

Adherence to the preventive strategies for nonsteroidal anti-inflammatory drug- or low-dose aspirin-induced gastrointestinal injuries

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Abstract As the aging of the population advances, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or low-dose aspirin (LDA) is increasing. Their use is accompanied by a risk of serious complications, such as hemorrhage or perforation of the gastrointestinal tract. Therefore, gastroprotective strategies upon the prescription of NSAIDs/LDA are outlined in several guidelines or recommendations. Because all NSAIDs including cyclooxygenase (COX)-2 inhibitors have cardiovascular (CV) toxicity, recent guidelines are based on not only GI risks but also CV risks of NSAID users. Assessment of the adherence to evidence-based guidelines or recommendations for the safe prescription of NSAIDs/LDA in clinical practice is an important issue. Here, we summarize randomized controlled trials (RCTs) on the preventive effects of antisecretory drugs for NSAID- or LDA-induced peptic ulcers. Then, we describe preventive strategies upon the prescription of NSAIDs/LDA outlined in several guidelines or recommendations, and describe studies on adherence and outcomes of adherence to these preventive strategies. Finally, we discuss strategies to increase the adherence rate, and changing pattern of GI events associated with NSAIDs/LDA. In Japan, the preventive strategies upon the prescription of NSAIDs/LDA are expected to spread rapidly because the use of proton pump inhibitors for the prevention of recurrence of NSAID- or LDA-induced

peptic ulcers and the use of COX-2 for the palliation of acute pain were recently approved under the national health insurance system. Further studies on adherence to the preventive strategies and the outcomes of adherence, which include both GI events and CV events, in the Japanese population are required.

Keywords Adherence · Preventive strategy · Nonsteroidal anti-inflammatory drug · Low-dose aspirin · Gastrointestinal injury

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the medicines most frequently prescribed in regular practice, and are used for the suppression of fever, pain, and inflammation in various acute and chronic diseases, such as headache, musculoskeletal pain, osteoarthritis, and rheumatoid arthritis. Low-dose aspirin (LDA), which is another of the most frequently prescribed medicines, is used for secondary prevention of ischemic heart disease and cerebrovascular disease. As the aging of the population advances, the number of patients with chronic pain, cardiovascular disease, or cerebrovascular disease is increasing, as is the number of prescriptions of NSAIDs and/or LDA.

However, it is well known that NSAIDs and LDA cause gastrointestinal mucosal injuries, and the prescriptions of NSAIDs and LDA are accompanied by the risk of serious complications, such as hemorrhage or perforation of the gastrointestinal tract. NSAID/LDA-induced gastrointestinal injuries are not often associated with gastrointestinal symptoms, whereas gastrointestinal symptoms often develop without mucosal injury in NSAID/LDA users. The

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first sign of NSAID/LDA-induced gastrointestinal injuries in asymptomatic individuals may be a life-threatening complication [1]. In addition, it is reported that NSAID- and LDA-induced hemorrhagic ulcers often require additional endoscopic hemostasis treatment, and their treatment is more difficult [2].

Upon the prescription of NSAIDs, gastroprotective strategies are outlined in several guidelines considering gastrointestinal (GI) risk factors that were identified in observational studies. Because it was found that NSAIDs including cyclooxygenase (COX)-2 inhibitors have cardiovascular (CV) toxicity, recent guidelines were developed on the basis of not only GI risks but also CV risks of NSAID users [3–6].

In Japan, guidelines for gastric ulcers were published in 2003, and were revised in 2007 [7]. In addition, peptic ulcer practice guidelines were published by the Japanese Society of Gastroenterology in 2009 [8]. In these guidelines, NSAID users with advanced age and/or peptic ulcer history were considered as high-GI-risk patients, and proton pump inhibitor (PPI) or prostaglandin analogue (PA) therapy is recommended for them for the prevention of NSAID-induced GI injury. In Japan, however, until the use of lansoprazole at 15 mg was approved for the prevention of recurrence of NSAID- or LDA-induced peptic ulcers in July 2010, the practice outlined in the guidelines could not be provided under the national health insurance system. In addition, PA or high-dose histamine type 2-receptor antagonist (H₂RA) therapy is not presently approved for the prevention of NSAID-induced peptic ulcers under the health insurance system in Japan.

The use of COX-2 inhibitors, which can decrease GI toxicity associated with nonselective COX inhibition, is a different strategy from the use of gastroprotective agents for high-GI-risk NSAID users. In Japan, however, the use of celecoxib under the health insurance system had been limited until the indication of celecoxib use was approved in the palliation of acute pain in December 2011.

Recently, reports based on studies of the adherence to preventive strategies for NSAID- or LDA-induced gastrointestinal injury have been accumulating [9–20]. In this review, we focus on the adherence to the preventive strategies for NSAID/LDA-induced gastrointestinal injuries, and the outcome of such adherence.

Preventive effects of PPIs for NSAID-induced peptic ulcers in at-risk patients

A summary of randomized controlled trials (RCTs) on the preventive effects of PPIs for NSAID-induced peptic ulcers in at-risk patients is shown in Table 1. Two studies conducted on patients with a history of peptic ulcers were

reported in Japan in 2012. Both low-dose lansoprazole [21] and esomeprazole [22] were more effective than gefarnate or placebo in reducing the risk of peptic ulcer recurrence, and hazard ratios (HRs) of 0.2510 (95 % confidence interval (CI) 0.1400–0.4499) and 0.09 (95 % CI 0.04–0.20) were reported, respectively.

In a trial of esomeprazole that was conducted outside of Japan, the estimated cumulative proportions of patients developing peptic ulcer at 6 months were reported as 17.0 % (95 % CI 13.2–20.8) with placebo, 5.2 % (95 % CI 3.0–7.4) with esomeprazole at 20 mg, and 4.6 % (95 % CI 2.6–6.6) with esomeprazole at 40 mg in at-risk patients using NSAIDs [23].

Chan et al. [24] reported that omeprazole was superior to the eradication of *Helicobacter pylori* in preventing recurrent upper GI bleeding in a 6-month treatment period in patients who were taking naproxen (omeprazole 4.4 % vs. placebo 24.4 %, $p = 0.005$). In addition, the efficacy of lansoprazole in the prevention of peptic ulcer relapse after eradication of *Helicobacter pylori* in naproxen users was reported by Lai et al. At 8 weeks, significantly fewer patients in the lansoprazole group (4.5 %) than in the group with *Helicobacter pylori* eradication alone (42.9 %) developed recurrence of ulcers [25].

