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Abstract

Upper gastrointestinal bleeding is a major adverse event of non-steroidal anti-inflammatory drugs (NSAIDs), and co-administration of proton pump inhibitors and H2 receptor antagonists has been established as a means of preventing such an eff ect. However, the incidence of bleeding associated with NSAID-induced ulcers under conditions where such strong anti-acid agents are used for prevention has yet to be clarified. We aimed to determine the annual incidence of serious upper gastrointestinal ulcer bleeding among Japanese patients in whom NSAIDs were used in our hospital. Before commencing the study, we recommended to all the physicians in our hospital the best method for caring for NSAID users, focusing on the concomitant use of proton pump inhibitors or H2 receptor antagonists. We conducted a cohort study involving 17,270 patients for whom NSAIDs had been newly prescribed. Bleeding from gastric ulcers was observed in 8 of the 17,270 patients using NSAIDs (0.05%). The pooled incidence rate for bleeding was calculated as 2.65 (95% confidence interval, 2.56-2.74) and 1.29 (1.27-1.31) per 1,000 patient years for low-dose aspirin and non-aspirin NSAID users, respectively. None of the bleeding ulcer patients required blood transfusion or were in serious condition. In conclusion, gastric ulcer bleeding occurred in low-dose aspirin or non-aspirin NSAID users, but its incidence was low and outcomes were not serious when adequate preventive measures were taken.

KEYWORDS: hemorrhage, non-steroidal anti-inflammatory drugs, peptic ulcer, prevention

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Original Article

Incidence of Serious Upper Gastrointestinal Bleeding in Patients Taking Non-steroidal Anti-inflammatory Drugs in Japan

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Upper gastrointestinal bleeding is a major adverse event of non-steroidal anti-inflammatory drugs (NSAIDs), and co-administration of proton pump inhibitors and H2 receptor antagonists has been established as a means of preventing such an effect. However, the incidence of bleeding associated with NSAID-induced ulcers under conditions where such strong anti-acid agents are used for prevention has yet to be clarified. We aimed to determine the annual incidence of serious upper gastrointestinal ulcer bleeding among Japanese patients in whom NSAIDs were used in our hospital. Before commencing the study, we recommended to all the physicians in our hospital the best method for caring for NSAID users, focusing on the concomitant use of proton pump inhibitors or H2 receptor antagonists. We conducted a cohort study involving 17,270 patients for whom NSAIDs had been newly prescribed. Bleeding from gastric ulcers was observed in 8 of the 17,270 patients using NSAIDs (0.05%). The pooled incidence rate for bleeding was calculated as 2.65 (95% confidence interval, 2.56–2.74) and 1.29 (1.27–1.31) per 1,000 patient years for low-dose aspirin and non-aspirin NSAID users, respectively. None of the bleeding ulcer patients required blood transfusion or were in serious condition. In conclusion, gastric ulcer bleeding occurred in low-dose aspirin or non-aspirin NSAID users, but its incidence was low and outcomes were not serious when adequate preventive measures were taken.

Key words: hemorrhage, non-steroidal anti-inflammatory drugs, peptic ulcer, prevention

Non-steroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin, are widely used. Their use can, however, cause gastrointestinal injury, and especially gastric or duodenal ulcers. In Western countries, many deaths due to hemorrhage and perforation from NSAID-induced ulcers have been reported [1, 2]. Several methods have been recommended to help prevent serious gastrointestinal complications, *i.e.*, use of cyclooxygenase (COX)-2 inhibitors [3, 4] and/or concomitant proton pump inhibitors (PPIs) [5, 6], high-dose H2 receptor antagonists (H2RAs) [7], or prostaglandins [8], especially in high-risk patients

