Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials

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Abstract

**Background:** Aspirin is recommended for secondary prevention after transient ischaemic attack (TIA) and ischaemic stroke based on trials showing about a 13% reduction in long-term risk of recurrent stroke. However, the risk of major stroke is very high for only the first few days after TIA and minor ischaemic stroke and observational studies show substantially greater benefits of early medical treatment in the acute phase. We hypothesised that the short-term benefits of early aspirin have been underestimated.

**Methods:** Using individual patient data from all randomised trials of aspirin vs placebo in secondary prevention after TIA or ischaemic stroke, we studied the time-course of effects on risk and severity (modified Rankin score - mRS) of recurrent stroke and myocardial infarction. To more reliably determine the very early time-course of effect of aspirin on risk of recurrent ischaemic stroke, we also studied trials in treatment of acute stroke stratified by severity of baseline neurological deficit. To understand possible mechanisms of action, we also studied the time-course of the interaction between effects of aspirin and dipyridamole in secondary prevention of stroke.

**Results:** Among 15,778 patients in 12 trials of aspirin vs. control in secondary prevention, aspirin reduced the 6-week risk of major ischaemic vascular events by 70-80% (disabling or fatal ischaemic stroke - HR=0.29,0.20-0.43, p<0.0001; acute myocardial infarction - HR=0.22, 0.09-0.53, p=0.0008), with greatest benefit in patients with TIA or minor stroke (disabling or fatal ischaemic stroke: 0-2 weeks-HR=0.07,0.02-0.31,p=0.0004; 0-6 weeks-HR=0.19,0.11-0.34,p<0.0001). The effect of aspirin on early recurrent ischaemic stroke was due partly to a substantial reduction in severity (mRS shift analysis: OR=0.43,0.26-0.72,p=0.001). These effects were independent of dose, patient characteristics or aetiology of TIA or stroke. Some further reduction in risk of ischaemic stroke on aspirin only vs control accrued from 6-12 weeks, but benefit after 12-weeks was limited (stroke risk-OR=0.97,0.84-1.12,p=0.67; severity-mRS ‘shift’ OR=1.00,0.77-1.29,p=0.97). In contrast, dipyridamole plus aspirin vs aspirin alone had no effect on risk or severity of ischaemic stroke within 12-weeks (OR=0.90,0.65-1.25,p=0.53; mRS shift: OR=0.90,0.37-1.72,p=0.99), but did reduce risk thereafter (OR=0.76, 0.63-0.92,p=0.005; disabling or fatal ischaemic stroke - OR=0.64,0.49-0.84,p=0.001). In trials of aspirin versus control in major acute stroke (40,531 participants in 3 trials), the reduction in risk of recurrent ischaemic stroke was most evident in patients with less severe baseline deficits (interaction-p=0.014), and was substantial by the second day after starting treatment (2-3 days-HR=0.37,0.25-0.57,p<0.0001).

**Interpretation:** Our findings confirm that medical treatment substantially reduces the risk of early recurrent stroke after TIA and minor stroke and identify aspirin as the key intervention. The considerable early benefit from aspirin warrants public education about self-administration after possible TIA. The previously unrecognised effect of aspirin on severity of early recurrent stroke, the diminishing benefit with longer-term use, and the contrasting time-course of effects of dipyridamole have implications for understanding mechanisms of action.
Introduction

The risk of major stroke is up to 10% in the days after a transient ischaemic attack (TIA) or minor stroke without appropriate treatment.\textsuperscript{1-4} Urgent medical treatment appears to reduce that risk by as much as 80%,\textsuperscript{5,6} but many patients delay seeking medical attention, often for several days or weeks, even when they make a correct self-diagnosis.\textsuperscript{7,8} Public education campaigns, such as the FAST test television campaigns, have decreased delays to presentation after major stroke,\textsuperscript{9,10} but there has been little improvement after TIA or minor stroke (webappendix p1).\textsuperscript{11} In a recent population-based study in the UK, half of recurrent strokes in the days after a TIA occurred prior to medical attention being sought for the initial event,\textsuperscript{11} and the situation is likely to be worse in many parts of the developing world in which access to emergency services is limited.

Antithrombotic treatment is important in the immediate management of most acute ischaemic vascular events.\textsuperscript{12,13} Since aspirin is available in many households public education materials recommend self-administration by patients who develop acute chest pain, in addition to seeking immediate medical attention.\textsuperscript{14,15} However, pre-hospital self-administration of aspirin is discouraged after stroke,\textsuperscript{15} due to concern about effects on possible intracerebral haemorrhage. However, haemorrhage is a rare cause of TIA symptoms and it accounts for less than 5% of minor strokes.\textsuperscript{16,17} Although public education should continue to persuade people with transient neurological symptoms to seek medical attention immediately, where this is possible, self-administration of aspirin after transient unfamiliar symptoms might also be appropriate, particularly in rural settings or in less developed countries where access to medical services will be delayed.

