# Indications for Early Aspirin Use in Acute Ischemic Stroke

## A Combined Analysis of 40 000 Randomized Patients From the Chinese Acute Stroke Trial and the International Stroke Trial

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***Background and Purpose***—Long-term daily aspirin is of benefit in the years after ischemic stroke, and 2 large randomized trials (the Chinese Acute Stroke Trial [CAST] and the International Stroke Trial [IST]), with 20 000 patients in each, have shown that starting daily aspirin promptly in patients with suspected acute ischemic stroke also reduces the immediate risk of further stroke or death in hospital and the overall risk of death or dependency. However, some uncertainty remains about the effects of early aspirin in particular categories of patient with acute stroke.

***Methods***—To assess the balance of benefits and risks of aspirin in particular categories of patient with acute stroke (eg, the elderly, those without a CT scan, or those with atrial fibrillation), a prospectively planned meta-analysis is presented of the data from 40 000 individual patients from both trials on events that occurred in the hospital during the scheduled treatment period (4 weeks in CAST, 2 weeks in IST), with 10 characteristics used to define 28 subgroups. This represents 99% of the worldwide evidence from randomized trials.

***Results***—There was a highly significant reduction of 7 per 1000 (SD 1) in recurrent ischemic stroke (320 [1.6%] aspirin versus 457 [2.3%] control, $2P<0.000001$) and a less clearly significant reduction of 4 (SD 2) per 1000 in death without further stroke (5.0% versus 5.4%, $2P=0.05$). Against these benefits, there was an increase of 2 (SD 1) per 1000 in hemorrhagic stroke or hemorrhagic transformation of the original infarct (1.0% versus 0.8%, $2P=0.07$) and no apparent effect on further stroke of unknown cause (0.9% versus 0.9%). In total, therefore, there was a net decrease of 9 (SD 3) per 1000 in the overall risk of further stroke or death in hospital (8.2% versus 9.1%, $2P=0.001$). For the reduction of one third in recurrent ischemic stroke, subgroup-specific analyses found no significant heterogeneity of the proportional benefit of aspirin ($\chi^2_{18}=20.9$, NS), even though the overall treatment effect ($\chi^2_1=24.8$, $2P<0.000001$) was sufficiently large for such subgroup analyses to be statistically informative. The absolute risk among control patients was similar in all 28 subgroups, so the absolute reduction of ≈7 per 1000 in recurrent ischemic stroke does not differ substantially with respect to age, sex, level of consciousness, atrial fibrillation, CT findings, blood pressure, stroke subtype, or concomitant heparin use. There was no good evidence that the apparent decrease of ≈4 per 1000 in death without further stroke was reversed in any subgroup or that in any subgroup the increase in hemorrhagic stroke was much larger than the overall average of ≈2 per 1000. Finally, there was no significant heterogeneity between the reductions in the composite outcome of any further stroke or death ($\chi^2_{18}=16.5$, NS). Among the 9000 patients (22%) randomized without a prior CT scan, aspirin appeared to be of net benefit with no unusual excess of hemorrhagic stroke; moreover, even among the 800 (2%) who had inadvertently been randomized after a hemorrhagic stroke, there was no evidence of net hazard (further stroke or death, 63 aspirin versus 67 control).

***Conclusions***—Early aspirin is of benefit for a wide range of patients, and its prompt use should be routinely considered for all patients with suspected acute ischemic stroke, mainly to reduce the risk of early recurrence. **(*Stroke*. 2000;31:1240-1249.)**

**Key Words:** aspirin ■ stroke, acute ■ stroke, ischemic ■ randomized controlled trials

Long-term daily aspirin is of benefit in the prevention of serious vascular events in survivors of ischemic stroke, reducing the recurrence rate and improving survival.[1] In addition, the Chinese Acute Stroke Trial (CAST)[2] and the International Stroke Trial (IST)[3] recently demonstrated that starting daily aspirin as soon as is practicable after the onset of suspected acute ischemic stroke moderately reduces the risk of recurrent stroke or death in hospital and improves

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**TABLE 1. Characteristics of the Two Large Trials of the Early Use of Aspirin in Acute Ischemic Stroke: CAST and IST**

| Design Features | CAST (n=20 655) | IST (n=19 435) |
|---|---|---|
| Aspirin | | |
| Daily dose, mg | 160 | 300 |
| Maximum duration, wk | 4 | 2 |
| Control | Placebo | Open |
| Time from onset, h | 0–48 | 0–48 |
| Random allocation to heparin | No | 50%* |
| Recruitment period | June 1993 to March 1997 | January 1991 to May 1996 |
| Location | China | 34 Other countries |

*IST was a 2×2 "factorial" trial of aspirin, heparin, neither, or both: of those allocated to receive heparin in IST, half were to receive 5000 U BID and half were to receive 12 500 U unfractionated heparin SC BID.

functional recovery. This suggests that for maximal benefit, aspirin should generally be started promptly after the onset of suspected ischemic stroke and continued indefinitely. There remains uncertainty, however, about the benefits of early aspirin in certain categories of patient with acute ischemic stroke (including the elderly, those with atrial fibrillation,[4–6] and those presenting after a prolonged delay from symptom onset),[7] as well as concerns about cerebral and other hemorrhage (particularly among the elderly, those with high blood pressure, those who have not had a CT scan to exclude preexisting cerebral hemorrhage, and those being treated with anticoagulants).[7–9] To help address these issues, a combined analysis of individual patient data from CAST and IST had been planned prospectively before any results were available from either study. Each trial involved ≈20 000 patients, and together they represent ≈99% of the worldwide evidence from randomized trials of early aspirin use in acute ischemic stroke.[10,11] Both studies assessed the same clinical outcomes, and the main purpose of combining their results was to obtain from analyses of all 40 000 patients highly reliable estimates of the effects of immediate aspirin on particular outcomes, such as recurrent ischemic stroke. Both studies also, however, recorded the same patient characteristics (using similar entry forms), and a subsidiary preplanned purpose of the meta-analysis was to determine whether these particular characteristics significantly modified the clinical effects of aspirin.

