

Primary prevention of CHD

Summary

Low-dose aspirin (typically 75-100mg/day) is recommended to reduce the risk of coronary events such as myocardial infarction in people who have not previously experienced such events when their risk exceeds a certain threshold. This forms one part of a wider strategy to reduce coronary risk that includes other medication and lifestyle change.

The available evidence suggests that primary prevention with low-dose aspirin reduces the risk of myocardial infarction by about one-third in men at increased coronary risk. Its impact on total mortality and other vascular events, including stroke, is less clear and clinical trials have produced conflicting results. More limited evidence shows that low-dose aspirin reduces the risk of stroke in middle-aged and older healthy women and reduces the risk of cardiovascular events in healthy women over 65 years old. However, there is currently insufficient evidence to justify the use of low-dose aspirin in people who are not at increased coronary risk.

In the UK, low-dose aspirin is recommended for individuals aged over 50 whose 10-year risk of cardiovascular disease is $\geq 20\%$ (equivalent to a $\geq 15\%$ coronary heart disease risk) whose blood pressure is controlled (systolic pressure < 150 mmHg and diastolic pressure < 90 mmHg) but who have end-organ damage (e.g. nephropathy) or type 2 diabetes.

In the United States, low-dose aspirin is recommended for men whose 10-year risk of coronary heart disease is at least 10% and for women whose 10-year risk is 20%; aspirin should be considered for women whose 10-year risk is 10 - 20%.

Key points

- Primary prevention with low-dose aspirin (75-100 mg/day) reduces the risk of myocardial infarction in people at increased risk by about one-third.
- It is less clear whether this strategy reduces the risk of death or other vascular events.
- In the UK, low-dose aspirin is recommended as primary prevention for men and women aged over 50 whose 10-year cardiovascular risk is $\geq 20\%$ (equivalent to a coronary risk of 15%) and who have other risk factors.
- In the US, low-dose aspirin is recommended for men whose 10-year coronary risk is 10% and for women whose 10-year risk is 20%.
- Primary prevention with aspirin is one part of a wider strategy to reduce cardiovascular risk that includes lifestyle change and other drug therapy.

Primary prevention of coronary heart disease

Low-dose aspirin is not explicitly licensed for the primary prevention of coronary heart disease (CHD) in many countries, including Germany, the United Kingdom and the USA, but it is in more than 30 countries worldwide, e.g. Belgium, Canada, Greece, Italy, Portugal, Korea, and Switzerland. Moreover, its use is recommended for people whose risk of coronary events (such as myocardial infarction) exceeds certain thresholds. Guidelines from various professional associations make broadly comparable recommendations on when aspirin should be used in this context, based on similar bodies of evidence. Note that aspirin is one part of a multifactorial approach to reducing coronary risk that involves lifestyle change and other drug treatment.

In the UK, low-dose aspirin is recommended for primary prevention in individuals aged over 50, whose blood pressure is controlled (<150/<90 mmHg) and who have end-organ damage (e.g. nephropathy), type 2 diabetes or a cardiovascular disease risk of $\geq 20\%$ over 10 years (1). (This is equivalent to a coronary disease risk of 15%.)

In the United States, guidelines from the American Heart Association and other professional associations recommend primary prevention with low-dose aspirin in men whose 10-year risk of a CHD event is 10% or greater (2). In women, US guidance recommends low-dose aspirin for women at high risk (10-year risk greater than 20%). Low-dose aspirin should be considered for women at intermediate risk (10 - 20%) provided blood pressure is controlled and the likely benefit outweighs the risk of adverse gastrointestinal effects (3). There is a lack of evidence on which to base guidance for women at lower risk, in whom the problems of gastrointestinal effects may outweigh any coronary benefit.

UK guidance followed the publication in 1998 of the results of the Thrombosis Prevention Trial (Lancet 1998; 351:233-41) and the HOT study (Hypertension Optimal Treatment) (4). In this study, patients were randomly assigned to one of three treatment groups with a target

diastolic pressure of ≤ 90 mmHg, ≤ 85 mmHg or ≤ 80 mmHg. In addition, they were then randomly assigned to either 75mg aspirin daily or placebo. When added to antihypertensive therapy, low-dose aspirin reduced major cardiovascular events by 15%, all myocardial infarction by 36%, but had no effect on the incidence of stroke or fatal bleeds. Non-fatal bleeds, however, were twice as common and mortality was not reduced.

