that prophylactic aspirin had no effect and cannot have averted much more than a third of all non-fatal myocardial infarctions. The United States trial, however, observed about three times as many non-fatal myocardial infarctions as the United Kingdom trial did, so the positive result from the United States carries more weight than the null result from the United Kingdom. If, therefore, the truth lies somewhat nearer to the United States than to the United Kingdom result then taken together these two primary prevention trials suggest that prophylactic antiplatelet treatment can probably avert about one third of all non-fatal myocardial infarctions. Such a reduction is plausible, for it is similar to the reductions of 35% and 31% in non-fatal myocardial infarction suggested by the overviews of results of antiplatelet trials in patients with cerebral and with cardiac vascular disease (see accompanying paper). But although a reduction in non-fatal myocardial infarction must presumably correspond to some reduction in fatal myocardial infarction, it does not necessarily correspond to a net reduction in overall vascular mortality. At present, neither the United States nor the United Kingdom trial results suggest any reduction whatever in overall vascular mortality, and both suggest some increase in the number of disabling strokes (which, in the United States trial, were attributed to cerebral haemorrhage).

Side effects of aspirin may be assessed in an unbiased way only with placebo control, so the present data on side effects add little to the data from the main placebo controlled studies.[4,5] The adverse effects on the stomach and oesophagus of daily doses of 1000 mg aspirin found in placebo controlled studies are appreciable but may largely be avoided by reducing the amount or frequency of dosage (UK-TIA Study Group trial, accompanying paper) or using an enteric coated aspirin preparation (which should dissolve in the intestine but not in the stomach). Some protection against various aches and pains was expected, but the reduction in the numbers of subjects reporting migraine on the final questionnaire was substantial and would presumably have been somewhat larger (that is, over 30%) had compliance with the allocated treatment been greater. Because of the lack of placebo control, however, this finding needs support, possibly from a placebo controlled prophylactic study in migraine clinics of the extent to which recurrence of migraine could be avoided (or its symptoms controlled) by some regimen such as 300 mg enteric coated aspirin daily. A small placebo controlled trial of aspirin in migraine sufferers found about a 50% reduction in headaches, but only 12 patients were studied.[6] The lack of support for suggestions that aspirin might help avoid cataract is similar to the findings in some[7] but not all[8] case-control studies. Conversely, the apparent shortfall in both fatal and non-fatal respiratory diseases offers no support to the suggestion that aspirin might aggravate such conditions.[9]

Thus though the prophylactic use of daily aspirin for "secondary" prevention of disease among patients at high risk of thrombotic disease has been shown to reduce the incidence both of non-fatal vascular events and of vascular death, and though it is still possible that apparently healthy people will, when fuller evidence is available, be found to derive comparable proportional reductions in risk, our study has provided no definite indication that any such benefits exist.

By far the greatest acknowledgment is to the doctors who participated in this study. In Oxford Brian Gribbin, Jane Kench, Gale Mead, David Skegg, Steve Sutherland, and Salim Yusuf helped in many different ways. The Aspirin Foundation (G N Henderson, G Fryers) provided financial support but with its ready agreement had throughout no contact with the study's conduct, results, or interpretation.

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United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results

UK-TIA STUDY GROUP

Abstract

From 1979 to 1985, 2435 patients thought to have had a transient ischaemic attack or minor ischaemic stroke were allocated at random to receive long term blind treatment with either aspirin 600 mg twice daily (n=815), aspirin 300 mg once daily (806), or placebo (814). Treatment continued with about 85% compliance until September 1986 (mean four years). The odds of suffering one or more of four categories of event—namely, non-fatal myocardial infarction, non-fatal major stroke, vascular death, or non-vascular death—were 18% less in the two groups allocated to receive aspirin than in the group allocated to receive placebo (2p=0·01). The more relevant but less frequent composite event of disabling stroke or vascular death was reduced by only 7%; this reduction was not significantly different from zero, but nor was it significantly different from a 25% reduction. There was no definite difference between responses to the 300 mg and 1200 mg daily doses, except that the lower dose was significantly less gastrotoxic.

