

Gastrointestinal Safety of Low-Dose Aspirin

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Abstract

The cardioprotective benefits of aspirin support the use of low-dose regimens for primary and secondary prevention of cardiovascular disease. However, these cardioprotective benefits must often be balanced against the well-documented gastrointestinal (GI) effects of aspirin. Recent research suggests that the GI effects of aspirin may be dose-dependent; however, even low-dose aspirin can cause significant GI sequelae. Similarly, the use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2 inhibitors, has also been shown to increase the risk of GI effects, and the concomitant use of aspirin and nonaspirin NSAIDs can significantly increase the risk of GI ulceration and bleeding. Therefore, clinicians should use the lowest effective dose of aspirin (ie, 75 to 150 mg/day) that affords cardiovascular benefits without increasing the risk of GI effects. Low-dose aspirin therapy can complicate the concurrent use of analgesics. When an analgesic is needed in addition to aspirin, concomitant use of aspirin and nonaspirin NSAIDs or COX-2 inhibitors should be used with caution, or with concomitant gastroprotective agents, to minimize the risk of GI complications. In contrast, because acetaminophen does not cause GI irritation, it should therefore be considered when an analgesic is needed.

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The cardioprotective benefits of aspirin therapy are well documented and do not appear to be dose-related. For example, a dose of 75 mg/day aspirin reduces thrombotic cardiovascular events as much as higher doses, such as 300 mg.¹ As a result, prophylactic low-dose aspirin therapy is now frequently used for the primary or secondary preven-

tion of cardiovascular disease (CVD). Of concern are the well-documented gastrointestinal (GI) effects of aspirin, including gastropathy, gastric and duodenal hemorrhage, and erosion and ulcer, especially with daily dosages of aspirin >325 mg. The risk of GI effects has been shown to rise with increasing dose^{2,3} and with regular³ or recent use.⁴ Furthermore, in contrast to popular belief, the use of buffered or enteric-coated aspirin does not minimize the risk of upper GI bleeding.^{5,6} Although the risks for GI effects may be reduced with low-dose aspirin, they are not eliminated. Several studies suggest that even low doses may still be associated with GI damage.^{3,7-9}

Prescribed or over-the-counter (OTC) nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) also have been shown to increase the risk for GI bleeding, and, when combined with aspirin, substantially increase such GI bleeding risk compared with either aspirin or nonaspirin NSAIDs alone. Although the risk for GI bleeding from NSAIDs is considerably lower with the use of cyclooxygenase (COX)-2 inhibitors, the GI protective effects of COX-2 inhibitors are significantly diminished when aspirin is taken concomitantly.¹⁰ Therefore, when low-dose aspirin therapy is indicated for the primary or secondary prevention of CVD and additional agents are needed for analgesic purposes, patients should be warned about the increased risks for GI side effects associated with the use of aspirin in combination with NSAIDs or COX-2 inhibitors and should be advised to use alternative analgesics, such as acetaminophen.

Table 1. Mechanisms of Aspirin-Induced Gastric Mucosal Injury

■ Alterations in gastric mucosal barrier
■ ↓ Prostaglandin synthesis
■ ↓ Mucus and bicarbonate secretion
■ ↓ Gastric cellular energy
■ ↓ Submucosal blood flow
■ ↓ Mucosal adenosine triphosphate
■ ↓ Cell turnover
■ ↓ Platelet function (irreversible)

Adapted with permission from Ivey KJ.¹¹

Mechanism of Aspirin-Induced Gastric Mucosal Injury

NSAID use, including aspirin therapy, induces GI effects ranging from an asymptomatic constellation of internal changes in the stomach mucosal lining, visible only upon endoscopic evaluation, to symptomatic gastroduodenal lesions and ulcers that may lead to acute or chronic bleeding.¹¹

Although the risk for GI bleeding from NSAIDs is considerably lower with the use of COX-2 inhibitors, the GI protective effects of COX-2 inhibitors are significantly diminished when aspirin is taken concomitantly.