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such as those with a history of peptic ulcer disease. Unfortunately, the use of COX-2 inhibitors was not authorized in Japan until June 2007. The use of prostaglandins is limited by the occurrence of gastrointestinal adverse effects, particularly diarrhea [9], and marketing authorization has not been granted for the use of high-dose H2RAs in Japan. Accordingly, we took the following steps to prevent serious gastrointestinal complication in our patients using NSAIDs. Arranged as a private meeting, 2 gastroenterologists, a cardiologist, an orthopedist, and 2 pharmacists met to discuss the risk of NSAID-induced ulcers and the adequate management of patients. From that meeting, they emphasized prevention using anti-ulcer agents and on December 2002 recommended concomitant use of PPIs for the prevention of NSAID-induced bleeding ulcers to all physicians working within our hospital (Table 1). However, the efficacy of such methods for preventing NSAID-induced gastroduodenal ulcers and bleeding from these lesions has yet to be clarified in Japan. In the present study, we aimed to determine the annual incidence of serious upper gastrointestinal bleeding among Japanese patients being treated with NSAIDs in our hospital, where steps had been undertaken to prevent serious complications of NSAID use.

Materials and Methods

Following the recommendation to manage NSAID users with concomitant PPIs, the Division for Medical Informatics at our hospital collected monthly data on patients given NSAIDs, and medical records included prior history of ulceration, endoscopic examination and hospitalization. Between January 2003 and December 2004, 18,048 patients (8,588 male and 9,460 female, mean age 51.5 ± 20.7 years) received NSAIDs in our hospital. Indications for NSAIDs included cardiovascular disease, cerebrovascular disease, arthritis, fever, and pain control.

Endoscopic examinations were performed for patients with hematemesis and/or tarry stools, as confirmed by hospital staff, for anemia from a blood examination. Bleeding ulcers were defined in accordance with Forrest's classification [10]. NSAID-induced ulcer was defined by the use of NSAID at the time of onset of ulcer bleeding, regardless of the duration of NSAID use. For patients with NSAID-induced ulcer bleeding, we investigated their characteristics and background, concomitant drug use including anticoagulants other than NSAIDs, and duration from the start of NSAID use to the time of bleeding. *Helicobacter pylori* (*H. pylori)* infection was assessed in these patients by the measurement of serum immunoglobulin G antibodies (Determiner *H. pylori* antibody J; Enteric products, Kyowa Medix, Tokyo, Japan [11], and E plate Eiken *H. pylori* antibody; Eiken Chemical, Tokyo, Japan [12]). The sites of bleeding ulcers were divided into the upper, middle, and lower stomach as well as the duodenum. For multiple ulcers occurring across several sites, the major bleeding lesion was selected. Re-bleeding was determined as recurrent bleeding after initial stabilization. The endpoint of this study was serious ulcer bleeding in need of urgent endoscopic examination using a hemostatic procedure such as clipping of the exposed vessel on the ulcer.

Statistical analysis. The incidence of bleeding associated with NSAID-induced ulcers was calculated

Table 1 Recommendation for the management of NSAID users in our hospital, submitted on December 2002

On prescription of low dose aspirin
First, ask the patient about their history of previous peptic ulcer disease.
If yes, use concomitant use PPIs*.
Even if no, use concomitant use PPIs* or H2RAs in patients with serious underlying disease such as ischemic heart disease, arrhythmia with cardiac valve disease, or cerebral infarction.
On prescription of other NSAIDs
First, ask the patient about their history of previous peptic ulcer disease.
If yes, use concomitant use PPIs*.
Discuss the possibility of adverse events associated with NSAID use, especially gastrointestinal injury, and if necessary, do not hesitate to consult with a gastroenterologist.

*Half-dose PPI is available.

in terms of patient years with a 95% confidence interval.

Results

A final assessment was conducted in June 2005. Patients were divided into the following 2 groups: patients taking low-dose aspirin, and those taking non-aspirin NSAIDs. We categorized the patients who continuously used low-dose aspirin and occasionally used non-aspirin NSAIDs as being in the low-dose aspirin group. A flow diagram in Fig. 1 shows the details of low-dose aspirin users and non-aspirin NSAIDs users focusing on concomitantly used anti-ulcer agents. Six hundred twenty-nine patients were lost to follow-up, 148 died of other diseases: 67 of their original malignant disease, 23 of cardiovascular disease, 21 of cerebrovascular disease, 17 of pneumonia, 10 of liver failure, 7 of renal failure, and 3 in traffic accidents, while 1 patient underwent *H. pylori* eradication therapy 2 days after administration of loxoprofen. We therefore analyzed 17,270 patients (8,105 male and 9,165 female, mean age 50.8 ± 20.7 years). Of these 17,270 patients, 8,815 periodically came for hospital visits, 7,613 returned to our hospital for follow-up after their last NSAID prescription, and 992 were interviewed by telephone. In the 17,270 NSAID users, 1,657 (9.6%) were taking low-dose aspirin and 15,613 were taking non-aspirin NSAIDs (90.4%). The NSAIDs used in this study were low-

