Community-Based Thrombolytic Therapy of Acute Ischemic Stroke in Helsinki

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Background and Purpose—Thrombolysis with alteplase is used in acute ischemic stroke within 3 hours after symptom onset in many stroke centers, but experience remains limited in Europe.

Methods—Using eligibility and management criteria similar to those published by the American Heart Association, we treated 75 consecutive patients aged 21 to 83 years (mean age, 63.6 years; median Scandinavian Stroke Scale score, 32/58) with hemispheric infarction with alteplase in 1998–2001. Their neuroradiological findings (ischemic and hemorrhagic changes) and functional outcome at 3 months were evaluated.

Results—Sixty-one percent of the patients had recovered functional independence (Barthel Index 95 to 100) at the 3-month follow-up. On the modified Rankin Scale (mRS), 37% (28/75) of patients had no or minimal symptoms (mRS 0 to 1), while 17% (13/75) remained dependent (mRS 4 to 5) and 5% (4/75) died. Cerebral parenchymal hematomas occurred in 8% (6/75) and hemorrhagic transformation in 8% (6/75) of the patients. Low initial diastolic blood pressure and administration of intravenous antihypertensive medication were associated with unfavorable outcome (mRS 3 to 6).

Conclusions—We conclude that our management protocol for thrombolytic therapy is safe. These rates of functional outcome, case fatality, and hemorrhagic cerebral events compare favorably with those of other published series of stroke thrombolysis with similar time windows and management guidelines. Associations between blood pressure and its treatment during thrombolysis with functional outcome deserve further analysis. (Stroke. 2003;34:1443-1449.)

Key Words: hemorrhage ■ outcome ■ stroke ■ stroke, ischemic ■ thrombolysis

Ultra-acute thrombolysis with intravenous alteplase (recombinant tissue plasminogen activator [rtPA]) is the only available pharmacological therapy to improve the outcome of acute ischemic stroke. Five randomized, placebo-controlled, multicenter clinical trials studying intravenous rtPA in acute stroke1–4 have been conducted. The National Institute of Neurological Disorders and Stroke (NINDS) trial conducted in the United States was positive and led to approval by the Food and Drug Administration, and stroke specialists in many countries adopted guidelines launched by the American Heart Association (AHA) to include thrombolysis as a treatment option in the management of acute ischemic stroke.5 However, outside North America thrombolytic therapy is generally considered justified only for selected patients in experienced centers, and its widespread use in routine clinical practice is not recommended.6

More scientific data of the clinical correlates of patients, who derive the greatest benefit and who are at greatest risk, are still needed.

Based on a modified protocol of the AHA guidelines,5 we provided intravenous thrombolysis with rtPA and describe here the outcome and factors associated with this treatment in an open series of the first 75 patients treated consecutively during 1998–2001.

Subjects and Methods

Hospital Setting

The Helsinki University Central Hospital (HUCH) is responsible for all acute neurological disorders in Helsinki (501 000 inhabitants in 2000) and is the only hospital in its catchment area of 1.5 million that provides 24-hour service of specialist neurological care, brain imaging, and neurosurgical care. All citizens of Helsinki who live at home independently and suffer an acute stroke are admitted to the Emergency Neurological Services of HUCH. To ensure that all eligible patients will be transported, the dispatchers and paramedics were trained to recognize initial stroke symptoms (ie, acute unilateral limb weakness and/or difficulty in speaking) and to use preselective criteria for rapid transport. Since 1998, each dispatcher and paramedic received continuing education on stroke for at least 2 and 3 hours, respectively. Previously independent patients with symptoms lasting <5 hours were dispatched for rapid transport.

