Circulation Reports
Circ Rep 2021; 3: 26–33
doi:10.1253/circrep.CR-20-0124

ORIGINAL ARTICLE
Cardiovascular Intervention

Effects of Vonoprazan on the Antiplatelet Function of Prasugrel Assessed by the VerifyNow P2Y12 Assay in Patients With Coronary Artery Disease

Seiji Koga, MD, PhD; Satoshi Ikeda, MD, PhD; Ryohei Akashi, MD;
Tsuyoshi Yonekura, MD; Hiroaki Kawano, MD, PhD; Koji Maemura, MD, PhD

Background: Vonoprazan is a potassium-competitive acid blocker increasingly used in Japan to prevent upper gastrointestinal bleeding in patients undergoing dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI). Cytochrome P450 (CYP) 3A4 is involved in the primary metabolism of both vonoprazan and prasugrel. This raises concern about the possibility of a CYP3A4-mediated drug-drug interaction between vonoprazan and prasugrel that may lead to attenuation of prasugrel's antiplatelet effect.

Methods and Results: We evaluated 88 PCI patients who were taking either vonoprazan (n=45) or proton pump inhibitors (PPIs; n=43) in combination with DAPT (aspirin and prasugrel). Platelet reactivity on prasugrel was assessed using the VerifyNow P2Y12 assay. The primary endpoint was comparison of P2Y12 reaction units (PRU) between patients on vonoprazan and PPIs. PRU >208 and <85 were defined as high (HPR) and low (LPR) on-treatment platelet reactivity for prasugrel. PRU was comparable between patients receiving vonoprazan and PPIs (169±52 vs. 179±61, respectively; P=0.75). There were no significant differences between the vonoprazan and PPI groups in the prevalence of HPR (22% vs. 37%, respectively; P=0.16) and LPR (4 vs. 7%, respectively; P=0.48). The results were consistent regardless of the type of clinical presentation and DAPT duration.

Conclusions: PRU under DAPT with aspirin plus prasugrel in patients receiving vonoprazan was not significantly different from that in patients receiving PPIs after PCI in routine clinical practice.

Key Words: P2Y12 receptors; Percutaneous coronary intervention; Platelet reactivity; Proton pump inhibitor

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor is the standard care for the prevention of cardiovascular events in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI).[1] Although clopidogrel is a widely used P2Y12 receptor inhibitor, it shows modest antiplatelet effects with significant interpatient variability, primarily because of the presence of cytochrome P450 (CYP) 2C19 *2 and/or *3 loss-of-function alleles.[2,3] This genetic variation is responsible for the variability in platelet reactivity on clopidogrel, which is more frequent in Japanese than Caucasian populations.[2,3] Prasugrel is a recently developed P2Y12 receptor inhibitor that causes more consistent, rapid and pronounced inhibition of platelet activity than clopidogrel. Because prasugrel is predominantly metabolized to its active form by CYP3A4, its antiplatelet effects are not affected by CYP2C19 polymorphisms.[3] In fact, despite the lower dose of prasugrel used in Japan compared with Western countries (3.75 vs. 10 mg for maintenance), platelet function tests showed potency of prasugrel compared with clopidogrel.[4] Therefore, prasugrel may be preferable in patients at a high ischemic risk, including for acute coronary syndrome (ACS), but is potentially associated with an increased risk of bleeding.[5]

Gastrointestinal bleeding (GIB) is the predominant cause of non-access site-related bleeding under DAPT after PCI, and is associated with all-cause mortality in hospital and after discharge.[6,7] Therefore, proton pump inhibitors (PPIs) in combination with DAPT are recommended, particularly in patients at high risk of GIB, such as those with a history of GIB or peptic ulcer.[8,9] However, PPIs need several days to achieve sufficient gastric acid suppression, and their effects vary depending on the genetic variation in CY2C19, the main enzyme responsible for their

Received November 18, 2020; accepted November 18, 2020; J-STAGE Advance Publication released online December 18, 2020 Time for primary review: 1 day
Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
K.M. is a member of *Circulation Reports*' Editorial Team.
Mailing address: Satoshi Ikeda, MD, PhD, Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. E-mail: sikeda@nagasaki-u.ac.jp
All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cr@j-circ.or.jp
ISSN-2434-0790

metabolism.[10] Since 2015, vonoprazan, a novel potassium-competitive acid blocker, has become clinically available in Japan for various indications, such as the treatment of gastroesophageal reflux disease and secondary prevention of low-dose aspirin-induced ulcers in patients with a history of peptic ulcer. Vonoprazan has several advantages over PPIs, including a rapid onset of action, greater potency, and long-lasting acid inhibitory effects.[11,12] In addition, because vonoprazan is predominantly metabolized by CYP3A4, the effect of CYP2C19 genotype status on its pharmacokinetics is considered minimal.[13] This, however, raises concern about the possibility of a CYP3A4-mediated drug-drug interaction (DDI) between vonoprazan and prasugrel, which may lead to attenuation of the antiplatelet effect of prasugrel.[14] However, such a relationship has not yet been fully investigated in daily clinical practice. Therefore, the aim of this study was to clarify the effect of vonoprazan on the antiplatelet function of prasugrel compared with PPIs in patients with CAD treated with PCI.