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Participants in the trial are listed at the end of this paper.

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Introduction

Patients who have had a transient ischaemic attack or have largely recovered from an ischaemic stroke are at risk not only of a recurrence but of a permanently disabling or fatal vascular event. The natural course of transient ischaemic attack and of mild ischaemic stroke is similar[1]; the subsequent incidence of stroke (about 4% a year) is the same as that of myocardial infarction (in-

cluding sudden presumed cardiac death).[2] Thus the serious vascular events in these patients are at least as often cardiovascular as cerebrovascular and many are thought to be due to the thrombotic and embolic complications of atheroma. Inhibition of thrombosis may therefore improve the prognosis after a transient ischaemic attack or mild ischaemic stroke, and aspirin, which has antiplatelet activity, may be clinically effective in this respect.

In 1978 a group of British neurologists decided to start a large multicentre trial of long term aspirin in patients thought to have had a transient ischaemic attack or minor ischaemic stroke. The aim was to test the clinical efficacy of the then conventional antithrombotic dose (1200 mg daily) and to see whether a lower dose (300 mg daily) might be at least as effective (both doses produce virtually complete inhibition of cyclo-oxygenase dependent platelet aggregation). Treatment was stopped in September 1986. This paper reports the interim results. A full report of the trial methodology with complete follow up is being prepared and will be submitted in due course.

Patients and methods

Between 25 July 1979 and 8 October 1985, 60 consultant neurologists (about a third of the total in the United Kingdom and Eire) working in 35 neurological centres recruited patients thought to have had a recent transient ischaemic attack or minor ischaemic stroke. We used standard and uncontroversial diagnostic criteria, which depended on the duration of symptoms rather than signs.[3] A transient ischaemic attack was defined by symptoms lasting less than 24 hours and a minor stroke by symptoms lasting at least 24 hours but less than a week. Computed tomography (CT) was not widely available but most of the minor strokes were presumably ischaemic and not due to primary intracerebral haemorrhage. By telephone to the clinical trial service unit at Oxford the patients were allocated at random to receive as blind treatment either aspirin 600 mg twice daily, aspirin 300 mg once daily, or placebo. No patient was subsequently withdrawn from follow up or analysis unless an intracranial tumour was discovered that was thought to have been responsible for the original symptoms. These tumours were generally recognised quite soon after randomisation, and the policy of excluding all such patients was adopted early in the trial. Patients were seen every four months and those unwilling to continue attending neurological clinics were followed up through their general practitioners. In addition, all deaths were monitored by flagging each patient's records at the Office of Population Censuses and Surveys. Details of all deaths and vascular events were sought and reviewed centrally without knowledge of the allocated treatment. When possible all patients continued with their allocated treatment until the last day of the trial (30 September 1986). All events occurring up to that date will eventually be reviewed and included in an "intention to treat" analysis.

We planned to review all patients again after the close of the trial to ensure that no major events had been missed, to inform them of the interim results, and to advise them whether to take aspirin in the future. To achieve this we also had to disclose the interim results (but not the individual treatment allocations) to the collaborating neurologists, and this was done on 29 and 30 September 1986. As so many neurologists had taken part it would have been impossible and indeed undesirable to keep the preliminary results confidential; moreover, the comparatively few further events that remained to be reported were unlikely to make any substantial difference to the trial results.

In 1979 we envisaged that the fundamental analysis would be of non-fatal major stroke, non-fatal myocardial infarction, vascular death, or non-vascular death taken as a composite event in a conventional log rank survival analysis,[4] with major stroke meaning any stroke causing symptoms for at least a week. We soon realised, however, that such an analysis might yield misleading results if, for example, aspirin decreased the incidence of non-disabling ischaemic strokes or non-fatal myocardial infarctions but increased the incidence of disabling or fatal haemorrhagic stroke or increased the likelihood of haemorrhage into an ischaemic cerebral infarct. In 1981, therefore, we decided that instead the fundamental analysis should be of disabling stroke or vascular death, disabling strokes being defined as those leaving definite functional disability six months after onset. It was because aspirin was not thought likely to have much influence on non-vascular deaths that we decided to assess efficacy on the basis of disabling stroke or vascular death, taken as a composite event, excluding non-vascular deaths. The full results for non-vascular deaths and for various other types of vascular event, both singly and in various combinations, will be included in our report.

