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Aspirin and myocardial infarction: is one positive study enough?

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Introduction

Acetylsalicylic acid, the active compound in aspirin, is the most widely sold drug in the world and is mainly used as a pain-killer, an anti-inflammatory agent and antipyretic drug. In 1980, 36,000 tons of aspirin were consumed in the western world, which averages approximately 20 tablets of 500 mg per person per year. During the last 15 years, aspirin has proven its efficacy as a mechanism of secondary prevention in patients with cerebrovascular and cardiovascular diseases. Aspirin slows down the aggregation of platelets, which is seen as the first step towards arterial thrombosis. Exaggerated platelet aggregation is frequently seen in patients with atherosclerosis of the larger arteries. The stimulus of this abnormal form of platelet aggregation is unknown, but has been shown that cerebral infarction, as well as myocardial infarction, are caused by complete thrombotic occlusion of a larger artery. Aspirin appears to be successful not only in the secondary prevention of these diseases, but also in the primary prevention of myocardial infarction in patients who also have symptoms of cerebrovascular disease. Retrospective studies have shown that patients who consumed large quantities of acetylsalicylic acid for rheumatic diseases reduced their likelihood of developing myocardial infarction. In the 1970s the idea was raised that this very cheap and effective drug could be valuable in the primary prevention of heart disease in healthy people. In this article, two studies, which attracted the attention of the public and in which the primary prevention of myocardial infarction with aspirin was studied, are discussed.

The American study (Physicians' Health Study)

In 1982 a letter was sent to 261,000 American physicians, all of whom were registered in the American Medical Association. They were asked to participate in a large national study on the prevention of myocardial and vascular disease with aspirin and the prevention of cancer by using beta-carotene. Fifty-nine thousand doctors agreed to participate. Physicians were excluded from the study if they had a personal history of myocardial infarction, stroke or cancer, liver, kidney and stomach diseases or gout. In addition those using anti-coagulants or vitamin A were excluded. In 1983, 33,000 doctors started a run-in phase lasting 4 months in which they were asked about complaints after taking medication. A total of 22,071 physicians between the ages of 40 and 84 were then randomized to the use of aspirin, beta-carotene, both or double placebo: 11,037 received aspirin in a dose of 325 mg every other day and 11,034 received placebo every other day. On the days that neither aspirin nor aspirin placebo were used, the physicians took beta-carotene or beta-carotene placebo.

Every 6 months for the first year and annually thereafter the physicians were sent a new supply of medication as well as a questionnaire asking about any complaints. When an end-point was reached, all information was examined by a committee of physicians, which included two internists, one cardiologist and one neurologist, all blinded to treatment assignment. The end-points were myocardial infarction, stroke and death. An external reviewing committee reported twice a year on the accumulated data and the ethical aspects of the trial. On 18 December 1987 the committee decided to report the results of the aspirin and placebo users, even though the trial was to continue until 1990. The preliminary results were then published in 1988 in The New England Journal of Medicine and the final results in 1989 in the same journal.

The English study

In 1978 an invitation was sent to about 20,000 male doctors in the United Kingdom asking them to take part in a study on the effects of aspirin in the primary prevention of myocardial infarction, stroke and death. The doctors had all replied to a questionnaire in 1951 about their smoking habits and were still listed in the 1977 Medical Directory. Eligible doctors taking aspirin, those with gastrointestinal ulcers and those who had had a myocardial infarction or a stroke, were excluded. Another 762 doctors, who were asked by other methods, also joined the study. Thus 5139 doctors were recruited for the study, of whom two-thirds (n=3149) received 500 mg aspirin daily and one-third (n=1790) were asked to avoid taking aspirin. Treatment was not blind. In an unknown percentage of doctors the aspirin dose was reduced from 500 mg to 300 mg because of side-effects. Every 6 months the doctors were sent a questionnaire asking about their health and use of aspirin.
When an end-point was reached, all information was screened by a cardiologist and a neurologist in Oxford. The study closed in November 1984, 6 years after starting. Because the results of the study were negative, it was decided not to publish them until the results of the important study of aspirin in patients with 'transient ischaemic attacks' (UK TIA trial[4]) were known. The results of both studies were published in the British Medical Journal 2 days after publication of the American study.

Results

The American study was, as earlier stated, prematurely stopped and published because of the favourable results in the aspirin group. Overall, there was a 44% reduction in the risk of myocardial infarction in the aspirin group (139 myocardial infarctions, including 10 deaths) compared to the placebo group (239 myocardial infarctions, including 26 deaths). This difference is statistically significant ($P<0.00001$). For stroke there was a non-significant 22% increase (in the aspirin group 119 strokes, including nine deaths, in the control group 98 strokes, including six deaths, $P=0.15$). The classification of stroke is not completely clear, because the diagnosis was made by a local neurologist unrelated to the study. Peptic ulcer was reported in 169 aspirin and 138 placebo subjects ($P=0.08$). Other side-effects attributable to aspirin were not reported. Total death was not significantly different in the treatment group: 217 in the aspirin group compared to 227 in the placebo group. The total death rate was barely 2% during a follow-up period of nearly 5 years, which is very low. Death from cardiovascular disease was identical in both groups and was also exceptionally low: 0.7% (3.5% is the norm for American white males). Details as regards risk groups who may have profited from aspirin or were more at risk are not available. The lack of effect of aspirin in cardiovascular disease in the aspirin group prompted the steering committee to bring out an interim report. In December 1987 it seemed unlikely that a statistically significant reduction in mortality could be achieved by December 1987.

