Should patients who have not had a cardiac event take ASA to prevent one?

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Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet* 2001;357:89-95.

Research question

Is acetylsalicylic acid or vitamin E effective in primary prevention of cardiovascular (CV) events in people with one or more major CV risk factors?

Type of article and design

Open-label, randomized controlled trial with a 2x2 factorial design.

Relevance to family physicians

Cardiovascular disease is the leading cause of death in Canada, accounting for 37% of all deaths.[1] Premature death from CV disease is responsible for an estimated 294 000 years of life lost; only injuries and cancer account for more years of life lost.[2] Physicians freqently prescribe ASA for prevention and treatment of CV disease; ASA is one of the most widely used pharmacologic agents in the United States.[3] In the United Kingdom, estimated yearly incidence among new patients per general practitioner of acute myocardial infarction (MI), previous MI, stable or unstable angina, and transient ischemic attacks (TIA) and strokes is 4.6, 1.0, 10.4, and 5.0, respectively.[4] Simple, accessible, safe preventive therapies that will decrease incidence and mortality of CV disease are expected to have a great effect on public health.

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail michael.evans@utoronto.ca or by fax (416) 603-5821.

Overview of study and outcomes

In this trial, 4495 patients (mean age 64.4 years) were recruited from general practice (95%) and hypertension clinics (5%). Inclusion criteria were older age (>50 years), hypertension (systolic blood pressure 160 mm Hg or diastolic 95 mm Hg), hypercholesterolemia (total blood cholesterol 6.4 mmol/L), diabetes mellitus, obesity (body mass index ≥30), and family history of MI before 55 years old in at least one parent or sibling. Exclusion criteria were treatment with antiplatelet drugs, history of vascular events or diseases, chronic use of anti-inflammatory agents or anticoagulants, contraindications to ASA, and diseases with predictable poor short-term prognoses.

Patients were randomly allocated to receive ASA (one 100-mg tablet of enteric-coated ASA daily) or no ASA, and vitamin E (one 300-mg capsule of synthetic tocopherol daily) or no vitamin E, following a 2x2 factorial design. Treatments were assigned with computer-generated randomization. At the beginning, and repeatedly during the trial, all patients received advice on compliance with background treatments and control of CV risk. Follow-up visits were scheduled yearly and included reassessment of presence and level of CV risk factors and recording of outcomes. The primary outcome was the cumulative rate of CV death, non-fatal MI, and non-fatal stroke. Secondary outcomes included CV deaths, total deaths, total CV events (CV death, non-fatal MI, non-fatal stroke, angina pectoris, TIAs, peripheral artery disease, and revascularization procedures).

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Table 1. Significant results of trials of ASA for primary prevention of cardiovascular events

TRIAL	DOSE (MG/D)	OUTCOMES	RESULTS (95% CI) RELATIVE RISK	RESULTS (95% CI) NUMBER NEEDED TO TREAT
Physicians' Health Study[7]	325	Fatal MI	.34 (.15-.75)	690
		Non-fatal MI	.59 (.47-.74)	131
		Total MI	.56 (.45-.70)	110
HOT trial[5]*	75	Major CV events†	.85 (.73-.99)	176
		All MI	.64 (.49-.85)	208
Thrombosis prevention trial[6]	75	Non-fatal MI	.65 (.44-.92)	49
Primary Prevention Project (study trial)	100	Total CV events‡	.77 (.62-.95)	53
		CV deaths	.56 (.31-.99)	167

CV—cardiovascular, MI—myocardial infarction.
**Six percent of participants had a history of coronary artery disease.*
†All MI, all strokes, and all other CV deaths.
‡Cardiovascular deaths, non-fatal MI, non-fatal strokes, transient ischemic attacks, angina pectoris, peripheral artery disease, and revascularization procedures.

Results

Baseline characteristics, except for hypercholesterolemia, were well-balanced across groups. Mean cholesterol concentrations were slightly higher in the ASA group. Most patients with hypertension and diabetes were treated with drugs (although treatment was not always well controlled), and 40% of patients with hypercholesterolemia received lipid-lowering drugs. Antihypertensive, antidiabetic, and lipid-lowering drugs were well-balanced across groups at baseline and at the end of the study.