There are, however, few published data from randomised trials on the effect of aspirin on risk of early recurrent stroke after TIA and minor stroke, and no data on severity; evidence of apparently major benefits of urgent medical treatment more generally comes only from observational studies.\textsuperscript{4,18} Randomised trials of aspirin vs. placebo in longer-term secondary prevention showed only a 13% relative reduction in risk of recurrent stroke.\textsuperscript{12,13,19} Trials of short-term treatment of hospitalised acute stroke also reported a 13% reduction in the 4 week risk of recurrent stroke or intracerebral haemorrhage, but the effect of aspirin on risk or severity of recurrence after more minor stroke was not reported.\textsuperscript{20-22} Yet, observational studies suggest potentially substantial early benefits of aspirin after TIA or minor stroke. In the EXPRESS study, urgent treatment with antiplatelet drugs, BP-lowering, and statins reduced the early risk of stroke by 80%,\textsuperscript{5,6} much of which benefit was hypothesised to have been due to aspirin.\textsuperscript{5} Severity of recurrent cerebral events was also reduced in EXPRESS (webappendix p2), which might also have been due to aspirin.

In the absence of published randomised evidence of the effect of aspirin on risk and severity of early recurrent stroke after TIA and minor stroke, we re-analysed individual patient data and reviewed original paper records on early outcomes from all available trials of aspirin vs. placebo in secondary prevention after TIA or ischaemic stroke. To more reliably estimate the very early time-course of onset of effects of aspirin, we also studied risk of recurrent ischaemic stroke in trials of aspirin in treatment of acute stroke, stratified by severity of the pre-randomisation neurological deficit. To inform on possible mechanisms of action, we also studied the time-course of the interaction between effects of aspirin and dipyridamole in secondary prevention of stroke.
Methods

Trials were eligible if they randomised: 1) patients with TIA or ischaemic stroke to regular aspirin (any dose, in the presence or absence of another antiplatelet agent) versus no antiplatelet or anticoagulant in the secondary prevention of stroke and other vascular events; 2) patients with acute ischaemic stroke to regular aspirin (any dose) versus no aspirin, in the presence or absence of another antithrombotic treatment, for acute treatment and prevention of early recurrence; or 3) patients with TIA or ischaemic stroke to regular dipyridamole (any dose) versus no dipyridamole (in the presence or absence of another antiplatelet agent) in the secondary prevention of stroke and other vascular events. Trials were identified from the Antithrombotic Trialists’ (ATT) Collaboration,13 subsequent systematic reviews, and the Cochrane Collaboration.24,25 In view of the ‘historical’ nature of the trials, no additional searches were made for ongoing trials or abstracts presented at meetings.

For all eligible trials of aspirin or dipyridamole in secondary prevention after TIA or stroke, we sought to obtain individual patient data. If these were not available, published data on vascular events were extracted from trial reports. Data were obtained on the following baseline variables: randomised treatment allocation, age, sex, prior diabetes, current smoking, history of hypertension, blood pressure at entry, time from most recent cerebrovascular event to randomisation, nature of the most recent cerebrovascular event prior to randomisation (TIA; “minor” or non-disabling stroke; “major” or disabling stroke), and pre-morbid disability (modified Rankin score). Data were also obtained on the nature and timing of the following outcome variables: any recurrent stroke, recurrent ischaemic stroke, acute myocardial infarction, intracerebral haemorrhage, fatal extracranial bleeding, and cause of any other deaths. If available, from either electronic or paper records, data were obtained on the severity/outcome of all recurrent strokes (modified Rankin score). There were minor differences in definition of recurrent stroke between trials, but designations made in the original trials were not changed.

For trials of aspirin in treatment of major acute stroke, we also sought to obtain individual patient data on the severity of stroke at entry (e.g. a severity score or other measure of the extent on the baseline neurological deficit) and on time to first recurrent ischaemic stroke during the trial period. In one small trial,26 only data on ‘progression’ of stroke were collected (defined as a worsening of at least 2 points on Scandanavian Stroke Progression Scale27). In the absence of any other data, this outcome was included for completeness.

Analysis

All analyses were by intention-to-treat based on the randomised treatment allocation. In trials in the secondary prevention of stroke, the effect of aspirin versus control and dipyridamole versus control was determined, with stratification by time from randomisation (0-6 weeks; 6-12 weeks, >12 weeks), for the following outcomes: recurrent ischaemic stroke, disabling or fatal recurrent ischaemic stroke; any recurrent stroke, any fatal stroke, intracerebral haemorrhage, and acute myocardial infarction. For each outcome, odds ratios were calculated in each trial and pooled estimates were obtained by fixed-effects meta-analysis (Mantel-Haenszel-Peto method) if there was no significant heterogeneity (chi-squared test) between trials.

In the absence of significant heterogeneity, individual patient data were pooled and Kaplan Meier curves (1 – proportion free of event) were generated for time to first event. Statistical significance of any effect of randomised treatment allocation was determined using the log-rank test stratified by trial and hazard ratios (95%CI) for events up to 12 weeks follow-up were generated using Cox proportional hazards models stratified by trial (the assumption of proportional hazards was violated if events after 12 weeks were included).
The severity of early recurrent strokes was compared between treatment groups based on modified Rankin scores (mRS) using ordinal regression (‘mRS-shift’) analysis. The assumption of proportional odds was assessed with the score test and was valid (p>0.3) for all analyses. However, odds ratios were also calculated for the traditional single cut point of mRS>2.

Stratified analyses of effect of treatment on recurrent ischaemic stroke and on disabling or fatal recurrent ischaemic stroke were also done for the following potential effect-modifiers: dose of aspirin (low <100mg vs ≥300mg - high), TIA or minor stroke only vs major stroke (usually defined as the presence of residual neurological signs) at baseline; time from last TIA or minor stroke to randomisation (≤14 days vs >14 days), age (<65 vs 65-74 vs ≥75 years), sex, diabetes, current smoking, and hypertension (prior diagnosis or BP≥160/90 at baseline assessment).

