# A randomized controlled trial of aspirin in the prevention of early mortality in myocardial infarction

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SUMMARY. A randomized controlled trial is reported in which a single dose of aspirin (300 mg) was given to patients with myocardial infarction on first contact with a general practitioner. A total of 1,705 patients with confirmed infarction were studied, and survival ascertained. There was no evidence of benefit from the aspirin.

## Introduction

THERE is growing evidence about the beneficial effect of aspirin on mortality from myocardial infarction, presumably through its inhibitory effect on platelet aggregation (Verstraete, 1976). No trial has yet reported results which are statistically significant, yet the available data show remarkable consistency. Thus a 24 per cent reduction in mortality by aspirin during the year after infarction was reported by Elwood and colleagues (1974) and subsequent trials have reported reductions of 30 per cent (Coronary Drug Project Research Group, 1976) and 42 per cent (Breddin *et al.*, 1977).

All this evidence relates to prevention, albeit secondary prevention. There are reasons, however, which make an effect on early mortality following infarction possible. These reasons relate to three possible mechanisms. First, an early dose of an anti-platelet drug could reduce the eventual size of a thrombus in the coronary circulation. Secondly, there is evidence that infarction can precede thrombosis (Warren, 1973) and in patients in whom this is the sequence, early aspirin could inhibit or limit thrombosis. Thirdly, Hughes and Tonks (1968) have described intravascular platelets clumping in experimental animals, and Haerem (1974) has described platelet aggregates and micro-thrombi in the intramyocardial vessels in fatal coronary disease in humans. While Haerem postulates that this may be a mechanism in sudden death from arrhythmia, it could be that an early dose of an anti-platelet drug could reduce further platelet aggregation and hence either reduce the eventual size of an infarct or reduce the risk of arrhythmia.

For these reasons we decided to set up a trial to test the hypothesis that a dose of aspirin given soon after the onset of symptoms of myocardial infarction would reduce mortality.

## Method

We wrote to all the members of the Royal College of General Practitioners. The trial was described and co-operation invited. Those who agreed to help were sent six sealed envelopes, each containing two capsules of either aspirin 300 mg or matching placebo, at random. These were to be given on first contact with any patient who it was believed might have suffered a myocardial infarct. A short record form was enclosed, with a stamped addressed envelope for its return, asking for identification details and a few clinical details. One month after the admission of a patient to the trial we wrote to the general practitioner to find out whether the patient had died or survived. In addition we asked the doctor whether or not any evidence confirming infarction had become available after the initial record had been sent in. Confirmatory evidence was sought at several levels of certainty and this was indicated in the enquiry, but we did not ask for fine detail. We accepted

**Table 1.** Cumulative mortality in males during the 28 days following the giving of 300 mg aspirin or matching placebo. (Percentages are given in brackets.)

| | Given aspirin | Given placebo |
|---|---|---|
| Number of confirmed myocardial infarctions | 608 | 671 |
| *Cumulative deaths* | | |
| Same day | 48 *(7.9)* | 53 *(7.9)* |
| Same day + 1 | 56 *(9.2)* | 68 *(10.1)* |
| Same day + 2 | 67 *(11.0)* | 76 *(11.3)* |
| Same day + 3 | 73 *(12.0)* | 80 *(11.9)* |
| Same day + 28 | 114 *(18.8)* | 129 *(19.1)* |

**Table 2.** Cumulative mortality in females during the 28 days following the giving of 300 mg aspirin or matching placebo. (Percentages are given in brackets.)

| | Given aspirin | Given placebo |
|---|---|---|
| Number of confirmed myocardial infarctions | 219 | 207 |
| *Cumulative deaths* | | |
| Same day | 18 *(8.2)* | 15 *(7.2)* |
| Same day + 1 | 23 *(10.5)* | 21 *(10.1)* |
| Same day + 2 | 25 *(11.4)* | 22 *(10.6)* |
| Same day + 3 | 27 *(12.3)* | 25 *(12.1)* |
| Same day + 28 | 45 *(20.5)* | 43 *(20.8)* |

any evidence judged by the doctor himself to have confirmed the occurrence of infarction. This included the course of the illness, the opinion of a hospital consultant physician, and ECG or enzyme changes judged to indicate infarction.

The certified cause of death was not ascertained for all deaths though it was given for many by the doctor. We assumed that deaths from causes other than coronary thrombosis were very few, which seems a reasonable assumption with regard to very early deaths.

