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Review Article

Is a Potassium-Competitive Acid Blocker Truly Superior to Proton Pump Inhibitors in Terms of *Helicobacter pylori* Eradication?

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Vonoprazan (VPZ), a new potassium-competitive acid blocker, has been approved and used for *Helicobacter pylori* eradication in Japan. To date, many studies, as well as several systematic reviews and meta-analyses (MAs), have compared VPZ-based 7-day triple therapy with proton pump inhibitor (PPI)-based therapy. An MA of randomized controlled trials (RCTs) comparing first-line VPZ- with PPI-based triple therapy, the latter featuring amoxicillin (AMPC) and clarithromycin (CAM), found that approximately 30% of patients hosted CAM-resistant *H. pylori*; however, the reliability was poor because of high heterogeneity and a risk of selection bias. VPZ-based triple therapy is superior to PPI-based triple therapy for patients with CAM-resistant *H. pylori*, but not for those with CAM-susceptible *H. pylori*. An MA of non-RCTs found that second-line VPZ-based triple therapies were slightly (~2.6%) better than PPI-based triple therapies (with AMPC and metronidazole). However, the reliability of that MA was also low because of selection bias, confounding variables and a risk of publication bias; in addition, it is difficult to generalize the results because of a lack of data on antibiotic resistance. VPZ-based triple therapy (involving AMPC and sitafloxacin) was more effective than PPI-based triple therapy in a third-line setting, but a confirmatory RCT is needed. Non-RCT studies indicated that VPZ-based triple therapy involving CAM and metronidazole may be promising. Any further RCTs must explore the antibiotic-resistance status when evaluating the possible superiority of a potassium-competitive acid blocker. **(Gut Liver 2021;15:799-810)**

Key Words: Potassium-competitive acid blocker; Proton pump inhibitors; *Helicobacter pylori*; Treatment outcome; Drug resistance, microbial

INTRODUCTION

Helicobacter pylori-induced signaling pathways contribute to the development of gastric carcinogenesis.[1] A systematic review (SR) and meta-analysis (MA) found that *H. pylori* eradication reduced the incidence and mortality rates of gastric cancer.[2] Many clinical trials have assessed the efficacy and safety of *H. pylori* eradication regimens.[3] An intention-to-treat (ITT) cure rate that is "excellent" (95% to 100%) is considered optimal, and a "good" cure rate (90% to 95%) is considered acceptable.[4] It is important to increase the gastric pH; *H. pylori* then enters an antibiotic-susceptible replicative state.[5] Several MAs have shown that high-dose proton pump inhibitors (PPIs) enhance eradication.[6-8] Vonoprazan (VPZ) is a new potassium-competitive acid blocker (P-CAB) approved in 2015 for *H. pylori* eradication in Japan.[9] Since that time, several SRs and MAs comparing VPZ- and PPI-based therapies have appeared,[10-12] but the same studies were reviewed among several of the MAs. Furthermore, few randomized controlled trials (RCTs) have been performed,[13] and many studies lacked data on antibiotic resistance. Here, we focus on study overlap and design and antibiotic resistance data. We pose the question: is P-CAB really superior to a PPI in terms of *H. pylori* eradication?

MECHANISM AND CLINICAL INDICATION OF P-CAB

1. Mechanism of P-CAB action in patients with various lesions

VPZ is a new P-CAB (other P-CABs include SCH28080) that inhibits H+/K+ ATPases in a manner described as rapid (the intragastric pH increased to over 4.0 within 4 hours[14]), strong (the intragastric pH increased to over 5 and was maintained for 99% of the time when VPZ [20 mg] was given twice daily[15]), or stable (not affected by the CP2C19 genotype[14,16]). VPZ was the second P-CAB to be approved worldwide (revaprazan was approved first, in South Korea).

At pH >5, *H. pylori* enters the growth phase. Clarithromycin (CAM) inhibits protein synthesis during growth, and amoxicillin (AMPC) inhibits cell wall biosynthesis; metronidazole (MNZ) targets DNA synthesis and acts during both the growth and stationary phases.[17] Thus, CAM and AMPC function at pH >5, whereas MNZ is pH independent.

SCH28080 is the prototype P-CAB that was developed in the 1980s. This drug is short-acting and was never approved. Linaprazan was found to be as effective as esomeprazole (40 mg) in patients with non-erosive reflux disease; however, its clinical development was later suspended.[18] Revaprazan (a P-CAB) was approved in South Korea in 2005 for the treatment of gastroduodenal ulcers and gastritis. However, endoscopic submucosal dissection revealed that the drug was no more efficacious than 20 mg rabeprazole for treating ulcers.[19] In 2018, a new P-CAB, tegoprazan, was approved for *H. pylori* eradication in South Korea. Tegoprazan was not inferior to lansoprazole when used to treat gastric ulcers[20] and non-inferior to esomeprazole in patients with erosive esophagitis.[21] However, no data on *H. pylori* eradication have been published. Tegoprazan may be valuable in this context.

2. P-CAB based data: mainly with VPZ, in Japan, and with triple therapy

P-CAB based data are mainly with VPZ based and in Japanese population. First-line VPZ based regimens compared to PPI based (Table 1), and second-line VPZ based regimens compared to PPI based (Table 2) are studies with Japanese population. In these studies, 7-day triple therapies are used. In Japan, 7-day first-line triple therapy consisting of VPZ or a PPI, AMPC, and CAM and 7-day second-line triple therapy consisting of VPZ or a PPI, AMPC, and MNZ are covered by national insurance. Esomeprazole, rabeprazole, lansoprazole, or omeprazole serves as the PPI. The approved doses are VPZ 20 mg bid (twice a day; 40 mg/day), esomeprazole 20 mg bid (40 mg/day), rabeprazole 10 mg bid (20 mg/day), omeprazole 20 mg bid (40 mg/day), AMPC 750 mg bid (1,500 mg/day), CAM 200 mg or 400 mg bid (400 mg/day or 800 mg/day), and MNZ 250 mg bid (500 mg/day).

