

Geographic differences in low-dose aspirin-associated gastroduodenal mucosal injury

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Abstract

Aspirin, even at low doses, has been known to cause upper gastro-intestinal complications, such as gastroduodenal ulcers, despite the definite benefits from its antithrombotic effects. *Helicobacter pylori* (*H. pylori*) is major pathogen responsible for gastroduodenal ulcer

formation. There have been conflicting results about the potential interaction between these two ulcerogenic factors and the geographic areas involved. In Western countries, the prevalence of gastroduodenal ulcers is consistently higher in *H. pylori*-positive low-dose aspirin (LDA) users than in *H. pylori*-negative ones, suggesting that *H. pylori* infection exacerbates LDA-induced gastroduodenal mucosal injury in these geographic areas. Meanwhile, previous studies from Japan have generally reported a similar prevalence of LDA-induced gastroduodenal mucosal injury regardless of the presence of *H. pylori* infection, indicating that the infection is not an overall exacerbating factor for drug-induced injury. *H. pylori* infection could have a synergistic or antagonistic interaction with LDA use in adverse gastroduodenal events depending on gastric acid secretion. It is well-recognized that the net effect of *H. pylori* infection on gastric acid secretion shows considerable geographic variation at the population level. While gastric acid secretion levels were not decreased and were well-preserved in most patients with *H. pylori* infection from Western countries, the majority of Japanese patients with *H. pylori* infection exhibited decreased gastric acid secretion. Such large geographic differences in the net effect of *H. pylori* infection on gastric acid secretion could be at least partly responsible for the geographically distinct interaction between LDA use and *H. pylori* infection on adverse gastroduodenal lesions.

Key words: *Helicobacter pylori*; Low-dose aspirin; Gastric acid secretion; Gastroduodenal ulcers; Geographic variation

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Core tip: There have been conflicting results about the potential interaction between these low-dose aspirin (LDA) use and *Helicobacter pylori* (*H. pylori*) infection on the gastroduodenal ulcers and the geographic areas involved. *H. pylori* infection could have a synergistic

or antagonistic interaction with LDA use in adverse gastroduodenal events depending on gastric acid secretion. Large geographic differences in the net effect of *H. pylori* infection on gastric acid secretion could be at least partly responsible for the geographically distinct interaction between LDA use and *H. pylori* infection on adverse gastroduodenal lesions.

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INTRODUCTION

Use of aspirin at relatively low doses (usually ranging from 75 to 325 mg/d) is now widespread as an anti-thrombotic drug for the prevention of cerebrovascular and cardiovascular diseases^[1-3]. Although the use of low-dose aspirin for primary and secondary prophylaxis is still less prevalent in Asia than in Western countries^[4], aspirin use has also become a common clinical practice among Asian patients with atherothrombotic diseases or multiple cardiovascular risk factors^[5]. However, despite the well-defined benefits from the antithrombotic effects, aspirin, even at a low dose, has been recognized to yield upper gastro-intestinal (GI) complications such as gastroduodenal ulcers^[6]. The identification of high-risk groups for low-dose aspirin (LDA)-induced GI mucosal injury and targeted administration of gastro-protective drugs to the high-risk groups is essential for stabilizing prolonged LDA administration, considering that numerous people are now taking aspirin prophylactically.

Helicobacter pylori (*H. pylori*) is major pathogen responsible for the formation of peptic ulcers in the upper GI tract. Currently, *H. pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs), including LDA, have been identified as the two major causes of peptic ulcers^[7]. It is well-recognized that the *H. pylori* infection rate is still higher in Asian than in Western populations, although the infection rate is decreasing in Asian countries^[8]. Considering that there could be a potential interaction between these two ulcerogenic factors^[9], the prevalence of adverse gastroduodenal mucosal injury in LDA users could be modulated by *H. pylori* infection rates that are different in Asia and Western countries.

As most LDA-induced ulcers are asymptomatic and small, ulcer complications (bleeding and perforation) are the real clinical problems in LDA-induced adverse upper GI events. However, as occurrences of ulcer complications are relatively rare in chronic LDA users^[6], endoscopic ulcers are frequently employed as an endpoint for LDA-induced upper GI injury in clinical studies. A recent review of the available literature

suggested that endoscopic ulcers could be a possible surrogate endpoint for upper GI injury^[10].

