Streptokinase in Acute Ischemic Stroke: An Individual Patient Data Meta-Analysis

The Thrombolysis in Acute Stroke Pooling Project

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Background and Purpose—Three major randomized controlled trials of streptokinase in acute ischemic stroke were curtailed because of safety concerns. The prospective Thrombolysis in Acute Stroke Pooling Project (TAS-PP) was established to examine the aggregate data to identify factors influencing the effect of streptokinase.

Methods—Individual patient data from the Australian Streptokinase Trial (ASK), Multicentre Acute Stroke Trial-Europe (MAST-E), Multicentre Acute Stroke Trial-Italy (MAST-I), and Glasgow Trial (Glasgow) were pooled. Multivariate modeling determined the interaction between treatment effect and delay from symptom onset to treatment, predicted baseline risk, age, concomitant aspirin or heparin use, and the presence of early CT signs on the outcomes of 10-day death, death and disability, or death alone at 3 or 6 months.

Results—Patients’ records were pooled (total 1292 patients; streptokinase, n = 653, no streptokinase n = 639). The subgroup analysis of treatment effect according to delay from symptoms to inclusion shows only a trend toward a better treatment effect with shorter delay, which is not statistically significant for any outcome. Heavier patients in MAST-E may have had a lower (non significant) risk from the fixed dose of 1.5 million units of streptokinase. Concomitant aspirin increased the excess mortality rates in streptokinase-treated patients (17% without aspirin versus 91% with aspirin, P = 0.005). The presence of early CT scan signs did not increase the detrimental effect of streptokinase.

Conclusions—Few factors influenced the response to streptokinase. However, earlier administration, lower doses of streptokinase, and avoidance of concomitant aspirin should be considered if further streptokinase trials in acute stroke are planned. (Stroke. 2000;31:1555-1560.)

Key Words: cerebral infarction ■ clinical trials ■ meta-analysis ■ streptokinase ■ stroke, acute ■ thrombolysis

Stroke is the second leading cause of death and a major cause of disability.1 Until recently, there was no effective therapy or management strategy to reduce stroke mortality and/or disability. Fortunately, some progress has now been made: Management in stroke units is associated with the avoidance of 70 death or dependency per 1000 patients treated,2 the commencement of aspirin within 48 hours with the avoidance of 12 death or dependency per 1000 patients treated, and an additional 10 per 1000 make a complete recovery from their stroke.3,4 Thrombolysis is being pursued vigorously, particularly since the logic of giving intravenous thrombolytic agents early after the onset of ischemic stroke is clear: Early cerebral tissue reperfusion is an independent predictor of outcomes,5 thrombolytic therapies are of proven benefit in myocardial ischemia,6 and preclinical experimental evidence for their efficacy is strong.7 Much of the available evidence comes from a series of acute stroke trials of thrombolysis conducted recently.8–15 In 4 of these,11–14 streptokinase (SK) was used in doses of 1.5 million units intravenously within 4 or 6 hours of stroke onset. All 3 major SK trials were terminated early because of safety concerns,11,13,14 A trend toward adverse outcome was noted in the Australian Streptokinase Trial (ASK) for those patients who received therapy after 3 hours but not for those who received therapy earlier than this.11 The Multicentre Acute Stroke Trial-Italy (MAST-Italy) was suspended and not recommenced.14 Conversely, 3 trials of tissue plasminogen activator tPA were completed,8–10 and one was stopped early because “treatment was unlikely to prove beneficial.”15 In the NINDS trial, 0.9 mg/kg tPA was given intravenously within 3 hours of stroke onset, and outcomes (those with minimal or no neurological deficit) were improved by ≈30% in the treatment group, with no increase in mortality rates.8 When a 6-hour time window was used with 1.1 mg/kg IV tPA in the European Cooperative

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Acute Stroke Study (ECASS), there was a nonsignificant trend toward better outcomes but at the cost of an increase in mortality rates. When the dose was reduced to 0.9 mg/kg in the second European Cooperative Acute Stroke Study (ECASS II), there was no increase in mortality rate and, again, a trend toward improving outcomes with therapy. A meta-analysis of published data from these trials shows that overall, there is a clear early hazard (an increase in fatal intracranial hemorrhage), but despite this there is a reduction in the number of patients dead or dependent at the end of follow-up (44 fewer dead or dependent patients per 1000 treated patients). Intravenous tPA looks slightly more promising than the overall estimate and SK rather than the overall estimate. tPA was approved in the United States for treating stroke patients within 3 hours from symptom onset, according to the strict NINDS protocol (ie, a selected subgroup of patients, expert teams). The questions now are whether tPA should be approved in other countries and how to select the ~6% of stroke patients who could benefit from a thrombolytic treatment. Finally, should a very large-scale trial be performed to assess the efficacy of thrombolysis in a large spectrum of stroke patients, with results generalizable to routine practice?