Inclusion and Exclusion Criteria

Inclusion criteria included mild to moderate hemispheric ischemic stroke and independence in daily activities. The AHA guidelines for
thrombolytic therapy were adopted but were modified in respect to the following 2 points. Since evidence from the Second European-Australasian Acute Stroke Study (ECASS II) trial suggested that extended early ischemic changes (EIC) were associated with parenchymal hemorrhages, we adopted the CT exclusion criteria from the ECASS trials of CT hypodensity of more than one third of the middle cerebral artery (MCA) territory. Most of our patients were treated within 3 hours after symptom onset, but a minority were treated between 3 and 4.5 hours, another deviation from the AHA guidelines. Exclusion criteria also included reduced consciousness with fixed gaze paresis and severe hemiplegia, mild symptoms on Scandinavian Stroke Scale (SSS) (SSS score >30/58); rapidly improving symptoms, uncertain timing of stroke onset, labetalol-resistant hypertension (>185/105 mm Hg), active bleeding disorder, or anticoagulant therapy and comorbidity with short life expectancy. Treatment decisions were made by stroke thrombolysis specialists, who participated either in the ECASS trials and/or in special training for stroke thrombolysis, which included reading of CT scans for EIC. A specialist neuroradiologist was often available, but the attending stroke thrombolysis specialist evaluated CTs and made treatment decisions and consulted the patients or next of kin to provide oral informed consent. Since we use a separate protocol involving MR angiography for thrombolysis of vertebrobasilar occlusions, we intended to treat only hemispheric infarctions in the present series.

Medical Management
According to an institutional protocol for acute stroke, which includes guidelines for thrombolysis, all thrombolysis candidates received continuous/repeated monitoring of blood pressure (BP) and intravenous labetalol as necessary to stabilize BP (<185/105 mm Hg) before and after rtPA administration. A total dose of 0.9 mg/kg rtPA (Actilyse, Boehringer Ingelheim Pharmaceuticals) was administered first as a bolus (10%) in 2 to 3 minutes, followed by a 1-hour infusion. During the next 24 hours, BP was monitored as in ECASS II, and antithrombotic agents were forbidden, as recommended. Outcome Evaluation
After thrombolysis, admission to our acute stroke unit included preventive therapy of ordinary poststroke complications, diagnostic workup, initiation of secondary prevention, and early rehabilitation. Patients were evaluated and treated by a multidisciplinary team for rehabilitation including physiotherapy, occupational therapy, speech therapy, and neuropsychological therapy. A 3-month follow-up evaluation included performance on SSS, Barthel Index (BI), and modified Rankin Scale (mRS) assessed by a physician and a stroke nurse familiar with these scales. In nearly all instances, scoring was performed independently by a physician not involved in the initial management of the patient. Patients in rehabilitation centers or nursing homes were scored by the treating personnel.

Post Hoc Evaluation of CT Scans
All initial (day 0) and follow-up (day 1) CT scans were evaluated post hoc by an experienced neuroradiologist (O.S.), who underwent training in the ECASS trials. The neuroradiologist was blinded to the day 1 CT scan and outcome but informed of the symptom laterality. Infarct size was graded in 3 categories: lacunar, less than one third of MCA territory, and more than one third of MCA territory. The following EIC were systematically recorded: (1) sulcus effacement; (2) cortical hypodensity (loss of gray-white matter distinction); (3) hypodensity (obscuration) of basal ganglia (lentiform and caudate nucleus); (4) hypodensity (obscuration) of insular cortical "ribbon"; and (5) hyperdense MCA sign. Hemorrhagic transformations (HTs) and parenchymal hematomas (PHs) were also registered. PH was defined as a solid, dense, typically confluent lesion; HT was defined as a nonhomogeneous, more subtle lesion with less density and a typical appearance of a trickle bleed or petechial hemorrhages within an infarcted area. A causal relationship between fluctuating neurological symptoms and a cerebral hemorrhagic change is reportedly ambiguous and may be limited to the most expansive solid PHs (so-called PH2). Therefore, and since we did not repeat neurological scores on detecting a hemorrhage, we could not classify "symptomatic hemorrhages." Hemorrhagic events recorded were too few to justify their further division into subclasses. Statistical Analysis
Distributions of the continuous variables were studied with Shapiro-Wilk W test, and univariate predictors of outcome were compared with the Student t test or Mann-Whitney U test, as appropriate. The x2 test (or Fisher exact test in case of small cell frequencies) was applied to univariate dichotomous variables. Fixed logistic regression was used to evaluate the significance of identified EIC for the dichotomized outcome. Stepwise logistic regression was performed to identify independent predictors of dichotomized outcome (mRS 0 to 2 versus 3 to 6), including predictors with associated probability values no greater than 0.20 in the univariate analyses or with expected clinical relevance. A similar sequential analysis was performed for the predictors of HT. Goodness of fit for the models was determined with the Hosmer-Lemeshow test. Because of the relatively small number of patients, multivariate models should be interpreted with caution.

