

# Outcomes after GERD Treatment Based on the Japanese GERD Management Guideline

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## Abstract

**Background:** In Japan, the GERD management guideline (GERD-GL) was issued by the Japanese Society of Gastroenterology in 2009. However, there have been few reports on the actual conditions of GERD treatment in Japan.

**Objective:** The aims of this study were to prospectively investigate the compliance of gastroenterology physicians with the GERD-GL and to clarify follow-up rates for long-term management, dropout rates in each stage, symptom improvement rates and secession rates.

**Method:** Between January 2010 and December 2010, patients with GERD who consecutively visited 12 medical institutes (5 hospitals and 7 clinics) in Sendai City were enrolled in this study. Medical treatment was conducted fully in accordance with the GERD-GL flowchart. A PPI was given in the range covered by the Japanese medical insurance. Subjects initially received Rabeprazole (RPZ) 10mg daily. When symptom improvement was not observed, they received RPZ 20mg daily. The FSSG, a GERD-specific questionnaire, was used for the diagnosis of GERD. Subjects with scores  $\geq 8$  were diagnosed with GERD. Symptom improvement was defined as scores of FSSG  $< 8$  or  $\geq 50\%$  score reduction after dosing.

**Design and Setting:** The Prospective study from multiple institutions.

**Results:** The number of cases was 211 (male 88, female 123). Mean age was  $53.5 \pm 16.4$  years (18 - 88). FSSG score at entry was  $16.8 \pm 7.3$  (8 - 45). The follow-up rate for long-term management was 43.1% (91/211). The highest dropout rate was observed in cases in which symptoms persisted in spite of RPZ 10mg daily dosing. The symptom improvement rate was 69.9% (107/153). No significant difference was observed between the prompt PPI treatment group (80.0% (16/20)) and the prompt endoscopy group (68.4% (91/133)) ( $p=0.43$ ). The symptom improvement rate in patients with non-erosive GERD was 60.0% (36/60), which tended to be lower than the 75.3% (55/73) observed in patients with erosive GERD ( $p=0.08$ ). The highest dropout rate was observed when the patients didn't visit hospital/clinic despite persisting symptoms after PPI treatment or when treated by an optional treatment. The final secession rate for long-term management after RPZ continuous treatment was 9.2% (14/153).

**Conclusions:** With gastroenterology physicians' treatment in accordance with the GERD-GL flowchart, 43.1% of the subjects could be followed-up for long-term management. The secession rate for long-term management after RPZ continuous treatment was 9.2%. Thus, few patients discontinued drug treatment if they were followed-up for long-term management of GERD. A major problem was a high dropout rate even when symptoms persisted.

**Key words:** Gastroesophageal Reflux Disease (GERD), Guideline, Proton Pump Inhibitor (PPI), Long-term management, Endoscopy

## Background

The reflux of gastric juice containing acid, bile, and pepsin into the esophagus is a causal factor of gastroesophageal reflux disease (GERD). It was reported that the incidence of GERD has increased significantly in each of the last two decades in western countries [1]. The incidence of GERD is also increasing in Japan as well as in the West [2] because of the decreasing prevalence of *H. pylori* infection and westernization of the diet in recent decades.

Proton pump inhibitors (PPIs) are commonly used as the first-line treatment because of their effectiveness and prolonged suppression of gastric acid secretion.

In Europe and America, guidelines for the treatment of GERD have been proposed. However, there have been few reports on the actual conditions of GERD treatment. In Japan, the GERD management guideline (GERD-GL) was issued by the Japanese Society of Gastroenterology in 2009 (Figure 1). However, until now, there have been few reports on the outcomes of patients treated in accordance with the GERD-GL.

The aims of this study were to prospectively investigate the compliance of gastroenterology physicians with the GERD-GL and to clarify follow-up rates to long-term management, dropout rates in each stage, symptom improvement rates and secession rates.