The mechanisms by which aspirin damages the gastric mucosa include alterations to the gastric mucosal barrier, interference with prostaglandin synthesis, reduction in gastric mucus and bicarbonate secretion, and decreases in gastric cellular energy and cell turnover rate (Table 1).¹¹ The gastric mucosal barrier prevents the absorption of hydrogen ions, which accounts for the concentration of acid

within the stomach. Aspirin disrupts the gastric mucosal barrier, thereby facilitating an increase in back-diffusion of hydrogen ions into the gastric mucosa, which in turn injures cells and damages capillaries and venules. The effect of aspirin on the gastric mucosa depends on the pH level of the solution into which the aspirin is introduced. When aspirin is introduced into an acidic medium, 90% of this drug remains in a nonionized form, resulting in a high degree of gastric absorption.¹¹

When found in the stomach, prostaglandins inhibit acid secretion and provide protection against mucosal injury. Aspirin interferes with the synthesis of prostaglandin, which is mediated by the inhibition of the COX enzyme. In addition to these effects, aspirin causes an irreversible decrease in platelet function (ie, related to COX inhibition at the level of the platelet).¹¹

Similar mechanisms are believed to cause the GI effects associated with use of nonaspirin NSAIDs, although the local irritative effects do not appear to be as dependent on pH levels as with aspirin. NSAIDs inhibit prostaglandin synthesis, increase the synthesis of leukotrienes, may increase toxic oxygen metabolites, and may reduce levels of protective endogenous sulfhydryls.¹¹

Gastrointestinal Safety of Aspirin Therapy

The GI effects of aspirin are apparent either from endoscopic evaluation, which frequently reveals predominantly asymptomatic and clinically nonsignificant alterations to gastric mucosa, or from symptomatic assessment, including clinical presentations ranging from minor GI symptoms to upper GI bleeding. The regular use of even short-term low-dose aspirin therapy can result in upper GI irritation and may predispose patients to GI hemorrhage.¹²

The microscopic effects of aspirin on gastric mucosa are evident within minutes of oral ingestion,¹³ even with low-dose aspirin therapy. Characteristic endoscopic features of recent aspirin use include a constellation of linear hemorrhages and

erosions distributed throughout the antrum of the stomach, especially more proximate to the body of the stomach (Figure 1). Although their appearance is of concern, these lesions are rarely of clinical significance, and many resolve quickly.¹³ Recent research suggests that although 11% of patients receiving daily low-dose aspirin therapy have endoscopic ulceration, this type of ulceration is frequently asymptomatic, does not present clinically, and rarely progresses to clinical sequelae, such as perforation or upper GI bleeding.¹⁴

The GI manifestations associated with aspirin use include stomach upset, nausea, constipation, and diarrhea. In one study, 400 healthy, elderly (ie, ≥ 70 years) adults participated in a double-blind, randomized, placebo-controlled trial to investigate the incidence of adverse effects from the use of low-dose (100 mg/day) aspirin therapy during a 12-month period.¹² GI symptoms were reported by 18% of subjects who received aspirin compared with 12.5% of subjects who received placebo (Table 2).¹² A significant difference ($P < .05$) was noted in the percentage of subjects experiencing clinically evident GI bleeding: 0% of those who received placebo compared with 3% of aspirin-treated subjects. In addition, those treated with aspirin had a significant decrease in mean hemoglobin levels compared with the placebo group (0.33 g/dL vs 0.11 g/dL, respectively; $P < .05$).¹² The excess of GI symptoms at even 100 mg/day challenges the benefit of low-dose aspirin therapy for the primary prevention of CVD.

