Lifestyle Factors and Efficacy of Lifestyle Interventions in Gastroesophageal Reflux Disease Patients with Functional Dyspepsia: Primary Care Perspectives from the LEGEND Study

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Abstract

Objective Although gastroesophageal reflux disease (GERD), a very common disorder worldwide, is considered to be a lifestyle disease, the pathogenic role of lifestyle factors and consequently the efficacy of lifestyle interventions, remains controversial. Lifestyle factors associated with GERD and the beneficial effect of specific recommended lifestyle interventions in the primary care setting were evaluated as a post-hoc analysis of the LEGEND study which investigated the effect of lansoprazole in patients with GERD who reported dyspeptic symptoms.

Methods GERD patients with dyspepsia were treated with lansoprazole 15 mg or 30 mg daily for four weeks. Reflux and dyspeptic symptoms were evaluated using patient-reported questionnaires before and four weeks after the administration of lansoprazole.

Results Among 12,653 patients, “feelings of continued stress” was the most common lifestyle factor (45.6% of patients), and >30% of the patients reported “eating sweet foods at least once every two to three days,” “eating greasy foods at least once every two to three days” and “drinking coffee almost daily.” Introducing lifestyle interventions had a significant effect on both reflux and dyspeptic symptoms.

Conclusion Lifestyle interventions are thus considered to be important in GERD patients with dyspepsia who receive a proton pump inhibitor.

Key words: GERD, dyspepsia, lifestyle, modification, lansoprazole, non-erosive reflux disease

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Introduction

Gastroesophageal reflux disease (GERD) is a multifactorial disease in which anatomical and functional factors both play a pathogenic role. Among related environmental factors, lifestyle factors, in particular dietary habits including alcohol and coffee intake, and smoking, and psychological factors, have frequently been suggested as possible risk factors for GERD (1-6).

It is well recognized that the most effective treatment strategy for GERD involves the use of proton pump inhibitors (PPIs); however, PPI therapy does not resolve all GERD symptoms. In addition, prior to the introduction of anti-secretory drugs, lifestyle interventions were the only treatment option for GERD, although the effectiveness of this option in cases of GERD has not been fully assessed.

Recently, the LEGEND (Lansoprazole Effectiveness on GERD patients with Dyspepsia symptoms) study was conducted in Japan to investigate the effects of the PPI lansoprazole in improving subjective symptoms in ≥10,000 patients with GERD who reported experiencing dyspeptic symptoms.
symptoms (7). As a post hoc analysis of this large-scale study, we evaluated whether lifestyle interventions, in combination with PPI therapy, improve reflux and dyspeptic symptoms in GERD patients with dyspepsia.

### Materials and Methods

The LEGEND study was performed at 1,611 clinics and hospitals in Japan. Patients with a clinical diagnosis of GERD, based on the Montreal definition, were enrolled in this study (from December 2008 to June 2010) if they reported experiencing heartburn and/or acid regurgitation in addition to dyspepsia (postprandial fullness, early satiation, epigastric pain, epigastric burning, upper abdominal bloating, nausea/vomiting, belching). Full details of the design and procedures of the LEGEND study have been described previously (7). Patients with endoscopically-proven erosive esophagitis were enrolled in the LEGEND study, even in the absence of reflux symptoms, provided they had dyspepsia.

All patients received lansoprazole (Takepron®; Takeda Pharmaceutical, Osaka, Japan) at a dose of 15 mg or 30 mg once daily, with the dose selection made arbitrarily by the attending physician. The coadministration of prokinetic and antisecretory agents was allowed. Esophagogastrroduodenoscopy was performed as needed prior to enrollment, and the physicians evaluated the endoscopic findings according to the Los Angeles classification incorporating Japanese modifications.