In this study, we surveyed the prevalence of gastroduodenal mucosal injury (mainly endoscopic ulcers and erosions) in chronic LDA users from various parts of the world; we compared the incidence between *H. pylori*-positive and -negative subjects; and we then attempted to estimate future trends of LDA-induced upper GI injury in Asia in the post-*H. pylori* era, where infection rates have decreased globally.

DIFFERENCES IN THE PREVALENCE OF LOW-DOSE ASPIRIN-INDUCED GASTRODUODENAL INJURY BETWEEN WESTERN COUNTRIES AND JAPAN

There have been 4 prospective studies reporting the prevalence of endoscopic ulcers/erosions in chronic LDA users in European and North American countries^[11-14]: 2 studies reported the prevalence of endoscopic ulcers^[12,13], 1 study reported the combined prevalence of endoscopic ulcers and/or erosions^[11], and the remaining study reported the prevalence of ulcers as well as ulcers and/or erosions^[14]. Overall, these studies reported a relatively high prevalence of endoscopic ulcers from 10.7% to 39.1% and a high combined prevalence of endoscopic ulcers/erosions (47.8% and 68%). However, because of the widespread availability of endoscopic examinations, there have been a relatively large number of studies, 7 in total, reporting the prevalence of endoscopic ulcers and/or erosions among chronic LDA users in Japan^[15-21]. All studies presented the prevalence of endoscopic ulcers^[15-21], and 4 studies also presented the combined prevalence of endoscopic ulcers and/or erosions^[16,18,19,21]. These studies showed a low prevalence of endoscopic ulcers, from 4% to 20%, although the combined prevalence of endoscopic ulcers and/or erosions was relatively high in the 4 studies, ranging from 29.2% to 57.3%. Taking all the results reported from each geographic area, 101 of 478 of chronic LDA users (21.1%) from Western countries and 266 of 3685 chronic LDA users (7.2%) from Japan suffered from peptic ulcers (Table 1). Thus, although it may be difficult to make a direct comparison due to variations in the study subjects (inclusion and exclusion criteria, proportion of concomitant administration of proton pump inhibitors: PPI) and the study design (*e.g.*, the definition of ulcer, retrospective or prospective sampling) among these studies, there appear to be differences in the prevalence of peptic ulcers among LDA users between Western countries and Japan; that is, the prevalence is likely to be lower in Japan than in Western countries. Meanwhile, the combined prevalence of endoscopic ulcers and/or erosions in LDA users is more comparable between Western countries and Japan (47.8% to 68% vs 29.2% to 57.3%) (Table 1).

Table 1 Differences in the prevalence of endoscopic ulcers and erosions in low-dose aspirin users between Western countries and Japan

Ref.	Countries	Study design	Sample size	Definition of ulcers	Prevalence of ulcers	Prevalence of ulcers and/or erosions
Kordecki <i>et al</i> ^[11] , 1997	Poland	Prospective	96	Greater than 5 mm	-	68.0%
Pilotto <i>et al</i> ^[12] , 2004	Italy	Prospective	245		25.7%	-
Yeomans <i>et al</i> ^[13] , 2005	Australia, United Kingdom, Canada, Spain, Israel	Prospective	187	Greater than 3 mm	10.7%	-
Niv <i>et al</i> ^[14] , 2005		Prospective	46	Greater than 3 mm	39.1%	47.8%
Subtotal			478 ulcers, 142 ulcers and/or erosions		21.1%	61.2%
Shiotani <i>et al</i> ^[15] , 2009	Japan	Prospective	305	Greater than 5 mm	12.4%	-
Nema <i>et al</i> ^[16] , 2009	Japan	Prospective	236	Greater than 5 mm	11.0%	48.4%
Kawai <i>et al</i> ^[17] , 2010	Japan	Prospective	101	Greater than 3 mm	15.8%	-
Tamura <i>et al</i> ^[18] , 2011	Japan	Prospective	150	Greater than 3 mm	4.0%	37.3%
Fujisawa <i>et al</i> ^[19] , 2011	Japan	Retrospective	1213	Greater than 5 mm	5.9%	57.3%
Kawamura <i>et al</i> ^[20] , 2013	Japan	Retrospective	226	Greater than 5 mm	6.2%	-
Uemura <i>et al</i> ^[21] , 2014	Japan	Prospective	1454	Greater than 5 mm	6.5%	29.2%
Subtotal			3685 for ulcers, 3053 for ulcers and/or erosions		7.2%	36.1%