Mean follow up was 3.6 years; 81% of patients randomized to ASA complied with treatment. There was a nonsignificant reduction in the primary outcome in the ASA group (relative risk [RR] 0.71, 95% confidence interval [CI] 0.48 to 1.04). There was a significant reduction in total CV events (RR 0.77, 95% CI 0.62 to 0.95) and in CV mortality (RR 0.56, 95% CI 0.31 to 0.99).

Analysis of methodology

This was a well designed trial with excellent follow up (92%). Most participants were recruited from general practice (95%). Analysis was based on intention to treat. The range of inclusion criteria increased the generalizability of the conclusions, especially for family medicine settings. This was an open-label trial, but a committee of experts masked to treatment assignment assessed outcomes, which minimized bias. After a mean follow up of 3.6 years, the trial was prematurely stopped on ethical grounds because newly available evidence from other trials on the benefit of ASA in primary prevention showed significant reductions in the main end point recorded in the planned interim analysis.[5,6]

Application to clinical practice

This trial showed a significant reduction in total CV events and CV deaths. Other large trials showed a significant reduction in fatal and non-fatal MIs and in major CV events (**Table 1**).[5-7] A trial of ASA (500 mg) in British male doctors,[8] however showed no significant reduction in incidence or mortality of MI or CV events. This trial and the HOT (Hypertension Optimal Treatment) trial[5] involved a large proportion of women, which enabled us to apply the conclusions of these large trials to our female patients. Most of these trials involved patients >50 years with one or more risk factors for coronary events.

Gastrointestinal bleeding was more frequent among patients in the ASA group (RR 3.5, number needed to harm [NNH] 184). In a large meta-analysis of 24 RCTs, ASA treatment was associated with a significant increase in gastrointestinal bleeding (odds ratio [OR] 1.68; 95% CI 1.51 to 1.88, NNH 106 based on an average of 28 months' therapy).[9]

No major differences were seen between groups in incidence or type of stroke, but the total number of strokes was small in this trial. In a large meta-analysis of 16 RCTs, ASA was associated with a significant increase in hemorrhagic stroke (NNH 833); in this meta-analysis, ASA was associated with a reduction in incidence of ischemic stroke (NNT 256).[10] Vitamin E appeared to have no effect on CV events, but this could be attributed to the inadequate power of a prematurely interrupted trial.

Bottom line

- Acetylsalicylic acid therapy should be considered for primary prevention of CV events in patients ≥50 years with one or more risk factors for coronary events and no contraindications to ASA therapy.
- This trial showed that ASA therapy is effective in primary prevention of coronary events in women.
- No reduction was seen in total mortality in this and the other large trials of primary prevention using ASA.

- Low-dose ASA should be used in primary prevention of coronary events (75 to 100 mg); it has been shown to be effective and to have fewer side effects than higher doses.[11,12]
- If ASA therapy is considered, blood pressure should be well controlled (<145/90 mm Hg). Patients with uncontrolled hypertension might derive no CV benefit from ASA and could risk serious bleeding.[13] Physicians and patients should discuss the potential benefits and risks of ASA therapy before starting it.

Points saillants

- La thérapie à l'aide de l'acide acétylsalicylique (AAS) devrait être envisagée comme traitement de prévention primaire des accidents vasculaires cérébraux chez les patients de ≥50 ans présentant un ou plusieurs facteurs de risque d'accidents coronariens et chez qui il n'est pas contre-indiqué de suivre une thérapie à l'AAS.
- La présente étude a fait valoir que la thérapie à l'AAS est efficace comme mesure de prévention primaire d'accidents coronariens chez les femmes.
- Aucune réduction de la mortalité totale n'a été observée dans la présente étude, ni dans d'autres de plus grande envergure, sur la prévention primaire à l'aide de l'AAS.
- L'AAS à faible dose (75 à 100 mg) devrait être utilisée comme mesure de prévention primaire des accidents coronariens; son efficacité a été éprouvée et ses effets secondaires sont moins grands que ceux de doses plus élevées[11,12].
- Si on envisage une thérapie à l'AAS, il importe de bien contrôler la pression artérielle (<145/90 mm Hg). Les patients chez qui l'hypertension est mal contrôlée pourraient ne tirer aucun bienfait sur le plan cardiovasculaire et courir un risque d'hémorragie grave[13]. Les médecins et leurs patients devraient discuter des avantages et des inconvénients éventuels avant de commencer une thérapie à l'AAS.

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