Selected Summaries

Risk of lower gastrointestinal bleeding with low-dose aspirin: To give or not to give?

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SUMMARY

This nationwide study investigated the risk of lower gastrointestinal bleeding (LGIB) in aspirin users in Taiwan. The study population consisted of 53 805 new low-dose (75–325 mg) aspirin users and 269 025 controls, matched for age (≥20 years) and sex and recruited between 1 January 2000 and 31 December 2006. This cohort was selected from 1 million randomly sampled individuals from the National Health Insurance Research Database, which has the healthcare data of more than 99% of the Taiwanese population (23 million enrollees). The exclusion criteria were: (i) active GI bleeding at enrolment; (ii) malignant tumour of the GI tract; (iii) disease associated with alcohol; (iv) inflammatory bowel disease; (v) radiation gastroenteritis or colitis; (vi) intestinal vascular insufficiency; and (vii) coagulopathy before low-dose acetylsalicylic acid (ASA) use.

The end-point of the study was onset of LGIB. Cox proportional hazard regression models were used to evaluate the predictors of LGIB with adjustments for age, sex, comorbid conditions and concomitant use of certain medications.

Comorbid conditions included coronary artery disease, ischaemic stroke, diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease, liver cirrhosis, chronic obstructive pulmonary disease, peptic ulcer disease without complication and a history of peptic ulcer bleeding. Medications included clopidogrel, ticlopidine, warfarin, non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, steroids, proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), nitrates, alendronate, selective serotonin reuptake inhibitors (SSRIs) and calcium channel blockers.

All conditions mentioned in the exclusion criteria and comorbid conditions were defined as per the codes of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Comorbid conditions were identified according to the receipt of the corresponding code once for hospitalization and emergency room claims or three times for outpatient claims before enrolment in the study.

Data on prescribed medications were retrieved from the database. Medication use was defined as hospitalization or outpatient prescription of medication for at least 2 weeks prior to the month before the index LGIB in patients with LGIB and at least 2 weeks during the observation period in patients without LGIB.

The low-dose aspirin group had a significantly higher incidence of LGIB within 1 year than the control group (0.20% *v.* 0.06%, $p<0.0001$). A univariate Cox proportional hazard regression model revealed that after adjustments for significant univariate independent predictors, low-dose aspirin (hazard ratio [HR] 2.75, 95% confidence interval [CI] 2.06–3.65), NSAIDs (HR 8.61, 95% CI 3.28–22.58), steroids (HR 10.50, 95% CI 1.98–55.57), SSRIs (HR 11.71, 95% CI 1.40–97.94), PPIs (HR 8.47, 95% CI 2.26–31.71) and H2RAs (HR 10.83, 95% CI 2.98–39.33) were significantly associated with LGIB.

For patients aged ≥75 years, only low-dose aspirin was significantly associated with LGIB. For patients aged <75 years, low-dose aspirin, NSAIDs, steroids, SSRIs, PPIs and H2RAs were significantly associated with LGIB.

As per the review of relevant literature done by the authors, this was the largest cohort used for specifically evaluating the risk of LGIB in low-dose ASA users. The incidence of LGIB of 0.2% within 1 year in low-dose aspirin users was consistent with a previous study on NSAIDs/ASA-related LGIB. However, it is uncertain whether low-dose ASA users with LGIB should discontinue ASA. The results on the risk of bleeding with NSAIDs, steroids and SSRIs were more or less in agreement with the existing literature. The authors unexpectedly found that PPIs and H2RA were independent risk factors for LGIB. Some studies were quoted in these contexts in which increased risk of bleeding was found in aspirin users who were also taking PPIs.

Some limitations were acknowledged for the study. The observational period was 1 year; therefore, the study results may not be applicable to long-term low-dose aspirin users. Patient compliance was not examined. The use of over-the-counter medications was not evaluated in this study; consequently, the risk of low-dose aspirin-related LGIB might have been under-estimated. More patients in the low-dose aspirin group experienced ischaemic stroke and used pro-bleeding drugs. Moreover, studies using ICD-10-CM (rather than ICD-9-CM) are warranted.

However, low-dose aspirin remained an independent risk factor for LGIB after adjustments for age, sex, comorbid conditions and pro-bleeding drugs.

COMMENT

Aspirin or ASA is one of the most commonly prescribed drugs in clinical practice. It acts by irreversible inhibition of the cyclo-oxygenase enzyme in a non-selective manner, leading to suppression of production of thromboxanes and prostaglandins. Apart from use as an analgesic and anti-inflammatory agent, it has cemented its place as a prophylactic agent against thromboembolic events in atherosclerosis. Daily low doses (75–325 mg) are used for the treatment and prophylaxis of ischaemic heart disease, ischaemic stroke and peripheral vascular disease.