Table 1. Dosage and Incidence of the Use of Vonoprazan and PPIs Among All Patients (n=88)

Vonoprazan	45 (51)
10 mg	41 (47)
20 mg	4 (5)
PPIs	43 (49)
Esomeprazole	
10 mg	5 (6)
20 mg	23 (27)
Lansoprazole	
15 mg	4 (5)
30 mg	4 (5)
Rabeprazole	
5 mg	1 (1)
10 mg	6 (7)

Data are given as n (%). PPIs, proton pump inhibitors.

Methods

Study Design

This was a single-center retrospective observational study at Nagasaki University Hospital conducted between October 2017 and October 2018. The study complied with the Declaration of Helsinki regarding ethical human investigations, and the Nagasaki University Hospital Ethics Committee approved the study protocol. All patients provided written informed consent before study enrollment.

Patient Population

Patients with CAD who were taking DAPT (aspirin and prasugrel) plus either vonoprazan or PPIs were enrolled in the study, including patients with the following clinical presentations: (1) those undergoing scheduled follow-up coronary angiography (CAG) after previous PCI; and (2) patients with stable angina pectoris (SAP) and ACS who were scheduled to undergo PCI. Patients were excluded if they were taking other antithrombotic agents, had a platelet count $\leq 10\times10^4/\mu$L, or had severe liver dysfunction (Child-Pugh Class C). SAP was defined as no change in the frequency, duration, or intensity of angina symptoms within the 6-week period before admission. ACS included acute myocardial infarction (AMI) and unstable angina pectoris. AMI was defined as acute myocardial injury with clinical evidence of acute myocardial ischemia and detection of a rise and/or fall in cardiac troponin values at least one value above the 99th percentile upper reference limit and at least one of the following: symptoms of myocardial ischemia, new ischemic changes on an electrocardiogram, the development of pathological Q waves, imaging evidence of a new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, or identification of coronary thrombus on angiography.[15] Unstable angina pectoris was defined as angina at rest, accelerated angina, or new-onset angina without an elevation in cardiac markers.

Dual Antiplatelet Therapy

In patients who underwent emergency PCI, loading doses of 200 mg aspirin and 20 mg prasugrel were administered just before PCI. Maintenance doses of 100 mg/day aspirin and 3.75 mg/day prasugrel were prescribed after PCI. In patients who underwent elective PCI, 100 mg/day aspirin and 3.75 mg/day prasugrel were administered before PCI and maintained after the procedure. Patients who underwent scheduled follow-up CAG after previous PCI had been routinely taking 100 mg/day aspirin and 3.75 mg/day prasugrel since the previous PCI. The duration of DAPT from initiation to the time of assessment using the VerifyNow $P2Y_{12}$ assay (Instrumentation Laboratory, Bedford, MA, USA) was evaluated.

Vonoprazan and PPIs

Vonoprazan or PPIs were newly administered in combination with DAPT if patients were not taking them before PCI. The choice of vonoprazan or PPIs was left to the discretion of the treating physician. If patients were already receiving vonoprazan or any kind of PPI at the time of PCI, these were continued at the same dose after PCI.

VerifyNow Assay

Blood collection for the VerifyNow assay was performed immediately before CAG or PCI. Before heparinization, whole blood samples (~2 mL) were drawn from the femoral or radial artery sheath and collected in tubes containing 3.2% sodium citrate after discarding the first 2–4 mL of blood to avoid using blood with arterial puncture-induced platelet activation. Samples were processed by laboratory personnel blinded to whether the patient was receiving vonoprazan or PPIs. The time between sample collection and assay performance was at least 10 min, but not more than 4 h. Platelet reactivity on prasugrel was evaluated using the VerifyNow $P2Y_{12}$ assay according to the manufacturer's instructions. The VerifyNow system was calibrated using electronic quality control to minimize interassay variance before starting the system. The VerifyNow system measures ADP-induced platelet function and reports the results as $P2Y_{12}$ reaction units (PRU). VerifyNow $P2Y_{12}$ baseline reactivity (BASE) and percentage inhibition of platelet aggregation (IPA) were also assessed. BASE is the estimated platelet reactivity without $P2Y_{12}$ receptor inhibition. IPA is calculated as $([\text{BASE}-\text{PRU}]/\text{BASE})\times100$. High (HPR) and low (LPR) on-treatment platelet reactivity on prasugrel were defined as PRU >208 and <85, respectively, based on the Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding $P2Y_{12}$ Receptor Inhibitor Treatment in Percutaneous Coronary