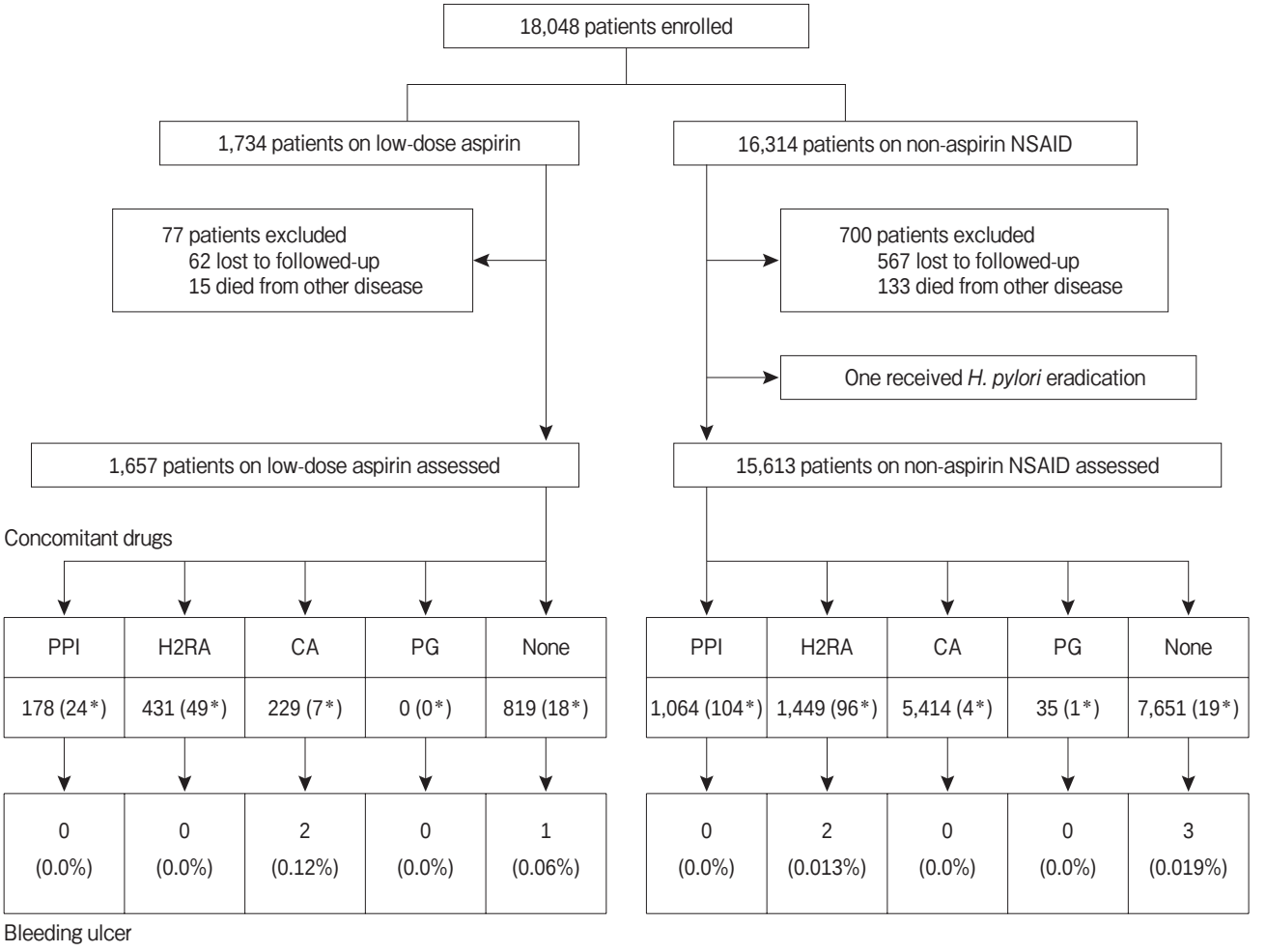

Fig. 1 Flow diagram of patients.
Asterisks represent the number of patients with a history of peptic ulcers.