## Results

Of the 2,530 patients admitted to the trial, no confirmatory evidence of myocardial infarction was later reported in 825 (422 were given aspirin, 403 placebo). Thus the analysis was based on 1,705 patients (about 67 per cent), 1,279 males and 426 females.

Table 1 sets out the mortality in males and Table 2 in females. There is no evidence of benefit in either sex. Tables 3 and 4 set out the same analysis for patients who had been seen initially, and who had received treatment within four hours of the onset of symptoms. Again there is no evidence of benefit from aspirin.

Based on the assumption that a low blood pressure indicates a serious infarct, Table 5 set out the deaths in patients who had had a blood pressure on first examination of 100 mm Hg systolic or less. The numbers are small, especially in females, but again there is no evidence of benefit.

**Table 3.** Cumulative mortality in males who had received treatment within four hours of the onset of symptoms. (Percentages are given in brackets.)

| | Given aspirin | Given placebo |
|---|---|---|
| Number of confirmed myocardial infarctions | 329 | 404 |
| *Cumulative deaths* | | |
| Same day | 33 *(10.0)* | 41 *(10.1)* |
| Same day + 1 | 39 *(11.9)* | 51 *(12.6)* |
| Same day + 2 | 45 *(13.7)* | 56 *(13.9)* |
| Same day + 3 | 47 *(14.3)* | 58 *(14.4)* |
| Same day + 28 | 70 *(21.3)* | 88 *(21.8)* |

**Table 4.** Cumulative mortality in females who had received treatment within four hours of the onset of symptoms. (Percentages are given in brackets.)

| | Given aspirin | Given placebo |
|---|---|---|
| Number of confirmed myocardial infarctions | 124 | 118 |
| *Cumulative deaths* | | |
| Same day | 11 *(8.9)* | 8 *(6.8)* |
| Same day + 1 | 14 *(11.3)* | 12 *(10.2)* |
| Same day + 2 | 15 *(12.1)* | 13 *(11.0)* |
| Same day + 3 | 16 *(12.9)* | 13 *(11.0)* |
| Same day + 28 | 23 *(18.5)* | 26 *(22.0)* |

## Discussion

These results give no encouragement to the use of aspirin in the early treatment of myocardial infarction. There are, however, several limitations to the study.

Although only a small dose of aspirin was used, it was about three times the dose usually found effective in preventing platelet aggregation. It has been shown repeatedly that doses of aspirin over about 100 mg have a profound effect on platelet aggregation (Rowan *et al.*, 1976). The effect occurs as early as 15 minutes after an oral dose (Stuart, 1970) and can be detected for at least two days subsequently (Burch *et al.*, 1977).

We decided to use a 300 mg dose of aspirin in this trial because it would probably not only be ethically acceptable to most doctors but also large enough to have the desired effect on platelets. It is possible that this dose, while sufficient to affect platelet aggregation in a normal person, may not be sufficient to suppress gross aggregation heralding an infarction. However, recent discussions on aspirin have noted an effect on the vessel wall which may not be beneficial, and the use of a low dose at infrequent intervals has been strongly recommended (Moncada and Vane, 1978).

A beneficial effect of aspirin in myocardial infarction has not been established beyond all reasonable doubt. Nevertheless, the evidence available to us when we proposed the trial was highly suggestive and since then further confirmatory evidence has been reported. This is

**Table 5.** Cumulative mortality in patients who had had an initial blood pressure of 100 mm Hg systolic or less. (Percentages are given in brackets.)

| | Males | | Females | |
|---|---|---|---|---|
| | Given aspirin | Given placebo | Given aspirin | Given placebo |
| Number of confirmed myocardial infarctions | 77 | 85 | 23 | 24 |
| *Cumulative mortality* | | | | |
| Same day | 10 *(13.0)* | 11 *(12.9)* | 3 | 1 |
| Same day + 1 | 12 *(15.6)* | 18 *(21.2)* | 0 | 0 |
| Same day + 2 | 16 *(20.8)* | 20 *(23.5)* | 0 | 0 |
| Same day + 3 | 17 *(22.1)* | 22 *(25.9)* | 0 | 0 |
| Same day + 28 | 26 *(33.8)* | 31 *(36.5)* | 9 | 2 |

all consistent with a preventive effect and comes from trials in patients who have already had one infarct.

The possibility remains that a drug which has a direct anti-arrhythmic effect might be of value in the acute situation following an infarct. It would be reasonable to consider the possibility of conducting a similar study using a drug with an anti-arrhythmic effect.

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