3. Antibiotic resistance background in a Japanese population

Studies reviewed in this article are based on a Japanese population, so the Japanese *H. pylori* antibiotic-resistance status is important to understanding the setting and limitation of this review. One MA found that CAM resistance reduced the eradication rate by 55% (95% confidence interval [CI], 33 to 78), and MNZ resistance reduced the rate by 37.7% (95% CI, 29.6 to 45.7); CAM/MNZ resistance is the principal cause of eradication failure.[22] Whereas the MNZ-resistance rate remains low,[23] the CAM-resistance rate has increased, from 23.7% (56/236) in 2017[24] to 27.9% (41/147) in 2018.[25] Table 1 lists the available data on antibiotic resistance. The CAM-resistance rates were 35.5% (215/605) in 2016,[9] 39.5% (45/114) in 2016,[26] 34.7% (143/412) in 2016,[27] 42.7% (123/288) in 2019,[28] and 25.6% (42/164) in 2020.[29] The data differed according to the lesion type evaluated; the average was 33.8% (665/1,996) (95% CI, 31.7 to 36.0). The CAM-resistance rate exceeds 15% in Japan, which is thus a high-CAM-resistance area. As shown in Table 2, MNZ-resistance data are scarce. Horie *et al.*[23] reported that the MNZ-resistance rate was less than 5% from 2005 to 2018. The AMPC-resistance rate is generally very low in Japan. In 2020, Suzuki reported that the minimal inhibitory concentration of AMPC was <0.03 μg/mL in 93.6% (306/327) of subjects, 0.03 μg/mL in 5.2% (17/327) of subjects, and 0.06 μg/mL in 1.2% (4/327) of subjects.[29] In summary, Japanese population-based eradication studies have found high rates (~33%) of CAM resistance, low rates (<5%) of MNZ resistance, and very low rates of AMPC resistance. This antibiotic resistance setting is the main limitation of this review in generalizing to clinical settings outside of Japan.

VPZ-COMPARED WITH PPI-BASED FIRST-LINE TRIPLE THERAPY CONSISTING OF AMPC AND CAM

As mentioned above, we ask: "is P-CAB really superior to a PPI in terms of *H. pylori* eradication?" in the context of first-line VPZ-based 7-day triple therapy consisting of AMPC and CAM. As shown in Table 1, many relevant studies have appeared.

Table 1. First-Line Vonoprazan-Based Compared to PPI-Based Eradication Regimen

First author (year)	Method	CAM susceptible	VPZ-based eradication regimen					PPI-based eradication regimen				
			Regimen	ITT/FAS analysis		PP analysis		Regimen	ITT/FAS analysis		PP analysis	
				No.	ER (95% CI), %	No.	ER (95% CI), %		No.	ER (95% CI), %	No.	ER (95% CI), %
Murakami (2016)[9†]	RCT	Sensitive	VPZ/AMPC/CAM	205	97.6 (94.4–99.2)*	NA	NA	LPZ/AMPC/CAM	185	97.3 (93.8–99.1)*	NA	NA
		Resistant	VPZ/AMPC/CAM	100	82.0 (73.1–89.0)*	NA	NA	LPZ/AMPC/CAM	115	40.0 (31.0–49.6)*	NA	NA
		NA	VPZ/AMPC/CAM	19	94.7 (74.0–99.9)*	NA	NA	LPZ/AMPC/CAM	20	85.0 (62.1–96.8)*	NA	NA
		Total	VPZ/AMPC/CAM	324	92.6 (89.2–95.2)*	NA	NA	LPZ/AMPC/CAM	320	75.9 (70.9–80.5)*	NA	NA
Noda (2016)[26†]	RST	Sensitive	VPZ/AMPC/CAM	NA	NA	44	100 (92.0–100)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	NA	NA	25	88.0 (68.8–97.5)
		Resistant	VPZ/AMPC/CAM	NA	NA	32	87.5 (71.0–96.5)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	NA	NA	13	53.8 (25.1–80.8)
		NA	VPZ/AMPC/CAM	NA	NA	70	84.3 (73.6–91.9)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	NA	NA	1,267	73.9 (71.4–76.2)
		Total	VPZ/AMPC/CAM	NA	NA	146	89.7 (87.9–91.3)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	NA	NA	1,305	73.9 (66.0–80.8)
Matsumoto (2016)[27†]	RST	Sensitive	VPZ/AMPC/CAM	NA	NA	57	100 (94.9–100)	LPZ or RPZ or EPZ/AMPC/CAM	NA	NA	212	87.8 (82.5–91.8)
		Resistant	VPZ/AMPC/CAM	NA	NA	97	40.2 (30.4–50.7)	LPZ or RPZ or EPZ/AMPC/CAM	NA	NA	46	76.1 (61.2–87.4)
		NA	VPZ/AMPC/CAM	125	89.6 (82.9–94.3)	125	89.6 (82.9–94.3)	LPZ or RPZ or EPZ/AMPC/CAM	295	71.9 (66.4–76.9)	290	73.1 (67.6–78.1)
		Total	VPZ/AMPC/CAM	125	89.6 (82.9–94.3)	279	74.6 (69.0–79.6)	LPZ or RPZ or EPZ/AMPC/CAM	295	71.9 (66.4–76.9)	548	79.0 (75.4–82.4)
Sugimoto (2017)[30]	RST	Sensitive	VPZ/AMPC/CAM	NA	NA	19	82.5 (66.9–98.7)	NA	NA	NA	NA	NA
		Resistant	VPZ/AMPC/CAM	NA	NA	14	78.6 (49.2–95.3)	NA	NA	NA	NA	NA
		NA	VPZ/AMPC/CAM	NA	NA	43	83.7 (69.3–93.2)	NA	NA	NA	NA	NA
		Total	VPZ/AMPC/CAM	NA	NA	76	82.9 (72.5–90.6)	NA	NA	NA	NA	NA
Sue (2017)[24†]	PST	Sensitive	VPZ/AMPC/CAM	NA	NA	180	88.9 (83.4–93.1)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	NA	NA	NA	NA
		Resistant	VPZ/AMPC/CAM	NA	NA	56	73.2 (59.7–84.2)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	NA	NA	NA	NA
		NA	VPZ/AMPC/CAM	623	84.9 (81.9–87.6)	376	87.2 (83.4–90.4)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	608	78.8 (75.3–82.0)	603	79.4 (76.0–82.6)
		Total	VPZ/AMPC/CAM	623	84.9 (81.9–87.6)	612	86.4 (83.5–89.1)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	608	78.8 (75.3–82.0)	603	79.4 (76.0–82.6)
Sue (2018)[25†]	RCT	Sensitive	VPZ/AMPC/CAM	55	87.3 (75.5–94.7)	54	88.9 (77.4–95.8)	LPZ or RPZ or EPZ/AMPC/CAM	51	76.5 (62.5–87.2)	45	86.7 (73.2–94.9)
		Resistant	VPZ/AMPC/CAM	41	82.9 (67.9–92.8)	41	82.9 (67.9–92.8)	NA	NA	NA	NA	NA
		Total	VPZ/AMPC/CAM	96	85.4 (76.7–91.8)	95	86.3 (77.7–92.5)	LPZ or RPZ or EPZ/AMPC/CAM	51	76.5 (62.5–87.2)	45	86.7 (73.2–94.9)

