

# Efficacy of vonoprazan for initial and maintenance therapy in reflux esophagitis, nonerosive esophagitis, and proton pump inhibitor-resistant gastroesophageal reflux disease

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## Abstract

Proton pump inhibitors (PPIs) have been the first line treatment for gastroesophageal reflux disease (GERD). The aim of this study was to evaluate the efficacy of vonoprazan (VPZ), a potassium-competitive acid blocker for reflux esophagitis (RE), nonerosive reflux disease (NERD), and PPI-resistant GERD patients.

An open-label, single-center, observational study in our hospital was performed from August 2016 to August 2017. All patients diagnosed with GERD were asked to self-report a questionnaire of frequency scale for the symptoms of GERD (FSSG) and rate their degree of satisfaction with the treatment of GERD during outpatient visit. A total of 200 (RE 47, NERD 49, PPI-resistant GERD 104) patients were included in the present study. The primary endpoint was the change of FSSG and the proportion of degree of satisfaction with the treatment at the end of the initial therapy. A percentage of improvement (improvement rate) and resolution (resolution rate) at the end of the initial therapy were evaluated. Secondary endpoint included the proportion of patients with symptomatic relapse in the 24-week maintenance phase.

FSSG and the degree of satisfaction were significantly improved after the initial therapy in every group. Improvement and resolution rate after the initial therapy were 83.0% and 67.0% in RE, 66.7% and 60.4% in NERD, and 76.0% and 60.4% in PPI-resistant group. There was no significance between after the initial therapy and 24 weeks in improvement and resolution rate. Thirty-two of the total 48 patients did not take VPZ at 24 weeks. Total FSSG score in each group was  $1.67 \pm 1.97$ ,  $2.71 \pm 4.91$ , and  $4.0 \pm 4.93$ . The nonrelapse rate at 24 weeks in each group was 66.7%, 60.0%, and 50.0%. The resolution rate at 24 weeks in each group was 38.9%, 45.0%, and 30.0%.

The VPZ therapy is effective for initial and maintenance therapy and improves heartburn and patient's satisfaction significantly in all 3 groups. Among patients who stopped taking VPZ during the maintenance period, 42.0% of RE and NERD group and 30% of PPI-resistant group experience complete remission from GERD at 24 weeks by introduction of VPZ.

**Abbreviations:** ARD = acid-related dyspepsia, BMI = body mass index, EPZ = esomeprazole, FSSG = frequency scale for the symptoms of GERD, GERD = gastroesophageal reflux disease, LPZ = lansoprazole, NERD = nonerosive reflux disease, PPI = proton pump inhibitor, PPI-rGERD = proton pump inhibitor-resistant GERD, QOL = quality of life, RE = reflux esophagitis, SD = standard deviation, VPZ = vonoprazan.

**Keywords:** nonerosive reflux esophagitis, potassium-competitive acid blocker, proton pump inhibitor-resistant gastroesophageal reflux esophagitis, reflux esophagitis, vonoprazan

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## 1. Introduction

Gastroesophageal reflux disease (GERD) is a common disorder that presents as heart burn and acid regurgitation as a result of reflux of stomach contents. Recently, the incidence is increasing in the background of westernization of eating habits and the decrease in the rate of *Helicobacter pylori* infection.<sup>[1]</sup> The range of GERD prevalence estimates were 18.1% to 27.8% in North America, 8.8% to 25.9% in Europe, 2.5% to 7.8% in East Asia, and 23.0% in South America.<sup>[2]</sup> And the prevalence increased since 1995, particularly in North America and East Asia. Incidence per 1000 person-years was approximately 5 among the UK and US populations.<sup>[2]</sup> Alcohol, smoking, consumption of fatty foods, obesity, hiatus hernia, and forward-bending positions are the known risk factors of GERD with mucosal injury.<sup>[1]</sup> Symptoms such as heartburn or regurgitation decrease the quality of life (QOL) of GERD patients. The occurrence of these symptoms at least once a week may considerably affect

QOL.<sup>[3]</sup> Proton pump inhibitors (PPIs) have been the first line treatment for GERD and are recommended in Japanese guidelines.<sup>[4]</sup> But 20% of patients with severe mucosal injury do not heal despite 8 weeks of continuous esomeprazole (EPZ) 40 mg once daily therapy.<sup>[5]</sup> Moreover, the severity of GERD symptoms does not correlate well with disease severity. It was reported that the symptoms of GERD are not proportional to the degree of the esophageal mucosal injury.<sup>[6]</sup> Approximately, a third of the patients with GERD are resistant or partial responders to PPIs.<sup>[7,8]</sup> The Japanese GERD guidelines recommend the additional use of prokinetics or herbal medicine for PPI-resistant GERD, but the effect is not absolute.<sup>[9]</sup> As a further problem, in the nonerosive reflux disease (NERD) patients without esophageal mucosal injury, the improvement rate of PPIs was lower (35%–45%) in several reports.<sup>[10–13]</sup> Previous reports have revealed that not only the regurgitation of gastric acid, but also the hyperesthesia of esophageal mucosa is a mechanism of NERD.<sup>[12]</sup> In addition, functional heart burn, which mainly occurs because of the hyperesthesia of the esophageal mucosa and psychological factors of patient, is not affected by PPIs and has difficulty in differential diagnosis. For this reason, a stronger acid inhibitor is necessary for the treatment of NERD and PPI-resistant GERD and differentiation against functional heart burn. But PPIs have several disadvantages. First, PPIs are affected by genetic polymorphisms of CYP2C19, a drug metabolizing enzyme in the liver. The differing levels of the activity of CYP2C19 in individuals result in clinically relevant differences between them, with the presence of extensive metabolizer and poor metabolizer phenotypes and drug interactions to warfarin or clopidogrel.<sup>[14]</sup> Second, PPIs are easily inactivated under acidic conditions and take a few days until the pharmacological action is expressed.<sup>[14]</sup> Therefore, initially, the patient does not get the satisfaction of relief from the symptoms.