## Subjects and Methods

### Trial Features

The designs of the 2 trials were similar (Table 1). A major eligibility criterion was the time from symptom onset, with both trials including only patients who were still within the first 48 hours (mean ≈24 hours) from symptom onset (or from sleep onset, if the stroke occurred while sleeping). A CT scan before randomization was mandatory only for those who were comatose at admission: the proportion of all patients scanned before randomization was, however, high (see later). In both trials, half of the patients were randomly allocated to receive medium-dose aspirin (160 mg/d for 4 weeks in CAST, 300 mg/d for 2 weeks in IST). In CAST, the control group were given inactive placebo tablets, but in IST, they were not, so IST was an "open" trial. For each patient who had not yet been irreversibly entered, however, proper concealment of the next random treatment allocation would be complete in both trials. In IST, half of the aspirin-allocated patients were also allocated subcutaneous heparin, as were half of the control patients, but this "factorial" design does not bias the present comparisons of all of those who were allocated aspirin versus all of those who were not.

### Individual Patient Data Collection

Information for each patient was obtained from both trials on several characteristics: hours since symptom onset, age, sex, level of consciousness (either alert or drowsy/comatose), presence of atrial fibrillation (yes/no), CT scan findings (infarct visible/not visible/not performed), systolic blood pressure, stroke syndrome (lacunar/other), and, in IST, whether the allocated treatment included heparin (yes/no). In addition, patients were subdivided into 3 similar-sized "prognostic categories" with respect to their risk of further (symptomatic) stroke or death in hospital, as estimated from a logistic model based on the data recorded at randomization for all patients (regardless of allocated treatment).[3]

Analyses are presented of recurrent ischemic stroke, of hemorrhagic stroke (including both hemorrhagic stroke and hemorrhagic transformation of the original infarct), of further stroke of unknown cause, of death without further stroke, of further stroke or death (ie, any of the above outcomes), and of any noncerebral hemorrhage that required transfusion or caused death. All analyses are based on allocated treatment and are of the numbers of patients with the relevant outcome at least once in the hospital (before first discharge) during the scheduled treatment period (days 0 to 28 in CAST, days 0 to 14 in IST).

Data from each trial were checked for internal consistency, with any apparent inconsistencies investigated and, if possible, corrected by the principal investigators. This process yielded only very minor discrepancies between the numbers reported here and those in the previous reports of these studies.[2,3]

### Statistical Analysis

The overall comparison of aspirin versus control in each particular subgroup is obtained by adding together the corresponding subgroup-specific results from CAST and from IST with use of the standard Mantel-Haenszel methods for meta-analyses of different trials.[1,12] These methods avoid any direct comparisons between patients in different trials or subgroups and involve no unjustifiable assumptions about similarities between the effects of aspirin in different trials. For a particular subgroup (eg, men) in a particular trial, the observed number of events among the aspirin-allocated patients is compared with the number expected from the combined experience among the aspirin-allocated and control-allocated patients in that subgroup. This is repeated for this same subgroup in the other trial, and these 2 "observed-minus-expected" (O−E) numbers of events, 1 from each trial, are then added together, as are their 2 variances, to yield a total (O−E) and its variance (V). From these 2 totals, ORs are calculated (using the standard formula exp[(O−E)/V] for the OR.[1,12] An OR of 0.70 would correspond to a 30% odds reduction among those allocated aspirin. The $\chi^2$ tests are calculated in the usual way[1,12] for heterogeneity between the odds reductions in subgroups with different characteristics (eg, age, sex, blood pressure, and so on). The summation of such $\chi^2$ tests yields a global $\chi^2$ test of heterogeneity on a number of *df* equal to the total number of subgroups minus the number of individual $\chi^2$ tests (eg, 10 characteristics divided into 28 subgroups yields a global heterogeneity test

**TABLE 2. Characteristics and Prognoses of Patients in CAST and IST**

| | CAST, %* | IST, %* |
|---|---|---|
| Prerandomization characteristics | | |
| Randomized 25–48 h after stroke onset | 47 | 34 |
| Age ≥75 y | 12 | 43 |
| Male | 63 | 54 |
| Drowsy/comatose | 13 | 23 |
| Atrial fibrillation | 7 | 16 |
| CT before randomization | 88 | 67 |
| Infarct visible on prerandomization CT, % of CT | 85 | 49 |
| Systolic blood pressure ≥190 mm Hg | 13 | 17 |
| Lacunar stroke syndrome | 30 | 24 |
| Final diagnosis of initial event was a hemorrhagic stroke | 1 | 3 |
| Event rates in hospital during scheduled treatment period | | |
| Recurrent ischemic stroke | 1.8 | 2.0 |
| Hemorrhagic stroke (or transformation) | 1.0 | 0.8 |
| Further stroke of unknown cause | 0.5 | 1.3 |
| Death without further stroke | 2.6 | 8.0 |
| Death (any cause) | 3.6 | 9.2 |
| Further stroke or death | 5.6 | 11.9 |
| Treatment time in survivors, mean/d | 26.2 | 13.5 |

*Percentages are of patients with data for the relevant characteristic.

on 28 minus 10 *df*). Because the individual tests for different characteristics may not be mutually independent, this global test is conservative; that is, it yields only a lower limit on the *P* value, with NS (not significant) indicating that the lower limit exceeds 0.1.

Even when there is clear overall evidence of benefit in an overview that involves several tens of thousands of patients, it can still be surprisingly difficult to reliably determine whether a treatment is either especially advantageous or relatively ineffective (or even dangerous) in some small subcategory of patients. Now that aspirin has been demonstrated to produces a significant overall reduction in recurrent ischemic stroke,[2,3] the statistically appropriate question for any particular category of patient is, in general, not whether the proportional risk reduction produced by aspirin in that category differs significantly from zero but instead whether (after due allowance for the fact that many categories have been analyzed) there is good evidence that the proven ability of aspirin to prevent ischemic stroke is absent in any particular category of patient with suspected acute ischemic stroke. Simple statistical formulas can help, but do not suffice, to answer such questions.

## Results

### Prerandomization Characteristics and Event Rates in the Hospital

In both trials, a wide range of patients with suspected ischemic stroke were randomized, with those in CAST tending to be younger and less likely to have impaired consciousness or atrial fibrillation than those in IST and hence having a somewhat better prognosis (Table 2). Overall, the mean time from symptom onset to randomization was ≈24 hours, but 5600 patients (14%) were randomized within the first 6 hours (and trial treatment began immediately after randomization). The mean age was 67 years (63 in CAST, 71 in IST), but 11 000 (28%) were aged ≥75 years. At randomization, 18% were drowsy or comatose, 12% had atrial fibrillation, and 15% had a systolic blood pressure of ≥190 mm Hg.