Table 1. Continued

First author (year)	Method	CAM susceptible	VPZ-based eradication regimen					PPI-based eradication regimen				
			Regimen	ITT/FAS analysis		PP analysis		Regimen	ITT/FAS analysis		PP analysis	
				No.	ER (95% CI), %	No.	ER (95% CI), %		No.	ER (95% CI), %	No.	ER (95% CI), %
Tanabe (2018)[31]	RST	Sensitive	NA	NA	NA	NA	NA	LPZ or RPZ or EPZ/AMPC/CAM	162	93.8 (90.1–97.5)	159	95.6 (90.1–97.5)
		Resistant	NA	NA	NA	NA	NA	LPZ or RPZ or EPZ/AMPC/MNZ	50	92.0 (80.8–97.8)	48	95.8 (85.7–99.5)
		NA	VPZ/AMPC/CAM	363	91.5 (88.6–94.3)	341	97.4 (95.7–99.1)	LPZ or RPZ or EPZ/AMPC/CAM	568	74.1 (70.3–77.7)	510	82.5 (79.0–85.7)
		Total	VPZ/AMPC/CAM	363	91.5 (88.6–94.3)	341	97.4 (95.7–99.1)	LPZ or RPZ or EPZ/AMPC/CAM	780	79.4 (76.5–82.2)	717	86.3 (83.8–88.8)
Shinmura (2019)[28†]	RST	Sensitive	VPZ/AMPC/CAM	NA	NA	165	93.2 (88.2–96.1)	NA	NA	NA	NA	NA
		Resistant	VPZ/AMPC/CAM	NA	NA	123	85.8 (78.5–91.0)	NA	NA	NA	NA	NA
		NA	VPZ/AMPC/CAM	NA	85.0 (81.8–87.8)	253	90.1 (85.8–93.5)	NA	NA	NA	NA	NA
		Total	VPZ/AMPC/CAM	NA	85.0 (81.8–87.8)	541	90.2 (87.4–92.5)	NA	NA	NA	NA	NA
Saito (2019)[32†]	RST	Sensitive	VPZ/AMPC/CAM	NA	NA	28	100 (88.9–100)	EPZ/AMPC/CAM	NA	NA	97	93.8 (87.0–97.7)
		Resistant	VPZ/AMPC/CAM	NA	NA	25	100 (88.7–100)	EPZ/AMPC/CAM	NA	NA	65	38.5 (26.7–51.4)
		NA	VPZ/AMPC/CAM	290	79.0 (73.8–83.5)	206	85.4 (79.9–90.0)	EPZ/AMPC/CAM	288	65.6 (59.5–70.8)	110	66.4 (56.7–75.1)
		Total	VPZ/AMPC/CAM	290	79.0 (73.8–83.5)	259	88.4 (83.9–92.0)	EPZ/AMPC/CAM	288	65.6 (59.5–70.8)	272	69.5 (63.6–74.9)
Suzuki (2020)[29†]	RCT	Sensitive	VPZ/AMPC/CAM	NA	NA	122	95.1 (89.6–98.2)	NA	NA	NA	NA	NA
		Resistant	VPZ/AMPC/CAM	NA	NA	42	76.2 (60.5–87.9)	NA	NA	NA	NA	NA
		NA	VPZ/AMPC/CAM	167	89.2 (83.5–93.5)	NA	NA	NA	NA	NA	NA	NA
		Total	VPZ/AMPC/CAM	167	89.2 (83.5–93.5)	164	90.2 (84.6–94.3)	NA	NA	NA	NA	NA
Suzuki (2016)[33†]	RST	NA (total)	VPZ/AMPC/CAM	175	89.1 (84.5–93.8)	171	91.2 (87.0–95.5)	LPZ or RPZ/AMPC/CAM	175	70.9 (64.1–77.6)	173	71.7 (64.9–78.4)
Shinozaki (2016)[34†]	RST	NA (Total)	VPZ/AMPC/CAM	117	82.9 (74.8–89.2)	114	85.0 (77.2–91.1)	LPZ or RPZ or EPZ/AMPC/CAM	456	70.6 (66.0–74.6)	435	74.0 (69.6–78.1)
Shichijo (2016)[35†]	RST	NA (total)	VPZ/AMPC/CAM	NA	NA	422	87.2 (83.6–90.2)	LPZ or RPZ or EPZ/AMPC/CAM	NA	NA	2,293	72.4 (70.5–74.2)
Yamada (2016)[36†]	RST	NA (total)	VPZ/AMPC/CAM	335	85.7 (81.5–89.2)	318	90.3 (86.4–93.3)	LPZ or RPZ or EPZ/AMPC/CAM	1,720	73.2 (71.0–75.3)	1,647	76.4 (74.3–78.4)
Tsujimae (2016)[37†]	RST	NA (total)	VPZ/AMPC/CAM	443	84.6 (81.4–88.3)	439	86.3 (82.8–89.4)	EPZ/AMPC/CAM	431	79.1 (75.0–82.9)	427	79.9 (75.7–83.6)
Katayama (2017)[38]	RST	NA (total)	VPZ/AMPC/CAM	NA	NA	258	90.6 (86.3–93.9)	NA	NA	NA	NA	NA
Kajihara (2017)[39†]	RST	NA (total)	VPZ/AMPC/CAM	111	94.6 (88.6–98.0)	110	95.5 (89.7–98.5)	RPZ/AMPC/CAM	98	86.7 (78.4–92.7)	98	86.7 (78.4–92.7)
Ono (2017)[40†]	RST	NA (total)	VPZ/MNZ/CAM	14	92.9 (66.1–99.8)	14	92.9 (66.1–99.8)	LPZ or RPZ/MNZ/CAM	13	46.2 (19.2–74.9)	11	54.6 (23.4–83.3)
Sakurai (2017)[41†]	RST	NA (total)	VPZ/AMPC/CAM	NA	NA	546	87.9 (84.9–90.5)	LPZ or RPZ or EPZ/AMPC/CAM	NA	NA	807	66.9 (63.5–70.2)
Maruyama (2017)[42†]	RCT	NA (total)	VPZ/AMPC/CAM	72	95.8 (88.3–99.1)	70	95.7 (88.0–99.1)	LPZ or RPZ/AMPC/CAM	69	69.6 (57.3–80.1)	63	71.4 (58.7–82.1)