In trials of aspirin in treatment of acute stroke, we determined the effect of aspirin versus control on risk of recurrent ischaemic stroke. Trials differed in duration of randomised treatment allocation (webappendix p8). To maximise comparativeness between the trials, we first determined the effect of aspirin up to day-14 after randomisation, stratified by the severity of the stroke at the baseline assessment. In the two largest trials, data on the extent of baseline neurological deficit had been collected in the same way based on the presence or absence of neurological deficits of the following types: face; arm/hand; leg/foot; dysphasia; visuospatial; brainstem/cerebellar; hemianopia; and other. We quantified the severity of stroke as follows: mild (≤2 deficits); moderately severe (3-4 deficits); severe (≥5 deficits). A third smaller trial had quantified baseline severity of stroke using approximate quartile categories of the Scandanavian Stroke Progression Scale27 (<9; 10-11; 12-13; 14-25). The distribution of severity that most closely matched that in the other two trials was: mild (<9); moderately severe (10-14); severe (14-25).

Odds ratios for the effect of aspirin on the 14-day risk of recurrent ischaemic stroke were calculated in each trial, with stratification by severity of initial stroke. Pooled estimates were obtained by fixed-effects meta-analysis (Mantel-Haenszel-Peto method) if there was no significant heterogeneity (p>0.05 on chi-squared test) between trials, or otherwise by random-effects meta-analysis. To determine the time-course of onset of effect of aspirin in the acute phase, we performed a pooled analysis stratified by time from randomisation to recurrent ischaemic stroke (days 0-1; 2-3; 4-6; 7-14; ≥15). This analysis covered the full period of randomised treatment allocation in the trials and was done both with and without the patients in the IST20 who had been taking aspirin prior to randomisation. Prior aspirin use was an exclusion criterion in the smaller trial26 and was rare in CAST.21

Role of sponsor: The sponsor was not involved in the design, analysis, reporting of the study or the decision to publish.
Results

We identified 12 trials (15,778 participants) of aspirin versus control in secondary prevention after TIA or ischaemic stroke (webappendix p3). Data on recurrent vascular events within 12 weeks of randomisation were available for all of these trials. Eleven trials included comparisons of aspirin alone vs placebo and 3 trials included comparisons of aspirin plus dipyridamole vs no aspirin.

Among 9635 patients in 11 trials of aspirin only vs. control in secondary prevention, aspirin reduced the 6-week risk of recurrent ischaemic stroke by about 60% (55/5213 vs 118/4422; HR=0.40, 95%CI 0.29-0.55, p<0.0001), with a similar effect at 12 weeks (table 1) and no heterogeneity between trials (webappendix p5, p_het=0.86).

Inclusion of comparisons of aspirin plus dipyridamole versus no aspirin did not change the result (any aspirin vs control: 6-week risk - 82/8452 vs 175/7326; HR=0.41, 0.32-0.54, p<0.0001, table 1). Benefit was greatest at 0-2 weeks (figure 1), but further benefit did accrue up to 12 weeks follow-up (table 1, figures 1 & 2).

Aspirin also reduced the severity (mRS) of recurrent ischaemic stroke during the six weeks after randomisation (any aspirin vs control: mRS ‘shift’ ordinal regression OR=0.43, 95%CI=0.26-0.72, p=0.001; aspirin alone vs control: 0.46, 0.26-0.82, p=0.009; figure 3), with a similar effect also seen at 12 weeks (figure 3) and when analysis was based just on mRS>2 (figure 3). Consequently, aspirin reduced the 6-week risk of disabling or fatal (mRS>2) ischaemic stroke by about 70% (any aspirin vs control: 36/8422 vs 110/7296, HR=0.29, 0.20-0.42, p<0.0001, p_het=0.91; aspirin only vs control: 26/5183 vs 78/4392, HR=0.29, 0.19-0.46, p<0.0001, p_het=0.91) and the risk of very severe (mRS=4-6) recurrent ischaemic stroke by about 75% (26/8422 vs 92/7296; HR=0.25, 0.16-0.39, p<0.0001), but had less effect on non-disabling (mRS≤2) recurrence (6-weeks: 46/8422 vs 64/7296; HR=0.63 0.43-0.92, p=0.017 ). Benefit continued to accrue for risk of disabling or fatal recurrent ischaemic stroke up to 12 weeks follow-up (table 1, figures 1 & 2), but the greatest reduction was seen within the first two weeks particularly in patients presenting with TIA and minor stroke (HR=0.07, 0.02-0.31, p=0.0004, figure 1).

Aspirin also reduced the early risks of any recurrent stroke (table 1), fatal recurrent stroke (table 1), and acute myocardial infarction (any aspirin vs control 6-weeks: 6 vs 25, HR=0.22, 0.09-0.53, p=0.0008; 12-weeks – 17 vs 50, 0.31, 0.18-0.53, p<0.0001). There was no increase in the 12-week risk of intracerebral haemorrhage on low-dose aspirin vs control (3/4125 vs 5/4137), but there was a trend towards higher risk on high-dose aspirin vs control (5/4297 vs 1/3159). However, four of the events on high-dose aspirin occurred as complications of carotid endarterectomy in the UK-TIA Aspirin Trial (3 on 1200mg; 1 on 300mg). There was only one fatal extracranial bleed within 12 weeks of randomisation in any of the trials (on aspirin plus dipyridamole in ESPS-2).