Results
Demographics
Between March 1998 and October 2001, 3498 patients were admitted to the Emergency Neurology Services with the diagnosis of acute ischemic stroke. This is not the number of patients who received rapid transport but also includes patients with substantial symptom duration, serious comorbidity, and other clear contraindications for thrombolysis. The results of 75 consecutive patients (2.14%) who fulfilled the thrombolysis criteria are reported here. A total of 61% of the patients were transported from Helsinki city, 21% from the 4 neighboring capital districts, and 18% from more remote municipalities. The majority (72%) of patients (54/75) were treated within 3 hours of symptom onset. The mean±SD SSS score before rtPA infusion was 30.3±10.0 (median, 32/58), as illustrated in Figure 1. Demographic data, baseline variables, and cardiovascular risk factors are given in Table 1.

Clinical Outcomes
Blood Pressure
Twenty-eight patients were treated for increased BP. In the majority, intravenous boluses of labetalol were sufficient, but some were given additional boluses of metoprolol or nitroglycerin if BP did not reach a level defined in the protocol. The initial BP on admission of these 28 treated patients was 169/92 mm Hg (95% CI, 159 to 179/87 to 97 mm Hg), but follow-up values >185/105 mm Hg detected during continuous/repeated BP monitoring triggered antihypertensive therapy in them. The initial BP was highly significantly lower in those 47 patients who did not receive antihypertensive medications: 151/87 mm Hg (95% CI, 145 to 157/84 to 90 mm Hg). During rtPA infusion, the averaged BP values were 165/90 mm Hg (95% CI, 156 to 173/86 to 94 mm Hg) (treated) and 150/87 mm Hg (95% CI, 145 to 155/84 to 90 mm Hg) (untreated). Accordingly, there was a reduction only in systolic BP in treated patients (−4.5 mm Hg; 95% CI, 0.2 to −9.2 mm Hg), while the systolic BP of untreated patients remained stable (−0.7 mm Hg; 95% CI, 2.8 to
Leukocyte counts showed a trend (P=0.06) but were significantly associated (P≤0.001) on day 1 with unfavorable outcome (Table 1). However, these associations did not reach significance on multiple logistic regression analysis. BP or additional cardiovascular risks or comorbidity had no significant associations with outcome in univariate analyses. Baseline SSS was associated with functional outcome (univariate P=0.009; multivariate P=0.013). Patients with favorable outcome (mRS 0 to 2) had higher initial diastolic BP (P=0.008) (Table 1), which was also significant in multivariate analysis (P=0.027) (Table 2). The use of antihypertensive medication was significantly associated with decreased likelihood of favorable outcome in univariate (P=0.028) and multivariate (P=0.001) analysis (Tables 1 and 2).

Individuals with EIC on day 0 (n=45) had a BI score of 77.1±31.9, which was significantly lower than the BI score in those without EIC (n=30), at 94.2±16.9 (univariate P=0.009). A similar association was confirmed in independent versus dependent/fatal outcome on mRS (0 to 2 versus 3 to 6) in both univariate (P=0.014) and multiple logistic regression analysis (P=0.011) (Tables 2 and 3). The dominant EIC that was associated with unfavorable outcome (mRS 3 to 6) was cortical hypodensity (univariate P=0.0001; multivariate P=0.004) (Tables 3 and 4). In contrast, obscuration of basal ganglia lacked any association, and sulcus effacement (univariate P=0.0017) and loss of insular “ribbon” (univariate P=0.037) lacked significance in multivariate analysis. Individuals with PH had a decreased likelihood of independent outcome on mRS (univariate P=0.004; Table 3). Although patients with HT had a worse BI score at 3 months (65.8±7.1) than those without hemorrhages (89.1±20.8), multivariate statistics revealed no significant association between HT and mRS score.