Vonoprazan (VPZ), a potassium-competitive acid blocker, is a new class of drug that competitively blocks the potassium-binding site of H<sup>+</sup> and K<sup>+</sup>-ATPase and reduces gastric acid secretion strongly without being deactivated by the gastric acid.<sup>[15–17]</sup> In healthy volunteers, a single use of VPZ produced a rapid, profound, and dose-related suppression of 24-hour gastric acid secretion.<sup>[18]</sup> Several reports refer to the superiority against PPIs for acid block.<sup>[19,20]</sup> Furthermore, VPZ is not affected by genetic polymorphisms of CYP2C19.<sup>[21]</sup> Ashida et al<sup>[22]</sup> have reported the noninferiority of VPZ to lansoprazole (LPZ) in erosive esophagitis, and the effectiveness in patients with severe esophagitis (Los Angeles classification grades C/D) and CYP2C19 extensive metabolizer. Sakurai et al<sup>[23]</sup> have reported, in 20 healthy Japanese adult male volunteers with CYP2C19 extensive metabolizer genotype, a more rapid and sustained acid-inhibitory effect of VPZ 20 mg vs EPZ 20 mg. Several reports also refer to the efficacy of VPZ for NERD and PPI-resistant GERD.<sup>[24,25]</sup>

On the contrary, GERD has a wide spectrum of symptoms and is found in varying degrees of severity and frequency. The evaluation of GERD symptoms sometimes becomes difficult in a clinical scene. For this reason, a quick and objective questionnaire is necessary to diagnose and evaluate the effect of treatment for GERD without repeating endoscopy. Frequency scale for the symptoms of GERD (FSSG) is the standard questionnaire in Japan and is widely used for the diagnosis of GERD and assessment of the response to treatment.<sup>[26]</sup> There are few reports that evaluate the efficacy for VPZ in both initial and maintenance therapy targeted for over 100 patients. The aim of the present study is to evaluate the efficacy and safety of VPZ for patients

with reflux esophagitis (RE), NERD, and PPI-resistant GERD using self-report questionnaire in both initial and maintenance therapy.

## 2. Methods

### 2.1. Study design

This is an open-label, single-center, observational study. The patients diagnosed with GERD at our hospital from August 2016 to August 2017 were included in the present study. All patients were asked to answer FSSG, a self-report questionnaire to evaluate the symptoms of GERD. At the same time, the patients were also asked the degree of satisfaction with GERD treatment. Degrees of satisfaction were classified into 5 categories (very dissatisfied, dissatisfied, neutral, satisfied, and very satisfied). The patient who had FSSG total score of  $\geq 8$ , or a degree of satisfaction of dissatisfied or very dissatisfied, even if the FSSG score was between 4 and 7, were eligible for inclusion in our study. A total of 200 patients were analyzed in present study. All patients underwent esophagogastroduodenoscopy and we evaluated esophageal mucosal injury according to the Los Angeles classification system before initiation of the treatment. The study consisted of initial phase and maintenance phase. All eligible patients were administered VPZ 20 mg once daily for 4 weeks for initial therapy. For adaptation in Japan, after 4 weeks, VPZ must be reduced to 10 mg before switching to maintenance therapy. If efficacy of VPZ was thought to be inadequate at 4 weeks, 20 mg VPZ was administered for another 4 weeks. Maintenance therapy continued for 24 weeks. During the maintenance therapy, if symptoms worsened, VPZ was again increased to 20 mg. The present study was performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before study enrollment. The data were analyzed at Shin Beppu Hospital under the approval of the institutional ethics committee (August 13, 2018. No 2018004).

### 2.2. Participants

The exclusion criteria were as follows: younger than 20 years of age; presence of another organic lesion on endoscopy; history of gastric or esophageal surgery; evidence of Zollinger–Ellison syndrome, a primary motility disorder, esophageal stricture, Barrett's esophagus ( $>3$  cm), evidence of upper gastrointestinal malignancy, or other severe disease. The following were investigated from the patients' medical records: age, sex, body mass index (BMI), smoking habits, alcohol consumption, *H. pylori* infection status (negative, positive, or negative after eradication therapy), findings of upper gastrointestinal endoscopy (hiatal hernia, endoscopic gastric mucosal atrophy, and baseline LA classification),<sup>[27]</sup> and use of PPIs before initiating VPZ therapy. BMI was calculated as the body weight divided by the square of body height in meters ( $\text{kg}/\text{m}^2$ ). *H. pylori* infection status was assessed by the 13C-urea breath test and/or the presence of serum antibodies against *H. pylori*. Endoscopic gastric atrophy was classified as none (C-0), closed type (C-1, C-2, C-3), or open type (O-1, O-2, O-3), using the Kimura–Takemoto classification system that identifies the location of the endoscopic atrophic border.<sup>[28]</sup>

### 2.3. Gastroesophageal reflux disease

FSSG is the standard questionnaire used in Japan for the diagnosis of GERD and assessment of the response to the

treatment.<sup>[27]</sup> The FSSG contains the 12 symptoms most commonly experienced by GERD patients. Each symptom is divided into 5 phases according to its frequency of expression (never = 0, occasionally = 1, sometimes = 2, often = 3, and always = 4) and divided into 2 subscales: acid reflux-related symptoms, including 7 of 12 items (Nos. 1, 4, 6, 7, 9, 10, and 12), and dysmotility, including 5 of 12 items (Nos. 2, 3, 5, 8, and 11). The FSSG score became a good correlation with the extent of endoscopic improvement and was useful for objectively evaluating the therapeutic response of GERD. When the cutoff score was set at 8 points, the FSSG showed a sensitivity of 62%, a specificity of 59%, and an accuracy of 60%.<sup>[27]</sup> For this reason, the cutoff score for GERD has been recognized as 8 points.

In the present study, the patients were divided into 3 groups: the RE group, NERD group, and PPI-resistant GERD group. The RE patients were defined as those who were administered VPZ as an initial therapy and had findings of grades A, B, C, or D according to the Los Angeles classification system before the treatment. The NERD patients were defined as those who were administered VPZ as an initial therapy and had findings of grade M or N before the treatment. The PPI-resistant GERD patients were defined as those in whom the GERD symptoms did not adequately improve even after a standard dose of PPI treatment for more than 8 weeks. As a subgroup analysis, PPI-resistant GERD group was divided into 2 groups: erosive group and nonerosive group. The patients suffering from erosive esophagitis (erosive group) were defined as those who had findings of grade A, B, C, or D before switching to VPZ. The patients suffering from nonerosive esophagitis (nonerosive group) were defined as those who had findings of grade M or N before switching to VPZ. All patients were administered VPZ 20 mg once daily for initial therapy. After the initial therapy, VPZ was decreased to 10 mg as a maintenance therapy. During the maintenance therapy, if symptoms worsened, VPZ was again increased to 20 mg.