DIVERSE EFFECTS OF *H. PYLORI* INFECTION ON LOW-DOSE ASPIRIN-INDUCED GASTRODUODENAL INJURY IN WESTERN COUNTRIES AND JAPAN

There have been some studies comparing *H. pylori*-negative and -positive subjects in terms of the prevalence of gastroduodenal mucosal injury among chronic LDA users. These comparisons of the presence or absence of *H. pylori* infection within the same study design should be more reliable than those of the prevalence of events among different studies (Table 2).

Four studies from Western countries have reported the prevalence of different outcomes of LDA-related adverse gastroduodenal events (endoscopic ulcers, endoscopic ulcers and/or erosions, and upper GI bleeding) separately in *H. pylori*-negative and -positive subjects^[11,12,22,23]. Feldman *et al*^[22] conducted a prospective comparative study in the United States in which either low-dose aspirin (81 or 325 mg/d) or placebo was administered to 61 healthy volunteers for 45 d. They found that erosive disease from LDA (erosions and/or ulcers) occurred in 50% of *H. pylori*-positive subjects, which was significantly higher than that observed in *H. pylori*-negative subjects (16%) ($P = 0.02$). Lanis *et al*^[23] conducted a case-controlled study in Spanish patients, in which 98 chronic users of LDA with peptic ulcer bleeding were enrolled as cases and 147 chronic users without the upper GI lesions were also enrolled as controls. They found a *H. pylori* infection rate of 90% in the cases, a rate that was significantly higher than in the controls (69%) ($P < 0.01$) and which corresponded to the prevalence of upper GI bleeding in 46% of *H. pylori*-positive subjects

and in 18% of *H. pylori*-negative ones. Similarly, Pilotto *et al*^[12] conducted an observational study in Italy, in which 245 chronic LDA users were enrolled and the prevalence of endoscopic ulcers was evaluated. A significantly higher prevalence of peptic ulcers was observed in *H. pylori*-positive than *H. pylori*-negative subjects (37% vs 16%, $P < 0.01$). In addition, Kordecki *et al*^[11] conducted a prospective observational study in Poland, in which 96 chronic LDA users were enrolled and the prevalence of endoscopic ulcers and/or erosions was evaluated. They found a very high prevalence of the lesions in *H. pylori*-positive patients compared with that in *H. pylori*-negative patients (75% vs 35%, $P < 0.01$). These studies consistently found large differences in the adverse gastroduodenal events between *H. pylori*-negative and -positive LDA users; there is, a significantly higher prevalence in *H. pylori*-positive LDA users than *H. pylori*-negative ones. Thus, *H. pylori* infection clearly exacerbates LDA-induced gastroduodenal mucosal injury in Western countries.

In contrast, the interaction between *H. pylori* infection and LDA use in gastroduodenal mucosal injury is considerably different in Japan than in Western countries. Five studies conducted in Japan investigated the prevalence of endoscopic ulcers in LDA users in the presence and absence of *H. pylori* infection^[15,18,21,24,25]. In a prospective observational study among 305 chronic LDA users, Shiotani *et al*^[15] reported a similar prevalence of endoscopic ulcers between *H. pylori*-positive and -negative subjects (13% vs 12%). Likewise, Iijima *et al*^[25] and Watanabe *et al*^[24] independently reported a similar prevalence of endoscopic ulcers in a relatively small number of LDA users between *H. pylori*-positive and -negative subjects (17% vs 13% and 20% vs 19%, respectively). In

Table 2 Diverse effects of *Helicobacter pylori* infection on low-dose aspirin-induced gastroduodenal injury between Western countries and Japan *n* (%)