Table 1. Continued

First author (year)	Method	CAM susceptible	VPZ-based eradication regimen					PPI-based eradication regimen				
			Regimen	ITT/FAS analysis		PP analysis		Regimen	ITT/FAS analysis		PP analysis	
				No.	ER (95% CI), %	No.	ER (95% CI), %		No.	ER (95% CI), %	No.	ER (95% CI), %
Nishizawa (2017)[43†]	RST	NA (total)	VPZ/AMPC/CAM	353	62.3 (57.0–67.4)	246	89.4 (84.9–93.0)	LPZ or RPZ/AMPC/CAM	2,173	47.1 (45.0–49.2)	1,532	66.8 (64.4–69.1)
Tanabe (2017)[44]	RST	NA (total)	VPZ/AMPC/CAM	694	82.7 (84.7–89.7)	641	94.4 (92.6–96.2)	NA	NA	NA	NA	NA
Ozaki (2018)[45]	RST	NA (total)	VPZ/AMPC/CAM	NA	NA	1,688	90.8 (89.3–92.2)	RPZ or EPZ/AMPC/CAM	NA	NA	147	72.8 (64.8–79.8)
Mori (2018)[46]	RST	NA (total)	VPZ/AMPC/CAM	308	NA	275	91.0 (86.9–94.0)	LPZ/AMPC/CAM	272	NA	249	84.7 (79.7–89.0)
Shinozaki (2018)[47]	RST	NA (total)	VPZ/AMPC/CAM	174	83.3 (76.9–88.5)	171	84.8 (78.5–89.8)	NA	NA	NA	NA	NA
Kusunoki (2019)[48†]	RST	NA (total)	VPZ/AMPC/CAM	NA	NA	415	92.5 (89.6–94.9)	LPZ or RPZ or EPZ/AMPC/CAM	NA	NA	757	83.9 (81.1–86.5)
Nishida (2019)[49]	RST	NA (total)	VPZ/AMPC/CAM	NA	NA	326	71.9 (68.3–75.2)	LPZ or RPZ/AMPC/CAM	NA	NA	644	90.2 (86.5–93.0)
Mori (2019)[50†]	RST	NA (total)	VPZ/AMPC/CAM	1,676	81.4 (79.4–83.2)	NA	89.1 (87.4–90.6)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	2,043	62.7 (60.6–64.8)	NA	69.4 (67.2–71.5)
Furuta (2019)[51]	RST	NA (total)	VPZ/AMPC/CAM	56	91.9 (80.4–97.0)	55	92.7 (82.4–98.0)	NA	NA	NA	NA	NA

All papers that investigated the efficacy of first-line vonoprazan-containing eradication therapy until January 2020 were listed. A total of 4 RCTs and 26 RSTs investigated the efficacy of first-line VPZ-containing therapy. There were many RSTs but few RCTs (Murakami 2016, Maruyama 2017, Sue 2018, Suzuki 2020). Because CAM resistance is becoming a global clinical problem for *Helicobacter pylori* eradication, eradication therapy that has been susceptibility tested may be an effective option. However, there were only 3 RCTs (Murakami 2016, Sue 2018, Suzuki 2020) containing CAM susceptibility information.

CAM, clarithromycin; VPZ, vonoprazan; PPI, proton pump inhibitor; ITT, intention-to-treat analysis; FAS, full analysis set; PP, per-protocol analysis; ER, eradication rate; CI, confidence interval; RCT, randomized controlled trial; PST, prospective interventional trial; RST, retrospective cohort trial; AMPC, amoxicillin; LPZ, lansoprazole; RPZ, rabeprazole; EPZ, esomeprazole; OPZ, omeprazole; MNZ, metronidazole; NA, not available.

*FAS; †Studies were used for meta-analyses.