The effect of aspirin on 12-week risk of recurrent ischaemic stroke was independent of dose and patient characteristics (webappendix p6), but the benefit tended to be larger after TIA and minor stroke than after major ischaemic stroke (table 2, figure 1). In trials where data were available, a similar effect on 12-week risk of disabling or fatal recurrent ischaemic stroke was found in patients with atrial fibrillation at baseline (HR= 0.28, 0.08-1.00, p=0.05) and in those with lacunar stroke (data in ESPS-2 only). There was also no interaction between time from the last TIA or stroke to randomisation and the effect of any aspirin vs. control on the 12-week risks of ischaemic stroke or of disabling or fatal ischaemic stroke (table 2). Aspirin reduced the 12-week risk of disabling or fatal recurrent ischaemic stroke in patients recruited <14 days after their last event (HR=0.48, 0.28-0.80, p=0.005), but there were too few patients recruited within 7-days to define the effect of treatment.
The absolute risk of recurrent ischaemic stroke fell with time from randomisation (p<0.0001, figure 2). In trials of aspirin only vs control, there was no reduction in risk of recurrent ischaemic stroke after 12 weeks (OR= 0.97, 0.84-1.12, p=0.67; p<0.0001 for <12 vs >12 weeks), with no heterogeneity between trials (webappendix p7). There was also no reduction in severity of post-12 week strokes (mRS ‘shift’ OR=1.00, 0.77-1.29, p=0.97).

Given the small numbers of patients randomised within 7 days of their last event in the trials of aspirin in secondary prevention after TIA or stroke, we studied the time-course of risk of recurrent ischaemic stroke in trials of aspirin in treatment of acute stroke, in which all patients were randomised within 48 hours of stroke onset. Among 3 eligible trials (40,531 participants, webappendix p8) individual patient data were available from the two largest (40,090 participants) and tabular data from the smaller trial (441 participants).

The effect of aspirin vs. control on the 14-day risk of recurrent ischaemic stroke differed (p=0.014) in relation to the severity of stroke, as indicated by the extent of the baseline neurological deficit (webappendix p9). Aspirin reduced the 14-day risk of recurrent ischaemic stroke in participants with mild neurological deficits at baseline, with a consistent effect across the trials, but had no effect in those with severe deficits at baseline. In participants with moderately severe deficits, there was a significant overall reduction in risk, but there was heterogeneity between trials. There was no interaction (p=0.92) between the effect of aspirin on recurrent ischaemic stroke and randomisation between heparin and no heparin in the International Stroke Trial (IST).

On pooled analysis of recurrent ischaemic stroke in patients with mild and moderately severe initial deficits, no effect of aspirin was found within the first 24 hours (day 0/1; figure 4) after randomisation, but risk was reduced on days 2 (HR=0.44, 0.25-0.76, p=0.0034) and 3 (0.31, 0.16-0.58, p=0.0003), with further reductions during days 4-6 (0.45, 0.31-0.67, p<0.0001) and 7-14 (0.64, 0.45-0.91, p=0.012), but not after 14 days (0.86, 0.58-1.27, p=0.45). Results were similar after inclusion of 3292 (21.3%) participants in IST who had received aspirin during the days prior to randomisation (webappendix p10). Of note, allocation to continued aspirin in this group did reduce the risk of recurrent ischaemic stroke in the first 24 hours (HR=0.31, 0.11-0.85, p=0.02).

We identified 8 trials (11,937 participants) of dipyridamole versus control (with or without aspirin) in secondary prevention after TIA or ischaemic stroke (webappendix p3). Three trials with comparisons of aspirin plus dipyridamole versus no antiplatelet were included in the any aspirin versus control analyses described above. Seven trials (9437 participants) included comparisons of dipyridamole plus aspirin versus aspirin alone, and one trial also included comparisons of dipyridamole versus aspirin and dipyridamole versus control (webappendix p3). Data on recurrent vascular events within 12 weeks of randomisation were obtained for all of these trials.

Adding dipyridamole to aspirin had no effect on the 12-week risk of recurrent ischaemic stroke (OR=0.90, 0.65-1.25, p=0.53; webappendix p11), with no heterogeneity between trials (p=0.31), and had no effect on severity of recurrent ischaemic stroke within 12-weeks of randomisation (mRS shift analysis: OR=0.90, 0.37-1.72, p=0.99. However, adding dipyridamole to aspirin did reduce the risk of recurrent ischaemic stroke after 12-weeks (OR=0.76, 0.63-0.92, p=0.005), particularly the risks of disabling or fatal ischaemic stroke (OR=0.64, 0.49-0.84, p=0.0010) and any disabling or fatal stroke (OR=0.65, 0.51-0.84, p=0.0008).

Dipyridamole versus control also had no effect of severity of 12-week recurrent ischaemic stroke in the ESPS-2 trial (mRS shift analysis: any dipyridamole vs control - OR=0.98 (0.58-1.66), p=0.95; dipyridamole only vs control – OR=1.11, 0.59-2.09, p=0.74).
Discussion

Our analyses of trials of aspirin in secondary prevention after TIA and ischaemic stroke show that the effect of aspirin on early recurrent events has been under-estimated. We identified substantial reductions in the early risks of all stroke, ischaemic stroke and acute myocardial infarction, with effect-sizes greater than after unstable angina or acute myocardial infarction.\textsuperscript{23} We also found that a major part of the early benefit of aspirin was due to an hitherto unrecognised reduction in severity of early recurrent ischaemic stroke, resulting in up to a 90% reduction in early risk of disabling or fatal recurrent ischaemic stroke after TIA and minor stroke.

