INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

# Proton Pump Inhibitor Treatment Decreases the Incidence of Upper Gastrointestinal Disorders in Elderly Japanese Patients Treated with NSAIDs

Yuki Sakamoto, Tadashi Shimoyama, Satoru Nakagawa,
Tatsuya Mikami and Shinsaku Fukuda

## Abstract

**Objective** The Japanese health insurance system approved the use of proton pump inhibitors (PPIs) for the prevention of peptic ulcers in patients using low-dose aspirin (LDA) and/or non-steroidal anti-inflammatory drugs (NSAIDs). However, many orthopedists and physicians do not prescribe PPIs to elderly patients with atrophic gastritis. The aim of this study was to determine whether PPIs are effective in preventing gastrointestinal mucosal injury in elderly Japanese patients with atrophic gastritis.

**Methods** We examined the associations between the use of antiulcer drugs and endoscopic findings in elderly Japanese patients using LDA or NSAIDs.

**Patients** We evaluated 100 patients using LDA and 58 patients using non-aspirin NSAIDs 65 years of age or older. All patients underwent upper GI endoscopy to detect the presence of open ulcers and hemorrhagic lesions and assess the extent of atrophic gastritis.

**Results** Among the patients using LDA, the prevalence of open ulcers was significantly lower in the patients using PPIs than in those using mucosal protective agent only and those not receiving antiulcer treatment ($p<0.001$). Among the patients using NSAIDs, the patients treated with PPIs exhibited a significantly lower incidence of open ulcers than the patients not receiving antiulcer treatment ($p=0.012$). Open-type atrophic gastritis was observed in nearly 70% of the patients.

**Conclusion** The use of PPI treatment is advisable in order to prevent the discontinuation of LDA or NSAIDs due to the development of gastrointestinal disorders in elderly patients with atrophic gastritis.

**Key words:** proton pump inhibitor, low-dose aspirin, non-steroidal anti-inflammatory drugs

**(Intern Med 53: 1107-1111, 2014)**
**(DOI: 10.2169/internalmedicine.53.2159)**

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat acute or chronic pain such as that observed in patients with lumbago or arthritis. Additionally, low-dose aspirin (LDA) is widely used to prevent cardiovascular and cerebrovascular diseases. The most common cause of discontinuation of NSAID and LDA therapy is upper gastrointestinal injury, such as the presence of peptic ulcers or gastrointestinal bleeding (1). In Japan, the frequency of hemorrhagic peptic ulcers associated with LDA is increasing in association with the increase in the number of LDA prescriptions (2). The American College of Cardiology Foundation (ACCF)/American College of Gastroenterology (ACG)/American Heart Association (AHA) 2008 expert consensus recommends discontinuing treatment with of NSAIDs in patients with gastrointestinal events, such as gastrointestinal bleeding (3). However, discontinuing NSAID and/or LDA therapy impairs the quality of life and increases the risk of thrombosis (4).

Proton pump inhibitors (PPIs) are recognized to be superior to histamine 2 receptor antagonists (H2RAs) in healing and preventing peptic ulcers associated with the use of

Department of Gastroenterology, Hirosaki University Graduate School of Medicine, Japan
Received for publication November 19, 2013; Accepted for publication December 16, 2013
Correspondence to Dr. Tadashi Shimoyama, tsimo-hki@umin.ac.jp

**Table 1. Characteristics of the Patients Taking LDA and non-aspirin NSAIDs (NANSAIDs)**

| | PPI | H2RA | MPA | no drug |
|---|---|---|---|---|
| LDA (n=100) | | | | |
| number | 39 | 19 | 12 | 30 |
| male/female | 26/13 | 14/5 | 8/4 | 18/12 |
| age | 73.3 ± 6.4 | 75.0 ± 6.6 | 76.8 ± 5.2 | 71.4 ± 4.5 |
| (range) | (65-88) | (65-89) | (69-87) | (65-88) |
| smoker (%) | 7.7 | 5.2 | 8.3 | 0 |
| atrophic gastritis (%) | 71.8 | 68.4 | 66.7 | 73.3 |
| NANSAIDs (n=58) | | | | |
| number | 9 | 15 | 22 | 12 |
| male/female | 5/4 | 7/8 | 10/12 | 6/6 |
| age | 73.2 ± 4.3 | 72.9 ± 3.5 | 71.0 ± 4.7 | 73.8 ± 4.6 |
| (range) | (68-81) | (67-79) | (65-80) | (65-81) |
| smoker (%) | 33.3 | 20.0 | 9.1 | 0 |
| atrophic gastritis (%) | 66.7 | 73.3 | 72.7 | 66.7 |