A CT scan was performed before randomization in 88% of those in CAST and 67% of those in IST; indeed, in CAST, eligibility was often decided only after a scan. Hence, of the prerandomization scans, 85% in CAST and 49% in IST already showed an infarct. Many patients were also scanned (or rescanned) after randomization: 97% in CAST and 96% in IST of those randomized were scanned either before entry or at some time during the scheduled treatment period. At the end of this, only 3% of all patients still did not have the type of the initial stroke determined reliably: 94% had had the initial diagnosis of ischemic stroke confirmed, 2% had been found retrospectively to have had a hemorrhagic stroke at randomization (and so trial treatment, but not trial follow-up, was stopped), and 2% had been found not to have had a stroke at all. All randomized patients were included in these analyses regardless of their compliance with study treatment and of their original or final diagnosis.

After randomization, the risk of having another stroke in the hospital was similar in the 2 trials (Table 2: 2% had a recurrent ischemic stroke, 1% had a hemorrhagic stroke, and 1% had another stroke of unknown cause), even though the follow-up duration was twice as long in CAST, because most of the recurrent strokes occurred in the first 7 days. The risk of death without further stroke was, however, only one third as high in CAST (2.6%) as in IST (8.0%), perhaps in part because the patients entering CAST tended to be younger and to have had smaller strokes.

### Main Outcomes in All Patients

Overall, allocation to early aspirin produced a very definite and substantial reduction of 7 (SD 1) per 1000 in the risk of having a fatal or nonfatal recurrent ischemic stroke in the hospital (Figure 1: 320 [1.6%] aspirin versus 457 [2.3%] control, $2P<0.000001$). Against this, there was a smaller increase of 2 (SD 1) per 1000 in the risk of having a hemorrhagic stroke or hemorrhagic transformation of the original infarct (202 [1.0%] aspirin versus 167 [0.8%] control, $2P=0.07$). There appeared to be no net difference in the overall risk of having another stroke of unknown cause, of which some would have been ischemic and some would have been hemorrhagic (178 [0.9%] aspirin versus 186 [0.9%] control). Finally, aspirin appeared to produce a reduction of 4 (SD 2) in death without further stroke, but this benefit is only just conventionally significant (1004 [5.0%] aspirin versus 1090 [5.4%] control, $2P=0.05$). Most of such deaths would have been due to the direct or indirect effects of the original stroke (but without good evidence of hemorrhagic transformation of it). A combination of these 4 outcomes (which hardly overlap) yields an overall risk reduction of 9 (SD 3) per 1000 for the composite outcome of any further stroke or death (1641 [8.2%] aspirin versus 1823 [9.1%] control, $2P=0.001$). For the composite outcome of death or dependency, the absolute benefit was slightly greater: 12 (SD 5) per 1000 (9153 [45.6%] aspirin versus 9391 [46.9%] control, $2P=0.01$). The assessment in Figure 1 of the net benefit of aspirin in hospital involves only the reduction of 9 per 1000 in further stroke or death, ignoring the increases or decreases

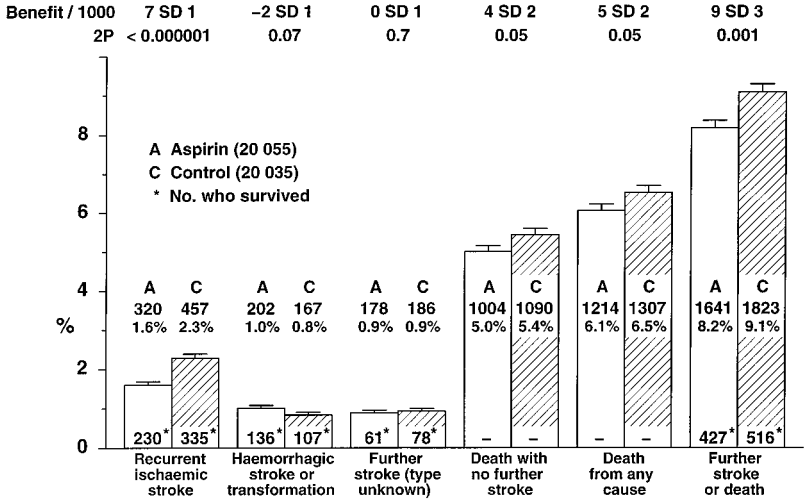


**Figure 1.** Absolute effects in CAST and IST of early use of aspirin in 40 000 randomized patients with suspected acute ischemic stroke. Numbers and percentages of patients with various outcomes during the scheduled treatment period, by allocated treatment: A indicates aspirin; C, control. The percentages are plotted as bars (with the SD of each bar plotted at the top). The difference between aspirin and control is given as the benefit per 1000, along with its SD and statistical significance (2*P*). A negative benefit indicates an apparent hazard. *Number of patients who experienced the relevant event and survived.

of 1 or 2 per 1000 in nonfatal transfused bleeds, nonfatal pulmonary emboli, and nonfatal myocardial infarcts. Any pulmonary emboli that were followed by death in hospital (39 aspirin versus 56 control) are already included in these deaths, but both these and other pulmonary emboli (30 aspirin versus 41 control) may have been substantially underreported. No systematic information was collected on nonfatal myocardial infarction (which, although already uncommon, might well be made slightly less common with aspirin).

## Recurrent Ischemic Stroke in Various Subgroups

For recurrent ischemic stroke, the absolute risk reduction of 7 per 1000 (1.6% versus 2.3%) corresponds to a proportional reduction of 30% (OR 0.70). This overall result is indicated by the broken vertical line in Figure 2, along with the separate results for each of 28 different subgroups of 10 characteristics recorded at baseline. Overall, the amount of heterogeneity between these 28 results is no greater than would be expected by chance alone if the proportional risk reduction was really about the same in all subgroups (global heterogeneity test on 18 *df*, 20.9, NS). Thus, for recurrent ischemic stroke, there is no good evidence that the proportional reduction is much larger or smaller in any subgroup than in the aggregate of all patients. In particular, the result for patients randomized 7 to 12 hours after stroke onset merely illustrates the statistical problems of subgroup analyses and does not indicate that aspirin is much less effective for such patients than for those randomized 0 to 6 or 13 to 48 hours after stroke onset. Likewise, the apparent difference between the effects in men and women is not conventionally significant, as long as due allowance is made for the number of different comparisons that have been made in Figure 2.

### *Atrial Fibrillation*

The absolute risk of recurrent ischemic stroke was similar for control patients with and without atrial fibrillation, so if the proportional risk reductions produced by aspirin are similar (as suggested in Figure 2), then atrial fibrillation will be of little relevance to the absolute reduction in recurrent ischemic stroke with early aspirin.