In 2004 the British Hypertension Guidelines were reassessed. No new evidence on the use of aspirin for primary prevention had been reported and the recommendations were unchanged (5).

In April 2001, Diabetes UK amended its guidance to state that individuals over the age of 30 with diagnosed diabetes should be offered aspirin prophylaxis if they have one or more of the following risk factors (6):

- Other conditions such as angina, previous heart attack, stroke, transient ischaemic attacks, atrial fibrillation and peripheral vascular disease
- Dyslipidaemia (high cholesterol levels, total cholesterol greater than 5.0 mmol/l, LDL more than or equal to 3.0 mmol/l, HDL less than or equal to 0.9 mmol/l).
- CVD risk $\geq 20\%$ (CHD risk $>15\%$) over the next 10 years from the coronary risk prediction chart.
- Raised blood pressure controlled to less than 150/90mmHg.
- Microalbuminuria or albuminuria.
- A family history of CHD.
- Smoking
- Overweight, with a Body Mass Index >25 .
- An Indo-Asian background.
- Diabetic retinopathy.

* The risk of cardiovascular disease (non-fatal MI, coronary death, stroke and new angina pectoris) is estimated from age, sex, presence of diabetes, smoking habit (including ex-smoker within the last 5 years), systolic blood pressure (pretreatment) and the total/HDL cholesterol

ratio (pretreatment). The risk can be calculated from charts published with the guidelines (5) or printed in the *British National Formulary* (1).

For individuals without known risk factors, there is insufficient evidence to recommend the use of aspirin for primary prevention of CHD. Two early primary prevention studies reported contradictory results. The English Physicians' Health study (7) was conducted in 5139 apparently healthy male physicians, half of whom were older than 60 years on inclusion. Compared with placebo, aspirin 500mg daily did not reduce the incidence of fatal or non-fatal MI, fatal or non-fatal stroke after 6 years. It reduced the frequency of transient ischaemic attacks (TIAs) by approximately 50%; mortality was reduced by 10% but this was not statistically significant.

The American Physicians' Health Study (8) was conducted in 22,071 male physicians aged 40 to 84 years and had an average follow-up of approximately 5 years. Compared with placebo, aspirin 325mg on alternate days significantly decreased the risk of fatal or non-fatal MI by 44%; this reduction was more marked in patients over 50 years old. Aspirin was associated with a slightly increased risk of haemorrhagic stroke but there was no overall change in cardiovascular mortality.

A meta-analysis of these studies concluded that primary prevention with aspirin reduced the rate of non-fatal MI by 33% but it did not reduce overall cardiovascular mortality. Aspirin did not reduce the risk of stroke overall though it may increase disabling stroke (9). A systematic review of the role of aspirin prophylaxis for primary prevention concluded that it is not possible to distinguish between asymptomatic individuals who would benefit and those who would be harmed (10).

A more recent meta-analysis (11) reached different conclusions. This analysis of five randomised studies (the Physicians' Health Study, the British Doctors' Trial, the Thrombosis Prevention Trial, the Hypertension Optimal Treatment Study and the Primary Prevention Project) involving a total of 55,580 participants (11,466 women), found that aspirin was associated with a statistically significant 32% reduction

in the risk of a first MI and a significant 15% reduction in the risk of all important vascular events; it had no significant effects on non-fatal stroke or vascular death. This analysis strongly supports the initial finding from the Physicians' Health Study that aspirin reduces the risk of a first MI. For apparently healthy individuals whose 10-year risk of a first coronary event is 10% or greater the benefits of long-term aspirin therapy are therefore likely to outweigh any risks.

Another recent review has also concluded from two meta-analyses of secondary and primary prevention trials that low-dose aspirin has a favourable benefit-to-risk profile supporting its widespread use in at-risk patients (12).

A trial of low-dose aspirin in the primary prevention of cardiovascular disease in women was carried out in 39,876 initially healthy women over 45 years of age (13). They were randomised to treatment with 100mg of aspirin on alternate days or placebo and were then monitored for 10 years. Overall, aspirin reduced the risk of ischaemic stroke by 24%. In the subgroup of women aged 65 or older, it also significantly reduced the risk of major cardiovascular events and myocardial infarction. This evidence suggests that primary prevention of CVD with aspirin is not effective in younger, otherwise healthy women. However, the overall benefit (which may include not only a reduced risk of stroke but also a reduction in the risk of colorectal cancer or breast cancer) may still be enough to persuade some women under the age of 65 to take daily, low-dose aspirin (14).

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