Graham et al. conducted a study that compared PPI with misoprostol in NSAID users without *Helicobacter pylori* infection who had a history of gastric ulcer. The estimated cumulative proportion of patients developing peptic ulcer at 3 months was reported to be 53 % in the placebo group, 21 % in the group with lansoprazole at 15 mg, 17 % in the group with lansoprazole at 30 mg, and 8 % in the group with misoprostol, indicating that lansoprazole is effective for the prevention of NSAID-induced peptic ulcers, but is not superior to misoprostol. However, poor compliance due to adverse events such as diarrhea was reported in the misoprostol group [26].

There have been three studies that compared COX-2 inhibitor with PPI plus nonselective NSAIDs in a high-GI-risk group with a history of bleeding peptic ulcer [27–29]. Chan et al. [27] reported that, in a 6-month treatment period, the proportions of patients who developed upper GI bleeding were 6.4 % in the omeprazole plus diclofenac group and 4.9 % in the celecoxib group ($p = 0.60$). Lai et al. [28] reported similar results using lansoprazole in a 6-month treatment period (lansoprazole plus naproxen 6.3 % vs. celecoxib 3.7 %, $p = 0.37$). Chan et al. [29] also reported that the proportions of patients who developed peptic ulcers confirmed by endoscopy at 6 months were 32.3 % in the omeprazole plus diclofenac group and 24.1 % in the celecoxib group ($p = 0.15$). These studies indicate that COX-2 inhibitor is as effective as PPI co-therapy.

A trial that compared the effect of PPI plus COX-2 inhibitor with that of COX-2 inhibitor was reported in 2007

Table 1 Randomized controlled trials on the preventive effects of PPIs for NSAID-induced peptic ulcers in at-risk patients

References	Treatment (number of patients)	Control (number of patients)	NSAIDs	Patient characteristics	Scheduled endoscopy	Incidence of peptic ulcers	HR (95 % CI)
Japan							
Sugano et al. [21]	Lansoprazole 15 mg (<i>n</i> = 185)	Gefarnate 100 mg (<i>n</i> = 181)	Any	Having a history of peptic ulcers	3, 6, 12 months	3.3 % (LPZ) vs. 18.7 % (GN) (3 months) 5.9 % (LPZ) vs. 28.5 % (GN) (6 months) 12.7 % (LPZ) vs. 36.9 % (GN) (12 months)	0.251 (0.1400–0.4499)
Sugano et al. [22]	Esomeprazole 20 mg (<i>n</i> = 175)	Placebo (<i>n</i> = 168)	Any	Having a history of peptic ulcers	1, 3, 6 months	4.0 % (EPZ) vs. 35.6 % (placebo) (6 months)	0.09 (0.04–0.20)
Overseas							
Chan et al. [24]	Omeprazole 20 mg (<i>n</i> = 75)	HP eradication therapy followed by placebo (<i>n</i> = 75)	Naproxen 1,000 mg	Having a history of gastrointestinal bleeding with HP infection	None	4.4 % (OPZ 20 mg) vs. 18.8 % (eradication) (6 months) (Upper-GI bleeding)	
Graham et al. [26]	Lansoprazole 30 mg (<i>n</i> = 132) Lansoprazole 15 mg (<i>n</i> = 136) Misoprostol 800 µg (<i>n</i> = 134)	Placebo (<i>n</i> = 133)	Any	Having a history of gastric ulcers	1, 2, 3 months	17 % (LPZ 30 mg) vs. 21 % (LPZ 15 mg) vs. 12 % (Misoprostol) vs. 53 % (placebo) (3 months)	
Chan et al. [27]	Omeprazole 20 mg (<i>n</i> = 143)	Celecoxib 400 mg (<i>n</i> = 144)	Diclofenac 150 mg (Omeprazole group) Celecoxib 400 mg (Celecoxib group)	Having a history of bleeding peptic ulcers	None	6.4 % (OPZ + Diclofenac) vs. 4.9 % (Celecoxib) (6 months) (Upper-GI bleeding)	
Lai et al. [25]	Lansoprazole 30 mg (<i>n</i> = 22)	None (<i>n</i> = 21)	Naproxen 750 mg	Having peptic ulcers with HP infection followed by ulcer healing and HP eradication	2 months	4.5 % (LPZ) vs. 42.9 % (control) (2 months)	
Chan et al. [29]	Omeprazole 20 mg (<i>n</i> = 106)	Celecoxib 400 mg (<i>n</i> = 116)	Diclofenac 150 mg (Omeprazole group) Celecoxib 400 mg (Celecoxib group)	Having a history of bleeding peptic ulcers	6 months	32.3 % (OPZ + Diclofenac) vs. 24.1 % (Celecoxib) (6 months) (Bleeding and endoscopic ulcers)	
Lai et al. [28]	Lansoprazole 30 mg (<i>n</i> = 122)	Celecoxib 200 mg (<i>n</i> = 120)	Naproxen 750 mg (Lansoprazole group) Celecoxib 200 mg (Celecoxib group)	Having a history of bleeding peptic ulcers	None	6.3 % (LPZ + Naproxen) vs. 3.7 % (Celecoxib) (6 months) (Upper-GI bleeding)	
Scheiman et al. [23]	Esomeprazole 40 mg (<i>n</i> = 467) Esomeprazole 20 mg (<i>n</i> = 459)	Placebo (<i>n</i> = 452)	nsNSAIDs or COX-2 inhibitor	Older age (≥60) and/or having a history of peptic ulcers	1, 3, 6 months	4.6 % (EPZ 40 mg) vs. 5.2 % (EPZ 20 mg) vs. 17.0 % (placebo) (6 months)	

Table 1 continued

References	Treatment (number of patients)	Control (number of patients)	NSAIDs	Patient characteristics	Scheduled endoscopy	Incidence of peptic ulcers	HR (95 % CI)
Chan et al. [30]	Esomeprazole 20 mg (n = 136)	Placebo (n = 137)	Celecoxib 400 mg	Having a history of bleeding peptic ulcers	None	0 % (EPZ + Celecoxib) vs. 8.9 % (Celecoxib) (13 months) (Upper-GI bleeding)	

LPZ lansoprazole, GN gefaminate, EPZ esomeprazole, OPZ omeprazole, GI gastrointestinal, HR hazard ratio, CI confidence interval, NSAID nonsteroidal anti-inflammatory drug, COX cyclooxygenase, nsNSAID nonselective nonsteroidal anti-inflammatory drug

in a high-GI-risk group with a history of bleeding peptic ulcer. In a 3-month treatment period, significantly fewer patients in the esomeprazole plus celecoxib group (0 %) than in the celecoxib group (8.9 %) developed upper GI bleeding events [30].

