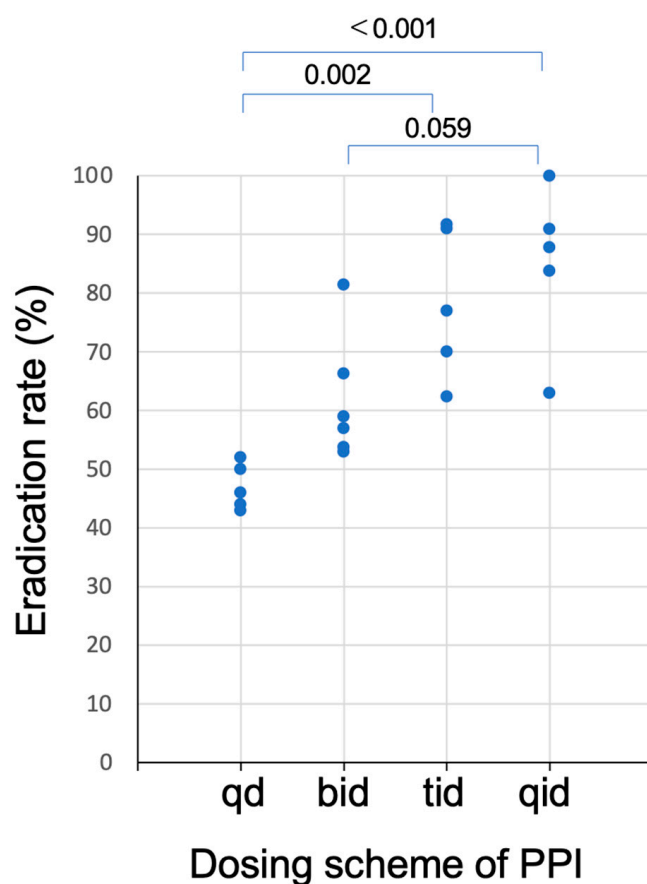


Figure 2. Plots of the eradication rates of studies of dual therapy with PPI and amoxicillin as a function of dosing schemes of PPI listed in Table 1. Eradication rates of regimen with three (tid) or four (qid) times daily dosing of PPI was significantly higher than those with once (qd) or twice (bid) daily dosing.

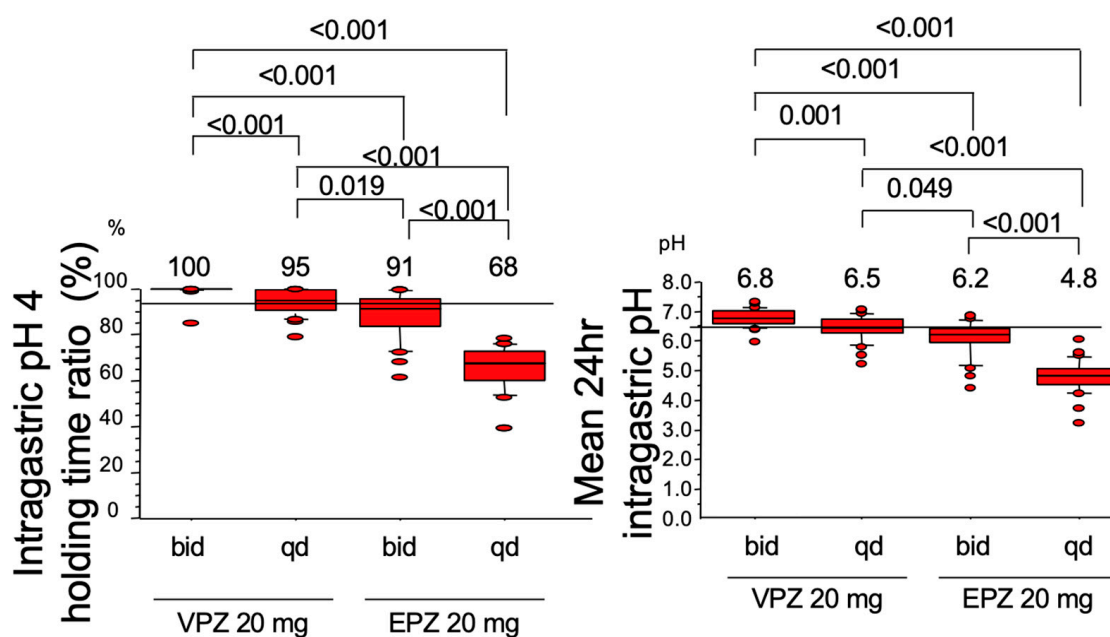


Figure 3. Intragastric pH 4 holding time ratio (Left panel) and mean 24 h intragastric pH (Right panel) attained by the twice (bid) or once (qd) daily dosing of 20 mg of vonoprazan (VPZ) or esomeprazole (EPZ) on day 7. VPZ 20 mg twice daily can attain both the intragastric pH 4 holding time ratio 100.0% and the mean 24 h intragastric pH 6.8.

3. Antibacterial Effect and Optimal Dosing Scheme of Amoxicillin

The relationship between the eradication rates and dosing scheme of AMOX is shown in Figure 4. When AMOX was dosed twice daily, the eradication rates were all less than 60%. To attain eradication rates higher than 90.0%, at least 3 times daily dosing seems necessary for AMOX in the dual therapy. Because the antibacterial effect of AMOX is time-dependent [33] and because it has no post antibiotic effect [34], its antibacterial activity depends on the percent time above MIC (%T > MIC) [35]. Since the plasma half-life of AMOX is as short as around 1 h, it will decrease below MIC in a few hours after dosing, and therefore, it is necessary to be dosed 3–4 times a day for AMOX to be effective. This is the reason why results of the twice-daily dosing regimens of AMOX are insufficient. In contrast, in reports that achieved high eradication rates, AMOX was administered 3–4 times daily when PPI was also administered at high doses 3–4 times a day.