At enrollment and four weeks after the start of lansoprazole administration, the patients reported their symptoms using questionnaires that contained questions related to reflux symptoms (heartburn and acid regurgitation) and seven dyspeptic symptoms (postprandial fullness, early satiation, epigastric pain, epigastric burning, upper abdominal bloating, nausea/vomiting, and belching). Symptoms were graded on a four-point Likert scale, as follows: ‘never,’ ‘sometimes/mild,’ ‘often/moderate’ or ‘frequent/severe.’ Changes in symptoms four weeks after the start of lansoprazole administration were classified into the following five categories: ‘disappearance of symptoms,’ ‘improvement,’ ‘no change,’ ‘worsened symptoms’ and ‘unclear.’ The rate of symptom improvement (i.e., the frequency of symptoms classified as ‘disappeared’ or ‘improved’) was calculated. Dyspeptic symptoms were classified into two groups, i.e., postprandial distress symptoms (PDS; postprandial fullness, early satiation) and epigastric pain symptoms (EPS; epigastric pain and burning).

At enrollment, the patients were also requested to complete 11 questions related to whether they had lifestyle risk factors for GERD. The physicians reported lifestyle interventions for each patient after four weeks of treatment. The body mass index (BMI) was also calculated prior to treatment and the patients were recommended to lose weight if their BMI was >25 kg/m².

This study was performed in compliance with Good Post-marketing Study Practices (GPSP), a ministerial ordinance concerning standards for implementing post-marketing surveys of drugs in Japan. In contrast to GPSP requirements for formal clinical trials, neither approvals from each institutional ethics committee nor written informed consent from the patients are mandatory for this type of study.

### Statistical analysis

The SAS software program (version 9.1.3, SAS Institute, Cary, USA) was used for the statistical analyses. For the analysis of categorical variables, the proportion (%) of relevant patients was calculated. The Chi-square test was used to compare the between-group symptom improvement rates. p values of <0.05 (two-sided) were considered to be statistically significant.

### Results

#### Patient demographics

A total of 12,653 patients were included in the analysis. The demographic characteristics of the subjects are shown in Table 1. The mean age of the patients was 60.5 years, and 34.0% of the patients were >70 years of age. A total of 58.6% of the enrolled patients were women. The BMI was >25 kg/m² and >30 kg/m² in 37% and 4.9% of the patients, respectively. In total, 505 of 12,653 (4.0%) patients had kyphosis, 3,035 of 5,195 (58.6%) patients had erosive esophagitis, 689 of 2,903 (23.7%) patients were H. pylori-positive and 2,498 of 9,626 (26.0%) patients had a history of GERD. The duration of dyspepsia was <1 month in 52.3% of the patients and >6 months in 12.9% of the patients.

#### Lifestyle risk factors for GERD and lifestyle interventions

As shown in Fig. 1, the risk factor “feelings of continued stress” was observed in 45.6% of the patients, “eating sweet food at least once every two to three days” in 41.1% of the patients.

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**Table 1. Clinical Background of Enrolled Gastroesophageal Reflux Disease (GERD) Patients in the Effectiveness Analysis Set (n=12,653)**

| Gender (Male/Female) | 5,236/7,417 |
|----------------------|-------------|
| Mean age (SD, years) | 60.5±16.0   |
| BMI <25 kg/m²        | 6,043       |
| 25-30 kg/m²         | 3,083       |
| >30 kg/m²           | 472         |
| Kyphosis +/-         | 505/12,148  |
| Erosive esophagitis +/- | 3,035/2,160 |
| H. pylori infection +/- | 689/2,214   |
| History of GERD +/- | 2,498/12,728 |
| Duration of dyspepsia: |            |
| <1 month             | 5,832       |
| 1-3 months           | 3,080       |
| 3-6 months           | 802         |
| >6 months            | 1,442       |

BMI: body mass index
Data shown are patient numbers, unless specified otherwise.
patients, “eating greasy foods at least once every two to three days” in 36.1% of the patients, “drinking coffee almost daily” in 32.9% of the patients, “eating until full” in 29.6% of the patients and “BMI ≥25 kg/m²” in 28.1% of the patients.

As shown in Fig. 2, the following lifestyle interventions were achieved by more than half of all patients: “do not keep eating until full” (62.9% of patients); “cut down on eating greasy foods” (59.1%); “do not lie down after eating/sleep with the head elevated/sleep on the left side” (57.9%); “cut down on smoking” (55.5%); “cut down on drinking alcohol” (54.7%); “cut down on eating sweet foods” (50.8%). In contrast, “lose weight” was achieved in only 15.6% of the patients.

