Outcome and Severe Hemorrhagic Complications of Intravenous Thrombolysis With Tissue Plasminogen Activator in Very Old (≥80 Years) Stroke Patients

Jörg Berrouschot, MD; Joachim Röther, MD; Jörg Glahn, MD; Thomas Kucinski, MD; Jens Fiehler, MD; Götz Thomalla, MD

Background and Purpose—Information on safety and efficacy of intravenous thrombolysis with tissue plasminogen activator (tPA) (IV-tPA) in very old acute ischemic stroke (AIS) patients is scarce. We studied outcome and severe hemorrhagic complications in patients aged 80 and older.

Methods—We analyzed data of AIS patients, treated with IV-tPA, in 3 German stroke centers. Neurologic deficit on admission was assessed using the National Institutes of Health Stroke Scale (NIHSS). Outcome was assessed after 90 days using the Modified Rankin Scale (MRS), and favorable outcome was defined as a MRS score of 0 to 1. Severe intracerebral bleeding complications were assessed on follow-up magnetic resonance imaging or cranial computed tomography. Data were compared between patients <80 years of age and patients aged ≥80 years.

Results—A total of 228 patients were treated with IV-tPA; 38 (16%) were 80 years or older. There was no difference in NIHSS on admission or onset to treatment time between younger and older patients. Less patients <80 years of age achieved a favorable outcome (26.3 versus 46.8%, \( P = 0.021 \)), and mortality was higher in older patients (21.1 versus 5.3%, \( P = 0.004 \)). There was no difference in the rate of parenchymal hemorrhage (6.3% <80 years versus 5.3% ≥80 years, \( P = 1.000 \)) and symptomatic intracerebral hemorrhage (2.6% <80 years versus 2.6% ≥80 years, \( P = 1.000 \)) between both groups.

Conclusion—There is no increase in severe intracerebral hemorrhage after IV-tPA in very old patients, but outcome is worse as compared with younger patients. There is no evidence to exclude ischemic stroke patients from thrombolysis based on a predefined age threshold. (Stroke. 2005;36:000-000.)

Key Words: stroke ■ thrombolytic therapy ■ treatment outcome

Intravenous thrombolysis with tissue plasminogen activator (IV-tPA) is the only approved therapy for acute ischemic stroke (AIS) and has been shown to improve clinical outcome in AIS patients.\(^1\) However, although stroke mainly affects the elderly, there is little information on efficacy and risk of IV-tPA in very old patients. Except for the NINDS study, all large clinical trials of tPA in stroke excluded patients over 80 years.\(^1-5\) and in Europe, IV-tPA is not recommended for patients over 80 years. Moreover, age is considered a reason not to treat with IV-tPA.\(^6\)

On the other hand, stroke incidence is clearly associated with age. Although incidence of a first-ever stroke is approximately 200 to 300 per 100 000 in the 55 to 64 years old, it is approximately 10-fold higher (2000 to 2500 per 100 000) in those over 85 years.\(^7\) At the same time, outcome is worse and mortality is higher in older patients. In large epidemiologic studies, short- and long-term mortality are approximately twice as high in patients over 85 years compared with those below 85 years.\(^8,9\)

In the centers participating in this study, IV-tPA was administered according to the NINDS criteria.\(^1\) As a consequence of this, also patients aged 80 and older were treated with IV-tPA. We studied outcome and severe hemorrhagic complications after thrombolysis IV-tPA in AIS patients below and 80 years and above.

Patients and Methods

Patients

We retrospectively analyzed data of prospectively studied consecutive AIS patients treated with IV-tPA during different time periods from 2000 to 2004 in 3 German stroke centers (Altenburg, Hamburg, and Minden). In all patients, diagnosis of AIS was confirmed by initial and follow-up cranial computed tomography (CCT) or magnetic resonance imaging (MRI).
Treatment
IV-thrombolysis with tPA was performed within 3 hours according to the NINDS criteria. In the 3- to 6-hour time period, IV-thrombolysis was performed as an individual decision of the treating neurologist and neuroradiologist based on multimodal CCT or MRI findings after informed consent according to the Declaration of Helsinki. The study was approved by the local Institutional Review Boards in all participating centers.

Clinical Assessment
Severity of neurologic deficit at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS). Outcome was assessed 90 days after stroke using the Modified Rankin Scale (MRS). According to the primary end points of the NINDS and ECASS II trials, favorable outcome was defined as a score of zero to one on the MRS.

Assessment of Hemorrhagic Transformation
Hemorrhagic transformation was assessed by neuroradiologists, blinded to clinical data, on follow-up CCT or MRI. Parenchymal hemorrhage (PH) and symptomatic intracerebral hemorrhage (SICH) was rated according to the definitions used in the ECASS trials, which means that SICH was defined as any signs of hemorrhage on follow-up imaging associated with clinical deterioration of 4 or more points on the NIHSS. As a result of the small numbers of hemorrhages in our sample, we summarized PH1 and PH2 for further analysis as PH.