Ref.	Countries	Subjects	Study design	Outcomes	Prevalence of outcomes (<i>H. pylori</i> -positive vs -negative)
Kordecki <i>et al</i> ^[11] , 1997	Poland	96 chronic LDA users	Observational	Endoscopic ulcers and erosions	49 (75) vs 11 (35)
Feldman <i>et al</i> ^[22] , 2001	United States	61 healthy volunteers	Interventional study (LDA vs placebo)	Endoscopic ulcers and erosions	11 (50) vs 4 (16)
Lanas <i>et al</i> ^[23] , 2002	Spain	245 chronic LDA users	Case-control	Upper gastrointestinal bleeding	88 (46) vs 10 (18)
Pilotto <i>et al</i> ^[12] , 2004	Italy	245 chronic LDA users	Observational	Endoscopic ulcers	41 (37) vs 21 (16)
Hart <i>et al</i> ^[31] , 2010	Australia, United Kingdom, Canada, Spain,	206 chronic LDA users	Observational	Endoscopic erosions	27 (40) vs 78 (64)
Shiotani <i>et al</i> ^[15] , 2009	Japan	305 chronic LDA users	Observational	Endoscopic ulcers	22 (13) vs 16 (12)
Tamura <i>et al</i> ^[18] , 2011	Japan	150 asymptomatic chronic LDA users	Observational	Endoscopic ulcers	3 (4.4) vs 3 (3.7)
Watanabe <i>et al</i> ^[24] , 2011	Japan	75 chronic LDA users	Observational	Endoscopic ulcers	7 (20) vs 8 (19)
Uemura <i>et al</i> ^[21] , 2014	Japan	1454 chronic LDA users	Observational	Endoscopic ulcers Endoscopic erosions	59 (8.4) vs 35 (4.6) 132 (19) vs 293 (39)
Iijima <i>et al</i> ^[25] , 2015	Japan	100 chronic LDA users	Observational	Endoscopic ulcers	10 (17) vs 5 (13)

H. pylori: *Helicobacter pylori*; LDA: Low-dose aspirin.

addition, Tamura *et al*^[18] reported a relatively low overall prevalence of endoscopic ulcers in 150 asymptomatic chronic LDA users, in which the prevalence was similar between *H. pylori*-positive and -negative subjects (4.5% vs 3.7%). Finally, in a multicenter, large-scale study comprising 1,454 chronic LDA users, Uemura *et al*^[21] demonstrated a higher but non-significant prevalence of endoscopic ulcers in *H. pylori*-positive subjects compared with *H. pylori*-negative ones (8.4% vs 4.6%), in which a multivariate regression analysis indicated a weak but significant positive association between *H. pylori* infection and LDA use for the risk of gastroduodenal ulcers. Nonetheless, this study also demonstrated a much lower prevalence of endoscopic erosions in *H. pylori*-positive subjects compared with *H. pylori*-negative ones (19% vs 39%, $P < 0.0001$). Thus, these studies from Japan generally reported a similar prevalence of LDA-induced gastroduodenal mucosal injury regardless of *H. pylori* infection status^[21].

Consequently, while the difference in the prevalence of LDA-induced gastroduodenal injury between Western countries and Japan was relatively small in *H. pylori*-negative subjects (e.g., 16% to 35% vs 4% to 19%), the difference became larger in *H. pylori*-positive subjects (e.g., 37% to 75% vs 5% to 20%). Thus, it seems that *H. pylori*-positive Japanese subjects are more resistant to LDA-induced gastro-duodenal mucosal injury than *H. pylori*-positive Westerners. Although there has recently been a marked decline in *H. pylori* infection rates among the general Japanese population, especially among the young and middle-aged populations, the infection rate is still high (60%) in the elderly^[26]. Hence, the fact that there are no additional exacerbating effects of *H. pylori* infection on gastroduodenal mucosal injury in Japanese LDA users will likely result in a notably lower prevalence of

gastroduodenal ulcers in Japanese LDA users overall.

The potential diverse effect of PPI administration on the LDA-induced gastroduodenal mucosal injury between *H. pylori*-negative and -positive subjects need to be addressed when comparing the prevalence between the Japanese and Westerners because many of these studies comprised a portion of LDA users with co-treatment of PPI. However, thus far, there has been no consistent conclusion on this issue; that is, although a study reported that PPI treatment is more efficient to suppress LDA-induced adverse gastroduodenal lesions in *H. pylori*-negative subjects than in *H. pylori*-positive ones^[27], another study reported the opposite result^[28], and the remaining studies have indicated that the treatment is efficient to the same degree regardless of the infection status^[29,30]. In addition, the different association of *H. pylori* infection with LDA-induced adverse gastroduodenal lesions between Western and Japanese subjects seems to persist in the three studies in which patients with co-treatment of PPI were excluded^[11,22,25]. Thus, the inclusion of PPI users could have a minimal impact on the geographic difference in LDA-induced adverse gastroduodenal lesions according to *H. pylori* infection status.