Table 2. Patient Characteristics

	All (n=88)	PPIs group (n=43)	Vonoprazan group (n=45)	P value
Age (years)	67±11	68±12	67±10	0.65
Male sex	67 (76)	30 (70)	37 (82)	0.21
Body weight (kg)	63 [52–72]	64 [56–70]	62 [49–72]	0.56
Body mass index (kg/m^2)	23.2 [20.5–26.3]	24.0 [21.7–26.5]	21.8 [20.4–26.1]	0.23
Hypertension	74 (84)	38 (88)	36 (80)	0.39
Dyslipidemia	66 (75)	31 (72)	35 (78)	0.63
Diabetes	34 (39)	19 (44)	15 (33)	0.38
Current smoking	18 (21)	7 (16)	11 (24)	0.43
Clinical presentation				0.89
Follow-up CAG	35 (40)	18 (42)	17 (38)	
PCI for SAP	37 (42)	18 (42)	19 (42)	
PCI for ACS	16 (18)	7 (16)	9 (20)	
Concomitant medications				
CCB	40 (46)	19 (44)	21 (47)	0.83
ACEI	21 (24)	8 (19)	13 (29)	0.32
ARB	35 (40)	17 (40)	18 (40)	0.96
β-blocker	39 (44)	19 (44)	20 (44)	1.00
Statin	68 (77)	33 (77)	35 (78)	1.00
DAPT				
Duration (days)	127 [3–297]	128 [4–293]	126 [3–299]	0.50
Duration <7 days	29 (33)	12 (28)	17 (38)	0.37
Loading	12 (14)	4 (9)	8 (18)	0.56
Time from last DAPT intake to blood sampling (min)	310 [243–354]	322 [268–361]	302 [225–344]	0.28
Laboratory data				
WBC (×10^3/μL)	6.1 [5.1–7.8]	5.9 [4.8–7.3]	6.4 [5.4–8.2]	0.16
Hemoglobin (g/dL)	13.6 [12.0–14.9]	13.3 [11.9–14.7]	13.9 [12.2–14.9]	0.68
Platelet count (×10^3/μL)	198 [171–240]	205 [175–240]	196 [162–240]	0.22
hsCRP (mg/L)	0.65 [0.29–2.59]	0.65 [0.22–2.48]	0.64 [0.29–2.71]	0.76
LDL-C (mg/dL)	85 [67–103]	80 [66–98]	87 [67–107]	0.62
HDL-C (mg/dL)	42 [35–53]	44 [36–54]	39 [34–51]	0.43
Triglyceride (mg/dL)	97 [75–147]	92 [70–136]	104 [79–158]	0.27
HbA1c (%)	6.0 [5.6–6.6]	6.1 [5.6–6.9]	5.9 [5.6–6.4]	0.15
eGFR (mL/min/1.73 m^2)	57 [44–77]	52 [44–65]	64 [43–84]	0.086

Data are given as the mean±SD, median [interquartile range], or n (%). ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CAG, coronary angiography; CCB, calcium channel blocker; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors; SAP, stable angina pectoris; WBC, white blood cell.

Intervention.[16] The VerifyNow assay wet quality control was assessed 5 times to determine our laboratory coefficient of variation (CV) for the VerifyNow P2Y$_{12}$ assay. The CV was 2.8% for quality control.

Risk Factors

Hypertension was defined as systolic/diastolic blood pressure of >140/90 mmHg in repeated measurements or the current use of antihypertensive medications. Dyslipidemia was defined as documented hyperlipidemia or the use of lipid-lowering medications. Diabetes was defined as an HbA1c concentration of >6.5% or the use of antihyperglycemic medications.

Endpoints

The primary endpoint was comparison of PRU between patients on vonoprazan and PPIs. Secondary endpoints were comparisons of the prevalence of HPR and LPR between the 2 drug groups.

Analysis of PRU in Various Settings

PRU was compared between patients on vonoprazan and PPIs in terms of the following variables: (1) type of PPI; (2) clinical presentation (follow-up CAG, PCI for SAP, or PCI for ACS); (3) DAPT duration (<7 or ≥7 days); and (4) comorbidities and concomitant medications.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA). Normality of data was assessed using the Shapiro-Wilk test. Continuous normally distributed data are presented as the mean±SD and were compared using unpaired t-tests. Data that were not normally distributed are presented the median with

Table 3. Results of the VerifyNow P2Y12 Analysis

	All (n=88)	PPIs group (n=43)	Vonoprazan group (n=45)	P value
PRU	171 [132–223]	175 [132–225]	167 [134–197]	0.75
HPR (PRU >208)	26 (30)	16 (37)	10 (22)	0.16
LPR (PRU <85)	5 (6)	3 (7)	2 (4)	0.48
IPA (%)	35 [19–49]	35 [16–50]	34 [22–48]	0.88

Values are shown as the median [interquartile range] or n (%). HPR, high on-treatment platelet reactivity; IPA, inhibition of platelet aggregation; LPR, low on-treatment platelet reactivity; PRU, P2Y12 reaction units; PPIs, proton pump inhibitors.

