

Review: Low-dose aspirin causes a small increase in gastrointestinal bleeding

Laine L. Review article: gastrointestinal bleeding with low-dose aspirin – what's the risk? *Aliment Pharmacol Ther.* 2006;24:897-908.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★☆☆ Gastroenterology ★★★★★☆☆ Neurology ★★★★★☆☆

QUESTION

What is the effect of low-dose aspirin on gastrointestinal (GI) bleeding and development of endoscopic ulcers?

METHODS

Data sources: MEDLINE (1966 to 2005).

Study selection and assessment: Randomized placebo-controlled trials (RCTs) and systematic reviews that evaluated aspirin, 75 to 325 mg/d and assessed upper GI bleeding or development of endoscopic ulcers. Cohort and case-control studies were also sought to identify risk factors for bleeding associated with low-dose aspirin.

Outcomes: GI bleeding and development of endoscopic ulcers.

MAIN RESULTS

14 RCTs of low-dose aspirin for cardiovascular indications and a meta-analysis of the 14 trials showed a pooled absolute increase of 0.12%/y (95% CI 0.07 to 0.19) in GI bleeding with low-dose aspirin (Table). A meta-analysis of 24 RCTs of low-dose aspirin used as an antiplatelet agent also showed an increase in GI bleeding (Table). Doses ranged from 50 to 1500 mg/d; when meta-analysis included trials of 50 to 162.5 mg/d only, the

increase in bleeding was similar to the overall results (odds ratio [OR] 1.59, CI 1.40 to 1.81). The Women's Health Initiative RCT showed 100 mg of aspirin every other day increased GI bleeding requiring transfusion by 0.018%/y (Table). Evidence was weak or inconclusive regarding increased development of endoscopic ulcers. 1 RCT ($n = 768$) of 81 mg/d of aspirin in patients with osteoarthritis showed a nonsignificant 1% absolute increase (CI -4.4% to 6.4%) in ulcer rate. Evidence from cohort and case-control studies shows that increased risk for GI bleeding from low-dose aspirin is associated with a previous history of ulcers or GI

bleeding, use of corticosteroids or anticoagulant therapy, and the addition of a nonsteroidal antiinflammatory drug (NSAID) to aspirin.

CONCLUSIONS

Low-dose aspirin produces a minor increase in serious gastrointestinal bleeding compared with the incidence of bleeding found with placebo. No difference is seen in rate of development of endoscopic ulcers.

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Low-dose aspirin vs placebo and risk for gastrointestinal bleeding*

Patient characteristics	Study characteristics	Aspirin dose (mg/d)	RR or OR (95% CI)	NNH/y (CI)
Cardiovascular indications	1 meta-analysis (14 RCTs)	75 to 325	RR 2.07 (1.61 to 2.66)	833 (526 to 1429)
Need for antiplatelet agent	1 meta-analysis (24 RCTs)	50 to 1500	OR 1.68 (1.51 to 1.88)	247
Cardiovascular prevention	1 RCT (> 39 000 women)	100 mg every other d	1.4 (1.1 to 1.8)	5556

*RCT = randomized controlled trial; RR = relative risk; OR = odds ratio. Other abbreviations defined in Glossary.

COMMENTARY

Low-dose aspirin increases the risk for GI bleeding, and several meta-analyses and reviews already exist on this topic. What information does the review by Laine add to our current knowledge? First, Laine used one of his studies to illustrate that even large-scale endoscopic studies are not good surrogates for evaluating clinical GI events with low-dose aspirin, unlike with nonaspirin NSAIDs (1).

Second, the reported rates of GI bleeding with aspirin vary considerably. Laine found that the higher rate of major GI bleeding attributable to low-dose aspirin in the observational study (0.23%) compared with the pooled RCTs (0.12%) may relate to the fact that the RCTs excluded patients at risk for GI bleeding. Another explanation is the inclusion of trials using higher-than-cardioprotective doses of aspirin. In a meta-analysis of placebo-controlled trials of low-dose aspirin (75 to 325 mg/d), the number needed to harm (NNH) was 833 (2). Another meta-analysis, which included trials of both low- and high-dose aspirin (50 to 1500 mg/d), reported an NNH of 247 (3).

Third, is "very-low-dose" aspirin safe? In a large RCT of young healthy women taking 100 mg of aspirin every other day, the increase in absolute incidence of major GI bleeding attributable to aspirin was 0.018% (4). This finding suggests that although the absolute risk is low, no dose of aspirin is completely free of GI bleeding risk even among low-risk patients.

Fourth, the risk factors for GI bleeding with low-dose aspirin are not identical to those for nonaspirin NSAIDs. Laine found that available

data do not support increasing age as a risk factor for low-dose-aspirin-induced bleeding. Nevertheless, he did not discuss other known but not widely recognized risk factors. Good evidence exists that the presence of *Helicobacter pylori* increases the risk for ulcer bleeding with low-dose aspirin (5).

Finally, one important yet unmentioned issue is whether other antiplatelet drugs, such as clopidogrel, can reduce the risk for GI bleeding. Current evidence suggests that the risk for GI bleeding with clopidogrel is similar to that with low-dose aspirin (6). Patients requiring antiplatelet therapy who are judged to be at significant risk for GI bleeding should receive low-dose aspirin and a proton-pump inhibitor rather than clopidogrel (7).

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