THE MARVEL OF INEXPENSIVE CARDIOVASCULAR DRUGS: ASPIRIN

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HOW DOES ASPIRIN WORK?

Aspirin irreversibly inhibits cyclo-oxygenase (COX_1 and COX_2). This leads to the inhibition of thromboxane A_2, rendering platelets unable to aggregate and initiate a thrombus. A dose of 100 mg aspirin will completely abolish the thromboxane A_2 effect. The antiplatelet effect of aspirin is maximal within 60 minutes after a dose of 160 mg. The antiplatelet effect of a single dose of aspirin can be detected before any drug can be measured in the blood (due to exposure of platelets to aspirin in the portal circulation). The antiplatelet effect lasts 7 - 10 days (the lifetime of platelet).

ASPIRIN AND MYOCARDIAL INFARCTION

The Antiplatelet Trialists Collaboration reported on 145 randomised control trials (RCT) and 102 459 patients on the effect of aspirin. Aspirin reduced non-fatal myocardial infarction (MI) by ± 34% and all-cause mortality was reduced by 16%. There was no important difference in subgroups of patients with prior MI, stroke, transient ischaemic attack (TIA), unstable angina, peripheral arterial disease (PAD), or difference in gender, age, diabetics or hypertensives.

In the International Study of Infarct Survival (ISIS-1), when aspirin was given for an acute MI, aspirin reduced mortality by 23% and reduced non-fatal MI and non-fatal stroke by 50%. The mortality benefit was subsequently shown to be maintained for 10 years after the original study. Streptokinase in ISIS-1 showed a relative risk reduction (RRR) of 25% mortality. Aspirin plus streptokinase when given together, reduced mortality by 42%. It seems that aspirin augments the effect of streptokinase (Fig. 1).

ASPIRIN IN PRIMARY PREVENTION

In primary prevention of cardiovascular disease, the use of aspirin for this purpose should be viewed as the balance of benefits and harm (GI and cerebral bleeds). This is most favourable in high-risk individuals (5-year risk ≥ 3%; 10-year risk >10%). The doses of aspirin for this purpose are 75 mg/day, 100 mg/day and 325 mg/day. In the United States Physicians Health Study 325 mg aspirin used on alternate days was tested against daily placebo. There was a 44% decrease in first MI, but there was an increase in haemorrhagic stroke. There was NO effect on mortality, however. The benefit of aspirin was more evident in older patients (> 50 years).

There is even more increased risk of serious bleeding due to the long-term use of aspirin in the following groups of patients:

- uncontrolled hypertensives
- concomitant use of NSAID
- concomitant use of warfarin.

What is the effectiveness of aspirin for primary prevention of coronary artery disease (CAD) in persons at risk?

In four trials, consisting of 48 540 patients, the relative risk reduction (RRR) of MI was 28 - 30% (95% CI: 20 - 38%). The effect on total mortality was a RRR of 6% (–3 - 14). This is a non-significant result on mortality. There was also a non-significant effect on stroke reduction. The bottom line was that the higher the risk of the individual, the better the benefit with fewer harmful effects.

In persons without vascular disease

What is the effectiveness of aspirin in reducing vascular events in persons without vascular disease? In 5 trials, consisting of 52 251 patients, there was a RRR of 26% for MI (95% CI: 18 - 32%). There was however an increased risk of developing a haemorrhagic stroke, RR of 1.35 (0.88 - 2.10). Total mortality showed a RRR of 6% (–1 - 13%). This was a non-significant result.

ASPIRIN IN SECONDARY PREVENTION

In various trials post-MI consisting of 1 000 000 patients, the RRR for non-fatal MI was ± 33% ($\frac{1}{3}$) and the RRR for non-fatal stroke ± 20% ($\frac{1}{5}$), while the RRR for vascular death was ± 17% ($\frac{1}{6}$). This is a highly significant result, making post-MI the strongest and most frequent indication for aspirin use. It is thus the duty of the practitioner to start all patients surviving their first event on aspirin therapy, unless otherwise contraindicated.

OTHER BENEFICIAL EFFECTS OF ASPIRIN

Prevention of colorectal cancer

Epidemiological data suggest that the use of aspirin will reduce the risk of colorectal cancer by 40 - 50%. It has also been demonstrated that the regular use of aspirin will reduce colorectal adenomas and thus prevent colorectal cancer.

