Original Article

Recent effectiveness of proton pump inhibitors for severe reflux esophagitis: the first multicenter prospective study in Japan

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(Received 9 December, 2014; Accepted 8 February, 2015; Published online 7 October, 2015)

Proton pump inhibitors are the first-line treatment for reflux esophagitis. Because severe reflux esophagitis has very low prevalence in Japan, little is known about the effectiveness of proton pump inhibitors in these patients. This prospective multicenter study assessed the effectiveness of proton pump inhibitors for severe reflux esophagitis in Japan. Patients with modified Los Angeles grade C or D reflux esophagitis were treated with daily omeprazole (10 or 20 mg), lansoprazole (15 or 30 mg), or rabeprazole (10, 20, or 40 mg) for 8 weeks. Healing was assessed endoscopically, with questionnaires administered before and after treatment to measure the extent of reflux and dyspepsia symptoms. Factors affecting healing rates, including patient characteristics and endoscopic findings, were analyzed. Of the 115 patients enrolled, 64 with grade C and 19 with grade D reflux esophagitis completed the study. The healing rate was 67.5% (56/83), with 15 of the other 27 patients (55.6%) improving to grade A or B. No patient characteristic or endoscopic comorbidity was significantly associated with healing rate. Reflux and dyspepsia symptoms improved significantly with treatment. The low healing rate suggests the need of endoscopic examination to assess healing of reflux esophagitis at the end of therapy. (UMIN000005271)

***Key Words*: proton pump inhibitor, severe reflux esophagitis, healing rate, asymptomatic reflux esophagitis**

Although the prevalence of reflux esophagitis (RE) has been reported lower in Japanese than in western populations, it has increased in Japan in recent years.[1] This may be a consequence of aging of the population, westernization of the diet, and/or decreased rates of *Helicobacter pylori* (*H. pylori*) infection.[2–6] The aging of Japanese society may also increase the problem of severe RE because the proportion of severe esophagitis is high in the elderly.[1]

Proton pump inhibitors (PPIs), which markedly inhibit the secretion of gastric acid, constitute the first-line treatment for RE. In Japan, omeprazole, lansoprazole, and rabeprazole have been available since 1991, 1992, and 1997, respectively. Treatment with a PPI for 8 weeks results in healing rates of 80% to 90% in patients with moderate to severe RE.[7] In Western patients with severe RE, graded C or D on the Los Angeles classification, standard-dose PPI therapy has been found to have healing rates of 63% to 92%.[8] Less is known, however, about the effectiveness of PPI treatment in Japanese patients with severe RE in clinical practice, and because the prevalence of severe RE is very low in Japan, there have been few prospective studies that have included sufficient numbers of patients.[1,9]

Severe RE can lead to complications, including esophageal stenosis, esophageal hemorrhage and Barrett's esophagus.[10,11] It is therefore important to investigate whether PPI therapy is effective in Japanese patients with severe RE. This prospective, multi-center study examined the healing rate achieved by 8 weeks of PPI therapy in Japanese patients with severe RE, rated grade C or D on the modified Los Angeles classification,[12,13] as well as assessing whether any patient characteristics could predict treatment outcomes.

Materials and Methods

Patients. Patients aged ≥20 years with endoscopically diagnosed severe RE, verified grade C or D on the modified Los Angeles classification, were enrolled. All patients had been evaluated at one of 32 institutions throughout Japan, to which one or more members of the Gastroesophageal Reflux Disease (GERD) Society, a Japanese collaborative research group, belonged (see Acknowledgments). Patients were enrolled between October 2010 and December 2011, and the study was performed between October 2010 and February 2012. The study protocol was approved by the ethics committee of each institution and of Nishi Hospital, Higashi-Osaka, Japan, and was conducted in accordance with the Declaration of Helsinki. All patients provided written or verbal informed consent.

Patients were excluded if they had (1) a history of gastrointestinal resection or vagotomy; (2) warning signs such as vomiting, hemorrhage of the digestive tract (including hematemesis, melena, and anemia) or rapid weight loss; (3) peptic ulcer complications excluding the scarring stage; (4) required continuation of drugs thought to interact with the study drugs; or (5) on-going treatment with a PPI within one week of enrollment.