To maximize the information accrued from these trials, meta-analyses of individual patient data are required to control for confounding patient characteristics, to explore the possible sources of heterogeneity between trials, and to attempt to identify subgroups of patients who may benefit, or be at particular risk, from thrombolytic therapy. To this end, the Thrombolysis in Acute Stroke Pooling Project (TAS-PP) was initiated. Here we report our initial findings, based on 4 trials of SK.

Subjects and Methods
The complete protocol of TAS-PP has been published elsewhere. Briefly, eligible trials were identified by searching prospective clinical trials registries, electronic database searching (MEDLINE), hand-searching conference abstracts, and direct contact with investigators who were involved in designing trials in acute stroke and the Cochrane Collaboration Stroke Review Group. For inclusion in TAS-PP, the selected clinical trials had to be randomized trials (with a precisely described randomization process ensuring that the next treatment could not be guessed), to include >10 patients, and to use a thrombolytic treatment in the acute phase of ischemic stroke (within 6 hours of symptom onset) at a dose that could be expected to achieve recanalization, to require a CT scan assessment before inclusion, and to exclude from treatment patients with signs of hemorrhagic stroke. When the project was initiated, 6 trials were eligible, 4 with SK and 2 with rtPA. To this stage, only data from the SK trials could be pooled (because of data release policies of the trialists): ASK, Glasgow, Multicentre Acute Stroke Trial-Europe (MAST-E), and MAST-I.

Definition of Variables
The efficacy outcomes were all-cause death and death or severe disability at the end of scheduled follow-up (3 months or 6 months). The safety outcomes were early death (within 10 days) and symptomatic cerebral hemorrhages. Data were combined after completion of the trials, once each study report was accepted for publication. Each study provided a data file containing the variables that were required for the project, with a description of the file. Data were checked for accuracy and consistency. The efficacy of the randomization and the completeness of the follow-up were controlled. After pooling, tabulated data were edited for each study and sent to the trials’ representatives for verification. Definitions of variables were systematically examined for homogeneity between trials. A common definition was looked for when heterogeneous definitions were used in each trial. Because different neurological scales were used for patient assessment at baseline, severity at entry was assessed on one hand with the item “consciousness” of each study as a categorical variable, that is, “alert” or “drowsy/stupor/coma,” and on the other hand with the definition of “severe” patients used in each study. There was no standard classification for early CT scan abnormalities. All the studies had a central CT scan committee. The procedures were similar between studies: The readers were blind to treatment and looked at the first CT without looking at the second. However, there was neither a common rule nor common training of the readers, and there was no common definition of “early signs” or “hypodensity.” Since this variable might explain part of the outcome, we decided to classify the patients into 2 categories, that is, “patients with early signs or hypodensity (any sign related to the present stroke) at entry,” according to each study’s committee decision, and patients without such signs. The primary outcome was a combined outcome of death and severe disability in all 4 studies; it was evaluated at 3 months in ASK and at 6 months in MAST-E and MAST-I. Severe disability at the end of follow-up was defined as a Rankin score ≥3 in MAST-E and MAST-I (the scale used was slightly different in the 2 trials, but for both scales, ≥3 implies dependency) and a Barthel score <90 in ASK, in which the Rankin scale was not used. Correspondence between the Barthel and Rankin scales was possible because both scores were available in MAST-E. The primary outcome “death or dependency” was available for all patients. For safety evaluation, death after 10 days of follow-up was chosen.

