Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)

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Summary

Background Thrombolysis for acute ischaemic stroke has been investigated in several clinical trials, with variable results. We have assessed the safety and efficacy of intravenous thrombolysis with alteplase (0.9 mg/kg bodyweight) within 6 h of stroke onset.

Methods This non-angiographic, randomised, double-blind, trial enrolled 800 patients in Europe, Australia, and New Zealand. Computed tomography was used to exclude patients with signs of major infarction. Alteplase (n=409) and placebo (n=391) were randomly assigned with stratification for time since symptom onset (0-3 h or 3-6 h). The primary endpoint was the modified Rankin scale (mRS) at 90 days, dichotomised for favourable (score 0-1) and unfavourable (score 2-6) outcome. Analyses were by intention to treat.

Findings 165 (40.3%) alteplase-group patients and 143 (36.6%) placebo-group patients had favourable mRS outcomes (absolute difference 3.7%, p=0.277). In a post-hoc analysis of mRS scores dichotomised for death or dependency, 222 (54.3%) alteplase-group and 180 (46.0%) placebo-group patients had favourable outcomes (score 0-2; absolute difference 8.3%, p=0.024). Treatment differences were similar whether patients were treated within 3 h or 3-6 h. 85 (10.6%) patients died, although symptomatic haemorrhages were increased in the actively treated group patients. Alteplase (n=409) was approved in the USA for use within 3 h of stroke onset.

Interpretation The results do not confirm a statistical benefit for alteplase. However, we believe the trend towards efficacy should be interpreted in the light of evidence from previous trials. Despite the increased risk of intracranial haemorrhage, thrombolysis with alteplase at a dose of 0.9 mg/kg in selected patients may lead to a clinically relevant improvement in outcome. Lancet 1998; 352: 1245-51

See Commentary page ???

Introduction

There have been several large, randomised, placebo-controlled trials of thrombolytic therapy in acute ischaemic stroke. Three of these trials, testing the effects of intravenous streptokinase given within 6 h of stroke onset, were terminated prematurely because there were more deaths and bleeding complications in the actively treated groups.1-3 The use of alteplase (recombinant tissue-type plasminogen activator) in acute ischaemic stroke has been investigated in two trials. The National Institute of Neurological Disorders and Stroke (NINDS) trial4 used a very short maximum interval from symptom onset to treatment (180 min), a dose of 0.9 mg/kg bodyweight, and very strict blood-pressure control. It found that 11-13% more patients in the alteplase group than in the placebo group had good functional outcome, with no increase in mortality, although symptomatic haemorrhages were increased ten-fold by thrombolysis. On the basis of these results, alteplase was approved in the USA for use within 3 h of onset of symptoms.

ECASS I,5 a European multicentre trial, used a maximum interval from onset to treatment of 6 h and a higher dose of alteplase (1.1 mg/kg). No significant differences between alteplase and placebo were seen in the median scores of the primary outcome measures, probably because a significant minority (17%) of patients included in the analysis had protocol violations (mostly with extensive ischaemic changes on the baseline computed tomography [CT] scan). The target population (per-protocol) analysis showed significant differences between the study groups in favour of alteplase, with effect sizes similar to those found in the NINDS trial. Mortality was increased in the alteplase group, however, and parenchymal haemorrhages were significantly more common in alteplase-treated than in placebo-treated patients.

ECASS II was therefore designed with a lower dose of alteplase (0.9 mg/kg, chosen to match NINDS criteria)
given intravenously within 6 h of onset of symptoms, more rigorous application of the CT eligibility criteria, and strict guidelines for blood-pressure control. The objective of ECASS II was to find out whether alteplase given within 6 h of symptom onset (patients were randomised equally to alteplase and placebo for both time strata of 0–3 h and 3–6 h) improved clinical outcome in comparison with placebo.

Patients and methods

ECASS II was carried out in 108 centres in 14 European countries and Australia and New Zealand. The trial was non-angiographic. Therefore, in most patients the precise location of the causative cardiovascular thrombus or embolus was not identified. The exception was if a hyperdense middle-cerebral-artery sign was seen on the initial CT scan.