## Methods

Between January 2010 and December 2010, patients with persistent symptoms suggestive of GERD who consecutively

visited 12 medical institutes (5 hospitals and 7 clinics) in which gastroenterological specialist physicians worked in Sendai City were enrolled in this study. Medical treatment was conducted fully in accordance with the GERD-GL flowchart (Fig 1) [3]. Patients suspected with GERD underwent prompt endoscopy before treatment or, initially, prompt PPI treatment before endoscopic examination. In the prompt PPI treatment group, the patients underwent endoscopy if their symptoms persisted. In the prompt endoscopy group, the patients were classified into erosive GERD and non-erosive GERD (NERD). A PPI was given in the range covered by the Japanese medical insurance. Subjects initially received Rabeprazole (RPZ) 10mg daily. When symptom improvement was not observed, they received RPZ 20mg daily. The frequency scale for symptoms of GERD (FSSG), a GERD-specific questionnaire was used for diagnosis of GERD [4]. Subjects with scores  $\geq 8$  were diagnosed with GERD. Symptom improvement was defined as scores of FSSG  $< 8$  or  $\geq 50\%$  score reduction after dosing [5]. Each dropout stage on GERD-GL flowchart was defined as: stage 1; the patients couldn't be evaluated symptoms improvement after prompt PPI treatment; stage 2; the patients didn't visit hospital/clinic before PPI treatment on prompt endoscopy group; stage 3: the patients couldn't be followed up to long-term management after symptoms improvement on prompt endoscopy; stage 4; the patients didn't visit hospital/clinic despite persisting symptoms after PPI treatment or were treated by the optional treatments; stage 5; PPI refractory GERD patients couldn't be followed up to long-term management after pathophysiologic evaluation (e.g. 24 hour pH monitoring). Recurrent GERD symptoms were defined as FSSG scores  $\geq 8$  or the score rose after GERD symptom improvement that was

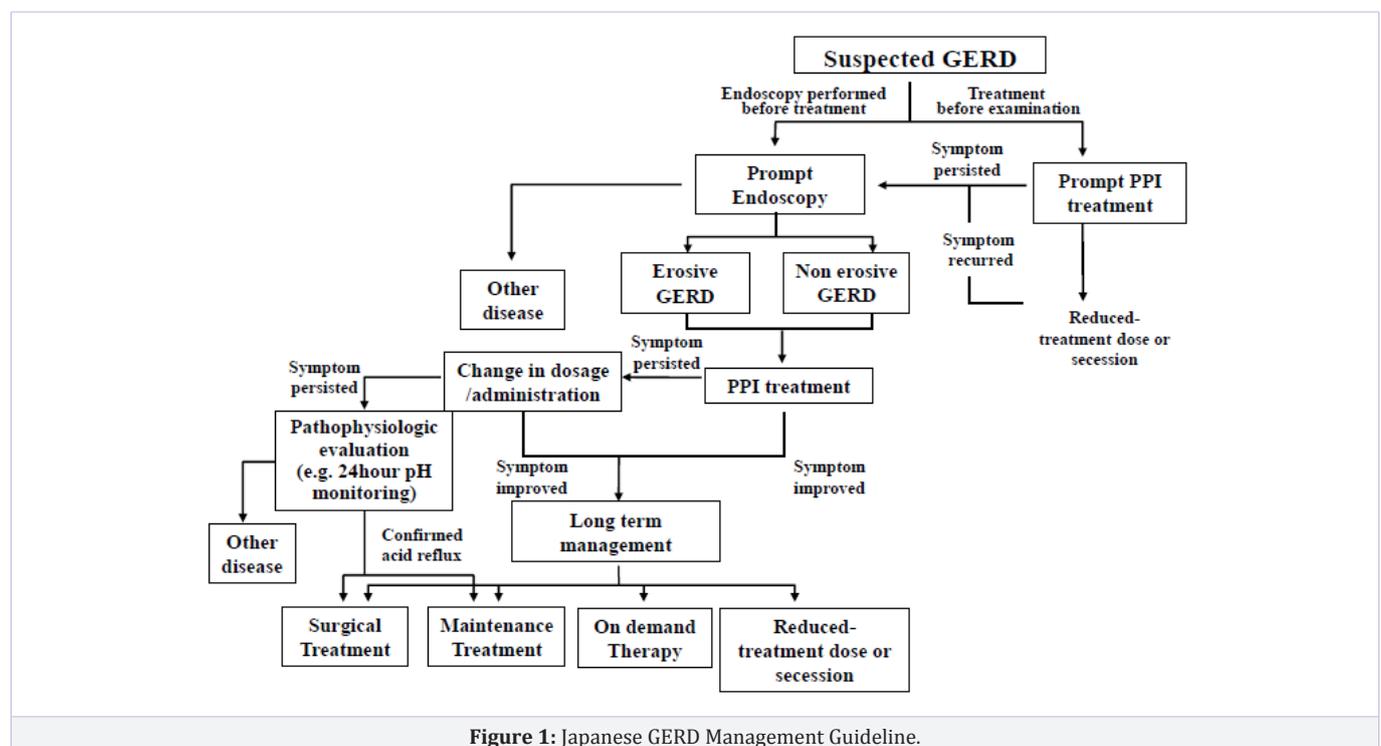


Figure 1: Japanese GERD Management Guideline.