dose aspirin (80–325 mg; Bufferin 81 mg and Bayaspirin, a 100 mg enteric-coated tablet) and other NSAIDs (loxoprofen, diclofenac sodium, aminosalicylic acid, zaltoprofen, serrapeptase, indomethacin, etodolac, tiaramide, or mefenamic acid) (Table 2). Loxoprofen was the most frequently used NSAID (44.2%).

Concomitantly used anti-ulcer agents included PPIs (lansoprazole 15 or 30 mg, omeprazole 20 mg, or rabeprazole 10 or 20 mg), H2RAs (famotidine 20 mg, ranitidine 150 mg or cimetidine 200 mg), prostaglandin (misoprostol), or cytoprotective anti-ulcer agents (ecabet sodium, sucralfate, teprenone, sodium alginate, polaprezinc, cetraxate, rebamipide, or sulfonic acid). The proportion of PPIs used in this study is shown in Fig. 2, and ordinary-dose lansoprazole (30 mg) or half-dose lansoprazole (15 mg) were the most frequently used PPIs with NSAIDs (32.5% and 30.2%, respectively).

Of the 1,657 patients on low-dose aspirin, 178 (10.7%) were given a PPI concomitantly, 431 (26.0 %) were given an H2RA, 229 (13.8%) were given a cytoprotective anti-ulcer agent, and 819 (49.4%) were not given anti-ulcer agents. Of the 15,613 patients on non-aspirin NSAIDs, 1,064 (6.8%) were given a PPI concomitantly, 1,449 (9.3%) were given an H2RA, 5,414 (24.7%) were given a cytoprotective anti-ulcer agent, and 35 (0.2%) were given prostaglandin, while 7,651 (48.8%) patients were not given any anti-ulcer agents (Fig. 1). Of the 17,270 NSAID users, 322 (1.9%) had a history of peptic ulcer (98 on low-dose aspirin and 224 on non-aspirin NSAIDs), and 128 of these patients were given a PPI (39.8%), 145 were given an H2RA (45.0%), and the remaining 49 were given other anti-ulcer agents or nothing at all (15.2%).

Bleeding gastric ulcers developed in 8 of the 17,270 NSAID users (0.05%), but none of the 8 had a history of a peptic ulcer or of anti-coagulant therapy other than low-dose aspirin. In the 1,657 low-dose aspirin users, when stratified by concomitant anti-ulcer agents, the proportion who developed bleeding ulcers was as follows: none in the PPI or H2RA groups, 0.12% in the cytoprotective anti-ulcer agent group, none in the prostaglandin group, and 0.06% in the no anti-ulcer agent group. In the 15,613 non-aspirin NSAID patients, the proportion who developed bleeding ulcers was as follows: none in the PPI group, 0.013% in the H2RA group, none in the cytoprotective anti-ulcer agent or prostaglandin groups, and 0.019% in the no anti-ulcer agent group. No bleeding ulcers developed in the NSAID users given concomitant PPIs (Fig. 1).

Table 3 shows the characteristics of NSAID users in whom bleeding ulcers developed, and the incidence rate of bleeding ulcers. The 8 patients with bleeding ulcers comprised 3 low-dose aspirin users (2 with cytoprotective agents and 1 without an anti-ulcer agent) and 5 non-aspirin NSAID users (2 with H2RAs and 3 without an anti-ulcer agent). Four of the 8 bleeding ulcers (50.0%) were located in the middle of the stomach, and 3 (37.5%) were located in the lower

