

## Alternate-day dosing

### *Key points*

- Alternate-day dosing with low-dose aspirin (75 mg) may provide adequate protection against cardiovascular events in some individuals.
- Current guidelines recommend daily dosing with aspirin and alternate-day administration for patients at cardiovascular risk must therefore be at the discretion of the prescriber.

The benefits of alternate-day dosing with aspirin were first demonstrated by The Physicians' Health Study (1,2). This randomised, double-blind, placebo-controlled trial evaluated the use of aspirin 325 mg on alternate days as primary prevention of cardiovascular disease in 22,071 male physicians aged 40 - 84 years. After a mean duration of follow-up of 5 years, the risk of myocardial infarction was reduced by 44% in the aspirin group (254.8 vs. 439.7 per 100,000 per year with placebo; relative risk, RR, 0.56; CI<sub>95%</sub> 0.45 - 0.70; p<0.00001). A slightly increased risk of stroke among those taking aspirin was not statistically significant; this trend was observed primarily in the subgroup with haemorrhagic stroke (RR 2.14; CI<sub>95%</sub> 0.96 - 4.77; p=0.06). Aspirin was not associated with a reduction in mortality from all cardiovascular causes (RR, 0.96; CI<sub>95%</sub> 0.60 - 1.54). Further analyses showed that the reduced risk of myocardial infarction was confined to those aged 50 or older. The risk reduction occurred at all blood levels of cholesterol, but appeared greatest at low levels. The investigators concluded that primary prevention of cardiovascular disease with aspirin reduces the risk of myocardial infarction but the evidence concerning stroke and total cardiovascular deaths remains inconclusive (because of low numbers of these endpoints). This study does not determine whether alternate-day dosing with aspirin is preferable to daily dosing.

A subgroup analysis of the Physicians' Health study suggested that alternate-day dosing with medium-dose aspirin reduced the risk of a first myocardial infarction (3). The subgroup included 333 men with chronic stable angina at baseline but no history of myocardial infarction, stroke or transient ischaemic attack. Aspirin was associated with a reduced risk of myocardial infarction (7/178 vs. 20/155 with placebo; RR 0.30, CI<sub>95%</sub> 0.14 - 0.63; p=0.003). After adjustment for other cardiovascular risk factors, the overall risk reduction was 87% (RR 0.13, CI<sub>95%</sub> 0.04 - 0.42; p<0.001). A similar risk reduction occurred in the subgroup of patients with chronic stable angina but no previous coronary bypass surgery or coronary angioplasty. Eleven strokes occurred in the aspirin group and 2 in the placebo group (RR 5.4, CI<sub>95%</sub> 1.3 - 22.1; p=0.02). No stroke was fatal, but 4 produced some long-term impairment of function; one stroke, in the aspirin group, was haemorrhagic. This analysis indicated that alternate-day aspirin therapy reduced the risk of a first myocardial infarction among patients with chronic stable angina, a group at high risk of cardiovascular death.

Although numbers were few, aspirin may be associated with an increased frequency of stroke.

Results are expected soon from the US Women's Health Study (4), a long-term placebo-controlled study of low-dose aspirin (100 mg on alternate days) in 40,000 healthy postmenopausal, women healthcare workers. In an acute, ex vivo study in healthy volunteers, this aspirin regimen achieved adequate inhibition of platelet function. In 22 healthy volunteers, 2 weeks' administration of standard or enteric-coated aspirin 100 mg on alternate days inhibited platelet aggregation and reduced mean thromboxane and prostacyclin levels to 7.5% and 15.6% of baseline respectively (both  $p < 0.001$ ). Platelet function and thromboxane and prostacyclin production returned to normal levels after discontinuation of aspirin. There were no important differences between standard and enteric-coated formulations or between men and women.

Alternate-day aspirin 125 mg does not inhibit prostacyclin synthesis and may offer advantages for patients with atrial fibrillation. In a non-blinded trial (5), 285 patients with primary atrial fibrillation (age 40 - 82 years) were randomised to treatment with aspirin 125 mg daily (group A1) or on alternate days (A2) or no treatment (C). Follow up ranged from 1 - 62 months. The most frequent final event was sudden cardiac death associated with heart failure or angina (4.8%, 1.1%, and 6.6% in groups A1, A2, and C respectively). Cardiovascular mortality rate and the incidence of main events less frequent with alternate-day aspirin than among controls (1.1% in group A2 vs. 6.6% in group C); the differences between group A1 and C were smaller and not statistically significant. Both regimens of aspirin were associated with fewer major cardiovascular events than among controls (group C, 7.7%; group A1, 2.2%; group A2, 5.5%). There were no significant differences for other endpoints. (Note that current guidelines for the management of atrial fibrillation do not recommend the use of aspirin unless warfarin is contraindicated.)

A recent multicentre, open-label, randomised controlled trial found no difference between alternate-day low-dose and daily low-dose aspirin in 751 hospitalised patients in preventing subsequent cardiovascular events for one month following acute myocardial infarction (6). Treatment with aspirin was initiated immediately at a dose of 162 mg on the first and second day after myocardial infarction, after which patients were randomised to aspirin 81mg on alternate days or 162 mg/day. The groups were well matched (no significant differences in age, sex, hours from onset to admission, Killip classification, number of thrombolytic therapies, percutaneous transluminal coronary angioplasty, and other drug treatment). After 30 days, there were no significant differences in the incidence of angina refractory to drug therapy, reinfarction, cerebral vascular accidents or adverse effects. Cardiac death occurred in 9 patients taking daily aspirin and in none of those taking the alternate-day regimen ( $p = 0.0037$ ). Fatal cerebral infarction occurred in 2 patients taking alternate-day aspirin and in none of those taking daily aspirin. Although this study was underpowered, the authors concluded that it showed no difference in the risk of in-hospital cardiovascular events between these aspirin regimens.

*References:*

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