≥50% score reduction after dosing. Remission maintenance was defined as patients without recurrent GERD symptoms after PPI treatment during the study period.

Subjects with peptic ulcer disease, malignant disease, a history of previous esophagogastric surgery, who had taken antibiotics and prokinetic drugs prior to the endoscopic examination were excluded from the analysis. Informed consent was obtained from all the subjects.

**Endoscopic Findings**

One hundred and seventy five patients underwent esophagogastroduodenoscopy (EGD) before treatment. According to the Los Angeles (LA) classification system, esophageal erosions were classified into grades A–D [6]. When no esophageal erosions and ulcers were present, these cases were defined as NERD [7].

**Statistical Analysis**

Parametric data were expressed as mean ± SD and non-parametric data as median (interquartile range). Mann – Whitney

U –test and Fisher’s exact test were used to compare differences between proportions. A P value of < 0.05 was considered to be significant. Analyses were carried out using SPSS software (version 20; IBM, Tokyo, Japan).

**Results**

**Patients’ Population**

All 211 patients (88 male; mean 53.5 years, range 18-88 years) with persistent symptoms suggestive of GERD were included in this study. FSSG at entry was 16.8±7.3 (8-45) and the initial prescription period was 36.3±24.0 days (Table 1). The dropout rates for each stage were: stage 1, 44.4% (16/36); stage 2, 24.0% (42/175); stage 3, 5.2% (5/96); stage 4, 73.8% (31/42) and stage 5, was 16.7% (1/6)(Figure 2).

**Prompt Endoscopy vs Prompt PPI treatment**

Comparisons of the patient backgrounds between the prompt endoscopy group and the prompt PPI treatment group are shown in Table 2. Of the 211 GERD patients, 175 (82.9%) were in the prompt endoscopy group and 36 (17.1%) were in the prompt PPI treatment group. Patients in the prompt endoscopy group (53.5±16.9) were significantly older than those in the prompt PPI treatment group (47.0±16.4)(p<0.01). The period of the initial prescription in the prompt endoscopy group (36.3±24.0) was significantly longer than that in the prompt PPI treatment group (25.0±17.4)(p<0.05). The FSSG scores after RPZ 10mg dosing in both the prompt endoscopy group (7.4±7.0) and the prompt PPI treatment group (6.3±5.5) were significantly lower than those before taking PPI(16.5±7.5, 15.9±5.5). The total symptom

**Table 1:** Patient background at entry.

No. patients	n=211
Age	53.5±16.4
Gender (M/F)	88/123
Initial FSSG	16.8 ± 7.3 (8-45)
Initial prescription period (clays)	36.3±24.0