Patients who present with upper GI bleeding are often likely to report recent use of an NSAID, either prescription or OTC, particularly formulations containing aspirin. Results of a survey on GI bleeding conducted by the American College of Gastroenterology of 635 patients with gastric bleeding and 600 control patients indicated that OTC analgesics were used significantly more often ($P < .05$) in patients with bleeding than in control patients.¹⁵ A later analysis of the survey revealed that the odds ratio (OR) for GI

Figure 1. Endoscopic Photograph of Gastric Ulcer

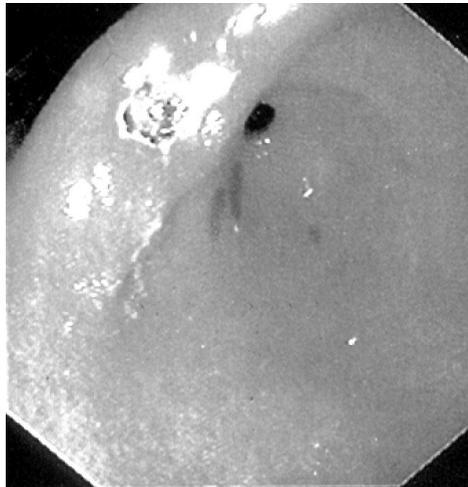


Table 2. Adverse Effects of Low-Dose Aspirin in the Elderly (Double-blind, Placebo-controlled Study of 400 Subjects Randomized to Aspirin 100 mg/day or Placebo)

	Subjects Reporting Symptoms (%)		Relative Risk
	Aspirin (n = 200)	Placebo (n = 200)	
Stomach upset	6.0	4.5	1.33
Nausea	4.0	1.5	2.67
Needed antacid	5.0	3.5	1.43
Constipation	6.0	4.5	1.33
Diarrhea	3.5	1.0	3.50
Any GI symptoms	18.0	12.5	1.44

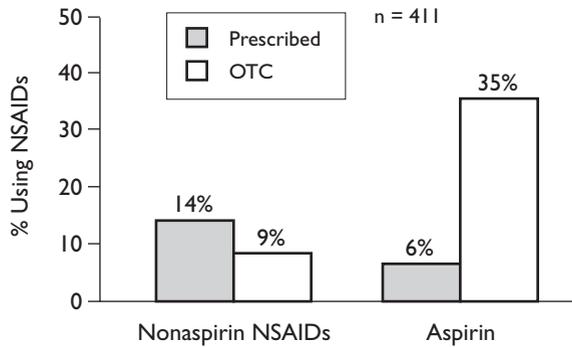
GI indicates gastrointestinal.

Adapted with permission from Silagy et al.¹²

bleeding was increased for aspirin (OR = 2.7) and ibuprofen (OR = 2.4), but did not increase for acetaminophen (OR = 0.9).¹⁶

A study of 421 consecutive patients who presented at an inner-city hospital during a 24-month period with upper GI hemorrhage revealed that the use of any NSAID was significantly associated with gastric hemorrhage compared with duode-

Figure 2. Percentage of Patients with Upper GI Bleeding Using NSAIDs



GI indicates gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over the counter.

Adapted with permission from Wilcox et al.¹⁷

nal ulcer hemorrhage ($P < .007$) as well as ulcer-related bleeding compared with variceal hemorrhage ($P < .001$).¹⁷ In addition, OTC aspirin and NSAID use was frequent and exceeded prescription use (Figure 2). More than one third of the patients reported using OTC aspirin during the week before their admission to the hospital.¹⁷

A case-control study in Spain compared 1122 consecutive patients hospitalized for bleeding from a peptic lesion with 2231 control subjects.¹⁸ The use of any NSAID, including low-dose (ie, ≤ 300 mg/day) aspirin, was associated with an increased

risk of GI bleeding from a peptic ulcer. In contrast, the use of a nitrovasodilator or antisecretory therapy was independently associated with a decrease in the risk of GI bleeding.¹⁸

Nitrates and/or agents that release nitric oxide appear to mitigate the vasoconstrictive properties of aspirin and NSAIDs within the GI mucosa, thereby minimizing the GI mucosal damage. However, nitrovasodilators inhibit platelet aggregation—which contributes to the GI bleeding caused by aspirin or other NSAIDs—and thus may not be appropriate for patients with gastroduodenal lesions.¹⁸ The concomitant use of aspirin with nitrovasodilators is common among patients with CVD but may confound an evaluation of the effects of aspirin. An important finding of this case-control study was the increased risk of bleeding associated with any dose of aspirin or NSAID for a short-term treatment (ie, ≤ 1 month) compared with longer treatment periods (ie, > 1 month; Table 3).¹⁸