Statistical analysis was by standard log rank tests[4] of time to first event (ignoring subsequent events), which for the treated patients contrasted the observed number of affected patients (O) with the number that would have been expected (E) in the absence of any real effect of treatment. The conditional variance (V) of O−E was used both for calculating the standard deviation (S) and for estimating the odds ratio (event rate ratio) and its 95% confidence iterval.[5]

Results

Out of 2448 patients randomised, 12 (0·5%) were soon found to have intracranial tumours that were thought to have caused their neurological symptoms; these patients were withdrawn. Seven survived to the end of the study period and five died, all from their tumours. None suffered a stroke or myocardial infarct. These deaths were evenly distributed among the withdrawals in the high dose, low dose, and placebo groups (2/5, 2/5, and 1/2, respectively). One other patient was lost to both flagging and follow up (a patient in the high dose group, lost immediately after randomisation), so that 2435 patients remained for analysis. These patients had been followed up for one to seven years (mean four).

BASELINE CHARACTERISTICS

The three treatment groups were well matched for all the important prognostic variables for stroke and myocardial infarction that were recorded at entry (table I). Most patients had experienced some kind of transient ischaemic attack. By definition none were disabled, but a few had minor residual neurological signs, usually as a result of a minor stroke. Like most hospital series of patients with transient ischaemic attack, the patients were elderly, were mostly male, and had a high prevalence of vascular risk factors and vascular disease.

TABLE I—*Summary of baseline characteristics*

	Placebo	Aspirin 300 mg daily	Aspirin 1200 mg daily	All patients
No of patients	814	806	815	2435
No (%) of men	575 (71)	603 (75)	600 (74)	1778 (73)
Mean (SD) age (years)	59·5 (9·0)	60·0 (8·9)	59·9 (9·2)	59·8 (9·0)
Mean (SD) systolic blood pressure (mm Hg)	151 (26)	150 (25)	150 (24)	150 (25)
Mean (SD) cholesterol (mmol/l)	6·1 (1·4)	6·1 (1·4)	6·0 (1·4)	6·0 (1·4)
No (%) of smokers	417 (51)	431 (53)	445 (55)	1293 (53)
No (%) with angina/past myocardial infarction	165 (20)	164 (20)	146 (18)	475 (20)
No (%) with transient ischaemic attack	586 (72)	561 (70)	573 (70)	1720 (71)
No (%) with amaurosis fugax	142 (17)	170 (21)	163 (20)	475 (19)
No (%) with minor stroke	186 (23)	171 (21)	178 (22)	535 (22)

DEVIATION FROM ALLOCATED TREATMENT AND SIDE EFFECTS

At each follow up about 85% of patients reported that they were taking the trial medication. To check on compliance of the active treatment groups and on contamination of the control group with non-trial aspirin, urine samples were collected at each follow up and tested for aspirin. Unfortunately, the ferric chloride test used was rather insensitive; nevertheless, very few persistent negatives were encountered among patients who reported that they were taking 1200 mg aspirin daily, so the self reported compliance was unlikely to have been substantially wrong. The main reason for stopping was side effects; table II presents the most common and relevant of these. There was a definite dose-response effect for upper gastrointestinal symptoms and gastrointestinal haemorrhage but not for constipation. Gastrointestinal haemorrhage or peptic ulceration was the underlying cause of death in three patients (one allocated to placebo, one allocated to 1200 mg aspirin daily who was continuing with treatment, and one allocated to 1200 mg aspirin who had stopped treatment several months earlier).