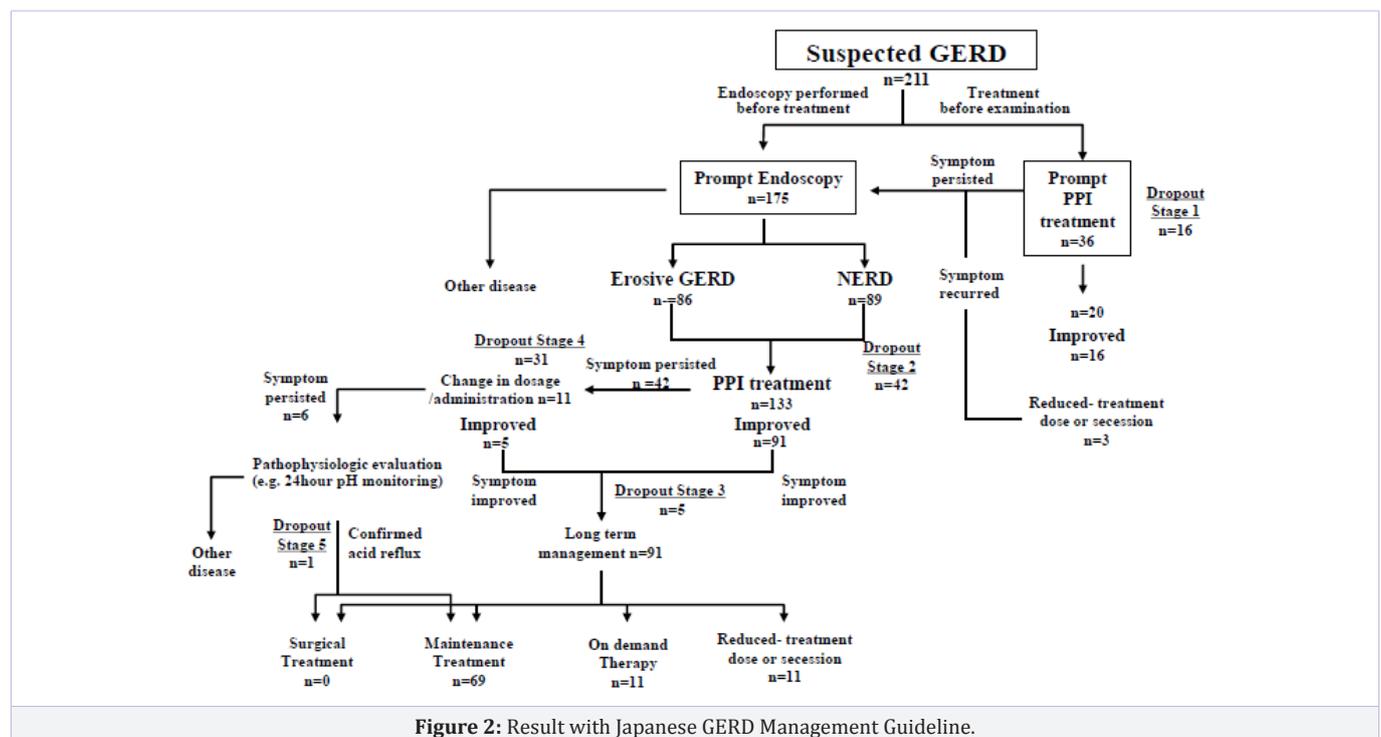


Figure 2: Result with Japanese GERD Management Guideline.

improvement rate was 69.9% (107/153)(Figure 3). No significant difference in the symptom improvement rate was observed in between the prompt PPI treatment group (80.0% (16/20)) and the prompt endoscopy group (68.4%(91/133))(p=0.43).

**Erosive GERD vs NERD**

Of the 175 patients who underwent EGD before PPI treatment, 86 (49.1%) were diagnosed with erosive GERD and 89 (50.9%) were with NERD (Table 3). The ratio of females with NERD was significantly higher than that of females with erosive GERD (p<0.05). The FSSG scores after RPZ 10mg dosing in both erosive GERD (9.0±7.8) and NERD (6.2±6.1) were significantly lower than those before, 17.9±8.0, 15.3±6.8) (p<0.01). The FSSG scores of NERD patients both before RPZ 10mg dosing (17.9±8.0) and after (9.0±7.8) were significantly higher than those with erosive GERD before (15.3±8.0) and after (6.2±6.1) (p<0.05, p<0.05). The symptom improvement rate of patients with NERD (60.0%) tended to be lower than in those with erosive GERD (75.3%), but not significantly (p=0.080) (Figure 4).

Eleven patients (NERD: 7, LA GradeA:1, B:2, C:1) who did not show symptom improvement after RPZ 10mg dosing, received RPZ 20mg daily. Their FSSG scores after RPZ 20mg dosing (8.8±1.6) was significantly lower than that before (17.6±2.4) and after RPZ 10mg dosing (14.5±1.7) (p<0.05, p<0.05)(Figure 5).