However, the trials of aspirin in secondary prevention recruited few patients in the acute phase after TIA or stroke. We found no significant diminution of effect in patients randomised early, but the acute effects might differ. For example, aspirin had no effect on death for the first 3 days after acute myocardial infarction in the ISIS-2 trial.\textsuperscript{28} We therefore studied trials of aspirin in treatment of acute stroke, aiming simply to estimate the time-course of onset of effect of aspirin on risk of recurrent ischaemic stroke, the overall balance of risk and benefit having been documented elsewhere.\textsuperscript{20-22} On stratification by severity of the baseline neurological deficit, we showed that in patients with less severe stroke the relative reduction in risk of recurrent ischaemic stroke on aspirin was similar to that in the secondary prevention trials and was evident by the second full day of treatment. Aspirin could also have reduced further thrombosis, or related processes, in patients with more major stroke, but such effects would probably be less clinically evident in the territory of an already large cerebral infarct.

Our results have implications for acute treatment after TIA and minor stroke. First, they confirm previous non-randomised studies of the impact of urgent treatment on the early risk of recurrent stroke,\textsuperscript{5,6,18} supporting recommendations for urgent assessment. Second, they suggest that most of the benefit of urgent treatment in these previous multi-intervention studies was simply due to aspirin. It is essential therefore patients with TIA or minor stroke are not sent home from the emergency department with advice to add aspirin to their next prescription; they should be treated acutely. Similarly, patients who telephone their family doctor or advice lines should be told to take aspirin immediately if TIA is suspected, in addition to obtaining medical attention. Aspirin could also be given by paramedics when they assess patients at home. Third, we showed that aspirin reduced early recurrent stroke in non-anticoagulated patients with atrial fibrillation at baseline.

Our findings also have implications for the choice of antithrombotic treatment early after TIA or ischaemic stroke. Most guidelines do not distinguish between the early and later phases of secondary prevention and several recommend clopidogrel monotherapy or other drugs as equal alternatives to aspirin.\textsuperscript{29,30} Our findings suggest that treatment in the first few days and weeks should include aspirin unless some other antithrombotic agent is shown to be superior. We found that dipyridamole monotherapy was inferior to aspirin in prevention of early recurrent stroke, and that addition of dipyridamole to aspirin did not enhance the effects of aspirin on risk or severity of early recurrent ischaemic stroke. Clopidogrel plus aspirin does appear to be more effective than aspirin alone in preventing early recurrent stroke after TIA and minor ischaemic stroke,\textsuperscript{31,32} but has no effect on severity of stroke,\textsuperscript{33} and the only trial of clopidogrel monotherapy versus aspirin plus dipyridamole in this patient group reported data that, in light of our findings, suggest increased severity of early recurrent stroke in the clopidogrel group.\textsuperscript{34} Indeed, although the PROFESS trial showed no difference in overall severity of recurrent stroke on aspirin plus dipyridamole versus clopidogrel in secondary prevention after TIA and ischaemic stroke,\textsuperscript{35} our findings suggest that risk and severity of early recurrent stroke might have been reduced on aspirin plus dipyridamole in patients who were randomised soon after their initial TIA or stroke, such that the early effects of
aspirin would not already be lost after prolonged pre-randomisation use. Diminishing benefit of aspirin with longer pre-randomisation use would also explain why the advantage of aspirin plus clopidogrel versus clopidogrel alone in the MATCH trial was only seen in patients randomised early after their TIA or stroke,\textsuperscript{36} and possibly why previous observational studies of severity of ischaemic stroke in relation to prior aspirin use have yielded conflicting results. Similar considerations will apply to trials of cilostazol, ticagrelor and other new anticoagulants in secondary prevention of stroke. In fact, survival curves in trials of aspirin vs cilostazol suggest that aspirin is superior for the first 3 months, but cilostazol is more effective thereafter.\textsuperscript{37,38} Future trials of new antiplatelet/antithrombotic drugs in prevention of early recurrent stroke should report data on severity of stroke and should avoid mixing patients on aspirin and patients on other antiplatelet drugs in the comparator arm.

Our findings also have implications for public education. First, confirmation in randomised trials that urgent treatment after TIA and minor ischaemic stroke reduces the early risk of disabling or fatal stroke by about 80% highlights the need to reduce delays in patients seeking medical attention. Second, since aspirin is available in many households, consideration should be given to promoting self-administration immediately after transient stroke-like neurological symptoms, as is recommended for people who have acute chest pain.\textsuperscript{14,15} Intracranial haemorrhage is rare in patients with TIA symptoms and accounts for less than 5% of minor strokes.\textsuperscript{16,17} Moreover, randomised trials of antithrombotic agents that have included patients with acute intracranial haemorrhage have not, in fact, shown any increase in risk of death or of recurrent haemorrhage.\textsuperscript{39} Similarly, there is no evidence that prior aspirin would worsen outcome in the small proportion of patients who still subsequently progressed to have a major stroke and required thrombolysis or thrombectomy.\textsuperscript{40,41} Indeed, given the substantial reductions in progression to disabling or fatal early recurrent ischaemic stroke that we observed on aspirin, prevention of the need for thrombolysis or thrombectomy will be the main benefit. Public education should continue to persuade people with transient unfamiliar neurological symptoms to seek medical attention immediately, where this is possible, but self-administration of aspirin would also be prudent, particularly in rural settings or in less developed countries where access to emergency services may be delayed. Some individuals would take an aspirin or two unnecessarily, as is the case with non-cardiac chest pain, but others would benefit.