Table 2. Second-Line Vonoprazan-Based Compared to PPI-Based Eradication Regimen

First author (year)	Method	MNZ susceptible	First-line	VPZ-based eradication regimen					PPI-based eradication regimen				
				Regimen	ITT/FAS analysis		PP analysis		Regimen	ITT/FAS analysis		PP analysis	
					No.	ER (95% CI), %	No.	ER (95% CI), %		No.	ER (95% CI), %	No	ER (95% CI), %
Murakami (2016)[9]	PST	Sensitive	VPZ	VPZ/AMPC/MNZ	45	NA	NA	NA	NA	NA	NA	NA	NA
		Resistant	VPZ	VPZ/AMPC/MNZ	4	NA	NA	NA	NA	NA	NA	NA	NA
		NA	VPZ	VPZ/AMPC/MNZ	1	NA	NA	NA	NA	NA	NA	NA	NA
		Total	VPZ	VPZ/AMPC/MNZ	50	98.0 (89.4–99.9)*	NA	NA	NA	NA	NA	NA	NA
Yamada (2016)[36]	RST	NA (total)	NA	VPZ/AMPC/MNZ	66	89.4 (79.4–95.6)	61	96.7 (88.7–99.6)	LPZ or RPZ or EPZ/AMPC/MNZ	386	89.9 (86.4–92.7)	374	92.8 (89.7–95.2)
Tsujimae (2016)[37]	RST	NA (total)	NA	VPZ/AMPC/MNZ	46	89.1 (76.4–96.4)	45	91.1 (78.8–97.5)	EPZ/AMPC/MNZ	54	83.3 (70.7–92.1)	51	88.2 (76.1–95.6)
Katayama (2017)[38]	RST	NA (total)	VPZ	VPZ/AMPC/MNZ	NA	NA	23	87.0 (66.4–97.2)	NA	NA	NA	NA	NA
Sakurai (2017)[41]	RST	NA (total)	NA	VPZ/AMPC/MNZ	NA	NA	76	96.1 (88.9–99.2)	LPZ or RPZ or EPZ/AMPC/MNZ	NA	NA	185	91.6 (86.3–95.0)
Nishizawa (2017)[43]	RST	NA (total)	NA	VPZ/AMPC/MNZ	85	71.8 (61.0–81.0)	63	96.8 (89.0–99.6)	LPZ or RPZ/AMPC/MNZ	650	73.7 (70.1–77.0)	529	90.5 (87.7–92.9)
Sue (2017)[24]	PST	NA (total)	NA	VPZ/AMPC/MNZ	216	80.5 (74.6–85.6)	211	82.4 (76.6–87.9)	LPZ or RPZ or EPZ/AMPC/MNZ	146	81.5 (74.2–87.4)	145	82.1 (74.8–87.9)
Tanabe (2017)[44]	RST	NA (total)	NA	VPZ/AMPC/MNZ	73	90.4 (83.7–97.2)	68	97.1 (93.0–101.1)	NA	NA	NA	NA	NA
Ozaki (2017)[45]	RST	NA (total)	VPZ	VPZ/AMPC/MNZ	NA	NA	94	86.3 (77.5–92.4)	NA	NA	NA	NA	NA
Mori (2018)[46]	RST	NA (total)	VPZ	VPZ/AMPC/MNZ	NA	NA	23	87.0 (66.4–97.2)	NA	NA	NA	NA	NA
			PPI	NA	NA	NA	NA	NA	RPZ/AMPC/MNZ	NA	NA	33	87.9 (71.8–96.6)
Kusunoki (2019)[48]	RST	NA (total)	NA	VPZ/AMPC/MNZ	NA	NA	48	93.8 (82.8–98.7)	LPZ or RPZ or EPZ/AMPC/MNZ	NA	NA	108	90.7 (83.6–95.5)
Mori (2019)[50]	RST	NA (total)	NA	VPZ/AMPC/MNZ	NA	80.0	1,292	90.1 (88.3–91.7)	LPZ or RPZ or OPZ or EPZ/AMPC/CAM	NA	77.6	2,280	86.6 (85.1–88.0)
Saito (2019)[32]	RST	NA (total)	NA	VPZ/AMPC/MMZ	60	81.7 (69.6–90.5)	54	90.7 (79.7–96.9)	EPZ/AMPC/MNZ	74	89.2 (79.8–95.2)	73	90.4 (81.2–96.1)

All papers that investigated the efficacy of second-line vonoprazan-containing eradication therapy up until March 2019 were listed. A total of 1 PST and 12 RSTs investigated the efficacy of second-line VPZ-containing therapy. There were many RSTs but no RCTs. In 8 studies (Yamada 2016, Tsujimae 2016, Sakurai 2017, Nishizawa 2017, Sue 2017, Kusunoki 2019, Mori 2019, Saito 2019), statistical significance was not found between the VPZ and PPI regimens. This may be because although CAM and AMPC are acid-sensitive antimicrobial agents, MNZ is not an acid-sensitive antimicrobial agent. However, there were no RCTs containing susceptibility information. The first-line regimen is important for the *Helicobacter pylori* eradication rate of the second-line regimen. However, there were few studies (Murakami 2016, Katayama 2017, Ozaki 2017, Mori 2018) that used a first-line regimen. One of the studies (Mori 2019) showed that the eradication rates were 90.1% and 63.2% for VPZ and PPI, respectively. Mori's study contained much larger populations (1,147 and 2,051), more than those in other studies, so this study had a strong influence on Shinozaki's meta-analysis (60.7%). However, it is dangerous to rely on this study completely. The VPZ and PPI regimens had different follow-up periods, there was no information about the number of MNZ-resistant strains, and this study was retrospective.

MNZ, metronidazole; VPZ, vonoprazan; PPI, proton pump inhibitor; ITT, intention-to-treat analysis; FAS, full analysis set; PP, per-protocol analysis; ER, eradication rate; CI, confidence interval; PST, prospective interventional trial; RST, retrospective cohort trial; AMPC, amoxicillin; LPZ, lansoprazole; RPZ, rabeprazole; EPZ, esomeprazole; OPZ, omeprazole; CAM, clarithromycin; NA, not available.

*FAS.

1. The need for CAM-resistance data

The CAM-resistance status is very important when exploring whether first-line 7-day triple therapy consisting of VPZ, AMPC, and CAM are superior to PPI-based regimens. Attempts to generalize results in the absence of CAM- and AMPC-resistance data[33-51] are both difficult and misleading. Generalization may be possible in very limited circumstances only (the trial sites and lesions are identical). The CAM-resistance rate is increasing in Japan, and antibiotic-resistance rates vary by lesion.[9,24-32] Generalization to other countries is even less appropriate.

