Korean J Gastroenterol Vol. 64 No. 2, 70-75
http://dx.doi.org/10.4166/kjg.2014.64.2.70
pISSN 1598-9992 eISSN 2233-6869

REVIEW ARTICLE

비스테로이드성 소염제 사용자에서의 헬리코박터 파일로리 감염

임윤정, 홍수진[1]
동국대학교 의과대학 내과학교실, 순천향대학교 의과대학 부천병원 내과학교실, 소화기질환연구소[1]

Helicobacter pylori Infection in Nonsteroidal Anti-inflammatory Drug Users

Yun Jeong Lim and Su Jin Hong[1]
Department of Internal Medicine, Dongguk University College of Medicine, Goyang, Digestive Disease Center and Research Institute, Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon[1], Korea

NSAID-induced upper gastrointestinal (GI) damage occurs easily in people with a prior history of complicated or uncomplicated ulcers. Many recent clinical studies have proved the benefit of *Helicobacter pylori* eradication in NSAID users; however, the exact pathophysiologic relationship between concomitant *H. pylori* infection and NSAID use has not yet been fully elucidated. Testing and eradication of *H. pylori* are generally recommended in patients who are at a high risk for NSAID-induced GI damage. However, in high-risk patients, ulcer prophylaxis with proton pump inhibitor or misoprostol is needed even if *H. pylori* has been successfully eradicated. In low-risk patients, it is still questionable whether or not eradication of *H. pylori* can reduce upper GI damage. However, in western countries, due to its cost effectiveness, testing and eradication of *H. pylori* is recommended before starting aspirin or NSAID irrespective of the risk level. In regions with a high prevalence of *H. pylori* infection (>20%), the usefulness of testing and eradication of *H. pylori* has not yet been determined. **(Korean J Gastroenterol 2014;64:70-75)**

Key Words: Anti-inflammatory agents, non-steroidal; *Helicobacter pylori*; Peptic ulcer

INTRODUCTION

NSAIDs and aspirin are prescribed worldwide. Upper gastrointestinal (GI) damage due to these drugs has been the main concern and its complication such as bleeding is a life-threatening condition. The risk of NSAID-induced upper GI damage is increased in the elderly, *Helicobacter pylori* infection, concomitant corticosteroid and anticoagulant use, and prior history of ulcers.[1] Detection and treatment of *H. pylori* is recommended in de novo long-term NSAID users because *H. pylori* seems to act synergistically with NSAID, causing upper GI damage. This report focuses on the pathophysiology, interaction of *H. pylori* with NSAID in NSAID-induced upper GI damage, cost effectiveness of *H. pylori* eradication, and clinical studies on *H. pylori* eradication in NSAID users, in order to propose the best therapeutic guidelines for management of *H. pylori* infection in NSAID users.

MAIN SUBJECTS

1. Pathophysiology

H. pylori and NSAIDs are the most important risk factors in the pathogenesis of gastric mucosal damage. Some studies have shown that the interaction between *H. pylori* and NSAIDs in ulcer development may be independent, synergistic, additive, or antagonistic.[2] In general, the harmful effects of NSAIDs are related to the reduction of prostaglandin synthesis through inhibition of the cyclooxygenase 1 (COX-1)

교신저자: 홍수진, 420-767, 부천시 원미구 조마루로 170, 순천향대학교 부천병원 내과
Correspondence to: Su Jin Hong, Department of Internal Medicine, Soonchunhyang University Hospital Bucheon, 170 Jomaru-ro, Wonmi-gu, Bucheon 420-767, Korea. Tel: +82-32-621-5087, Fax: +82-32-621-5080, E-mail: sjhong@schmc.ac.kr

Financial support: None. Conflict of interest: None.