MAJOR EVENTS

Table III gives the main results in such a way that various combinations of event can be extracted. For example, among the non-fatal cases of myocardial infarction in the placebo group three patients subsequently died of a non-vascular cause, none died of a stroke, nine died of other vascular causes (mostly cardiac), and 31 were not known to have died; thus 43 patients allocated to the placebo group had experienced a non-fatal myocardial infarction by September 1986. Figures 1 to 4 show the results of

TABLE II—*Numbers (percentages) of patients in the three groups ever reporting gastrointestinal side effects*

	Basic data			No of standard deviations (Z) comparing:	
	Placebo (n=814)	Aspirin 300 mg daily (n=806)	Aspirin 1200 mg daily (n=815)	Placebo *v* both aspirin groups	Aspirin 300 mg *v* 1200 mg
Indigestion, nausea, heartburn, vomiting	198 (24·3)	237 (29·4)	316 (38·8)	4·9***	4·0***
Constipation	19 (2·3)	45 (5·6)	49 (6·0)	3·8***	0·4
Any gastrointestinal bleeding	13 (1·6)	21 (2·6)	38 (4·7)	2·8**	2·2*
Serious gastrointestinal bleeding (that is, requiring admission to hospital)	7 (0·9)	12 (1·5)	19 (2·3)	2·0*	1·2

*2p<0·05. **2p<0·01. ***2p<0·001.

TABLE III—*State of patients in the three groups at end of trial (September 1986 interim analysis)*

	Definite non-vascular death			Definite fatal stroke			Other deaths, mostly cardiac*			Not known to be dead in September 1986		
	Daily dose of aspirin (mg)			Daily dose of aspirin (mg)			Daily dose of aspirin (mg)			Daily dose of aspirin (mg)		
Patients with:	0	300	1200	0	300	1200	0	300	1200	0	300	1200
Non-fatal stroke† Minor	0	0	2	0	1	0	4	2	0	20	16	14
Non-fatal stroke† Non-disabling major	2	1	2	1	2	0	2	4	4	46	35	34
Non-fatal stroke† Disabling major	7	3	4	4	1	3	6	9	6	17	13	15
Non-fatal myocardial infarction	3	3	1	0	4	0	9	5	4	31	22	16
Neither non-fatal stroke nor non-fatal myocardial infarction	24	16	18	10	12	16	52	48	52	586	613	626
Total‡	36	22	27	15	18	19	71	68	65	692	698	704

*Includes a few deaths of unknown cause, a few due to gastrointestinal haemorrhage, a few due to ruptured aortic aneurysms, and many definitely or probably due to heart disease.
†Patients with more than one category of non-fatal stroke counted only for most serious event.
‡Totals may be less than sum of columns because a few patients had both a non-fatal stroke and a non-fatal myocardial infarction.

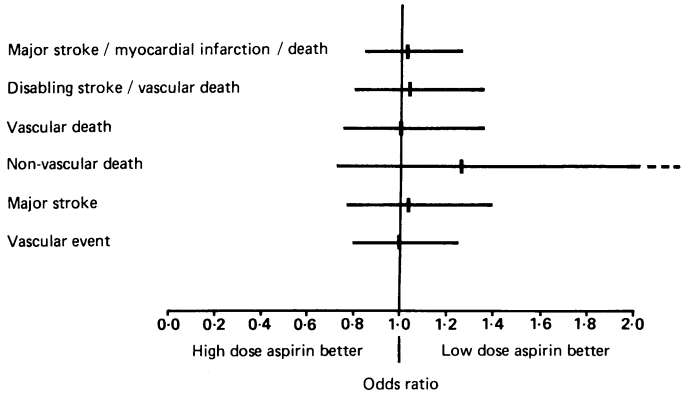

FIG 1—Odds ratios (vertical bars) and 95% confidence intervals (horizontal bars) for various categories of event. Results for all patients: 1200 mg aspirin *v* 300 mg aspirin daily. (*Vascular deaths* included those due to stroke, myocardial infarction, sudden presumed cardiac death, cardiac failure, ruptured aortic aneurysm, and gastrointestinal haemorrhage or peptic ulceration. *Vascular events* included non-fatal stroke, non-fatal myocardial infarction, all cardiac deaths, deaths due to stroke, and gastrointestinal haemorrhage.)