### *Heparin*

Early aspirin yielded a highly significant reduction in recurrent ischemic stroke both when subcutaneous heparin was given as part of the IST trial (1.3% aspirin plus heparin versus 2.2% heparin alone, $2P=0.0004$) and when it was not given (1.7% aspirin alone versus 2.3% nil, $2P=0.0002$; Figure 2). Thus, early aspirin is of substantial value for the prevention of recurrent ischemic stroke, regardless of the use of heparin. Moreover, Figure 5 of the original IST report[3] showed that aspirin reduced recurrent ischemic stroke to a similar extent in those allocated medium-dose heparin and in those allocated low-dose heparin, with little effect in either case on intracranial hemorrhage.

### *Prognostic Index*

The 10th characteristic in Figure 2 is an overall prognostic index, which combines information from several of the other characteristics to produce 3 equal-sized groups, good, average, and poor prognoses, that differ as much as possible in their overall risk of further stroke or death in hospital[2,3] (see later). However, they do not differ substantially with respect to their absolute risk of recurrent ischemic stroke or with respect to the proportional reductions in this outcome that are produced by aspirin (Figure 2). Hence, early aspirin appears to produce about the same absolute reduction in recurrent ischemic stroke in all 3 of these prognostic categories.

### *Definite Benefit in All Subgroups*

Because recurrent ischemic stroke is not a composite outcome, because the absolute risk is fairly similar for all of these 28 subgroups, and because the $\chi^2$ for overall risk reduction is large enough ($\chi^2_1=24.8$) to be informative when shared between a few subgroups, the lack of significant heterogeneity between the proportional risk reductions in Figure 2 provides strong evidence that aspirin will produce fairly similar proportional and absolute reductions in recurrent ischemic stroke for all of these patient categories. Hence, in each category, aspirin produces an absolute reduction of several per 1000 in the risk of recurrent ischemic stroke.

## Further Stroke of Unknown Type

Overall, there was no apparent effect of aspirin allocation on the subsequent incidence of strokes of unknown type, either

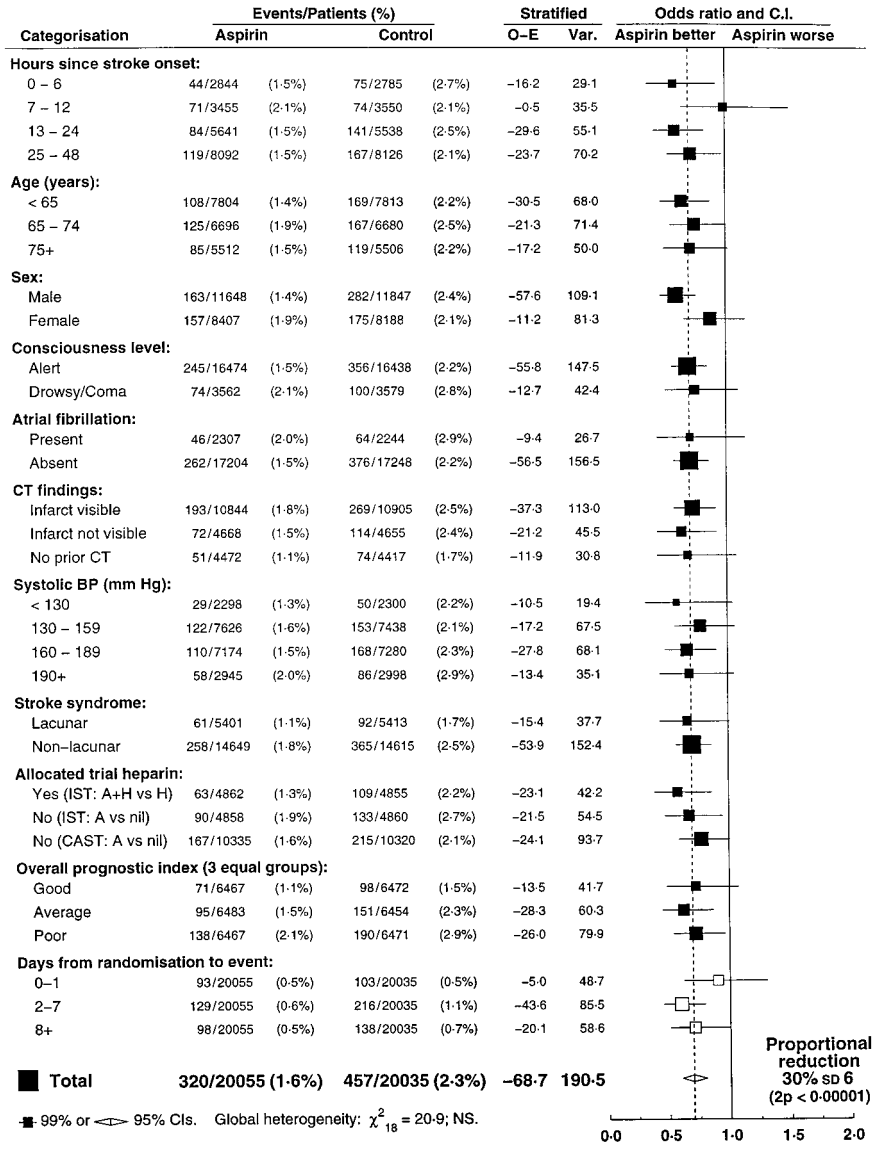


**Figure 2.** Proportional effects of early aspirin on recurrent ischemic stroke. Fatal and nonfatal events are included. For each particular subgroup, the O−E number of events among aspirin-allocated patients, its variance, and the OR (■, with area proportional to the total number of patients with an event) are given. A square to the left of the solid vertical line suggests benefit, significant at $2P<0.01$ only if the entire 99% CI (horizontal line) is to the left of the solid vertical line. ◆ indicates overall result and its 95% CI. Summation of the 10 separate $\chi^2$ heterogeneity test statistics (1 for each baseline characteristic but not for "days" [□]) yields the global test for heterogeneity between the 28 subgroups: $\chi^2_{18}=20.9$, NS). Here and elsewhere, results for those with missing information on particular characteristics are not listed separately (except for CT findings), but numerators and denominators for them can be obtained through subtraction of the subgroup results from the total (eg, the numbers with no prognostic index calculated were 16 of 638 aspirin vs 18 of 638 control). A indicates aspirin; H, heparin.

overall (Figure 1) or in any particular subgroup (global heterogeneity test: $\chi^2_{18}=17.3$; NS).