Age is expressed as the mean ± SD (years old).
Atrophic gastritis is expressed as the prevalence of O-1, O-2 and O-3.
No significant differences in gender, age, the proportion of smokers or the prevalence of atrophic gastritis were observed between the groups.

NSAIDs (5). Moreover, the effects of PPIs are superior to those of misoprostol in preventing peptic ulcer recurrence in patients taking NSAIDs (6). Although gastric acid secretion is lower in Japanese than in Western populations, both lansoprazole and esomeprazole significantly reduce the recurrence of peptic ulcers compared with mucosal protective agents (MPAs) in NSAID users (7, 8). Lansoprazole is also superior to MPAs in reducing the recurrence of peptic ulcers associated with LDA (9). In 2010, the Japanese health insurance system approved the use of PPIs for the prevention of gastric and/or duodenal ulcer recurrence in patients taking LDA or NSAIDs.

Gastric acid secretion decreases with age in patients with *H. pylori* infection due to the progression of atrophic gastritis (10). Indeed, a recent study showed an association between an age of 65 or older and a reduced risk of gastroduodenal ulcers (11). In addition, the rate of *H. pylori* seropositivity has been found to be nearly 70% among elderly people living in an agricultural area in northern Japan, more than 60% of whom had atrophic gastritis (12). In this population, the use of LDA is frequent because the incidence of cerebrovascular disease is high. NSAIDs are also frequently used to treat lumbago or arthralgia. However, few studies have examined whether gastric acid suppression with PPI therapy is required in elderly Japanese patients with reduced gastric acid secretion due to atrophic gastritis.

The aim of this study was to determine whether the use of PPIs is adequate in preventing gastrointestinal mucosal injury associated with the discontinuation of NSAID and LDA therapy. We examined the associations between the use of antiulcer drugs and endoscopic findings in elderly Japanese patients receiving treatment with LDA or NSAIDs.

**Table 2. Type and Dose of LDA**

| | daily dose | n |
|---|---|---|
| enteric coated aspirin | 100 mg | 83 |
| | 200 mg | 4 |
| buffered aspirin | 81 mg | 10 |
| | 162 mg | 1 |
| aspirin bulk powder | 100 mg | 1 |
| | 200 mg | 1 |

## Materials and Methods

### Patients

The Japanese health insurance system defines elderly people as those 65 years of age or older. Therefore, the subjects of this study included 158 consecutive patients 65 years of age or older. All patients underwent upper gastrointestinal endoscopy between October 2006 and March 2011 at Hirosaki University Hospital. We excluded patients with renal failure or gastrointestinal cancer and those receiving corticosteroids or anticoagulants (other than LDA). We considered a patient to be under LDA therapy if they received a daily dose of aspirin of 200 mg or less for at least three months. We considered a patient to be under NSAID therapy if they received an NSAID for at least two weeks. We also inquired about each patient's smoking habits at the time of endoscopy. An open ulcer was defined as a mucosal break of significant depth, measuring at least 3 mm over its longest diameter. A hemorrhagic lesion was defined as any ulcers accompanied by bleeding and/or mucosal hemorrhage of grade 2 to 4 according to the Lanza score (13). The extent of atrophic gastritis was defined based on the Kimura-Takemoto classification (14), and the prevalence of open-type atrophic gastritis (O-1, O-2 and O-3) was compared between the groups. During endoscopy, the presence of *H. pylori* infection was tested using the rapid urease test (RUT) in patients not receiving LDA or PPI therapy. Among patients receiving LDA, but not a PPI, an *H. pylori* stool antigen test was performed (15). This study was approved by the ethics committee of Hirosaki University.

