



March 2005

NEWS BRIEFS from the Aspirin Foundation

'Aspirin – the developing story'

The Aspirin Foundation are holding a conference at the Royal College of Physicians, London on Tuesday 12th April 2005. Healthcare professionals, medical students, members of the media are invited to attend the one day conference – there is no fee to attend. Professional accreditation has been granted.

Professor Peter Elwood, University of Wales College of Medicine will chair the meeting. Other eminent specialists will be talking on colds and flu, pain and headache, the safety of OTC aspirin, dementia, Alzheimer's and stroke. For more information or to register please contact: aspirin@healthcom.eu.com or visit our website at www.aspirin-foundation.com

Aspirin reduces stroke risk in women

Although the effectiveness of low-dose aspirin in preventing cardiovascular events is well established, most of the evidence has been obtained in men. Now, US investigators have shown that low-dose aspirin reduces the risk of ischaemic stroke in women too (*N Engl J Med* 2005;352:published online March 7th on www.nejm.org).

In the Women's Health Study, nearly 40,000 women over 45 were randomised to take placebo or aspirin 100 mg on alternate days for 10 years. The absolute incidence of major cardiovascular events (defined as nonfatal myocardial infarction or stroke, or cardiovascular death) was 2.62 percent with placebo and 2.39 percent with aspirin – a relative risk reduction of 9 percent that was not statistically significant.

Aspirin prophylaxis had no effect on the risk of fatal or nonfatal myocardial infarction, cardiovascular death or fatal stroke but it was associated with a 24 percent reduction in the risk of ischaemic stroke (RR 0.76; CI_{95%} 0.63 - 0.93, p=0.009).

This benefit, which emerged early in the trial and did not diminish with time, was slightly offset by an increased risk of haemorrhagic stroke. The overall reduction in stroke risk was 17 percent, though it remained statistically significant (OR 0.83; CI_{95%} 0.69 - 0.99, p=0.04). Aspirin was also associated with a statistically significant 22 percent reduction in the risk of transient ischaemic attack.

Women over 65 derived consistently greater benefits from aspirin than younger women, with significant reductions in the risk of major cardiovascular events overall (by 26 percent), ischaemic stroke (30 percent) and myocardial infarction (34 percent). The investigators used alternate-day doses of aspirin to minimise gastrointestinal effects. Gastrointestinal bleeding (4.6 vs. 3.8 percent), bleeding requiring transfusion (0.6 vs. 0.5 percent) or peptic ulcer (2.7 vs. 2.1 percent) were significantly more common among aspirin users but the incidence of symptomatic gastric upset was the same as with placebo. There was no evidence that concurrent use of NSAIDs reduced the efficacy of aspirin. This study also showed that vitamin E supplementation (600 IU on alternate days) did not modify any of the effects of aspirin.

Stopping aspirin risks coronary event

Stopping aspirin prophylaxis may precipitate acute coronary syndrome (ACS) in some patients with coronary heart disease (CHD), according to a US study (*J Am Coll Cardiol* 2005;45:456-9).

They asked 1,236 patients admitted to hospital with ACS over a 2.5-year period whether they had interrupted their aspirin prophylaxis - to be sure, every patient was asked three times. 383 patients had known CHD and should have been taking aspirin; 51 cases of ACS (13.3 percent) occurred within one month of discontinuing aspirin, with an average lag time of 10 days. Ten of these patients had thrombosis associated with an uncoated stent. The coronary event was associated with ST-segment elevation in 39 percent of patients

who stopped aspirin compared with 18 percent among those who continued to take it.

The reasons for discontinuing aspirin were minor surgery or other procedures in 28 cases, bleeding in 3 cases and non-compliance in the remainder. There were no apparent differences in age, sex or other medication between the patients who stopped aspirin and others. The authors point out that both patients and doctors should be made aware of the risks associated with stopping low-dose aspirin and they recommend that compliance with prophylaxis should be improved.

Receptor status determines aspirin effect against breast cancer

Aspirin reduces the risk of breast cancer among women with oestrogen receptor-positive tumours, say US investigators (*J Am Med Assoc* 2004;291:2433-40).

One mechanism by which aspirin and other NSAIDs may lower the risk of breast cancer is to reduce prostaglandin-dependent aromatase gene expression. The final step in the synthesis of oestrogen is catalysed by aromatase cytochrome P450, so aspirin use should be associated with reduced oestrogen synthesis in breast tissue. If this mechanism underlies the lower risk of breast cancer observed among women who frequently use aspirin, it's likely that the benefit will be confined to women with hormone receptor-positive tumours.

The latest study confirmed that aspirin use is associated with a lower incidence of breast cancer. Comparing 1442 women with breast cancer with 1420 controls, it found that any use of aspirin or other NSAIDs at least once a week for at least 6 months was associated with a 20 percent reduction in the odds of having breast cancer (20.9% vs. 24.3%; odds ratio, OR, 0.80; CI_{95%} 0.66 - 0.97). Among women taking at least 7 aspirin tablets per week, the risk was reduced by 28 percent. Aspirin's effect was greater among postmenopausal than premenopausal women.

When the results were analysed by the hormone receptor status of the tumour, it was shown that the effects of aspirin were confined to women with hormone receptor positive tumours (OR 0.74; CI_{95%} 0.60 - 0.93), with no significant protection in women with hormone receptor-negative disease (OR 0.97; CI_{95%} 0.67 - 1.40).

The authors say their findings bolster the case for aspirin and NSAIDs in the chemoprevention of breast cancer, provided the balance of benefit and risk is favourable. Prospective trials are now needed to confirm their findings.

International Aspirin Award 2004 winners announced

The winners of the Bayer Healthcare International Aspirin Award for 2004 are Dr Nina Großer from Halle-Wittenberg University, Germany and Dr Leon Iri Kupferwasser from Cedars-Sinai Medical Center in Los Angeles. The award was made in recognition that their research could lead to new uses for aspirin in the future.

Dr Großer's work revealed a previously unknown mechanism for the protective effect of aspirin on vascular endothelial cells (*Arterioscler Thromb Vasc Biol* 2003;23:1345-51). She showed that, in vitro, pre-incubating endothelial cells with aspirin protected them against the toxicity of hydrogen peroxide.

Aspirin enhanced intracellular nitric oxide synthesis and the accumulation of cyclic GMP. This protective effect was abolished by a scavenger of nitric oxide, an inhibitor of the enzyme guanylyl cyclase and an L-arginine antagonist.

These findings suggest that aspirin may protect the vascular endothelium against oxidative stress by activating the nitric oxide - cyclic GMP pathway. Dr Großer concludes that this could be an important mechanism that complements aspirin's antiplatelet effects in reducing the risk of myocardial infarction, stroke and death.

Dr Kupferwasser showed that salicylate, the metabolite of aspirin, attenuates the virulence of the bacterium *Staphylococcus aureus* by modifying the genetic regulation of two key characteristics - its ability to colonise host tissues and propagate, and to breakdown host tissues (*J Clin Invest* 2003;112:222-33). In vitro, salicylate down-regulated expression of the genes regulating these process and Dr Kupferwasser confirmed that this reduced bacterial virulence in an experimental model of endocarditis.

The prevalence of multiple antibiotic resistance among *S aureus* strains is proving a clinically important problem; this research shows that the effectiveness of antibiotics in the treatment of hospital or community-acquired infections may be improved by additional treatment with aspirin.

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