## Hemorrhagic Stroke (Table 3)

Given the definiteness and size of the reduction in recurrent ischemic stroke produced by early aspirin, the lack of apparent reduction in further strokes of unknown etiology (Figure 1) reinforces the evidence from this and other sources[1] that there also is some real adverse effect of such treatment, even though the increase of 2 (SD 1) per 1000 in clinically diagnosed hemorrhagic stroke (or transformation) was not conventionally significant ($2P=0.07$). The left part of Table 3 provides the results for hemorrhagic stroke (or hemorrhagic transformation of the original infarct) in the 28 subgroups considered previously. However, because the overall result is not clearly significant, these subgroup-specific analyses are insensitive, so a subgroup-specific hazard would have to be very large to be reliably demonstrably greater than the average hazard. For only 3 of the 28 subgroups in Table 3 is the apparent excess of hemorrhagic stroke >3 per 1000, but none of these excesses are clearly significantly greater than the average (after allowance for the number of subgroups considered), and no particularly large hazard would be expected for any of these 3 subgroups (those randomized 7 to 12 hours after stroke onset, those aged <65 years, and those with low blood pressure). Moreover, aspirin appears to produce no special excess risk of hemorrhagic stroke in those with a more severe stroke at entry (ie, those with "poor prognosis").

Hence, in all such subgroups, it is appropriate to conclude that the absolute increase in hemorrhagic stroke or transformation is no more than a few (overall 2 SD 1) per 1000. This hazard can reliably be taken to be smaller than the absolute decrease of several (overall 7 SD 1) per 1000 in recurrent ischemic stroke that is produced by early aspirin use.

## Major Noncerebral Hemorrhage

The right part of Table 3 gives the number of patients who received a blood transfusion or died because of bleeding from a noncerebral site. Overall, aspirin was associated with a

**TABLE 3. Absolute Effects of the Early Use of Aspirin on Hemorrhagic Stroke and Major Noncerebral Hemorrhage**

| | Hemorrhagic Stroke (or Hemorrhagic Transformation of Infarct) | | | Major (Transfused or Fatal) Noncerebral Hemorrhage | | |
|---|---|---|---|---|---|---|
| Categorization | Aspirin | Control | Difference per 1000 (SD) | Aspirin | Control | Difference per 1000 (SD) |
| Time from stroke onset to randomization, h (%) | | | | | | |
| 0–6 | 46 (1.6) | 40 (1.4) | −2 (3) | 27 (1.0) | 10 (0.8) | −2 (3) |
| 7–12 | 40 (1.2) | 25 (0.7) | −5 (2) | 26 (0.8) | 24 (0.7) | −1 (2) |
| 13–24 | 53 (0.9) | 46 (0.8) | −1 (2) | 51 (0.9) | 26 (0.5) | −4 (2) |
| 25–48 | 62 (0.8) | 56 (0.7) | −1 (1) | 91 (1.1) | 44 (0.5) | −6 (1) |
| Age, y (%) | | | | | | |
| <65 | 100 (1.3) | 62 (0.8) | −5 (2) | 36 (0.5) | 34 (0.4) | −1 (1) |
| 65–74 | 52 (0.8) | 62 (0.9) | 2 (2) | 72 (1.1) | 42 (0.6) | −4 (2) |
| 75+ | 49 (0.9) | 42 (0.8) | −1 (2) | 87 (1.6) | 39 (0.7) | −9 (2) |
| Sex, n (%) | | | | | | |
| Male | 138 (1.2) | 106 (0.9) | −3 (1) | 108 (0.9) | 64 (0.5) | −4 (1) |
| Female | 64 (0.8) | 61 (0.7) | 0 (1) | 87 (1.0) | 51 (0.6) | −4 (1) |
| Level of consciousness, n (%) | | | | | | |
| Alert | 139 (0.8) | 96 (0.6) | −3 (1) | 128 (0.8) | 77 (0.5) | −3 (1) |
| Drowsy/comatose | 63 (1.8) | 70 (2.0) | 2 (3) | 67 (1.9) | 38 (1.1) | −8 (3) |
| Atrial fibrillation, n (%) | | | | | | |
| Yes | 39 (1.7) | 37 (1.6) | 0 (4) | 41 (1.8) | 18 (0.8) | −10 (3) |
| No | 154 (0.9) | 125 (0.7) | −2 (1) | 149 (0.9) | 97 (0.6) | −3 (1) |
| CT findings, n (%) | | | | | | |
| Infarct visible | 103 (0.9) | 77 (0.7) | −2 (1) | 104 (1.0) | 51 (0.5) | −5 (1) |
| Infarct not visible | 54 (1.2) | 47 (1.0) | −1 (2) | 47 (1.0) | 32 (0.7) | −3 (2) |
| No prior CT | 43 (1.0) | 40 (0.9) | −1 (2) | 42 (0.9) | 30 (0.7) | −3 (2) |
| Systolic blood pressure, mm Hg (%) | | | | | | |
| <130 | 34 (1.5) | 17 (0.7) | −7 (3) | 25 (1.1) | 17 (0.7) | −3 (3) |
| 130–159 | 83 (1.1) | 63 (0.8) | −2 (2) | 72 (0.9) | 37 (0.5) | −4 (1) |
| 160–189 | 64 (0.9) | 57 (0.8) | −1 (2) | 67 (0.9) | 44 (0.6) | −3 (1) |
| 190+ | 21 (0.7) | 29 (1.0) | 3 (2) | 31 (1.1) | 17 (0.6) | −5 (2) |
| Stroke syndrome, n (%) | | | | | | |
| Lacunar | 33 (0.6) | 23 (0.4) | −2 (1) | 32 (0.6) | 17 (0.3) | −3 (1) |
| Nonlacunar | 169 (1.2) | 144 (1.0) | −2 (1) | 163 (1.1) | 98 (0.7) | −4 (1) |
| Allocated trial heparin, n (%) | | | | | | |
| Yes (IST: A+H vs H) | 61 (1.3) | 59 (1.2) | 0 (2) | 86 (1.8) | 43 (0.9) | −9 (2) |
| No (IST: A vs nil) | 26 (0.5) | 15 (0.3) | −2 (1) | 23 (0.5) | 14 (0.3) | −2 (1) |
| No (CAST: A vs nil) | 115 (1.1) | 93 (0.9) | −2 (1) | 86 (0.8) | 58 (0.6) | −3 (1) |
| Overall prognostic index (3 equal groups), n (%) | | | | | | |
| Good prognosis | 33 (0.5) | 17 (0.3) | −3 (1) | 30 (0.4) | 19 (0.3) | −2 (1) |
| Average prognosis | 52 (0.8) | 32 (0.5) | −3 (1) | 57 (0.9) | 34 (0.5) | −4 (2) |
| Poor prognosis | 107 (1.7) | 107 (1.7) | 0 (2) | 102 (1.6) | 60 (0.9) | −7 (2) |
| Time from randomization to hemorrhage, d (%) | | | | | | |
| 0–1 | 31 (0.2) | 29 (0.1) | 0 (0) | 25 (0.1) | 13 (0.1) | −1 (0) |
| 2–7 | 64 (0.3) | 53 (0.3) | −1 (1) | 90 (0.4) | 44 (0.2) | −2 (1) |
| 8+ | 107 (0.5) | 85 (0.4) | −1 (1) | 80 (0.4) | 58 (0.3) | −1 (1) |
| Total, n (%) | 202 (1.0) | 167 (0.8) | −2 (1) | 195 (1.0) | 115 (0.6) | −4 (1) |