### Statistical analysis

The SPSS ver.12.0J software program (SPSS Inc., Chicago, IL, USA) was used for the data input and analysis. The statistical analysis was conducted using the *t*-test, $\chi^2$ test or Fisher's exact test, and significance was considered after performing Bonferroni correction.

## Results

### Patients taking LDA

One hundred patients received LDA (66 men and 34 women, 65-89 years old) (Table 1). PPIs were used in 39 patients and H2RAs were used in 19 patients, while 12 pa-

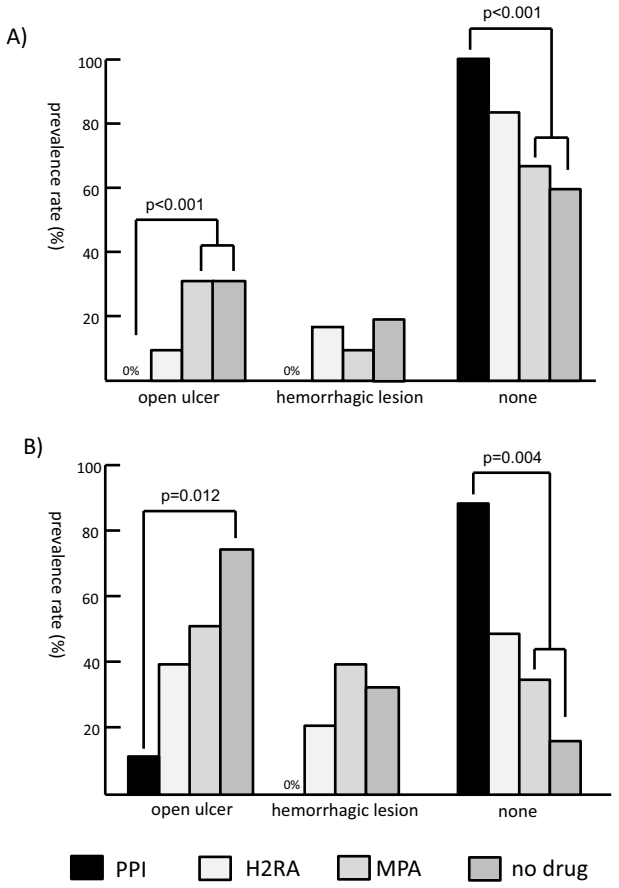


**Figure. Prevalence of open ulcers and hemorrhagic lesions in the patients using LDA (A) and NANSAIDs (B). PPI: proton pump inhibitor, H2RA: histamine 2 receptor antagonist, MPA: mucosal protective agent**

tients received MPA only. Thirty patients did not receive any antiulcer drugs. There were no significant differences in the prevalence of open-type atrophic gastritis or the mean age between the patients treated with different medications. The type and dose of LDA are shown in Table 2.

The associations between the use of antiulcer agents and endoscopic findings in the patients taking LDA are shown in Figure A. The prevalence of open ulcers was 0% in 39 patients treated with PPIs, 10.5% in 19 patients treated with H2RAs, 33.3% in both the patients treated with MPA only and the patients who did not receive any antiulcer agents. The prevalence of open ulcers was significantly lower in the patients using PPIs than in the patients using MPA only and those not receiving any antiulcer treatment ($p<0.001$). The incidence of hemorrhagic lesions was 0% (0/39 patients), 15.8% (3/19 patients), 8.3% (1/12 patients) and 23.3% (7/30 patients) among the patients using PPIs, H2RAs and MPA only and those not receiving any antiulcer treatment, respectively. The lack of both ulcers and hemorrhagic lesions was significantly more frequent among the patients taking PPIs than among the patients taking MPA only and those not receiving any antiulcer treatment ($p<0.001$).