Eligible patients were men and women aged 18–80 years who had a clinical diagnosis of moderate to severe ischaemic hemispheric stroke, who could be treated within 6 h of symptom onset, who showed no or only minor early signs of infarction on the initial CT scan, and who could be followed up for the 90-day study period. As in ECASS I, we excluded patients with signs of intracerebral haemorrhage or parenchymal hypodensification exceeding a third of the middle-cerebral-artery territory. In contrast to ECASS I (in which a diffuse swelling of one entire brain hemisphere was an exclusion criterion), patients were excluded from ECASS II if brain swelling exceeded 33% of the middle-cerebral-artery territory. Other exclusion criteria for ECASS II included: subarachnoid haemorrhage; time of stroke onset not exactly known (eg, awakening with stroke symptoms); coma or stupor; hemiplegia plus fixed eye deviation; minor stroke symptoms (>50 of the maximum 58 points on the Scandinavian stroke scale [SSS]) before randomisation, or rapid improvement of symptoms; seizure during the previous 6 months; hypertension at the time of randomisation (systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg); any traumatic brain injury within the previous 14 days; recent (within 3 months) surgery on the central nervous system; haemorrhage of the gastrointestinal or urinary tract; current therapy with intravenous or subcutaneous heparin to raise the clotting time; known hereditary or acquired haemorrhagic diathesis (eg, activated partial thromboplastin time or prothrombin time greater than normal, uncorrected coagulation-factor deficiency, oral anticoagulant therapy, or haemorrhagic retinopathy); lactation; pregnancy or recent parturition (within the previous 30 days); lack of a medically approved means of contraception in women of childbearing age; baseline blood glucose concentrations below 2.75 mmol/L (50 mg/dL) or above 22.0 mmol/L (400 mg/dL); baseline platelet counts below 100×10^5 /L; packed-cell volume below 25%; and current or recent (within 3 months) participation in another trial of an investigational drug. Pretreatment with aspirin was permitted. Control of blood pressure by use of a standard protocol was enforced.

Methods

Before ECASS II and during the trial, courses were run to improve the quality of both the CT-scanning procedure and CT-scan assessment. All investigators took part in these training courses.

A computer-generated randomisation procedure in blocks of four was used, with each centre allocated at least one block of the treatment groups at 0–3 h and 3–6 h to ensure a stratified distribution. At each centre, eligible patients were randomly assigned treatment at baseline by means of sequential patient numbers. The randomisation schedule was known only to the Clinical Trial Support Unit at Boehringer Ingelheim and to one member of the External Safety Committee. Treatment allocation was concealed from all investigators, but in emergencies, investigators had access to sealed opaque envelopes containing treatment allocation. Five such emergencies occurred. Investigators could end a patient’s participation in the trial for any medical reason, if the patient withdrew consent, or for administrative reasons. Each patient was followed up at 90 days if possible. Follow-up at 90 days was carried out at each local centre by one of the local investigators. Measures were taken in the planning and conduct of the trial to reduce the risk that the examiner would be able to identify the treatment received at this stage—eg, investigators did not receive the results of coagulation tests.

Alteplase (Boehringer Ingelheim, Ingelheim, Germany) and placebo were identical in appearance; they were sealed in vials containing 50 mg drug or placebo, reconstituted in 50 mL water for injection. The dose of alteplase was 0.9 mg/kg bodyweight, with an upper dose limit of 90 mg per patient. (The assessment of bodyweight was based on the patient’s or relative’s report, the clinician’s best guess, or actual weight, in a minority.) A bolus of 10% of the total dose was given over 1–2 min, followed by a 60 min intravenous infusion of the remaining dose. Administration of intravenous heparin, oral anticoagulants, antiplatelet agents, haemorrhagic agents, potential neuroprotective drugs, and volume expanders was prohibited during the first 24 h. Subcutaneous heparin (not exceeding 10 000 IU) was allowed during the first 24 h for prophylaxis of deep-vein thrombosis. Osmotic agents could be given if the intracranial pressure was raised.