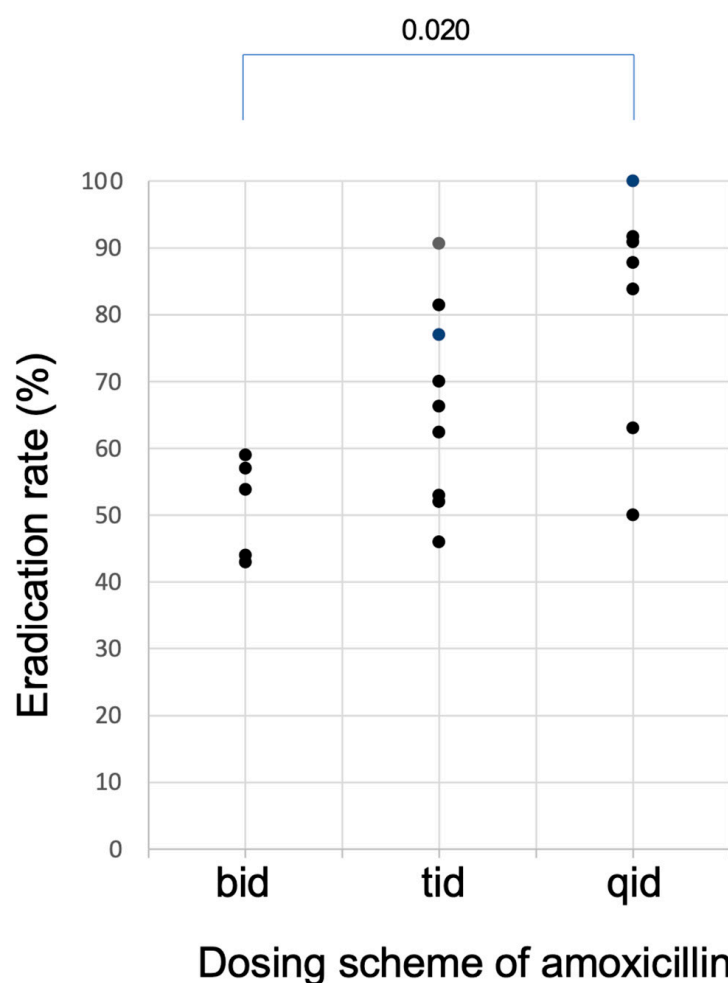


Figure 4. Plots of the eradication rates of studies of dual therapy with PPI and amoxicillin listed in Table 1 as a function of dosing schemes of amoxicillin. Eradication rates higher than 90.0% can be attained when amoxicillin was dosed at least three time daily (tid).

There was no significant correlation between the total daily dose of AMOX and eradication rates in the regimens listed in Table 1 ($p = 0.414$).

Accordingly, to attain the sufficient eradication rates by the dual therapy with AMOX and an acid inhibitor, it is considered necessary to administer AMOX in 3 or more divided doses under the potent acid inhibition that can be attained by the higher doses of PPI dosed 3 or 4 times daily or VPZ 20 mg twice daily. Because the acid inhibitory effect of PPI is influenced by CYP2C19 polymorphism, but not for VPZ, VPZ is ideal and should be used for the dual therapy.

It is obvious that the time above the MIC obtained with 3 doses of AMOX 500 mg is longer than the time above the MIC obtained with 2 doses of AMOX 750 mg (Figure 5). Furthermore, since the MIC is lowered by strongly suppressing gastric acid, it is speculated that the time above the MIC will be even longer when an ultra-potent acid inhibitor, such as VPZ, is used.