Statistical Analysis
Patients were stratified into 2 age groups: <80 and ≥80 years. All values are presented as median (interquartile ranges [IQR]) for continuous variables and counts (percentage) for categorical variables. Group comparisons were made using the Mann–Whitney U test for continuous variables and Fisher exact test for categorical variables; for correlations, Spearman rank correlations were used. To identify independent predictors of favorable outcome and death, logistic regression analysis was performed. After univariate analysis, covariates with P < 0.15 were entered into a multiple regression model (SPSS 9.0.1; SPSS Inc).

Results
In total, 228 patients were treated with IV-tPA, with age ranging from 27 to 91 years. Of these, 38 patients (16%) were aged 80 years or older, with a median age of 83 years (see Table 1). There was no difference in the proportion of patients treated within 3 hours or after 3 to 6 hours or in the NIHSS score on admission between the groups. The proportion of female patients was higher in the group of very old patients.

The number of patients with a favorable outcome, defined by a MRS score of zero to one, was smaller in older patients (10 of 190 (5.3%) versus 89 of 190 (46.8%), P = 0.004; see figure). At 90 days after stroke, 8 of 38 (21.1%) patients ≥80 years had died. The cause of death was noncerebral in 5 patients (pneumonia, cardiac arrest) and cerebral (space-occupying middle cerebral artery infarction) in 3 patients. The mortality at day 90 was higher in the very old patients compared with patients below 80 years (10 of 190 (5.3%, P = 0.004). One third of the patients aged 80 or older was functionally independent (as defined by an MRS score ≤2) after 3 months. The frequency of severe hemorrhagic complications was comparable between both groups. PH was found in 2 of 38 (5.3%) patients 80 years or older compared with 12 of 190 (6.3%) in patients <80 years (P = 1.000), and the rate of SICH was 2.6% for both groups (5 of 190 < 80 years versus one of 38 ≥ 80 years, P = 1.000).

There were strong positive correlations between age and NIHSS score on admission (r = 0.191, P = 0.004), age, and MRS score at day 90 (r = 0.303, P < 0.001), and also between

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*Mann–Whitney U test.
†Two-tailed Fisher exact test.
NA indicates not applied.

Modified Rankin Scale at day 90

![Modified Rankin Scale at day 90](http://stroke.ahajournals.org/)

Outcome assessed by the Modified Rankin Scale at day 90. All values are given in percentage. Values do not equal 100% because of rounding.
NIHSS score on admission and MRS score at day 90 (r=0.559, P<0.001). Age (P=0.001) and NIHSS on admission (P<0.001) were predictors of outcome in univariate analysis, whereas onset to treatment time (OTT) (P=0.581) and sex (P=0.204) were not. Both NIHSS on admission and age were identified as independent predictors by multiple regression analysis (see Table 2). In other words, the likelihood of reaching a favorable outcome decreases by 25% for every 10 year of increase in age and by approximately 91% for an increase of 5 points on the NIHSS on admission. Age (P=0.004) and NIHSS on admission (P=0.002) were also predictors of death at day 90 in univariate analysis, whereas OTT (P=0.576) and sex (P=0.313) were not. Both age and NIHSS were retained in the model after multiple regression analysis. Odds ratios (see Table 2) translate into an increased risk of death at day 90 of 72% for every 10-year increase in age and of 69% for an increase of 5 points on the NIHSS on admission.

Discussion
There are no consistent recommendations regarding the use of intravenous thrombolysis in very old patients.1–5 Because an increased risk of hemorrhagic complications is feared with increasing age, thrombolysis is withheld in older people. However, the aged population is more frequently and more severely struck by ischemic stroke,7–9 and by this, they might have even more to gain from thrombolysis than younger patients.

Only few patients aged 80 or older have been included into the large clinical trials of tPA in stroke. Until now, there exists no evidence whether very old patients benefit from treatment with IV-tPA comparable to younger patients and whether the risk of severe intracerebral bleeding complications is higher in the very old patients. In our analysis, mortality was higher and the proportion of patients with favorable outcome was smaller 90 days after stroke in patients age 80 or older, whereas the rate of severe intracerebral bleeding complications did not differ between very old and younger patients.

A small number of case series report on the use of IV-tPA in old patients. A retrospective survey of patients treated at 13 U.S. hospitals included 30 patients aged 80 or older and compared patients ≥80 or older and <80 years.13 They found no significant differences in the number of patients with favorable outcome at hospital discharge (37 versus 30%), symptomatic intracerebral hemorrhage (3 versus 6%), and only a tendency toward a higher inhospital mortality in older patients (20 versus 8%). These results are contrary to our data with significant differences between patients ≥80 and <80 years regarding favorable outcome and mortality. This may partially be explained by the different time points for the assessment of outcome, being 90 days in our study and a rather short-term outcome (hospital discharge) in the U.S. tPA Stroke Survey Experience.13 Moreover, outcome of the patients below 80 years in our study appears remarkably good with 46.8% patients reaching a favorable outcome after 90 days, which leads to a stronger contrast to the outcome in the older people.