The primary endpoint was the proportion of patients who had a favourable outcome (score 0 or 1) on the modified Rankin scale (mRS—a seven-point scale that assesses overall function; death is rated as 6) 90 (±14) days after treatment. A post-hoc analysis of mRS scores dichotomised for dependency (in which scores of 0, 1, and 2 were classified as favourable) was also done. Secondary endpoints were the change from baseline to day 30 on the National Institutes of Health stroke scale (NIHSS—a 46-point scale that assesses neurological deficit) and the combination of Barthel index (BI—a 100-point scale that assesses activities of daily living) and the mRS at day 90 (as defined in ECASS I). Further endpoints were the BI at day 90, the SSS (a 48-point scale that assesses neurological deficit) at day 90, the duration of hospital stay, and quality of life at day 90 (short-form-36 [SF-36]) rated by the patient. Other endpoints (the infarct volume assessed by CT at days 1 and 7, and the combination of various endpoints) will be the subject of future detailed analyses.
in the NIHSS score of 4 or more points. (eg, drowsiness, increase of hemiparesis) or causing a decrease in the CT reading panel, independently of the assessment by the CT scans of the brain were done and assessed before treatment started, 22–36 h after the infusion of trial medication (three). The alteplase treated, because they withdrew consent (two), and placebo groups were similar in terms of baseline variables (table 1). 72 protocol violations (34 in the alteplase group and 39 in the placebo group) were reported, because they withdrew consent (two), deteriorated (two), or improved clinically before infusion of alteplase or placebo (three). The alteplase and placebo groups were similar in terms of baseline variables (table 1). 72 protocol violations (34 in the alteplase group, 38 in the placebo group) were reported during the study; most were violations of the CT criteria.

Safety variables included mortality at days 30 and 90, haemorrhagic infarction, parenchymal haemorrhage as defined in ECASS I, symptomatic haemorrhage, and other adverse events. Haemorrhagic events were classified according to clinical and CT criteria. Haemorrhagic infarction 1 (H11) was defined as small petechiae along the margins of the infarct; haemorrhagic infarction 2 (H12) as confluent petechiae within the infarcted area but no space-occupying effect; parenchymal haemorrhage (PH1) as blood clots in 30% or less of the infarcted area with some slight space-occupying effect; and parenchymal haemorrhage (PH2) as blood clots in more than 30% of the infarcted area with substantial space-occupying effect. Symptomatic intracranial haemorrhage was defined as blood at any site in the brain on the CT scan (as assessed by the CT reading panel, independently of the assessment by the investigator of clinical deterioration, or adverse events indicating clinical worsening (eg, drowsiness, increase of hemiparesis) or causing a decrease in the NIHSS score of 4 or more points.

Alteplase (n=409) Placebo (n=391)

Demography
Median age (years) 68 68
M/F 248/161 221/170

Onset-to-treatment interval
0-3 h 81 (19.8%) 77 (19.7%)
3-6 h 328 (80.2%) 314 (80.3%)

Median total score
NIHSS 11 11
SSS 31 30

Clinical
Aspirin therapy 84 (20.5%) 99 (25.3%)
Subcutaneous heparin with first 24 h 218 (53.6%) 242 (62.7%)
Atrial fibrillation 89 (21.8%) 98 (25.3%)
Hypertension 216 (52.8%) 196 (50.1%)
History of stroke 79 (19.3%) 79 (20.3%)
Diabetes 87 (21.3%) 82 (21.0%)
Transient ischaemic attack 34 (8.3%) 29 (7.4%)
Previous myocardial infarction 57 (13.9%) 29 (7.4%)
Valvular heart disease 1 (0.2%) 2 (0.5%)

Table 1: Demographic and baseline features

Safety variables included mortality at days 30 and 90, haemorrhagic infarction, parenchymal haemorrhage as defined in ECASS I, symptomatic haemorrhage, and other adverse events. Haemorrhagic events were classified according to clinical and CT criteria. Haemorrhagic infarction 1 (H11) was defined as small petechiae along the margins of the infarct; haemorrhagic infarction 2 (H12) as confluent petechiae within the infarcted area but no space-occupying effect; parenchymal haemorrhage (PH1) as blood clots in 30% or less of the infarcted area with some slight space-occupying effect; and parenchymal haemorrhage (PH2) as blood clots in more than 30% of the infarcted area with substantial space-occupying effect. Symptomatic intracranial haemorrhage was defined as blood at any site in the brain on the CT scan (as assessed by the CT reading panel, independently of the assessment by the investigator of clinical deterioration, or adverse events indicating clinical worsening (eg, drowsiness, increase of hemiparesis) or causing a decrease in the NIHSS score of 4 or more points.

