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Authors' reply

SIR—In response to Petroski's comments, we did not suggest that enteric-coated or buffered aspirin carries a higher risk of upper gastrointestinal bleeding than plain aspirin. Nor did we include individuals who had already had an episode of upper gastrointestinal bleeding. We disagree that the number of cases (550) was small: ours is one of the largest published epidemiological studies of upper gastrointestinal bleeding. Use of high doses of enteric-coated aspirin was infrequent in our study population, and we lacked the data to evaluate its association with upper gastrointestinal bleeding at doses greater than 325 mg. The potential biases Petroski mentions were considered in our report, as were disparities between our findings and those of those of endoscopic studies. Since ours is the first observational study, we emphasise, as we state in the report, that our results need to be confirmed by others.

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SIR—Kelly and colleagues[1] report that low doses of enteric-coated or buffered aspirin can promote upper gastrointestinal bleeding to the same extent as plain aspirin. Although gastric damage by aspirin is not prevented by buffering, the comparative safety of enteric-coated preparations has been controversial because of endoscopic studies reporting fewer gastric erosions and less bleeding than with regular aspirin. The enteric-coated drug may be less harmful to the stomach during very short-term administration since there may be little or no contact with the gastric mucosa, but untoward gastric effects are likely after repeated administration.[2-4] Aspirin is thought to injure the gastric mucosa through local and systemic effects, the latter being due to inhibition of gastric cycloxygenase (with blockade of gastric prostaglandin production) after the drug is absorbed, irrespective of route of administration or formulation given.[4]

Prophylaxis against aspirin-associated gastroduodenal damage, even when enteric-coated preparations are used, is necessary. H_2-receptor antagonists can prevent duodenal (but not gastric) lesions by non-steroidal anti-inflammatory drugs, but specific data concerning aspirin are not available. By contrast, co-prescription of misoprostol can protect both stomach and duodenum from the harmful effects of NSAIDs. The protective effect of misoprostol against low-dose aspirin has been described by UK investigators: 100 μg daily misoprostol was better than placebo in preventing gastric haemorrhagic lesions induced by a 4-week course with aspirin 300 mg daily.[5] These data suggest that high-risk patients with strong indications for antiplatelet treatment with low-dose aspirin may benefit from prophylactic intake of a very low dose of the prostaglandin analogue.

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SIR—With prolonged daily use of aspirin, gastrointestinal loss of iron is likely, even when bleeding is so occult as to be detectable only by sensitive methods. A perspective on aspirin-induced iron loss is gained by comparison with menstruation, which has undeniable impact on iron status. Iron lost from regular aspirin use can cumulatively exceed usual menstrual losses. Averaged over the month, typical menstrual blood losses amount to 1–2 mL per day. One aspirin (325 mg) tablet can cause 1–10 mL of bleeding from the stomach, with much individual variation.[1] Adults without chronic blood loss store 300–1000 mg of iron, and blood contains about 0·5 mg of iron per mL. With aspirin-associated iron losses of 0·5–5 mg per day, iron stores could be exhausted in months, depending on the initial size of the iron load and the rate of blood loss.

Induction of iron depletion may be an important second mode of action of aspirin used long-term, rather than an undesirable side-effect. Loss of stored iron is an increasingly likely mechanism of protection against heart disease[2] and cancer.[3] For the protective action of aspirin against cancer, the most plausible previously proposed mechanisms remain essentially speculative.[4] Prolonged use of aspirin is thought necessary for protection against cancer, and there is an apparently increasing effectiveness against heart disease with duration of treatment. These patterns are consistent with an iron-loss mechanism since they suggest a cumulative protective effect (progressive lessening of iron stores over time).

The benefits of daily aspirin Symmons[5] discusses in his Nov 23 Commentary were all associated with treatments that do not eliminate gastrointestinal bleeding. Is a daily aspirin beneficial in spite of, or because of gastrointestinal blood loss? Studies are uninformative on this fundamental question. The clinical trials were inescapably a test of the global effects of aspirin. What is the empirical basis for the conclusion that benefit is only a direct result of intravascular platelet inhibition and not a consequence of occult bleeding?

Efforts to minimise bleeding are founded not on empirically based conclusions, but on the assumption that aspirin-associated bleeding is an undesirable side-effect under all circumstances. A new aspirin designed to be harmless to the stomach may turn out to be a less effective aspirin. Without new trials of efficacy there is a danger that ineffectiveness might never be detected if so-called safe versions of aspirin are prescribed for prevention of heart disease and cancer. Until the contributions of all possible mechanisms are known, those with aspirin-induced iron depletion should be cautioned against supplemental iron.

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