Denominators as in Figure 2. Negative difference indicates an apparent hazard.

definite (2$P$=0.00001) excess of such bleeds. The absolute excess produced by aspirin was larger among patients allocated heparin in half of IST (1.8% allocated aspirin plus heparin versus 0.9% heparin alone; excess 9 SD 2 per 1000, 2$P$=0.0001) than among other patients (0.7% allocated aspirin alone versus 0.5% nil; excess 2 SD 1 per 1000, 2$P$=0.01, and because some of these received nontrial anticoagulants, the excess with aspirin on its own may have been still less). These excesses chiefly involved nonfatal bleeds in patients who were subsequently discharged alive (1.42% aspirin plus heparin versus 0.68% heparin alone, excess 7 per 1000; 0.43% aspirin versus 0.26% nil, excess 2 per 1000).

### Patients Inadvertently Randomized After a Hemorrhagic Stroke

Seven hundred seventy-three patients (2%) were subsequently found to have been randomized, inadvertently, after an intracerebral hemorrhage rather than an ischemic stroke. Among them, the overall risk of further stroke or death was high (17%), but there was no good evidence of an adverse effect of aspirin, rather the reverse, if anything (Table 4). Aspirin had no significant effect on the incidence of another symptomatic cerebral hemorrhage (29 [7.3%] versus 26 [6.9%], NS) and appeared to reduce the incidence of other strokes (1 [0.3%] versus 8 [1.1%], 2$P$=0.04).

### Death Without Further Stroke

Taking all patients together, aspirin was associated with a proportional reduction of 8% (SD 4) in deaths without any further stroke (1004 [5.0%] aspirin versus 1090 [5.4%] control, 2$P$=0.05). Figure 3 shows this overall treatment effect (vertical broken line), together with the results observed in the 28 subgroups. Because the overall effect of treatment on this outcome is not highly significant, the subgroup-specific treatment effects are not statistically reliable, but at least none provide good evidence of hazard. This, together with the apparently favorable overall effect of treatment on these deaths, provides a margin of safety for the earlier evidence, based on the favorable balance between recurrent ischemic stroke and hemorrhagic stroke, that aspirin is of net value in all subgroups.

Deaths without further stroke were mainly due to the direct or indirect effects of the original stroke (which might not be much affected by aspirin), and many of the characteristics recorded at entry were strongly predictive of the absolute risk. Overall, the risk of such deaths in poor-prognosis patients was >10 times that in good-prognosis patients. If the relative risk (aspirin versus control) were constant, then this wide variation in absolute risk would imply wide variation in absolute benefit, but the subgroup-specific analyses of the effects of aspirin are not sufficiently stable to determine whether the absolute benefits really do vary widely. For example, the 8% proportional risk reduction in poor-prognosis patients corresponds to an absolute risk reduction of 9 per 1000, whereas the 8% proportional risk reduction in good- or average-prognosis patients corresponds to an absolute risk reduction of only 2 per 1000, but these absolute benefits are not significantly different from each other.

**TABLE 4. Effects of the Early Use of Aspirin Among the 773 Patients Who Were Inadvertently Randomized With a Recent Hemorrhagic Stroke (Rather Than an Ischemic Stroke)**

| Outcome | Aspirin (n=398) | Control (n=375) |
|---|---|---|
| Further hemorrhagic stroke | 29 | 26 |
| Ischemic stroke | 0 | 4 |
| Further stroke of unknown type | 1 | 4 |
| Death without further stroke | 35 | 37 |
| Death (from any cause) | 44 | 44 |
| Further stroke or death | 63 (16%) | 67 (18%) |

### Further Stroke or Death

Taking all patients together, aspirin was associated with a highly significant proportional reduction of 11% (SD 3) in further stroke or death in hospital (1641 [8.2%] aspirin versus 1823 [9.1%] control, 2$P$=0.001). Figure 4 shows this overall treatment effect (broken vertical line), together with the results observed in the 28 subgroups. There was no significant heterogeneity between the 28 proportional risk reductions ($\chi^2_{18}$=16.5, NS), and the erratic result for patients entered 7 to 12 hours after stroke onset can plausibly be dismissed as a chance finding (as discussed earlier). Because the overall result for further stroke or death involves a much smaller $\chi^2$ than that for recurrent ischemic stroke ($\chi^2_1$=10.8 instead of 24.8) and because further stroke or death is a composite outcome, involving both benefit and hazard, the subgroup analyses in Figure 4 are less reliable than those in Figure 2. They are, however, readily compatible with the earlier conclusions from the separate analyses of recurrent ischemic stroke and of hemorrhagic stroke that early aspirin is of net benefit in all of these subgroups (including patients with impaired consciousness, those with atrial fibrillation or hypertension, those without a prior CT scan, and those allocated heparin). There is an apparent tendency for the absolute benefit to be bigger for poor- than for good-prognosis patients, but this is not statistically significant.

### Days From Randomization to Outcome

The findings during days 0 to 1, days 2 to 7, and later after randomization are given separately at the foot of each set of subgroup results (Figures 2 to 4, open squares, and Table 3). For none of the analyzed outcomes was there significant heterogeneity between the proportional effects in these 3 time periods, so although the benefit appears chiefly to be seen after days 0 to 1, there might in fact be some net benefit during days 0 to 1 (and treatment during days 0 to 1 may have been a cause of some of the subsequent benefit).