**Improvement in subjective symptoms after treatment with lansoprazole and lifestyle interventions**

The rates of improvement at four weeks for both reflux and dyspeptic symptoms are shown in Tables 2-4. For all lifestyle interventions, although the difference in the rate of improvement ranged from 3.7% to 9.2%, a significantly greater degree of improvement in reflux symptoms was observed in the group of patients who received lifestyle interventions compared with those who did not. With the exception of “avoid tight-fitting girdles or corsets” in patients with PDS and “lose weight” in patients with PDS and EPS, significantly greater improvements in dyspeptic symptoms were also observed in the patients who received lifestyle interventions.

**Discussion**

To our knowledge, this is the first large-scale study to confirm that lifestyle interventions are effective in the primary care setting for improving reflux and dyspeptic symptoms in GERD patients with dyspepsia who receive a PPI. The most effective treatment for GERD is recognized to be a PPI; however, a significant proportion of patients experi-
ence persistent symptoms or exhibit endoscopic evidence of esophagitis despite the use of PPIs. In addition, approximately 10% to 20% of patients with GERD fail to respond symptomatically, either partially or completely, to standard-dose PPI therapy (8-10). Options for patients with PPI-resistant or refractory GERD include doubling the PPI dose or adding an H2-receptor antagonist, antacids or prokinetics, although these treatment options are not cost effective and among lifestyle interventions were the only viable treatment option for GERD; however, the effectiveness of lifestyle interventions has not been fully assessed. In our five-year prospective study in community medicine (14), reflux symptoms were controlled by lifestyle modifications in a proportion of GERD patients.

Although lifestyle interventions are frequently recommended for the treatment for GERD in the primary care setting, there is little evidence that they are of benefit. Losing weight and avoiding lying down within three hours of a meal as well as eating large, greasy or sweet foods, consuming alcohol, smoking, drinking coffee and using tight girdles or corsets are generally considered to be useful interventions by physicians. However, when patients are asked about the advice they have received from physicians, lifestyle interventions are only modestly recommended. A study by Nowak and colleagues (15) indicated that most general practitioners (GPs) believe that lifestyle changes are beneficial, although they do not think that their patients would change their behavior. In addition, most GPs recommend fewer than half the lifestyle changes their peers believe to be effective in the treatment of GERD. Kitchin and Castell (16) concluded that, although there were few well-designed, placebo-

