

Aspirin for primary prevention of cardiovascular disease in women: does sex matter?

Recommendations for primary prevention in women need to be different

The efficacy of low-dose aspirin for the secondary prevention of cardiovascular disease among men and women is established.^{1,2} However, the risk-to-benefit ratio for aspirin in primary prevention is much less clear.^{2,3} The National Heart Foundation has recommended that low-dose aspirin be considered for people without symptoms but at increased (>1% annual) risk of a coronary heart disease event.⁴ This recommendation is based on earlier primary prevention trials, with over 55 000 participants, showing a significant 32% reduction in the risk of myocardial infarction, but no significant change in risk of stroke or cardiovascular death.³ However, women comprised only 20% of trial participants, and fewer than 180 of the 2402 cardiovascular events occurred in women.^{3,5} Until recently, there has been limited direct evidence for the efficacy of aspirin in primary prevention among women.

The Women's Health Study (see Box) not only addressed this important sex issue, but suggested a significant difference in the cardiovascular response to aspirin between women and men.⁵ In this study, confined to healthy women aged 45 years or older, aspirin prophylaxis did not lower the risk of a first major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes) — the primary endpoint. However, it did significantly reduce the risk of all strokes by 17%, and ischaemic stroke by 24%, without affecting the risk of myocardial infarction or cardiovascular death.⁵ This differs from previous aggregate data derived from mostly middle-aged men, and confirmed by a recent sex-specific meta-analysis, which showed that aspirin therapy significantly reduced the risk of myocardial infarction but not ischaemic stroke in men.⁶

Are there any apparent reasons for the seemingly opposite results for stroke and myocardial infarction in men and women? One possibility is that aspirin lowered the risk of stroke in women, but not men, simply because women have a higher risk of stroke than myocardial infarction. For instance, the ratio of incident stroke to myocardial infarction was 1.4 : 1 among women in the placebo group of the Women's Health Study, compared with 0.4 : 1 among men of a similar age in the placebo group of the Physicians' Health Study (a randomised, double-blind, placebo-controlled trial examining whether low-dose aspirin [325 mg every second day] decreases cardiovascular mortality and whether β -carotene reduces the incidence of cancer).⁷ Conversely, the Women's Health Study may have lacked statistical power with respect to the risk of myocardial infarction. The study enrolled a group of largely healthy women, 85% of whom had a 10-year Framingham coronary risk score of less than 5%. Women also have a lower age-adjusted incidence of coronary heart disease than men; the rate of myocardial infarction among women in the Women's Health Study was 97.3 per 100 000 person-years, about one-fifth the rate of myocardial infarction among men in the Physicians' Health Study.⁷

Women tend to develop heart disease between 10 and 15 years later than men. This may explain why consistent benefits of aspirin on all major cardiovascular endpoints, including myocardial infarction and stroke, were observed only among women aged 65

Summary of the Women's Health Study⁵

- A large randomised placebo-controlled trial of aspirin (100 mg on alternate days) for primary prevention among 38 876 initially healthy women, aged 45 years or older, followed for 10 years for the occurrence of a first major cardiovascular event (myocardial infarction, stroke, or death from cardiovascular causes).
- The study recruited healthy women, 85% of whom had a 10-year Framingham risk score of less than 5%.
- The 10-year absolute cardiovascular event rate was low, and among placebo recipients there were more strokes than myocardial infarctions (266 v 193).
- At the end of the trial, major cardiovascular events (the primary endpoint) occurred in a non-significant 9% fewer aspirin recipients than placebo recipients (2.4% v 2.6%; $P=0.13$).
- With regard to secondary endpoints, there was a significant 17% reduction in the risk of stroke in the aspirin group (1.1% v 1.3% with placebo; $P=0.04$), owing to a 24% reduction in risk of ischaemic stroke; the two groups did not differ significantly in their incidence of myocardial infarction or cardiovascular death.
- Subgroup analyses showed that aspirin significantly lowered the risk of major cardiovascular events, ischaemic stroke, and myocardial infarction among women 65 years of age or older (6.4% v 8.5% with placebo; $P=0.008$).
- The aspirin group had a higher frequency of gastrointestinal bleeding (4.6% v 3.8% with placebo; $P<0.001$), and a non-significant increase in risk of haemorrhagic stroke (0.26% v 0.21% with placebo; $P=0.31$).
- Overall, this trial indicates that caution is necessary when advising apparently healthy women to take low-dose aspirin for cardiovascular disease prevention. ◆

years or older in the Women's Health Study.⁵ This subgroup comprised 10% of the study population, but accounted for nearly a third of all cardiovascular events. In this subgroup, aspirin, compared with placebo, led to 44 fewer myocardial infarctions, strokes, or deaths from cardiovascular causes, but also caused 16 more gastrointestinal haemorrhages requiring transfusion, emphasising again the importance of balancing benefits and risks.⁵ A recent overview has also suggested that the risk of gastrointestinal and other bleeding with aspirin use may increase with age, and that the true balance of risks and benefits in the healthy aged population has not yet been established by randomised trials.⁸

The 100 mg alternate-day dose of aspirin used in the Women's Health Study is lower than doses employed in previous trials. However, this regimen of aspirin was sufficient to reduce the risk of ischaemic stroke, and hence is likely to be an adequate dose for cardiovascular prevention. Nonetheless, sex differences in salicylate metabolism, platelet responses, vascular reactivity, and the nature of atherosclerotic disease may well cause different biological responses between men and women.⁹⁻¹¹ This further highlights the need for women to be well represented in cardiovascular trials.

What are the clinical implications of the Women's Health Study? Overall, this study indicates that clinicians should be very

cautious about advising women under the age of 65 years to take low-dose aspirin for primary prevention unless their global risk score is high. Even the benefit of aspirin for prevention of stroke in women needs to be carefully weighed against the increased risk of bleeding complications, and the low risk of stroke and other major cardiovascular events among apparently healthy women. To put this into perspective, the absolute risk reduction with aspirin therapy was about two stroke events per 1000 women treated.⁵ Thus, as with men, any decision about the use of aspirin for primary prevention among women requires an assessment of the net absolute benefit of therapy in an individual, and such a decision should be made only in association with an overall program of lifestyle measures to reduce cardiovascular risk.² Reflecting these developments, the National Heart Foundation of Australia has recently amended its position statement on aspirin for cardiovascular disease prevention.¹²

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