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Optimizing cardiovascular and chemopreventive benefits of aspirin: what role for the proton-pump inhibitors?

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INTRODUCTION

Aspirin has been studied as a means of primary and secondary prevention of cardiovascular events. In those with a history of cardiovascular disease (CVD), a meta-analysis of six trials involving 6300 patients found that the use of low-dose aspirin (≤ 325 mg/day) reduced all-cause mortality by 18%, the number of strokes by 20%, myocardial infarction by 30% and other 'vascular events' by 30%.[1] The benefits of aspirin in those without a history of CVD have not been as clear[2] with its use in these individuals remaining controversial.

The role of aspirin as a potential chemopreventive agent for colorectal and other gastrointestinal cancers continues to evolve, supported by the results of epidemiological observations and randomized-controlled studies.[3–5]

Doctors are often unaware of a patient's use of aspirin therapy because of patients' perception of the safety of aspirin as well as its widespread promulgation as an anticancer agent. Clinically, the use of chronic aspirin therapy can have serious ramifications. Regardless of the indication for use, aspirin imparts an inherent and significant increased risk for adverse gastrointestinal events. A systematic review of 17 epidemiological studies found that the overall relative risk of serious upper gastrointestinal complications with aspirin use was 2.2 [95% confidence interval (CI): 2.1–2.4] in cohort and nested case–control studies and 3.1 (95% CI: 2.8–3.3) in non-nested case–control studies.[6] The risk for upper gastrointestinal events was elevated even with low-dose aspirin or the use of buffered formulations.[6] In those receiving non-steroidal anti-inflammatory drugs (NSAIDs), the concurrent use of aspirin substantially increases (one- to twofold) the risk for gastrointestinal events.[7]

Several strategies exist to reduce the gastrointestinal effects of aspirin alone or in combination with another NSAID. These include eradication of *Helicobacter pylori* infection and/or the use of proton-pump inhibitor (PPI) co-therapy.[7–9] In a randomized trial of *H. pylori*-positive patients with complicated ulcers receiving aspirin therapy (≥325 mg/day), Lai *et al.*[7] observed that nearly 15% of patients given *H. pylori* eradication therapy who resumed aspirin therapy (dose of 100 mg/daily) experienced recurrent ulcer complications after 1 year. In contrast, an ulcer recurrence rate of <2% was observed in those treated for *H. pylori* and given co-therapy with a PPI following the re-initiation of aspirin therapy (Figure 1). The use of a PPI or misoprostol co-therapy has been found to significantly reduce the risk for recurrent peptic ulceration in patients receiving NSAIDs[10] as well as those receiving an NSAID plus low-dose aspirin (Figure 2).[8]

Workshop Consensus on Clinical Management Issues

Is the role of aspirin for cardiovascular prophylaxis or as chemoprevention of colorectal cancer justifiable given its risks for gastrointestinal events? While the literature supports the benefits of aspirin in those with a history or CVD, its use as primary prevention must be weighed against the risk for serious gastrointestinal events.[2] In either case, in those patients in whom cardioprotective aspirin use is warranted the use of PPI co-therapy should be considered to reduce the risk for gastric injury and complications.

The role of aspirin as a chemopreventive strategy for oesophageal or colorectal cancer is still emerging and its

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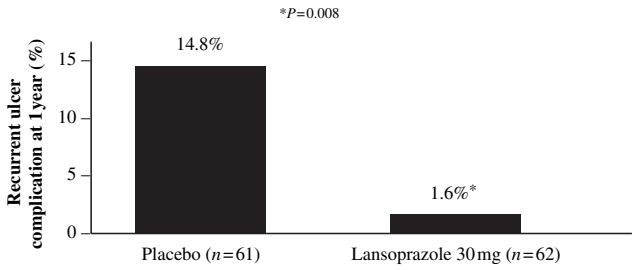

Figure 1. Placebo-controlled trial of lansoprazole for prevention of recurrent ulcer complications on low-dose aspirin. Patients who experienced an ulcer following at least 1 month of aspirin therapy were treated for *Helicobacter pylori*, resumed aspirin therapy at a dose of 100 mg/daily, were significantly less likely to experience recurrent ulcer complications with lansoprazole co-therapy compared with placebo. Adapted from Lai *et al.*[7]

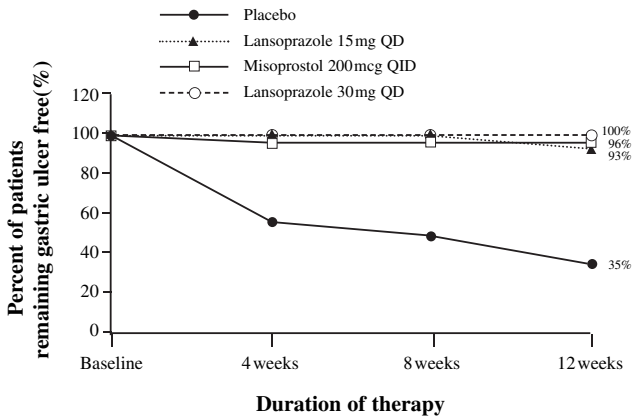

Figure 2. Patients remaining ulcer-free on chronic non-steroidal anti-inflammatory drug (NSAID) plus daily low-dose aspirin. A subanalysis of aspirin taking patients receiving NSAIDs revealed a lower risk for ulcer recurrence with lansoprazole 15 mg, lansoprazole 30 mg or misoprostol 200 mcg/day compared with placebo. Adapted from Goldstein *et al.*[8]

use cannot be considered a substitute for screening or surveillance. In the case of oesophageal cancer,[3] an association was demonstrated between aspirin use and the incidence of malignancy only. The case for secondary prophylaxis of colorectal cancer is stronger, especially in those who have undergone curative surgery and in those with familial adenomatous polyposis coli. Because the evidence for colorectal cancer prevention comes only from secondary prevention trials, it is premature to recommend the use of aspirin or any NSAID as a primary cancer chemopreventive strategy.

Does the addition of aspirin to a COX-2 selective NSAID reduce the gastrointestinal safety of the NSAID? All workshop participants felt that the addition of aspirin to a cyclo-oxygenase (COX)-2 selective NSAID regimen reduced the safety profile of the anti-inflammatory agent – 88% of these strongly agreed and 12% agreed with reservation.

Is there enough evidence to suggest aspirin for the secondary prevention of colon polyps? This proved to be a difficult issue for workshop participants to agree upon: 38% strongly agreed that there is enough evidence to suggest aspirin for the secondary prevention of colon polyps, 31% agreed with reservation and 31% felt that there is not enough evidence to warrant this management strategy.

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