### Table 2. Improvement Rate of Reflux Symptoms according to Lifestyle Measures

| Lifestyle factor                      | Lifestyle measure                      | Yes/No | No. of patients | Achievement rates | Improvement rates at 4 weeks (disappear + improve) | p value | odds ratio | 95% CI          |
|--------------------------------------|----------------------------------------|--------|----------------|-------------------|-------------------------------------------------|---------|------------|----------------|
| keep on eating                       | do not keep on eating                  | Yes    | 2,325          | 63.0%             | 77.1%                                           | p < 0.005 *** | 1.248     | 1.070-1.455     |
| until full                           |                                        | No     | 1,363          |                   | 72.9%                                           |         |            |                |
| eat greasy food at least once in 2 to 3 days | cut down on eating greasy food         | Yes    | 2,674          | 59.2%             | 77.3%                                           | p < 0.001 *** | 1.301     | 1.135-1.491     |
|                                       |                                        | No     | 1,844          |                   | 72.4%                                           |         |            |                |
| eat sweet food at least once in 2 to 3 days | cut down on eating sweet food          | Yes    | 2,603          | 50.8%             | 78.0%                                           | p < 0.001 *** | 1.328     | 1.168-1.508     |
|                                       |                                        | No     | 2,517          |                   | 72.8%                                           |         |            |                |
| eat spicy food at least once in 2 to 3 days | cut down on eating spicy food          | Yes    | 1,081          | 45.9%             | 78.4%                                           | p = 0.001 **  | 1.368     | 1.131-1.654     |
|                                       |                                        | No     | 1,276          |                   | 72.6%                                           |         |            |                |
| drink alcohol almost daily            | cut down on drinking alcohol           | Yes    | 1,376          | 54.7%             | 77.1%                                           | p = 0.036 *  | 1.218     | 1.015-1.461     |
|                                       |                                        | No     | 1,141          |                   | 73.4%                                           |         |            |                |
| drink coffee almost daily             | cut down on drinking coffee            | Yes    | 1,781          | 43.5%             | 75.7%                                           | p = 0.001 **  | 1.259     | 1.093-1.449     |
|                                       |                                        | No     | 2,315          |                   | 71.3%                                           |         |            |                |
| smoke 10 or more cigarettes a day    | cut down on smoking                    | Yes    | 995            | 55.8%             | 79.6%                                           | p < 0.001 *** | 1.480     | 1.188-1.843     |
|                                       |                                        | No     | 789            |                   | 72.5%                                           |         |            |                |
| wear girdles or corsets              | avoid tight wear girdles or corsets     | Yes    | 432            | 36.2%             | 79.9%                                           | p < 0.001 *** | 1.640     | 1.237-2.175     |
|                                       |                                        | No     | 762            |                   | 70.7%                                           |         |            |                |
| have a bent-forward posture          | avoid having a bent-forward posture     | Yes    | 1,132          | 35.1%             | 78.7%                                           | p < 0.001 *** | 1.364     | 1.148-1.620     |
|                                       |                                        | No     | 2,089          |                   | 73.0%                                           |         |            |                |
| lie down soon after eating           | do not lie down after eating/sleep with head elevated/sleep on left side | Yes    | 1,789          | 57.9%             | 77.1%                                           | p < 0.001 *** | 1.328     | 1.128-1.564     |
|                                       |                                        | No     | 1,303          |                   | 71.8%                                           |         |            |                |
| feel continued stress                | do not feel stress or change the feeling| Yes    | 2,486          | 43.5%             | 77.8%                                           | p < 0.001 *** | 1.511     | 1.339-1.705     |
|                                       |                                        | No     | 3,229          |                   | 69.9%                                           |         |            |                |
| BMI ≥25 kg/m²                        | lose weight                            | Yes    | 553            | 15.7%             | 82.5%                                           | p = 0.013 *  | 1.346     | 1.063-1.704     |
|                                       |                                        | No     | 2,965          |                   | 77.7%                                           |         |            |                |

95%CI: 95 percent confidence interval
controlled trials, lifestyle interventions are effective in treating GERD. In contrast, Galmiche et al. (17) reported that, while appropriate for promoting general health, many of lifestyle changes are not of benefit in alleviating GERD symptoms. Salyers et al. (18) also reported that only 12% of 502 GERD patients received documented counseling regarding lifestyle modifications.

In the current analysis, all 12 lifestyle interventions were effective in improving both reflux and dyspeptic symptoms. There is currently no established evidence with respect to the use of lifestyle interventions for dyspepsia, although stress, the lipid levels and possibly other foods are associated with the pathogenesis of functional dyspepsia. The most effective lifestyle intervention in the current analysis was “avoiding tight-fitting girdles or corsets,” resulting in improvements in reflux symptoms in 9.2% more patients who received this advice versus those who did not. “Cut down on smoking” and “reduce stress” were also highly effective in treating reflux symptoms (7.1% and 7.9%, respectively). Moreover, previous studies have reported an association between GERD and metabolic syndrome/obesity (19), and between NERD and the serum lipid levels (20), which may explain why lifestyle interventions, such as losing weight and reducing the intake of eating greasy foods were linked to improvements in GERD and dyspeptic symptoms in our analysis. A systematic review of the English-language literature by Kaltenbach and colleagues, who investigated the effect of lifestyle interventions on GERD, found that only weight loss, elevating the head of the bed and using the left lateral decubitus position were associated with improvements in GERD variables (21). In a study that reviewed evidence for potentially modifiable lifestyle risk factors for GERD, Dibley et al. (22) concluded that data obtained from other chronic disease programs showed that life-

