Low-Dose Acetylsalicylic Acid and the Use of Gastroprotectors among Older Adults

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Introduction
Acetylsalicylic acid (ASA) is a non-steroidal anti-inflammatory drug (NSAID) that produces an antithrombotic effect via irreversible acetylation of a serine amino acid in cyclo-oxygenase 1 (COX-1) in platelets. Consequently, production of thromboxane A2 and platelet aggregation is abolished. Low-dose ASA, usually defined as 75–325 mg/d, is commonly used for the primary and secondary prevention of cardiovascular (CV) events such as myocardial infarction and cerebrovascular disease. The American Heart Association recommends that daily low-dose ASA be used by all persons considered to be at increased coronary risk, determined as a 10-year risk of CV event of >10%, whereas the U.S. Preventive Services Task Force recommends that the person’s underlying risk for CV disease and the relative values the person attaches to the main outcomes should be considered when deciding whether to use low-dose ASA.

Although there are CV benefits, ASA is associated with upper gastrointestinal (GI) toxicity. Low-dose ASA results in fewer upper GI side effects than high-dose ASA and other NSAIDs, but the risk is still substantial. In this review, we explain the GI effects of low-dose ASA use and discuss GI risk factors and therapeutic strategies that can be used to increase the risk benefit for individuals who need ASA.

Upper GI Effects
Low-dose ASA therapy is associated with a variety of upper GI side effects, ranging from dyspepsia and acute mucosal damage to upper GI complications (UGIC) and death. Dyspepsia is commonly reported among persons treated with NSAIDs and ASA but is not necessarily associated with the presence of mucosal lesions. Approximately half of individuals with dyspeptic symptoms have mucosa of normal appearance; there is little literature available on the association between dyspepsia and ASA use. In a multicountry prospective study of a small number of individuals receiving low-dose ASA for CV disease prophylaxis, 20% reported dyspeptic symptoms. In addition, there was a poor correlation between the presence of epigastric symptoms and that of gastroduodenal ulcers or erosions. Most people taking ASA develop acute mucosal lesions, particularly relating to damage of the gastroduodenal mucosa such as petechiae and erosions. Although petechiae and erosions are not clinically relevant, some erosions may develop into ulcers or have associated complications; in some cases, these complications can be fatal. The negative effects of low-dose ASA on the gastroduodenal mucosa have been proven in short-term endoscopic studies involving healthy volunteers and patients. One study demonstrated that 60% (28 out of 47) of individuals taking low-dose ASA had gastroduodenal mucosal lesions on endoscopy.

Data on the incidence or point prevalence of endoscopic gastroduodenal ulcers among persons taking low-dose ASA are scarce. In one study, the prevalence of endoscopically detected gastric and duodenal ulcers was 11% (95% confidence interval [CI] 6.3–15.1%) for those receiving low-dose ASA for CV disease prophylaxis. In the same study, the ulcer incidence in 113 persons followed up for 3 months was 7% (95% CI 2.4–11.8%). In the only available placebo-controlled trial to assess ulcers, the difference in 12-week ulcer incidence observed between those with arthritis treated with placebo (5.8%) and those treated with enteric-coated ASA 81 mg/d (7.3%) was not statistically significant.

In placebo-controlled studies designed to evaluate the efficacy of low-dose ASA for the prevention of CV complications, the incidence of endoscopic ulcer complications was lower in those treated with ASA compared to those receiving placebo.
events, individuals receiving low-dose ASA had a higher incidence of GI bleeding than did placebo recipients. Odds ratios for the risk of GI bleeding in these studies ranged from 1.5 to 3.1. However, these studies have limitations. In many studies, the GI bleeding was not defined or was defined in vague terms—for example, the presence of melena was reported as an event and not investigated per se. Both major and minor bleeding were considered in the same way, and most studies had criteria that excluded individuals at risk, including “ulcer disease or individuals with intolerance to ASA,” suggesting that the populations included in these trials may have been at lower risk than the actual population that needs ASA. On the contrary, some other small studies including people taking low-dose ASA for other indications have shown no differences in GI bleeding compared with those taking placebo.

