

## SHORT REPORT

## Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia

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**Abstract**

There is continuing debate about the relative efficacy of low (< 100 mg per day), medium (300 to 325 mg per day), and high (> 900 mg per day) doses of aspirin in patients after a transient ischaemic attack or non-disabling stroke. The purpose of this study was to resolve the issue. Thus a minimeta-analysis was performed on data from 10 randomised trials of aspirin only *v* control treatment in 6171 patients after a transient ischaemic attack or non-disabling stroke. The data on the trials were listed in an appendix of the report on the second cycle of the Antiplatelet Trialists' Collaboration. There was virtually no difference in relative risk reduction for low, medium, and high doses of aspirin (13%, 9%, and 14% respectively). This equivalence corresponds with the results of the UK-TIA trial in a direct comparison of 300 and 1200 mg. The Dutch TIA trial showed no difference in efficacy of 30 and 283 mg. It is concluded that aspirin at any dose above 30 mg daily prevents 13% (95% confidence interval 4-21) of vascular events and that there is a need for more efficacious drugs.

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The vast majority (85%) of neurologists in the United States prescribe one tablet (325 mg) of

aspirin a day for the secondary prevention of stroke.<sup>1</sup> In an inquiry among 44 leading neurologists 42 (95%) preferred a dose of 325 mg or less; nine (20%) prescribed 100 mg or less for this indication.<sup>2</sup> Nevertheless the efficacy of low or medium dose aspirin ( $\leq$  325 mg per day) has been questioned.<sup>3</sup> This has again fuelled a debate on the relative efficacy of low or medium *v* high doses of aspirin.<sup>4</sup>

In the second cycle of the Antiplatelet Trialists' Collaboration 18 randomised trials in patients with cerebral ischaemia were included in the analyses and the raw tabular data on single trials were provided in an appendix.<sup>5</sup> We performed a minimeta-analysis with these data to try and resolve the controversy.

**Methods**

The present analysis is restricted to the efficacy of various doses of aspirin only, without interference from other antiplatelet drugs. Therefore we selected those trials in which aspirin only was compared with control treatment. The composite outcome of vascular death, stroke, or myocardial infarction was chosen for the analysis because we agree with the Antiplatelet Trialists' Collaboration that this measure of outcome is the most relevant from the patient's point of view and also provides the largest number of events for analysis which are likely to be influenced by antiplatelet treatment. The relative risk and corresponding relative risk reduction ( $(1 - \text{relative risk}) \times 100\%$ ) were used as the effect measure rather than the odds ratio and relative odds

Table 1 List of randomised trials of aspirin only, number of patients randomised and vascular events, selected baseline risk factors, and annual risk of vascular event in the control group

Trial	Year of publication	Dose (mg/day)	No of patients		Vascular events		Mean age (y)	TIA (%)	Previous MI (%)	Annual risk (%)*
			Aspirin	Control	Aspirin	Control				
AITIA <sup>9,10</sup>	1977	1300	162	157	26	35	67	100	19	15.7
Reuther <sup>11</sup>	1978	1500	30	30	2	5	66	33	—	8.3
Canadian Coop <sup>12</sup>	1978	1300	144	139	32	30	—†	40	15	7.6
Toulouse TIA <sup>13</sup>	1982	900	147	156	11	16	63	45	10	3.6
AICLA <sup>14</sup>	1983	900	198	204	31	46	64	58	10	7.5
Danish Coop <sup>15</sup>	1983	1000	101	102	23	27	59	76	7	9.6
Britton <sup>16</sup>	1987	1500	253	252	59	55	68	0	9	10.9
Danish Low <sup>17</sup>	1988	50-100	150	151	21	21	59	51	13	7.3
UK-TIA <sup>18,19</sup>	1988	300	806	814	174	193	60	77	11	5.7
		1200	815	814	168	193				
SALT <sup>20</sup>	1991	75	676	684	163	193	67	33	11	10.6

\*Risk of a vascular event (vascular death, stroke, or MI) in the control group; MI = Myocardial infarction; — = no data received.

†Age  $\geq$  70 years in 17%.

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Figure 1 Relative risks (RRs) and corresponding relative risk reductions with 95% CIs for all aspirin trials separately, two low (< 100 mg/day) dose trials combined, one medium dose trial, all high (>900 mg/day) dose trials combined, and all aspirin trials combined. ASA = acetylsalicylic acid (aspirin).