For longer-term secondary prevention after TIA and ischaemic stroke, aspirin had no significant effect on risk or severity of recurrent ischaemic stroke after 12 weeks. It is important to stress, however, that the early benefit of aspirin was maintained on longer-term follow-up even though no additional benefit accrued. More detailed analyses of trials in a broader range of secondary prevention settings, and including all relevant outcomes, are underway to establish the longer-term balance of risk and benefit (personal communication, Rothwell), and new trials may be required to determine the risk and benefits of stopping aspirin. The lack of additional benefit after 12 weeks does, however, necessitate re-interpretation of trials of long-term secondary prevention of stroke with other antithrombotic drugs vs aspirin which have shown either no benefit of the other drug,\textsuperscript{42} or only a small benefit.\textsuperscript{43} The interpretation that these drugs are ‘as effective’ as aspirin is less positive if aspirin is ineffective.

We found no evidence that adding dipyridamole to aspirin reduced the risk or severity of early recurrent ischaemic stroke. However, dipyridamole plus aspirin vs aspirin alone did reduce the risk of later recurrent ischaemic stroke and this effect was particularly marked for disabling or fatal events. Further work is required to fully understand the nature of this late effect in the trials that we studied here and in the PROFESS trial.\textsuperscript{35}

Our results do have limitations. First, the trials of aspirin in secondary prevention were done in the 1980s and 1990s. Medical care has since changed, with more detailed investigations and more intensive blood pressure
and lipid lowering. However, the effect of urgent treatment after TIA and minor stroke that was observed in more recent observational studies\textsuperscript{5,6,18} is very similar to that in the previous trials (webappendix p2). Changes in medical care would also impact less on the effectiveness of pre-hospital self-administration. Second, most patients in the secondary prevention trials were already beyond the very early high risk period after their initial TIA or minor stroke when recruited.\textsuperscript{44} However, delayed inclusion is likely to have underestimated the absolute reduction in risk of early recurrent stroke, as might the lack of a loading dose in the trials of low-dose aspirin, but relative risk reductions are likely to be generalizable to the acute phase. The absolute reduction in risk of ischaemic stroke in the EXPRESS study in which patients were treated more acutely was about 8% (NNT=12; webappendix p2).\textsuperscript{5} We did not find a reduction in recurrent ischaemic stroke during the first 24 hours in trials of aspirin in the acute treatment of major stroke, but early deterioration after major stroke is multifactorial and recurrent stroke is difficult to distinguish from progression of existing pathological processes. There was no evidence of a delay in onset of the benefit of acute treatment after TIA and minor stroke in observational studies in the acute phase.\textsuperscript{5,6,18} Third, some patients in the trials of aspirin in secondary prevention were treated with aspirin or other antithrombotic drugs for a short time after their initial TIA or stroke but prior to inclusion. However, we found no evidence that such treatment influenced the effect of subsequent randomised treatment, either in the SALT trial, which had a short on-treatment run-in, or in the other secondary prevention trials. However, prior aspirin use was associated with benefit within the first 24 hours in the IST trial. Finally, we did not report data on whether non-compliance with trial treatment might explain the diminishing longer-term benefit of aspirin. However, preliminary analyses show little evidence of this (personal communication, Rothwell) and compliance was clearly sufficient to show the late benefits of dipyridamole plus aspirin versus aspirin alone.

Our findings raise questions about the mechanism(s) by which aspirin reduces the risk and severity of early recurrent ischaemic stroke and by which effectiveness diminishes with longer-term use. It is unusual for preventive treatments to reduce the risk of disabling stroke more than non-disabling stroke, which might suggest a ‘neuroprotective’ effect of aspirin, possibly due to prostaglandin-mediated effects on the microvasculature.\textsuperscript{45,46} However, the similarly large reduction in the early risk of myocardial infarction suggests reversal of short-term systemic platelet activation, but other antiplatelet drugs do not appear to reduce severity of stroke. The loss of benefit of aspirin on longer term use is at odds with the maintenance of platelet COX-1 inhibition,\textsuperscript{47} although time-course data on bleeding time are less clearcut.\textsuperscript{48} It is possible that aspirin is only clinically effective during periods when platelets are activated, or that platelets ‘adapt’ to aspirin via upregulation of non-COX-mediated pathways, or that acetylation of other proteins has effects on other important pathways.\textsuperscript{49}

In conclusion, we have demonstrated the validity of previous non-randomised studies that showed the considerable impact that medical treatment has on the early risk of recurrent stroke after TIA and minor ischaemic stroke and we have identified aspirin as the key component. It is essential that aspirin is given to patients with TIA or minor stroke immediately. Indeed, a case can be made for public education about self-administration after transient unfamiliar neurological symptoms. The previously unrecognised reduction in severity of early recurrent ischaemic stroke by aspirin, has important implications for clinical guidelines, interpretation of previous and future trials, and for understanding mechanism of action. More generally, our findings highlight the fact that to understand the effects of newer drugs in comparison to, or in combination with, older drugs, it is first necessary to fully understand the effects of the older drug.
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Contributions of authors
Rothwell conceived the study, administered the collection of data, did analyses, interpreted results, did literature searches and wrote the manuscript. Mehta assisted in preparation and analysis of data and created the tables and figures. Other authors were Lead Investigators on the large trials included in the analyses, made the individual patient data available, and commented on drafts of the manuscript.