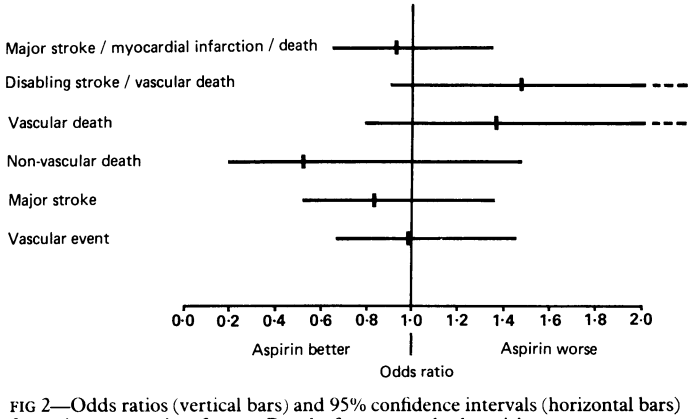

FIG 2—Odds ratios (vertical bars) and 95% confidence intervals (horizontal bars) for various categories of event. Results for women: both aspirin treatment groups *v* placebo. (Vascular death and vascular event defined as in fig 1.)

the main statistical analyses (all by allocated treatment). Estimates of the odds ratios and 95% confidence intervals were derived from log rank survival analyses.[4,5]

High versus low dose aspirin (fig 1)—The number of events was comparatively small and the confidence intervals of the odds ratios wide for each category of event that was analysed. There were, however, no significant differences between the two dose levels of aspirin. Though we could not definitely exclude a real difference between the two active treatment arms, it seemed reasonable to consider both doses together in subsequent analyses, especially given the evidence that 300 mg aspirin may have a significant protective effect (see accompanying paper).

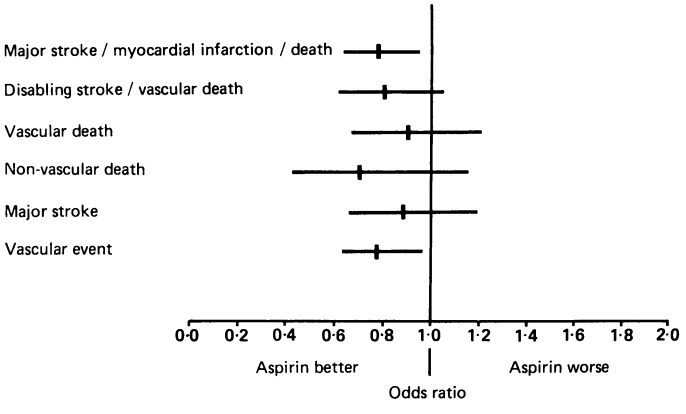

FIG 3—Odds ratios (vertical bars) and 95% confidence intervals (horizontal bars) for various categories of event. Results for men: both aspirin treatment groups *v* placebo. (Vascular death and vascular event defined as in fig 1.)

Aspirin versus placebo: women (fig 2)—As only a quarter of the patients were women, the number of events was small and the confidence intervals for the odds ratios correspondingly wide. There were no significant effects of treatment, and though some analyses tended to favour aspirin, others tended to favour placebo.

Aspirin versus placebo: men (fig 3)—Among men there was a significant advantage for aspirin with respect to any major event (non-fatal major stroke, non-fatal myocardial infarction, vascular death, and non-vascular death) (odds reduction 22%; 95% confidence interval 5% to 36%) and with respect to any major vascular event (non-fatal major stroke, non-fatal

myocardial infarction, or vascular death) (odds reduction 22%; 95% confidence interval 4% to 37%). There were trends in the same direction for the other categories of event but these did not reach conventional levels of significance.