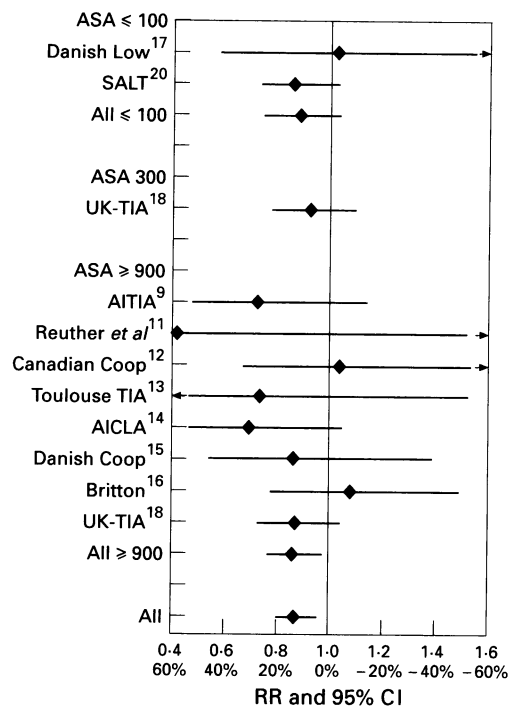


Figure 2 Cumulative meta-analysis in chronological order (1977 to 1991) with relative risks (RRs) and corresponding relative risk reductions with 95% CIs. Each line represents the relative risk and 95% CI of that study combined with all previous studies.

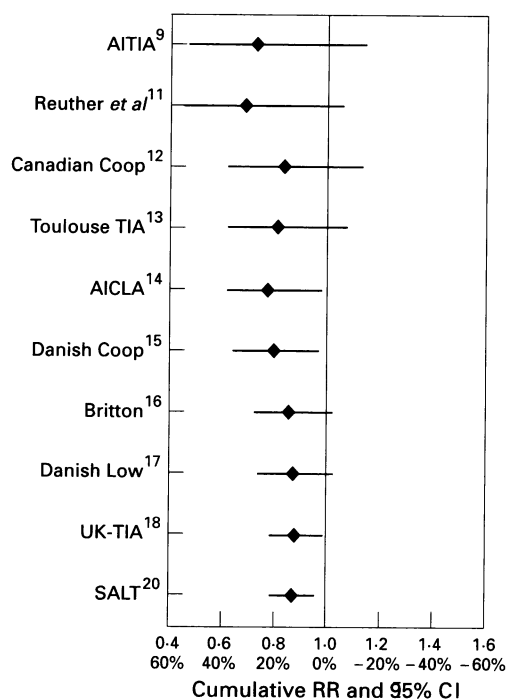


Table 2 Side effects in the United Kingdom and Dutch TIA trials

	Daily dose of aspirin			
	1200 mg	300/283 mg*	30 mg	placebo
UK-TIA trial <sup>19</sup> (No of patients)	815	806	—	814
Proved haemorrhagic stroke (%)	0.9†	0.9	—	0.2
Gastrointestinal haemorrhage (%)	4.8	3.1	—	1.1
Bruising (%)	1.6	1.5	—	0.4
Upper gastrointestinal symptoms (%)	41.5	31.4	—	25.7
Constipation (%)	6.9	6.0	—	2.5
Dutch TIA trial <sup>22</sup> (No of patients)	—	1555	1576	—
Major bleeding complications (%)	—	3.4†	2.6	—
Minor bleeding complications (%)	—	5.3	3.2	—
Gastric discomfort (%)	—	11.4	10.5	—

\*300 mg in the UK-TIA trial and 283 mg in the Dutch TIA trial.

†Percentages should only be compared between doses within one trial because of different follow up periods and definitions of side effects between trials.

reduction. The main reason for this choice is that risks are more directly linked with clinical thinking than odds. Odds reductions are often misinterpreted as risk reductions, but in that case the effect is overestimated as we shall illustrate in the results. The data from the different trials were combined by means of the Mantel-Haenszel method.<sup>6</sup> Cumulative meta-analysis by date of publication was performed according to methods described by Lau *et al.*<sup>7</sup> Poisson regression was employed to test for a statistically significant difference in the efficacy of low, medium, and high dose aspirin.<sup>8</sup>

## Results

Table 1 lists the 10 controlled trials with aspirin only that were eligible for the analysis.<sup>9-20</sup> With the exception of the Toulouse TIA trial all studies were placebo controlled. The trials are listed according to year of publication. The early trials used high doses, whereas the later trials studied lower doses. In the UK-TIA trial both 300 and 1200 mg regimens were compared with placebo. The table also provides data on the number of patients randomised and vascular events as well as the frequency of some important baseline risk factors. The proportion of patients with a transient ischaemic attack ranged from 0% to 100%, and the event rates in the control groups ranged from 3.6% to 15.7% a year.