Another study, including 16 patients aged 80 years or older, reported no significant difference in favorable outcome between very old and younger patients (29 versus 41%) nor in the number of symptomatic hemorrhages, but the small sample size may be responsible for the failure to detect significant differences between the groups.14 Recently Simon et al15 reported a series of 62 patients aged 80 and over treated by IV-tPA and found 20% patients with favorable outcome at 3 months, a mortality at 3 months of 33%, and a 9.7% rate of symptomatic intracerebral hemorrhage.

Considering the results from all reports of thrombolysis in very old patients together with our analysis, the proportion of IV-tPA patients 80 years or older with a favorable outcome is approximately 20% to 30% and by this appears smaller than in younger patients or in the pooled treatment group from the large tPA trials, in which favorable outcome was found in approximately 35% to 40% of patients.16 This is not surprising because outcome after stroke in general is related to age.7–9

It is remarkable that with a median NIHSS on admission of 16, the old patients in our study represent a group of very severely affected AIS patients, a trend that was also found in previous reports of thrombolysis in the very old, in which 50% of patients presented with a NIHSS score of ≥15.15 In line with this, age, severity of neurologic deficit on admission, and outcome were strongly correlated in our study. Age was also identified as a strong independent predictor of outcome after IV-thrombolysis with tPA in our sample, with a 72% increased risk of death and a 25% decrease in the likelihood of reaching a favorable outcome for every 10-year increase in age.

Mortality of thrombolysis in patients 80 years or older (most commonly being rated at 3 months after stroke) ranges between 15% and 30% and is approximately twice as high as in patients below 80 years. It is well documented that mortality after stroke increases with age7–9 relating to general age-related factors and increased comorbidity in older patients.17 In the European BIOMED study, 3-month mortality without thrombolysis was as high as 45% in patients aged 80 and older.18 Obviously, there is no excess in mortality in old patients receiving thrombosis.

A presumed increased risk of intracerebral hemorrhage is often cited as the reason to exclude very old patients from thrombolysis. Amyloid angiopathy, a decreased renal tPA clearance, and frail vasculature in the elderly are asserted as explanations for a possibly increased risk of intracerebral hemorrhage.19 In the pooled analysis of the ATLANTIS,
NINDS, and ECASS trials, multivariate analysis identified age as an independent predictor of intracerebral hemorrhage. In the NINDS study, however, no association between age and severe hemorrhagic complications was found. These results were approved in a large survey of 1205 patients treated with IV-tPA in the clinical setting, in which age also was not found to be a predictor of secondary intracerebral hemorrhage. In line with our data and previous reports of thrombolysis in patients aged 80 or over, the rate of severe intracerebral hemorrhages was not increased in the groups of very old patients.

There are limitations to our study and results have to be interpreted cautiously. Our data do not result from a randomized, controlled trial of IV-tPA in the very old. The decision whether to treat was left to the treating neurologist, and we cannot exclude that some bias may be introduced by this. It is well conceivable that, especially in the population of the very old, patient selection was performed very carefully. Symptomatic intracranial hemorrhage occurred in only one patient aged 80 or older, therefore any conclusions regarding the risk of SICH are limited. Moreover, part of our study population was treated beyond the 3-hour time window using multimodal computed tomography or magnetic resonance imaging as a selection tool, and we cannot exclude a bias introduced thereby. Additionally, it appears worthwhile remarking that the majority of patients in the very old group was aged 80 to 85 years (n=30), whereas only 8 patients were >85 years. Furthermore, our analysis is restricted to a selected set of covariates (age, sex, onset to treatment time, NIHSS on admission), but there are numerous other parameters that are known to be correlated with outcome after stroke such as blood pressure, blood glucose level, and body temperature on admission, or the presence of arterial hypertension and diabetes mellitus. We cannot exclude that imbalances in these parameters in our patients confound our results.

It is a matter of fact that the Western world faces demographic changes with a continuous increase of the proportion of old and very old people. In Europe, the number of people aged 80 or above is expected to grow by 180% by 2050. Therefore, the number of very old acute stroke patients will increase dramatically, and it appears unjustifiable to exclude this increasing patient population a priori from the only approved and effective treatment of acute ischemic stroke. Moreover, there are clear indications that older stroke patients are not resistant to therapy but may well benefit from state-of-the-art acute stroke therapy. In a post hoc subgroup analysis of the NINDS study, the number of patients with a favorable outcome in the treatment group was approximately twice as high (n=117) in the subgroup of patients >75 years than in the placebo group (n=57). This result even exceeds the treatment effect for the younger patients.

Conclusion
In our study with a limited number of patients, we found no increase in symptomatic intracerebral hemorrhage after thrombolysis in patients aged 80 or older. Outcome is worse in very old patients after IV-tPA compared with younger patients, which mirrors the well-documented interaction between age and outcome after stroke, independent from treatment. We find it therefore justifiable to use IV-tPA in carefully selected old and very old patients according to established protocols. However, randomized, controlled trials of IV-tPA including patients aged 80 or over are needed before definite recommendations regarding thrombolysis in the very old can be made.

In the future, demographic changes will force stroke physicians to rethink current treatment concepts and to adjust acute stroke treatment to the increasing population of old and very old stroke patients.

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References


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