Low-dose aspirin (75-100 mg/day) is an inexpensive and readily available prophylactic that is well established in the reduction of ischemic heart disease and stroke, but its use in healthy subjects is debatable. The perception is that chronic aspirin use instigates gastrointestinal (GI) and cerebral bleeds and that, if everyone began taking low-dose aspirin daily at the onset of middle age, gastroenterologists would be unable to cope with the overwhelming number of patients who would be expected to experience complications. Accumulating evidence suggests otherwise. Indeed, evidence is growing that aspirin prophylaxis is associated with reductions in colorectal and possibly other solid tumor cancers.2,3 The wider use of aspirin prophylaxis could, therefore, make an important contribution to the preservation of health and the increase in survival in communities across the world.

Concerns over GI and cerebral bleeding attributable to aspirin remain, although marked differences exist between general perceptions about bleeding and evidence from randomized trials and population samples of persons using aspirin prophylactically. Although an iatrogenic GI bleed is a crisis and a cerebral bleed is a disaster, the seriousness of these events and any resultant aftereffects should be evaluated against the benefits attributable to aspirin prophylaxis.

The odds ratio (OR) of a GI bleed attributable to low-dose aspirin based on 18 randomized trials is 1.5 (95% CI, 1.2-1.8),4 translating into an absolute risk of 1 or 2 extra bleeds per 1000 subjects per year.5 This risk is age-sensitive,5 but the extent to which the proportion of bleeds attributable to aspirin increases with age is unknown.

In evaluating the relationship between aspirin use and bleeds, it is important to distinguish between bleeding in relation to short-term use of aspirin, as reported in most of the published trials, and bleeding in relation to long-term use. Shortly after commencement of aspirin prophylaxis, the risk of a GI bleed is high but decreases thereafter.2 In an overview of 17 randomized studies, the relative risk (RR) of a bleed in the first month of aspirin use was 4.4 (95% CI, 3.2-6.1), and this RR fell rapidly thereafter.6 Data from long-term studies have shown an OR for GI bleeding attributable to aspirin of 1.95 (95% CI, 1.47-2.59) in the first 3 years, decreasing within the next 3 years (OR, 1.37; 95% CI, 0.87-2.14) and showing no significant excess risk 5 and more years later (OR, 0.63; 95% CI, 0.34-1.16).2

Although an iatrogenic GI bleed is a crisis ... the seriousness ... should be evaluated against the benefits attributable to aspirin prophylaxis.

The incidence and severity of GI bleeding are highly sensitive to the presence of gastric pathology,5 but the extent to which untreated pathology might explain the observed excess bleeding attributed to aspirin is unknown. Although gastric and intestinal mucosal damage can be seen on endoscopic examination with short-term aspirin administration, this appears to improve during continuous aspirin taking,7 and, in longer-term observations, aspirin appears not to be responsible for peptic ulceration.8 On the other hand, the presence of an untreated peptic ulcer can lead to a large...
increase in bleeding from aspirin (OR, 15.2; 95% CI, 3.8-60.1).9 Helicobacter pylori infection, which is relatively common, especially in less-privileged communities,10 has been suggested as a common causal factor in many of the bleeds attributed to aspirin, and it increases the risk of bleeding from aspirin (OR, 4.7; 95% CI, 2.0-10.9).9

The most serious bleeds are those that lead to death, and despite frequent comments to the contrary, there appears to be no valid evidence that fatal GI bleeds are increased by low-dose aspirin.1,2,11 Consider that in the Antithrombotic Trialists’ overview, there were 9 fatal GI bleeds in patients on aspirin and 20 in those on placebo, giving an OR of 0.48 (95% CI, 0.17-1.34).1 In another study based on these same trials, deaths attributable to bleeding in patients randomized to aspirin were 3.9 per 100,000 patients per year and 5.1 per 100,000 per year in those on placebo, giving an OR of 0.79 (95% CI, 0.38-1.64).11

In a long-term follow-up of 34 trials, 8 (4%) of 203 GI bleeds in patients on aspirin were fatal, and 15 (11%) of 132 GI bleeds in patients on placebo were fatal, for an OR of 0.32 (95% CI, 0.12-0.83).2 In another review of 35 trials involving 87,000 patients, the OR for a fatal GI bleed with aspirin was 0.94 (95% CI, 0.47-1.87).12

The absence of any increase in fatal bleeds attributable to aspirin within clinical trials could, of course, be due to the selection of subjects at low risk for a bleed.3 This seems unlikely, however, because the rate of bleeds that are fatal within randomized trials (5.2% and 4%) is very similar to the proportion of fatal bleeds attributable to aspirin that are identified in community-based studies. In 3000 patients admitted to the hospital because of adverse drug reactions (ADRs) to aspirin, 162 (5.4%) patients had been taking low-dose aspirin and 7 (4.3%) of these died.13 In 2 community-based cohorts, the mortality rates from GI complications, stated to be mostly upper GI bleeding, were 5.7% and 5.6%.14 The United Kingdom’s Yellow Card Scheme facilitates the reporting of suspected ADRs to the Medicines and Healthcare Products Regulatory Agency (similar to the US Food and Drug Administration’s MedWatch program). Although under-reporting is likely in any such scheme, this is likely to be low for life-threatening and fatal ADRs. Sixty (3.8%) of the 1572 GI bleeds that have been reported since 1963 were fatal [Medicines and Healthcare Products Regulatory Agency, personal communication].