Table 3. Improvement Rate of PDS Symptoms according to Lifestyle Measures

| Lifestyle factor | Lifestyle measure | Yes/No | No. of patients | Achievement rates | Improvement rates at 4 weeks (disappear + improve) | p value odds ratio 95% CI |
|------------------|-------------------|--------|----------------|-----------------|---------------------------------|----------------------|
| keep on eating   | do not keep on eating | yes    | 2,109          | 63.7%           | 69.4%                           | p < 0.001 ***        | 1.314 1.132-1.526 |
| until full       | until full        | no     | 1,200          |                 | 63.3%                           |                      |                     |
| eat greasy food at least once in 2 to 3 days | cut down on eating greasy food | yes    | 2,435          | 59.8%           | 70.0%                           | p < 0.001 ***        | 1.348 1.180-1.539 |
|                 |                   | no     | 1,635          |                 | 63.4%                           |                      |                     |
| eat sweet food at least once in 2 to 3 days | cut down on eating sweet food | yes    | 2,362          | 51.6%           | 71.0%                           | p < 0.001 ***        | 1.377 1.217-1.559 |
|                 |                   | no     | 2,219          |                 | 63.9%                           |                      |                     |
| eat spicy food at least once in 2 to 3 days | cut down on eating spicy food | yes    | 983            | 46.3%           | 70.1%                           | p < 0.001 ***        | 1.381 1.151-1.656 |
|                 |                   | no     | 1,141          |                 | 62.9%                           |                      |                     |
| drink alcohol almost daily | cut down on drinking alcohol | yes    | 1,252          | 55.5%           | 71.2%                           | p = 0.003 **        | 1.308 1.094-1.563 |
|                 |                   | no     | 1,002          |                 | 65.4%                           |                      |                     |
| drink coffee almost daily | cut down on drinking coffee | yes    | 1,618          | 44.1%           | 69.1%                           | p < 0.001 ***        | 1.311 1.142-1.506 |
|                 |                   | no     | 2,048          |                 | 63.0%                           |                      |                     |
| smoke 10 or more cigarettes a day | cut down on smoking | yes    | 902            | 56.0%           | 71.3%                           | p = 0.002 **        | 1.408 1.141-1.738 |
|                 |                   | no     | 710            |                 | 63.8%                           |                      |                     |
| wear girdles or corsets | avoid tight wear girdles or corsets | yes    | 391            | 36.1%           | 68.3%                           | p = 0.163          | 1.210 0.930-1.575 |
|                 |                   | no     | 692            |                 | 64.0%                           |                      |                     |
| have a bent-forward posture | avoid having a bent-forward posture | yes    | 1,019          | 35.2%           | 69.5%                           | p = 0.005 **        | 1.269 1.077-1.494 |
|                 |                   | no     | 1,878          |                 | 64.2%                           |                      |                     |
| lie down soon after eating | do not lie down after eating/sleep with head elevated/sleep on left side | yes    | 1,623          | 58.2%           | 70.3%                           | p = 0.002 **        | 1.297 1.104-1.522 |
|                 |                   | no     | 1,167          |                 | 64.6%                           |                      |                     |
| feel continued stress | do not feel stress or change the feeling | yes    | 2,299          | 43.8%           | 70.8%                           | p < 0.001 ***        | 1.507 1.341-1.693 |
|                 |                   | no     | 2,948          |                 | 61.6%                           |                      |                     |
| BMI ≥25 kg/m² | lose weight | yes    | 497            | 15.9%           | 73.0%                           | p = 0.550          | 1.073 0.865-1.331 |
|                 |                   | no     | 2,636          |                 | 71.6%                           |                      |                     |

PDS: postprandial distress symptoms (postprandial fullness, early satiation)

95% CI: 95 percent confidence interval

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style education interventions that include self-management strategies are highly effective in improving well-being and reducing health care costs, although there was no conclusive evidence showing that modulating these factors is either effective or ineffective in patients with GERD.

There are a number of limitations in the current analysis. For example, this study was not a randomized controlled trial, and the lifestyle interventions were performed according to the patient’s own determination and the physician’s judgment. In addition, the level of patient adherence to the lifestyle interventions was not assessed. Due to the fact that potential confounding factors (e.g., the co-administration of histamine H₂-receptor antagonists with lansoprazole, presence of esophageal hiatal hernias) and/or sample selection bias (e.g., missing values) may have influenced the findings, larger prospective randomized controlled trials are required in order to draw more definitive evidence-based conclusions.