CT scans of the brain were done and assessed before treatment started, 22–36 h after the infusion of trial medication started, and at day 7. Other CT scans were done if necessary. The CT scans were assessed by each member of the CT reading panel, with quality assessed as not readable, poor, moderate, and good. If the members disagreed, they reviewed and discussed the scan until consensus was reached. All baseline CT scans were assessed by the reading panel without access to the follow-up scans of individual patients but with information about the location of symptoms.

ECASS II was carried out according to the principles of good clinical practice. Independent auditors (Parexel GmbH, Berlin, Germany) undertook audits at individual study sites, at Boehringer Ingelheim operative units, and at the independent data-management centre (Covance, Maidenhead, UK).

The trial protocol was reviewed and approved by local independent ethics committees or institutional review boards according to the regulatory requirements of the participating country, and carried out in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each patient (or from his or her legally authorised representative) before enrolment in the study.

Analysis
The sample-size estimation for the primary endpoint was based on a two-sample test of proportions with \( \alpha = 0.05 \) and a power probability of 80%. The study was powered to detect or disprove an absolute difference of about 10% between the treatment groups in the percentage of patients with a favourable outcome. We calculated that at least 350 evaluable patients in each treatment group would be required for the study to achieve this power, assuming that 30% of placebo-treated patients would have a favourable outcome. 800 patients were recruited to compensate for possible violations of the protocol.

The primary analysis was by intention to treat, of all randomised patients. The primary endpoint (mRS) was dichotomised according to the NINDS criteria and analysed by Fisher’s exact test (p=0.05), with scores of 0 or 1 taken to indicate a favourable outcome and scores of 2–6 taken to indicate an unfavourable outcome (death rated as 6). Secondary endpoints were analysed by the Wilcoxon rank-sum test.

Mortality was analysed by the log-rank test. Kaplan-Meier estimates were plotted over the observation period of 90 days. The frequency and severity of adverse events, especially of intracranial haemorrhages, were analysed by Fisher’s exact test.

If values were missing, the last observation was carried forward. For the mRS and the BI, a worst-case imputation (mRS=5, BI=0) was made for missing values at day 90.

The Safety Monitoring Committee carried out continuous masked safety monitoring, with an interim analysis for the primary endpoint after 175 evaluable patients in each group had been treated.

Results

Patients

Patients were recruited for ECASS II between October, 1996, and January, 1998; 409 patients were assigned to the alteplase group and 391 to the placebo group (figure 1). All randomised patients were included in the intention-to-treat analysis, including seven patients (two alteplase, five placebo) who were randomised but not treated, because they withdrew consent (two), deteriorated (two), or improved clinically before infusion of alteplase or placebo (three). The alteplase and placebo groups were similar in terms of baseline variables (table 1). 72 protocol violations (34 in the alteplase group, 38 in the placebo group) were reported during the study; most were violations of the CT criteria.

At baseline, 341 (42.6%) patients had no signs of infarction on the CT scan. 414 (51.8%) patients had hypodensity of 33% or less of the middle-cerebral-artery territory, and 37 (4.6%) patients had hypodensity of more than 33% of that territory; the CT scan of eight patients was not available or readable because of low quality.

Endpoints

The overall distribution of the primary endpoint, mRS scores, is shown for all randomised patients in figure 2. A favourable outcome (mRS score 0 or 1) was seen in 165 (40.3%) [95% CI 35.6–45.4] patients in the alteplase group and 143 (36.6%) [31.8–41.6] in the placebo group (table 2). The absolute difference in favour of alteplase treatment was 3.7% (p=0.277).
The proportion of patients in ECASS II who had a baseline CT scan showing hypodensity in more than the first 7 days. After day 7, the causes of death in the two groups were similar, and most were non-cerebral (cardiac arrest, pulmonary embolism, pneumonia). In the subgroup treated within 3 h of symptom onset, there were more deaths up to day 102 in the alteplase group than in the placebo group (11 [14%] vs six [8%]). The corresponding numbers in the subgroup treated 3–6 h after symptom onset were 31 (9.5%) and 35 (11.3%).