Preventive effects of antisecretory drugs for LDA-induced peptic ulcers

A summary of RCT on the preventive effects of antisecretory drugs for LDA-induced peptic ulcers is shown in Table 2. Three studies were conducted using PPIs (low-dose lansoprazole, rabeprazole, and esomeprazole) in patients with a history of peptic ulcers in Japan [31–33], and two studies have so far been published [31, 33]. All of low-dose lansoprazole, rabeprazole, and esomeprazole were more effective than gefarnate or placebo in reducing the risk of peptic ulcer recurrence, and HRs were reported to be 0.099 (95 % CI 0.042–0.230), 0.179 (95 % CI 0.082–0.394), and 0.09 (95 % CI 0.02–0.41), respectively. In the trial of rabeprazole, the cumulative rate of ulcer recurrence at 12 weeks in the rabeprazole 20 mg group (3.7 %) was lower than that in the rabeprazole 10 mg group (7.4 %), although there was no significant difference between them [33].

Two trials of esomeprazole were conducted outside of Japan on at-risk patients using LDA, and significant risk reductions of ulcer development were reported in 2008 and 2011 [34, 35]. Two doses of esomeprazole were used in the trial of 2011, but a dose-dependent preventive effect was not identified [35].

Taha et al. reported the efficacy of a normal dose of H₂RA for the prevention of peptic ulcers and esophagitis in LDA users. At 3 months, the proportions of patients who developed gastric ulcers were 3.4 % in the famotidine 40 mg group and 15.0 % in the placebo group (HR 0.20, 95 % CI 0.09–0.47). In addition, the proportions of patients who developed duodenal ulcers were 0.5 % in the famotidine 40 mg group and 8.5 % in the placebo group (HR 0.05, 95 % CI 0.01–0.40) [36].

Chan et al. [24] reported that omeprazole was not statistically superior to the eradication of *Helicobacter pylori* in preventing recurrent upper GI bleeding in a 6-month treatment period in LDA users (omeprazole 0.9 % vs. placebo 1.9 %). However, the efficacy of lansoprazole in the prevention of peptic ulcer relapse after eradication of *Helicobacter pylori* in LDA users was reported by Lai et al. in 2002. In a 12-month treatment period, significantly fewer patients in the lansoprazole group (1.6 %) than in the group with *Helicobacter pylori* eradication alone (14.8 %) developed recurrence of ulcer complications [37].

Table 2 Randomized controlled trials on the preventive effects of antisecretory drugs for LDA-induced peptic ulcers

References	Treatment (number of patients)	Control (number of patients)	Patient characteristics	Scheduled endoscopy	Incidence of peptic ulcers	HR (95 % CI)
Japan						
Sugano et al. [31]	Lansoprazole 15 mg (<i>n</i> = 226)	Gefarnate 100 mg (<i>n</i> = 235)	Having a history of peptic ulcers	3, 6, 12 months	1.5 % (LPZ) vs. 15.2 % (GN) (3 months) 2.1 % (LPZ) vs. 24.0 % (GN) (6 months) 3.7 % (LPZ) vs. 31.7 % (GN) (12 months)	0.099 (0.042–0.230)
AstraZeneca ^a [32]	Esomeprazole 20 mg (<i>n</i> = 182)	Placebo (<i>n</i> = 182)	Having a history of peptic ulcers	3, 6, 9, 12, 15, 18 months	1.7 % (EPZ) vs. 18.8 % (placebo) (12 months)	0.09 (0.02–0.41)
Sanuki et al. [33]	Rabeprazole 20 mg (<i>n</i> = 89) Rabeprazole 10 mg (<i>n</i> = 87)	Gefarnate 100 mg (<i>n</i> = 85)	Having a history of peptic ulcers	3 months	5.5 % (RPZ) vs. 26.7 % (GN) (3 months) 3.7 % (RPZ 20 mg) 7.4 % (RPZ 10 mg)	0.179 (0.082–0.394)
Overseas						
Chan et al. [24]	Omeprazole 20 mg (<i>n</i> = 125)	HP eradication therapy followed by placebo (<i>n</i> = 125)	Having a history of gastrointestinal bleeding with HP infection	None	0.9 % (OPZ 20 mg) vs. 1.9 % (eradication) (6 months) (Upper-GI bleeding) Statistically not significant	
Lai et al. [37]	Lansoprazole 30 mg (<i>n</i> = 62)	Placebo (<i>n</i> = 61)	Having ulcer complications with HP infection followed by ulcer healing and HP eradication	None	1.6 % (LPZ 30 mg) vs. 14.8 % (placebo) (12 months) (ulcer complications: bleeding, perforation, or obstruction)	
Yeomans et al. [34]	Esomeprazole 20 mg (<i>n</i> = 493)	Placebo (<i>n</i> = 498)	Older age (≥ 60)	2, 6.5 months	1.8 % (EPZ) vs. 6.2 % (control) (6.5 months)	
Taha et al. [36]	Famotidine 40 mg (<i>n</i> = 204)	Placebo (<i>n</i> = 200)	Aged ≥ 18	3 months	3.4 % (Famotidine) vs. 15.0 % (placebo) (GU, 3 months) 0.5 % (Famotidine) vs. 8.5 % (placebo) (DU, 3 months)	0.20 (0.09–0.47) (GU) 0.05 (0.01–0.40) (DU)
Ng et al. [38]	Pantoprazole 20 mg (<i>n</i> = 65)	Famotidine 80 mg (<i>n</i> = 65)	Having a history of upper gastrointestinal bleeding or dyspepsia due to peptic ulcers/erosion	None	0 % (PPZ) vs. 20.0 % (FAM) (12 months) (Dyspeptic or bleeding ulcers/erosion)	
Bhatt et al. [40]	Omeprazole 20 mg (<i>n</i> = 1,876)	Placebo (<i>n</i> = 1,885)	Having acute coronary syndrome or percutaneous coronary intervention receiving aspirin and clopidogrel	None	1.1 % (OPZ) vs. 2.9 % (placebo) (6 months) (GI events: overt or occult bleeding, symptomatic gastroduodenal ulcers or erosion, obstruction, or perforation)	0.34 (0.18–0.63)
Scheiman et al. [35]	Esomeprazole 40 mg (<i>n</i> = 817) Esomeprazole 20 mg (<i>n</i> = 804)	Placebo (<i>n</i> = 805)	Older age (≥ 65), older age (≥ 60) with one or more risk factors, aged ≥ 18 with a history of peptic ulcers	2, 6.5 months	1.5 % (EPZ 40 mg) vs. 1.1 % (EPZ 20 mg) vs. 7.4 % (control) (6.5 months)	0.19 (0.10–0.37) (EPZ 40 mg) 0.14 (0.07–0.30) (EPZ 20 mg)