Strategy for Statistical Analysis
The statistical analysis was conducted according to the intention-to-treat principle. Baseline population characteristics were described for each trial and overall in the 2 treatment groups. Computation of the treatment effect and its variance across the trials was performed with the Mantel-Haenszel method (fixed-effect model), which combined on a log scale the trial-specific relative risks with weights proportional to the inverse of their variance. The test for heterogeneity of treatment effect between subgroups was obtained by logistic regression with the trial entered as a dummy variable, the treatment group, the variable of interest (subgroup) entered as an ordinal (ranked) variable, and an interaction term between this variable and the treatment group. Assessment of the treatment effect according to baseline risk of 3-month death was conducted as follows. Patient’s predicted baseline risk of 3-month death was computed by means of a prediction function established with a multivariable logistic model established on the data from the control group. Five categories of risk then were created with approximately an equal number of patients in each. All analyses were repeated with the use of multivariable logistic models with adjustment on severity, drowsiness, atrial fibrillation, systolic blood pressure, diastolic blood pressure, age, sex, concomitant aspirin use, with a trial factor as a fixed effect. Glasgow data were grouped with MAST-E data, which had the most similar design, because the data of this study were too limited to be analyzed separately.

Study Organization
The TAS-PP Steering Committee was constituted before all trials were completed, with representatives from all of the eligible trials. This Committee is responsible for the protocol and plan for analysis, access to the common data file, and publications. The common data file is held at the Data Handling Unit in the Department of Clinical Pharmacology, EA643, Claude Bernard University, Lyon, France.

Results
Among the 1292 patients whose records were pooled in the common file of TAS-PP, 653 were randomized to SK and 639 to control (placebo or no treatment). Concomitant aspirin was
given in 330 patients in the SK group and in 319 in the control group (100 mg in ASK and 300 mg in MAST-I for 10 days, nonrandomized and dose not known in other studies). SK or placebo was injected according to the protocol in 86% patients in the SK group as compared with 98% in the control group (P < 0.0001). Heparin was administered within 48 hours of randomization in 404 (31%) patients, of which 8% were in ASK and 46% each in MAST-E and MAST-I.

The mean (± SD) delay from onset of stroke to randomization was 3.8 ± 1.08 hours (range 0.4 to 5.0), and 304 patients were included within 3 hours (60% from MAST-I, 23% from ASK, and 17% from MAST-E plus Glasgow).

The patient baseline characteristics differed among the trials (Table). Patients from MAST-E had a more severe neurological deficit (51% drowsy or comatose patients in MAST-E compared with 9% to 15% in the other studies). Early CT signs of ischemia were present in 64% of patients in MAST-E and 5% in MAST-I.

Outcomes
SK was associated with a significantly greater early death (within 10 days) (relative risk [RR] 1.94, 95% confidence interval [CI] 1.55 to 2.42, P < 0.001) and 3-month mortality (RR 1.46, 95% CI 1.24 to 1.73, P < 0.001). There was no evidence that the combined outcome death or Rankin ≥3 differed between the 2 groups (RR 0.99, 95% CI 0.92 to 1.06, P = 0.72). However, there were significantly more patients with hemorrhagic transformation (RR 1.85, 95% CI 1.58 to 2.17, P < 0.001). After adjustment for drowsiness, atrial fibrillation, systolic blood pressure, diastolic blood pressure, age, sex, and aspirin use, the results remained unchanged.

Delay From Onset of Symptoms to Treatment
The histogram of the patient population by time to treatment indicates that MAST-I was a major contributor to data of patients included within 3 hours of treatment (Figure 1). When dichotomized into 0 to 3 hours and ≥3-hour epochs, the subgroup analysis of treatment effect according to delay from symptoms to inclusion shows only a trend toward a better treatment effect with shorter delay, which is not statistically significant for any outcome (Figure 2).

Clinical Severity of Neurological Deficit at Baseline and Age
When patients were categorized according to the severity at baseline (defined by their predicted baseline risk of 3-month death, see section "Definition of Variables"), the treatment effect was not shown to be different on death or severe disability, in the initial "minimal" (RR 0.89 [0.66 to 1.21]) and "very severe" (RR 0.97 [0.91 to 1.04]) risk categories, on death at 10 days (RR 1.59 [0.79 to 3.31]) and at 3 months (RR 1.59 [0.79 to 3.31]).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASK (n=340)</th>
<th>MAST-E (n=310)</th>
<th>MAST-I (n=622)</th>
<th>Glasgow (n=20)</th>
<th>SK (n=653)</th>
<th>No SK (n=639)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay symptom inclusion, h</td>
<td>3.47±0.63</td>
<td>4.13±1.03</td>
<td>3.81±1.16</td>
<td>4.37±1.91</td>
<td>3.82±1.09</td>
<td>3.79±1.08</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.9±12.0</td>
<td>68.9±13.2</td>
<td>69.1±11.8</td>
<td>67.7±8.3</td>
<td>69.3±11.5</td>
<td>68.5±12.4</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>152.5±22.8</td>
<td>153.6±22.8</td>
<td>156.7±23.9</td>
<td>161.6±12.1</td>
<td>154.6±22.2</td>
<td>155.2±24.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>86.8±12.5</td>
<td>85.1±13.0</td>
<td>89.1±11.7</td>
<td>89.6±9.8</td>
<td>87.5±11.9</td>
<td>87.5±12.8</td>
</tr>
</tbody>
</table>

