



Critical Appraisal

Does low-dose ASA help prevent cardiovascular events in women?

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Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women [The Women's Health Study]. *N Engl J Med* 2005;352:1293-304.

Research question

Is acetylsalicylic acid effective in primary prevention of cardiovascular (CV) events in women?

Type of article and design

Randomized, blinded, placebo-controlled trial using a 2x2 factorial design to allow separate assessment of low-dose ASA (100 mg every other day) and vitamin E (600 international units every other day). The factorial design allows investigators to evaluate the separate effects of 2 interventions in one study (in this trial, low-dose ASA and vitamin E).

Relevance to family physicians

Cardiovascular disease (CVD) is the leading cause of death in Canada. In men of all ages, 36% of deaths are attributable to CVD. In women, the percentage is slightly higher at 38%.¹ Acetylsalicylic acid is widely prescribed for prevention and treatment of CVD and is one of the most widely used pharmacologic agents in the United States.² Five large randomized controlled trials have evaluated the role of ASA in primary prevention of CVD. A meta-analysis of these trials showed that ASA could substantially reduce risk of coronary artery disease events (number needed to treat [NNT] 194).³ Direct evidence for use of ASA for primary prevention of CVD in women is limited, however, because only 20% of the patients studied in these trials were women.

Overview of study and outcomes

For this large trial, 39876 female health professionals (mean age 54 years) were recruited in the United States. Women were eligible if they were 45 years old or older; had no history of coronary artery disease, cerebrovascular disease, cancer, or other major chronic illnesses; had no history of side effects from any of the

study medications; were not taking ASA or nonsteroidal anti-inflammatory drugs more than once a week; were not taking anticoagulants or corticosteroids; and were not taking individual supplements of vitamins A or E or beta-carotene more than once a week.

Patients were randomly allocated to receive ASA (100 mg every other day) or placebo. Treatments were centrally assigned with computer-generated randomization. Study medications and end-point assessments were continued in a blinded fashion through to the end of the trial. Follow-up and validation of reported end points were completed in February 2005. Rates of follow-up with respect to morbidity and mortality were high (97.2% and 99.4%, respectively).

The primary end point was the cumulative rate of major CV events, including non-fatal myocardial infarction, non-fatal stroke, and death from CV causes. Secondary end points included the individual end points of fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, ischemic stroke, hemorrhagic stroke, and death from CV causes. Additional analyses included incidence of death from any cause, transient ischemic attacks, and the need for coronary revascularization.

Results

The large sample size and good randomization system used in this trial produced well-balanced ASA and placebo groups. Mean follow-up was 10.1 years. There was a non-significant reduction in major CV events in the ASA group (relative risk [RR] 0.91, 95% confidence interval [CI] 0.80 to 1.03). The most important significant results of this trial are shown in **Tables 1** and **2**. There was a non-significant increase in risk of hemorrhagic stroke in the ASA group (RR 1.24, 95% CI 0.82 to 1.87). Compared with placebo, ASA had no significant effect on risk of fatal or non-fatal myocardial infarction (RR 1.02, 95% CI 0.84 to 1.25) or death from CV causes (RR 0.95, 95% CI 0.74 to 1.22). Among women 65 years old or older, however, subgroup analyses showed that ASA substantially reduced risk of major CV events (RR 0.74, 95% CI 0.59 to 0.92), ischemic stroke (RR 0.70, 95% CI 0.49 to 1.00), and

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Table 1. Potential benefits of ASA therapy in the Women's Health Study

OUTCOMES	NUMBER NEEDED TO TREAT	95% CONFIDENCE INTERVAL
All strokes	444	227-10 563
Ischemic strokes	392	223-1618
Non-fatal strokes	434	229-4000
Transient ischemic attacks	385	217-1704