### *Patients taking NSAIDs*

Fifty-eight patients used non-aspirin NSAIDs (NANSAIDs) (28 men and 30 women, 65-81 years old) (Table 1). PPIs and H2RAs were used in nine and 15 patients, respectively, while 22 patients received MPA only. Twelve patients did not receive any antiulcer agents. No significant differences were observed in the prevalence of open-type atrophic gastritis or the mean age between the groups (Table 1). Loxoprofen was administered in 38 patients (65.5%), diclofenac was administered in 11 patients (19.0%) and lornoxicam was administered in seven patients (12.0%). Naproxen and etodolac were each administered in one patient.

As shown in Figure B, open ulcers were observed in 11.1% of nine patients using PPIs, 40.0% of 15 patients using H2RAs, 50.0% of 22 patients using MPA only, and 75.0% of 12 patients not receiving any antiulcer treatment. The patients using PPIs had a significantly lower incidence of open ulcers than the patients not receiving antiulcer treatment ($p=0.012$). In contrast, the difference was not significant between the patients receiving H2RAs and the patients not receiving any antiulcer treatment. The incidence of hemorrhagic lesions in the patients treated with PPIs, H2RAs and MPA only was 0%, 20.0% and 40.9%, respectively. The incidence of hemorrhagic lesions was 33.3% in 12 patients not receiving any antiulcer treatment. The patients treated with PPIs exhibited the lowest incidence of hemorrhagic lesions, although the difference was not statistically significant. The lack of both ulcers and hemorrhagic lesions was significantly more frequent in patients receiving PPIs than among the patients receiving MPA only and those not receiving with any antiulcer treatment ($p=0.004$).

### *H. pylori infection and smoking*

*H. pylori* infection was positive in 52.2% and 40.0% of the patients taking LDA and NANSAIDs, respectively. No significant associations were observed between the presence of *H. pylori* infection and the endoscopic findings.

Five patients using LDA were smokers, none of whom presented with open ulcers or hemorrhagic lesions. Open ulcers and hemorrhagic lesions were observed in 13.8% and 10.0% of non-smokers, respectively. Among the patients taking NANSAIDs, 62.5% and 12.5% of the smokers presented with open ulcers and hemorrhagic lesions, respectively, while 26.2% and 31.0% of the non-smokers presented with open ulcers and hemorrhagic lesions, respectively. No significant associations were observed between smoking and the endoscopic findings in either the patients taking LDA or NANSAIDs.

## Discussion

The results of the present study indicate that gastric ulcers and hemorrhagic lesions can develop following the administration of LDA or NANSAIDs in elderly Japanese patients

with severe atrophic gastritis. Only PPIs appeared to be useful for preventing upper gastrointestinal disorders in these patients.

A study of emergency endoscopy found that the prevalence of LDA users among patients with bleeding ulcers increased from 9.9% in 2000-2003 to 18.8% in 2004-2007 (3). In a recent Japanese study, the rates of upper gastrointestinal bleeding and related death declined significantly in association with an increase in PPI use, although the use of LDA and NSAIDs also increased significantly (16). Furthermore, another study showed that continuing aspirin therapy after the development of bleeding ulcers significantly reduces mortality rates among patients with cardiovascular or cerebrovascular diseases, whereas the recurrence of bleeding ulcers did not increase significantly (17). Therefore, in patients with cardiovascular or cerebrovascular diseases, LDA therapy should be continued even if bleeding ulcers are detected. In the present study, more than half of elderly patients taking LDA had open-type atrophic gastritis. However, neither peptic ulcers nor hemorrhagic lesions were observed only in the PPI only users. The suppression of gastric acid with PPI treatment should be considered in order to avoid discontinuing LDA therapy due to the presence of gastrointestinal injury even in elderly patients with atrophic gastritis.