*Aspirin given within 4 hours from SK infusion; †randomized 150 to aspirin alone and 150 to aspirin plus SK; ‡any signs, including early signs or hypodensity, according to each study CT committee.
3.19] and 1.20 [0.97 to 1.49], respectively). Similar results were obtained when patients were classified according to their age at inclusion.

Concomitant Antiplatelet Treatment

Concomitant aspirin use had a detrimental effect on the risk of 3-month death ($P=0.005$) (Figure 3). However, concomitant aspirin use did not significantly alter the effect of SK on the risk of “death or severe disability” ($P=0.28$). Hence, the negative effect of the combination of aspirin and SK on mortality rates was compensated by a positive effect on the functional outcome in surviving patients. The same results were observed when the analysis was extended to any antiplatelet drug taken during or up to 48 hours after thrombolysis.

Concomitant Heparin Therapy

One hundred sixty-seven (25.6%) patients in the SK group received heparin within 48 hours along with 237 (37.1%) patients in the control group. Patients who received SK without heparin appeared to have a worse outcome. The risk of 3-month mortality in the SK group was increased by 56% in these patients as compared with a 4% increase in patients with heparin ($P=0.03$). The same trend was observed for early deaths and death/disability at trial completion.

Dose of SK

In all trials, a dose of 1.5 million units of SK was given to patients randomized in the active group, regardless of the patient’s body weight. An indirect analysis of the relation between the treatment effect and the dose of SK was performed by classifying the patients according to their body weight, with heavier patients having received a proportionally lower dose of treatment. Data were available only in the MAST-E trial. No differences were observed between the subgroups with regard to the combined outcome death/severe disability (Figure 4). However, there was a marked trend (although not statistically significant, $P=0.12$) for a detrimental treatment effect on the risk of early death in patients with lower body weight and thus a higher relative dose of SK.

Early CT Scan Signs

There was a marginally significant trend ($P=0.07$) for a greater deleterious effect of SK on early death in patients with no early signs at admission (RR 2.27 95% CI 1.65 to 3.13), as compared with the effect in patients with early signs (RR 1.47 95% CI 1.06 to 2.05). There was no evidence that the presence of early signs at entry interfered with the effect of SK on the risk of 3-month death and of death or severe disability.

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**Figure 2.** Treatment effect in the 2 delay subgroups.

**Figure 3.** Treatment effect according to concomitant aspirin administration.
The main aim of this meta-analysis was to facilitate targeting of thrombolysis after acute ischemic stroke. Unfortunately, the outcome was unpredictable among patients who received SK. However, there were interesting trends and observations. In particular, there was a trend toward better outcomes in the patients who received therapy within 3 hours compared with those who received therapy later. This trend was observed despite a lack of interaction between delay to therapy and outcomes when 1-hour time epochs were considered up to 6 hours. Also, the ECASS II study, which aimed to evaluate this issue, did not show any greater benefit in patients treated earlier. Nevertheless, the 3-hour time window was chosen for specific attention because of the benefit of tPA when given within this time frame. This trend is consistent with what has been clearly demonstrated in myocardial infarction by the Fibrinolytic Therapy Trialists group. Also, earlier administration of therapy after onset of ischemic stroke is more likely to be beneficial, given the known time dependence of the “ischemic penumbra” and our understanding of the cascade of neurochemical events that occur after vessel occlusion.