It should also be noted that the prevalence of exclusive endoscopic erosions is significantly lower in *H. pylori*-positive subjects than in *H. pylori*-negative ones not only in Japan but also in Western countries. Uemura *et al*^[21] reported a significantly lower prevalence of endoscopic erosions in Japanese *H. pylori*-positive LDA users compared with *H. pylori*-negative ones as described above (19% vs 39%, $P < 0.0001$). Similarly, in a multinational study comprising Canada, Australia, England, and Spain, Hart *et al*^[31] reported a significantly lower prevalence of endoscopic erosions in *H. pylori*-positive LDA users compared with

that in *H. pylori*-negative ones (40% vs 64%, $P = 0.03$). Hence, *H. pylori* infection may play a protective role in the formation of gastroduodenal erosions in LDA users regardless of the geographic area; however, the infection affects the subsequent process of ulcer formation differently in Western countries and Japan. The infection could exacerbate the small, eroded mucosal injury (erosions) initially created by LDA more aggressively in Western countries than in Japan.

ESSENTIAL ROLE OF GASTRIC ACID IN PROVOKING ASPIRIN-INDUCED GASTRODUODENAL MUCOSAL INJURY

Gastric acid plays an essential role as an aggressive factor in upper GI mucosal injury through hydrochloric (HCl) acid back-diffusion into the epithelium, which is also true for aspirin-induced gastric mucosal damage^[7,32]. In a previous animal model study, parenteral aspirin produced extensive gastric mucosal injury in the presence of luminal acid (pH 1.3), but did not induce gastric mucosal injury with the intragastric instillation of saline (pH 3.7), suggesting that aspirin-induced gastric mucosal injury only occurs in the presence of acid^[33]. In addition, we recently clarified that individual gastric acid secretion levels in human chronic LDA users is pivotal in determining the extent of aspirin-induced gastric mucosal injury. Whereas the administration of LDA showed only a modest increase in the risk of gastric mucosal injury in the absence of a sufficient level of gastric acid secretion, the dosing greatly elevated the risk in those with sufficient gastric acid secretion^[34]. Similarly, Nishino *et al.*^[35], using 24-h pH monitoring in healthy volunteers, demonstrated that the extent of LDA-related gastroduodenal mucosal injury is positively associated with gastric acidity. Furthermore, the preventive effect of a potent inhibitor of gastric acid secretion, a PPI, on aspirin-induced gastroduodenal mucosal injury also supports this point of view^[27-30]. Taken together, these studies in an animal model and in humans indicated an essential role of gastric acid in provoking LDA-induced gastroduodenal mucosal injury.

BIPHASIC EFFECT OF *H. PYLORI* INFECTION ON LOW-DOSE ASPIRIN-INDUCED GASTRODUODENAL INJURY

H. pylori infection is known to diversely affect gastric acid secretion; that is, infection could yield an elevation, decline, or no change in gastric acid secretion according to the distribution of inflammation or atrophy within the stomach^[36]. Given the essential role of gastric acid in the formation of LDA-induced gastroduodenal injury, such diverse effects of *H. pylori* infection on the gastric acid secretion could modulate

the interaction between *H. pylori* infection and LDA use on adverse gastroduodenal lesions.

H. pylori infection may be synergistic with LDA use in adverse gastroduodenal events through several plausible mechanisms. NSAIDs/aspirin reduce mucosal capillary blood flow and cause ischemic changes by inducing the adhesion of neutrophils to endothelial cells, leading to neutrophil-mediated tissue injury^[7,37,38]. Hence, as the neutrophil chemotaxis induced by *H. pylori* infection in the gastric mucosa may exacerbate gastric mucosal injury in aspirin users as shown in a previous animal model study that indicated that although *H. pylori* infection potentiated aspirin-induced gastric mucosal injury, pre-treatment with anti-neutrophil serum attenuated the synergistic action^[39]. Otherwise, *H. pylori* infection could potentiate LDA-induced gastric mucosal injury by hampering the gastric adaptation to the agent. The normal gastric mucosa could become more tolerant or adapted in response to the repeated administration of noxious agents such as aspirin^[40,41]. A previous study demonstrated that the presence of *H. pylori* infection significantly impaired such an adaptive response to aspirin, and its eradication restored the response^[42]. Thus, *H. pylori* infection and aspirin could synergistically potentiate the gastric mucosal injury.