Table 2 continued

References	Treatment (number of patients)	Control (number of patients)	Patient characteristics	Scheduled endoscopy	Incidence of peptic ulcers	HR (95 % CI)
Ng et al. [39]	Esomeprazole 20 mg (<i>n</i> = 163)	Famotidine 40 mg (<i>n</i> = 148)	Having acute coronary syndrome or ST elevation myocardial infarction receiving aspirin, clopidogrel, and enoxaparin or thrombolytics	None	0.6 % (EPZ, 19.2 weeks) vs. 6.1 % (FAM, 17.6 weeks)	0.095 (0.005–0.504)

LPZ lansoprazole, GN gefarnate, EPZ esomeprazole, RPZ rabeprazole, OPZ omeprazole, PPZ pantoprazole, FAM famotidine, GU gastric ulcer, DU duodenal ulcer, GI gastrointestinal, HR hazard ratio, CI confidence interval, LDA low-dose aspirin

^a Not only the Japanese patients but also the foreign patients were included in this study

Ng et al. [38, 39] reported two trials that compared the effect of PPI with that of H₂RA for the prevention of upper GI complications in LDA users. In a trial reported in 2010, the effect of pantoprazole at 20 mg was compared with that of high-dose famotidine (80 mg) in LDA users with a history of upper GI bleeding or dyspepsia due to peptic ulcer/erosion. In a 12-month treatment period, significantly fewer patients in the pantoprazole group (0 %) than in the famotidine group (20 %) developed dyspeptic or bleeding ulcer/erosion [38]. Furthermore, in another trial reported in 2012, the effect of esomeprazole at 20 mg was compared with that of famotidine at 40 mg in patients with acute coronary syndrome or ST elevation myocardial infarction receiving a combination of aspirin, clopidogrel, and either enoxaparin or thrombolytics. In a mean follow-up period of approximately 5 months, 0.6 % of patients in the esomeprazole group and 6.1 % of patients in the famotidine group developed upper GI bleeding, perforation, or obstruction from ulcer/erosion (HR 0.095, 95 % CI 0.005–0.504) [39].

Bhatt et al. also reported the preventive effect of PPI for GI events in patients receiving dual antiplatelet therapy (aspirin plus clopidogrel). At 6 months, the gastrointestinal event rates were 1.1 % with omeprazole and 2.9 % with placebo (HR 0.34, 95 % CI 0.18–0.63) [40].

Definitions of high-risk NSAID users and recommended preventive strategies in recent guidelines

The definitions of GI risk and CV risk and recommended preventive strategies in recent guidelines on NSAID therapy are shown in Table 3. A history of peptic ulcer complication, a history of peptic ulcer disease, advanced age, concomitant use of anticoagulants, concomitant use of aspirin, concomitant use of corticosteroid, and high-dose NSAIDs are consistently considered as definite GI

risk factors in the guidelines. *Helicobacter pylori* infection, concomitant use of selective serotonin reuptake inhibitors, and concomitant use of bisphosphonate are also identified as GI risk factors in some observational studies [4, 5]. Lanza et al. [5] recently reported guidelines that stratified the GI risk into low- (no risk factors), moderate- (1–2 risk factors), and high-risk groups [multiple (≥ 3) risk factors, or a history of peptic ulcer complications, or concomitant use of corticosteroids or anticoagulants] by the type and number of risk factors. The use of COX-2 plus PPI/misoprostol is consistently recommended for high-GI-risk patients in guidelines, although misoprostol is not recommended, owing to the occurrence of GI side effects [43], in several guidelines [4, 6].

High CV risk is defined as the requirement for LDA for prevention of serious CV events. In several guidelines, an estimated 10-year risk of a fatal CV event of more than 10 % or more than 20 % in patients without established CV disease is considered as a high CV risk [3, 6].

Both COX-2 inhibitors and nonselective NSAIDs share similar CV risks, with an increase in acute myocardial infarction, congestive heart failure, and sudden death [1]. In a recent review on the cardiovascular risk associated with NSAIDs, however, it was suggested that naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk [41]. Therefore, the use of naproxen as an NSAID is consistently recommended for high-CV-risk patients in guidelines.

Adherence to evidence-based guidelines for the safe prescription of NSAIDs

Assessment of the adherence to evidence-based guidelines for the safe prescription of NSAIDs in clinical practice is an important issue. A summary of several studies on