Aspirin versus placebo: all patients (fig 4)—Figure 4 presents our preferred main analysis; on the basis of the above results and those of an overview (see accompanying paper) we were not convinced that there was a definite difference between men and women in the response to aspirin. There was a significant reduction (2p=0·01) in the odds of non-fatal major stroke, non-fatal myocardial infarction, vascular death, and non-vascular death (18%; 95% confidence intervals 31% to 2%) but only a non-significant reduction in the odds of disabling stroke or vascular death (7%; 95% confidence intervals: 26% reduction, 18% increase). The discrepancy between these two analyses was largely due to a deficit of deaths from cancer among the patients allocated to receive aspirin (21 cases (2·6%) among the patients allocated to placebo, 25 cases (1·5%) among patients allocated to aspirin; no particular type of cancer predominated).

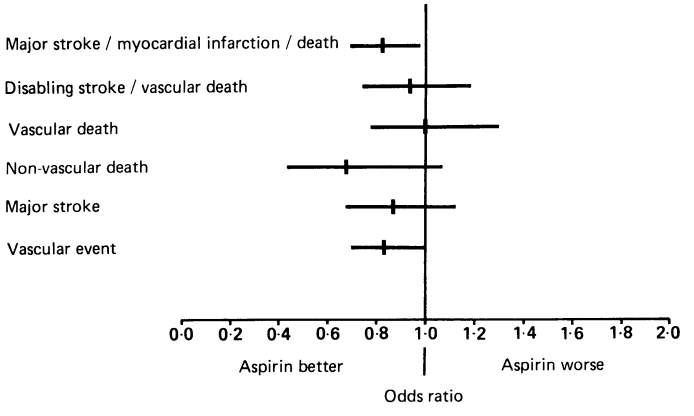

FIG 4—Odds ratios (vertical bars) and 95% confidence intervals (horizontal bars) for various categories of event. Results for all patients: both aspirin treatment groups *v* placebo. (Vascular death and vascular event defined as in fig 1.)

Intracranial haemorrhage—Very few patients who suffered a stroke after randomisation either came to necropsy or had a CT scan early enough to distinguish reliably between cerebral infarction and primary intracerebral haemorrhage. The number of definite intracranial haemorrhages recorded was very small and presumably underestimated the true state of affairs. There were three cases (including one fatal) recorded in the placebo group and 13 (including nine fatal) in the combined aspirin treated groups. Though this represented a twofold increase in the odds of haemorrhage attributable to aspirin, and the trend was in the expected direction, the numbers were too small for the difference to be significant (2p=0·2).

Discussion

Analysis of the two different daily doses studied (300 mg and 1200 mg) showed highly significantly greater gastrotoxicity with the high dose regimen but no clear differences in therapeutic effect. The degree of inhibition of cyclo-oxygenase dependent platelet aggregation is similar over a range of daily doses of aspirin from about 50 mg to well over 1500 mg,[6] and trials of 300 mg aspirin daily have shown at least as great a therapeutic effect as trials of 1000-1500 mg daily (see accompanying paper). We therefore combined the two active treatment arms for analysis. Similarly we merged the data for men and women, for though there was direct evidence of benefit only for men, the number of women was too small for their results to be separately reliable.

Overall among the patients who survived the study the effects of aspirin on the numbers of non-fatal vascular events were much as hoped for; in the two active treatment groups there were fewer non-fatal strokes and fewer non-fatal myocardial infarctions than among the controls, but there was no apparent difference between the two aspirin dose levels. Among survivors the total numbers in the control and low dose and high dose aspirin treatment groups suffering non-fatal major or minor stroke or non-fatal myocardial infarction were 106, 85, and 78 respectively (table III). This difference between the control and combined active treatment groups was 2·2 standard deviations, which is only marginally significant (2p=0·03); nevertheless, the avoidance of non-fatal strokes and non-fatal myocardial infarctions that it indicates was strongly confirmed by other trial results (see accompanying paper).