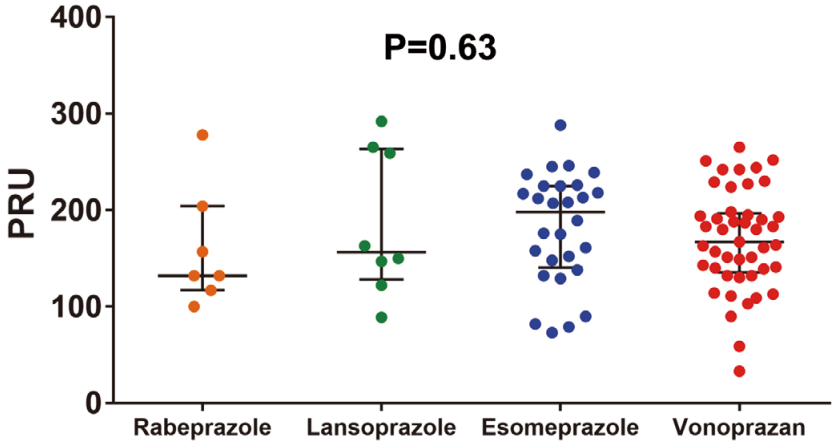

Figure 1. Comparison of P2Y12 reaction units (PRU) between patients receiving vonoprazan and those receiving different types of proton pump inhibitors. Symbols represent individual participants. The horizontal lines indicate median values and the error bars show the interquartile range.

interquartile range (IQR) and were compared using the Mann-Whitney U-test. Categorical variables were compared using Chi-squared or Fisher's exact tests, as appropriate. Multiple comparisons were performed using the Kruskal-Wallis test. A 2-tailed test of significance was performed for all analyses, and P<0.05 was considered statistically significant.

Results

Patient Characteristics

In all, 88 patients who were taking DAPT plus either vonoprazan (n=45) or PPIs (n=43) were assessed. These included 35 patients who underwent scheduled follow-up CAG and 37 SAP and 16 ACS patients who were scheduled to undergo PCI. The scheduled follow-up CAG was performed a median of 279 days (IQR 119–332 days) after the index PCI. The PPIs prescribed included esomeprazole in 28 patients, lansoprazole in 8 patients, and rabeprazole in 7 patients. The doses of vonoprazan and the PPIs used are listed in **Table 1**. Clinical characteristics of the patients are summarized in **Table 2**. There were no significant differences in clinical characteristics between patients receiving vonoprazan and PPIs (**Table 2**).

Analysis of PRU

The main results of the VerifyNow P2Y12 assessment are summarized in **Table 3**. PRU in patients on vonoprazan was comparable to that in patients on PPIs. There were no significant between-group differences in the prevalence of HPR and LPR. IPA was also comparable between the groups.

PRU values among patients on vonoprazan and the different PPIs are summarized in **Figure 1**. Median (IQR) PRUs were similar across all groups: 132 (117–204) with rabeprazole, 157 (128–264) with lansoprazole, 198 (141–225) with esomeprazole, and 167 (134–197) with vonoprazan (P=0.63). PRU values in each type of clinical presentation are shown in **Figure 2**. Median (IQR) PRUs in patients on vonoprazan were comparable with those in patients on PPIs with all the presentations: 151 (132–191) vs. 207 (157–225), respectively, in the PCI for ACS group (P=0.17); 191 (151–229) vs. 170 (134–223), respectively, in the PCI for SAP group (P=0.58); and 157 (122–186) vs. 150 (121–229), respectively, in the follow-up CAG group (P=0.65). Furthermore, there were no significant differences in the median (IQR) PRU between patients receiving vonoprazan or PPIs stratified according to DAPT duration (<7 or ≥7 days; **Figure 3**): 161 (132–211) vs. 191 (152–260), respectively, in patients with DAPT duration <7 days (P=0.23); and 174 (140–196) vs. 163 (129–218), respectively, in those with DAPT duration ≥7 days (P=0.99). In addition, there were no significant differences in PRU between patients on vonoprazan and PPIs stratified according to various factors, including background characteristics, comorbidities, and concomitant medications (**Table 4**).

Discussion

There are 2 main findings of this study in patients with CAD under treatment with DAPT (aspirin and prasugrel) plus either vonoprazan or PPIs: (1) there were no significant