The primary endpoint was the change of FSSG and the proportion of degree of satisfaction to treatment at end of initial therapy. Changes in the FSSG score in RE, NERD, and PPI-resistant GERD groups at the end of initial therapy and from

baseline were evaluated. In addition, we evaluated the change in the FSSG score in the 2 subscale groups: acid reflux-related symptoms group and dysmotility group. Changes of proportions for 2 groups (very satisfied, satisfied) in the degree of satisfaction at 4 and 24 weeks of VPZ therapy were evaluated. The improvement was defined as a score below 8 points or decrease over 2 points compared with baseline if the FSSG score was between 4 and 7 points. The resolution was defined that the score about chest burn score (FSSG question nos. 1, 4, 6, and 12) was reduced to 0. A percentage of improvement (improvement rate) and resolution (resolution rate) after having VPZ at the end of initial therapy were evaluated. Secondary endpoint included the proportion of patients with symptomatic relapse in the 24-week maintenance phase. The relapse was defined as a score that rises over 8 points until 24 weeks. A percentage of nonrelapses (nonrelapse rate) at 24 weeks was evaluated. The outcome for patients who discontinued taking VPZ after initial therapy was also analyzed.

The safety of VPZ was monitored by recording adverse events, laboratory evaluations, and vital signs throughout the administration of VPZ. An adverse event was defined as unintended sign that was considered to be related to the study medication.

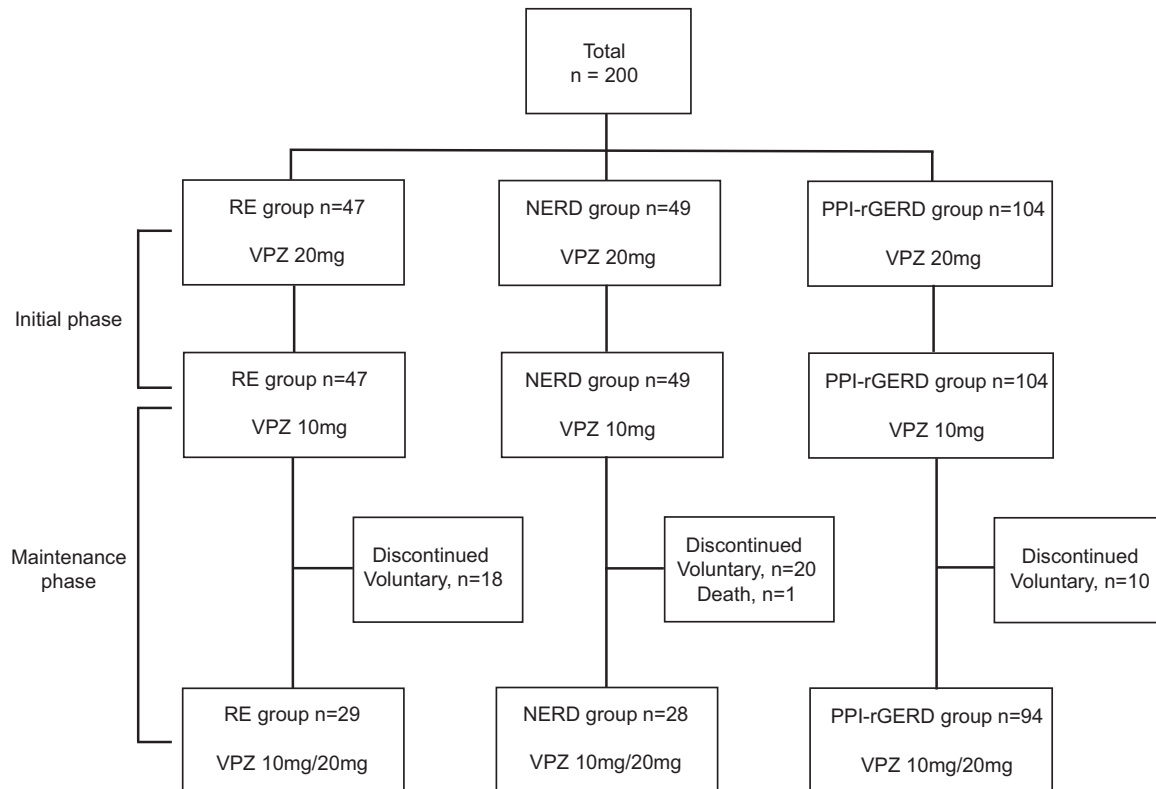
#### 2.4. Statistical analysis

The clinical characteristics were presented as means  $\pm$  standard deviation or as number (%) of patients. To compare clinical characteristics of each group, the analysis of variance test and  $2 \times 2$  Chi-squared test was used. To compare FSSG scores at measure points, Wilcoxon rank sum test was used. To compare proportions of 2 groups (very satisfied, satisfied) in the degree of satisfaction at measure points, the  $2 \times 2$  Chi-squared test was used. To assess normality of distribution of continuous variables, Kolmogorov–Smirnov test was used. Statistical analysis was performed using SPSS 22.0 software (IBM, SPSS, Armonk, NY). Differences between variable with  $P < .05$  were considered statistically significant.

**Table 1**  
Background characteristics of 3 groups of patients (n=200).

Characteristics	Total (n=200)	RE (n=47)	NERD (n=49)	PPI-rGERD (n=104)	P
Age, years, mean $\pm$ SD	70.8 $\pm$ 12	72.1 $\pm$ 9.3	67.8 $\pm$ 15	71.6 $\pm$ 11	.23
Gender, male, n (%)	72 (36)	18 (38)	18 (37)	36 (35)	.962
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	23.2 $\pm$ 3.3	23.6 $\pm$ 3.5	22.9 $\pm$ 3.1	23.1 $\pm$ 3.3	.61
Smoker, n (%)	12 (6)	2 (4)	4 (8)	6 (5.8)	.718
Alcohol consumption, n (%)	59 (30)	16 (34)	15 (31)	28 (27)	.633
<i>Helicobacter pylori</i> infection, n (%)					
Positive	36 (18)	7 (15)	15 (31)	14 (13)	.03
Negative	106 (53)	26 (55)	17 (35)	63 (61)	.009
Negative after eradication	27 (14)	5 (11)	8 (16)	14 (13)	.01
Not measured	31 (16)	9 (19)	9 (18)	13 (13)	
Endoscopic mucosal atrophy, n (%)					
Non	49 (25)	9 (19)	11 (22)	21 (20)	.46
Closed-type	48 (24)	19 (40)	8 (16)	54 (52)	.01
Open-type	103 (52)	19 (40)	30 (61)	29 (28)	.081
Baseline LA classification					
Grade A/B/C/D	47/25/11/6	25/13/6/3		22/12/5/3	
PPI before starting VPZ, n (%)					
EPZ 20 mg/LPZ 15 mg/RPZ 10 mg				34/26/44	

BMI = body mass index, EPZ = esomeprazole, GERD = gastroesophageal reflux disease, LPZ = lansoprazole, NERD = nonerosive reflux disease, PPI = proton pump inhibitor, PPI-rGERD = proton pump inhibitor-resistant GERD, RE = reflux esophagitis, RPZ = rabeprazole, SD = standard deviation, VPZ = vonoprazan.