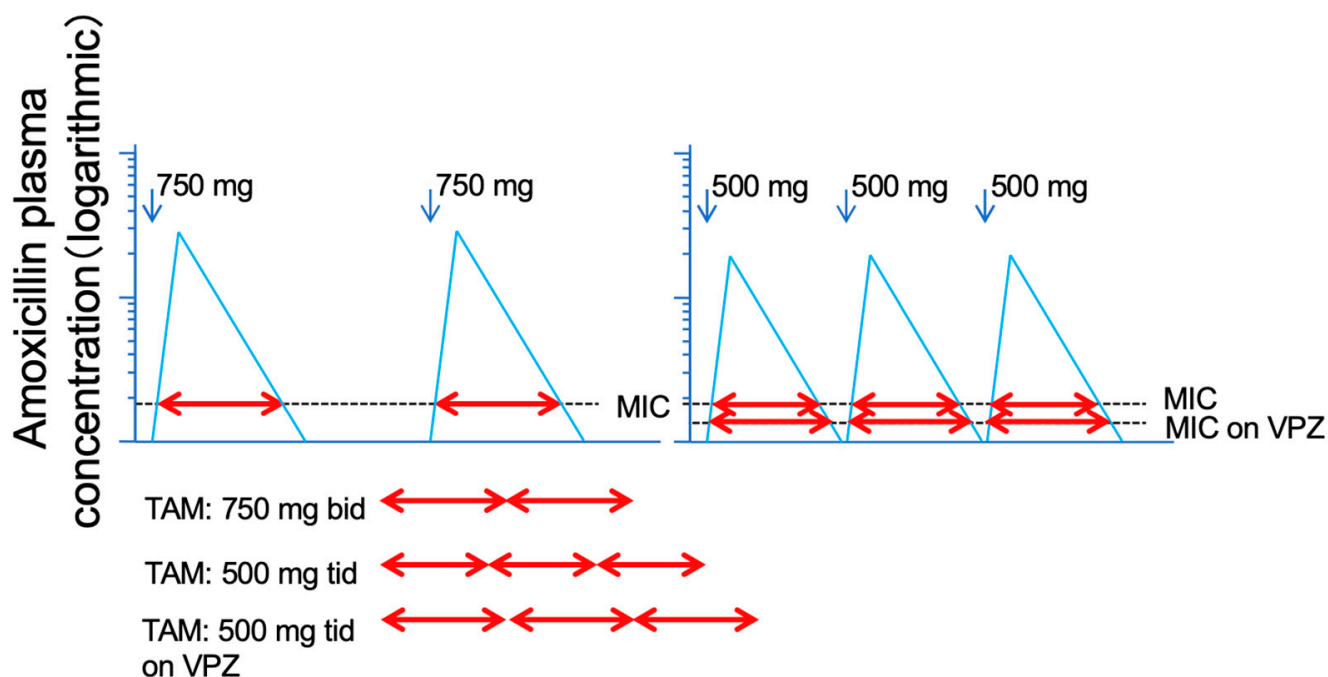


Figure 5. Logarithmic model of Time above MIC ($T > MIC$) of plasma level of amoxicillin 750 mg dosed twice and 500 mg three times daily. The total of $T > MIC$ of amoxicillin 500 mg three times daily is longer than that of 750 mg twice daily. By using the vonoprazan, MIC is expected to be lowered, resulting in the further elongation of $T > MIC$ of amoxicillin.

4. Eradication Rates of Dual Therapy with Vonoprazan and Amoxicillin

The eradication rate reported in the first study of the dual therapy with VPZ and AMOX was 92.9%, which was identical to that of the triple therapy with VPZ, AMOX, and CAM [36]. In this report, there were no statistically significant differences in adverse events between dual therapy and triple therapy, but tended to be less with dual therapy. Therefore, it was considered that the dual VPZ/AMOX therapy could be a regimen for the first-line eradication therapy.

Since this report, there have been several studies on the dual therapy with VPZ and AMOX as listed in Table 2 [37–45]. Although the sufficient eradication rate could be attained by the first study [36], the eradication rates of the dual VPZ/AMOX therapies varies by different dosing schemes of AMOX and treatment periods as in the cases of PPIs.

As the duration of the treatment period, Lin et al. [42] reported that the dual VPZ/AMOX therapies for 7 days could not achieve an acceptable eradication rates (58.3% and 60.7%). Hu et al. [45] compared the 7 day and 10 day regimen with different AMOX dosing schemes and found that none of the 7 or 10 day regimens could attain the sufficient eradication rates. However, they reported that a 14 day regimen could attained a sufficient eradication rate (89.1%) [37]. However, studies by Suzuki et al. [38] Gotoda et al. [39] and Sue et al. [40], which were all from Japan, demonstrated that 7 days seemed a sufficient treatment period for the dual VPZ/AMMOX therapy. The optimal treatment periods for the dual VPZ/AMOX therapy seem to differ among different regions and ethnic groups.

Table 2. Lists of reports of dual therapy with VPZ and AMOX.

Author	Year	Dosing Scheme of AMOX	Dosing Scheme of VPZ	Duration	n	Eradication Rate (%) (ITT)
Furuta [36]	2019	500 mg tid	20 mg bid	7 days	56	92.9%
Suzuki [38]	2020	750 mg bid	20 mg bid	7 days	168	84.5%
Gotoda [39]	2020	750 mg bid	20 mg bid	7 days	60	85.0%
Sue [40]	2022	500 mg qid	20 mg bid	7 days	20	90.0%
Lin [42]	2022	750 mg qid	20 mg bid	7 days	84	58.3%
Lin [42]	2022	500 mg qid	20 mg bid	7 days	61	60.7%
Hu [45]	2022	1000 mg bid	20 mg bid	7 days	24	66.7%
Hu [45]	2022	1000 mg bid	20 mg bid	10 days	37	89.2%
Hu [45]	2022	1000 mg tid	20 mg bid	7 days	21	81.0%
Hu [45]	2022	1000 mg tid	20 mg bid	10 days	37	81.1%
Qian [41]	2022	750 mg qid	20 mg bid	10 days	125	93.4%
Qian [41]	2022	1000 mg bid	20 mg bid	10 days	125	85.1%
Hu [37]	2022	1000 mg bid	20 mg bid	14 days	55	89.1%
Hu [37]	2022	1000 mg tid	20 mg bid	14 days	55	87.3%
Zuberi [44]	2022	1000 mg bid	20 mg bid	14 days	92	93.5%
Chey [46]	2022	1000 mg tid	20 mg bid	14 days	324	78.5%
Gao [43]	2022	1000 mg tid/750 mg qid	10 mg bid	14 days	43	95.3%
Gao [43]	2022	1000 mg tid/750 mg qid	20 mg bid	14 days	143	91.6%

Abbreviations: VPZ = vonoprazan AMOX = amoxicillin, bid = twice daily, tid = three times daily, qid = 4 times daily.

Qian et al. [41] compared two types of ten-day dual VPZ/AMOX therapies with bismuth-containing quadruple therapy. The dual therapy with VPZ 20 mg bid and AMOX 750 mg qid attained the 93.4% of eradication rate, which was as high as that of the quadruple therapy (90.9%). Interestingly, the incidence of side effects of the dual therapy was significantly lower than that of the quadruple therapy. Zuberi [44] also reported that dual VPZ/AMOX therapy provides an acceptable and higher eradication rate (93.5%) with fewer adverse events in comparison with the triple therapy with omeprazole, CAM, and AMOX. Gao [43] reported that the dual VPZ/AMOX therapies were useful as the rescue therapy. However, the eradication rate of the report by Chey [46] was 78.5%, although the regimen was almost the same as that of study of Gao [43]. Accordingly, the optimal dosing schemes of the dual VPZ/AMOX therapy remains to be determined. The best regimens of the dual VPZ/AMOX therapy should be developed for each region and ethnicity.