NANSAIDs are frequently prescribed in the field of orthopedics. More than 80% of Japanese orthopedists have experienced patients under NSAID therapy with abdominal symptoms (18). However, orthopedists prescribe prostaglandin analogs and PPIs along with NSAIDs in only 17.4% and 10.8% of patients, respectively (18). A survey conducted in 2007 revealed that only 20% of 409 Japanese physicians prescribed PPI while 54% prescribed MPA along with NSAIDs (19). Before 2010, neither orthopedists nor physicians prescribed PPIs due to medical insurance restrictions. However, both lansoprazole and esomeprazole significantly reduce the recurrence of peptic ulcers in Japanese patients using NANSAIDs. Furthermore, at present, the use of PPIs to prevent peptic ulcer recurrence in patients using NSAIDs is approved by the Japanese health insurance system in patients using NSAIDs (7, 8). The results of our study indicate that PPIs, but not H2RAs, prevent the occurrence of peptic ulcers and hemorrhagic lesions in elderly patients receiving NANSAIDs. Therefore, in elderly patients with atrophic gastritis, the use of PPIs should be considered to prevent gastrointestinal mucosal injury in order to allow the patient to continue NANSAID treatment and maintain their quality of life.

In this study, the dose of H2RA was maximal under the rules of Japanese health insurance system in eight patients taking LDA. Among these patients, one receiving LDA had a hemorrhagic gastric ulcer. Although the maximal dose of H2RA was also used in two-thirds of the 15 patients taking NANSAIDs, the incidence of gastric ulcers did not differ from that observed in the patients not taking any acid suppressive agents. These results would demonstrate that suppressing gastric acid secretion is insufficient to prevent gastric mucosal injury caused by NSAIDs, even if H2RAs are used at high doses.

In the present study, we detected *H. pylori* using only one RUT or stool antigen test, which may have been associated with the lower prevalence of *H. pylori* infection observed in the study population. The lower prevalence of *H. pylori* infection may preclude us from identifying any associations between *H. pylori* infection and the occurrence of gastric mucosal lesions. In elderly patients with severe atrophic gastritis, *H. pylori* colonization is significantly decreased or even absent. Therefore, there is a possibility that many patients evaluated in this study showed false-negative results or had a history of past infection with *H. pylori*. Several Japanese studies have shown that infection of *H. pylori* increases the risk of peptic ulcers and/or upper gastrointestinal bleeding in NSAID users (11, 20, 21). In contrast, a previous observation of long-term NSAID users suggested that *H. pylori* infection is not necessarily a cofactor of hemorrhagic peptic ulcers associated with NSAID use (22). The Japanese guidelines for the management of *H. pylori* infection indicate that eradication therapy would decreases the risk of peptic ulcer bleeding, although the administration of such therapy alone is insufficient in high-risk patients (23). In order to minimize the risk of ulcers or bleeding associated with the use of LDA or NANSAIDs, it is necessary to inhibit acid secretion after *H. pylori* eradication using PPI therapy.

It is known that smoking increases the risk of gastroduodenal ulcers and gastrointestinal bleeding (11, 21). In the present study, no significant associations with smoking were found in the patients taking LDA or NANSAIDs. The low frequency of smokers among our patient population accounts for these results. In this study, 7.5% of men and 0% of women among LDA users and 25.0% of men and 3.3% of women among NANSAIDs users were smokers. These rates are lower than those observed in an investigation by the Japanese Ministry of Health, Labour and Welfare conducted in 2010 (42.6% among men and 12.9% among women). In particular, most of the patients in that study treated with LDA had either cardiovascular or cerebrovascular diseases or had stopped smoking.

In conclusion, the use of PPIs significantly prevents the occurrence of both open ulcers and hemorrhagic lesions compared with gastric mucosal protective drugs and that observed in patients treated without antiulcer therapy. Therefore, our results indicate that the administration of PPI treatment is advisable in order to prevent the discontinuation of LDA or NSAIDs due to the development of gastrointestinal disorders in elderly patients with atrophic gastritis.

**The authors state that they have no Conflict of Interest (COI).**

## *References*

**1.** Kasanuki H. Guidelines for management of anticoagulant and an-

tiplatelet therapy in cardiovascular disease (JCS 2004). Circulation J **68** (Suppl IV): 1153-1219, 2004 (in Japanese).