Table 2 Details of NSAIDs used in this study

Drug	Case number (%)
Loxoprofen	7,640 (44.2%)
Diclofenac Na	3,187 (18.5%)
Low dose aspirin	1,657 (9.6%)
Aminosalicylic acid	1,609 (9.3%)
Zaltoprofen	908 (5.3%)
Serrapeptase	716 (4.1%)
Indomethacin	568 (3.3%)
Etodolac	563 (3.3%)
Tiaramide	259 (1.5%)
Mefenamic acid	127 (0.7%)
Other	36 (0.2%)
Total	17,270 (100%)

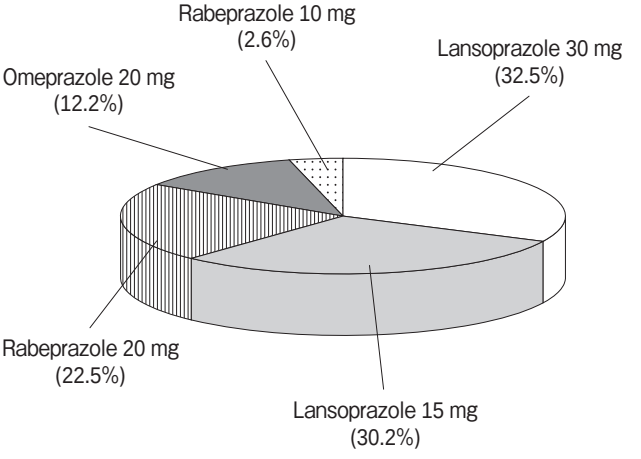

Fig. 2 Details of concomitant PPIs used in this study.

region. We conducted endoscopic hemostasis for all patients, and none of the bleeding ulcer patients required blood transfusion or were in serious condition. Serum anti-*H. pylori* antibody was detected in 5 of the 8 (62.5%) patients with bleeding ulcers. One patient was a low-dose aspirin user, and 4 were non-aspirin NSAID users (Table 3).

As shown in Table 3, the incidence rates for bleeding per 1,000 patient years (95% confidence interval) for all NSAID users, low-dose aspirin users, and non-aspirin NSAID users were 1.60 (1.58–1.61), 2.65 (2.56–2.74), and 1.29 (1.27–1.31), respectively. For the patients taking low-dose aspirin, the incidence rate stratified by concomitantly used anti-ulcer agents was as follows: 0 for the PPI and H2RA groups, 1.72 (1.58–1.86) for the no anti-ulcer agent group, and 14.4 (12.7–16.1) for the cytoprotective anti-ulcer agent group. Because none of the patients taking low-dose aspirin received prostaglandin, we could not calculate the incidence rate. In patients using non-aspirin NSAIDs, the incidence rate was as follows: 0 for the PPI, cytoprotective anti-ulcer agent and prostaglandin groups; 1.57 (1.53–1.61) for the no anti-ulcer agent group; and 5.54 (5.13–5.94) for the H2RA group.

Discussion

To prevent serious adverse events associated with NSAID use, *i.e.,* gastrointestinal bleeding, in December 2002, we recommended to all physicians in our hospital that they manage NSAID users with concomitant PPIs or H2RAs. In the present study, we determined the annual incidence of serious upper gastrointestinal bleeding in 17,270 patients taking newly prescribed NSAIDs in our hospital, after the time of the above recommendation. We found that upper gastrointestinal ulcer bleeding occurred in low-dose aspirin or non-aspirin NSAID users, but its incidence was low and outcomes did not become serious when ade-