In addition to randomized clinical trials, numerous observational studies have shown increased risk of UGIC (perforation and overall bleeding) in the order of greater than twofold with low-dose ASA. The use of enteric-coated or buffered formulations does not appear to reduce the risk of UGIC, suggesting that the upper GI side effects of ASA are the result of a systemic rather than a topical action. Furthermore, a recent nationwide observational study from Spain has reported that at least 12% of all upper and lower GI complications and ensuing deaths are attributed to low-dose ASA use.

**Risk Factors for UGIC**

The risk factors for UGIC associated with NSAID therapy are well known and include advanced age, a history of ulcer or ulcer complications, the use of two or more NSAIDs, high NSAID dose, concurrent use of corticosteroids or anticoagulants, and the presence of severe disease. Few studies, however, have considered risk factors associated with UGIC among persons receiving low-dose ASA alone. Not surprisingly, many of the factors identified for other NSAIDs have also been suggested as risk factors for low-dose ASA, including higher ASA dose (see Table 1).

Although age has not been shown to predict hospitalization for upper GI bleeding in case-control and cohort studies, older adults have a much higher baseline risk of UGIC. For example, the risk of UGIC was approximately 6% per year among controls over 80 years of age and nearly 4% among those 70–79 years old compared with <0.5% among those <50 years old. Hence, the twofold increased risk of UGIC with low-dose ASA shown in observational studies leads to a significantly higher absolute risk. Among persons <60 years the risk was similar between men and women, but among persons >60 years the risk was somewhat higher for men. A review of the changes in the upper GI tract with age suggested that atrophy of the gastric mucosa, probably attributed to an increase in the prevalence of Helicobacter pylori, and prolonged GI transit time may also partly explain these differences.

This is a concern, given that population-based studies in the United Kingdom have demonstrated that admission rates for peptic ulcer have fallen for younger individuals but increased for older people with hemorrhage (especially those >74 years).

Helicobacter pylori infection and NSAID use are independent risk factors for ulcer bleeding, but Helicobacter pylori eradication alone is insufficient to eliminate the risk of GI complications related to NSAID use. However, Helicobacter pylori infection is associated with an increased risk of gastroduodenal damage among low-dose ASA users, and eradication of Helicobacter pylori among individuals with GI ulcers or bleeding is associated with a reduction in the occurrence of UGIC in both non-ASA and ASA users.

**Minimizing the Upper GI Side Effects of Low-Dose ASA**

Several strategies have been proposed for minimizing the upper GI side effects of low-dose ASA (see Table 2). These include the use of an alternative platelet inhibitor, such as clopidogrel, and cotherapy with a gastroprotective agent; also, as discussed previously, strong consideration should be given to eradicating Helicobacter pylori. Approximately 20% of persons taking low-dose ASA also use NSAIDs; among these persons, the use of NSAIDs with better upper GI tolerability has been proposed.

**Alternative Antiplatelet Agents**

Current cardiology guidelines recommend the antithrombotic agent clopidogrel for people who are unable to take ASA owing to previous GI intolerance. Clopidogrel does not inhibit COX but exerts its antithrombotic effect by targeting platelet adenosine diphosphate receptors. In a study comparing the use of 75 mg clopidogrel with 325 mg ASA, clopidogrel was slightly more effective for the secondary prevention of thrombotic CV events than was ASA (annual risk 5.32% versus 5.83%, respectively) and conferred a moderately lower rate of upper GI bleeding (0.52% versus 0.72%, respectively). However, a small retrospective study has suggested that a history of GI bleeding is an important risk factor for GI bleeding during clopidogrel therapy. It appears that impairment of

