

Primary Prevention of Cardiovascular Disease

4 Answers on ASA



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The role of acetylsalicylic acid (ASA) for patients with atherosclerotic disease is now uncontested. Recent meta-analysis showed ASA reduces the risk of relapse by about 20% to 30% for subjects with conditions such as angina and intermittent claudication and for those who have had an infarction or a stroke.¹

The benefits of ASA use as a primary prevention tool for individuals without a clinical or paraclinical manifestation of atherosclerotic disease are less clear.

Table 1

Effectiveness of ASA in primary prevention

| Issues | Relative Risk (IC95%) | NNT/year (Number needed to treat/year) NNH/an (Number needed to harm/year) |
|---------------------------|-----------------------|---|
| Benefits | | |
| Myocardial infarction | 0.72 (0.60-0.87) | 875 |
| Total mortality | 0.87 (0.70-1.09) | NS |
| Total strokes | 1.02 (0.85-1.23) | NS |
| Deaths from all causes | 0.93 (0.84-1.02) | NS |
| Risks | | |
| Haemorrhagic stroke | 1.4 (0.9-2.0) | NS |
| Gastrointestinal bleeding | 1.7 (1.4-2.1) | 950 |

NS: Not significant

Hayden M, Pignone M, Phillips C, et al: Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; 136(2):161-71.

➤ 1. What about women?

There is much less evidence for the use of ASA as primary prevention for women. Only two of the five major studies in primary prevention included women.

- In the Primary Prevention Project (PPP), benefit seemed identical for men and women.
- In the Hypertension Optimal Treatment trial (HOT), infarction incidences did not significantly decrease for women.
- The Nurses' Health Study (a 1991 observation study of 88,000 women) showed one to six doses of ASA/week reduced the number of myocardial infarctions by 25%.²

However, no major total decreases were recorded for vascular incidents (cardiac deaths, infarctions or strokes) or total deaths.² The definite response to whether ASA is beneficial in primary prevention for women is currently the objective of a major study of 40,000 patients (Women's Health Study).³

Survey says...

Five randomized studies carried out between 1988 and 2001 evaluated the effectiveness of ASA in primary prevention.

These studies brought forth very similar results—ASA use significantly reduces the occurrence of MI by approximately 28% (for the five studies, the number needed to treat/year varied between 364 and 2,265). On the other hand, total mortality, cardiac deaths and occurrences of strokes were not significantly reduced (Table 1).

Although these studies focused on high-risk subjects (*e.g.*, mostly men over 50, often with other risk factors), the annual risk of major cardiovascular events (cardiac deaths, infarctions, strokes) is remarkably low: between 0.72% and 1.54%/year.

Followup monitoring for these studies is relatively short (three to seven years) and more long-term effects remain undetermined.

In HOT, ASA use significantly reduced occurrences of clinical MI. However, when silent infarctions (detected from an electrocardiogram [ECG]) were included, this decrease ceased to be significant.⁹

So, does ASA only reduce the symptoms of an infarction without reducing the real incidence? This remains to be seen.



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➤ 2. Does diabetes play a role?

Patients with diabetes are known to be at higher risk for cardiovascular events. A diabetes patient who has never had an MI is at equal risk as a patient who has.⁴

That said, the Canadian Working Group on Dyslipidemia recommends low-density lipoprotein (LDL) targets be identical for patients with atherosclerotic disease or diabetes.⁵ In this sense, ASA use for diabetes patients seems appropriate. However, no study to date has evaluated the effectiveness of ASA on major clinical issues in diabetes patients who do not have atherosclerotic disease.

Subanalyses of major studies indicate a benefit, although the total number of events showing a benefit remains small.⁶

Another study of diabetes patients with retinopathy, either with or without coronary heart disease, showed a tendency of decreased total mortality and infarctions. Nevertheless, there is no present study on primary prevention in the “pure” diabetic.⁷

➤ 3. What are the risks?

The price to pay for a decrease of MI is an increase in bleeding, especially gastrointestinal (relative risk 1.7). For 1,000 men receiving ASA over five years, about three will have major gastrointestinal bleeding and one will have a hemorrhagic stroke.⁸

Blood pressure is an important factor; many studies show the higher the blood pressure, the less effective ASA is. Blood pressure should thus be well-controlled.

Many other effects of ASA are being investigated. Incidences of neoplasia (particularly colorectal) could possibly be decreased, although this has not been confirmed by randomized studies. A negative interaction between angiotensin-converting enzyme (ACE) inhibitors and ASA, especially at high doses, is also the subject of controversy.

Moreover, certain patients manifest ASA resistance, which probably prevents them from drawing the same treatment benefit. However, a clinical observation of this effect is not presently feasible.

No current studies analyse primary prevention on the new clopidogrel or ticlopidine antiplatelet agents.

► 4. Any recommendations?

The U.S. Preventive Services Task Force recommends ASA use in primary prevention for patients with high risk of coronary heart disease ($\geq 3\%$ in a five-year period).⁸

The American Heart Association (AHA) and the American College of Chest Physicians (ACCP) recommend the use of ASA if the cardiovascular risk is $\geq 10\%$ in a 10-year period.^{10,11} A recent article of the *New England Journal of Medicine* recommends using ASA if:

- the risk of coronary heart disease in a 10-year period is $\geq 15\%$;
- 7% to 14% risk is diagnosed in conjunction with essential hypertension with target organ damage, diabetes, a poor physical condition; or
- patient shows preference and tolerance for ASA.^{11,12}

Cardiac risk can be evaluated with the Framingham tables or with other similar tools (Sheffield tables, Prospective Cardiovascular Munster Risky Factors, *etc.*).

The latest recommendations by the Canadian Task Force on the Periodic Health Examination date back to 1994 and these neither encourage nor discourage the use of ASA in primary prevention.

As for diabetes patients, the American Diabetes Association (ADA) suggests ASA use for high-risk individuals over 30 years of age.¹³ The ADA estimates the benefits of ASA for patients with diabetes probably outweigh the risks.

Take-home message



- ASA for patients considered at risk of atherosclerotic disease is a foreseeable option.
- The only proven benefit is a decrease of MIs.
- Optimal dose has not yet been fully determined, but is estimated to be at 80 mg/day to 325 mg/day.
- ASA should not be used as primary prevention for anticoagulated subjects; prudence is also advised for those using non-steroidal anti-inflammatory drugs, prednisone or other medications that increase overall risk.
- Taking charge of other risk factors remains primordial. These include:
 - smoke-free lifestyle,
 - healthy diet and body weight, and
 - physical exercise.

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