Table 2. Potential harm of ASA therapy in the Women's Health Study

OUTCOMES	NUMBER NEEDED TO HARM	95% CONFIDENCE INTERVAL
All gastrointestinal bleeding	125	84-245
Gastrointestinal bleeding requiring transfusion	553	307-2773
Peptic ulcer	154	105-287
Hematuria	124	66-899
Easy bruising	10	9-11
Epistaxis	41	32-60

myocardial infarction (RR 0.66, 95% CI 0.44 to 0.97). The authors of this study also did a meta-analysis that included the female populations in the previous primary prevention trials that evaluated the role of ASA in primary prevention of CVD in women. In this meta-analysis, ASA therapy was associated with a substantial reduction in risk of stroke (RR 0.81, 95% CI 0.69 to 0.96) and no reduction in risk of myocardial infarction (RR 0.99, 95% CI 0.83 to 1.19). Results of this meta-analysis were influenced mainly by the results of the Women's Health Study, which represented 71% of the population included in this meta-analysis.

Analysis of methodology

This was a well designed trial with excellent follow-up. Analysis was based on the intention-to-treat principle. Two limitations of this study can explain the lack of benefit of ASA in prevention of major CV events and myocardial infarction. First, the general health of the study population was not representative of the health of the general population. This trial enrolled a very healthy and health-conscious group of women; 84.4% of them had a 10-year Framingham risk score lower than 5%. The United States Preventive Services Task Force systematically reviewed the role of ASA in primary prevention of CVD and concluded that the net benefit of ASA was small in patients with a 5-year Framingham risk score lower than 5%.³ The second limitation is that this trial used 100 mg of ASA every other day, which is lower than doses

used in previous primary prevention trials.⁴ The US Preventive Services Task Force and the European Society of Cardiology recommend use of low-dose ASA (75 to 100 mg/d).^{3,5} Several human studies have shown no or minimal differences between men and women in the antithrombotic effects of ASA, which makes sex-based differences an unlikely explanation of the lack of benefit of ASA in prevention of major CV events.^{6,7}

Application to clinical practice

The balance of risks and benefits of ASA in this trial does not look favourable, as indicated by the large NNT with very wide 95% CIs and the smaller number needed to harm for several serious complications (Tables 1 and 2). The NNT found in this trial was much larger and less attractive than that reported in previous primary prevention trials.⁴ In this trial, women at high risk of CVD, for example those 65 years old and older, benefited more consistently from ASA. These results should not be a surprise, as several papers have confirmed that the balance of benefit and harm of ASA therapy for primary prevention of CVD is less favourable in people at low risk (those with a 10-year risk lower than 5%). The balance of benefit and harm of ASA therapy is most favourable among people at high risk (those with a 10-year risk at or greater than 5%).^{3,8} As a general guide, men older than 40 and postmenopausal women with risk factors for coronary artery disease (eg, hypertension, diabetes, hyperlipidemia, or smoking) have a 10-year risk at or greater than 5%. Several CVD risk-prediction charts are available and can be used in clinical practice to estimate individual patients' 10-year risk of CVD.

Bottom line

- The balance of risks and benefits of ASA therapy for primary prevention of CVD does not look favourable among women and men at low risk of CVD.
- In women 65 years old or older, ASA therapy substantially reduced major CV events.
- Decisions to start patients on ASA therapy for primary prevention of CVD should take into account overall risk of CVD.
- Patients have to be involved in the decision to start ASA therapy and have to understand the potential risks and benefits of ASA therapy.
- Funding agencies should push more to include women in clinical trials evaluating interventions for prevention and treatment of CVD.



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Points saillants

- L'analyse comparative des risques et des bienfaits d'une thérapie à l'AAS pour la prévention primaire des maladies cardiovasculaires (MCV) chez les femmes et les hommes à faible risque de contracter ces maladies ne semble pas pencher en faveur de la thérapie.
- Chez les femmes de 65 ans et plus, la thérapie à l'AAS a réduit considérablement les accidents cardiovasculaires majeurs.
- La décision d'amorcer une thérapie à l'AAS pour la prévention primaire des MCV devrait prendre en compte le risque global de MCV.
- Les patients doivent participer à la décision de commencer une thérapie à l'AAS et comprendre les risques et les avantages potentiels d'une telle thérapie.
- Les organismes de financement devraient insister davantage sur l'inclusion de femmes dans les études cliniques qui évaluent les interventions de prévention et de traitement des MCV.

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