Table 4 shows the incidence and classification by CT criteria of intracranial haemorrhages up to day 7. The alteplase and placebo groups did not differ significantly in the incidence of haemorrhagic infarction. By contrast, parenchymal haemorrhage of any kind was roughly four times more common in the alteplase group than in the placebo group (11/8 vs 3/1). Large, confluent, space-occupying intracranial haemorrhage (PH2) was ten times more common in the alteplase group (table 4). The difference in the rate of PH2 haemorrhages was apparent in both time-to-treatment subgroups. The frequency of all symptomatic intracranial haemorrhage showed a 2.5-fold excess with alteplase compared with placebo.

Up to day 30, 1804 adverse events were reported in the alteplase group and 1591 were reported in the placebo group. After day 30, only serious adverse events were reported and assessed. Overall, most events were mild (alteplase group 65.8%; placebo group 66.6%). The most common adverse events (incidence >20%) were non-specific disorders, gastrointestinal disorders, central and peripheral nervous system disorders, cardiovascular disorders, and urinary system disorders. There were no clinically or statistically significant differences in the frequency of adverse events between the treatment groups, except those related to platelet, bleeding, and clotting disorders.

Discussion

The proportion of patients in ECASS II who had a baseline CT scan showing hypodensity in more than...
33% of the middle-cerebral-artery territory is smaller than that in ECASS I (4·6% vs 8·3%). The difference probably reflects both the increased experience in diagnosing acute ischaemic changes on CT scans gained by the investigators since ECASS I, and the benefits of the training programmes undertaken in preparation for ECASS II.\(^6\) This increased diagnostic sensitivity did not lead to the selection of more patients with normal CT scans at baseline (42·6% in ECASS II, 54·8% in ECASS I), but it has probably led to the recruitment of more patients with small hypodensities (51·8% and 34·4%, respectively).

We found no significant difference between the alteplase and placebo groups in the primary endpoint (mRS at day 90: favourable versus unfavourable outcome) in this study. However, for the secondary post-hoc endpoint (death or dependence, mRS 3–6), there was a significant effect in favour of alteplase—an 8·3% decrease, which is equivalent to 83 per 1000 fewer patients dead or dependent after alteplase. Only one secondary endpoint showed a significant difference between the groups, and that was a difference of only 1 point in the change from baseline to day 30 on the 46-point NIHSS scale. The other secondary endpoint and some of the further endpoints showed trends in favour of alteplase, but none was significant. The unexpectedly high response to placebo seen in this study (mRS scale at day 90, favourable versus unfavourable outcome) was higher in the alteplase group than in the placebo group among patients randomised within 3 h of stroke onset: no such difference was observed in the patients treated 3–6 h after stroke onset. The apparent difference may reflect the small number of patients in the 0–3 h subgroup. The overall frequency of intracranial haemorrhages was higher in the alteplase group than in the placebo group (48·4 vs 40·2%) and was within the range reported in other studies.\(^4,5,7,8\) Severe intracranial haemorrhages (PH 2) were significantly more common in the alteplase group than in the placebo group, but this difference did not lead to an overall increase in morbidity or mortality in the alteplase group. The overall frequency of intracranial haemorrhage was similar in ECASS I and II, but parenchymal haemorrhage was less frequent in ECASS II than in ECASS I. The frequency of symptomatic intracranial haemorrhage in the placebo group was higher than that seen in the NINDS trial (3·4 vs 0·6%), probably because different definitions of haemorrhage were used and different populations of patients were selected. Treatment with alteplase clearly leads to an excess of early severe intracranial haemorrhage with clinical deterioration, but this is counterbalanced by a lower frequency of postischaemic space-occupying oedema, which may reflect haemorrhagic transformation of large infarcts with severe brain oedema in patients treated with alteplase.

The most likely reason for the better placebo response and lower mortality rate in ECASS II than in ECASS I or the NINDS trial is selection bias. The ECASS II patients had less severe neurological deficits at entry to the study: the median baseline NIHSS scores in the

### Table 4: Cases of intracranial haemorrhage up to day 7 in patients who actually received treatment

<table>
<thead>
<tr>
<th>CT criterion*</th>
<th>0–3 h</th>
<th>3–6 h</th>
<th>Total (n=793)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alteplase (n=81)</td>
<td>Placebo (n=77)</td>
<td>Alteplase (n=326)</td>
</tr>
<tr>
<td>Petechial haemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH2</td>
<td>6 (7%)</td>
<td>1 (1%)</td>
<td>27 (8·3%)</td>
</tr>
<tr>
<td>PH1</td>
<td>1 (1%)</td>
<td>3 (4%)</td>
<td>14 (4·3%)</td>
</tr>
<tr>
<td>Haemorrhagic infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI2</td>
<td>10 (12%)</td>
<td>12 (15%)</td>
<td>52 (16·0%)</td>
</tr>
<tr>
<td>HI1</td>
<td>15 (19%)</td>
<td>22 (29%)</td>
<td>65 (19·9%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
<td>0</td>
<td>4 (1·2%)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (43%)</td>
<td>38 (49%)</td>
<td>162 (49·6%)</td>
</tr>
</tbody>
</table>