5. Merits of the Dual Therapy with Vonoprazan and Amoxicillin

One of merits of the dual VPZ/AMOX therapy is to reduce the incidence of adverse events. As noted above, the incidence of adverse events observed in the dual therapies was lower in comparison with the triple therapy and quadruple therapy [36,41].

Pharmacologically, the greatest advantage of the dual therapy is that fewer drugs are used, reducing the risk of drug–drug interactions. CAM, which is often used in triple therapy, is a potent inhibitor of CYP3A4 and p-glycoprotein [47]. CAM has been reported to increase plasma levels of drugs metabolized and transported by these enzymes [29]. However, CAM is not involved in the dual VPZ/AMOX therapy. Therefore, the risk of drug–drug interactions related to CAM can be avoided. Of course, AMOX and VPZ are not without risk of interaction. VPZ has also been reported to affect the antiplatelet effects of Clopidogrel and Prasugrel [48], and has also been reported to affect CYPs [49]. Therefore, it cannot be said that the dual VPZ/AMOX is completely safe. However, it is considered safer than triple therapy from the viewpoint of drug–drug interactions. CAM also has an arrhythmia risk [50]. Therefore, dual therapy with VPZ and AMOX is particularly useful in patients with a risk of arrhythmia, such as QT prolongation.

6. Dual Therapy with Vonoprazan and Amoxicillin with Reference to Clarithromycin Susceptibility

Suzuki et al. investigated influence of the CAM resistance in the comparative study of the dual therapy with VPZ 20 mg bid + AMOX 750 mg bid for 1 week and the triple therapy with VPZ 20 mg bid + CAM 20 mg bid + AMOX 750 mg bid for 1 week. In their study in patients infected with CAM-sensitive strains of *H. pylori*, the eradication rates of the dual and triple therapies were 85.5% and 95.1%, respectively. However, in patients infected with CAM-resistant strains of *H. pylori*, the respective eradication rates were 92.3% and 76.2% ($p < 0.05$). In other words, CAM has a negative effect on patients infected with CAM-resistant strains of *H. pylori*. There are many possible reasons, but one possible explanation is the pharmacodynamic antagonism between CAM and APMC.

In other bacteria, the combination of AMOX and CAM has been reported to be antagonistic [51,52]. The target of AMOX is PBP as noted above, which is the enzyme involved in biosynthesis of bacterial cell wall. When *H. pylori* grows, the expression of PBP is enhanced, which means that the expression of target of AMOX is increased, resulting in the bactericidal effect of AMOX being enhanced. In contrast, when the growth of *H. pylori* is inhibited, the expression of PBP is decreased. In this situation, the bactericidal effect of AMOX is decreased because the expression of target of AMOX is decreased. CAM is known as the inhibitor of rRNA, indicating that CAM inhibits the protein synthesis including PBP. Then, the sensitivity to AMOX is decreased by CAM.

However, if the patient is infected with CAM-sensitive strains, there is no problem because they can be killed by CAM. However, in cases infected with CAM-resistant strains of *H. pylori*, there might be some problems. MIC ranges of CAM-resistant strains of *H. pylori* are very wide (e.g., from 1 µg/mL to >32 µg/mL). In cases infected with CAM-weakly resistant strains of *H. pylori*, CAM will work halfway. Although *H. pylori* strains cannot be killed by CAM, the inhibitory effect of CAM on rRNA may affect the subsequent protein synthesis including PBP, leading to the reduced sensitivity to AMOX [53]. This seems to be the reason why the eradication rates attained by a PPI, AMOX, and CAM were reportedly very low in patients infected with CAM-resistant strains of *H. pylori* [54,55], although AMOX-resistant strains of *H. pylori* are rare.

7. Strategy for Patients Allergic to Penicillin

The dual therapy with VPZ and AMOX cannot be used for patients allergic to penicillin. Gao et al. [56] performed dual therapy with VPZ 20 mg bid and tetracycline 500 mg tid (body weight < 70 kg) or 500 mg qid (body weight ≥ 70 kg) for 14 days in patients who were allergic to penicillin or who had failed before. The eradication rate was 93.5%. Therefore, it is suggested that if one antibacterial agent with high susceptibility is selected besides AMOX, *H. pylori* eradication can be achieved with dual therapy with VPZ plus single effective antibacterial agent.

8. Conclusions

As mentioned above, the greatest merit of the dual VPZ/AMOX therapy is to reduce the risk of adverse events without lowering the eradication rates. In this regimen, CAM is not used, indicating the risk reduction of drug–drug interactions, arrhythmia, and other adverse events caused by CAM. The regimen is simple. There is also a report of the effective dual therapy with VPZ and single antimicrobial agent other than AMOX, such as tetracycline.

Now that we have vonoprazan in our hands, it is expected that eradication therapy will be reconstructed into a simpler regimen, such as dual therapy with VPZ and one antibacterial agent with high susceptibility (i.e., AMOX) in the optimal dosing scheme. It is also expected that we can break away from the stereotype of using multiple antibiotics to eradicate *H. pylori*.

Unfortunately, the use of VPZ is not widespread worldwide. It is hoped that VPZ will become widely available around the world in the future, and new drugs with similar effects will be developed, leading to the simplification of eradication regimens in many countries.