In addition, the achievement rates were low for several interventions, including “lose weight” (15.6%), “avoid having a bent-forward posture” (34.9%) and “avoid tight-fitting girdles or corsets” (36.1%). However, from the primary care perspective, it is important that a 3.7-9.2% additional improvement was achieved by introducing lifestyle interventions to significantly improve both reflux and dyspeptic symptoms in patients with GERD, as GERD and functional dyspepsia are very common diseases requiring long-term medical treatment, particularly the use of PPIs. Moreover, lifestyle interventions are completely safe and cost effective in addition to being useful for promoting general health. Furthermore, evidence from the management of other long-term illnesses such as chronic obstructive pulmonary disease, bronchial asthma, diabetes mellitus and rheumatoid arthritis, confirms that educating patients about their condition, as well as changes in lifestyle, may ease symptoms and improve well-being.

### Table 4. Improvement Rate of EPS Symptoms according to Lifestyle Measures

| Lifestyle factor                  | Lifestyle measure                  | Yes/No | No. of patients | Achievement rates | Improvement rates at 4 weeks (disappear + improve) | p value | odds ratio | 95%CI |
|----------------------------------|------------------------------------|--------|----------------|------------------|--------------------------------------------------|--------|------------|-------|
| keep on eating until full        | do not keep on eating until full   | yes    | 1,934          | 63.2%            | 75.0%                                            | p < 0.001 *** | 1.270 | 1.078-1.497 |
| eat greasy food at least once in 2 to 3 days | cut down on eating greasy food | yes    | 2,222          | 59.5%            | 75.5%                                            | p < 0.001 *** | 1.297 | 1.120-1.502 |
| eat sweet food at least once in 2 to 3 days | cut down on eating sweet food | yes    | 2,150          | 51.5%            | 76.3%                                            | p < 0.001 *** | 1.382 | 1.204-1.585 |
| eat spicy food at least once in 2 to 3 days | cut down on eating spicy food | yes    | 904            | 46.4%            | 76.1%                                            | p < 0.001 *** | 1.464 | 1.197-1.789 |
| drink alcohol almost daily       | cut down on drinking alcohol       | yes    | 1,161          | 55.3%            | 76.8%                                            | p < 0.001 *** | 1.338 | 1.100-1.629 |
| drink coffee almost daily        | cut down on drinking coffee        | yes    | 1,467          | 44.3%            | 73.4%                                            | p < 0.001 *** | 1.322 | 1.136-1.538 |
| smoke 10 or more cigarettes a day | cut down on smoking               | yes    | 867            | 57.1%            | 78.2%                                            | p < 0.001 *** | 1.545 | 1.225-1.950 |
| wear girdles or corsets          | avoid tight wear girdles or corsets | yes    | 352            | 36.6%            | 75.3%                                            | p = 0.010 *   | 1.482 | 1.103-1.991 |
| have a bent-forward posture      | avoid having a bent-forward posture | yes    | 926            | 35.3%            | 74.3%                                            | p < 0.001 *** | 1.294 | 1.081-1.549 |
| lie down soon after eating       | do not lie down after eating/sleep with head elevated/sleep on left side | yes    | 1,486          | 58.5%            | 76.3%                                            | p < 0.001 *** | 1.394 | 1.167-1.665 |
| feel continued stress            | do not feel stress or change the feeling | yes    | 2,123          | 44.1%            | 76.5%                                            | p < 0.001 *** | 1.583 | 1.392-1.800 |
| BMI ≥25 kg/m² lose weight        |                                   | yes    | 474            | 16.4%            | 76.7%                                            | p = 0.188 | 1.182 | 0.928-1.506 |

EPS: epigastric pain symptoms (epigastric pain, and epigastric burning)
95%CI: 95 percent confidence interval
promote a feeling of well-being (23-27). Such effects can be achieved by shifting the patient’s perception of the severity of their condition.

In summary, the results of the current large-scale analysis indicated that lifestyle interventions are effective for the improving reflux and dyspeptic symptoms, possibly representing an initial therapeutic option for GERD patients with dyspepsia who receive treatment with lansoprazole.

**Author’s disclosure of potential Conflicts of Interest (COI).**

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