<table>
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<th>Table 1: Risk Factors for Upper Gastroduodenal Damage in Persons Receiving Low-Dose ASA Therapy</th>
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<tr>
<td><strong>ASA dose</strong></td>
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<td><strong>Helicobacter pylori infection</strong></td>
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<td><strong>Advanced age (especially &gt;70 years)</strong></td>
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<td><strong>Presence of severe disease</strong></td>
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**Sources:** Weil J et al., 1995; Lanas A et al., 2000; Ibanez L et al., 2006; de Abajo FJ, 2001; Kelly JP et al., 1996; Serrano P et al., 2002; Newton JL, 2004; Hernández-Díaz S, 2006; Hurlen M et al., 2002.
Table 2: Recommendations to Reduce the Risk of Upper Gastrointestinal Complications Associated with Low-Dose ASA among Older Adults

<table>
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<th>Recommendation</th>
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<tr>
<td>Ensure ASA is indicated on the basis of cardiovascular risk.</td>
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<td>Use the lowest effective ASA dose (preferably ≤100 mg/d).</td>
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<tr>
<td>Consider cotherapy with gastroprotective drug, preferably a PPI at standard doses, especially in those patients with a past history of gastrointestinal events.</td>
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<tr>
<td>Eradicate Helicobacter pylori, especially in at-risk patients.</td>
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<tr>
<td>Add a gastroprotectant for patients receiving concomitant antiplatelets (e.g., clopidogrel), nonselective or COX-2-selective NSAIDs.</td>
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ASA = acetylsalicylic acid; COX-2 = cyclooxygenase 2; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

Sources: Patrono C et al., 2005; Lanas A et al., 2000; Serrano P et al., 2002; Hernández-Díaz S, 2006; Chan FK et al., 2001; Chan FK et al., 2002.

ulcer healing and inhibition of platelet aggregation may be the mechanisms by which antiplatelet agents, such as clopidogrel and ASA, may cause existing asymptomatic ulcers to bleed. Thus, while such agents, which impair angiogenesis, may not be the primary cause of ulcers, they may impair healing of background ulcers. In two case-control studies, clopidogrel has been found to carry an increased risk of ulcer bleeding. In the first study, the adjusted relative risks were 2.8 (95% CI 1.9–4.2) for clopidogrel/ticlopidine and 2.7 (95% CI 2.0–3.6) for ASA 100 mg/d. In the second study, the relative risks were 2.3 (95% CI 0.9–6.0) and 4.0 (95% CI 3.2–4.9) for clopidogrel and low-dose ASA, respectively. Thus, while guidelines recommend the use of clopidogrel, evidence suggests that the risk of upper GI side effects is similar to that with low-dose ASA; therefore, we advise caution in its use for at-risk individuals.

Gastroprotectors

Two cotherapy approaches have been investigated for the prevention of upper GI side effects associated with low-dose ASA therapy. The first, which has been investigated very little in this setting, is coadministration of a mucosal protectant, such as misoprostol, a prostaglandin analogue, which addresses the depletion of prostaglandins that are associated with GI toxicity among individuals taking ASA or other NSAIDs. The second option is coadministration of acid-suppressive therapies such as histamine 2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). These agents reduce gastric acid secretion, which plays a key role in the mucosal damage associated with ASA and other NSAIDs. However, to date, relatively few clinical studies have been performed to assess the efficacy of these approaches in low-dose ASA users.

Misoprostol

Misoprostol is an analogue of prostaglandin E1. In an endoscopic study, misoprostol 100 µg/d significantly reduced the development of erosions among healthy volunteers taking ASA 300 mg/d. However, misoprostol, especially doses ranging between 600 and 800 µg/d, is associated with side effects, particularly diarrhea, that often lead to treatment discontinuation. For example, in a study of more than 8,000 persons with rheumatoid arthritis, 20% of those receiving misoprostol withdrew within the first month of treatment because of diarrhea. So far, no studies looking at higher end points (e.g., peptic ulcers or ulcer bleeds) in actual patients who need ASA have been carried out with misoprostol. Consequently, due to the lack of studies and the probable nonadherence, cotherapy with misoprostol is unlikely to be used in the near future for the prevention of upper GI side effects in low-dose ASA users.