**Figure 1.** Clinical course of 3 groups. GERD = gastroesophageal reflux esophagitis, NERD = nonerosive reflux disease, PPI-rGERD = proton pump inhibitor resistant GERD, VPZ = vonoprazan.

### 3. Results

#### 3.1. Clinical characteristics

The clinical characteristics of total 200 patients are shown in Table 1. We divided patients into 3 groups: RE, NERD, and PPI-resistant GERD group. The total number of patients in each group were 47 (23.5%), 49 (24.5%), and 104 (52.0%), respectively. We found 18 patients in the RE group, 20 patients in the NERD group, and 10 patients in the PPI-resistant GERD group that voluntarily aborted VPZ therapy during the period of maintenance therapy because symptoms improved significantly. Finally, a total of 151 patients were administered VPZ at 24 weeks (Fig. 1).

#### 3.2. Analysis for initial therapy

**3.2.1. RE group.** FSSG at baseline and after initial therapy was  $11.8 \pm 7.2$  and  $3.8 \pm 4.3$ , respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 2A). In the acid reflux-related symptoms and dysmotility groups, the mean FSSGs at baseline and after initial therapy were  $6.8 \pm 4.0$  and  $2.0 \pm 2.6$ ,  $5.0 \pm 4.2$  and  $1.9 \pm 2.4$ , respectively; this difference was statistically significant ( $P < .001$ ; Fig. 2B). Proportions for the 2 groups (very satisfied and satisfied) in the degree of satisfaction at baseline and after initial therapy were 4.65% and 70.2%, respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 2C). Improvement and resolution rates after initial therapy were 83.0% and 67.0%, respectively (Fig. 2D).

**3.2.2. NERD group.** FSSG at baseline and after initial therapy was  $10.9 \pm 6.1$ ,  $4.9 \pm 4.3$ , respectively, and this difference was

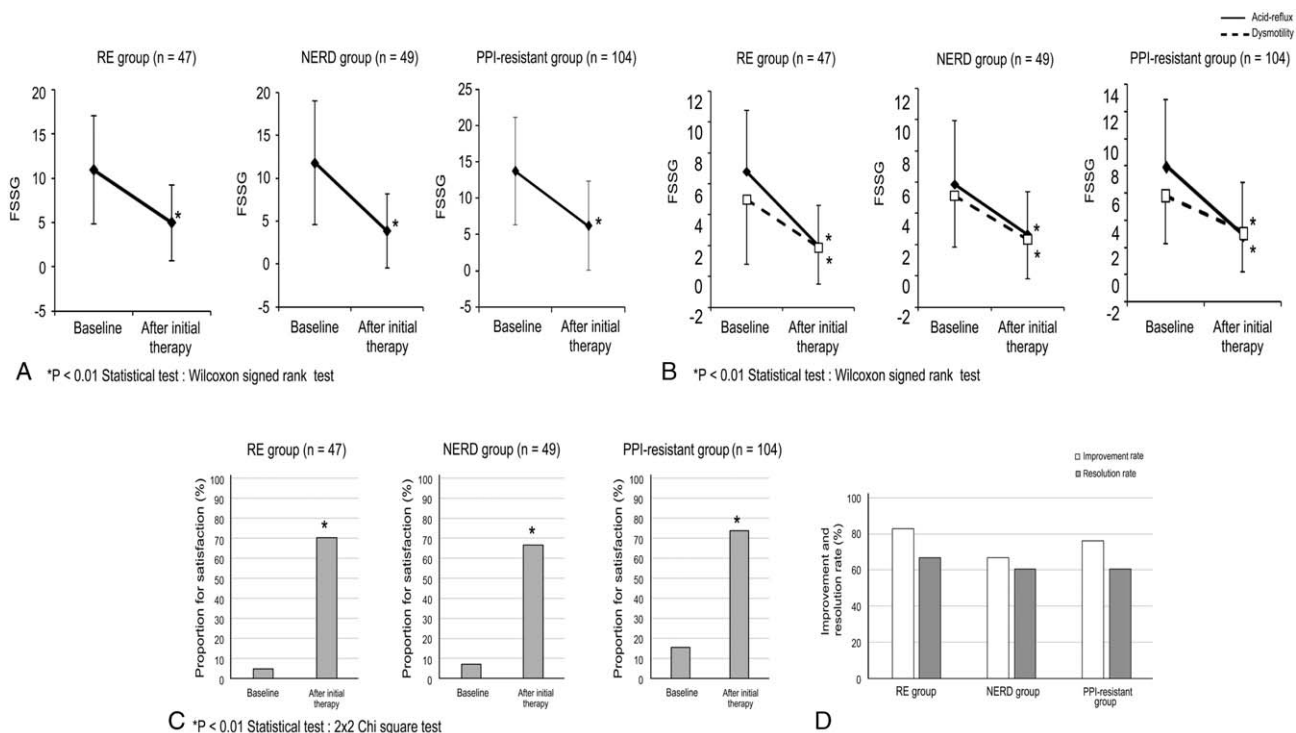
statistically significant ( $P < .001$ ; Fig. 2A). In the acid reflux-related symptoms and dysmotility groups, the mean FSSGs at baseline and after initial therapy were  $5.9 \pm 4.1$  and  $2.6 \pm 2.7$ ,  $5.1 \pm 3.3$  and  $2.3 \pm 2.5$ , respectively; this difference was statistically significant ( $P < .001$ ; Fig. 2B). Proportions for the 2 groups (very satisfied and satisfied) in the degree of satisfaction at baseline and after initial therapy were 6.98% and 66.7%, respectively, and the difference was statistically significant ( $P < .001$ ; Fig. 2C). Improvement and resolution rates after initial therapy were 66.7% and 60.4%, respectively (Fig. 2D).