Table 3 Definitions of high-risk NSAID users in recent guidelines

References	GI risk factors	Definition of GI risk	Definition of CV risk	Recommended preventive strategy
Chan et al. [3]	Aged ≥70 Prior upper-GI event Concomitant use of aspirin Concomitant use of anticoagulants Concomitant use of corticosteroids	High: having any GI risk factor Average: no GI risk factors	High: established coronary artery disease, any CV disease that required prophylactic LDA, an estimated 10-year CV risk of greater than 20 % Average: no CV risk factors	High GI risk with High CV risk: avoid NSAID if possible, naproxen + PPI/misoprostol High GI risk with Average CV risk: nsNSAID + PPI/misoprostol or COX-2 inhibitor + PPI/misoprostol Average GI risk with High CV risk: naproxen (if not on aspirin) or naproxen + PPI/misoprostol (if on aspirin) Average GI risk with Low CV risk: nsNSAID alone
Rostom et al. [4]	Aged ≥60–75 History of upper GI symptoms History of peptic ulcer History of GI bleeding High-dose NSAID Multiple NSAIDs Concomitant use of aspirin Concomitant use of anticoagulants Concomitant use of corticosteroids Concomitant use of SSRI Severe RA disability History of cardiovascular disease <i>Helicobacter pylori</i> positive	Very High: having history of GI bleeding High: having any GI risk factor other than history of GI bleeding Low: no GI risk factors	High: requirement for prophylactic LDA Low: no requirement for prophylactic LDA	Very High GI risk: COX-2 inhibitor + PPI High GI risk with High CV risk: avoid NSAID if possible or naproxen + PPI High GI risk with Low CV risk: COX-2 inhibitor alone or nsNSAID + PPI Low GI risk with High CV risk: naproxen + (PPI) Low GI risk with Low CV risk: nsNSAID Eradication of <i>Helicobacter pylori</i> infection if positive
Lanza et al. [5]	History of peptic ulcer complication History of peptic ulcer disease Aged >65 High-dose NSAID Concomitant use of aspirin, corticosteroids or anticoagulants <i>Helicobacter pylori</i> positive	High: 1. history of peptic ulcer complication or anticoagulants 2. concomitant use of corticosteroids 3. multiple (≥3) GI risk factors Moderate: 1-2 GI risk factors Low: no GI risk factors	High: requirement for prophylactic LDA Low: no requirement for prophylactic LDA	High GI risk with High CV risk: avoid NSAID if possible High GI risk with Low CV risk: alternative therapy if possible or COX-2 inhibitor + PPI/misoprostol Moderate GI risk with High CV risk: naproxen + PPI/misoprostol Moderate GI risk with Low CV risk: NSAID + PPI/misoprostol Low GI risk with High CV risk: naproxen + PPI/misoprostol Low GI risk with Low CV risk: NSAID alone Eradication of <i>Helicobacter pylori</i> infection if positive
Burmesster et al. [6]	Previous upper-GI event Aged ≥65 Continuous NSAID use Concomitant use of aspirin, anticoagulants or corticosteroids	Increasing GI risk is related to the number of GI risk factors	High: 10-year risk of fatal CV event ≥ 10 % Low: 10-year risk of fatal CV event <10 %	High GI risk with High CV risk: avoid any NSAID if possible, if needed: diclofenac/naproxen + PPI or COX-2 inhibitor + PPI High GI risk with Low CV risk: ibuprofen/diclofenac + PPI or COX-2 inhibitor + PPI Moderate GI risk with High CV risk: naproxen + PPI Moderate GI risk with Low CV risk: COX-2 inhibitor or nsNSAID + PPI Low GI risk with High CV risk: naproxen + PPI Low GI risk with Low CV risk: nsNSAID alone

GI gastrointestinal, CV cardiovascular, NSAID nonsteroidal anti-inflammatory drug, LDA low-dose aspirin, nsNSAID nonselective nonsteroidal anti-inflammatory drug, COX cyclooxygenase, PPI proton pump inhibitor, SSRI selective serotonin reuptake inhibitor, RA rheumatoid arthritis

adherence to preventive strategies for NSAID-induced gastrointestinal injury is shown in Table 4.

In two retrospective cross-sectional studies in the USA, which were conducted on 76,765 NSAID users from the database of the Tennessee Medicaid program and 707,244 NSAID users from the database of Veterans Affairs, it was shown that the rate of adherence to preventive strategies for NSAID-induced gastrointestinal injury was low [9, 10]. Smalley et al. [9] reported that the proportions of patients who received gastroprotective therapy recommended in the guidelines were 18 % in the NSAID users with a single GI risk factor and 30 % in the NSAID users with two or more GI risk factors. Abraham et al. reported that the rates of adherence to preventive strategies were 27.2 % in the NSAID users with at least 1 GI risk factor, 39.7 % in those with at least 2 GI risk factors, and 41.8 % in those with at least 3 GI risk factors. In addition, it was reported that NSAID prescription ≥ 90 days was a predictor of non-adherence [10].

In the Netherlands, a similar retrospective study on 50,126 NSAID users from the Integrated Primary Care Information database was carried out. In that study, although 43.3 % of NSAID users had GI-associated risk, the rate of adherence to preventive strategies was reported to be 21.9 % in high-risk NSAID users. This rate rose from 6.9 % in 1996 to 39.4 % in 2006 in high-risk NSAID users, but was still at a low level [11].

Recently, a prospective cross-sectional observational study that evaluated both GI risk and CV history in 17,105 osteoarthritis (OA) patients who visited 1,760 doctors throughout the Spanish National Health System in a single day was conducted [12]. Among these OA patients, 93.4 % had more than one GI risk factor, 60.3 % were in the high-GI-risk group, and 32 % had a CV history. Approximately four-fifths of patients received NSAID therapy. Although 25.3 % had both high GI risk and CV history, 74.4 % of this subpopulation received nonselective NSAIDs (94.5 % of them also received gastroprotective agents) or COX-2 inhibitors (82.4 % of them also received gastroprotective agents), which are prescriptions that should be avoided according to the guidelines. In addition, 61.8 % of patients with high GI risk and no CV history were treated with COX-2 inhibitors alone or nonselective NSAIDs plus PPI, although the use of COX-2 inhibitors plus PPI is recommended for those patients in the guidelines. These data suggest that assessments of CV risk and stratified GI risk are not fully implemented in routine clinical practice, and show the difficulty in translating guidelines into clinical practice [12].

On the other hand, over-prescription of PPI and/or COX-2 inhibitors in patients with no risk factors was indicated in studies in both the Netherlands and Spain [11, 12].

Outcomes of adherence to preventive strategies for the safe prescription of NSAIDs

A summary of several recent studies on the outcomes of adherence to preventive strategies for NSAID-induced GI injury is shown in Table 5. Goldstein et al. conducted a retrospective cross-sectional study using a managed-care database in the USA. Of 2,634 NSAID users (nonselective NSAIDs 1,312, COX-2 inhibitors 1,322) receiving concomitant PPI or H₂RA therapy, 463 NSAIDs users (nonselective NSAIDs 161, COX-2 inhibitors 302) developed upper-GI events (peptic ulcer and/or bleeding). Of NSAID users receiving concomitant PPI therapy, 68 % had a PPI coverage rate of 80 % or more over the course of NSAID treatment. A significantly higher risk of upper-GI events was observed in nonselective NSAID users with a PPI coverage rate of less than 80 % than in those with a PPI coverage rate of 80 % or more (OR 2.4, 95 % CI 1.0–5.6), but no such relationship was observed in COX-2 inhibitor users [13].