Histamine 2 Receptor Antagonists

Histamine 2 receptor antagonists include ranitidine, cimetidine, famotidine, and nizatidine, and they reduce gastric acid output as a result of histamine 2 receptor blockade. These agents have been shown in studies to significantly increase intragastric pH and reduce ASA-induced gastric bleeding. However, these were carried out with healthy volunteers and looked at local mucosal aspects or occult mucosal bleeding but not clinical expression of upper GI toxicity. Therefore, they are difficult to apply to a real-world setting. Two observational case-control studies reported a risk reduction of upper GI bleeding with H2RAs of 0.40 (95% CI 0.19–0.73). However, apart from these two studies, there are no data from chronic ASA users and, given the data demonstrating superiority of PPI to H2RA therapy for reducing ulcer risk in NSAID users, the former is likely to be a more rational approach.

Proton Pump Inhibitors

Proton pump inhibitors inhibit the parietal cell proton pump, thus exerting a suppressive effect on gastric acid. PPIs appear to be the gastroprotectant of choice. In a randomized trial, individuals taking ASA 100 mg/d for 12 months after the eradication of *H. pylori* and healing of ulcers used lansoprazole 30 mg/d compared with placebo for the recurrence of ulcer complications. Those in the lansoprazole group were less likely than those in the placebo group to have a recurrence of ulcer complications (1.6% versus 14.8%, p = .008), suggesting that PPI therapy plus *H. pylori* eradication is superior to *H. pylori* eradication alone. In one study, omeprazole therapy among individuals with *H. pylori* infection and a history of upper GI bleeding was equivalent to the eradication of *H. pylori* in preventing recurrence of bleeding (0.9% versus 1.9%, respectively), albeit with a relatively short follow-up time (6 months).
an absolute risk reduction of peptic ulcers by 36.6% in acute and 34.6% among chronic users of NSAIDs/ASA; indeed, the number needed to treat to avoid one peptic ulcer among older adults assigned to NSAIDs/ASA was three both in acute and chronic users.\(^{38}\)

These results were confirmed by epidemiological studies in which concomitant antisecretory therapy, especially PPI therapy, was associated with a significant reduction in the relative risk of upper GI bleeding among persons receiving low-dose ASA (0.2 \([95\%\ CI\ 0.1–0.9]\) for omeprazole\(^{13}\) and 0.22 \([95\%\ CI\ 0.07–0.75]\) for antisecretory therapy, which included PPI therapy\(^{20}\)). An observational study reported a low incidence of UGIC among high-risk individuals receiving low-dose ASA plus omeprazole (1.2% \([95\%\ CI\ 0.3–3.5\%]\)), translating to 1.0 events/100 persons/year, which was similar to the rate observed in studies involving non-high-risk individuals taking low-dose ASA alone.\(^{39}\) In a study from Hong Kong, the cumulative incidence of recurrent bleeding of persons with a history of ASA-associated bleeding during a 12-month period was 8.6% (95% CI 4.1–13.1%) among individuals who received clopidogrel and 0.7% (95% CI 0.2–2.0%) among those who received ASA plus esomeprazole (difference 7.9 percentage points \([95\%\ CI\ 3.4–12.4\%],\ p = .001\)).\(^{37}\) This was confirmed in a second trial among individuals intolerant of ASA monotherapy, in which the cumulative incidence of recurrent ulcer complications was 0% among those receiving esomeprazole and ASA and 13.6% among those receiving clopidogrel (absolute difference 13.6 percentage points \([95\%\ CI\ 6.3–20.9\%],\ p = .0019\)).\(^{40}\) These results, together with epidemiological data, suggest that those patients with ASA-associated GI side effects benefit from the co-prescription of a PPI.\(^{14,31}\)