Table 1. Recommended Guidelines for *Helicobacter pylori* Eradication in NSAID or Aspirin Users

	High risk for peptic ulcer	Low risk for peptic ulcer
Naïve NSAID users	*H. pylori* eradication irrespective of *H. pylori* prevalence	*H. pylori* eradication in population with a low prevalence because of cost effectiveness *H. pylori* eradication in population with a high prevalence is controversial
Chronic NSAID users	*H. pylori* eradication and PPI maintenance	Not recommended
Low-dose aspirin users	*H. pylori* eradication and/or PPI maintenance	Controversial

PPI, proton pump inhibitor.

pathway or direct topical injury.[3] On the other hand, *H. pylori* can damage the mucosa by inducing an inflammatory response. It triggers a substantial inflammatory response in the mucosa, involving cytokines and neutrophils and lymphocyte infiltration.[4] A variety of virulence factors also appear to play a role in the pathogenesis of NSAID-induced upper GI damage. These include the cytotoxin-associated proteins (CagA), vacuolating cytotoxin (VacA), urease and motility.[4]

Thus, NSAID use and *H. pylori* infection may impair the gastric mucosal defense by different mechanisms: *H. pylori* infection induces mucosal inflammation, whereas NSAIDs mainly inhibit synthesis of gastric prostaglandin. Because these two factors induce gastroduodenal injury through different mechanisms, they may have additive effects in terms of producing ulcers. Another theory is gastric adaptation, which is the attenuation of mucosal damage with prolonged NSAID use. Therefore, *H. pylori* is thought to impair the adaptation of gastric mucosa to repeated administration of NSAIDs. *H. pylori* infection and NSAIDs can also induce a synergistic effect on inflammatory cytokines. Both *H. pylori* and NSAIDs induce production of pro-inflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-1β, IL-8, and leukotriene B4, which play a critical role in development of gastroduodenal mucosal injuries, including erosion and ulceration.[3] On the other hand, some studies have reported that the interaction between *H. pylori* and NSAIDs is antagonistic.[5] Some studies emphasized that *H. pylori* enhances gastric mucosal prostaglandin synthesis, whereas NSAIDs suppress it.[5] Although a few studies have demonstrated the protective effect of *H. pylori* against NSAID-induced gastric ulceration, the results of many well-designed clinical trials have strongly demonstrated that *H. pylori* can be an aggravating factor for NSAID-induced upper GI damage.

In summary, both *H. pylori* infection and NSAID use significantly increase the risk of gastric mucosal damage, and these two risk factors affect ulcer formation synergistically, independently, or additively. However, the exact relationship between *H. pylori* infection and NSAID use in patients with gastric mucosal damage has not yet been fully elucidated.

2. Cost effectiveness (Table 1)

The role of *H. pylori* eradication in prevention of GI damage is not well defined, despite the well-established role of proton pump inhibitor (PPI) in NSAID users. Testing for *H. pylori* is recommended only if there is a reasonable option for treatment. Therefore, a definite consensus on screening and eradication of *H. pylori* in NSAID users infected with *H. pylori* according to the level of risk should be determined.

Eradication of *H. pylori* is generally regarded as a cost-effective method for preventing peptic ulcer disease associated with NSAID treatment in Western countries, where the prevalence of *H. pylori* is low ($<20\%$).[1] The American College of Gastroenterology guidelines recommend *H. pylori* screening and treatment with *H. pylori* eradication therapy for patients in need of long-term NSAID therapy regardless of the associated risk factors.[6] Health technology assessments by the National Institute for Health and Clinical Excellence have also demonstrated that *H. pylori* screening/eradication is the most cost-effective strategy.[7]

In Asian countries, which have a higher prevalence of *H. pylori* infection, there is controversy over the general application of screening and eradication of *H. pylori* infection. Some Asian studies have reported on cost-effectiveness analysis of *H. pylori* screening/eradication in NSAID users.[8,9] One Korean study reported that *H. pylori* screening/eradication strategy was found to be less expensive and more effective compared to the no-screening strategy among patients.[8] This finding was more apparent in younger individuals.[8] However, as already known, NSAID-induced toxicity is mainly a concern

in the elderly. A randomized study conducted in China also demonstrated that eradication therapy prior to initiation of long-term NSAID therapy, when compared to no *H. pylori* eradication, resulted in lowering the mean cost per patient and was more effective in prevention of symptomatic ulcers in *H. pylori*-infected patients with a history of peptic ulcer.[9] This study showed that *H. pylori* eradication is beneficial only before starting NSAID treatment, whereas in those who are already long-term NSAID users there is no clear benefit.[10]