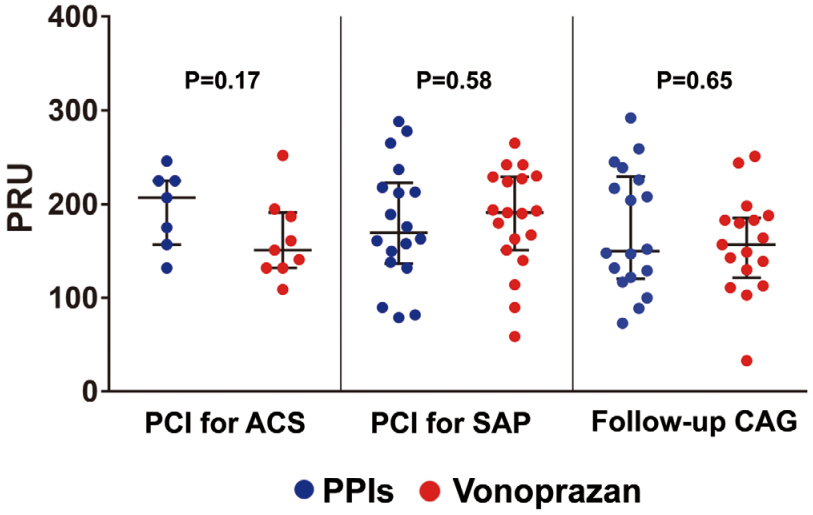

Figure 2. Comparison of P2Y12 reaction units (PRU) between patients receiving vonoprazan and those receiving proton pump inhibitors (PPIs) according to the type of clinical presentation. Symbols represent individual participants. The horizontal lines indicate median values and the error bars show the interquartile range. ACS, acute coronary syndrome; CAG, coronary angiography; PCI, percutaneous coronary intervention; SAP, stable angina pectoris.

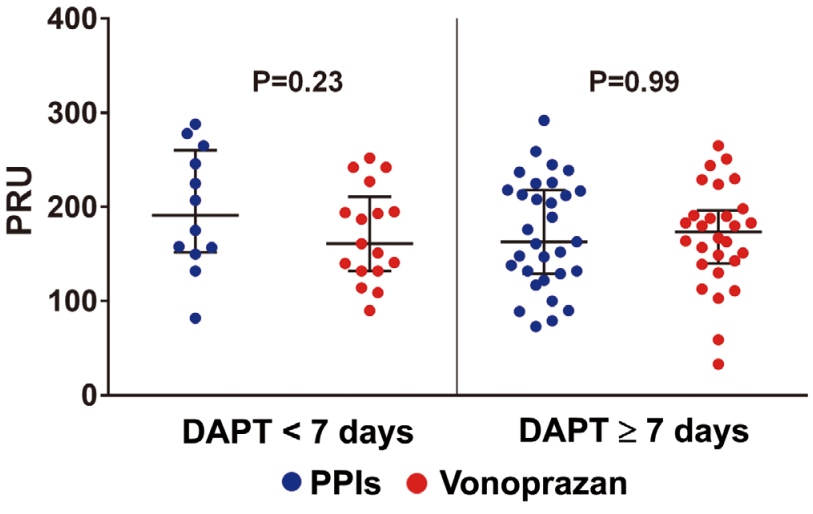

Figure 3. Comparison of P2Y12 reaction units (PRU) between patients receiving vonoprazan and those receiving proton pump inhibitors (PPIs) according to dual antiplatelet therapy (DAPT) duration. Symbols represent individual participants. The horizontal lines indicate median values and the error bars show the interquartile range.

differences in PRU between patients on vonoprazan and those on PPIs; and (2) the prevalence of HPR and LPR was comparable between the 2 groups. To the best of our knowledge, this is the first clinical study to demonstrate that the effect of vonoprazan on the antiplatelet function of prasugrel appears to be comparable to that of PPIs in CAD patients treated with PCI.

Recently, Kagami et al conducted a comparative study to investigate the effects of vonoprazan and the PPI esomeprazole on the antiplatelet effects of prasugrel using a VerifyNow P2Y12 assay in 31 healthy Japanese volunteers (mean age 21 years).[14] In that study, Kagami et al demonstrated that vonoprazan decreased the inhibitory effect of prasugrel on platelet aggregation more potently than did esomeprazole, and speculated that a CYP3A4-mediated DDI between vonoprazan and prasugrel attenuated its antiplatelet function.[14] To clarify this issue, Nishihara et al investigated the in vitro inhibitory potential of vonoprazan on the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5), and its effect on the metabolism of R-138727, the radiolabeled active metabolite of prasugrel, using pooled human liver microsomes, and whether the effects were direct (reversible) or time dependent (irreversible).[17,18] Vonoprazan showed no significant reversible inhibition of any of the major CYP isoforms (IC_{50} ≥16 μmol/L), and exhibited only weak time-dependent inhibition of CYP2B6, CYP2C19 and CYP3A4.[18] However, these time-dependent effects were weaker than those of the corresponding reference compounds (ticlopidine, esomeprazole, and verapamil). In addition, vonoprazan did not significantly inhibit the formation of R-138727 at concentrations up to 10 μmol/L, a concentration over 100-fold higher than that of the clinical maximum plasma concentration after therapeutic oral doses.[17] Therefore, theoretically, the inhibitory effect of vonoprazan on the metabolism of prasugrel would probably be limited at clinical doses. Nishihara et al concluded that pharmacodynamic interaction between vonoprazan and prasugrel is