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doi: 10.3164/jcbn.14-144

Table 1. Patient characteristics

Variable		*n* = 83
Sex	Male	53 (63.9%)
n (%)	Female	30 (36.1%)
Age† (years) mean ± SD		65.3 ± 15.4
BMI† (kg/m^2) mean ± SD		24.5 ± 3.7
Duration of GERD†	<1 month	25 (30.1%)
n (%)	1 month to 1 year	36 (43.4%)
	≥1 year	20 (24.1%)
	Not answered	2 (2.4%)
PPI dosage during the study	Standard‡	70 (84.3%)
n (%)	Double	11 (13.3%)
	Half	2 (2.4%)
Use of low-dose aspirin during the study	Yes	7 (8.4%)
n (%)	No	76 (91.6%)
Kyphosis	Yes	16 (19.3%)
n (%)	No	67 (80.7%)
H. pylori infection	Yes	4 (4.8%)
n (%)	No	27 (32.5%)
	Unknown	52 (62.7%)

†At time of first endoscopy. ‡Omeprazole 20 mg once daily, lansoprazole 30 mg once daily, or rabeprazole 10 mg once daily. SD, standard deviation; BMI, body mass index; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Treatment. Patients were treated for 8 weeks with one of the PPIs approved for RE in Japan before October 2010: omeprazole (10 or 20 mg daily), lansoprazole (15 or 30 mg daily), or rabeprazole (10, 20, or 40 mg daily). After 8 weeks, the healing of esophagitis was investigated by endoscopy. Concomitant treatment with PPIs other than the study drugs, H_2-receptor antagonists, prokinetic agents, mucosal protective factor enhancing agents, and anticholinergic drugs was prohibited. Other drugs thought to interact with the study drugs were also prohibited.

Endpoints. The primary endpoint was the RE healing rate after 8 weeks of PPI therapy, where the healing was defined as grades M (minimal change) and N (normal mucosa) on the modified Los Angeles classification.

Secondary endpoints included the intensity and frequency of the symptoms of reflux (heartburn and acid regurgitation) and dyspepsia (postprandial fullness, early satiation, epigastric pain, and epigastric burning), which were assessed by questionnaires before and after 8 weeks of PPI therapy. The intensity of each symptom was scored as none, mild, moderate, and severe; the frequency of each symptom was scored as 0, 1, 2–3, and ≥4 times per week. Adherence to PPI therapy was assessed in the questionnaire administered after 8 weeks.

Sex, age, body mass index (BMI), duration of GERD, PPI dose, use of low-dose aspirin during the study, kyphosis, and *H. pylori* infection were evaluated. In addition to Los Angeles classification grade, the presence of comorbidities, including atrophic gastritis, superficial gastritis, and hiatal hernia, were determined at the time of endoscopic examination. Atrophic gastritis was classified as open and closed types according to the Kimura-Takemoto classification.[14] Kyphosis and all endoscopic findings were diagnosed by gastroenterologists. Adverse events, their time of onset, seriousness, corrective measures taken and outcomes were also recorded.

Statistical analysis. The distribution of Los Angeles classification grades before and after PPI therapy were compared using the Wilcoxon signed-rank test, and the healing rates of grade C and grade D RE patient groups were compared using the chi-square test. To analyze factors that may influence healing, differences in healing rates in subgroups of patients, classified by patient characteristics (except for age and BMI), and the presence or absence of endoscopic comorbidities, were compared using chi-square tests. Age and BMI were compared in patients with and without healing using Student's *t* tests. The intensity and frequency of reflux and dyspepsia symptoms before and after PPI therapy were compared using the Wilcoxon signed-rank test. The difference in healing rates between patients with and without symptom resolution was compared using the chi-square test. All statistical analyses were performed with JMP ver. 11.0.0 (SAS Institute Inc., Cary, NC) statistical software.

Results

Study population. Of the 115 patients who met the inclusion criteria, 32 were excluded; of these, one did not attend after PPI therapy; five did not undergo endoscopy after PPI therapy; and 26 took PPIs for <49 or >63 days. Thus, the study cohort consisted of 83 patients.

Patient characteristics. Patient characteristics are shown in Table 1. The mean and standard deviation of age were 65.3 and 15.4 years, respectively. Duration of GERD was less than one month in 30% of patients and more than one month but less than one year in approximately 40%. More than 80% of the patients received standard doses of PPIs. Kyphosis was observed in 16 patients, of whom 15 were women.