In the recent Celecoxib Long-term Arthritis Safety Study (CLASS), investigators compared the rate of ulcer complications and symptomatic ulcers associated with the use of NSAIDs (ie, ibuprofen or diclofenac) or a COX-2 inhibitor (ie, celecoxib), with or without aspirin.¹⁰ The results demonstrated a lower risk of upper GI complications with the COX-2 inhibitor than with traditional NSAIDs; however, with concomitant use of aspirin the incidence of symptomatic ulcers and/or ulcer complications was not significantly different in patients taking celecoxib compared with traditional NSAIDs.¹⁰ These findings suggest that the deleterious effects of aspirin on the stomach are greater than the protective benefits of the COX-2 inhibitor, and the combination of aspirin plus a COX-2 inhibitor will still induce upper GI complications. The Food and Drug Administration (FDA) recently ruled that the CLASS results demonstrated no safety advantage in upper GI events for celecoxib compared with either ibuprofen or diclofenac.¹⁹

Table 3. GI Bleeding and Frequency of Medication Use

Type of Medication	Odds Ratio for GI Bleeding (95% CI)	
	≤ 1 month	> 1 month
Aspirin at any dose	8.9 (6.6-14.5)	2.8 (1.6-4)
Nonaspirin NSAID at any dose	7.6 (5.8)-9.2)	2.4 (1.8-3.9)

GI indicates gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; CI, confidence interval.

Adapted from Lanas et al.¹⁸

Dose-Related Effect of Aspirin on GI Bleeding

The role of aspirin dose in GI bleeding has been controversial. Many early studies involved high-dose aspirin regimens (ie, ≥ 325 mg/day), and the risk for GI bleeding was consistently elevated. Less information was known regarding the effect of lower-dose regimens, particularly regimens of < 100 mg/day.

A case-control study specifically examined the dose-related effect of aspirin on the risk of peptic ulcer bleeding.³ Prophylactic low-dose aspirin regimens generally involve doses of ≤ 325 mg/day. This study examined the risk of GI bleeding from nonaspirin NSAIDs as well as 3 low-dose regimens of aspirin (ie, 75, 150, and 300 mg/day) among 1121 patients presenting with gastric or duodenal ulcer bleeding compared with hospital or community controls. As shown in **Table 4**,³ the OR for ulcer bleeding rose with increasing aspirin dose. In addition, patients who used aspirin (ie, any dose) on a daily basis (ie, ≥ 5 days/week) were at increased risk for GI bleeding if they had used aspirin for < 1 month (OR = 9.2) compared with longer-term users (OR = 3.2). Patients who used nonaspirin NSAIDs concomitantly with daily aspirin had a significantly greater risk for GI bleeding than those who used daily aspirin alone (OR = 7.7 vs 3.3, respectively; $P < .05$). Despite a dose-response relationship, none of the aspirin doses (ie, 75-300 mg/day) was free of the risk for inducing gastric or duodenal bleeding. Patients receiving aspirin at any of the 3 doses had an increased risk for hospitalization for ulcer bleeding compared with either hospital or community controls.³

Other studies have not found a dose-response relationship with aspirin for upper GI bleeding. A recent meta-analysis of 24 randomized, controlled studies involving approximately 66 000 participants compared long-term use (ie, > 1 year) of aspirin 50 to 1500 mg/day with either placebo or no treatment.²⁰ Meta-regression analysis demonstrated GI hemorrhage in 2.47% of patients receiving

Table 4. Daily Aspirin Dose and Admission for Ulcer Bleeding

Aspirin Dose	Odds Ratio (95% CI)
75 mg (n = 27)	2.3 (1.2-4.4)
150 mg (n = 22)	3.2 (1.7-6.5)
300 mg (n = 62)	3.9 (2.5-6.3)

CI indicates confidence interval.

Adapted with permission from Weil et al.³

aspirin (ie, at all doses) compared with 1.42% of patients receiving placebo; GI hemorrhage occurred in 2.30% of patients receiving aspirin at doses < 163 mg/day compared with 1.45% of patients receiving placebo (**Table 5**).²⁰ The authors concluded that long-term aspirin therapy, even at low doses, was associated with a significantly increased rate of GI hemorrhage ($P < .0001$).²⁰ No evidence exists to support the notion that modified-release formulations would be safer.