## Discussion

The overall results (and subgroup analyses) published for CAST[2] and for IST[3] were consistent with each other in suggesting a net benefit for a wide range of patients, and the combined analyses of both trials further support this. Despite differences in the types of patient randomized, both studies indicated a substantial proportional reduction in recurrent ischemic stroke. Together, they show that if aspirin is started early in suspected acute ischemic stroke and continued for the next few weeks, it produces a definite reduction in

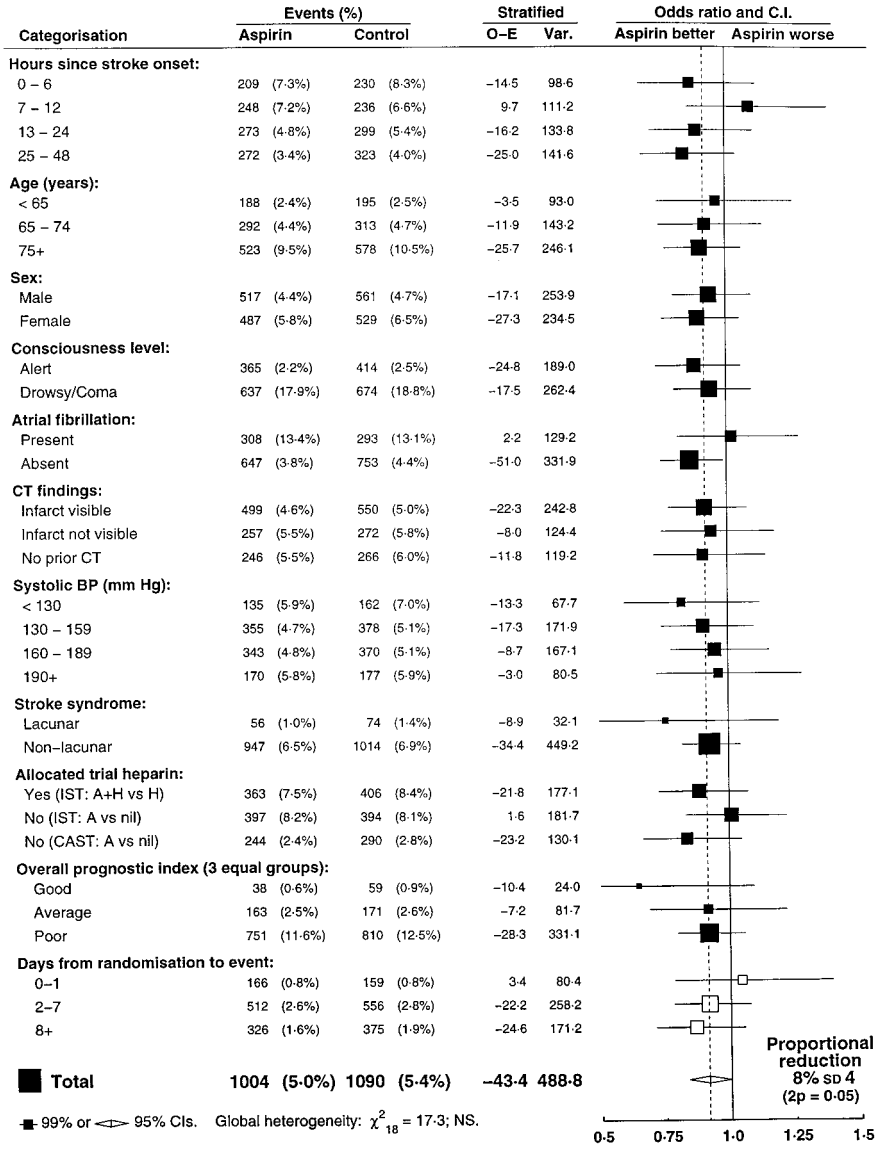


**Figure 3.** Proportional effects of early aspirin on death without any further stroke. Format as in legend for Figure 2 (global test for heterogeneity: $\chi^2_{18}$=17.3, NS).

recurrent ischemic stroke, and hence in the combined outcome of further stroke or death, and that it is of net benefit for a wide range of patients. If, as may well be the case, the absolute benefit is generally somewhat greater for those at a greater absolute risk, then the benefit with the widespread use of early aspirin therapy may well be somewhat greater than that suggested by these trials. For although a wide range of patients were included in both trials, the overall risk of further stroke or death may have been somewhat lower than that in routine practice.

The proportional reduction in recurrent ischemic stroke was not significantly affected by any of the factors examined (eg, age, sex, blood pressure, stroke syndrome, presence of atrial fibrillation, or whether a CT scan had been performed before randomization), as long as appropriate allowance is made for the number of characteristics analyzed. Older patients and hypertensive patients were not at particular risk of recurrent ischemic stroke or, perhaps surprisingly,[13] of hemorrhagic stroke, so the absolute net benefits of early aspirin appear to be about as great for them as for other types of patients. Indeed, the absolute risk of recurrent ischemic stroke was not very strongly related to any of the prognostic factors that were recorded, and the same is likely to be true for the reduction with aspirin in this risk. In particular, the apparent difference in benefit between men and women in Figure 2 is not good evidence of any real difference in benefit, especially because 1 month of aspirin therapy in acute myocardial infarction is of substantial and similar value for men and women,[14] as is long-term antiplatelet therapy.[1] It is therefore concluded that for the prevention of recurrent ischemic stroke, starting daily aspirin early and continuing for the long term are of definite benefit for both sexes.

## When to Start Aspirin

An overemphasis on the urgency of other treatments for ischemic stroke (eg, fibrinolytic therapy)[15] may lead to an underemphasis on the importance of prompt aspirin use.[16,17] The patients in these 2 trials were all randomized within 48 hours of the onset of symptoms, with definite benefit for those entered either 0 to 24 or 25 to 48 hours from the onset. The second of the results does not,