*For definitions see methods. 1Seven patients were randomised but not treated.
alteplase and placebo groups were 13 and 12 in ECASS I, 14 and 15 in the NINDS trial, and 11 in both groups in ECASS II. Furthermore, in ECASS II, patients showed fewer signs of early major infarction on the baseline CT scan, presumably as a result of better CT-scan surveillance. We intend to investigate other possible contributors to the good placebo response in future analyses; these factors include clinical history (for example, hypertension, diabetes, atrial fibrillation, previous strokes, transient ischaemic attacks, and myocardial infarctions), and more rigorous application of best acute-stroke management (eg, to control blood pressure, temperature, and blood glucose concentrations and to prevent complications). Such interventions are typical of the stroke-unit or stroke-team model.617 The lower dose of alteplase chosen may have contributed to both the better safety and the lower efficacy in ECASS II.

The trends seen in ECASS II should be interpreted in the light of existing clinical experience with thrombolytic agents. An important concept introduced in ECASS I was the exclusion of patients with substantial ischaemic oedema on the baseline CT scan, who were at higher risk of haemorrhagic transformation.34 No benefit of alteplase was seen in the intention-to-treat analysis of the primary endpoint, though the per-protocol analysis showed a significant difference in favour of alteplase. A post-hoc analysis, based on the NINDS method of dichotomising outcomes, showed a positive result for ECASS I; however, this analysis was not prespecified.62 Furthermore, the alteplase group had a higher mortality and incidence of parenchymal haemorrhages than the placebo group. These adverse results were particularly evident among patients whose inclusion violated the protocol because they had major early ischaemic changes on the CT scan. Hence, the results of ECASS I suggested that alteplase is effective in patients with small infarctions but probably not safe in patients with large infarctions, thus raising serious questions about selection of patients and safety.

The NINDS trial26 used a lower dose of alteplase and a shorter maximum interval between symptom onset and treatment. A significant benefit was observed for the alteplase group at 3 months in all four outcome measures (BI, mRS, Glasgow outcome scale, NIHSS). The occurrence of intracranial haemorrhages within the 3 h of stroke onset was increased substantially with alteplase but, as in ECASS II, mortality was not affected. This evidence therefore supported the use of alteplase therapy at 0·9 mg/kg within 3 h of stroke onset in a predefined subpopulation of patients with good hypertension control. However, less than 33% of patients reach hospital within 2 h.14 To recruit 624 hypertensive patients in ECASS II, only one in five patients (158) could be enrolled. The reasons for this were the exclusion of patients with substantial ischaemic oedema, and also the lower dose of alteplase chosen (9 mg/kg within 3 h of stroke onset) which may have contributed to both the better safety and the lower efficacy in ECASS II.

ECASS II study organisation

The following centres and principal investigators participated in ECASS II:

- Australia (25 patients)—Goldford (D Crimmins); Heidelberg (G Donnan 6); Melbourne (S Davis, R Gerraty); Perth (G Hankey).
- Austria (40 patients)—Graz (K Niederkorn); Linz (E Deisenhammer); Salzburg (G Ladurner); Vienna (W Grisold, I Podreka, C Alf, E Sluga, B Brücke, W Kistlerfirsch).
- Belgium (five patients)—Edegem (P Cras).
- Denmark (11 patients)—Ålborg (M Baggesen); Copenhagen (S Vorstrup); Glostrup (J Olesen).
- Finland (89 patients)—Espoo (A M uuronen); Helsinki (M Kade); Jyväskylä (A Rissanan); Kuopio (J Sivenius); Lahti (C Edman); Lappeenranta (H Numminen); Mikkeli (J Lukkonen); Oulu (K Kotonen); Seinäjoen (K Kolvisto); Tampere (T Erila).
- France (82 patients)—Auch (P Arabi); Dijon (R Dumas); Lyon (P T Rouillas); Montpellier (J-B Llard); Nancy (M Weber); Nantes (J-R Faw); Nizza (M-H M ahagne); Paris (P Amarenco, G Rancurel, M Zuber); Toulouse (F Chollet, V Larrue); Tours (D Saudeau).
- Germany (147 patients)—Bamberg (P K rausenbeck); Berlin (A Villenberg); Böchum (T Buttnер); Cologne (W Heiss, M Grond); Dresden (H Reichmann); Fulda (K Klotz); Göttingen (H Prange); Greifswald (M Wiersbitzky); Heidelberg (W M acke, T Steiner); Kassel (A Ferbert); Leipzig (O Schneider); Lübeck (M Kaps); Ludwigshafen (K Kowitzhch); Mannheim (B Tettlen); München (O Busse); München (G Harrer, J Klingelhofer); Regensburg (U Bodahn); Würzburg (W M ulges).
- Italy (52 patients)—Aosta (E Bottacchi); Florence (C Cappelletti, L Lagi); Genoa (O Regesta); Reggio Emilia (F Solime); Vicenza (V Toss); Pavia (G Righa); Udine (G Ferrari).
- Netherlands (13 patients)—Amsterdam (J Stam); Groningen (J M de Keijzer); Rotterdam (P Koudstaal); Tilburg (PLM de Kort).
- New Zealand (14 patients)—Dunedin (G Hammond-Tooke).
- Norway (28 patients)—Bergen (L Thomsen); Nordbyhagen (O Rosjo); Oslo (J Rygh); Trondheim (B Indredavik).
- Portugal (18 patients)—Coimbra (B Cunha); Oporto (C Correia).
- Spain (203 patients)—Coruna (J Castillo); Barcelona (F Rubio, A Chamorro, J Alvarez Sabin, J-L Marti Vilata); Bilbao (J Zarranz); Girona (A Davalos); Madrid (E Dieg-Tecedor, A Egido, J Vivancos Mora); Pamplona (P Gérgo); Seville (A G-Peralta); Valencia (J Lainez); Zaragoza (O M ostacore).
- Sweden (36 patients)—Linköping (J Radberg); Örebro (H Pantaleo); Stockholm (C Carlström, V Costulas, N-G Wahlgren).
- UK (14 patients)—Belfast (S Hawkins); Bristol (M Campbell).
- Venezuela (14 patients)—Bogotá (J-B Sava); Caracas (J-M Zuber); Valencia (J Lainez).
- Switzerland (13 patients)—Basel (P Lyer); Lausanne (J Bogousslavsky).
- UK (14 patients)—Belfast (S Hawkins); Bristol (M JC Campbell).
- Vancouver (14 patients)—Toronto (W M bindon).
- New Zealand (14 patients)—Dunedin (G Hammond-Tooke).
- Hamilton (T Timmins).
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- Norway (28 patients)—Bergen (L Thomsen); Nordbyhagen (O Rosjo); Oslo (J Rygh); Trondheim (B Indredavik).
- Portugal (18 patients)—Coimbra (B Cunha); Oporto (C Correia).
- Spain (203 patients)—Coruna (J Castillo); Barcelona (F Rubio, A Chamorro, J Alvarez Sabin, J-L Marti Vilata); Bilbao (J Zarranz); Girona (A Davalos); Madrid (E Dieg-Tecedor, A Egido, J Vivancos Mora); Pamplona (P Gérgo); Seville (A G-Peralta); Valencia (J Lainez); Zaragoza (O M ostacore).
- Sweden (36 patients)—Linköping (J Radberg); Örebro (H Pantaleo); Stockholm (C Carlström, V Costulas, N-G Wahlgren).
- UK (14 patients)—Belfast (S Hawkins); Bristol (M Campbell).
- Vancouver (14 patients)—Toronto (W M bindon).

We conclude that alteplase at a dose of 0·9 mg/kg does not increase mortality or morbidity, despite a 2-5-fold increase in symptomatic intracranial haemorrhage. The safety data are consistent with those of the NINDS trial. These results support the view that alteplase should be part of the routine management of acute ischaemic stroke within 3 h of symptom onset, and probably beyond, in selected patients and in experienced centres.
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References