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Abbreviations

AMOX = amoxicillin, CAM = clarithromycin, CYP = cytochrome P450, EPZ = esomeprazole, RPZ = rabeprazole, T>MIC = time above MIC, VPZ = vonoprazan.

References

1. Sasaki, M.; Ogasawara, N.; Utsumi, K.; Kawamura, N.; Kamiya, T.; Kataoka, H.; Tanida, S.; Mizoshita, T.; Kasugai, K.; Joh, T. Changes in 12-Year First-Line Eradication Rate of *Helicobacter pylori* Based on Triple Therapy with Proton Pump Inhibitor, Amoxicillin and Clarithromycin. *J. Clin. Biochem. Nutr.* **2010**, *47*, 53–58. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Fasciana, T.; Calà, C.; Bonura, C.; Di Carlo, E.; Matranga, D.; Scarpulla, G.; Manganaro, M.; Camilleri, S.; Giammanco, A. Resistance to clarithromycin and genotypes in *Helicobacter pylori* strains isolated in Sicily. *J. Med. Microbiol.* **2015**, *64*, 1408–1414. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Tsuda, M.; Watanabe, Y.; Oikawa, R.; Watanabe, R.; Higashino, M.; Kubo, K.; Yamamoto, H.; Itoh, F.; Kato, M. Clinical evaluation of a novel molecular diagnosis kit for detecting *Helicobacter pylori* and clarithromycin-resistant using intragastric fluid. *Helicobacter* **2022**, *27*, e12933. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Sue, S.; Ogushi, M.; Arima, I.; Kuwashima, H.; Nakao, S.; Naito, M.; Komatsu, K.; Kaneko, H.; Tamura, T.; Sasaki, T.; et al. Vonoprazan- vs. proton-pump inhibitor-based first-line 7-day triple therapy for clarithromycin-susceptible *Helicobacter pylori*: A multicenter, prospective, randomized trial. *Helicobacter* **2018**, *23*, e12456. [\[CrossRef\]](#)
5. Furuta, T.; Shirai, N.; Takashima, M.; Xiao, F.; Hanai, H.; Nakagawa, K.; Sugimura, H.; Ohashi, K.; Ishizaki, T. Effects of genotypic differences in CYP2C19 status on cure rates for *Helicobacter pylori* infection by dual therapy with rabeprazole plus amoxicillin. *Pharmacogenetics* **2001**, *11*, 341–348. [\[CrossRef\]](#)
6. Furuta, T.; Shirai, N.; Takashima, M.; Xiao, F.; Hanai, H.; Sugimura, H.; Ohashi, K.; Ishizaki, T.; Kaneko, E. Effect of genotypic differences in CYP2C19 on cure rates for *Helicobacter pylori* infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. *Clin. Pharmacol. Ther.* **2001**, *69*, 158–168. [\[CrossRef\]](#)
7. Malfertheiner, P.; Megraud, F.; O’morain, C.A.; Gisbert, J.P.; Kuipers, E.J.; Axon, A.T.; Bazzoli, F.; Gasbarrini, A.; Atherton, J.; Graham, D.Y.; et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* **2017**, *66*, 6–30. [\[CrossRef\]](#)
8. Furuta, T.; Shirai, N.; Xiao, F.; Takashita, M.; Sugimoto, M.; Kajimura, M.; Ohashi, K.; Ishizaki, T. High-dose rabeprazole/amoxicillin therapy as the second-line regimen after failure to eradicate *H. pylori* by triple therapy with the usual doses of a proton pump inhibitor, clarithromycin and amoxicillin. *Hepatogastroenterology* **2003**, *50*, 2274–2278.
9. Tai, W.-C.; Liang, C.-M.; Kuo, C.-M.; Huang, P.-Y.; Wu, C.-K.; Yang, S.-C.; Kuo, Y.-H.; Lin, M.-T.; Lee, C.-H.; Hsu, C.-N.; et al. A 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy regimen achieves a high eradication rate as first-line anti-*Helicobacter pylori* treatment in Taiwan: A prospective randomized trial. *J. Antimicrob. Chemother.* **2019**, *74*, 1718–1724. [\[CrossRef\]](#)
10. Shirai, N.; Sugimoto, M.; Kodaira, C.; Nishino, M.; Ikuma, M.; Kajimura, M.; Ohashi, K.; Ishizaki, T.; Hishida, A.; Furuta, T. Dual therapy with high doses of rabeprazole and amoxicillin versus triple therapy with rabeprazole, amoxicillin, and metronidazole as a rescue regimen for *Helicobacter pylori* infection after the standard triple therapy. *Eur. J. Clin. Pharmacol.* **2007**, *63*, 743–749. [\[CrossRef\]](#)