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**Research in context**

**Evidence before this study**
Previous systematic reviews of randomised trials of aspirin vs. placebo in secondary prevention after TIA or ischaemic stroke reported only a 13% relative reduction in risk of recurrent stroke. Systematic reviews of trials of aspirin in hospitalised acute stroke also reported a 13% reduction in the short-term risk of recurrent stroke or intracerebral haemorrhage. Yet, observational studies have suggested much more substantial benefits of urgent medical treatment after TIA or minor stroke, with the early risk of recurrent stroke reduced by as much as 80%, and a possible reduction in severity of stroke. However, the time-course of benefit of aspirin had not been studied in randomised trials. We re-analysed individual patient data and reviewed original paper records on early outcomes from all available trials of aspirin vs. placebo in secondary prevention after TIA or ischaemic stroke and we studied risk of recurrent ischaemic stroke in trials of aspirin in treatment of acute stroke. Trials were identified from the Antithrombotic Trialists’ (ATT) Collaboration, the Cochrane Collaboration, and other published systematic reviews.

**Added value of this study**
Our analyses of trials of aspirin in secondary prevention after TIA and ischaemic stroke show that the effect of aspirin on risk early recurrent events has been under-estimated. We identified substantial reductions in the early risks of all stroke, ischaemic stroke and acute myocardial infarction. We also found that a major part of the early benefit of aspirin was due to an hitherto unrecognised reduction in severity of early recurrent ischaemic stroke, resulting in 80-90% reductions in the early risk of disabling or fatal recurrent ischaemic stroke after TIA and minor stroke. Although these trials recruited few patients in first few days after TIA or stroke, we found similar reductions in risk of recurrent ischaemic stroke on aspirin in trials done in patients with acute ischaemic stroke.

**Interpretation of all available evidence**
Our results support the finding in observational studies that urgent medical treatment substantially reduces the risk of early recurrent stroke after TIA and minor stroke and have identified early use of aspirin as the key intervention. These results highlight the need for medical services to give aspirin as soon as possible and for public education about self-administration after unaccustomed transient neurological symptoms suggestive of ‘threatened stroke’.
Table 1. Pooled analysis of the early risk of recurrent vascular events in trials of aspirin versus control in secondary prevention after TIA and ischaemic stroke. Analysis of any aspirin versus control includes comparisons of aspirin plus dipyridamole versus control.

| Event Description | 0-6 weeks | 6-12 weeks | 0-12 weeks |
|-------------------|-----------|------------|------------|
|                   | Events    | HR (95% CI) | p          | Events    | HR (95% CI) | p          | Events    | HR (95% CI) | p          |
| Any aspirin vs control |           |            |            |            |            |            |            |            |            |
| Any ischaemic stroke | 257       | 0.41 (0.32-0.54) | <0.0001 | 119       | 0.61 (0.42-0.88) | 0.0084 | 376       | 0.47 (0.38-0.58) | <0.0001 |
| Disabling or fatal ischaemic stroke | 146       | 0.29 (0.20-0.42) | <0.0001 | 63        | 0.50 (0.30-0.84) | 0.0084 | 209       | 0.35 (0.26-0.47) | <0.0001 |
| Any stroke | 266       | 0.44 (0.34-0.57) | <0.0001 | 123       | 0.59 (0.41-0.86) | 0.0050 | 389       | 0.49 (0.39-0.60) | <0.0001 |
| Any fatal stroke | 58        | 0.36 (0.20-0.63) | 0.0005 | 22        | 0.71 (0.30-1.65) | 0.43 | 80        | 0.44 (0.27-0.70) | 0.0006 |
| Acute myocardial infarction | 32        | 0.21 (0.09-0.51) | 0.0006 | 36        | 0.39 (0.19-0.81) | 0.011 | 68        | 0.30 (0.17-0.52) | <0.0001 |
| Aspirin only vs control |           |            |            |            |            |            |            |            |            |
| Any ischaemic stroke | 173       | 0.40 (0.29-0.55) | <0.0001 | 70        | 0.62 (0.38-1.00) | 0.048 | 243       | 0.46 (0.35-0.60) | <0.0001 |
| Disabling or fatal ischaemic stroke | 104       | 0.29 (0.19-0.46) | <0.0001 | 39        | 0.51 (0.27-0.98) | 0.044 | 143       | 0.35 (0.24-0.50) | <0.0001 |
| Any stroke | 180       | 0.42 (0.31-0.58) | <0.0001 | 73        | 0.61 (0.38-0.97) | 0.036 | 253       | 0.47 (0.36-0.61) | <0.0001 |
| Any fatal stroke | 33        | 0.46 (0.22-0.95) | 0.035 | 12        | 0.53 (0.17-1.69) | 0.28 | 45        | 0.48 (0.26-0.88) | 0.018 |
| Acute myocardial infarction | 25        | 0.23 (0.09-0.63) | 0.0038 | 25        | 0.35 (0.15-0.85) | 0.020 | 50        | 0.29 (0.15-0.56) | 0.0002 |
Table 2. Pooled analysis of the effect of any aspirin vs control in secondary prevention after TIA and ischaemic stroke on the early risk of any recurrent ischaemic stroke and on disabling or fatal ischaemic stroke stratified by the nature of the presenting event (TIA and minor stroke versus major stroke) and by time from presenting event to randomisation (≤14 days vs >14 days). Data on time since last event were only available in 12,909 patients.