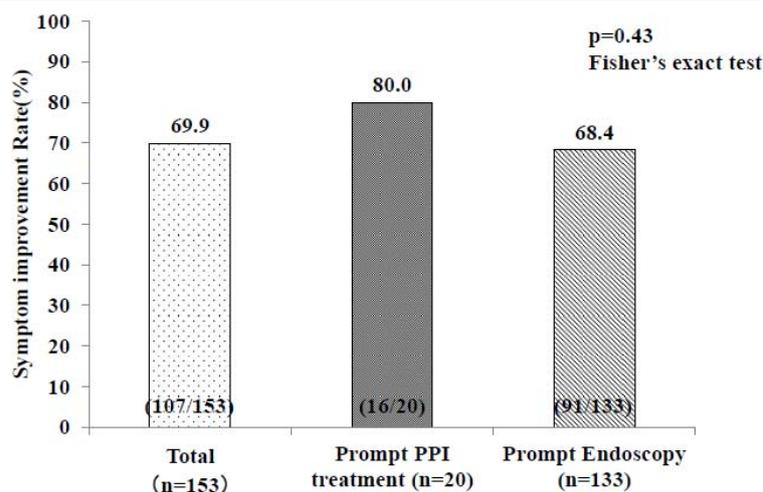
**Dropout Rates at Each Stage**

Dropout rates at stage 1 (the patients who couldn't be evaluated for symptoms improvement after prompt PPI treatment), 2 (the prompt endoscopy patients who didn't visit hospital/clinic for PPI treatment), 3 (the prompt endoscopy patients who couldn't be followed up for long-term management after symptom improvement), 4 (the patients who didn't visit hospital/clinic despite persisting symptoms after PPI treatment or were treated by optional treatments.) and 5 (the PPI refractory GERD patients who couldn't be followed up for long-term management after pathophysiologic evaluation (e.g. 24 hour pH monitoring)) were 44.4%(16/36),24.0%(42/175), 5.2%(5/96), 73.8%(31/42) and 16.7%(1/6), respectively.

**Table 2:** Patient background with the prompt endoscopy group and the prompt PPI treatment group.

	Prompt Endoscopy	Prompt PH treatment	P value
No. patients	175 (82.9%)	36 (17.1%)	P<0.01 <sup>1)</sup>
Age	53.5±16.9	47.0 ± 16.4	
Gender (IVI/F)	75/100	13/23	NS <sup>2)</sup>
Initial FSSG	16.8±7.3	16.5±7.1	NS <sup>3)</sup>
Initial prescription period (days)	36.3 ±24.0	25.0±17.4	P<0.05 <sup>1)</sup>

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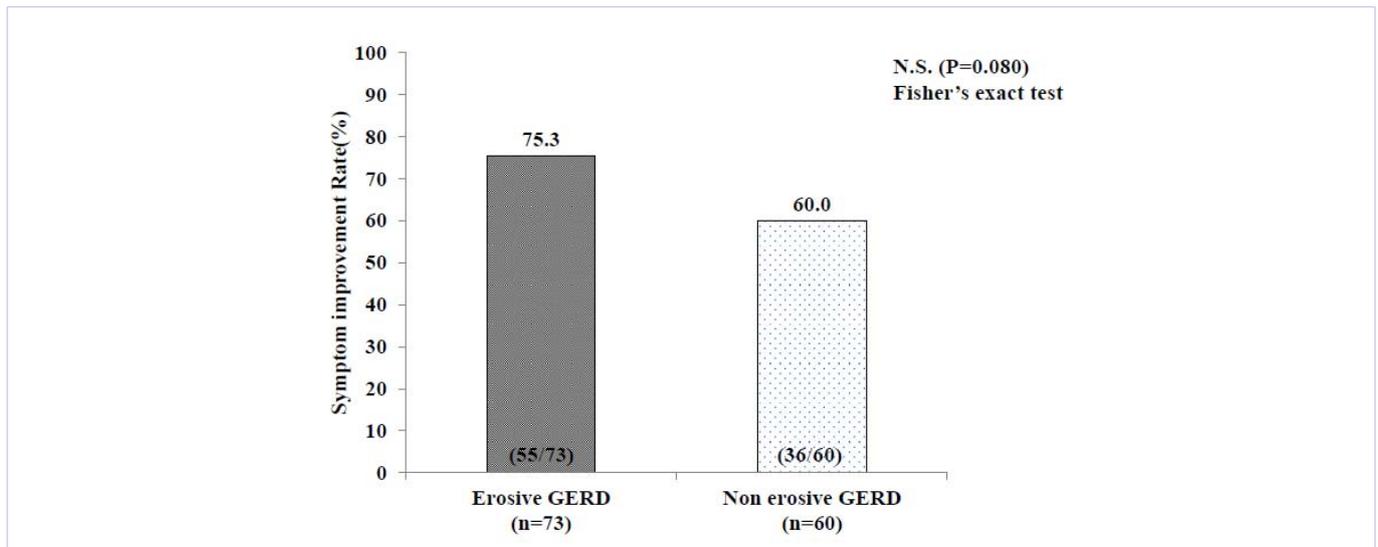


**Figure 3:** Symptom improvement Rate( Total, Prompt Endoscopy and prompt PPI treatment)

Total symptom improvement rate was 69.9% (107/153).