The identification of patients at increased risk for GI bleeding would be a valuable contribution to clinical care and could also help in deciding whether or not to recommend a gastroprotective drug along with prophylactic aspirin. Age, female sex, cigarette smoking, excessive alcohol use, a history of peptic ulceration, prior bleeding, hypertension, diabetes, prior vascular disease, evidence of congestive heart failure, and renal insufficiency have all been identified as factors positively associated with an increased bleeding risk.15,16

If gastric pathology is suspected or if there is any evidence of an increased risk of GI bleeding, the use of gastroprotective medication is justified. Proton pump inhibitors (PPIs) substantially reduce gastric bleeding, and although the value of a seek-and-treat policy for H pylori is controversial, there is a substantial reduction in the risk of bleeding with elimination of the infection and by maintaining the patient on a gastroprotective drug.17 Gastroprotective drugs seem, however, to be seriously underused; in one study, only 40% of patients with a history of peptic ulceration and only 23% with other risk factors for gastric bleeding were receiving a PPI together with aspirin.18

The natural response to a vascular bleed is to stop the aspirin. This, however, risks a rebound in vascular disease incidence. In an overview of 6 randomized trials with more than 50,000 patients who were taking aspirin for coronary artery disease, the OR of a major coronary event 8 to 10 days after the withdrawal of aspirin was 3.14 (95% CI, 1.75-5.61).19 A small randomized trial took the issue of aspirin withdrawal further and put 156 patients who had had bleeds on a PPI.20 A random half of these patients were then put back on aspirin. Mortality was 1.3% in patients receiving a PPI plus aspirin compared with 10.3% in patients who were not taking aspirin (hazard ratio, 0.2; 95% CI, 0.05-0.90).

Enormous differences exist in the risk of death, adverse outcomes, and the beneficial physical and psychological outcomes associated with aspirin prophylaxis. Therefore, evaluations should not be based on numbers of events alone. Consideration should also be given to the risk-benefit balance in settings in which the underlying gastric pathology is better identified and managed in settings in which gastroprotective agents are used.

Several recent evaluations of the risk-benefit balance of low-dose aspirin prophylaxis have taken into account effects on cancer incidence as well as vascular protection. One report concludes that “even a 10% reduction in overall cancer incidence beginning during the first 10 years of treatment could tip the balance of benefits and risks favorably in average-risk populations.”21 Another evaluation states that there would be further reduction in colorectal cancer deaths and further cost savings per life-year saved.
if aspirin prophylaxis was recommended alongside invita-
tions to the screening procedure.22

Finally, there are fundamental differences between treat-
ment, which has been delegated to healthcare practi-
tioners, and prevention, which is the responsibility of
the patient. The prime responsibility of healthcare profes-
sionals is to present evidence on risks and benefits in sufficient
detail to enable patients to make an informed decision
about the protection of their own health “ . . . even before
there is agreement amongst doctors.”23

References

1. Antithrombotic Trialists’ Collaboration. Aspirin in the primary and secondary
prevention of vascular disease: collaborative meta-analysis of individual participant

2. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on
cancer incidence, mortality and non-vascular death: analysis of the time course of

3. Cook NR, Lee IM, Zang SM, Moothy MV, Buring JE. Alternate-day, low-dose
aspirin and cancer risk: long-term observational follow-up of a randomized trial.

Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: a
meta-analysis of randomized clinical trials and observational studies. Can J Gastro-


use and upper gastrointestinal complications: systematic review of epidemiologic stud-

7. Graham DY, Smith JL, Dobbs SM. Gastric adaptation occurs with aspirin

8. Laine L, Maller ES, Yu C, Quan K, Simon T. Ulcer formation with low-dose
enteric-coated aspirin and the effect of COX-2 selective inhibition: a double blind

increases the risk of upper gastrointestinal bleeding in patients taking low-dose

10. Everhart JE, Kruzson-Moran D, Perez-Perez GI, Tralka TS, McQuillan G.
Seroprevalence and ethnic differences in Helicobacter pylori infection among adults

11. Morgan G. Aspirin for the primary prevention of vascular events? Public

12. Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase
2011;9(9):762-768.

of admission to hospital: prospective analysis of 18 820 patients. BMJ.

ated with hospital admission due to severe GI events and those associated with

15. Subberwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in
non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid
risk stratification of Unstable angina patients Suppress ADverse outcomes with
Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation.

16. Lanas A, Polo-Thomas M, Casado-Arroyo. The aspirin cardiovascular/gastro-
intestinal risk calculator—a tool to aid clinicians in practice. Aliment Pharmacol
Ther. 2013;37(7):738-748.

17. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recur-
2002;346(26):2033-2038.

18. Targownik LE, Metge CJ, Leung S. Underutilization of gastroprotective strate-
gies in aspirin users at increased risk of upper gastrointestinal complications. Aliment


prevention of colorectal cancer with low-dose aspirin in combination with endos-

Epidemiol Community Health. 2010;64(9):761-764.