**3.2.3. PPI-resistant GERD group.** FSSG at baseline and after initial therapy was  $13.7 \pm 7.4$  and  $6.2 \pm 6.1$ , respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 2A). In the acid reflux-related symptoms and dysmotility groups, the mean FSSGs at baseline and after initial therapy were  $8.0 \pm 4.9$  and  $3.0 \pm 3.8$ ,  $5.8 \pm 3.5$  and  $3.2 \pm 3.0$ , respectively; this difference was statistically significant ( $P < .001$ ; Fig. 2B). Proportions for the 2 groups (very satisfied and satisfied) in the degree of satisfaction at baseline and after initial therapy were 15.4% and 73.8%, respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 2C). Improvement and resolution rates after initial therapy were 76.0% and 60.4%, respectively (Fig. 2D).

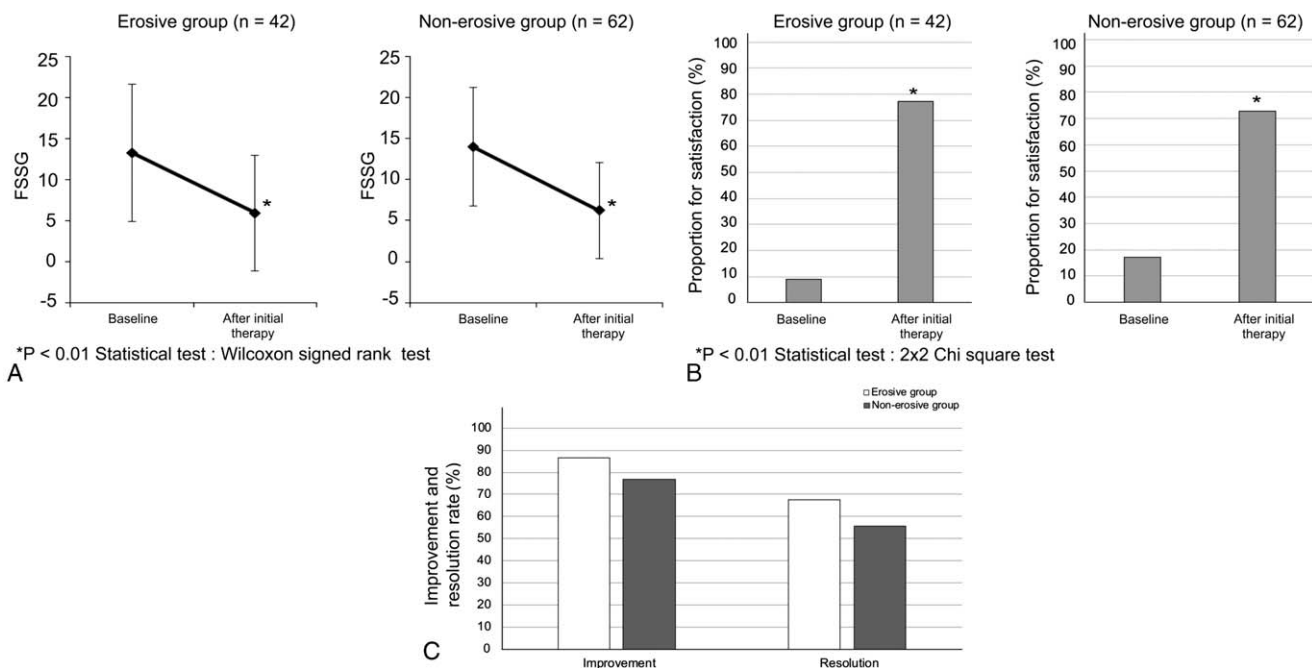
#### 3.3. Subgroup analysis in PPI-resistant GERD

**3.3.1. Erosive group.** The total number of patients in the erosive group was 42. FSSG at baseline and after initial therapy was  $13.3 \pm 8.4$  and  $5.9 \pm 7.1$ , respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 3A). Proportions for





**Figure 2.** Analysis for initial therapy. (A) Changes of total FSSG score at baseline and after initial therapy. (B) Change of FSSG score in 2 subscales (acid reflux-related symptoms, dysmotility). (C) Proportion for satisfaction at baseline and after initial therapy. (D) Improvement and resolution rate in each group after initial therapy. FSSG = frequency scale for the symptoms of GERD, NERD = nonerosive reflux disease, PPI = proton pump inhibitor, RE = reflux esophagitis.



**Figure 3.** Subgroup analysis in PPI-resistant GERD. (A) Changes of total FSSG score at baseline and after initial therapy. (B) Proportion for satisfaction at baseline and after initial therapy. (C) Improvement and resolution rate in each group after initial therapy. FSSG = frequency scale for the symptoms of GERD, GERD = gastroesophageal reflux esophagitis.

2 groups (very satisfied, satisfied) in the degree of satisfaction at baseline and after initial therapy were 9.10% and 77.3%, respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 3B). Improvement and resolution rates after initial therapy were 86.4% and 67.5%, respectively (Fig. 3C).

**3.3.2. Nonerosive group.** The total number of patients in erosive group was 62. FSSG at baseline and after initial therapy was  $14.0 \pm 7.2$  and  $6.2 \pm 5.9$ , respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 3A). Proportions for 2 groups (very satisfied, satisfied) in the degree of satisfaction at baseline and after initial therapy were 17.1% and 72.8%, respectively, and this difference was statistically significant ( $P < .001$ ; Fig. 3B). Improvement and resolution rates after initial therapy were 76.8% and 55.7%, respectively (Fig. 3C).

**3.4. Analysis for maintenance therapy at 24 week**

**3.4.1. RE group.** FSSG at baseline, after initial therapy, and at 24 week was  $11.7 \pm 8.3$ ,  $5.4 \pm 4.7$ , and  $4.2 \pm 5.1$ , respectively, and these differences were statistically significant ( $P < .001$ ; Fig. 4A).

Proportions for 2 groups (very satisfied, satisfied) in the degree of satisfaction at baseline, after initial therapy, and at 24 week were 8.0%, 65.5%, and 81.8%, respectively, and these differences were statistically significant ( $P < .001$ ; Fig. 4B). Improvement, resolution, and nonrelapse rates at 24 week were 72.7%, 63.0%, and 89.3%, respectively (Fig. 4C).