2. MAs of RCTs

MAs of RCTs evaluated high-quality evidence. In 2019, Lyu *et al.*[13] concluded that VPZ-based triple therapies were superior to PPI-based triple therapies based on ITT analysis (91.4% [95% CI, 88.5 to 93.8] vs 74.8% [95% CI, 70.5 to 78.8]) and per-protocol (PP) analysis (92.6% [95% CI, 89.8 to 94.9] vs 76.4% [95% CI, 72.1 to 80.3], respectively). Three RCTs were analyzed,[9,25,42] of those, one[42] had a risk of bias because of allocation concealment, as randomization was based on personal medical record numbers (odd or even). A risk of selection bias was involved during the assignment of 141 of 1,482 chronic gastritis cases (72 and 69 to the VPZ- and PPI-based treatments, respectively). In another of the three RCTs, all subjects were CAM susceptible.[25] The final RCT evaluated was a phase III trial conducted prior to approval of a new drug in Japan (performed before VPZ approval);[9] such trials usually exhibit selection bias. Heterogeneity was moderate in the ITT analysis (I^2=46%) and high in the PP analysis (I^2=61%), indicating that the MA was not reliable. If an MA is generalizable, information on antibiotic resistance is important. Two of the above RCTs contained such data,[9,25] whereas the third did not.[42] Of those receiving VPZ-based therapy, 259 were CAM susceptible, 100 were CAM resistant, and 73 were labeled "not applicable;" of those receiving PPI-based therapy, 230 were CAM susceptible, 115 were CAM resistant, and 64 were labeled "not applicable." The CAM-resistance rates were approximately 27.9% and 33.3% among those receiving VPZ-based and PPI-based therapies, respectively; thus, it might be possible to generalize the result to populations containing approximately 30% CAM-resistant subjects. However, the CAM-resistance rate was lower in the VPZ-treated than PPI-treated group (27.9% vs 33.3%), biasing the results. We thus focused on the treatment efficacy in CAM-susceptible and -resistant subjects in sections 3.4 and 3.5 below. In summary, one MA of RCTs indicated that VPZ-based therapy may be superior to PPI-based therapy in populations exhibiting approximately 30% CAM resistance, but the reliability of that MA was low given the high heterogeneity and risk of selection bias (lack of allocation concealment).

3. MAs of non-RCTs

Table 1 shows that many non-RCTs have been performed, but retrospective cohort studies lacking information on antibiotic resistance are misleading, as the CAM-resistance rates might have differed. Several MAs lack antibiotic-resistance data and are as misleading as single retrospective cohort studies lacking this information. The MA by Dong *et al.* (2017)[10] discussed two RCTs,[9,42] and 12 non-RCTs.[24,26,27,33-37,39-41,43] One study[33] performed propensity score matching in the absence of antibiotic-resistance data. Another[40] featured triple therapy consisting of CAM, MNZ or MNZ, and sitafloxacin (STFX; 88 of 13,495 cases); we discuss this in the sixth chapter. That retrospective study lacking antibiotic-resistance data was misleading. The eradication rate was 85.1% in VPZ-treated patients versus 68.0% in PPI-treated patients ($p<0.00001$) in the ITT analysis and 89.0% versus 74.2% in the PP analysis ($p<0.00001$).[10] Heterogeneity was high in the non-RCT analysis (I^2=65%) and low-to-moderate in the RCT analysis (I^2=26%), suggesting that the non-RCT data are unreliable. Jung *et al.* (2017)[11] discussed one RCT[9] and nine non-RCTs[26,27,33-36,39,41] Heterogeneity was high in the non-RCT analysis (I^2=72%), suggesting that the MA was as unreliable as that by Dong *et al.*

The MA by Li *et al.*[12] discussed two RCTs,[9,25] and three non-RCTs[24,26,27] with a focus on CAM-resistant and CAM-susceptible subjects separately. We discuss that MA in the next section.

No MA presented a funnel plot; we suspect that publication bias explains many of the differences between RCTs and non-RCTs. Many retrospective studies have been presented in Japanese conferences in Japanese, of which few are published. Most studies are neither prospective nor registered. Well-designed, registered, prospective studies with pre-planned analysis methods would reduce publication bias. In summary, MAs that include non-RCTs are unreliable given their high heterogeneity and publication bias, and it is difficult to generalize the results when antibiotic-resistance data are lacking.

4. CAM-resistant subjects

In 2017, Dong *et al.*[10] published an MA of CAM-resistant subgroups given first-line triple therapy consisting of AMPC and CAM. The eradication rate was 81.5% (95% CI, 75.0 to 86.9) in the VPZ-based group versus 40.9% (95% CI, 34.4 to 47.6) in the PPI-based group (odds ratio [OR], 5.92; 95% CI, 3.70 to 9.45). Three studies were analyzed: one RCT (VPZ phase III)[9] and two retrospective

studies.[26,27] Heterogeneity was very low (I^2=0%), indicating high reliability. In 2018, Li *et al.*[12] published an MA of one RCT (eradication rate of VPZ vs PPI: 82.0% vs 40.0%; OR, 6.83; 95% CI, 3.63 to 12.86), and two retrospective studies (eradication rate: 80.8% vs 41.8%; OR, 4.98; 95% CI, 2.47 to 10.03). We did not compare VPZ- and PPI-based therapies for CAM-resistant patients in our RCT[25] for ethical reasons. PPI-based therapies are associated with poor eradication rates in subjects with CAM-resistant *H. pylori*, and such patients should receive VPZ-based therapy. We explored the utility of VPZ-based therapy for CAM-resistant patients in a prospective study; the eradication rate was 82.9% (95% CI, 67.9 to 92.8),[25] thus in the range of "poor" (81% to 84%).[4] In 2020, Suzuki *et al.*[29] performed a prospective study (of the control arm of an RCT); the eradication rate was 76.2% (95% CI, 60.5 to 87.9) in CAM-resistant patients given VPZ-based therapy.