11. Bayerdörffer, E.; Miehke, S.; Mannes, G.A.; Sommer, A.; Höchter, W.; Weingart, J.; Heldwein, W.; Klann, H.; Simon, T.; Schmitt, W.; et al. Double-blind trial of omeprazole and amoxicillin to cure *Helicobacter pylori* infection in patients with duodenal ulcers. *Gastroenterology* **1995**, *108*, 1412–1417. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Furuta, T.; Sugimoto, M.; Kodaira, C.; Nishino, M.; Yamade, M.; Uotani, T.; Ikuma, M.; Shirai, N. The dual therapy with 4 times daily dosing of rabeprazole and amoxicillin as the 3rd rescue regimen for eradication of *H. pylori*. *Hepatogastroenterology* **2010**, *57*, 1314–1319. [\[PubMed\]](#)
13. Miehke, S.; Kirsch, C.; Schneider-Brachert, W.; Haferland, C.; Neumeyer, M.; Bastlein, E.; Papke, J.; Jacobs, E.; Vieth, M.; Stolte, M.; et al. A Prospective, Randomized Study of Quadruple Therapy and High-Dose Dual Therapy for Treatment of *Helicobacter pylori* Resistant to Both Metronidazole and Clarithromycin. *Helicobacter* **2003**, *8*, 310–319. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Schwartz, H.; Krause, R.; Sahba, B.; Haber, M.; Weissfeld, A.; Rose, P.; Siepmann, N.; Freston, J. Triple versus dual therapy for eradicating *Helicobacter pylori* and preventing ulcer recurrence: A randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. *Am. J. Gastroenterol.* **1998**, *93*, 584–590. [\[CrossRef\]](#)
15. Miehke, S.; Hansky, K.; Schneider-Brachert, W.; Kirsch, C.; Morgner, A.; Madisch, A.; Kuhlisch, E.; Bästlein, E.; Jacobs, E.; Bayerdörffer, E.; et al. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Aliment. Pharmacol. Ther.* **2006**, *24*, 395–403. [\[CrossRef\]](#)
16. Miyoshi, M.; Mizuno, M.; Ishiki, K.; Nagahara, Y.; Maga, T.; Torigoe, T.; Nasu, J.; Okada, H.; Yokota, K.; Oguma, K.; et al. A randomized open trial for comparison of proton pump inhibitors, omeprazole versus rabeprazole, in dual therapy for *Helicobacter pylori* infection in relation to CYP2C19 genetic polymorphism. *J. Gastroenterol. Hepatol.* **2001**, *16*, 723–728. [\[CrossRef\]](#)
17. Nishizawa, T.; Suzuki, H.; Maekawa, T.; Harada, N.; Toyokawa, T.; Kuwai, T.; Ohara, M.; Suzuki, T.; Kawanishi, M.; Noguchi, K.; et al. Dual therapy for third-line *Helicobacter pylori* eradication and urea breath test prediction. *World J. Gastroenterol.* **2012**, *18*, 2735–2738. [\[CrossRef\]](#)
18. Isomoto, H.; Inoue, K.; Furusu, H.; Enjoji, A.; Fujimoto, C.; Yamakawa, M.; Hirakata, Y.; Omagari, K.; Mizuta, Y.; Murase, K.; et al. High-dose rabeprazole-amoxicillin versus rabeprazole-amoxicillin-metronidazole as second-line treatment after failure of the Japanese standard regimen for *Helicobacter pylori* infection. *Aliment. Pharmacol. Ther.* **2003**, *18*, 101–107. [\[CrossRef\]](#)
19. Wong, B.; Xiao, S.; Hu, P.; Qian, S.; Huang, N.; Li, Y.; Manan, C.; Lesmana, L.; Carpio, R.; Perez, J.Y.; et al. Comparison of lansoprazole-based triple and dual therapy for treatment of *Helicobacter pylori*-related duodenal ulcer: An Asian multicentre double-blind randomized placebo controlled study. *Aliment. Pharmacol. Ther.* **2000**, *14*, 217–224. [\[CrossRef\]](#)
20. Attumi, T.A.; Graham, D.Y. High-Dose Extended-Release Lansoprazole (Dexlansoprazole) and Amoxicillin Dual Therapy for *Helicobacter pylori* Infections. *Helicobacter* **2014**, *19*, 319–322. [\[CrossRef\]](#)
21. Koizumi, W.; Tanabe, S.; Hibi, K.; Imaizumi, H.; Ohida, M.; Okabe, H.; Saigenji, K.; Okayasu, I. A prospective randomized study of amoxicillin and omeprazole with and without metronidazole in the eradication treatment of *Helicobacter pylori*. *J. Gastroenterol. Hepatol.* **1998**, *13*, 301–304. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Furuta, T.; Ohashi, K.; Kamata, T.; Takashima, M.; Kosuge, K.; Kawasaki, T.; Hanai, H.; Kubota, T.; Ishizaki, T.; Kaneko, E. Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann. Intern. Med.* **1998**, *129*, 1027–1030. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Bell, G.D.; Bate, C.M.; Axon, A.T.R.; Tildesley, G.; Kerr, G.D.; Green, J.R.B.; Emmas, C.E.; Taylor, M.D. Addition of metronidazole to omeprazole/amoxicillin dual therapy increases the rate of *Helicobacter pylori* eradication: A double-blind, randomized trial. *Aliment. Pharmacol. Ther.* **1995**, *9*, 513–520. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Cottrill, M.R.B.; Kinnon, C.M.C.; Mason, I.; Chesters, S.A.; Slatcher, G.; Copeman, M.B.; Turbitt, M.L. Two omeprazole-based *Helicobacter pylori* eradication regimens for the treatment of duodenal ulcer disease in general practice. *Aliment. Pharmacol. Ther.* **1997**, *11*, 919–927. [\[CrossRef\]](#)
25. Kagaya, H.; Kato, M.; Komatsu, Y.; Mizushima, T.; Sukegawa, M.; Nishikawa, K.; Hokari, K.; Takeda, H.; Sugiyama, T.; Asaka, M. High-dose ecabet sodium improves the eradication rate of *Helicobacter pylori* in dual therapy with lansoprazole and amoxicillin. *Aliment. Pharmacol. Ther.* **2000**, *14*, 1523–1527. [\[CrossRef\]](#)
26. Sakurai, Y.; Mori, Y.; Okamoto, H.; Nishimura, A.; Komura, E.; Araki, T.; Shiramoto, M. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—A randomised open-label cross-over study. *Aliment. Pharmacol. Ther.* **2015**, *42*, 719–730. [\[CrossRef\]](#)
27. Murakami, K.; Sakurai, Y.; Shiino, M.; Funao, N.; Nishimura, A.; Asaka, M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: A phase III, randomised, double-blind study. *Gut* **2016**, *65*, 1439–1446. [\[CrossRef\]](#)
28. Marcus, E.A.; Inatomi, N.; Nagami, G.T.; Sachs, G.; Scott, D.R. The effects of varying acidity on *Helicobacter pylori* growth and the bactericidal efficacy of ampicillin. *Aliment. Pharmacol. Ther.* **2012**, *36*, 972–979. [\[CrossRef\]](#)
29. Furuta, T.; Graham, D.Y. Pharmacologic Aspects of Eradication Therapy for *Helicobacter pylori* Infection. *Gastroenterol. Clin. N. Am.* **2010**, *39*, 465–480. [\[CrossRef\]](#)
30. Sugimoto, M.; Furuta, T.; Shirai, N.; Kodaira, C.; Nishino, M.; Ikuma, M.; Ishizaki, T.; Hishida, A. Evidence that the Degree and Duration of Acid Suppression are Related to *Helicobacter pylori* Eradication by Triple Therapy. *Helicobacter* **2007**, *12*, 317–323. [\[CrossRef\]](#)