The results of this trial with respect to mortality were not supported by the overview (see accompanying paper). In this trial aspirin appeared to offer some protection against death from non-vascular causes (for example, cancer) but not against death from vascular causes. The overview, however, showed clearly that aspirin offers little or no protection against non-vascular death. For example, in the Aspirin Myocardial Infarction Study Research Group trial the number of deaths attributed to non-vascular causes was 32 aspirin *v* 21 control,[7] which is the opposite of the result in this trial, and when all the trials are reviewed together no overall difference in non-vascular mortality remains. Hence the apparent protection against such deaths in this study must have been largely or wholly due to chance.

The lack of any apparent reduction in total vascular mortality was also at variance with the overview and at variance with the ability of such treatment to protect against non-fatal stroke and non-fatal myocardial infarction. Possibly ours was a chance finding or treatment may have been protecting against death from myocardial infarction but increasing the likelihood of death from stroke. The total numbers of deaths attributed to stroke were 15 in the control group, 18 in the low dose aspirin group, and 19 in the high dose aspirin group (table III); and of these, the numbers of deaths ascribed to intracranial haemorrhage were one in the control group and nine in the aspirin treated groups. Further evidence on the likely size of any adverse effect on cerebral haemorrhage will emerge when a more detailed overview becomes available. In the mean time, however, if aspirin is being considered for patients with stroke then it would seem sensible to seek evidence on whether any intracranial haemorrhage has occurred and to avoid such treatment if it may have done.

Whatever the true explanation for these results it appears that aspirin has less effect on fatal than on non-fatal events. For cerebral events this may be because aspirin causes cerebral haemorrhage, which is more likely to prove fatal than is the cerebral infarction that aspirin may prevent. For heart disease it may be that aspirin fails to protect against arrythmias which may cause death but which rarely lead to a diagnosis of non-fatal myocardial infarction.

The patients in this trial were mostly male, aged about 60, usually with a transient ischaemic attack rather than stroke, with a high prevalence of vascular risk factors, and often with evidence of generalised vascular disease. The patients were probably younger than the general population of patients with a transient ischaemic attack (many elderly patients with the condition would not be referred to hospital in Britain) and on the whole were randomised and began treatment weeks rather than days after presentation to their general practitioner. Thus they were probably reasonably representative of the type of patient with acute but mild cerebrovascular disease coming to British neurology clinics. But whether or not they were truly representative of this or of any other defined population the results of the trial should be relevant to hospital neurology, general practice, and a range of other settings; "representativeness" of the population studied is not a prerequisite for trial results to be of practical value. Indeed, though antiplatelet trials have chiefly been of long term treatment, the protection obtained in those circumstances strongly suggests that such treatment should also be of some value in the immediate management of transient ischaemic attack.

Having spent nearly 10 years designing, funding, conducting, and analysing this study, we are frustrated to conclude that its results cannot stand alone. But the best estimate of the true effects of antiplatelet treatment in patients with transient ischaemic attack, stroke, myocardial infarction, or angina is that which comes from a proper overview of all the important relevant trial evidence and not by undue emphasis on one particular trial result. At least this study contributes substantially to the overview of all available randomised trials (see accompanying paper), which shows conclusively that

antiplatelet treatment reduces the risk of non-fatal vascular events and, to a lesser extent, vascular death.

The trial was funded by the British Medical Research Council. Aspirin was supplied by Beechams Products through the Aspirin Foundation. We are particularly grateful for the help of the pharmacists, clinical chemists, and chemical pathologists in the collaborating centres.

PARTICIPANTS AND COLLABORATING CENTRES in the trial were as follows:

Collaborating centres—Aberdeen: Dr Allan Downie, Dr John Hern; Belfast: Dr Joe Lyttle, Dr Michael Swallow; Birmingham: Dr Milne Anderson, Dr Simon Nightingale; Bristol: Dr Malcolm Campbell; Coventry: Dr Richard Ponsford; Dublin: Dr Michael Hutchinson, Dr Edward Martin; Exeter: Dr Christopher Gardner-Thorpe; Ipswich: Dr Christopher Hawkes; Leeds: Dr Simon Currie; Keighley: Dr Jim Howe; Leicester: Dr Brian Kendall, Dr Paul Millac, Dr Ian Pye; Liverpool: Dr Lance Blumhardt, Dr Andrew Bowden, Dr David Chadwick, Dr Peter Humphrey, Dr Peter Sandercock; London: (Atkinson Morley's) Dr Maurice Gross, Dr Pauline Monro, Dr Steve Wilson, (Brook) Dr Tim Fowler, (Chase Farm) Dr Peter Harvey, (Guy's) Dr Richard Hughes, Dr Richard Kay, Dr Michael O'Brien, (London Hospital) Dr Chris Kennard, (Middlesex/UCH) Dr Michael Harrison, Dr Gerald Stern, (Royal Free) Dr Tony Wilson, (St Mary's) Dr David Thomas, Dr Michael Johnson, (Whittington) Dr Andrew Lees, Dr John Scadding; Manchester: Dr Wolfgang Schady, Dr David Shepherd, Dr George Yuill; Newcastle: Dr David Bates, Dr Niall Cartlidge, Professor David Shaw, Dr Graham Venables, Dr Chris Gray; Norwich: Dr John Pilling; Nottingham: Dr David Jefferson, Dr Alan Whiteley; Oxford: Dr Chris Davis, Dr Peggy Frith, Dr Richard Greenhall, Dr Nigel Hyman, Professor Bryan Matthews, Professor Charles Warlow; Plymouth: Dr David Thrush; Romford: Dr Rudi Capildeo, Dr Les Findley; Sheffield: Dr Aelwyn Davies-Jones, Dr Patricia Edney, Dr Peter Jackson; Southampton: Dr Bridget Burrell, Dr Nick Lawton, Dr Nigel Leigh, Professor Lindsay McLellan, Dr Christopher Newman, Mr John Pickard; Swansea: Dr Richard Weiser, Dr Stuart Williams; Wakefield: Dr Louis Loizou; West Sussex: Dr John Rees, Dr Margaret Rice-Oxley.

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Clinical audit committee—Dr Brian Gribbin, Dr Michael Harrison, Professor Charles Warlow.

Policy and monitoring committee—Professor Peter Armitage, Professor Sir Richard Doll (chairman), Dr Ralph Ross Russell.

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Secondary prevention of vascular disease by prolonged antiplatelet treatment

ANTIPLATELET TRIALISTS' COLLABORATION

Abstract

Thirty one randomised trials of antiplatelet treatment for patients with a history of transient ischaemic attack, occlusive stroke, unstable angina, or myocardial infarction were identified. Six were still in progress, and the results of the remaining 25 were reviewed. They included a total of some 29 000 patients, 3000 of whom had died. Overall, allocation to antiplatelet treatment had no apparent effect on non-vascular mortality but reduced vascular mortality by 15% (SD 4%) and non-fatal vascular events (stroke or myocardial infarction) by 30% (4%). This suggested that with good compliance these treatments might reduce vascular mortality by about one sixth, other vascular events by about a third, and total vascular events by about a quarter. There was no significant difference between the effects of the different types of antiplatelet treatment tested (300-325 mg aspirin daily, higher aspirin doses, sulphinpyrazone, or high dose aspirin with dipyridamole), nor between the effects in patients with histories of cerebral or cardiac disease. Thus antiplatelet treatment can reduce the incidence of serious vascular events by about a quarter among a wide range of patients at particular risk of occlusive vascular disease. The balance of risk and benefit, however, might be different for "primary" prevention among people at low absolute risk of occlusive disease if antiplatelet treatment produced even a small increase in the incidence of cerebral haemorrhage.

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Introduction

Patients with a history of myocardial infarction, stroke, transient ischaemic attack, or unstable angina are at particular risk of vascular death or of a further cardiac or cerebral event. To discover whether this risk can be reduced many randomised clinical trials of various types of antiplatelet treatment have been conducted (table I).[1-36] Such treatment need not be particularly expensive or toxic, so that even risk reductions that were only moderate—for example, altering 16% into 12% recurrences within two years—might be well worth knowing about when considering how to manage an individual patient.

Though such risk reductions might be of some practical relevance,