2. Nakayama M, Iwakiri R, Hara M, et al. Low-dose aspirin is a prominent cause of bleeding ulcers in patients who underwent emergency endoscopy. J Gastroenterol **44**: 912-918, 2009.
3. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Am J Gastroenterol **103**: 2890-2907, 2008.
4. Louthrenoo W, Nilganuwong S, Aksaranugraha S, Asavatanabodee P, Saengnipanthkul S; Thai Study Group. The efficacy, safety and carry-over effect of diacerein in the treatment of painful knee osteoarthritis: a randomised, double-blind, NSAID-controlled study. Osteoarthritis Cartilage **15**: 605-614, 2007.
5. Yeomans ND, Tulassay Z, Juhász L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med **338**: 719-726, 1998.
6. Hawkey CJ, Karrasch JA, Szczepañski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. N Engl J Med **338**: 727-734, 1998.
7. Sugano K, Kontani T, Katsuo S, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term non-steroidal anti-inflammatory drug (NSAID) therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. J Gastroenterol **47**: 540-552, 2012.
8. Sugano K, Kinoshita Y, Miwa H, Takeuchi T. Randomised clinical trial: esomeprazole for the prevention of nonsteroidal anti-inflammatory drug-related peptic ulcers in Japanese patients. Aliment Pharmacol Ther **36**: 115-125, 2012.
9. Sugano K, Matsumoto Y, Itabashi T, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of prospective, multi-center, double-blind, randomized, double-dummy, active-controlled trial. J Gastroenterol **46**: 724-735, 2011.
10. Haruma K, Kamada T, Kawaguchi H, et al. Effect of age and *Helicobacter pylori* infection on gastric acid secretion. J Gastroenterol Hepatol **15**: 277-283, 2000.
11. Uemura N, Sugano K, Hiraishi H, et al; The MAGIC Study Group. Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study. J Gastroenterol (in press).
12. Shimoyama T, Aoki M, Sasaki Y, Matsuzaka M, Nakaji S, Fukuda S. ABC screening for gastric cancer is not applicable in a Japanese population with high prevalence of atrophic gastritis. Gastric Cancer **15**: 331-334, 2012.
13. Lanza FL, Graham DY, Davis RE, Rack MF. Endoscopic comparison of cimetidine and sucralfate for prevention of naproxen-induced acute gastroduodenal injury. Effect of scoring method. Dig Dis Sci **35**: 1494-1499, 1990.
14. Kimura K, Satoh K, Ido K, Taniguchi Y, Takimoto T, Takemoto T. Gastritis in the Japanese stomach. Scand J Gastroenterol **214** (Suppl): 17-20, 1996.
15. Sato M, Shimoyama T, Takahashi R, et al. Characterization and usefulness of stool antigen tests using a monoclonal antibody to *Helicobacter pylori* catalase. J Gastroenterol Hepatol **27** (Suppl 3): 23-28, 2012.
16. Miyamoto M, Haruma K, Okamoto T, Higashi Y, Hidaka T, Manabe N. Continuous proton pump inhibitor treatment decreases upper gastrointestinal bleeding and related death in rural area in Japan. J Gastroenterol Hepatol **27**: 372-377, 2012.
17. Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med **152**: 1-9, 2010.
18. Tsumura H, Tamura I, Tanaka H, et al. Prescription of nonsteroidal anti-inflammatory drugs and co-prescribed drugs for mucosal protection: analysis of the present status based on questionnaires obtained from orthopedists in Japan. Intern Med **46**: 927-931, 2007.
19. Arakawa T, Fujiwara Y, Sollano JD, et al; IGICS study group. A questionnaire-based survey on the prescription of non-steroidal anti-inflammatory drugs by physicians in East Asian countries in 2007. Digestion **79**: 177-185, 2009.
20. Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sáinz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Aliment Pharmacol Ther **16**: 779-786, 2002.
21. Sakamoto C, Sugano K, Ota S, et al. Case-control study on the association of upper gastrointestinal bleeding and nonsteroidal anti-inflammatory drugs in Japan. Eur J Clin Phamacol **62**: 765-772, 2006.
22. Agrawal NM, Campbell DR, Safdi MA, Lukasik NL, Huang B, Haber MM. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multi-center study. Arch Intern Med **160**: 1455-1461, 2000.
23. Asaka M, Kato M, Takahashi S, et al; Japanese Society for Helicobacter Research. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. Helicobacter **15**: 1-20, 2010.