Table 4. Comparison of PRU in Various Patient Subgroups

	PRU		P value
	PPIs group (n=43)	Vonoprazan group (n=45)	
Age (years)			
≥75	158 [81–205]	188 [120–237]	0.36
<75	189 [135–232]	164 [136–197]	0.24
Sex			
Male	151 [127–219]	161 [132–192]	0.93
Female	213 [175–231]	212 [189–239]	0.92
Body weight (kg)			
≥50	176 [132–225]	162 [137–193]	0.36
<50	161 [124–258]	191 [114–244]	0.83
Diabetes			
Present	158 [138–225]	167 [114–190]	0.41
Absent	176 [125–226]	172 [140–228]	0.87
eGFR (mL/min/1.73 m^2)			
≥60	182 [145–228]	191 [157–230]	0.70
<60	157 [127–222]	151 [126–185]	0.63
CCB			
Present	204 [147–259]	167 [136–230]	0.29
Absent	159 [130–216]	172 [134–191]	0.98
ACEI			
Present	143 [113–173]	183 [135–191]	0.30
Absent	204 [132–226]	166 [134–229]	0.51
ARB			
Present	217 [131–243]	184 [128–233]	0.64
Absent	159 [132–212]	164 [139–191]	0.80
β-blocker			
Present	148 [122–207]	174 [132–189]	0.65
Absent	218 [157–244]	164 [137–236]	0.31
Statin			
Present	161 [132–225]	180 [130–224]	0.92
Absent	206 [120–245]	156 [141–194]	0.28

Values are the median (interquartile range). Abbreviations as in Tables 1,3.

unlikely to be caused by CYP inhibition by vonoprazan.[17,18] In contrast, Wang et al reported that vonoprazan could inhibit CYP3A4 both in vitro and in vivo, suggesting that the coadministration of vonoprazan with CYP3A4 substrates should be performed cautiously in clinical settings.[19] However, Wang et al did not investigate the CYP3A4-mediated DDI between vonoprazan and prasugrel. These apparent discrepancies in findings may be due to the heterogeneity of the different experimental methods. Clarification of these issues is vital before further clinical use of the combination of prasugrel and vonoprazan.

In the present study we compared the effects of vonoprazan and PPIs on the antiplatelet function of prasugrel using the VerifyNow P2Y$_{12}$ assay in patients with CAD treated by PCI. We found no significant differences in PRU and the prevalence of HPR and LPR between patients receiving vonoprazan or PPIs with prasugrel. In addition, the PRU between patients on vonoprazan and PPIs were comparable regardless of the type of PPI. It has been reported that platelet activation differs significantly depending on the type of clinical presentation, with the highest activation seen in ACS.[20] In the present study, PRU in patients on vonoprazan was comparable to that in patients receiving PPIs regardless of the type of clinical presentation, including PCI for ACS, SAP, and follow-up CAG. Because stent thrombosis occurred most commonly during the first 4 weeks, particularly during the first 7 days after PCI,[21] a sufficient antiplatelet effect is required during this period. We demonstrated that there were no significant differences in PRU between patients receiving vonoprazan or PPIs regardless of DAPT duration (i.e., in both the <7 and ≥7 days groups). It is unclear why our results are not consistent with the findings of Kagami et al[14] described above. However, several factors may explain the discordance. First, the study by Kagami et al was a prospective randomized cross-over study, whereas the present study was retrospective and observational in nature. Second, although both studies used the VerifyNow assay, the parameter used to assess platelet reactivity on prasugrel was different. The primary measurement in the study of Kagami et al was the IPA, whereas PRU was assessed in the present study. PRU is the most widely used bedside test and the best studied parameter to determine the correlation between platelet reactivity and ischemic or bleeding outcomes.[16] Conversely, Price suggested that the IPA reported by VerifyNow as a surrogate for the degree of P2Y$_{12}$-mediated inhibition

without a baseline pre-prasugrel sample may be inaccurate compared with the actual change in PRU.[22] A third possible explanation may be differences in inclusion criteria. Kagami et al enrolled healthy young volunteers, whereas we investigated CAD patients with several comorbidities who were treated with PCI in daily clinical practice. On-treatment platelet reactivity is not only a measure of drug response, but also a global integrator of responses to $P2Y_{12}$ receptor inhibitors. Certain patient characteristics and comorbidities (e.g., advanced age, diabetes, and renal insufficiency) may interfere with platelet activation.[23] Indeed, the median value of IPA on prasugrel in the present study was 35%, which is relatively low compared with the results reported by Kagami et al (47% with prasugrel plus esomeprazole and 37% with prasugrel plus vonoprazan).[14] In addition, certain concomitantly administered drugs can affect platelet activation. Calcium channel blockers and statins can attenuate the antiplatelet effect of clopidogrel through inhibition of CYP3A4.[24] Beta-blockers lower platelet reactivity under clopidogrel by inhibiting platelet β-adrenergic receptors.[25] In the present study, these confounding factors did not affect PRU when comparing patients receiving vonoprazan and PPIs (**Table 4**). Taken together, it is likely that vonoprazan does not attenuate the antiplatelet effects of prasugrel compared with PPIs. Further clinical assessment in larger patient populations is needed to corroborate our results.