The English study had a completely different outcome. This open study showed a small and statistically not significant reduction in myocardial infarction: 2% for non-fatal and 5% for fatal myocardial infarction. There was also a small increase in the incidence of stroke in the aspirin group, 13% for non-fatal and 25% for fatal strokes (statistically not significant). In contrast to the American study, cases of non-fatal gastrointestinal bleeding were more frequently reported in the aspirin group, though this finding is less reliable in an open study. The total death and vascular death rates were closer to the expected numbers. The death rate was 10% in the aspirin group and 6% in the placebo group (statistically insignificant difference).

The differences in outcome

The differences in outcome between the studies relate to the occurrence of myocardial infarction, one of the three important end-points. Why this is so is obscure. First, the subjects in both studies differ completely from each other. Total death in the American study was 2% during the whole study period compared to 8% in the English study. Apparently, the American physicians taking part in the study were healthier. A second difference is the relatively small control in the English study. The total man-years of the control subjects in the English study was 9470 compared to 54 865 in the American study. All end-points in the man-years of aspirin users were compared to the control group. The American study had six times as many man-years and, therefore, six times more power.

A third important difference was the design of both studies. The American study was double-blind, while the English study was open. This was an important limitation in the value of the English study. A less important reason for the difference in outcome between the studies may have been the difference in the aspirin dosage. The average daily dose in the American study was 162.5 mg and in the English study 500 mg. It is well known that aspirin in a dose of 500 mg or more can have important gastrointestinal side effects. There are theoretical viewpoints, that aspirin has a paradoxical dose-response curve: the lower the dose, the more effective the anti-thrombotic action. This, however, has never been clinically proven, but there are reasons to believe that it is true and presumably these two primary prevention trials are an example of this.

Although the total death rate was quite different between the two studies, it was not reduced by aspirin in either study. The English study showed a 10% lower death rate in the aspirin group, but this difference was not statistically significant. It could be expected that the prevention of myocardial infarction, still the most important cause of death in both countries, also has a direct effect on the total death rate. This is not the case and it may be that cause of death has been reshuffled from one organ to another. In both trials there was a higher risk for stroke in the aspirin group. Though these differences are statistically not significant, they should be taken note of. If one claims that aspirin can prevent myocardial infarction, it can also be presumed that aspirin can prevent stroke. The pathophysiology of both diseases seem identical: thrombosis on an atherosclerotic plaque. Perhaps there is a smaller incidence of ischaemic stroke, but this gain seems to be abolished by haemorrhagic stroke. Due to a vague definition of stroke in both studies this cannot be proven. Possibly the preventive effect of aspirin, if it exists, applies in particular to myocardial infarction.

Applicability to the general population

Both studies have been carried out and reported on by excellent researchers and have a high scientific value.
There is no doubt about their results, but the studies differ in design, dosage of aspirin, man-years and all-cause mortality, so they can hardly be compared. The only significant finding is the large benefit from aspirin in the prevention of myocardial infarction in the American study. Severe side-effects caused by aspirin cannot be found in either study.

Should the public be advised to take aspirin in the prevention of myocardial infarction? The American numbers were found in an extremely healthy male population, who in 5 years only reported a 2% death rate. The death rate in the ordinary population is much higher and whether aspirin can prevent death in this group is completely unclear. The results of the English study do not argue against this theory either. It would have been better if a similar study had been carried out in the general population. Because of lack of motivation in the population such a study will probably never be carried out and the question, whether aspirin in the general population has a preventive effect, cannot be answered. The turmoil over the publication of the American study results has led to the presumption in the general population that aspirin prevents myocardial infarction.

The risks in the general use of aspirin in the prevention of myocardial infarction does not lie in the side-effects of aspirin, as reported in both studies. These are small and not proven. Self-medication is a much larger risk and could arise from the media exposure. Every practising physician knows that one acetylsalicylic acid tablet of 500 mg can cause a severe peptic ulcer in a patient with or without symptomatic gastrointestinal disease. In both studies, subjects with gastrointestinal disease were not included, but general advice should be given to the public, that aspirin used to prevent heart disease is more likely to cause stomach ulcers than prevent myocardial infarctions.

Conclusions

The fact that myocardial infarction can be prevented with aspirin in healthy men was proven in the American study, but not in the English study. The first study had a better design, a longer control period and a lower dose of aspirin. The number of myocardial infarctions in the placebo group in the American study was so small that the question arises as to whether the results are applicable to the general population. Preventive studies with aspirin in the population as a whole is probably impossible and therefore there may never be an answer. Although the results are of scientific value, their applicability is small; maybe only high risk individuals will benefit. The preventive effect of aspirin in women should also be investigated. Both issues are being studied now. As a preventive measure, the value of aspirin has not been proven in the general population, and it must be used with caution. Self administration of acetylsalicylic acid for the purpose of primary prevention includes many risks.

References