A cohort study from Denmark involving nearly 27 700 people taking aspirin also found an increased risk of hospitalization due to upper GI bleeding associated with use of either plain or enteric-coated low-dose aspirin (ie, 100 or 150 mg/day).⁶ No difference in risk was noted for use of

Table 5. Risk of Gastrointestinal Hemorrhage with Long-Term Use of Aspirin: Meta-analysis of 24 Randomized Controlled Trials (n ~66 000) and GI Hemorrhage Incidence

	GI Hemorrhage Incidence (%)	Odds Ratio (95% CI)
Aspirin (overall)	2.47	1.68 (1.51-1.88)
Placebo	1.42	
Aspirin (< 163 mg/day)	2.30	1.59 (1.40-1.81)
Placebo	1.45	

$P \leq .0001$.

GI indicates gastrointestinal; CI, confidence interval.

Adapted with permission from Derry S, Loke YK.²⁰

100-mg tablets compared with 150-mg tablets. However, the addition of an NSAID to low-dose aspirin therapy more than doubled the standardized incidence rate for GI bleeding, from 2.6 for low-dose aspirin alone to 5.6 for the combination regimen.⁶

Although these results appear contradictory, neither the meta-analysis nor the cohort study definitively negates the possibility of a dose-response relationship,

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as doses of 75 to 81 mg/day were either combined with doses of 150 mg/day in the low-dose category²⁰ or not examined.⁶ According to a quote by Lawrence Goldkind, MD, deputy director of the anti-inflammatory division of the FDA, “A failure to show a difference is not the same as showing that things are the same.”²¹ The “totality of evidence” suggests a dose-response relationship for aspirin, so that aspirin regimens of 75 to 81 mg/day are more often associated with a lower risk and incidence of GI bleeding than regimens >325 mg/day.

Enteric-Coated or Buffered Aspirin and Risk of Upper GI Bleeding

The GI effects of short-term aspirin therapy can be mediated with as little as 1428 mg (ie, one-third teaspoon) of sodium bicarbonate (ie, baking soda).¹¹ However, OTC buffered aspirin products do not contain a sufficient amount of antacid to counteract the GI effects of low doses of aspirin. A 4-way, crossover, blinded endoscopic study compared the gastric effects of aspirin (325 mg/day), buffered aspirin (325 mg/day), acetamino-

phen (325 mg/day), and placebo in 10 healthy volunteers aged 20 to 30 years.¹³ All patients had a normal medical history, unremarkable physical examination, and gastroduodenoscopy.¹³ Study participants received 2 tablets of study drug or placebo 4 times during a 24-hour period and a 5th dose before gastroscopy. Both aspirin formulations (ie, plain and buffered) caused significant gastric ($P < .005$) and duodenal ($P < .05$) erosions compared with baseline and placebo, and the difference between plain and buffered aspirin was not significant. No significant gastric or duodenal mucosal damage was identified with the acetaminophen administration.¹³

A multicenter case-control study examined the suggestion that enteric-coated or buffered aspirin formulations are associated with lower rates of upper GI bleeding than plain aspirin formulations.⁵ A total of 550 patients with upper GI bleeding and 1202 controls were interviewed regarding their use of aspirin and NSAIDs during the 7 days before the onset of bleeding (ie, GI cases) or the interview (ie, controls). The relative risks of upper GI bleeding for plain, enteric-coated, or buffered aspirin (ie, average dose ≤ 325 mg/day) were 2.6, 2.7, and 3.1, respectively, and for higher-dose formulations (ie, >325 mg/day), the relative risks were 5.8 for plain and 7.0 for buffered aspirin (data for high-dose enteric-coated formulations were insufficient).⁵ These results confirm endoscopic evaluations indicating that buffered aspirin formulations afford no protection of the gastric mucosa compared with plain aspirin, but contradict other findings that suggest a protective benefit of enteric coating. In addition, the study highlighted the greater risk of upper GI bleeding associated with high-dose (ie, >325 mg/day) than with low-dose (ie, ≤ 325 mg/day) aspirin, while emphasizing that none of the aspirin formulations or doses studied had a reduced risk of upper GI bleeding.⁵