Interesting associations between the hemorrhagic changes (PH/HT) and baseline variables were revealed by multivariate analysis (Table 2). Blood glucose concentration (P=0.021) and peak systolic BP during rtPA infusion were directly (odds ratio >1) associated with increased risk of hemorrhagic changes. Unexpectedly, patients with longer treatment delays (symptom-to-needle time [SNT]) had a decreased risk of hemorrhagic changes (P=0.023). The use of antihypertensive medication, despite association with decreased likelihood of favorable outcome (Table 2), was not associated with the risk of hemorrhagic changes. Sixteen of 75 patients (21%) used antithrombotic agents. Hemorrhagic changes occurred in 12 patients, but only 2 (17%) used antithrombotic agents.

Radiological Outcome
EIC exceeding one third of the MCA territory on day 0 CT was present in 1 patient, and in 2 others the infarct was in the vertebrobasilar territory. In 30 patients (40%), the initial CT was normal, but in the majority of cases (56%; 42/75), the EIC did not exceed one third of the MCA territory (Figure 2A). On day 1, a large infarct had developed in 13% (10/75) of the patients. The 3 most frequent EIC on day 0 were cortical hypodensity (43%; 32/75), sulcus effacement (29%; 22/75), and obscuration of basal ganglia (27%; 20/75) (Figure 2B). On day 1, HTs and PHs were found in 8% (6/75) and 8% (6/75), respectively.

Functional Outcomes
At 3 months, a total of 37% (28/75) of the patients had no or minimal symptoms (mRS 0 to 1), and 23% (17/75) were either dead or moderately/severely disabled (mRS 2 to 6)(Figure 3A). On BI, 61% (46/75) were independent (BI 95 to 100), while 8% (6/75) were severely disabled or fully dependent (BI 0 to 50) (Figure 3B). The mean±SD BI score of the 71 survivors was 87.4±21.6. On SSS, the mean±SD improvement was 18.6±13.1, and 36% (27/75) recovered fully (58/58 on SSS). Four died (5%).
Alteplase (rtPA) has been licensed for the treatment of acute ischemic stroke and is used widely in North America but has been conditionally approved only recently by European Union health authorities, which still limits its use in Europe. Furthermore, health authorities worldwide have recommended collection of postmarketing phase 4 databases of stroke thrombolysis. Outside North America and Germany, no large series have been published on the feasibility, safety, and efficacy of stroke thrombolysis in a community-based setting. Building on training and experience gained during the ECASS trials,1,3 we started thrombolysis in 1998 according to an institutional protocol and report here our results of the first 75 rtPA-treated patients.

Sixty-one percent of patients (46/75) were independent in daily life (BI 95 to 100) at 3 months, which is among the highest percentages reported (Figures 1 and 3B). This pertains not only to comparisons with randomized controlled trials1–3,10 but also to comparisons with single-center series from both North America and Europe.11–13 Accordingly, a high percentage (37%) of treated patients had mRS of 0 to 1, which is greater than in the NINDS placebo cohort (26%).2 The percentages of patients with the 3 poorest scores (mRS 4 to 6; 23%) and mortality alone (5%) compare favorably with the community-based series from Cologne,11 the recent Canadian Activase for Stroke Effectiveness Study (CASES)10 (12% and 26%, respectively), the 3-hour cohort of the ECASS trial,14 and the NINDS trial2 (Figure 3A). We conclude that thrombolysis at our Emergency Neurological Services was safe and that the impressive proportion of patients reaching functional independence (61%) was not achieved at the expense of increased death rate. These results are probably influenced by the somewhat comparably better neurological status of our cohort (baseline mean SSS 30.3; median 32) (Figure 1) and the combination of thrombolysis with stroke unit care. Our patients also had a mean age of 63.6 years, which is lower than that of some other cohorts.2,13 On the other hand, patients in our series received thrombolysis much later (mean SNT, 2 hours 40 minutes) than those in

**Discussion**

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other series (Figure 1), which may have decreased the percentage (37%) with mRS score 0 to 1 (Figure 3A).