In summary, for high-risk individuals in Western and Asian countries, eradication of *H. pylori* is generally regarded as a cost- effective method for prevention of peptic ulcer disease associated with NSAID treatment. In western countries, where the prevalence of *H. pylori* is low, because of its cost effectiveness, *H. pylori* screening/eradication can be recommended in even low-risk patients. However, *H. pylori* screening/eradication in low-risk patients is still questionable in regions with high prevalence of *H. pylori*. *H. pylori* screening/eradication in chronic users of NSAIDs is still optional instead of mandatory, although *H. pylori* eradication can reduce the risk of GI complications in NSAID users.

3. Clinical studies of *H. pylori* eradication in NSAID users

There is a difference in the benefits of eradicating *H. pylori* between naïve users and those receiving chronic long-term NSAID treatment.

Three randomized trials showed that eradication of *H. pylori* before NSAID therapy reduces the occurrence of NSAID-induced peptic ulcers.[11,12] One of the studies assessed patients with a previous history of ulcers.[11] Results of this study showed that the rate of endoscopic ulcers was 12% in the eradication group and 34.4% (relative risk, 0.65; p=0.0085) in the placebo group. The incidence of complicated ulcers was also reduced in the eradication group compared with the placebo group (4.2% *vs.* 27.1%; relative risk, 0.85; p= 0.0026). In another randomized study reported by Labenz et al.,[12] patients with no prior history of ulcers also showed a reduction in the occurrence of ulcers after *H. pylori* eradication. They also reported that both *H. pylori* eradication and PPI were equally effective in reducing the risk of ulcer in naïve NSAID users.[12] However, this is quite controversial, with conflicting results in patients who are already receiving NSAIDs. The meta-analysis by Vergara et al.[13] showed that eradication seems less effective than treatment with a maintenance PPI for prevention of NSAID-induced ulcers. They included 385 patients and compared the eradication group *vs.* the PPI group; five of 196 (2.6%) patients developed a peptic ulcer in the eradication group *vs.* 0 of 189 (0%) patients in the PPI group (OR, 7.43; 95% CI, 1.27-43.6). This result showed that PPI is more effective than *H. pylori* eradication alone in prevention of ulcers in patients who are already receiving NSAIDs. This meta-analysis also showed a significant reduction of the ulcer risk for NSAID-naïve patients (OR, 0.26; 95% CI, 0.14-0.49) but not for patients previously treated with NSAIDs (OR, 0.95; 95% CI, 0.53-1.72).[13]

In several randomized trials in chronic NSAID users, *H. pylori* eradication did not reduce the risk of ulcers or ulcer complications.[14-17] In one randomized placebo-controlled trial, *H. pylori* eradication therapy in patients on long-term NSAID treatment had no beneficial effect on the occurrence of ulcers, erosions, or dyspepsia.[14] On endoscopy, gastroduodenal ulcers were diagnosed in six (4%) and eight (5%) patients in the eradication and placebo groups, respectively (p =0.65). In addition, no significant differences were found in development of gastroduodenal erosions, dyspepsia, or in quality of life.