**3.4.2. NERD group.** FSSG at baseline, after initial therapy, and at 24 week was  $11.3 \pm 6.9$ ,  $5.6 \pm 4.2$ , and  $5.0 \pm 5.6$ , respectively, and these differences were statistically significant ( $P < .001$ ; Fig. 4A). Proportions for 2 groups (very satisfied, satisfied) in the

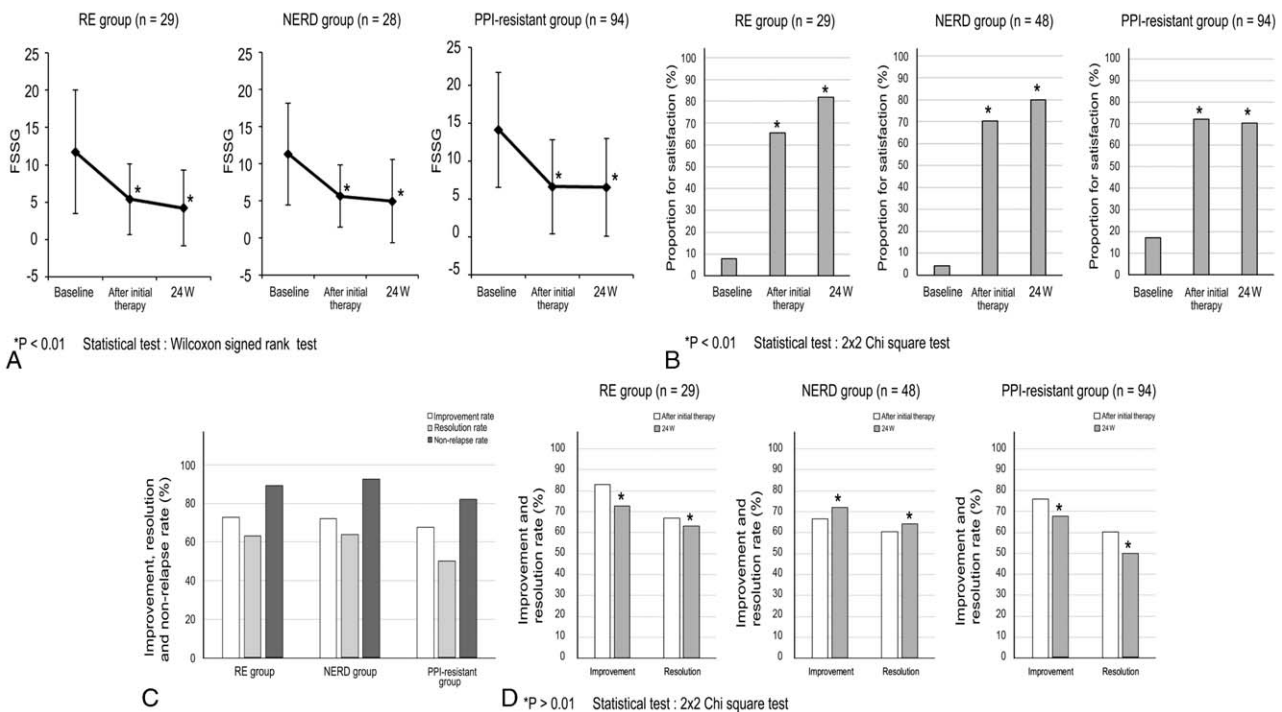
degree of satisfaction at baseline, after initial therapy, and at 24 week were 4.3%, 70.4%, and 80.0%, respectively, and these differences were statistically significant ( $P < .001$ ; Fig. 4B). Improvement, resolution, and nonrelapse rates at 24 week were 72.0%, 64.0%, and 92.6%, respectively (Fig. 4C).

**3.4.3. PPI-resistant GERD group.** FSSG at baseline, after initial therapy, and at 24 week was  $14.1 \pm 7.6$ ,  $6.6 \pm 6.2$ , and  $6.5 \pm 6.5$ , respectively, and these differences were statistically significant ( $P < .001$ ; Fig. 4A). Proportions for 2 groups (very satisfied, satisfied) in the degree of satisfaction at baseline, after initial therapy, and at 24 week were 17.0%, 72.0%, and 70.3%, respectively, and these differences were statistically significant ( $P < .001$ ; Fig. 4B). Improvement, resolution, and nonrelapse rates at 24 week were 67.7%, 50.0%, and 82.1%, respectively (Fig. 4C).

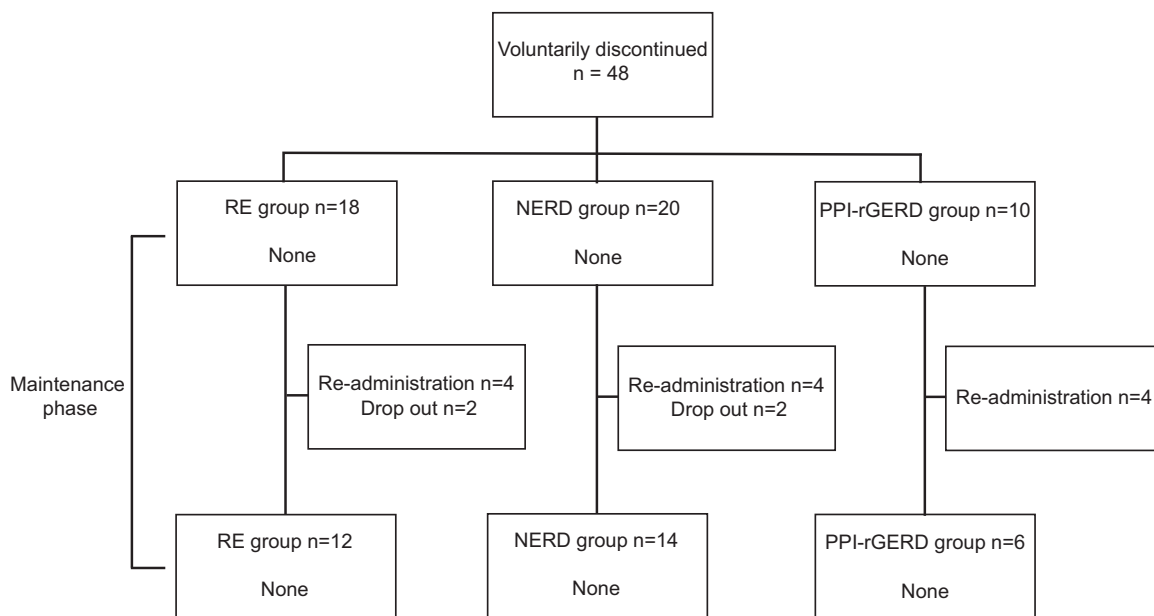
We noted no significant difference between findings obtained after initial therapy and at 24 week regarding improvement and resolution rates in the 3 groups (Fig. 4D).