Although an interpretation of the data from this meta-analysis clearly indicates that intravenous SK at doses of 1.5 million units is deleterious, it has been shown previously that reperfusion at the tissue level is increased, as are arterial recanalization rates based on data with single-photon emission computed tomography and transcranial Doppler sonography, respectively. However, it does seem likely that these changes are induced too infrequently or too late to result in clinical improvement, as evidenced by increased rates of nonnutritional reperfusion also measured by single-photon emission computed tomography.

Whereas age and severity of initial deficit appeared to have no impact on the deleterious effect of SK on outcome, the concomitant use of aspirin was significantly associated with death. The reasons for this are unclear and, on the basis of evidence from animal model data, somewhat surprising. In a rat embolic stroke model, Overgaard et al showed that whereas thrombolytic therapy significantly and dose dependently reduced infarct volume, improved clinical score, and increased angiographically verified reperfusion, aspirin coadministration conferred no additional benefit. Thomas et al, with the use of a rabbit model of embolic stroke, showed that preadministration of aspirin significantly antagonized the rate and extent of tPA-induced clot lysis by up to 70%.

The effect of concomitant use of anticoagulants within 48 hours of stroke onset cannot be disregarded, given the known risk of hemorrhage into acute cerebral infarcts in anticoagulated patients. It should be noted that there was a marked imbalance between therapy and control groups for anticoagulant use; perhaps used less frequently in the SK group because of the early development of cerebral hemorrhages. Because of this, the case for a potential interaction between anticoagulant and thrombolytic agent use remains unproved.

The impact of early ischemic changes, seen on initial CT, on the SK effect on outcome was minimal. Indeed, there was a counterintuitive trend toward increased early deaths for those with a normal CT scan and no effect on 3-month death or death and disability combined. The influence of CT changes on the development of cerebral hemorrhage was similar in the treated and control groups in this data set. It is of interest that CT changes were associated with increased hemorrhage rates after thrombolysis in MAST-E, and the NINDS trial, although not with poor clinical outcomes at 3 months in the latter. There was no common centralized reading panel for all SK trials, and rates of early CT changes varied considerably between trials. This heterogeneity renders interpretation of these findings difficult, unless standardized assessment becomes possible.

The role of SK should also be considered, now that tPA is “proven” to be effective. A recent meta-analysis of SK and tPA trials demonstrates that for the combined end point of death and disability, the SK trials are internally consistent and produce a neutral result; the tPA trials are internally consistent and produce a positive result; and the results of the SK trials are significantly different from the tPA trials. Pharmacological properties of SK may contribute to this difference.

SK has antigenic properties and frequently is associated with hypotension when used after acute myocardial infarction: Ten percent of patients in the ISIS-2 trial developed hypotension compared with 2% of the placebo group. Recorded hypotension varied from 20% of the treated group in the ASK trial, through 1.9% in MAST-I, to only 0.6% in the MAST-E study. Hypotension may have been a reason for incomplete infusion in the SK -treated patients in the stroke trials reported here (14% SK versus 2% for placebo). Acute blood pressure reductions could theoretically impair blood flow in the penumbral region, are consistently associated with poorer outcome in preclinical models of ischemic stroke, and have been significantly associated with poorer outcome in recent stroke trials. Also, the prolonged fibrinogen depletion and anticoagulant effect of SK could be responsible for a greater tendency to hemorrhagic transformation of infarction when compared with tPA; alternatively, this could be construed as an advantage.

An important consideration in the search for reasons for increased mortality rates and lack of efficacy among all trials was that the dose of SK may have been too high. Since doses were not individualized and a standard amount of 1.5 million units was given in all cases, a surrogate of dosage was used by inserting individual patient weights in the outcome model.
Although this approach was only possible with the MAST-E data, the observed trend toward worse outcomes in lighter patients would tend to support the view that higher equivalent doses of SK contributed to the increase in mortality rates. However, it would be unwise to select a dose for further study at random: Detailed dose-ranging studies would be required to establish an optimal dose and whether adjustment of dose by weight is preferable.

Further trials with SK could be justified, but the cost-effectiveness and risks of pursuing such trials will need to be carefully weighed against the likelihood of improving on the benefits and costs of rtPA. Also, the exact influence of outcome of the delay from stroke onset, the presence of early CT signs, and severity at baseline could be assessed with the use of meta-analysis on individual data from all thrombolysis stroke trials. This knowledge would help designing any further trial that would also primarily consider the issues of drug dose, timing of treatment, and avoidance of concomitant aspirin.

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References


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