Table 3 Characteristics of patients who developed a bleeding ulcer

Concomitant anti-ulcer agent	Low dose aspirin						Non-aspirin NSAID						Total
	none	PPI	H2RA	CA	PG	total	none	PPI	H2RA	CA	PG	total	
No. of patients	1	0	0	2	0	3	3	0	2	0	0	5	8
Sex (male/female)	1/0	0	0	1/1	0	2/1	2/1	0	1/1	0	0	3/2	5/3
Age	61	0	0	55, 86	0	61 (55–86)*	62, 76, 81	0	38, 77	0	0	76 (38–81)*	69 (38–86)*
HP infection	0	0	0	1	0	1	3	0	1	0	0	4	5
Underlying disease													
Cardiovascular disease	1	0	0	1	0	2	0	0	0	0	0	0	2
Cerebrovascular disease	0	0	0	1	0	1	0	0	1	0	0	1	2
Arthritis	0	0	0	0	0	0	2	0	1	0	0	3	3
Others	0	0	0	0	0	0	1	0	0	0	0	1	1
Time until bleeding (day)	480	0	0	63, 94	0	94 (63–480)*	4, 28, 144	0	15, 39	0	0	28 (4–144)*	51 (4–480)*
Site of bleeding ulcer													
Upper stomach	1	0	0	0	0	1	0	0	0	0	0	0	1
Middle stomach	0	0	0	2	0	2	1	0	1	0	0	2	4
Lower stomach	0	0	0	0	0	0	2	0	1	0	0	3	3
Duodenum	0	0	0	0	0	0	0	0	0	0	0	0	0
Forrest's classification	Ib			Ib, IIa			Ia, Ib, IIa		IIa, IIa				
Patient-year of exposure	580.5	107.5	305.5	139	0	1,132.5	1,915.25	267.5	361.25	1,329	7.75	3,880.75	5,013.75
Bleeding events	1	0	0	2	0	3	3	0	2	0	0	5	8
Incidence rate per 1,000 patients/year	1.72	0	0	14.4	NC	2.65	1.57	0	5.54	0	0	1.29	1.60
(95% Confidence Interval)	1.58–1.86	0	0	12.7–16.1	NC	2.56–2.74	1.53–1.61	0	5.13–5.94	0	0	1.27–1.31	1.58–1.61

CA, cytoprotective anti-ulcer agent; NC, not calculated; PG, prostaglandin.
*median (range).

quate measures were taken to prevent bleeding.

The association between NSAID use and the development of peptic ulcers may involve several mechanisms. Aspirin acts locally in the stomach through the release of salicylic acid, which directly injures the gastric epithelial cells and promotes topical inflammation by inducing the recruitment of leukocytes [13]. The systemic gastrotoxic effects of aspirin are related to the inhibition of COX-1, which disrupts prostaglandin production, as seen with other NSAIDs [3, 13]. Because aspirin possesses an anti-platelet function that promotes bleeding complications, in this study we analyzed low-dose aspirin separately from other NSAIDs.

Of the 17,270 patients using low-dose aspirin and non-aspirin NSAIDs, gastric ulcer bleeding was observed in 8 patients (0.05%). The pooled incidence rates in low-dose aspirin and non-aspirin NSAID users for bleeding per 1,000 patient years were calculated as 2.65 (95% confidence interval: 2.56–2.74) and 1.29 (1.27–1.31), respectively. The 2 largest randomized clinical trials [14 ,15] on low-dose aspirin reported an incidence of upper gastrointestinal bleeding of 7 per 1,000 patient-years and 3 per 1,000 patient-years respectively. On the other hand, Serrano *et al.* [16] have reported an incidence of 12 per 1,000 patient-years associated with low-dose aspirin use in patients suffering from cardiovascular disease in a clinical setting, a higher rate than reported previously. In randomized clinical trials, patients with risk factors for gastrointestinal bleeding (*e.g.* ulcer history) are excluded; the incidence rate of 2.65 per 1,000 patient years in our study is similar to that of the randomized trials.

Although many studies have shown that there is a risk of NSAID-associated bleeding peptic ulcers [17, 18], there is very little information available regarding the incidence of non-aspirin NSAID-induced upper gastrointestinal bleeding. Taha *et al.* [19] have recently reported, using 2,002 data from Scotland where PPI or H2RA are commonly prescribed with NSAIDs, and where one-third of the non-aspirin NSAID users were also taking COX-2 selective inhibitors, that the incidences of upper gastrointestinal bleeding in low-dose aspirin and non-aspirin NSAID users were 0.266 and 0.133 per 1,000 patient years, respectively. These figures are approximately one-tenth lower than ours.