**3.5. Analysis at 24 week for patients who discontinued taking VPZ after the initial therapy**

After the initial therapy, 48 patients (18 in RE group, 20 in NERD group, and 10 in PPI-resistant group) voluntarily aborted taking VPZ therapy at the end of the initial therapy because their symptoms had improved. All 48 patients obtained  $< 8$  points of FSSG and answered very satisfied or satisfied in the degree of satisfaction at the stop of the medication. Four of the 18 RE patients, 4 of the 20 NERD patients, and 4 of the 10 PPI-resistant GERD patients readministered VPZ again until 24 weeks because



**Figure 4.** Analysis for maintenance therapy at 24 weeks. (A) Changes of total FSSG score at baseline, after initial therapy and 24 weeks. (B) Proportion for satisfaction at baseline, after initial therapy and 24 weeks. (C) Improvement, resolution, and nonrelapse rate in each group at baseline and 24 weeks. (D) Changes of improvement and resolution rate at after initial therapy and 24 weeks in each group. FSSG = frequency scale for the symptoms of GERD, NERD = nonerosive reflux disease, PPI = proton pump inhibitor, RE = reflux esophagitis.



**Figure 5.** Clinical course of patients who discontinue taking VPZ at 24 weeks. NERD = nonerosive reflux disease, PPI-rGERD = proton pump inhibitor-resistant GERD, RE = reflux esophagitis, VPZ = vonoprazan.

the symptoms had recurred. Finally, 32 patients (12 in RE group, 14 in NERD group, and 6 in PPI-resistant GERD group) did not take VPZ at 24 week (Fig. 5).

Total FSSG score in the 3 groups were  $1.67 \pm 1.97$ ,  $2.71 \pm 4.91$ , and  $4.0 \pm 4.43$ . The acid reflux symptoms score was  $0.67 \pm 0.89$ ,  $0.93 \pm 1.82$ , and  $1.33 \pm 1.97$ . The dysmotility score was  $1.0 \pm 1.48$ ,  $1.79 \pm 3.99$ , and  $1.50 \pm 1.97$ . The number of nonrelapse (FSSG score was not exceeding 8 points or no readministration) at 24 week was 12 (66.7%) in RE, 12 (60.0%) in NERD, and 5 (50.0%) in PPI-resistant GERD. The number of resolution (chest burn symptom [FSSG question nos. 1, 4, 6, and 12] score become 0 point) at 24 week was 7 (38.9%) in RE, 9 (45.0%) in NERD, and 3 (30%) in PPI-resistant GERD. Among patients whose symptoms disappeared and who stopped taking VPZ during the maintenance period, 42.0% of RE and NERD group and 30% of PPI-resistance group could achieve a drug-free status and complete remission of GERD until 24 week by initial introduction of VPZ, a strong acid inhibitor (Table 2).

**3.6. Safety**

Four patients experienced adverse events, including diarrhea (n = 2), itching (n = 1), and epigastric discomfort (n = 1). All events were considered to be mild and improved without further

medication. No serious adverse events were reported during the study.

**4. Discussion**

The results of the present study demonstrate the improvement of FSSG score and the degree of satisfaction for RE, NERD, and PPI-resistant GERD at the initial and maintenance therapies using VPZ.

In the present study, FSSG score was reduced significantly after the initial therapy using VPZ compared with baseline in each of the 3 groups. Especially, in PPI-resistant GERD group, FSSG score improved by more than 50% on an average after the initial therapy. A previous report recommended that VPZ improved symptoms significantly in PPI-resistant GERD. Shinozaki et al<sup>[29]</sup> reported that VPZ 10 mg daily improved symptoms of patients with PPI-resistant GERD significantly after 4 weeks. Hoshino et al<sup>[30]</sup> have reported that FSSG score was significantly lower at the 4th week after initial therapy of VPZ than before its administration in PPI-resistant RE. Among various symptoms of GERD, improvement of heartburn was the first goal for the treatment for GERD. The rate of complete remission of heartburn was 67.0% in RE, 60.4% in NERD, and 60.4% in PPI-resistant GERD in the present study. A previous report states that the

**Table 2**  
**Analysis for patients who discontinued taking vonoprazan at 24 weeks.**

Group	Readministration n (%)	Nonrelapse n (%)	Resolution n (%)	Total FSSG score, mean ± SD	Acid reflux-related, mean ± SD	Dysmotility, mean ± SD
RE group (n = 18)	4/18 (22.2)	12/18 (66.7)	7/18 (38.9)	$1.67 \pm 1.97$	$0.67 \pm 0.89$	$1.0 \pm 1.48$
NERD group (n = 20)	4/20 (20.0)	12/20 (60.0)	9/20 (45.0)	$2.71 \pm 4.91$	$0.93 \pm 1.82$	$1.79 \pm 3.99$
PPI-resistant GERD (n = 10)	4/10 (40.0)	5/10 (50.0)	3/10 (30.0)	$4.0 \pm 4.43$	$1.33 \pm 1.97$	$1.50 \pm 1.97$

FSSG = frequency scale for symptoms of GERD, GERD = gastroesophageal reflux disease, NERD = nonerosive reflux disease, PPI = proton pump inhibitor, PPI-rGERD = proton pump inhibitor-resistant GERD, RE = reflux esophagitis, SD = standard deviation.

resolution rate in RE at 4 weeks was 68.1% using EPZ 20 mg,<sup>[31]</sup> and 51.1% in mild RE and 35.8% in NERD using rabeprazole 20 mg.<sup>[32]</sup> Our data certified a higher achievement of complete heartburn relief. The definition of resolution slightly differs in each report, and it should not be a numerical comparison.