Aspirin in diabetes mellitus type 2 (T_2DM)

- Secondary prevention in T_2DM with any evidence of vascular disease.
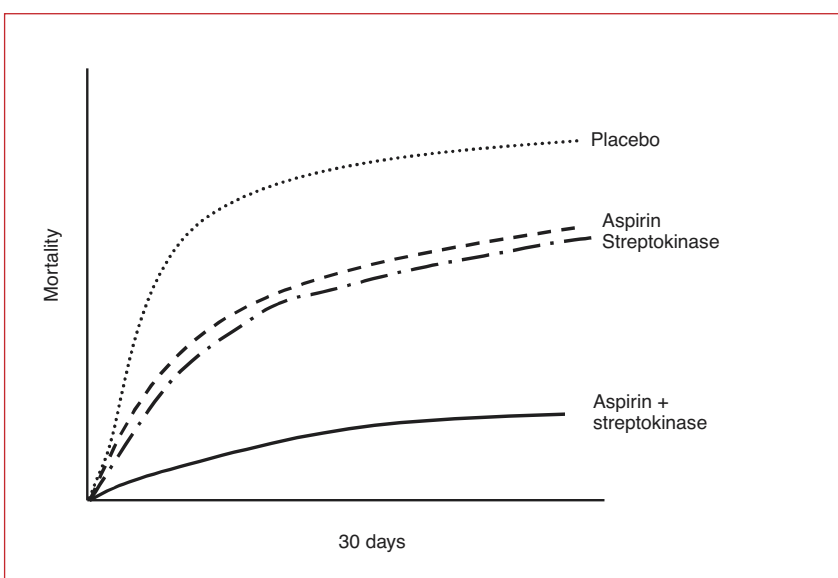- High-risk T_2DM.

Fig. I. Aspirin and acute MI.

Aspirin is not for people below the age of 21 years due to the risk of Reye's syndrome. Aspirin has not been tested in diabetes mellitus patients younger than 30 years of age and should not routinely be used in this young age group.

Well-controlled hypertension (high-risk patients)

Low-dose aspirin (75 mg/day) has been shown in the HOT study to reduce the risk of MI in those patients whose blood pressure was well controlled. It should not be used in patients whose blood pressure is not controlled or in hypertensives who have a low risk of developing cardiovascular disease.

DOSE OF ASPIRIN

- For acute MI: initial dose of 160 - 325 mg, chewed and swallowed.
- Unstable angina: initial dose 160 - 325 mg and subsequent daily dose 75 - 100 mg.
- Secondary prevention: daily dose of 75 - 325 mg (every other day)(lowest dose with proven benefit was 75 mg/day).
- Primary prevention: no clear indication of correct dose — consider 75 - 160 mg/day in 'high-risk' patients.

ADVERSE EFFECTS
GI toxicity (bleeding)
Bleeding can occur with doses from 30 mg to 1 300 mg. The risk of a major GI bleed was 2 - 4/1 000 in the middle-aged and 4 - 10/1 000 in the elderly given aspirin for 5 years.

Haemorrhagic stroke
A meta-analysis of 16 trials consisting of 55 462 patients showed a RR of 1.84 with 12 haemorrhagic strokes per 10 000 patients treated with aspirin. This harmful effect is seen as unacceptable when it occurs in patients at a very low risk of developing cardiovascular disease, but when given to a high-risk patient, benefit far outweighs harm.

Other adverse effects
Aspirin can interfere with blood pressure control in high doses (1 500 mg/day). It can interfere with ACE-I in doses of more than 100 mg/day, and can induce asthma.

ALTERNATIVES TO ASPIRIN
About 5 - 10% of patients will not tolerate aspirin. The following alternatives are available in those cases:
- Clopidogrel (Plavix). In the Caprie study, 325 mg/day aspirin versus 75 mg/day clopidogrel showed a significant increase in benefit from clopidogrel after 2 years (p = 0.04). Neutropenia occurred as a side-effect in 0.1% of patients treated with clopidogrel.
- Dipyridamole. For recurrent stroke prevention, this drug is equally effective.

The problem of the two alternative options for aspirin-intolerant patients is that they are much more expensive.

CONCLUSION
Aspirin decreases mortality and reinfarction when given in acute MI, unstable angina, and for long-term secondary prevention. Despite the strength of the data, 20 - 50% of patients with clear indications for aspirin are not receiving it. There is still much to be done by general practitioners to increase the use of highly effective drugs like aspirin.

THE MARVEL OF INEXPENSIVE CARDIOVASCULAR DRUGS: THIAZIDE DIURETICS

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The drugs in this group are called thiazides, benzothiadiazides or sulphonamide diuretics. Chlorothiazide is the