As we noted in "2.1. Mechanism of P-CAB action in patients with various lesions," the mechanism of this superiority is that rapid, strong, and stable acid block by P-CAB results in AMPC and CAM becoming more effective, because at pH >5, *H. pylori* enters the growth phase. This is also supported by recent VPZ-AMPC dual therapy results.

In summary, VPZ-based therapy is superior to PPI-based therapy in patients with CAM-resistant *H. pylori*, but the eradication rate remains unacceptably low.

5. CAM-susceptible subjects

In 2017, Dong *et al.*[10] published an MA evaluating first-line triple therapy consisting of AMPC and CAM in a CAM-susceptible subgroup; the eradication rate was 94.9% (95% CI, 92.5 to 96.6) in the VPZ-based group versus 89.6% (95% CI, 86.9 to 91.9) in the PPI-based group (OR, 2.02; 95% CI, 1.23 to 3.32). Four studies were analyzed: one RCT (VPZ phase III),[9] one prospective study,[24] and two retrospective studies.[26,27] Heterogeneity was moderate (I^2=45%), indicating moderate reliability. In 2018, Li *et al.*[12] published an MA based on five studies, consisting of one RCT[25] plus the four studies evaluated by Dong *et al.*[10] VPZ-based therapy was not superior to PPI-based therapy when the two RCTs were combined (eradication rate of VPZ vs PPI: 95.4% vs 92.8%) or when the three non-RCTs were combined (eradication rate of VPZ vs PPI: 92.9% vs 86.2%). The ORs were 1.63 (95% CI, 0.74 to 3.61; p=0.225) and 4.58 (95% CI, 0.67 to 31.45; p=0.122), respectively.

We performed an RCT to explore whether a clinically significant difference was apparent between VPZ-based and PPI-based triple therapies for CAM-susceptible *H. pylori* eradication. The eradication rates were 87.3% (95% CI, 75.5 to 94.7) for VPZ-based therapy and 76.5% (95% CI, 62.5 to 87.2) for PPI-based therapy in the ITT analysis (p=0.21) and 88.9% (95% CI, 77.4 to 95.8) and 86.7% (95% CI, 73.2 to 94.9), respectively, in the PP analysis (p=0.77).[25] There was no clinically significant difference.

Non-RCTs are at risk of several forms of bias that are lacking in RCTs. The differences between RCT and non-RCT analyses reflect these biases.

Rapid, strong, and stable acid block by P-CAB results in AMPC and CAM becoming more effective, because at pH >5, *H. pylori* enters the growth phase. The major reason for VPZ-based superiority with CAM-resistant *H. pylori* is that AMPC works more effectively, as evidenced by the VPZ-AMPC dual therapy result.[29] On the other hand, in a CAM-susceptible situation, PPI-induced acid suppression may be sufficient to be effective with the AMPC-CAM combination. The main reason for the failure of PPI-based or P-CAB-based eradication for CAM-susceptible *H. pylori* is based on the limit of the 7-day triple therapy regimen used in Japan. The results of VPZ-based therapy are not superior to those of PPI-based therapy, which shows that the limit of the 7-day triple therapy did not resolve the situation with P-CAB use, and improvement of the administration frequency and dose of AMPC, and the treatment period of P-CAB-based triple therapy is necessary.

In summary, VPZ-based triple therapies are not superior to PPI-based SSTs in terms of eradicating CAM-susceptible *H. pylori*.

VPZ-COMPARED WITH PPI-BASED SECOND-LINE TRIPLE THERAPY CONSISTING OF AMPC AND MNZ

Two MAs of non-RCTs comparing 7-day triple therapy consisting of VPZ, AMPC, and MNZ with 7-day triple therapy consisting of a PPI, AMPC, and MNZ have appeared. In 2017, Dong *et al.*[10] published a MA of non-RCTs and concluded that VPZ was not superior to PPIs when incorporated into a second-line therapy. In the ITT analysis, the eradication rates were 83.4% (95% CI, 79.8 to 86.5) for VPZ-based therapy versus 81.2% (95% CI, 79.5 to 83.5) for PPI-based therapy (p=0.79); in the PP analysis, the respective figures were 89.3% (95% CI, 86.2 to 92.0) versus 90.1% (95% CI, 88.3 to 91.6) (p=0.06).[10] Six studies[24,36,37,40,41,43] were evaluated. One study[40] principally employed PPI-based triple therapy consisting of MNZ and STFX; 31 of total of 1,941 cases were reviewed in the MA. The heterogeneity was very low (I^2=0%), indicating that the MA was highly reliable.

In 2020, Shinozaki *et al.*[52] published an MA of non-RCTs concluding that VPZ was superior to PPI when incorporated into second-line therapies. In the PP analysis,

the eradication rates were 91.1% (95% CI, 89.8 to 92.2) for VPZ-based therapy compared with 88.2% (95% CI, 87.2 to 89.2) for PPI-based therapy (p<0.001). Sixteen studies[24,32,36,37,41,43,48,50,53-60] were evaluated.[52] Heterogeneity was very low (I^2=0%), suggesting that the MA was very reliable. However, the latter seven studies[54-60] are not listed in PubMed, indicating that they may be of poor quality and have not been critically apprised; none of those seven studies were included in several other MAs.[10-12] After excluding those studies, the average eradication rates in the nine remaining studies were 90.9% (95% CI, 89.6 to 92.1) for VPZ-based triple therapy and 88.3% (95% CI, 87.2 to 89.3) for PPI-based triple therapy. The 2.6% difference lacks clinical significance. Also, most retrospective studies are at high risk of bias, lack pre-planned analyses, and used arbitrary numbers in the PPI-based arm that serve as historical controls. Another MA excluded most studies, considered "low-quality studies with poorly defined populations."[12] In the MA, two propensity score-matched analyses[52,53] were included. However, both works lacked antibiotic-resistance data, and this was not remedied by propensity score matching.