About subgroup analysis of PPI-resistant GERD in our study, in both erosive and nonerosive groups, FSSG score was reduced significantly at after initial therapy compared with baseline and improved by more than 50% on an average after initial therapy. Moreover, the improvement and resolution rates in each group were 83.3% and 67.5%, respectively, in the erosive group, and 76.8% and 55.7%, respectively, in nonerosive group. The improvement and resolution rates of the erosive group tended to be superior to the nonerosive group. Hence, mechanism of the erosive group is mainly regarded as regurgitation of gastric acid and insufficient acid suppression by PPIs. On the other hand, mechanism of the nonerosive group is the regurgitation of gastric acid along with hyperesthesia of the esophageal mucosa. Furthermore, functional heart burn, which mainly occurs because of the hyperesthesia of the esophageal mucosa and psychological factors of patient, may exist in nonerosive group. Shinozaki et al<sup>[33]</sup> have reported that improvement and resolution rates in the nonerosive PPI-resistant GERD were 83% and 28%, respectively, even when taking VPZ 10 mg daily. This data was in accordance to that from the present study. Hence, nonerosive PPI-resistant GERD is thought to be the most difficult to treat. VPZ could be the most effective drug for treating PPI-resistant GERD.

About subscale group analysis, not only the acid reflux-related symptom score but also dysmotility score improved significantly in each of the 3 groups. Hori et al<sup>[34]</sup> have indicated a high prevalence of functional dyspepsia and irritable bowel syndrome in GERD patients. Kusano et al<sup>[35]</sup> has also indicated that acid-related dyspepsia (ARD) has high correlation for reflux symptoms and high response to PPIs in GERD patients. There are several reasons that ARD responds to PPI. One reason is that gastric emptying is impaired in GERD patients. Delayed gastric emptying in GERD patients can be improved by PPI therapy. Second, gastric acid stimulates the sensitivity of esophagus and stomach and impairs the close functional interaction between the fundus and the lower esophagus. So PPIs can improve dyspepsia as well as acid reflux symptoms by acid inhibition.

Concerning maintenance therapy, in the present study, the FSSG scores were significantly lower at 24 week as well as at the end of initial therapy, and a high percentage of nonrelapse rates have been proven at 24 week. Many clinical trials have confirmed the low percentage of relapse late of PPIs treatment for GERD in maintenance therapy. Kawamura et al<sup>[36]</sup> have reported the recurrence rate of erosive esophagitis with LPZ 15 mg daily as 23.2% at 24 week. Kinoshita et al<sup>[37]</sup> have also reported the recurrence rate with EPZ 20 mg as 8.0% at 24 week. Moreover, several reports have revealed the recurrence rate in maintenance therapy with 10 or 20 mg of VPZ was numerically lower than that with regular dose of PPIs. Ashida et al have reported the recurrence rate with VPZ 10 and 20 mg as 6.0% and 4.1%, respectively.<sup>[23]</sup> Mizuno et al<sup>[38]</sup> have reported that the symptomatic nonrelapse rate for the acid reflux-associated symptoms and dysmotility scores of FSSG were 86.5% and 80.8%, respectively, at 24 weeks of treatment with VPZ 10 mg. In the study, the symptomatic nonrelapse rate in FSSG at 24 weeks was 89.3% in RE group and 82.1% in PPI-resistant GERD group. Hsu et al<sup>[39]</sup> have reported that longer and stronger

treatment at initial therapy significantly decreased the incidence of symptom relapse in maintenance therapy. Therefore, the strong activity of VPZ in initial phase plays an important role in the initial as well as maintenance therapy.

The main goals of GERD treatment were to relieve symptoms, heal GERD and maintain remission, prevent complications, and improve the QOL. Increasing the level of satisfaction is essential to improve the QOL. Surprisingly, several publications report that the proportion of patient dissatisfaction who are treated by conventional PPIs was approximately 30%.<sup>[7,8]</sup> Labenz et al has stated that in patients with GERD and a PPI therapy of at least 1 year, 39% of the patients still suffered from heartburn at least 2 days a week.<sup>[40]</sup> Twenty percent of the patients were very dissatisfied with the current PPI therapy.<sup>[40]</sup> In the present study, the proportion of patient satisfaction rose up to about 70% after initial therapy, and up to about 70% to 80% at 24 weeks (RE group 81.8%, NERD group 80.0%, PPI-resistant group 71.3%). There are few reports that described the patient's satisfaction regarding the effect of VPZ therapy. This is because, unlike the PPIs, VPZ is not easily inactivated under acidic conditions and has rapid onset of action for acid suppression. The speed of expression regarding the effect makes it possible to raise the proportion of satisfaction at initial therapy. Moreover, the strong effect of VPZ makes it possible to maintain the proportion of satisfaction at 24 weeks.

In the present study, we reported the analysis for patients who discontinued taking medicine. We often experience that patients undergoing treatment cease to come to outpatient visits after their symptoms had improved significantly. We are concerned about how the condition of the patients will progress and whether the disease will recur. In the present study, the nonrelapse rate at 24 weeks in each group was 66.7%, 60.0, and 50.0%, and the resolution rate at 24 weeks was 38.9%, 45.0%, and 30%. Hsu et al<sup>[39]</sup> have suggested that 8 weeks of PPI therapy reduced symptom relapse, compared with that in 4 weeks, in patients with mild erosive gastritis (even in those that switched to on-demand therapy until 20 weeks). Our data suggest that among patients whose symptoms disappeared and stopped taking VPZ during the maintenance period, 42.0% of RE and NERD group and 30% of PPI resistant group could achieve a drug-free status and complete remission of GERD until 24 weeks by introduction of VPZ, a strong acid inhibitor.

## 5. Limitations

There are several limitations to our study. First, there was no control group. The changes compared with the baseline in a single group are presented. Second, patients and providers were not blinded. Third, there were no strict criteria for discontinuing VPZ in the maintenance therapy. We decided to stop the medication mainly for the patient's wish and FSSG score. Forth, there was no consideration as to the presence of the CYP2C19 genotype. Case-controlled, double-blinded, and multicenter study is required to confirm these results.

## 6. Conclusion

The present study showed that the VPZ therapy was effective for initial and maintenance therapy in 3 groups (RE, NERD, and PPI-resistant GERD). Especially, VPZ therapy improved heartburn and patient's satisfaction significantly even in the PPI-resistant GERD group. Among patients whose symptoms disappeared and



stopped taking VPZ during the maintenance period, 42.0% of RE and NERD group and 30% of PPI resistant group had no relapse of symptom after stopping the medication of VPZ at 24 weeks. The complete remission of GERD can be achieved by introduction of VPZ.

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