Abraham et al. conducted a retrospective cohort study to examine the effect of PPI gastroprotection on the risk of NSAID-related upper-GI events in 481,980 NSAID users in the Veterans Affairs database. In that cohort, PPIs were co-prescribed for 19.8 %, and 2,753 upper-GI events occurred in 220,662 person-years of follow-up. HR (95 % CI) of upper-GI events on traditional NSAIDs alone, coxib alone, traditional NSAIDs plus PPI, and coxib plus PPI were estimated to be 1.8 (1.6–2.0), 1.8 (1.5–2.0), 1.1 (0.7–4.6), and 1.1 (0.6–5.2), respectively. In addition, an inverse relationship between PPI coverage rate and HR of upper-GI events was reported [15]. Moreover, Abraham et al. reported a retrospective cohort study of 3,566 NSAID users who had suffered an NSAID-related upper-GI event by using the Veterans Affairs database. Hospitalization occurred in 47.5 % of that cohort, and PPI therapy was associated with a 30 % reduction in hospitalization compared with that in those with no PPI. As a result, although it was associated with higher pharmacy costs, a substantial reduction of five-year medical costs was observed with PPI therapy [17].

Van Soest et al. conducted a nested case-control study by using the Integrated Primary Care Information database in the Netherlands, and reported a strong inverse relationship between the gastroprotective agent coverage rate over the course of NSAID treatment and the risk of upper-GI complications (symptomatic upper-GI ulcer and/or upper-GI bleeding/perforation) in high-GI-risk NSAID users. Compared with NSAID users with a gastroprotective agent coverage rate of ≥ 80 %, NSAID users with gastroprotective agent coverage rates of 20–80 % and of < 20 % had 2.5-fold and 4.0-fold increased risks of upper-GI complications, respectively [14]. Moreover, van Soest et al. [18]

Table 4 Studies on adherence to evidence-based guidelines for the prescription of NSAIDs

References	Database of patients	Number of NSAID users	Study design	Number of NSAID users with GI risk (%)	Adherence to guidelines
Smalley et al. [9]	Tennessee Medicaid program (from January 1999 to June 2000)	76,765 (nsNSAIDs 71,839, Coxibs 4,926)	Retrospective cross-sectional study	Any single GI risk factor: 15,587 (20.3 %) Two or more GI risk factors: 1,692 (2.2 %)	Any single GI risk factor: 18 % (gastroprotectant 9 %, Coxibs 9 %) Two or more GI risk factors: 30 % (gastroprotectant 11 %, Coxibs 19 %)
Abraham et al. [10]	Veterans Affairs database (from January 1999 to December 2002)	707,244	Retrospective cross-sectional study	At least 1 GI risk factors: 303,787 (43.0 %) At least 2 GI risk factors: 30,133 (4.3 %) Three or more GI risk factors: 1,503 (0.2 %)	At least 1 GI risk factor: 27.2 % (gastroprotectant 17.8 %, Coxibs 9.4 %) At least 2 GI risk factors: 39.7 % Three or more GI risk factors: 41.8 %
Valkhoff et al. [11]	Integrated Primary Care Information database (from January 1996 to December 2006)	50,126	Retrospective cross-sectional study	At least 1 GI risk factor: 21,685 (43.3 %)	At least 1 GI risk factors: 21.9 % (gastroprotectant 14.6 %, Coxibs 7.3 %) Adherence to guidelines rose from 6.9 % in 1996 to 39.4 % in 2006
Lanas et al. [12]	Osteoarthritis patients that visited 1,760 doctors in the Spanish National Health System in a single day (25 March 2009)	13,515 (nsNSAIDs 7,916, Coxibs 5,599) 17,105 OA patients	Prospective cross-sectional study	Moderate GI risk: 5,511 (32.2 %) OA patients High GI risk: 10,311 (60.3 %) OA patients CV history positive: 5,256 Low GI risk with CV history positive: 62 Low GI risk with CV history negative: 1,144 Moderate GI risk with CV history positive: 871 Moderate GI risk with CV history negative: 4,373 High GI risk with CV history positive: 4,323 High GI risk with CV history negative: 5,697	Moderate GI risk: 88.7 % (nsNSAIDs + gastroprotectant 49.8 %, Coxibs 18.0 %, Coxib + gastroprotectant 20.9 %) High GI risk: 95.6 % (nsNSAIDs + gastroprotectant 52.0 %, Coxibs 10.3 %, Coxib + gastroprotectant 33.3 %) High GI risk with CV history positive: 25.6 % (no use of NSAIDs) High GI risk with CV history negative: 27.3 % (Coxib + gastroprotectant)

GI gastrointestinal, CV cardiovascular, NSAID nonsteroidal anti-inflammatory drug, nsNSAID nonselective nonsteroidal anti-inflammatory drug

Table 5 Studies on the outcomes of adherence to preventive strategies for NSAID users