Healing rates. Prior to PPI therapy, 64 of the 83 patients (77.1%) had Los Angeles classification grade C and 19 (22.9%) had grade D RE. After 8 weeks of PPI therapy, 30 patients (36.1%) were classified as grade N and 26 (31.3%) as grade M, making the overall healing rate 67.5%. Of the 27 patients whose esophagitis did not heal, 15 (55.6%) showed improvement to grade A or B. Overall, Los Angeles grades significantly improved after PPI therapy (Fig. 1, $p<0.001$, Wilcoxon signed-rank test). Healing rates were similar in patients with pre-treatment grades C [70.3% (45/64)] and D [57.9% (11/19)] esophagitis (Fig. 2, $p = 0.213$, chi-square test).

doi: 10.3164/jcbn.14-144

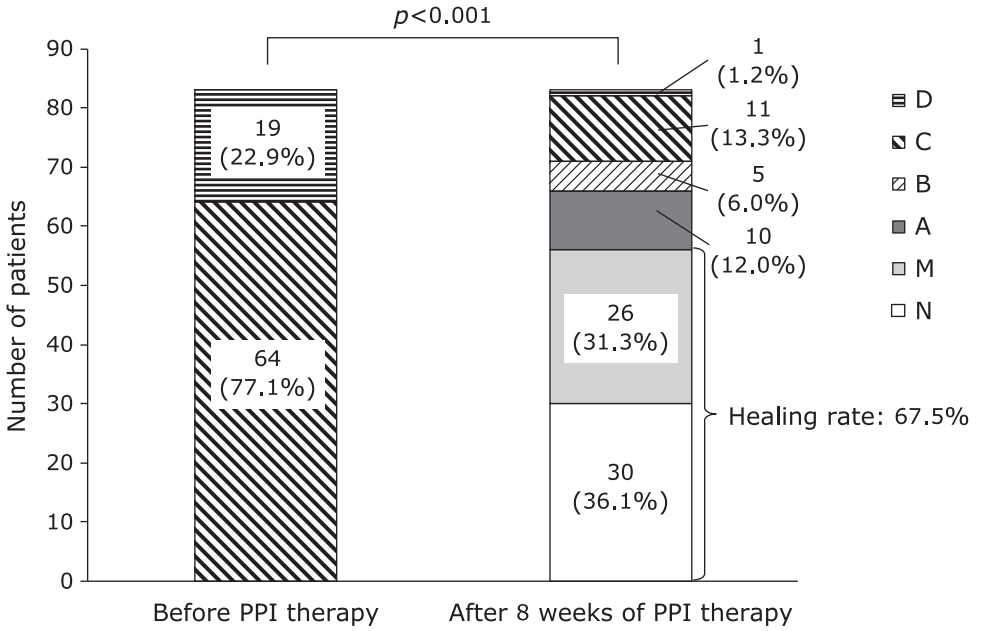

Fig. 1. The distribution of Los Angeles classification grades before and after proton pump inhibitor therapy. The *p* value was determined by the Wilcoxon signed-rank test.

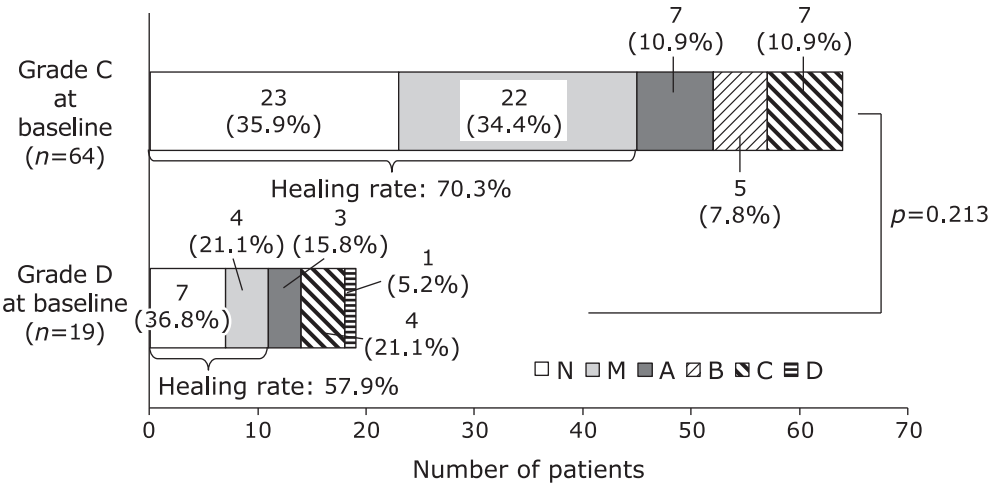

Fig. 2. The distribution of Los Angeles classification grades after proton pump inhibitor therapy by pre-treatment classification grades. The *p* value was determined by the chi-square test.