Several MAs seem to be very reliable in terms of low heterogeneity, but the conclusions differ. Publication bias may be in play, as retrospective studies with negative results may not be accepted by journals. Indeed, many positive results were published after one MA;[55] one MA of retrospective studies published in 2020[52] contained high numbers of subjects (1,147/2,293 cases of VPZ-based therapy and 2,251/3,854 cases of PPI-based therapy). Selection bias and confounding variables may be in play in other retrospective studies.

As shown in Table 2, that MA was almost entirely based on retrospective cohort trials and lacked data on antibiotic resistance; the groups were thus not matched in this context. Antibiotic-resistance data are essential when generalizing the results to countries or regions that vary in terms of the MNZ- or AMPC-resistance rate. In addition, the MA divided the patients into two groups based on VPZ- or PPI-based first-line therapy. Most studies do not do this; any assumption that the two groups are similar may be misleading. If first-line VPZ-based therapy is superior to PPI-based therapy, eradication is more difficult in those who fail first-line VPZ-based therapy. In summary, the finding of slight (~2.6%) superiority of VPZ-based therapy was unreliable given the selection bias, confounding variables, and risk of publication bias, and the results are difficult to generalize because of a lack of antibiotic-resistance data.

VPZ- VERSUS PPI-BASED TRIPLE THERAPIES CONSISTING OF AMPC AND STFX FOR THIRD-LINE ERADICATION

In 2019, we reported an RCT comparing third-line VPZ- with PPI-based 7-day triple therapies consisting of AMPC after first-line triple therapy (AMPC and CAM) and second-line triple therapy (AMPC and MNZ) failures.[61] The VPZ and AMPC doses were the same as those of the first- and second-line regimens; the STFX dose was 100 mg bid (200 mg/day). The eradication rates were 75.8% (95% CI, 57.7 to 88.9) for VPZ therapy versus 53.3% (95% CI, 34.3 to 71.7) for PPI therapy in the ITT analysis (p=0.071), and 83.3% (95% CI, 65.3 to 94.4) versus 57.1% (95% CI, 37.2 to 75.5), respectively, in the PP analysis (p=0.043). In a retrospective study, Saito *et al.*[32] reported eradication rates of 93.0% (95% CI, 83.0 to 98.1) for VPZ therapy versus 54.2% (95% CI, 32.8 to 74.4) for PPI therapy (esomeprazole) in the ITT analysis (p<0.001), and 93.0% (95% CI, 83.0 to 98.1) versus 56.5% (95% CI, 34.5 to 76.8), respectively, in the PP analysis (p<0.001). In summary, a third-line VPZ-based triple therapy consisting of AMPC and STFX is more effective than a PPI-based regimen, but a confirmatory RCT is required.

VPZ- VERSUS PPI-BASED TRIPLE THERAPIES INVOLVING CAM AND MNZ

In 2017, Ono *et al.*[40] published a retrospective study comparing 7-day triple therapy consisting of VPZ, CAM, and MNZ with 7-day triple therapy consisting of PPI, CAM, and MNZ. The VPZ-based regimen was associated with a higher eradication rate than that of the PPI-based treatment, thus 92.9% (n=14) versus 46.2% (n=13) in the ITT analysis (p=0.0128) and 92.9% versus 54.6% in the PP analysis. In 2017, we reported a registered, prospective, non-randomized study comparing VPZ-based and PPI-based regimens, as mentioned above. The eradication rate was 100% (95% CI, 86.1 to 100) for the VPZ-based therapy versus 83.3% (95% CI, 65.3 to 94.4) for the PPI-based therapy in the ITT analysis, and 100% (95% CI, 86.1 to 100) versus 82.7% (95% CI, 64.2 to 94.2), respectively, in the PP analysis.[62] Thus, VPZ-based triple therapy involving CAM and MNZ seems to be superior to PPI-based therapy. In summary, a VPZ-based triple therapy (CAM and MNZ) may be better than a PPI-based regimen, but both studies were non-RCTs and lacked data on antibiotic resistance.

CONCLUSIONS AND FUTURE DIRECTIONS

Any attempt to answer the question "Is P-CAB really superior to a PPI in terms of *H. pylori* eradication?" is limited by the setting in which we work. VPZ (a P-CAB) was used in 7-day triple therapies at the dose covered by the Japanese national insurance system. The CAM-resistance rate was approximately 33%, whereas the MNZ-resistance rate was low (<5%) and the AMPC-resistance rate was very low. Tegoprazan and other P-CABs should be trialed in terms of *H. pylori* eradication in the future. In addition, the study was performed mainly in Japan. Diet and human genetics are also influence the stomach pH. Thus, further studies outside Japan are needed to generalize the result to global populations.

An MA of RCTs comparing VPZ- and PPI-based first-line triple therapies consisting of AMPC and CAM may be generalizable to populations comprising approximately 30% of CAM-resistant subjects, but reliability is poor because of high heterogeneity and a risk of selection bias (poor allocation concealment). First-line VPZ-based triple therapy involving AMPC and CAM are superior to PPI-based regimens in patients with CAM-resistant *H. pylori*, but the eradication rate remains unacceptably low. First-line VPZ-based triple therapies consisting of AMPC and CAM are not superior to PPI-based regimens in patients with CAM-susceptible *H. pylori*, as revealed by two RCTs. The slightly (~2.6%) higher success rate of second-line VPZ-based triple therapy compared with PPI-based triple therapy (AMPC and MNZ) is unreliable given the selection bias, confounding variables and risk of publication bias, and it is difficult to generalize the results because of the lack of antibiotic-resistance information. Further RCTs are required. Third-line VPZ-based triple therapies involving AMPC and STFX may be more effective than PPI-based regimens, but a confirmatory RCT is required. VPZ-based triple therapies involving CAM and MNZ may be better than PPI-based regimens, but only non-RCT data are available, and information on antibiotic resistance is lacking. Finally, more RCTs with antibiotic-resistance data are required in populations outside Japan if P-CABs are to replace PPIs worldwide.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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