References	Database of patients	Number of NSAID users	Study design	Number of NSAID users receiving gastroprotectant	Upper-GI events	Outcome of adherence to gastroprotective therapy	Notes
Goldstein et al. [13]	PharMetrics Integrated Outcomes database (Information collected from approximately 75 commercial managed-care plans) (from January 2000 to December 2002)	92,833 (nsNSAID) 51,370 (Coxibs)	Retrospective cross-sectional study	1,312 (1.4 %) in nsNSAID users 1,322 (2.6 %) in Coxibs users	161 (12.3 %) in nsNSAID users receiving gastroprotectant 302 (22.8 %) in Coxibs users receiving gastroprotectant	Higher risk of upper-GI events in nsNSAID users with adherence rate <80 % of PPI therapy	OR (95 % CI): 2.4 (1.0–5.6) (compared with nsNSAID users with adherence rates of 80 % or more)
Van Soest et al. [14]	Integrated Primary Care Information database (from January 1996 to September 2005)	31,944 (nsNSAID) 2,602 (Coxibs) 3,546 (Diclofenac/Misoprostol, fixed combination)	Nested case-control study	2,735 (8.6 %) in nsNSAID users 359 (13.8 %) in Coxibs users	169 cases in NSAID users (48,046 matched controls in NSAID users)	Strong inverse relationship between adherence to gastroprotectant and the risk of upper-GI complications	OR (95 % CI): 2.5 (1.0–6.7) in nsNSAID users receiving gastroprotectant with adherence 0.2–0.8 OR (95 % CI): 4.0 (1.2–13.0) in nsNSAID users receiving gastroprotectant with adherence <0.2 (compared with nsNSAID users receiving gastroprotectant with adherence rates of 80 % or more)
Abraham et al. [15]	Veterans Affairs database (from January 2000 to December 2002)	440,547 (nsNSAID) 41,433 (Coxibs)	Retrospective cross-sectional study	53,031 (12.0 %) PPI therapy in nsNSAID users 33,124 (79.9 %) PPI therapy in Coxibs users	2,753 upper-GI events in 220,662 person-years of follow-up	Higher risk of upper-GI events in NSAID users with no PPI therapy	OR (95 % CI): 1.8 (1.6–2.0) on NSAID alone OR (95 % CI): 1.8 (1.5–2.0) on Coxib alone OR (95 % CI): 1.1 (0.7–4.6) on NSAID + PPI OR (95 % CI): 1.1 (0.6–5.2) on Coxib + PPI (reference category is no exposure)
Tsumura et al. [16]	NSAID users who had undergone upper gastrointestinal endoscopy (from April 2006 to March 2007)	254 (regular users 128, on-demand users 126)	Retrospective cross-sectional study	25 (31.7 %) PPI or PA therapy in high risk regular NSAID users 16 (24.6 %) PPI or PA therapy in high risk on-demand NSAID users	17 endoscopic GU in regular NSAID users 9 endoscopic GU in on-demand NSAID users	Higher incidence of endoscopic GU in NSAID users with non-adherence to guidelines for the prescription of NSAIDs	OR (95 % CI): 3.0 (2.6–3.7) in NSAID users receiving PPI with adherence >0–20 % OR (95 % CI): 1.8 (1.5–2.3) in NSAID users receiving PPI with adherence 20–40 % OR (95 % CI): 1.8 (1.5–2.2) in NSAID users receiving PPI with adherence 40–60 % OR (95 % CI): 1.3 (1.1–1.6) in NSAID users receiving PPI with adherence 60–80 % OR (95 % CI): 1.1 (1.0–1.3) in NSAID users receiving PPI with adherence 80–100 % (reference category is no exposure to PPI)
Abraham et al. [17]	Veterans Affairs database (from January 2001 to December 2004) Veterans Affairs-Medicare dataset		Retrospective cohort study		3,566 (nsNSAIDs 93.8 %, Coxib 6.2 %) (PPI + 41.8 %, PPI– 58.2 %) (Hospitalized for UGIE 47.5 %)	Higher risk of hospitalization due to upper-GI events, and higher medical cost in NSAID users with no PPI therapy	OR (95 % CI): 1.4 (1.1–1.7) (compared with NSAID users with PPI therapy) Medical cost: \$9,948,738 (PPI +) vs. \$18,686,081 (PPI–) (5-year medical costs)

Table 5 continued

References	Database of patients	Number of NSAID users	Study design	Number of NSAID users receiving gastroprotectant	Upper-GI events	Outcome of adherence to gastroprotective therapy	Notes
Van Soest et al. [18]	General Practice Research Database (UK 1998–2008) Integrated Primary Care Information database (the Netherlands 1996–2007) Health Search/CSD Longitudinal Patient Database (Italy 2000–2007)	618,684 NSAID users 1,107,266 nsNSAID episodes	Nested case-control study	117,307 nsNSAID episodes receiving gastroprotectants	339 cases in nsNSAID plus gastroprotectant cohort (71,380 matched controls in nsNSAID plus gastroprotectant cohort)	Higher risk of upper-GI events in nsNSAID users with adherence rate <80 % of PPI therapy	OR (95 % CI): 1.35 (1.05–1.73) in nsNSAID users receiving gastroprotectant with adherence 0.2–0.8 OR (95 % CI): 2.39 (1.66–3.44) in nsNSAID users receiving gastroprotectant with adherence <0.2 (compared with nsNSAID users receiving gastroprotectant with adherence rates of 80 % or more)

GI gastrointestinal, *CV* cardiovascular, *NSAID* nonsteroidal anti-inflammatory drug, *nsNSAID* nonselective nonsteroidal anti-inflammatory drug, *GU* gastric ulcer, *OR* odds ratio, *CI* confidence interval, *PPI* proton pump inhibitor, *PA* prostaglandin analogue

conducted a similar nested case-control study by using three European databases (from the UK, the Netherlands, and Italy), and a similar relationship between gastroprotective agent coverage rate over the course of NSAID treatment and the risk of upper-GI events was identified.

To date, no large-scale observational studies on the outcomes of adherence to preventive strategies for NSAID-induced GI injury have been reported in Japan. In a retrospective study by Tsumura et al. [16], however, the association between adherence to guidelines for safe prescription of NSAIDs and the incidence of gastric mucosal lesions in NSAID users who had undergone endoscopy was examined, and it was reported that gastric ulcers were more frequently observed in the non-adherence group than in the adherence group (29.6 vs. 4.0 %).

Recommended preventive strategies in at-risk LDA users

The use of LDA for cardioprophylaxis is associated with a 2- to 4-fold increase in the risk of an upper-GI event [42]. As for LDA-induced GI injury, similar factors identified for NSAID-induced GI injury have been suggested as GI risk factors in LDA users [43], although there have been far fewer studies on the risk of LDA therapy. In the ACCF/ACG/AHA 2008 expert consensus document, a history of peptic ulcer complication, a history of peptic ulcer disease, GI bleeding, dual antiplatelet therapy, concomitant use of anticoagulant, concomitant use of corticosteroid, age ≥60, and dyspepsia/gastroesophageal reflux disease (GERD) symptoms were considered as risk factors in LDA users, and PPI therapy was recommended for the prevention of LDA-induced GI injury in at-risk LDA users [42]. Before starting chronic LDA therapy, testing for and eradicating *Helicobacter pylori* in patients with a history of ulcer disease is also recommended [42].