### Eradication of \(H.\ pylori\)

\(H.\ pylori\) is a risk factor of upper GI ulcers or ulcer complications in low-dose ASA use\(^{26}\); its eradication can be seen as another therapeutic strategy to minimize the risk of developing ulcer or ulcer complications in such users. \(H.\ pylori\) eradication has been associated with risk reductions of ulcers and ulcer bleeding in naive NSAID users, but no such studies are available for low-dose ASA users.\(^{41}\) Among individuals at high risk who have had previous ulcer bleeding, \(H.\ pylori\) eradication alone does not seem to be enough to provide protection in the long-term—cotherapy with PPIs seems necessary.\(^{25,36}\) Conversely, \(H.\ pylori\) infection itself does lead to an increased risk of gastroduodenal damage in low-dose ASA users; therefore, clinicians should consider additional investigations to reduce the risks of bleeding and complications.\(^{25,26,42–5}\) The risk that \(H.\ pylori\) poses is often overlooked by physicians prescribing low-dose ASA to high-risk individuals. Physicians may not be aware of the simple tests available to determine \(H.\ pylori\) status or of the benefits of eradication.

### Prevention Strategies for Persons Taking Low-Dose ASA and Concomitant NSAIDs

More than 20% of persons who need NSAIDs also take low-dose ASA long term. This represents a new challenge for prevention strategies as coprescription may increase the incidence of GI symptomatic and complicated ulcers, and may also reduce or even suppress the GI benefits of COX-2-selective over nonselective NSAIDs.\(^{27,31}\) A clear explanation of these findings does not exist, but it is reasonable to assume that taking a selective COX-1 inhibitor (low-dose ASA) and a selective COX-2 inhibitor would be similar to taking a potent dual COX inhibitor.

### Use of Gastroprotectors among Older Adults

Vonkeman et al.\(^{45}\) found that although up to 33% of persons with no risk factors who receive NSAIDs (including low-dose ASA) overuse GI preventive therapies, underuse of gastroprotective therapy is more prevalent among those...
with risk factors, of which the most frequent is age. Over 30% of persons are nonadherent, and the lowest rate of nonadherence is associated with the first NSAID prescription; this increases the risk of ulcer bleeding compared with the risk in those who are fully adherent. Although the use of low-dose ASA was a predictor of adherence in the study by Vonkeman et al., there is a lack of data examining the use of gastroprotection among the general population and older adults taking low-dose ASA. Other observational studies have demonstrated that 47% of individuals still did not use adequate gastroprotection.

Another important aspect is self-medication (including over-the-counter ASA): this is common among older adults, who also have several risk factors for UGIC, and may be a factor in over one third of all NSAID-related complications. Older adults also appear to be at a high risk for GI toxicity when ASA is substituted for other antiplatelet agents. In the only trial that studied solely older adults, the number needed to treat to avoid one peptic ulcer among older users of NSAIDs/ASA was three, both in acute and chronic users. Extrapolating data from this and other studies, PPIs appear to be the gastroprotectant of choice.

**Conclusion**

In summary, low-dose ASA is frequently prescribed to older adults. Although useful, especially in a CV secondary prevention setting, it is important that it is appropriately prescribed. Older adults are at high risk for GI events, especially those adults who have other risk factors, including *H. pylori* infection. In addition to appropriate GI risk stratification, prevention strategies should be used, especially among older adults. Treatment strategies include the use of alternative antiplatelet agents, such as clopidogrel, concomitant gastroprotection, or both. Clopidogrel appears to lead to similar levels of gastrotoxicity and, hence, is not advocated currently. Mucosal protectants such as misoprostol have been used in the past, but side effects lead to nonadherence. Antisecretory agents, especially PPIs, have an evidence base and appear to be the concomitant agent of choice. The use of gastroprotectors with low-dose ASA definitely should be considered for older adults. *H. pylori* eradication may be considered as an additional therapy to reduce the risk of ulcer bleeding.

Dr. Bhala has no competing financial interests to declare. Dr. Lanas is a consultant for AstraZeneca, Cogenus, and Pfizer.

**References**

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