A difference between our study and that of Taha *et al.* [19] is that COX-2 selective inhibitors, which have been proven to have a better gastrointestinal safety profile than traditional non-selective NSAIDs, were not granted marketing authorization in Japan until June 2007. Thus, the NSAIDs used in our study were non-selective NSAIDs. The use of COX-2 selective inhibitors may reduce the incidence of upper gastrointestinal bleeding in Japan. However, despite the general decline in gastrointestinal adverse events, there is evidence to suggest that there is an increased relative risk for cardiovascular events associated with COX-2 selective inhibitors [20], and rofecoxib has been withdrawn from the market as a result. Thus, the trend is currently in favor of a non-selective NSAID plus a gastroprotective agent [21] such as PPIs and prostaglandins. We have recommended the concomitant use of PPIs in our hospital, especially for patients with a history of peptic ulcer. Indeed, ulcer bleeding was not observed in patients who were taking concomitant PPIs either with low-dose aspirin or non-aspirin NSAIDs. In contrast, ulcer bleeding developed in 2 of 1,449 patients who were taking non-aspirin NSAID with concomitant H2RAs. There is some concern regarding the interaction between warfarin and PPIs, both of which are metabolized by cytochrome P450 2C19 in the liver [22]. Therefore, we allowed the use of H2RAs, which is supported by a recent report in Japan that normal-dose H2RAs may be effective in the prevention of low-dose aspirin-induced ulcers because of low gastric acidity [23]. Indeed, H2RAs were effective in preventing ulcer bleeding in patients taking low-dose aspirin, but they were not sufficiently effective for non-aspirin NSAID users. Our findings support the use of PPIs or prostaglandins in non-aspirin NSAID users.

Another probable explanation for the higher incidence of ulcer bleeding in our study is the high prevalence of *H. pylori* infection in Japan, especially in older people; more than 80% of people over 50 years of age are infected with the bacterium. *H. pylori* infection [24] is another important cause of peptic ulcer, and it acts synergistically with NSAIDs to induce peptic ulcer development and bleeding. The risk of ulcer bleeding has been shown to be increased 1.8-fold by *H. pylori* infection, 4.85-fold by NSAID use, and 6.1-fold by the presence of both factors, compared to the risk of bleeding among *H. pylori*-neg-

ative subjects not taking NSAIDs [24]. Conflicting results have been reported regarding the effects of *H. pylori* eradication therapy on the prevention of upper gastrointestinal adverse events in NSAID users [25, 26]. Further studies are needed to clarify the preventative effects of eradication therapy on gastric ulcer bleeding in our NSAID patients. However, given the fact that *H. pylori* eradication may reduce the risk of gastric cancer [27, 28], as well as prevent recurrence of peptic ulcers and their bleeding, it should be considered as an appropriate means of preventing upper gastrointestinal adverse events in patients treated with NSAID and selective COX-2 inhibitors with concomitant administration of PPIs, especially in those with a high prevalence of *H. pylori* infection.

In Japanese patients with a previous history of peptic ulcer disease, a trial will soon be underway that will examine whether PPIs can suppress the development of NSAID-induced ulcers. The endpoint for our investigation was NSAID-induced ulcer bleeding. The results of our study suggest that inhibitory effects of PPIs on the development of NSAID-induced ulcers will likely be demonstrated in the aforementioned trial. However, our study also indicates the need for a more effective treatment strategy in the eradication of NSAID-induced peptic ulcer bleeding. In Japan, the clinical use of COX-2 selective inhibitors has now become possible for the prevention of NSAID-induced ulcers. However, in Japan, investigations regarding the efficacy and toxicity profile such as cardiovascular events of COX-2 selective inhibitors have not yet been fully realized. Therefore, further study is necessary regarding the prophylaxis of NSAID-induced ulcers in a Japanese population.

In summary, the objective of our study was not to compare preventive effects against NSAID-induced ulcer bleeding of the drugs concurrently administered with NSAIDs. Rather, our study purpose was to elucidate the incidence of NSAID-induced ulcer bleeding when appropriate prophylactic procedures are practiced by charge physicians in settings where the use of a COX-2 selective inhibitor is not an option. Our study showed that the pooled incidence rate for bleeding is as low as 2.65 and 1.29 per 1,000 patient years for low-dose aspirin and non-aspirin NSAID users, respectively.

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