We defined HPR and LPR on prasugrel as PRU >208 and <85, respectively, based on the Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding $P2Y_{12}$ Receptor Inhibitor Treatment in Percutaneous Coronary Intervention.[16] However, it is unclear whether these cut-off values are suitable in Japanese patients, because East Asian patients have different profiles for both ischemic and bleeding risks compared with Caucasian patients.[3] Recently, the results of the Platelet Reactivity in Patients with Drug Eluting Stent and Balancing Risk of Bleeding and Ischemic Event (PENDULUM) registry, which investigated ischemic or bleeding events and platelet reactivity in real-world Japanese patients undergoing PCI and determined associations between HPR, LPR, and clinical outcomes, were published.[26] In the PENDULUM registry, HPR (PRU>208) was independently associated with the incidence of major adverse cardiac and cerebrovascular events. Notably, the same trend was observed in patients with and without ACS.[26] In contrast, bleeding events were not associated with LPR (PRU ≤85). Therefore, it is probably reasonable to use PRU >208 as a cut-off for HPR on prasugrel related to cardiovascular events, even in Japanese patients undergoing PCI. However, it is unclear whether PRU ≤85 is appropriate as a cut-off value of LPR in relation to bleeding events in Japan. Further studies with a longer follow-up period are required to confirm the clinical impact of our results on ischemic and bleeding events.

The present study detected a wide interindividual variability in PRU on prasugrel. Similar findings were reported in the PRASugrel compared with clopidogrel For Japanese patIenTs with Acute Coronary Syndrome undergoing PCI (PRASFIT-ACS) study, a carefully monitored double-blind clinical trial with uniform assessment of PRU among patients with ACS. The variability in PRU would be expected to be more pronounced in clinical practice, where potential biasing factors, such as drug compliance, timing of the dose, and/or drugs interacting with prasugrel bioactivation, are not controlled and close monitoring and genetic data may not be routine. Indeed, the PENDULUM registry also showed a wide interindividual variability in PRU (PRU 163.5±74.5).[26] In the present study, clinical presentation, DAPT duration, timing of blood sampling, and the non-randomized study design for selection of vonoprazan and PPIs, all of which may influence prasugrel response, were heterogeneous. Other possible causes of the wide interindividual variability in PRU on prasugrel, such as problems with sampling or manipulation, also have to be considered. Therefore, data variation was wide and unmeasured confounders may still be present, adding some degree of imprecision to the results.

Study Limitations

There are several limitations to the present study. First, this retrospective observational study was performed at a single center with a small patient cohort. There was no patient randomization, no established algorithm for the selection of vonoprazan or PPIs, and the study did not follow a cross-over design (e.g., from vonoprazan to PPIs to vonoprazan). Patients were recruited to the study after they had already been treated by vonoprazan or PPIs, as prescribed by their attending physician or primary care physician. This is the main limitation of this study. Further analysis in a randomized cross-over study including a larger number of patients is needed to validate our results. Second, we performed VerifyNow measurements only once in each patient. Platelet function testing at a single time point may not be sufficient to guide antiplatelet therapy. However, a single test, as performed in the present study, is most relevant in clinical practice and has been included in most prior clinical studies using VerifyNow for risk prediction of bleeding or thrombotic events or for guidance of antithrombotic therapy. Testing results depend on many extrinsic and intrinsic variables and may change over time, as the influencing variables are subject to change over time. Thus, the optimal frequency and timing of testing in relation to the PCI remain controversial. Third, PRU at true baseline without medication was not evaluated. In addition, PRU with prasugrel alone without vonoprazan or PPIs was not investigated. Therefore, we cannot comment on the DDI of prasugrel with PPIs or vonoprazan. Fourth, plasma concentrations of the active metabolite of prasugrel and CYP polymorphisms were not evaluated. Fifth, the results cannot be directly extrapolated to other ethnic groups with different ischemic or bleeding risks and CYP polymorphisms.

Conclusions

PRU values in patients treated with prasugrel and vonoprazan were comparable to those in patients receiving prasugrel and PPIs. These findings suggest that the effect of vonoprazan on the antiplatelet function of prasugrel appears to be comparable to that of PPIs after PCI in routine clinical practice.

Acknowledgments

The authors thank Saori Usui for assistance with data and sample collection.

Sources of Funding

This study did not receive any specific funding.

Disclosures

K.M. is a member of *Circulation Reports*' Editorial Team and has received lecture fees and a scholarship from Daiichi-Sankyo. S.I. has received lecture fees from Daiichi-Sankyo. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Nagasaki University Hospital Clinical Research Ethics Committee (Reference no. 17101607-3).

Data Availability

The anonymized participant data will not be shared.