Another double-blind, placebo-controlled trial showed that eradication of *H. pylori* in patients receiving long-term treatment with NSAIDs did not prevent ulcer development.[15] Endoscopy at 12 weeks showed peptic ulcer development in five (7%; 95% CI, 2-16) patients among those who received triple therapy and in six (9%; 95% CI, 3-18) patients among those who received placebo (p=1.00). No significant difference in development of ulcers was observed between these two groups. However, the common observation in the two previous studies was that the rate of ulcer development was very low, although a larger sample size is required in order to confirm this finding. Helicobacter eradication for lessen prevention (HELP) NSAID study[16] demonstrated that *H. pylori* eradication in long-term users of NSAIDs did not affect the rate of peptic ulcers or dyspepsia over six months. Patients were randomized to receive eradication therapy or omeprazole with placebo antibiotics. Ulcer-free patients continued NSAIDs but did not receive an anti-ulcer treatment for up to six months. No difference in the relapse of dyspeptic symptoms or ulcers was observed between the two groups.[16] Chan et al.[17] examined the risk of recurrent ulcer bleeding. In this

study, *H. pylori*-positive patients received eradication therapy followed by naproxen alone, and naproxen and PPI. In six months, 18.8% of patients receiving eradication therapy, compared to 4.4% of patients receiving omeprazole, had recurrent ulcer bleeding (p=0.005), demonstrating that PPI was superior to eradication therapy in prevention of recurrent bleeding in patients taking NSAIDs except for aspirin.

In summary, in naïve NSAID users, it is clearly beneficial to eradicate *H. pylori*. Primary prophylaxis with *H. pylori* eradication or PPI therapy is equally effective in reducing the risk of ulcer in naïve NSAID users. However, *H. pylori* eradication alone does not reduce the incidence of gastroduodenal ulcers in patients who are already receiving long-term NSAID treatment. *H. pylori* eradication alone is less effective in secondary prevention of recurrent ulcers and ulcer complications in chronic NSAID users, and the use of a gastroprotective agent is mandatory in patients with a history of peptic ulcers.

4. Clinical studies of *H. pylori* eradication in aspirin users

Like NSAIDs, aspirin can also cause upper GI damage. Low-dose aspirin (75-325 mg) is widely used for prevention of cardiovascular or cerebrovascular events in at-risk patients. Even low-dose aspirin is an important predisposing factor for peptic ulcer bleeding and intestinal injuries such as small bowel bleeding.[18] Although the mechanism of ulceration is complex, it appears that reduced production of COX-generated cytoprotective prostaglandins induces ulceration. The risk of bleeding is also increased because of platelet dysfunction. Low-dose aspirin-induced GI complications are sometimes manifested as sudden onset of upper GI bleeding, particularly in the elderly. Aspirin itself can directly damage gastric epithelial cells. However, enteric-coated aspirin that escapes local direct toxicity can cause GI toxicity due to the systemic effect of reduced production of prostaglandins. *H. pylori* infection is associated with an increased risk of uncomplicated and complicated gastroduodenal ulcers in low-dose aspirin users. Eradication of *H. pylori* reduces the risk of complicated and uncomplicated gastroduodenal ulcers associated with low-dose aspirin use.

A systematic review of the impact of *H. pylori* on upper GI bleeding risk in aspirin users indicated that the current data are not sufficient to allow a meta-analysis or to draw firm conclusions.[19] In a case control study by Lanas et al.,[20] *H. pylori* infection was found to be an independent risk factor for ulcer bleeding in patients taking low-dose aspirin (OR, 4.7; 95% CI, 2.0-10.9). One study showed that eradication of *H. pylori* is equivalent to treatment with omeprazole in prevention of recurrent ulcer bleeding in aspirin users.[19] Among patients taking aspirin, the probability of recurrent bleeding during the six-month period was 1.9% for those who received eradication therapy and 0.9% for those who received omeprazole (absolute difference, 1.0%; 95% CI, −1.9-3.9).[18]

In a large-scale, long-term, prospective cohort study, the incidence of ulcer bleeding (per 100 patient-years) in the *H. pylori*-eradicated cohort (0.97; 95% CI, 0.53-1.80) did not differ significantly from that of the average-risk cohort (0.66; 95% CI, 0.38-0.99).[21] In contrast, the study showed that the concomitant use of NSAIDs, steroids, anticoagulants, and other antiplatelet drugs significantly increased the risk of ulcer bleeding. These data indicate that the risk of recurrent ulcer bleeding with low-dose aspirin use can be decreased after *H. pylori* eradication alone.