No significant difference in the symptom improvement rate was observed between the prompt PPI treatment group (80.0%, 16/20) and the prompt endoscopy group (68.4%, 91/133)(p=0.43).

PPI, proton pump inhibitor



**Figure 4:** Symptom improvement Rate (Erosive GERD and NERD)  
No significant difference in the symptom improvement rate was observed between erosive GERD patients (75.3%) and NERD (60.0%) (p=0.080).  
GERD, gastroesophageal reflux; NERD, non-erosive reflux disease

**Table 3:** Patient background with Erosive GERD and NERD.

	Erosive GERD	NERD	P value
No. patients	86 (49.1%)	89 (50.9%)	
Age	56.5 ± 14.4	53.4 ± 18.3	N.S. <sup>1)</sup>
Gender (M/F)	43/43	32/57	P<0.05 <sup>2)</sup>
Initial FSSG	15.7 ± 7.1	17.9 ± 7.6	P<0.05
Initial prescription period (days)	41.1±21.9	34.7±27.4	N.S. <sup>1)</sup>

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### Long-term management

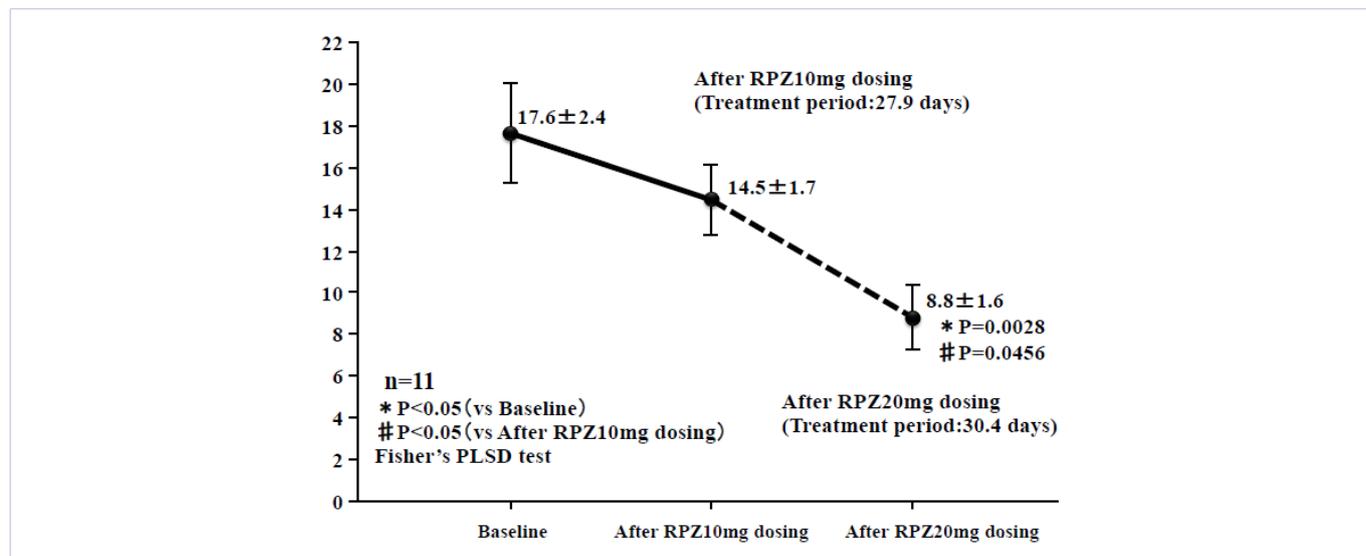
The follow-up rate for long-term management was 43.1% (91/211) in this study. Of the 91 patients, 69 patients (75.8%) received maintenance medical treatment, 11 patients (12.1%) received on demand therapy, 11 patients (12.1%) received reduced treatment dose or discontinued treatment and no patient underwent surgical treatment.

The FSSG scores of patients who received long-term management with maintenance treatment both before long-term management (3.7±2.0) and after (3.5±3.0) were significantly lower than those before taking RPZ (14.0±5.2) (p<0.05, p<0.05). With on demand therapy, the FSSG scores both before long-term management (2.5±1.6) and after (2.7±3.8) were significantly lower than those before taking RPZ (12.3±3.6) (p<0.05, p<0.05). In addition, with both maintenance therapy and on demand therapy, no significant differences in FSSG scores were observed between before (3.7±2.0, 2.5±1.6) and after long-term management (3.5±3.0, 2.7±3.8) (N.S, N.S.).