Factors affecting the healing of esophagitis. None of the patient characteristics, including sex, age, BMI, duration of GERD, PPI dose, use of low-dose aspirin during the study, or kyphosis, was significantly associated with healing rate (Table 2). The healing rates were also compared between patients with and without endoscopic comorbidities, including atrophic gastritis, superficial gastritis, and hiatal hernia. Healing rates tended to be higher in patients with than without hiatal hernia (74.1% vs 55.2%, $p = 0.080$, chi-square test; Table 3). Subgroup analysis revealed that the healing rate was significantly higher in men with open-type atrophic gastritis [100.0% (7/7)] than in men with closed-type or non-atrophic gastritis [60.0% (27/45), $p = 0.039$, chi-square test].

Changes in reflux and dyspepsia symptoms. The intensity and frequency of reflux and dyspepsia symptoms improved significantly after PPI therapy (Fig. 3). Reflux symptoms defined as "troublesome" by the Montreal classification, including ≥2 mild reflux episodes per week or ≥1 moderate or greater reflux episodes per week,[15] were observed in 37 patients (44.6%) before PPI treatment, but in only three (3.6%) after treatment. Before PPI therapy, 33 patients (39.8%) did not experience heartburn, 31 (37.3%) did not experience acid regurgitation symptoms, and 18 (21.7%) did not experience either. Of the 65 patients with reflux symptoms at baseline, 19 (29.2%) experienced symptoms after PPI therapy. Healing rates were similar in patients with [69.6%, (32/46)] and without [57.9%, (11/19)] symptom resolution ($p = 0.366$, chi-square test).

Adverse events. During the study, five patients experienced one adverse event each. One patient experienced a serious adverse event, pneumonia thought to be caused by aspiration, which led to death. One patient each experienced rash, pneumonia, urinary tract infection, and fever.

Table 2. Relationships between patient characteristics and healing rate in patients with reflux esophagitis

Variable		Healed patients $n = 56$	Non-healed patients $n = 27$	Healing rate†	p value
Sex	Male	31	19	63.3%	0.391‡
n (%)	Female	22	8	73.3%	
Age†† (years) mean ± SD		66.8 ± 14.5	62.3 ± 17.1	—	0.236§
BMI†† (kg/m^2) mean ± SD		24.2 ± 3.6	25.2 ± 3.7	—	0.224§
Duration of GERD††	<1 month	19	6	76.0%	0.513‡
n (%)	1 month to 1 year	25	11	69.4%	
	≥1 year	12	8	60.0%	
	Unanswered	0	2	—	—
PPI dosage during the study	Standard¶	46	24	65.7%	0.495‡
n (%)	Double	9	2	81.8%	
	Half	1	1	50.0%	
Use of low-dose aspirin during the study	Yes	4	3	57.1%	0.542‡
n (%)	No	52	24	68.4%	
Kyphosis	Yes	10	6	62.5%	0.637‡
n (%)	No	46	21	68.7%	

†Proportion of patients without erosion of esophageal mucosa (LA grade N or M) after 8 weeks of PPI therapy. ‡Chi-square test. §Student's t test. ¶Omeprazole 20 mg once daily, lansoprazole 30 mg once daily, or rabeprazole 10 mg once daily. ††At time of first endoscopy. SD, standard deviation; BMI, body mass index; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Table 3. Relationships between healing rate and pre-treatment Los Angeles grade and endoscopic findings

Variable		Healed patients $n = 56$	Non-healed patients $n = 27$	Healing rate†	p value‡
LA grade before PPI therapy	C	45	19	70.3%	0.310
n (%)	D	11	8	57.9%	
Atrophic gastritis	Open type	9	2	81.8%	0.300
n (%)	Closed type/without atrophic gastritis	47	24	66.2%	
	Unknown	0	1	—	
Superficial gastritis	Yes	8	4	66.7%	0.949
n (%)	No	48	23	67.6%	
Hiatal hernia	Yes	40	14	74.1%	0.080
n (%)	No	16	13	55.2%	

†Percentage of patients without erosion of esophageal mucosa (LA grade N or M) after 8 weeks of PPI therapy. ‡Chi-square test. LA, Los Angeles; PPI, proton pump inhibitor.