However, such a synergistic interaction could only occur in the presence of sufficient amounts of gastric acid. In the absence of sufficient amounts of gastric acid, this potential synergistic effect could be completely offset, and the *H. pylori* infection could even repress aspirin-induced gastric mucosal injury. Our recent study noted this biphasic effect of *H. pylori* infection on LDA-induced gastric injury^[43]. In that study, we determined *H. pylori* status and individual gastric acid secretion levels in 93 chronic LDA users, and we classified the drug users into 3 groups: *H. pylori*-negative subjects, *H. pylori*-positive non-hyosecretors, and *H. pylori*-positive hyosecretors. Consequently, setting *H. pylori*-negative patients as the reference, *H. pylori* infection was positively associated with intensive gastric mucosal injury among non-hyosecretors with an odds ratio (OR) of 4.2 and 95%CI of 1.1-17.1, whereas the infection was negatively associated with the injury among hyosecretors with an OR of 0.3 and a 95%CI of 0.1-0.9^[43]. These findings were supported by those of another study conducted by Shiotani *et al.*^[15] in Japanese patients, which demonstrated that corpus atrophy serologically defined by the serum pepsinogen value, a well-known surrogate for hypochlorhydria, decreased the risk of aspirin-induced ulcers.

It is well-recognized that the net effect of *H. pylori* infection on gastric acid secretion shows considerable geographic variation at the population level. Gastric acid secretion levels were not decreased and were well-preserved in most patients with *H. pylori* infection from Western countries^[44-46]. In contrast, the majority

of Japanese patients with *H. pylori* infection exhibited decreased gastric acid secretion^[47,48], and the overall gastric acid secretion in *H. pylori*-positive Japanese subjects was half of that in *H. pylori*-negative ones^[49]. In addition, gastric acid secretion further declines with age in the *H. pylori*-positive Japanese subjects with the advance of gastric atrophic changes^[47]. Accordingly, gastric acid secretion is profoundly decreased in *H. pylori*-positive Japanese subjects, especially in the elderly, who are frequently administered anti-thrombotic therapy with LDA for the prevention of cerebrovascular and cardiovascular diseases. Thus, such a large geographic difference in the influences of *H. pylori* infection on gastric acid secretion could at least partly account for the different prevalence of adverse gastroduodenal lesions observed in *H. pylori*-positive LDA users in Western countries and Japan.

HOMOLOGY OF *H. PYLORI*-INDUCED GASTRITIS IN JAPAN AND OTHER EAST ASIAN COUNTRIES

Thus far, there have been no reports from other Asian countries regarding either the prevalence of gastroduodenal ulcers in LDA users and the presence or absence of *H. pylori* infection or the effects of *H. pylori* infection on gastric acid secretion. The distribution of inflammation and mucosal atrophy determine the outcomes of *H. pylori* infection on gastric acid secretion^[36,50]. There are some studies evaluating international comparisons of histological findings in *H. pylori*-positive subjects. In comparisons among 4 Asian countries (Japan, China, Thailand, and Vietnam), histological findings were similar between *H. pylori*-positive Chinese and Japanese subjects, which were different from those of Thai and Vietnamese subjects^[51,52]. Another study indicated that the pattern of *H. pylori* infection-induced gastritis may differ between Korean and Japanese patients compared with Americans^[53]. These results indicated histological homology in *H. pylori*-infected subjects among East Asian countries. This notion is also supported by the fact that a high prevalence of non-cardiac gastric carcinoma is common in *H. pylori*-positive subjects from East Asian countries^[54]. The strain diversity of *H. pylori* could be responsible for the histological homology in East Asia. For example, *H. pylori*-related virulence factor cytotoxin-associated antigen A (CagA), particularly the more virulent East Asian subtype, is highly prevalent in East Asian countries^[55]. Hence, gastric acid secretion should supposedly decrease in the presence of the infection in other East Asian populations, such as in Japan, implying that LDA-induced gastroduodenal mucosal injury could be suppressed in *H. pylori*-positive aspirin users in these geographic areas.