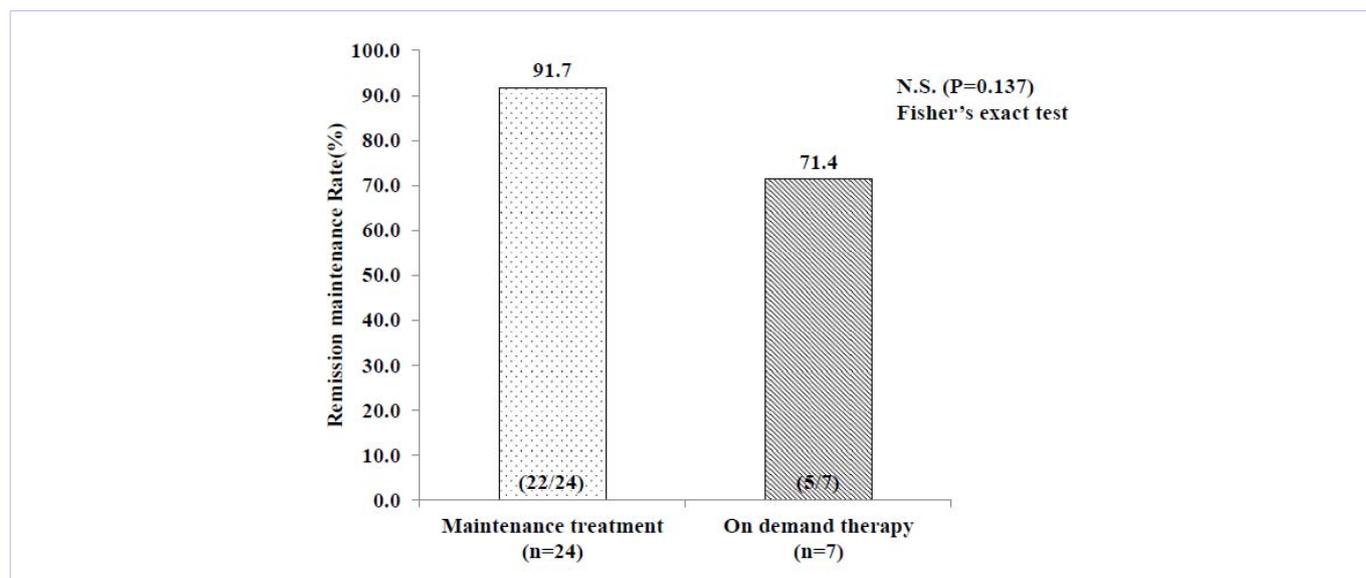
No significant difference in the remission maintenance rate was observed between maintenance treatment (91.7%) and on demand therapy (71.4%) (p=0.137) (Figure 6).

### Discussion

The worldwide consensus for GERD was developed by the Genval Workshop in 1999 [7] for the first time and issued as the Montreal Definition in 2006 [8]. In America, guidelines for the diagnosis and treatment of GERD were issued in 1995 for the first time [9] and updated in 1999 [10]. The previous guidelines were intended to apply to all healthcare providers who treated GERD, but it was considered that the treatment should be based on the course best suited to the individual patient depending on variables that existed when the treatment was decided. The GERD-GL was published in America by the American College of Gastroenterology in 2005 [11]. The GERD-GL was evaluated using strength of evidence score for the diagnosis and treatment. It was reported that endoscopic examination is a technique for identifying suspected Barrett's esophagus and for diagnosing complications of GERD, but not for excluding GERD because more than half of symptomatic patients will lack visible esophageal mucosal injury endoscopy [12]. Such symptomatic patients lacking visible esophageal mucosal injury at endoscopy are identified as NERD or functional heartburn (FH). NERD patients are defined as those with abnormal distal esophageal



**Figure 5:** Change in FSSG after RPZ20mg dosing  
FSSG score with those after RPZ 20mg dosing (8.8±1.6) was significantly lower than that before taking RPZ (17.6±2.4) and after RPZ 10mg dosing (14.5±1.7), respectively (p=0.0028, p=0.0456).  
FSSG, The frequency scale for symptoms of gastroesophageal reflux disease; RPZ, Rabeprazole