Discussion

This is the first large-scale multicenter study assessing the effectiveness and safety of PPIs for severe RE patients in Japan. Following 8 weeks of PPI treatment, the healing rates of patients with Los Angeles grades C and D RE were 70.3 and 57.9%, respectively. A similarly low healing rate was also reported in a western trial with 1,001 severe RE patients (grade C or D), in which the healing rate was <80% after 8 weeks of PPI treatment.[16] In addition, a trial assessing the efficacy of lansoprazole (30 mg once daily) for 8 weeks in Japanese patients with endoscopically-confirmed RE found that the healing rate in the 20 patients with grades C and D RE was 45.0%.[17] Since this study was designed to investigate the effectiveness of PPI for severe RE patients in clinical practice, patients were not subdivided by type and dose of PPI.

The low healing rate in our patients was comparable with the findings of a recent retrospective survey in Japan: the healing rates of patients with Los Angeles grades C and D RE were 50 and 42%, respectively, after more than 8 weeks of PPI therapy.[18] Our prospective study suggests the need for higher doses of PPIs, or the use of more potent drugs, when treating Japanese patients with severe RE. Of the 27 patients whose esophagitis was not healed, 15 (55.6%) showed improvements from grade C or D to grade A or B. These patients were considered at least partially responsive to PPI therapy, suggesting that treatment with a higher dose or stronger PPI could have healed their esophagitis.[19,20]

While we observed no significant associations between the healing rates and patient characteristics or endoscopic comorbidities in this cohort, patients with hiatal hernia tended to have a higher healing rate, suggesting that a significant association between concomitant hiatal hernia and RE healing after PPI therapy may be demonstrated if larger studies are conducted. Subgroup analysis showed that the healing rate was significantly higher in men with than without open-type atrophic gastritis, probably as a direct consequence of the suppression of gastric acid secretion.[21] A significantly higher healing rate in patients with RE and open-type atrophic gastritis was also reported in the aforementioned retrospective survey.[18]