| Presenting event                      | Events | 0-6 weeks | HR (95% CI) | p    | Events | HR (95% CI) | p    | Events | HR (95% CI) | p    | p       |
|---------------------------------------|--------|-----------|-------------|------|--------|-------------|------|--------|-------------|------|---------|
| **Any ischaemic stroke**              |        | 0-6 weeks |             |      | 6-12 weeks |             |      | 0-12 weeks |             |      | (interaction) |
| TIA or minor stroke                   | 168    | 0.38 (0.27-0.52) | <0.0001    | 91   | 0.64 (0.42-0.98) | 0.039   | 259 | 0.46 (0.35-0.59) | <0.0001 | 0.84 |
| Major stroke                          | 89     | 0.49 (0.32-0.76) | 0.0014     | 28   | 0.51 (0.23-1.10) | 0.088   | 117 | 0.49 (0.34-0.72) | 0.0003 |
| **Disabling or fatal ischaemic stroke** |        |            |             |      |            |             |      |            |             |      |         |
| TIA or minor stroke                   | 74     | 0.19 (0.11-0.34) | <0.0001 | 40   | 0.45 (0.23-0.87) | 0.017   | 114 | 0.27 (0.17-0.41) | <0.0001 | 0.16 |
| Major stroke                          | 72     | 0.42 (0.25-0.69) | 0.0007 | 23   | 0.59 (0.25-1.36) | 0.21    | 95  | 0.46 (0.30-0.70) | 0.0004 |
| **Time since last event**             |        | 0-6 weeks |             |      | 6-12 weeks |             |      | 0-12 weeks |             |      | (interaction) |
| Any ischaemic stroke                  |        |            |             |      |            |             |      |            |             |      |         |
| Time since last event ≤14             | 80     | 0.54 (0.34-0.85) | 0.0082 | 33   | 0.71 (0.36-1.42) | 0.33    | 113 | 0.59 (0.40-0.86) | 0.0059 | 0.10 |
| Time since last event >14             | 115    | 0.33 (0.22-0.50) | <0.0001 | 56   | 0.55 (0.32-0.94) | 0.029   | 171 | 0.39 (0.28-0.54) | <0.0001 |
| Disabling or fatal ischaemic stroke   |        |            |             |      |            |             |      |            |             |      |         |
| Time since last event ≤14             | 43     | 0.41 (0.21-0.78) | 0.0071 | 20   | 0.65 (0.27-1.59) | 0.35    | 63  | 0.48 (0.28-0.80) | 0.0055 | 0.10 |
| Time since last event >14             | 71     | 0.21 (0.12-0.39) | <0.0001 | 31   | 0.42 (0.20-0.90) | 0.025   | 102 | 0.27 (0.17-0.43) | <0.0001 |
Figure 1. Pooled analysis of the early risk of recurrent vascular events in trials of any aspirin (thick line) versus control (thin line) in 12 trials in secondary prevention after TIA and ischaemic stroke. Hazard ratio (95%CI) is given for 0-2, 0-6 and 0-12 weeks, with statistical significance by the logrank test.

Patients with TIA and minor stroke only

Any ischaemic stroke

0-2 weeks: 0.35, 0.20-0.60, p=0.0001
0-6 weeks: 0.38, 0.27-0.52, p<0.0001
0-12 weeks: 0.46, 0.35-0.59, p=0.0001

Disabling or fatal ischaemic stroke

0-2 weeks: 0.07, 0.02-0.31, p=0.0004
0-6 weeks: 0.18, 0.11-0.34, p=0.0001
0-12 weeks: 0.27, 0.17-0.41, p=0.0001

Disabling or fatal ischaemic stroke and acute myocardial infarction

0-2 weeks: 0.11, 0.04-0.31, p=0.0001
0-6 weeks: 0.19, 0.11-0.31, p<0.0001
0-12 weeks: 0.27, 0.19-0.39, p<0.0001

All patients

0-2 weeks: 0.56, 0.31-0.90, p=0.0002
0-6 weeks: 0.41, 0.32-0.54, p=0.0001
0-12 weeks: 0.47, 0.38-0.58, p<0.0001
Figure 2. Pooled analysis of the effect of aspirin only vs control in secondary prevention after TIA and ischaemic stroke on the absolute risk (events per 100 person years) of any recurrent ischaemic stroke and of disabling or fatal ischaemic stroke, stratified by period of follow-up. Time-course of treatment effect interaction: $p_{int}<0.0001$ for both outcomes.
Figure 3. Pooled analysis of the effect of aspirin versus control (any aspirin vs control; aspirin only vs control) on the severity (modified Rankin score on follow-up – mRS) of recurrent ischaemic strokes in the first 6 week and the first 12 weeks after randomisation in trials in secondary prevention after TIA and ischaemic stroke. Odds ratios (95%CI) for effect of treatment on severity of stroke are given for ordinal regression analyses and also for the single cut point of mRS>2.
Figure 4. Pooled hazard ratios for the effect of aspirin vs control on risk of recurrent ischaemic stroke in patients with mild and moderately severe initial neurological deficits during early follow-up (days 0-1; 2-3,4-6; 7-14; >15) in two large trials of aspirin in treatment of acute stroke.20,21

This analysis excludes 3292 (21.3%) patients with mild or moderately severe stroke in the International Stroke trial who had received aspirin during the days prior to randomisation. The equivalent analysis with these patients included is shown in webappendix page 6.