In summary, although there is no definite relationship between aspirin use and *H. pylori* eradication, several studies reported that *H. pylori* eradication may prevent the long-term occurrence of ulcer bleeding.

5. What is the best option for prevention of upper GI toxicity in high-risk individuals?

A meta-analysis showed that *H. pylori* eradication seems to be less effective than treatment with a maintenance PPI for prevention of NSAID-associated ulcers. A long-term NSAID user with a history of complicated ulcers requires continued PPI treatment as well as eradication treatment, although the long-term incidence of peptic ulcer complications is low after eradication even in the absence of gastroprotective treatment. However, in a long-term user of PPI, there are concerns about its adverse effects and drug interactions.[22-24] PPIs may increase the risk of *Clostridium difficile*-associated diarrhea and fractures. Omeprazole may interfere with the metabolism of clopidogrel, although studies demonstrating that there is no clinical interaction between PPIs and clopidogrel in terms of cardiovascular events have been reported.[22] Long-term PPI administration may promote the progression of *H. Pylori*-related atrophy and precancerous lesion.[25,26] Hence, in long-term PPI users, *H. pylori* eradication is

recommended. It would be reasonable to consider co-administration of PPI and aspirin or NSAID in case the benefit of GI protective effect outweighs the potential harm of long-term PPI use. COX-2 inhibitor and alternative analgesics such as tramadol and acetaminophen could be used in high-risk patients.[27,28] Other antiplatelet agents such as clopidogrel or cilostazol can be substituted for aspirin to prevent cardiovascular or cerebrovascular accidents. However, clopidogrel can also cause upper GI damage in patients with a history of peptic ulcer bleeding.[29,30] Until now, PPI and low-dose aspirin has been the best option for prevention of cardiovascular or cerebrovascular accidents in patients with complicated peptic ulcers.[31]

CONCLUSIONS

H. pylori infection and NSAID use are independent risk factors for development of peptic ulcer disease, and there is an increased risk when both of these factors are present. There is a difference in the benefits of testing and eradication of *H. pylori* between naive users and those receiving long-term NSAID treatment. In naïve users, it is clearly beneficial to eradicate *H. pylori*, whereas in those who are long-term users there is no clear benefit. In Asian countries, where the prevalence of *H. pylori* is high, testing and eradication of *H. pylori* has been recommended only in high-risk patients, including those with complicated or uncomplicated peptic ulcers, contrary to western countries.