In this study, both reflux and dyspepsia symptoms improved

doi: 10.3164/jcbn.14-144

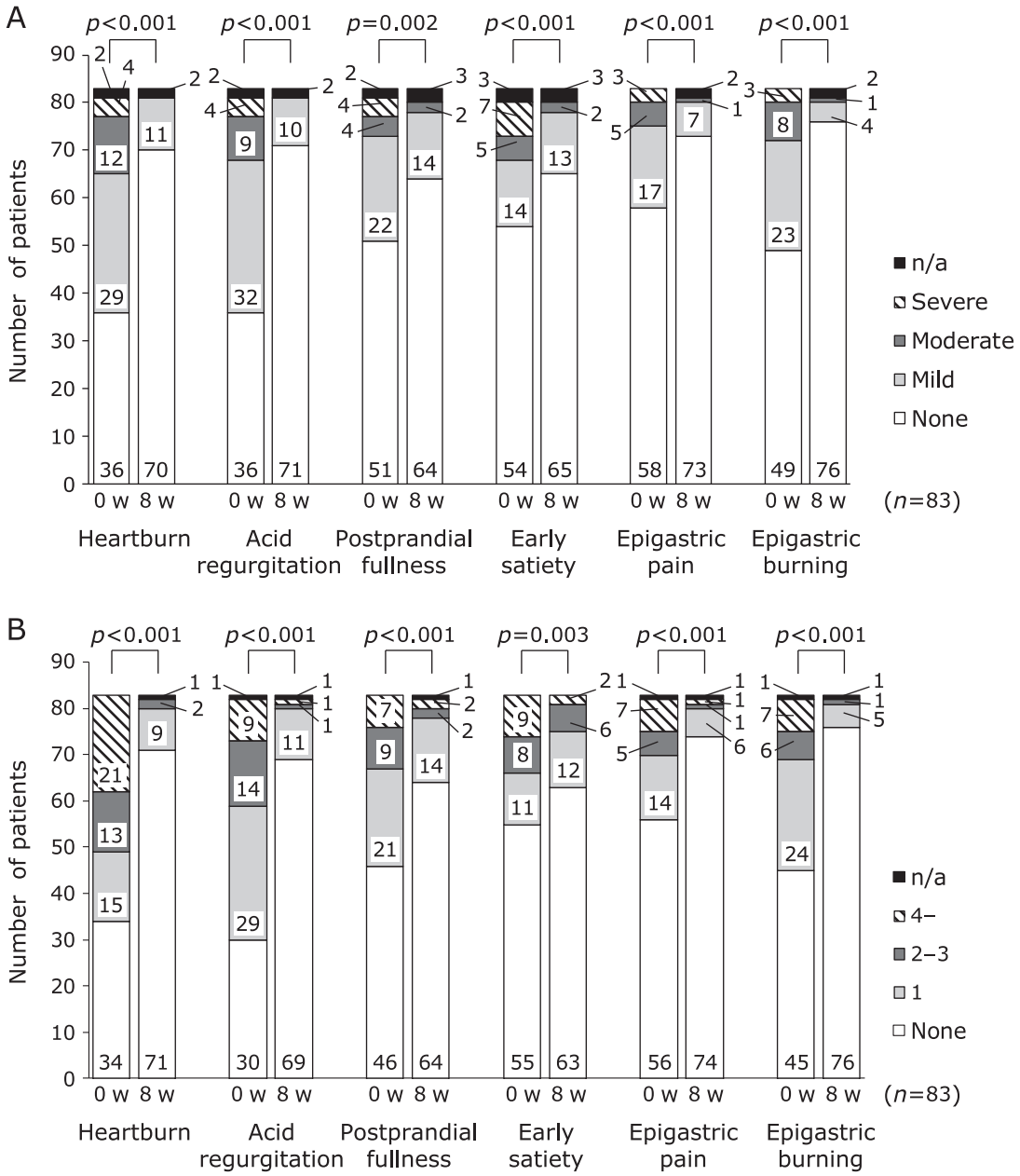

Fig. 3. Comparison of symptoms before and after proton pump inhibitor therapy. The *p* value was determined by the Wilcoxon signed-rank test. (A) Intensity of symptoms. (B) Frequency of symptoms. Patients were categorized by the number of symptomatic days per week. n/a, not answered.

following 8 weeks of PPI therapy. However, ≥20% of the patients reported that they did not experience reflux symptoms before treatment, despite having severe RE. Asymptomatic RE is common in elderly Japanese patients, and was reported to account for 24–54% of all patients with GERD.[22–24] Although most patients with asymptomatic RE are regarded as having mild esophagitis,[25] our results indicate that some patients with severe mucosal damage may be asymptomatic. Patients with severe RE may therefore go untreated owing to their lack of awareness of reflux symptoms. Thus, proactive endoscopic examinations, during routine care or regular check-ups, are an important means of identifying and treating these patients promptly. Our findings also underline the importance of post-treatment endoscopic examination to confirm healing of RE, as no significant relationship was found between the resolution of reflux symptoms and endoscopic healing of mucosal damage after PPI therapy.

In the study cohort, there were two patients treated with half-dose PPI, which was not usually used for severe RE patients, and two nonadherent patients. We did not exclude them, because we aimed to evaluate clinical effectiveness of PPI for severe RE. It should be noted that we confirmed that none of factors was associated with healing rate as the results shown in Table 2 and 3 even in the analysis excluding these patients.

A possible limitation of this study is that we did not investigate a kind of PPI administered for each patient. Therefore, the difference of effectiveness between PPIs cannot be discussed. Another limitation of the study is that the diagnostic criteria for hiatal hernia and kyphosis were not regulated by the protocol, and depended on each participating center.

In conclusion, Japanese patients with severe RE had a healing rate of 67.5% after 8 weeks of PPI treatment, comparable with rates reported in studies of western patients with severe RE. For

severe RE patients, it is therefore important to conduct endoscopic examination after PPI treatment to assess the extent of response to treatment.

Acknowledgments

The authors would like to thank the study participants, the physicians and other involved parties at the participating institutions for their cooperation in this study. Support for statistical analysis and medical editing was provided by Satoshi Osaga of MC&P Co., Ltd. (Osaka, Japan), and funded by AstraZeneca K.K. (Osaka, Japan) based on the contract between the GERD Society and AstraZeneca K.K.

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Abbreviations

BMI	body mass index
GERD	gastroesophageal reflux disease
PPI	proton pump inhibitor
RE	reflux esophagitis

Conflict of Interest

Nobuyuki Matsuhashi received lecture fees from AstraZeneca K.K. and Eisai Co., Ltd. Kazuhide Higuchi received lecture fees and scholarship grants from Daiichi-Sankyo Co., Ltd. and Eisai Co., Ltd. Ken Haruma received lecture fees and scholarship grants from AstraZeneca K.K., Daiichi-Sankyo Co., Ltd, Eisai Co., Ltd. and Takeda Pharmaceutical Co., Ltd. Takashi Joh received scholarship grants from AstraZeneca K.K., Daiichi-Sankyo Co., Ltd. and Eisai Co., Ltd. The other authors have no potential conflicts of interest.

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doi: 10.3164/jcbn.14-144