**Figure 6:** Remission maintenance rate (Maintenance treatment and on demand therapy)  
No significant difference in the remission maintenance rate was observed between maintenance treatment (91.7%) and on demand therapy (71.4%) (p=0.137).

acid exposure times or who present reflux symptoms with symptomatic reflux by 24 hour pH monitoring [13]. On the other hand, FH is defined according to the Rome criteria as the presence of reflux symptoms with no evidence of symptomatic reflux by multichannel intraluminal impedance monitoring [13]. It is considered that endoscopic examination for GERD does not necessarily indicate either less severe symptoms or a more easily controlled form of GERD in western countries [12].

It is suspected that Barrett's esophagus and Barrett's esophageal cancer is also increasing secondarily to GERD. Accordingly, the guideline applicable to Japanese, the GERD-GL was issued by the Japanese Society of Gastroenterology in 2009. The GERD-GL was based mainly on high quality published evidence and the flowchart was based on individual evidence. However, until now, there have been few reports on the outcomes of treatment based on the GERD-GL flowchart in Japan.

In Japan, the incidence of GERD is increasing as in the West and

There are differences in the standard doses of PPI between

Japan and western countries. Furthermore, are where differences in access to endoscopic examination between Japan and Western countries, where patients are initially given prompt PPI treatment followed ambulatory monitoring such as pH monitoring. In fact, in Japan the proportion of prompt endoscopy (82.9%) is larger than prompt PPI treatment (17.1%) in medical institutes with gastroenterological specialists.

In the gastroenterology physicians' treatment, which was in accordance with the GERD-GL flowchart, 43.1% (91/211) of the subjects could be followed-up for long-term management. The long-term management rate was relatively favorable in this study.

The highest dropout rate was observed when the patients didn't visit hospital/clinic despite persisting symptoms after PPI treatment or when treated by optional treatments. In the stage 4 cases, patients with persistent symptoms despite PPI treatment were generally recognized as PPI-refractory GERD patients. These patients are characterized by PPI-refractory erosive-GERD, PPI-refractory NERD and FH. In this study, these PPI-refractory GERD patients couldn't be distinguished by endoscopic re-examination or ambulatory pH monitoring from PPI-refractory erosive-GERD, PPI-refractory NERD and FH. In Japan, ambulatory pH monitoring is much less common than endoscopy because ambulatory pH monitoring is used only in a limited number of hospitals. The PPI-refractory GERD patients with persistent symptoms appeared to be less sensitive to PPI treatment because such patients could be treated without an accurate evaluation of the pathogenesis. Therefore, the highest dropout rate was observed in stage 4.

In patients with GERD, the FSSG score could be used to not only diagnose GERD but also assess the efficacy of PPI treatment for GERD [5]. The symptom improvement rate of RPZ10mg daily dosing was 69.9% (107/153), a relatively favorable rate. No significant differences were observed between the prompt PPI treatment group (80.0%, 16/20) and the prompt endoscopy group (68.4%, 91/133) ( $p=0.43$ ). However, performing prompt endoscopy can exclude malignant disorders and enable the diagnosis of GERD. For this reason, gastroenterological doctors believe that it is safe to prescribe PPI initially for a long period.

Several studies have demonstrated that NERD patients are less sensitive to PPI treatment than patients with erosive reflux disease [14, 15, 16]. In this study, no significant differences in the symptom improvement rate were observed between NERD and erosive GERD. However, the symptom improvement in patients with NERD tended to occur at a lower rate than in patients with erosive GERD, possibly because NERD may include some functional heart FH in this study.

The follow-up rate for long-term management was 43.1% (91/211). In long-term management patients, the secession rate after RPZ continuous treatment was 9.2%. Thus, it is difficult for patients to quit drug treatment if they are followed-up for long-term management of GERD treatment. In light of the good

remission maintenance rate (71.4%) of on demand therapy, this may be a relatively favorable form of maintenance treatment.

In conclusion, in the gastroenterology physicians' treatment in accordance with the GERD-GL flowchart, 43.1% of the subjects could be followed-up for long-term management. The secession rate of long-term management after RPZ continuous treatment was 9.2%. Thus, it is difficult for patients to quit drug treatment if they are followed-up long-term for the management of GERD treatment. Additionally, the problem in GERD-GL was a high dropout rate when symptoms persisted.

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