Predictors of In-hospital Mortality and the Risk of Symptomatic Intracerebral Hemorrhage after Thrombolytic Therapy with Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke

Mohamed Al-Khaled, MD,* Christine Matthis, MD,† and Jürgen Eggers, MD*

Recombinant tissue-plasminogen activator (rt-PA) therapy improves functional outcome in patients with acute ischemic stroke (AIS) but is associated with serious complications, including symptomatic intracerebral hemorrhage (sICH). This study aimed to determine the independent predictors of in-hospital mortality (IHM) and the risk of sICH after rt-PA therapy. A total of 1007 patients (mean age, 72 ± 12 years; 52% women; mean National Institutes of Health Stroke Scale [NIHSS] score, 11.6 ± 5.6) with AIS treated with rt-PA were enrolled in this study during a 42-month period beginning in November 2007. Univariate and multivariate regression analyses were performed to estimate the predictors of IHM. Eighty-three of the 1007 patients (8.2%) died during hospitalization (mean duration of hospitalization, 10 ± 1.8 days). Logistic regression estimated the following independent predictors for IHM: age ≥80 years (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.1-3.0; $P = .031$), aphasia (OR, 2.0; 95% CI, 1.1-3.4; $P = .017$), altered consciousness (OR, 3.6; 95% CI, 2.0-6.2; $P < .001$), hypertension (OR, 4; 95% CI, 1.4-11.6; $P = 0.012$), sICH (OR, 5.9; 95% CI, 2.9-11.9; $P < 0.001$), and pneumonia during hospitalization (OR, 3.0; 95% CI, 1.8-5.0; $P < .001$). After rt-PA therapy, 58 patients (5.8%) sustained sICH, 16 (28%) of whom died. Increased age ($P = .008$), higher NIHSS score ($P = .011$), and atrial fibrillation ($P = .025$) were correlated with sICH. The findings from this study may help clinicians estimate the prognosis and risk of sICH in patients with AIS treated with rt-PA. **Key Words:** Stroke treatment—prognosis—outcome—complication—epidemiology.

Thrombolysis with intravenous (IV) recombinant tissue-plasminogen activator (rt-PA) is the only medically approved treatment for patients with acute ischemic stroke (AIS) that improves functional outcome after stroke and prevents disability caused by stroke.[1,2] Based on the findings of the European Cooperative Acute Stroke Study (ECASS) III, rt-PA therapy is effective when administered within 3-4.5 hours after symptom onset.[3] Two previous studies (ECASS I and ECASS II) failed to demonstrate the efficacy of administering IV rt-PA up to 6 hours after symptom onset.[4,5] However, patients who were treated with IV rt-PA had an higher rate of symptomatic intracerebral hemorrhage (sICH) and greater mortality compared with patients with AIS in general, possibly related to the selection of more severely affected patients for IV rt-PA therapy.[6,7]

The aims of the present population-based study were to estimate the short-term risk and predictors of early in-hospital mortality (IHM) after IV rt-PA therapy, and to determine the risk of sICH in patients treated with IV rt-PA.

From the *Department of Neurology; and †Institute of Social Medicine, University of Lübeck, Lübeck, Germany.

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Address correspondence to Mohamed Al-Khaled, MD, Department of Neurology, University of Lübeck, Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. E-mail: Mohamed.al-khaled@neuro.uni-luebeck.de.

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Methods

Study Design

This study is a part of the benchmarking project Quality of Treatment of Stroke in Schleswig-Holstein (QugSS2), which has been described previously.[8] The German federal state of Schleswig-Holstein has 2.8 million inhabitants. Of the 15 participating sites, 2 were university departments of neurology, 8 were departments of neurology at nonuniversity hospitals, and 5 were departments of internal medicine at nonuniversity hospitals. Ten of the hospitals had a stroke unit certified by the German Stroke Society.

All patients provided written informed consent for inclusion in this study. Inclusion criteria included treatment of AIS with IV rtPA for up to 4.5 hours after symptom onset and main residence in the state of Schleswig-Holstein. Patients who received local thrombolytic therapy with rtPA were excluded.

The documentation and data collection procedures followed a uniform study manual, in accordance with recommendations of the German Stroke Register Study Group. Baseline characterizations at admission—sex, age, National Institutes of Health Stroke Scale (NIHSS) score, neurologic deficits at admission, vascular risk factors, history of stroke, and complications during hospitalization—were documented and analyzed. sICH was defined as any bleeding that was not detected on a previous computed tomography (CT) scan and was associated with a worsening NIHSS score of at least 4 points. All patients underwent a head CT scan before and 24 hours after IV rt-PA treatment as part of the clinical routine of administering thrombolytic therapy. Approval for the study was obtained from the local Ethics Committee of the University of Lübeck.

Statistics

Data analysis was done using SPSS PASW Statistics 18 (IBM, Armonk, NY). Correlations between categorical variables were identified using the χ^2 test, and correlations between continuous variables were determined using the Student t test. The Wilcoxon test was used to compare modified Rankin Scale (mRS) scores at admission and at discharge. Logistic regression was performed to estimate odds ratios (ORs) for predictors of mortality. Baseline characteristics found to be significantly associated with mortality on univariate analysis, sICH and pneumonia, were evaluated by logistic regression. A P value of $<.05$ was considered statistically significant.

Results

Between November 2007 and March 2011, a total of 1007 patients (mean age, 72 ± 12 years; 52% women; mean NIHSS score, 11.6 ± 5.6) with AIS received treatment with IV rt-PA. Eighty-three patients (8.2%) died during hospitalization (mean duration of hospitalization, 10 ± 1.8 days). Table 1 presents the baseline characteristics

Table 1. *Baseline characteristics and risk factors*

Baseline characteristic/risk factor	All (n = 1007)	IHM mortality (n = 83)	*P* value
Age, years, mean (SD)	71.5 (12.2)	78.9 (8.4)	<.001
Age ≥80 years, n (%)	247 (25)	36 (44)	<.001
Female sex, n (%)	508 (51)	47 (57)	.22
NIHSS score, mean (SD); median (IQR)	11.6 (5.6); 11 (7-15)	16.4 (5.2); 17 (14-20)	<.001
mRS score, mean (SD); median (IQR)	4 (1.1); 4 (3-5)	4.5 (0.8); 5 (4-5)	.001
Paresis, n (%)	933 (94)	79 (98)	.15
Aphasia, n (%)	549 (56)	60 (74)	.001
Dysarthria, n (%)	672 (69)	61 (77)	.10
Dysphagia, n (%)	462 (49)	56 (71)	<.001
Altered unconsciousness, n (%)	136 (14)	29 (36)	<.001
Time to rt-PA, n (%)			
<2 hours	367 (75)	24 (66)	
2-3 hours	96 (20)	8 (22)	
3-4.5 hours	25 (5)	4 (11)	.19
Admission on weekday, n (%)	717 (72)	56 (69)	
Admission on weekend, n (%)	285 (28)	26 (32)	.49
Hypertension, n (%)	795 (81)	77 (95)	0.001
Diabetes mellitus, n (%)	198 (20)	25 (31)	0.01
Hypercholesteremia, n (%)	477 (51)	30 (41)	0.06
Atrial fibrillation, n (%)	387 (40)	42 (54)	0.01
History of stroke, n (%)	197 (20)	15 (19)	0.79
Hospital stay, days, mean (SD)	10 (1.8)	3 (2.8)	<0.001

Abbreviations: IHM, in-hospital mortality; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue-plasminogen activator; SD, standard deviation.