The upper part of fig 1 shows the results of the two trials in which doses of aspirin less than 100 mg per day were used (1661 patients). The overall relative risk reduction for these two low dose trials was 13% (95% confidence interval (95% CI) -3 to 27). A medium dose (300 mg per day) was used in the UK-TIA trial (1620 patients) yielding a relative risk reduction of 9% (95% CI -9 to 24; middle of fig 1). All the eight high dose trials taken together (3704 patients; the UK-TIA placebo group is counted both with medium and high dose) showed a 14% relative risk reduction (95% CI 2 to 24; lower part of fig 1). The ranges of efficacy of low, medium, and high doses almost completely overlap; the P values of the tests for a statistical difference in the Poisson model were 0.75 (low *v* medium), 0.99 (low *v* high), and 0.71 (medium *v* high). Hence, the results of all trials could be combined in one overall effect estimate as shown at the bottom of fig 1. The overall relative risk reduction was 13% (95% CI 4 to 21%); the corresponding odds reduction was 16% (95% CI 5 to 26). Figure 2 shows the results of the cumulative meta-analysis, in chronological order, regardless of the dose of aspirin.

Table 2 shows direct comparisons of side effects with different doses of aspirin.

## Discussion

There could be objections to combining the results of the 10 trials selected for this minimeta-analysis. Some will argue that this is merely a post hoc subgroup analysis of the data collected by the Antiplatelet Collaboration by separating the effects of aspirin from

those of other antiplatelet agents, and only for patients after cerebral ischaemia. However, discussants of low and medium dose aspirin after cerebral ischaemia base their arguments on even more incomplete reviews of trials (some including other antiplatelet treatments).<sup>3</sup> To bring the dispute on the dose of aspirin into focus we reanalysed *all* trials with aspirin only in patients after cerebral ischaemia. Moreover, it is a matter of judgement whether to analyse the data of all atherosclerotic diseases combined or in separate disease categories. A second objection could be that the 10 trials are too different to be combined. Table 1, however, shows that major baseline risk factors are no more different between trials than within large trials. For example, in the Dutch TIA trial the annual risk of a vascular event in the average female patient with a transient ischaemic attack who was younger than 65 years and had no history of myocardial infarction was 1.3%, against 11.9% in a man with a non-disabling stroke who was 65 years or older and who did have a history of myocardial infarction.<sup>21</sup>

Our minimeta-analysis shows similar efficacy of low, medium, and high doses of aspirin, although for all regimens the 95% CI of the risk reduction ranges from about 25% to about 0%. Theoretically a true difference might still be hidden between these extremes. But a similar efficacy between medium and high doses is corroborated by the data of the UK-TIA trial which showed hardly any difference between 300 and 1200 mg daily, the point estimate of the relative risk being almost unity.<sup>19</sup> The direct comparison between 30 (low dose) and 283 mg (medium dose) in the Dutch TIA trial again showed no major differences.<sup>22</sup> Hence, we conclude that the efficacy in secondary prevention after cerebral ischaemia is similar for any dose of aspirin between 30 and 1500 mg a day.

In a recent review Barnett *et al* also included a minimeta-analysis of aspirin trials in patients after cerebral ischaemia.<sup>23</sup> Although non-fatal myocardial infarction was not included in their analysis a similar, low efficacy of aspirin was found with hardly any differences between different doses. Their recommendation to start with an initial dose of no less than 650 mg daily, however, is at variance with the conservative principle of medicine "primum non nocere". Given equal efficacy of low, medium, and high dose aspirin, the harmful side effects at high doses tilt the balance towards low doses (table 2).<sup>19, 22</sup>

The cumulative meta-analysis shows the historical development of the magnitude of relative risk reduction which was generally attributed to treatment with aspirin. At the end of the 1970s the perceived relative risk reduction was about 30%, but the confidence interval was wide. In the mid-1980s, after the publication of AICLA and the Danish cooperative study, the cumulative evidence shifted to a relative risk reduction of just over 20%. After the publication of SALT in 1991 the overall

relative risk reduction arrived at 13% with a 95% CI of 4 to 21%.

Because the point estimate of the risk reduction with aspirin is a modest 13%, the main message of this minimeta-analysis is that more potent approaches for secondary prevention after cerebral ischaemia are needed. For this reason we have launched SPIRIT (Stroke Prevention In Reversible Ischemia Trial) which compares anticoagulation and aspirin.<sup>24</sup>

We are grateful to professor CP Warlow and professor R Peto for criticisms on earlier drafts of this paper; we think it only fair to add that professor Peto considers that only the collective evidence (all arterial disease and all antiplatelet agents) should be reviewed, partial reviews being potentially misleading. We thank Dr FR Rosendaal for his remarks on this partial meta-analysis.

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