REFERENCES

1. Malfertheiner P, Megraud F, O'Morain CA, et al; European Helicobacter Study Group. Management of *Helicobacter pylori* infection–the Maastricht IV/ Florence Consensus Report. Gut 2012;61:646-664.
2. Leung Ki EL, Chan FK. *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug use: eradication, acid-reducing therapy, or both? Clin Gastroenterol Hepatol 2012;10: 831-836.
3. Tang CL, Ye F, Liu W, Pan XL, Qian J, Zhang GX. Eradication of *Helicobacter pylori* infection reduces the incidence of peptic ulcer disease in patients using nonsteroidal anti-inflammatory drugs: a meta-analysis. Helicobacter 2012;17:286-296.
4. Backert S, Clyne M. Pathogenesis of *Helicobacter pylori* infection. Helicobacter 2011;16(Suppl 1):19-25.
5. Hawkey CJ. What consideration should be given to *Helicobacter pylori* in treating nonsteroidal anti-inflammatory drug ulcers? Eur J Gastroenterol Hepatol 2000;12(Suppl 1):S17-S20.
6. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009;104:728-738.
7. Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess 2007;11:iii-iv, 1-164.
8. Song HJ, Kwon JW, Kim N, Park YS. Cost effectiveness associated with *Helicobacter pylori* screening and eradication in patients taking nonsteroidal anti-inflammatory drugs and/or aspirin. Gut Liver 2013;7:182-189.
9. You JH, Lau W, Lee IY, et al. *Helicobacter pylori* eradication prior to initiation of long-term non-steroidal anti-inflammatory drug therapy in Chinese patients-a cost-effectiveness analysis. Int J Clin Pharmacol Ther 2006;44:149-153.
10. Chan FK, Sung JJ, Chung SC, et al. Randomised trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet 1997;350:975-979.
11. Chan FK, To KF, Wu JC, et al. Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomised trial. Lancet 2002;359:9-13.
12. Labenz J, Blum AL, Bolten WW, et al. Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in *Helicobacter pylori* positive patients: a randomised, double blind, placebo controlled, clinical trial. Gut 2002;51: 329-335.
13. Vergara M, Catalán M, Gisbert JP, Calvet X. Meta-analysis: role of *Helicobacter pylori* eradication in the prevention of peptic ulcer in NSAID users. Aliment Pharmacol Ther 2005;21:1411-1418.
14. de Leest HT, Steen KS, Lems WF, et al. Eradication of *Helicobacter pylori* does not reduce the incidence of gastroduodenal ulcers in patients on long-term NSAID treatment: double-blind, randomized, placebo-controlled trial. Helicobacter 2007;12:477-485.
15. Lai KC, Lau CS, Ip WY, et al. Effect of treatment of *Helicobacter pylori* on the prevention of gastroduodenal ulcers in patients receiving long-term NSAIDs: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2003;17:799-805.
16. Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. Helicobacter Eradication for Lesion Prevention. Lancet 1998; 352:1016-1021.
17. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. N Engl J Med 2001;344:967-973.
18. Leung WK, Bjarnason I, Wong VW, Sung JJ, Chan FK. Small bowel enteropathy associated with chronic low-dose aspirin therapy. Lancet 2007;369:614.
19. Fletcher EH, Johnston DE, Fisher CR, Koerner RJ, Newton JL, Gray CS. Systematic review: *Helicobacter pylori* and the risk of

upper gastrointestinal bleeding risk in patients taking aspirin. Aliment Pharmacol Ther 2010;32:831-839.
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 2002;16:779-786.
21. Chan FK, Ching JY, Suen BY, Tse YK, Wu JC, Sung JJ. Effects of *Helicobacter pylori* infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. Gastroenterology 2013;144:528-535.
22. McCarthy DM. Adverse effects of proton pump inhibitor drugs: clues and conclusions. Curr Opin Gastroenterol 2010;26:624-631.
23. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol 2010;8:504-508.
24. Chan FK. Proton-pump inhibitors in peptic ulcer disease. Lancet 2008;372:1198-1200.
25. Chan FK, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet 2010;376:173-179.
26. Hagiwara T, Mukaisho K, Nakayama T, Sugihara H, Hattori T. Long-term proton pump inhibitor administration worsens atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with *Helicobacter pylori*. Gut 2011;60:624-630.
27. Wang X, Tian HJ, Yang HK, Wanyan P, Peng YJ. Meta-analysis: cyclooxygenase-2 inhibitors are no better than nonselective nonsteroidal anti-inflammatory drugs with proton pump inhibitors in regard to gastrointestinal adverse events in osteoarthritis and rheumatoid arthritis. Eur J Gastroenterol Hepatol 2011;23:876-880.
28. Goldstein JL, Chan FK, Lanas A, et al. Haemoglobin decreases in NSAID users over time: an analysis of two large outcome trials. Aliment Pharmacol Ther 2011;34:808-816.
29. Liu CP, Chen WC, Lai KH, et al; Formosa Acid-Related Disease (FARD) Study Group. Esomeprazole alone compared with esomeprazole plus aspirin for the treatment of aspirin-related peptic ulcers. Am J Gastroenterol 2012;107:1022-1029.
30. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005;352:238-244.
31. Almadi MA, Barkun A, Brophy J. Antiplatelet and anticoagulant therapy in patients with gastrointestinal bleeding: an 86-year-old woman with peptic ulcer disease. JAMA 2011;306:2367-2374.