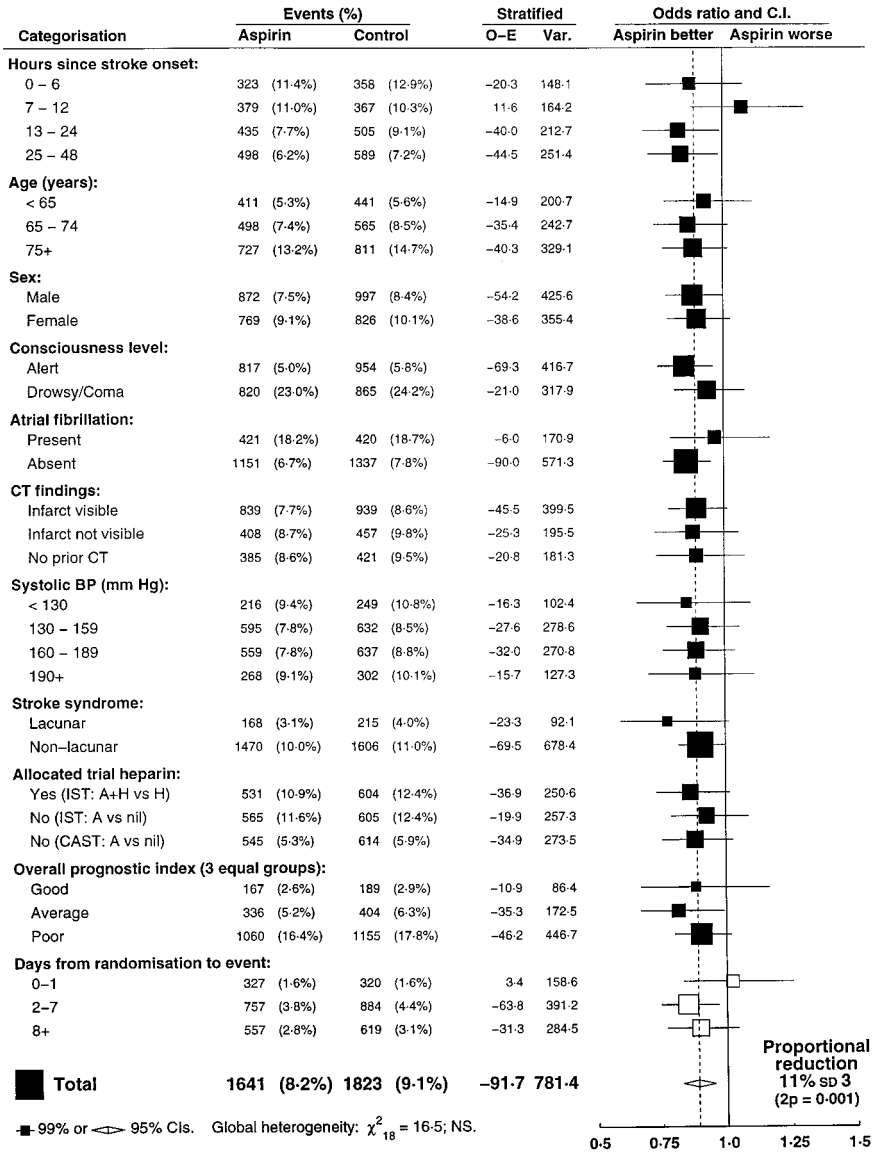


**Figure 4.** Proportional effects of early aspirin on further stroke or death. Format as in legend for Figure 2 (global test for heterogeneity: $\chi^2_{18}$=16.5, NS).

however, provide any good reason to delay the start of aspirin promptly in patients who present early (particularly because the incidence of hemorrhagic stroke or transformation was low during days 0 to 1, whereas that of recurrent ischemic stroke was relatively high), but it does mean that even patients who present somewhat later can still benefit from prompt treatment. Indeed, given that aspirin has been shown to be effective in the long-term secondary prevention of stroke after hospital discharge,[1] the prompt initiation of aspirin would also be of net benefit even for patients who present >48 hours after the onset of their symptoms. This conclusion is in accord with that of a recent review[17] of antiplatelet therapy in acute cerebral ischemia (which, however, mistakenly suggested that CAST and IST did not enter patients within the first 6 hours).

The reduction in further stroke or death from just a few weeks of early aspirin use is 9 per 1000 within 1 month, which compares favorably with the absolute monthly benefits of antiplatelet therapy in nonacute settings. For example, in the trials of antiplatelet treatment given on a long-term basis (eg, for some years) to patients who have already had a stroke or an episode of transient cerebral ischemia, the average monthly benefit was only 1 per 1000, even though the cumulative benefit eventually became substantial (≈38 per 1000 after 3 years of antiplatelet treatment).[1]

## Atrial Fibrillation

Patients admitted with suspected ischemic stroke and atrial fibrillation in CAST and IST had, in comparison with patients without this arrhythmia, ≈3 times the risk of death without further stroke (Figure 3: most such deaths were due to the original stroke), being older and more likely to have impaired consciousness or a large infarct. Perhaps surprisingly, their risk of recurrent ischemic stroke was not particularly elevated (Figure 2). Hence, the ability of aspirin to prevent recurrent ischemic stroke appears to be about as great for those with as for those without atrial fibrillation. Given that early aspirin is of net benefit, patients with acute ischemic stroke and atrial fibrillation could at least be treated safely with aspirin for the first few

weeks, regardless of whatever else is administered and regardless of the anticoagulant (or other) treatment that they will eventually receive for long-term secondary prevention.[18] In deciding whether some form of early anticoagulation should be administered in addition to early aspirin to acute stroke patients with atrial fibrillation, it should be borne in mind that their risk of recurrent ischemic stroke is not particularly high and that the increase in hemorrhagic stroke (and in transfused bleeds) is strongly related to the dose of heparin.[3]

### Treatment If CT Scanning Is Unavailable

About 10% to 15% of the acute strokes treated in countries such as Britain are hemorrhagic,[19] whereas the corresponding proportion in China appears to be about twice this.[20] Early aspirin use in both CAST and IST was associated with only a small increase in the risk of hemorrhagic stroke or hemorrhagic transformation. In the present overview, ≈9000 (22%) of the patients were randomized without a prior CT scan, and among them, the net benefits of aspirin appeared to be about the same as for those who had had a CT scan before randomization. Furthermore, in ≈800 patients whose presenting event was subsequently discovered to have been a hemorrhagic stroke, there was no evidence of any particular adverse effect of aspirin (Table 4), so any net hazard of early aspirin use in patients with a misdiagnosed hemorrhagic stroke is not substantial. Even so, because it would be preferable to limit the number of such patients who are inadvertently given antiplatelet therapy, if reasonably rapid CT scanning is available locally, then it may well be preferable to delay aspirin until after a CT scan has been performed. However, the results from CAST and IST give no good reason to withhold early aspirin treatment when ischemic stroke is suspected and rapid CT scanning is not conveniently available.

In summary, the present overview of 2 large randomized trials with ≈40 000 patients shows that early aspirin is beneficial in a wide range of patients with suspected acute ischemic stroke, confirming[17,21] that such treatment should routinely be considered for all patients who present with signs and symptoms of acute ischemic stroke, provided that no strong contraindications are apparent and that hemorrhagic stroke can be excluded with reasonable probability (with or without prior CT scan).

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# Indications for Early Aspirin Use in Acute Ischemic Stroke: A Combined Analysis of 40 000 Randomized Patients From the Chinese Acute Stroke Trial and the International Stroke Trial

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