Analysis of baseline variables associated with functional outcome revealed interesting relationships (Table 2), among which the EIC and SSS are self-evidently interacting. The limited number of patients did not allow statistical adjustment for each outcome variable with potential interaction with SSS. However, the 2 other variables (Table 2) significantly associated with favorable outcome, the initial diastolic BP (higher values predictive of better outcome) and the use of antihypertensives (predictive of decreased chances of good outcome), underscore the significance of BP and cerebral perfusion. Initially low BP and perithrombolytic antihypertensives may decrease perfusion pressure and compromise collateral circulation, which may have a bearing on recommendations for treating BP such as those in the AHA guidelines. In fact, these guidelines, by referring to NINDS trial practices, are quite permissive in stating that patients with BP 180 to 230/105 to 120 mm Hg should be treated. This has, however, been interpreted rigorously, as in our

Figure 2. A, Percentages of patients with EIC on day 0 CT and maturation of these findings as evaluated on day 1 CT. B, Percentages of patients with EIC item by item on day 0 CT.

Figure 3. A, Functional outcome on mRS at 3 months. Included is comparable information from the placebo and rtPA cohorts of randomized controlled trials in NINDS and the 3-hour cohort of the ECASS trial and from open community-based cohorts from Cologne and Canada (CASES). B, Dependency in daily activities on BI at 3 months. Comparison is made to similar data available from the placebo and rtPA cohorts of the NINDS trial and from the community-based open cohort from Cologne.
management protocol (≥185/105 mm Hg) and in ECASS II (≥185/110 mm Hg), which may be overreaching. Thrombolysis is recommended to be followed by BP monitoring (with treatment as necessary) during the next 24 hours, which should perhaps also be investigated. Our data are the first to support a previously suggested relationship between pharmacological BP reduction and poor outcome in a thrombolysis study. Although antihypertensives may moderate peak systolic BP, which we found borderline predictive of hemorrhagic changes (Table 2), this may occur at the expense of viable penumbral tissue with insufficient collaterals and may compromise long-term outcome, as suggested in previous nimodipine trials. We suggest that larger thrombolysis databases be reanalyzed, including delayed BP values and longer treatment delays were associated with decreased likelihood (OR>1) of hemorrhagic changes.

The frequencies of both HT and PH were 8%, which is similar to the open series from Cologne. Both frequencies are far lower than those in the ECASS 3-hour cohort. Excluding patients with EIC greater than one third of the MCA territory may decrease the hemorrhage rates, as suggested. On the other hand, Patel et al reported that EIC greater than one third of the MCA territory was not independently associated with the risk of adverse outcome or symptomatic ICH. These results contradict those of ECASS II, in which hypoattenuating CT changes were associated with hemorrhages. In an extension of the results suggesting that CT hypodensity is independently associated with PH, our results also suggest that hypodensity of cerebral cortex, but not that of basal ganglia, may predict unfavorable outcome.

Predictors of hemorrhagic events have been reported to include antithrombotic drugs, but in our cohort they were more common in patients without hemorrhages (21% versus 17%). In a Canadian series, asymptomatic hemorrhages were more common in patients treated beyond 3 hours, which we did not find. However, similar to our results, there were no symptomatic/fatal hemorrhages in the late treatment group. In fact, we found longer delay to be inversely associated with the probability of hemorrhagic changes (Table 2). Patients with dense ischemic symptoms tended to be admitted quickly (Figure 1) and may have had more ischemic tissue prone to hemorrhage if they underwent thrombolysis.

When our patients were treated, stroke thrombolysis with rtPA had not yet been approved in the European Union. Correspondingly, the percentage of stroke patients who un-
derwent thrombolysis was low (approximately 2%) because of the delay in seeking medical attention, which is the most prevalent contraindication for thrombolysis. A minority of patients (28%) were recruited despite a SNT somewhat more than allowed in the AHA guidelines, but only if they met the ECASS trial CT criteria of EIC not exceeding one third of the MCA territory. Although this protocol modification may have influenced the results, a preliminary analysis of pooled results of NINDS, ECASS I and II, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trials has suggested that there is benefit in rtPA therapy beyond 3 hours up to 4.5 hours,20 a time window into which all our patients fit. An ECASS III trial will be initiated to determine the potential extension of the time window.

References
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