References

1. Nakamura M, Kimura K, Kimura T, Ishihara M, Otsuka F, Kozuma K, et al. JCS 2020 Guideline focused update on antithrombotic therapy in patients with coronary artery disease. *Circ J* 2020; **84:** 831–865.
2. Mangieri A, Gallo F, Sticchi A, Khokhar AA, Laricchia A, Giannini F, et al. Dual antiplatelet therapy in coronary artery disease: From the past to the future prospective. *Cardiovasc Interv Ther* 2020; **35:** 117–129.
3. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol* 2014; **11:** 597–606.
4. Nakamura M, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Optimal cutoff value of $P2Y_{12}$ reaction units to prevent major adverse cardiovascular events in the acute periprocedural period: Post-hoc analysis of the randomized PRASFIT-ACS study. *Int J Cardiol* 2015; **182:** 541–548.
5. Saito Y, Kobayashi Y, Tanabe K, Ikari Y. Antithrombotic therapy after percutaneous coronary intervention from the Japanese perspective. *Cardiovasc Interv Ther* 2020; **35:** 19–29.
6. Genereux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol* 2015; **66:** 1036–1045.
7. Koskinas KC, Räber L, Zanchin T, Wenaweser P, Stortecky S, Moschovitis A, et al. Clinical impact of gastrointestinal bleeding in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv* 2015; **8:** e002053.
8. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GY, Verheugt FW, et al. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J* 2013; **34:** 1708–1713, 1713a–1713b.
9. Ozaki Y, Katagiri Y, Onuma Y, Amano T, Muramatsu T, Kozuma K, et al. CVIT expert consensus document on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) in 2018. *Cardiovasc Interv Ther* 2018; **33:** 178–203.
10. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: From CYP2C19 pharmacogenetics to precision medicine. *Expert Opin Drug Metab Toxicol* 2018; **14:** 447–460.
11. Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T, et al. 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.
12. Hori Y, Matsukawa J, Takeuchi T, Nishida H, Kajino M, Inatomi N. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. *J Pharmacol Exp Ther* 2011; **337:** 797–804.
13. Yamasaki H, Kawaguchi N, Nonaka M, Takahashi J, Morohashi A, Hirabayashi H, et al. In vitro metabolism of TAK-438, vonoprazan fumarate, a novel potassium-competitive acid blocker. *Xenobiotica* 2017; **47:** 1027–1034.
14. Kagami T, Yamade M, Suzuki T, Uotani T, Hamaya Y, Iwaizumi M, et al. Comparative study of effects of vonoprazan and esomeprazole on antiplatelet function of clopidogrel or prasugrel in relation to CYP2C19 genotype. *Clin Pharmacol Ther* 2018; **103:** 906–913.
15. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *Circulation* 2018; **138:** e618–e651.
16. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, et al. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding $P2Y_{12}$ Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2019; **12:** 1521–1537.
17. Nishihara M. Inhibitory effect of vonoprazan on the metabolism of [^{14}C]prasugrel in human liver microsomes. *Eur J Drug Metab Pharmacokinet* 2019; **44:** 713–717.
18. Nishihara M, Czerniak R. CYP-mediated drug-drug interaction is not a major determinant of attenuation of antiplatelet function of clopidogrel by vonoprazan. *Clin Pharmacol Ther* 2018; **104:** 31–32.
19. Wang Y, Wang C, Wang S, Zhou Q, Dai D, Shi J, et al. Cytochrome P450-based drug-drug interactions of vonoprazan in vitro and in vivo. *Front Pharmacol* 2020; **11:** 53.
20. Ault KA, Cannon CP, Mitchell J, McCahan J, Tracy RP, Novotny WF, et al. Platelet activation in patients after an acute coronary syndrome: Results from the TIMI-12 trial. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol* 1999; **33:** 634–639.
21. Kimura T, Morimoto T, Kozuma K, Honda Y, Kume T, Aizawa T, et al. Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: Observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). *Circulation* 2010; **122:** 52–61.
22. Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. *Circulation* 2009; **119:** 2625–2632.
23. Aradi D, Storey RF, Komócsi A, Trenk D, Gulba D, Kiss RG, et al. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2014; **35:** 209–215.
24. Bates ER, Lau WC, Angiolillo DJ. Clopidogrel-drug interactions. *J Am Coll Cardiol* 2011; **57:** 1251–1263.
25. Lee S, Durstberger M, Eichelberger B, Kopp CW, Koppensteiner R, Panzer S, et al. Beta-blockers are associated with decreased leucocyte-platelet aggregate formation and lower residual platelet reactivity to adenosine diphosphate after angioplasty and stenting. *Eur J Clin Invest* 2016; **46:** 1041–1047.
26. Nakamura M, Kadota K, Takahashi A, Kanda J, Anzai H, Ishii Y, et al. Relationship between platelet reactivity and ischemic and bleeding events after percutaneous coronary intervention in East Asian patients: 1-year results of the PENDULUM registry. *J Am Heart Assoc* 2020; **9:** e015439.