31. Sugimoto, M.; Furuta, T.; Shirai, N.; Kajimura, M.; Hishida, A.; Sakurai, M.; Ohashi, K.; Ishizaki, T. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. *Clin. Pharmacol. Ther.* **2004**, *76*, 290–301. [\[CrossRef\]](#)
32. Kagami, T.; Sahara, S.; Ichikawa, H.; Uotani, T.; Yamade, M.; Sugimoto, M.; Hamaya, Y.; Iwaizumi, M.; Osawa, S.; Miyajima, H.; et al. Potent acid inhibition by vonoprazan in comparison with esomeprazole, with reference to CYP2C19 genotype. *Aliment. Pharmacol. Ther.* **2016**, *43*, 1048–1059. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Craig, W.A. State-of-the-Art Clinical Article: Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men. *Clin. Infect. Dis.* **1998**, *26*, 1–10, quiz 11–12. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Craig, W.A. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diagn. Microbiol. Infect. Dis.* **1995**, *22*, 89–96. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Craig, W.A. Choosing an antibiotic on the basis of pharmacodynamics. *Ear Nose Throat J.* **1998**, *77* (Suppl. S6), 7–11. [\[PubMed\]](#)
36. Furuta, T.; Yamade, M.; Kagami, T.; Uotani, T.; Suzuki, T.; Higuchi, T.; Tani, S.; Hamaya, Y.; Iwaizumi, M.; Miyajima, H.; et al. Dual Therapy with Vonoprazan and Amoxicillin Is as Effective as Triple Therapy with Vonoprazan, Amoxicillin and Clarithromycin for Eradication of *Helicobacter pylori*. *Digestion* **2019**, *101*, 743–751. [\[CrossRef\]](#)
37. Hu, Y.; Xu, X.; Liu, X.-S.; He, C.; Ouyang, Y.-B.; Li, N.-S.; Xie, C.; Peng, C.; Zhu, Z.-H.; Xie, Y.; et al. Fourteen-day vonoprazan and low- or high-dose amoxicillin dual therapy for eradicating *Helicobacter pylori* infection: A prospective, open-labeled, randomized non-inferiority clinical study. *Front. Immunol.* **2022**, *13*, 1049908. [\[CrossRef\]](#)
38. Suzuki, S.; Gotoda, T.; Kusano, C.; Ikehara, H.; Ichijima, R.; Ohyauchi, M.; Ito, H.; Kawamura, M.; Ogata, Y.; Ohtaka, M.; et al. Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line *Helicobacter pylori* treatment: A multicentre randomised trial in Japan. *Gut* **2020**, *69*, 1019–1026. [\[CrossRef\]](#)
39. Gotoda, T.; Kusano, C.; Suzuki, S.; Horii, T.; Ichijima, R.; Ikehara, H. Clinical impact of vonoprazan-based dual therapy with amoxicillin for *H. pylori* infection in a treatment-naïve cohort of junior high school students in Japan. *J. Gastroenterol.* **2020**, *55*, 969–976. [\[CrossRef\]](#)
40. Sue, S.; Kondo, M.; Sato, T.; Oka, H.; Sanga, K.; Ogashiwa, T.; Matsubayashi, M.; Kaneko, H.; Irie, K.; Maeda, S. Vonoprazan and high-dose amoxicillin dual therapy for *Helicobacter pylori* first-line eradication: A single-arm, interventional study. *JGH Open* **2023**, *7*, 55–60. [\[CrossRef\]](#)
41. Qian, H.-S.; Li, W.-J.; Dang, Y.-N.; Li, L.-R.; Xu, X.-B.; Yuan, L.; Zhang, W.-F.; Yang, Z.; Gao, X.; Zhang, M.; et al. Ten-Day Vonoprazan-Amoxicillin Dual Therapy as a First-Line Treatment of *Helicobacter pylori* Infection Compared with Bismuth-Containing Quadruple Therapy. *Am. J. Gastroenterol.* **2022**, *118*, 627–634. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Lin, Y.; Xu, H.; Yun, J.; Yu, X.; Shi, Y.; Zhang, D. The efficacy of vonoprazan combined with different dose amoxicillin on eradication of *Helicobacter pylori*: An open, multicenter, randomized clinical study. *Ann. Transl. Med.* **2022**, *10*, 987. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Gao, W.; Teng, G.; Wang, C.; Xu, Y.; Li, Y.; Cheng, H. Eradication rate and safety of a “simplified rescue therapy”: 14-day vonoprazan and amoxicillin dual regimen as rescue therapy on treatment of *Helicobacter pylori* infection previously failed in eradication: A real-world, retrospective clinical study in China. *Helicobacter* **2022**, *27*, e12918. [\[PubMed\]](#)
44. Zuberi, B.F.; Ali, F.S.; Rasheed, T.; Bader, N.; Hussain, S.M.; Saleem, A. Comparison of Vonoprazan and Amoxicillin Dual Therapy with Standard Triple Therapy with Proton Pump Inhibitor for *Helicobacter pylori* eradication: A Randomized Control Trial. *Pak. J. Med. Sci.* **2022**, *38*, 965–969. [\[CrossRef\]](#)
45. Hu, Y.; Xu, X.; Ouyang, Y.B.; He, C.; Li, N.S.; Xie, C.; Peng, C.; Zhu, Z.H.; Xie, Y.; Shu, X.; et al. Optimization of vonoprazan-amoxicillin dual therapy for eradicating *Helicobacter pylori* infection in China: A prospective, randomized clinical pilot study. *Helicobacter* **2022**, *27*, e12896. [\[CrossRef\]](#)
46. Chey, W.D.; Mégraud, F.; Laine, L.; López, L.J.; Hunt, B.J.; Howden, C.W. Vonoprazan Triple and Dual Therapy for *Helicobacter pylori* Infection in the United States and Europe: Randomized Clinical Trial. *Gastroenterology* **2022**, *163*, 608–619. [\[CrossRef\]](#)
47. Zhou, S.; Chan, S.Y.; Goh, B.C.; Chan, E.; Duan, W.; Huang, M.; McLeod, H.L. Mechanism-Based Inhibition of Cytochrome P450 3A4 by Therapeutic Drugs. *Clin. Pharmacokinet.* **2005**, *44*, 279–304. [\[CrossRef\]](#)
48. Kagami, T.; Yamade, M.; Suzuki, T.; Uotani, T.; Hamaya, Y.; Iwaizumi, M.; Osawa, S.; Sugimoto, K.; Umemura, K.; Miyajima, H.; et al. Comparative study of effects of vonoprazan and esomeprazole on anti-platelet function of clopidogrel or prasugrel in relation to CYP2C19 genotype. *Clin. Pharmacol. Ther.* **2017**, *103*, 906–913. [\[CrossRef\]](#)
49. Wang, Y.; Wang, C.; Wang, S.; Zhou, Q.; Dai, D.; Shi, J.; Xu, X.; Luo, Q. Cytochrome P450-Based Drug-Drug Interactions of Vonoprazan In Vitro and In Vivo. *Front. Pharmacol.* **2020**, *11*, 53. [\[CrossRef\]](#)
50. Kang, J.; Kim, Y.-J.; Shim, T.S.; Jo, K.-W. Risk for cardiovascular disease in patients with nontuberculous mycobacteria treated with macrolide. *J. Thorac. Dis.* **2018**, *10*, 5784–5795. [\[CrossRef\]](#)
51. Drago, L.; Nicola, L.; Rodighiero, V.; Larosa, M.; Mattina, R.; De Vecchi, E. Comparative evaluation of synergy of combinations of beta-lactams with fluoroquinolones or a macrolide in *Streptococcus pneumoniae*. *J. Antimicrob. Chemother.* **2011**, *66*, 845–849. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Medscape. Drug Interaction Checker. Available online: <https://reference.medscape.com/drug-interactionchecker> (accessed on 3 March 2023).