Outcomes of recommended preventive strategies in at-risk LDA users

Regarding the outcomes of preventive strategies in at-risk LDA users, only a few studies have so far been carried out. Ng et al. conducted a retrospective cohort study on the effect of treatment with antisecretory agents for upper-gastrointestinal bleeding in 987 patients with LDA and clopidogrel co-therapy. The risk of upper-GI bleeding was reported to be marginally reduced by H₂RA (OR 0.43, 95 % CI 0.18–0.91) and significantly reduced by PPI (OR 0.04, 95 % CI 0.002–0.21), compared with that in a control group [19]. In addition, Hsiao et al. conducted a population-based, retrospective cohort study of 14,627 antiplatelet

users (12,001 LDA users, 2,627 clopidogrel users) who had a history of hospitalization for GI complications before the initiation of antiplatelet therapy using the Taiwanese National Health Insurance database. The incidences of recurrent hospitalization for major GI complications were reported to be 0.125 per person-year in LDA users and 0.103 per person-year in LDA plus PPI users (HR 0.76, 95 % CI 0.64–0.91), indicating a significant preventive effect of PPI [20].

Strategies to increase adherence rate

Education for physicians is important to raise the rate of adherence to preventive strategies for NSAID/LDA-induced GI injuries. Laine et al. [44] reported the efficacy of an intervention using a written reminder and required written response regarding preventive strategies in NSAID users. After the intervention, the rate of adherence to preventive strategies was improved from 43 to 61 % in NSAID users with GI risk. Among the patients who were not provided gastroprotective agents, however, 42 % of patients did not wish to take them, which indicates that education for patients is also important.

Lanas et al. conducted a prospective, observational, longitudinal study of 1,232 NSAID users with GI-related risk who were co-prescribed NSAID and gastroprotective agents for at least 15 days, and investigated adherence to these agents by telephone interviews. In terms of the reasons for non-adherence to these agents, patients most frequently cited forgetfulness [46]. Taking of NSAIDs/LDA does not necessarily cause GI symptoms, and a lack of symptoms might lead to non-adherence to gastroprotective agents due to forgetfulness, which also highlights the need for patient education.

Furthermore, Lanas et al. [45] reported that short-term treatment and adverse events were associated with poor adherence to preventive strategies. Because PPI and H₂RA have been proved to be effective for preventing GI symptoms as adverse events due to NSAIDs/LDA, antisecretory therapy might help to improve the rate of adherence to NSAIDs/LDA, and might provide a better quality of life via pain control and prevention of thrombosis.

Another strategy to increase the adherence rate is to use drugs in fixed-dose combination. Several drugs including diclofenac/misoprostol, naproxen/lansoprazole, naproxen/esomeprazole, ibuprofen/high-dose famotidine, and LDA/esomeprazole have been developed [46–48].

Changing pattern of GI events associated with NSAIDs/LDA

A decline (from 1.5 to 0.5 %) in the rate of GI-related hospitalization from 1992 to 2000 was reported for

rheumatoid arthritis patients in the USA [49]. A similar result showing a decline (from 2.1 to 1.2 %) in the rate of GI events was observed in a prospective observational study conducted in the Netherlands [50]. In addition, in a population-based study of patients hospitalized because of GI complications in 10 hospitals between 1996 and 2005 in Spain, a clear decreasing trend in upper-GI events and a significant increase in lower-GI events were demonstrated [51]. These trends over time appear to be associated with stricter adherence to preventive strategies for NSAID-induced GI injuries.

Casado Arroyo et al. conducted a prospective observational cohort study on the incidence of GI bleeding in patients on dual antiplatelet therapy who were receiving PPI co-therapy. They reported that lower-GI bleeding occurred more frequently than upper-GI bleeding (74 % lower vs. 26 % upper), and that this changing pattern of bleeding might reflect the success of gastroprotection [52].

Recently, a novel composite endpoint to evaluate the GI effects of NSAIDs through the entire GI tract, namely, clinically significant upper- and lower-GI events (CSULGIE), has been developed by a team of experts [53]. In the CONDOR trial, in which CSULGIE was used as the primary endpoint for evaluation of the GI effects of celecoxib or diclofenac plus omeprazole, 20 (0.9 %, upper GI: 8, lower GI: 12) patients receiving celecoxib and 81 (3.8 %, upper GI: 24, lower GI: 57) patients receiving diclofenac plus omeprazole met the criteria for the primary endpoint in a 6-month treatment period (HR 4.3, 95 % CI 2.6–7.0), indicating that lower-GI events occurred more frequently than upper-GI events, and that the risk of GI events associated with celecoxib was significantly lower than that associated with diclofenac plus omeprazole [54]. In addition, clinically significant anemia (hemoglobin drop ≥ 2 g/dL and/or hematocrit drop ≥ 10 %) was reported to be the most frequent event associated with NSAID-induced lower-GI injuries [54].

Conclusions and perspectives

The efficacy of gastroprotective agents including PPIs for NSAID-induced peptic ulcers has been proved in RCT, and preventive strategies for safe prescription of NSAIDs are outlined in several guidelines. The rate of adherence to preventive strategies was reported to be low in typical practice, but has been increasing recently. Observational studies demonstrated that there is an inverse relationship between adherence to PPI therapy and the risk of upper-GI events in NSAID users. In addition, it is reported that both the risk of hospitalization due to upper-GI events and the medical cost are lower in NSAID users receiving PPI therapy than in those without PPI therapy.

Because all NSAIDs are associated with CV-related risk, recent guidelines for the prescription of NSAIDs require patient assessments of both GI risks and CV risks when making appropriate choices of NSAIDs and gastro-protective agents. However, the assessments of CV risk and stratified GI risk are not fully implemented in routine clinical practice.

The efficacy of antisecretory drugs for LDA-induced peptic ulcers has also been proved in RCT. PPI therapy is recommended for the prevention of LDA-induced peptic ulcers in at-risk groups, and is reported to be associated with lower risks of upper-GI bleeding and hospitalization due to GI complications.

Furthermore, as gastroprotection spreads, the bleeding pattern due to NSAID/LDA-induced GI injuries appears to be changing from upper GI to lower GI. Further studies to identify the risk factors for NSAID/LDA-induced lower-GI injuries are required. As for the safe prescription of NSAIDs/LDA, preventive strategies for lower-GI risk are also required, in addition to CV risk and upper-GI risk.

In Japan, the preventive strategies upon the prescription of NSAIDs/LDA are expected to spread rapidly because the use of proton pump inhibitors for the prevention of recurrence of NSAID- or LDA-induced peptic ulcers and the use of COX-2 for the palliation of acute pain were recently approved under the national health insurance system. Further studies on the adherence to preventive strategies and the outcomes of adherence, which include both GI events and CV events, in the Japanese population are required.

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