NSAIDs and Lower GI Risk: Diverticular Bleeding

In a recent 3-year study, 710 patients diagnosed with asymptomatic diverticula through flexible sigmoidoscopy or

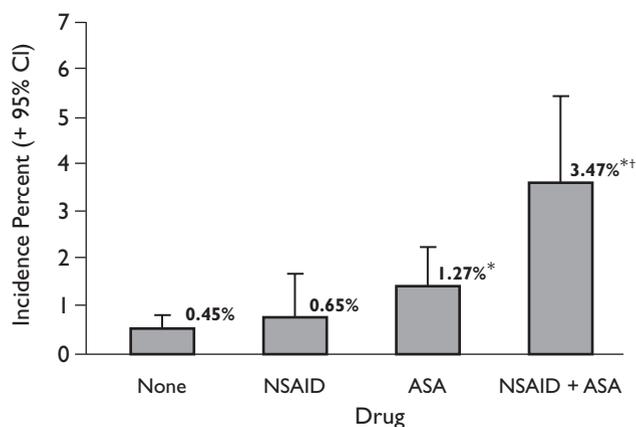
colonoscopy were followed-up either until the end of the study or till an episode of diverticular bleeding occurred.²² Diverticular bleeding was defined as major hematochezia, where colonoscopy identified no other cause for lower GI bleeding. Patients were then grouped according to their exposure to aspirin or to other NSAIDs: no exposure, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin ≤ 325 mg/day, or concurrent nonaspirin NSAID plus low-dose aspirin. As shown in **Figure 3**, patients who were exposed only to NSAIDs had a rate of diverticular bleeding relatively comparable to that of patients not exposed to any aspirin or NSAID.²² However, patients taking aspirin, either alone or in combination with another NSAID, were at an increased risk for diverticular bleeding. As with upper GI bleeding, the addition of an NSAID to low-dose aspirin therapy appears to have a synergistic effect, substantially increasing the incidence of lower GI bleeding compared with the use of either agent alone.²²

Conclusions

Aspirin therapy has become an integral component in the primary and secondary prevention of CVD. The benefits of aspirin therapy must often be balanced against the increased risk for GI effects and bleeding associated with the use of aspirin. Although low-dose regimens (ie, <100 mg/day) induce GI effects, recent studies suggest that the risk for GI bleeding from aspirin use may be dose-responsive, and clinicians are therefore advised to prescribe the lowest effective dose of aspirin therapy beneficial for CVD (ie, 75 to 81 mg/day) to minimize the risk of GI bleeding.

The use of nonaspirin NSAIDs has also been shown to induce deleterious upper GI sequelae. Although COX-2 inhibitors do not appear to increase the risk of—and may in fact protect against—upper GI bleeding, the concomitant use of aspirin with either nonaspirin NSAIDs or COX-2 inhibitors increases the risk for upper GI bleeding. Furthermore, the combination of nonaspirin NSAIDs and aspirin has a synergistic effect on the risk and incidence of both upper and lower GI

Figure 3. Rates of Diverticular Bleeding (Events per Patient-Years)



* $P = .04$ by Fisher exact test.

† $P = .01$ by Fisher exact test.

CI indicates confidence interval; NSAID, nonsteroidal anti-inflammatory drug; ASA, aspirin.

Adapted with permission from Cryer et al.²²

bleeding. In contrast, studies consistently demonstrate the lack of GI effects associated with acetaminophen use. Consequently, to reduce the risk of GI bleeding in patients requiring daily prophylactic low-dose aspirin therapy, concomitant therapy with gastroprotective agents such as proton pump inhibitors should be given. In addition, when an

When an analgesic is needed for pain relief or as concomitant therapy with aspirin, therapy should be directed away from OTC or prescription NSAIDs and toward nonaspirin formulations, including acetaminophen.

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