Gastric mucosal injury and consequent upper GI bleeding is a well-documented adverse effect of aspirin use, often necessitating the use of concomitant PPIs or prostaglandin analogues. Should this be a cause of worry? The relative risk of major GI bleeding with low-dose aspirin in a meta-analysis of placebo-controlled trials of vascular protection was 2.07 (95% CI 1.61–2.66). The absolute rate of increase with aspirin above placebo was 0.12% per year (95% CI 0.07–0.19%).[1] In another study, aspirin, warfarin and SSRI users tended to suffer more severe GI bleeds than non-users of these drugs.[2] Other studies have differed in this regard. A systematic review and meta-analysis found no significant increase

in the risk of fatal GI bleed in those who received aspirin versus those who did not. However, the risk of developing cerebral haemorrhage instead was found to be substantial.[3] In another observational prospective cohort study involving 104 patients, it was shown that the use of antiplatelet agents such as long-term low-dose aspirin did not significantly alter the hospital course or outcome in patients admitted with acute GI bleeding.[4]

Although aspirin may cause bleeding from any part of the gut, LGIB has not been a major area of concern, presumably because of a low incidence as compared to upper GI bleeding. However, with an increasing number of patients on long-term low-dose aspirin for various indications, it may be prudent to look at LGIB with renewed concern. Adding to the need for scrutiny is the fact that many such patients are on multiple other medications, which may be associated with this adverse effect either independently or in addition with aspirin.

In this large study by Chen *et al.*, the incidence of LGIB in 1 year was 0.2%. A similar result was found in a previous study by Lanas *et al.* on NSAIDs/aspirin-related LGIB.[5] It must be noted, however, that the low-dose aspirin group had a statistically significant larger proportion of patients taking other medications which are independent risk factors for bleeding such as NSAIDs, steroids and other antiplatelet agents such as clopidogrel and ticlopidine. The authors of the present study chose to control the confounding factors using statistical methods and concluded that after adjustments for age, sex, comorbid conditions, NSAIDs, clopidogrel, ticlopidine, warfarin, steroids and SSRIs, aspirin was still a significant independent risk factor for bleeding. Taha pointed out that it would have been wiser to exclude such 'multidrug' patients from the aspirin group.[6]

An interesting result of the study was the implication of PPIs and H2RAs as risk factors for LGIB. These agents are used to prevent bleeding and heal ulcers in the upper GI tract. Studies have found that when combined with aspirin or NSAIDs, PPIs might be damaging the intestinal mucosa.[7,8] However, no study has clearly implicated PPIs alone as a cause of bleeding.

Should the prophylactic use of low-dose aspirin be discontinued once LGIB occurs? There is no equivalent of PPIs for the lower GI tract, nor is endoscopic haemostasis done routinely for such bleeds. In a retrospective study of 295 patients over a 5-year period, LGIB recurred in 18.9% of aspirin users (95% CI 13.3%–25.3%) versus 6.9% of non-users (95% CI 3.2%–12.5%; p=0.007). However, serious cardiovascular events occurred in 22.8% of aspirin users (95% CI 16.6%–29.6%) versus 36.5% of non-users (95% CI 27.4%–45.6%; p=0.017). Multivariable analysis showed that aspirin use was an independent predictor of rebleeding, but protected against cardiovascular events and death.[9] The American College of Gastroenterology recommends maintaining patients with established high-risk cardiovascular disease (CVD) and LGIB on aspirin.[10]

If a decision has been taken to discontinue aspirin, should it be restarted after the LGIB has been controlled? If so, when? These questions remain difficult to answer.

It is also relevant to address another issue: how useful is aspirin as a preventive measure against CVD? For primary prevention, various randomized controlled trials have produced mixed results; therefore, controversy persists.[11] In a systematic review with meta-analysis, it was shown that aspirin had only a modest effect on the prevention of CVD, largely due to reduction in the number of non-fatal events of myocardial infarction. Even this small benefit could be negated by a significant increase in bleeding events. Miedema and Virani recommended that low-dose aspirin therapy should be reserved for middle-aged patients with a high (>10%) 10-year CVD risk and acceptable bleeding risk.[12] On the other hand, for secondary prevention, RCTs have shown benefit. In patients with non-variceal upper GI bleeding, current guidelines recommend continuation of aspirin in patients taking it for secondary prophylaxis.[13]

The authors advise to develop a strategy to prevent and monitor LGIB in patients for whom aspirin prophylaxis is justified. However, they have not given the outline of that strategy.

Conclusion

Since GI bleeding is a risk, low-dose aspirin must be used with caution. It is suitable for prophylaxis only in carefully selected patients. In those who develop bleeding, regardless of its anatomical origin, the benefits of protection against CVDs, stroke and cancer would have to be weighed against the risk of recurrent bleeding. If the purported benefits are too large to be ignored, the risk of bleeding must be explained to the recipient.

Relevance to India

Misuse of prescription medications is a major problem in India. Aspirin is a particular concern, since it is prescribed often without an adequate assessment of risk factors for CVD and stroke. Multiple pro-bleeding medications are usually found on a single prescription. Thus, there is a need to create and sustain awareness about the risk of bleeding from any part of the gut with the long-term use of aspirin. In case of patients in whom aspirin prophylaxis cannot be avoided, the physician must be vigilant for bleeding during long-term follow-up.

Conflicts of interest. None declared

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