IDENTIFICATION OF HIGH-RISK GROUPS OF ADVERSE GASTRODUODENAL EVENTS AMONG *H. PYLORI*-POSITIVE LDA USERS

The vulnerability of chronic LDA-users to the drug-induced gastric mucosal injury seemed to be largely defined by the individual gastric acid secretion level of *H. pylori*-positive patients. Accordingly, a *H. pylori*-positive gastric hypersecretor could be classified in a high-risk group for adverse gastroduodenal events; hence, these patients should be assigned to concomitant treatment with PPIs even without conventional risk factors (e.g., a history of peptic ulcers) when physicians commence prolonged LDA therapy. Otherwise, eradication therapy might lead to significant long-term preventive effects on LDA-induced gastric mucosal injury among *H. pylori*-positive chronic LDA users with gastric hypersecretion, as in patients with ulcer history^[56,57]. The extraction of high-risk groups from the general *H. pylori*-positive LDA users by estimating the individual's gastric acid secretion level would be particularly effective in a country such as Japan where the *H. pylori* infection rate is high in the elderly^[26] and the majority of *H. pylori*-positive subjects exhibit decreased acid secretion levels^[48-50].

Gastric acid secretion levels can be roughly estimated by simple serum measurements of pepsinogen concentrations^[58,59], and we found that *H. pylori*-positive LDA users with a pepsinogen (PG) I/II ratio of 3.3 or higher, a surrogate marker of gastric hypersecretion, had an extremely high risk for drug-induced gastropathy^[25]. Moreover, endoscopic findings could also provide some useful information for estimating gastric acid secretion levels. We reported that among non-LDA users, erosion and hematin formation in the antrum could be useful markers for gastric hypersecretors; in particular, the co-existence of these findings identified *H. pylori*-positive gastric hypersecretors with a specificity of 95%^[60]. Accordingly, the implementation of these tests for *H. pylori*-positive patients before the commencement of prolonged LDA treatment would be helpful to identify a high-risk group of adverse gastroduodenal events.

FUTURE TREND OF LOW-DOSE ASPIRIN-INDUCED GASTRODUODENAL INJURY IN ASIA

Aspirin is one of the most effective antiplatelet agents for long-term vascular disease prevention in those with a high risk of cardio/cerebrovascular diseases^[61], and the administration of aspirin for prevention is consistently recommended by international guidelines^[1-3]. The mortality and morbidity of acute

coronary diseases are increasing in Asia, and the dominant pattern of cerebrovascular disease in Asia has shifted from hemorrhagic stroke to ischemic stroke^[4]. Hence, although prophylactic aspirin is still underutilized in Asian countries and is at present prescribed at a 20% to 30% lower rate than in Western countries^[4,5], it will be expected to further increase in Asia in the near future. In addition, the accumulating evidence supporting the benefits of aspirin in the prevention of colorectal and other cancers^[62,63] will likely enhance the demand for aspirin use worldwide further.

In recent decades, the *H. pylori* infection rate has declined in Asian countries, especially among the younger populations; furthermore, the infection rate is likely to also substantially decrease in the elderly^[8]. Accompanying this change, the prevalence of ordinary *H. pylori*-positive peptic ulcer is declining in Japan^[64]. However, during this period, the proportion of drug (mainly NSAIDs/aspirin)-induced ulcers has increased^[65,66]. Considering that *H. pylori* infection could play a protective role in LDA-induced gastroduodenal mucosal injury in the majority of infected subjects in East Asia, we believe that the prevalence of LDA-induced ulcer will not decrease despite the declining rate of *H. pylori* infection. Rather, the increasing use of the drug is likely to increase the prevalence of LDA-induced ulcers in Asian countries. Currently, because *H. pylori* infection could have diverse effects on the LDA-induced adverse gastroduodenal lesions, especially in Eastern Asia, appropriate measures to extract high-risk groups among these patients and administer the concomitant gastro-protective drugs to the targeted subjects need to be established.

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