53. Furuta, T.; Yamade, M.; Kagami, T.; Suzuki, T.; Higuchi, T.; Tani, S.; Hamaya, Y.; Iwaizumi, M.; Miyajima, H.; Umemura, K.; et al. Influence of clarithromycin on the bactericidal effect of amoxicillin in patients infected with clarithromycin-resistant strains of *H. pylori*. *Gut* **2020**, *69*, 2056. [[CrossRef](#)] [[PubMed](#)]
54. Murakami, K.; Sato, R.; Okimoto, T.; Nasu, M.; Fujioka, T.; Kodama, M.; Kagawa, J.; Sato, S.; Abe, H.; Arita, T. Eradication rates of clarithromycin-resistant *Helicobacter pylori* using either rabeprazole or lansoprazole plus amoxicillin and clarithromycin. *Aliment. Pharmacol. Ther.* **2002**, *16*, 1933–1938. [[CrossRef](#)] [[PubMed](#)]
55. Kawabata, H.; Habu, Y.; Tomioka, H.; Kutsumi, H.; Kobayashi, M.; Oyasu, K.; Hayakumo, T.; Mizuno, S.; Kiyota, K.; Nakajima, M.; et al. Effect of different proton pump inhibitors, differences in CYP2C19 genotype and antibiotic resistance on the eradication rate of *Helicobacter pylori* infection by a 1-week regimen of proton pump inhibitor, amoxicillin and clarithromycin. *Aliment. Pharmacol. Ther.* **2003**, *17*, 259–264. [[CrossRef](#)]
56. Gao, W.; Xu, Y.; Liu, J.; Wang, X.; Dong, X.; Teng, G.; Liu, B.; Dong, J.; Ge, C.; Ye, H.; et al. A real-world exploratory study on the feasibility of vonoprazan and tetracycline dual therapy for the treatment of *Helicobacter pylori* infection in special populations with penicillin allergy or failed in previous amoxicillin-containing therapies. *Helicobacter* **2023**, *28*, e12947. [[CrossRef](#)]

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