Effects of Ultraearly Intravenous Thrombolysis on Outcomes in Ischemic Stroke

The STEMO (Stroke Emergency Mobile) Group

Alexander Kunz, MD
Christian H. Nolte, MD
Hebun Erdur, MD
Jochen B. Fiebach, MD
Frederik Geisler, MD
Michal Rozanski, MD
Jan F. Scheitz, MD
Kersten Villringer, MD
Carolin Waldschmidt, MD
Joachim E. Weber, MD
Matthias Wendt, MD
Benjamin Winter, MD
Katja Zieschang, MD
Ulrike Grittner, PhD
Sabina Kaczmarek
Matthias Endres, MD
Martin Ebinger, MD
Heinrich J. Audebert, MD

The effects of intravenous thrombolysis (IVT) in ischemic stroke are time dependent.[1,2] Because of delays in conventional stroke workup, previous randomized IVT trials were unable to include patients with onset-to-treatment time (OTT) ≤60 minutes of symptom onset. With the invention of computed tomography–equipped mobile stroke units (MSUs), a relevant proportion of patients treated on such ambulances receive IVT within this ultraearly time window.[3] In this study, we assessed the effects of IVT on 3-month functional outcome and mortality in different OTT intervals, including the first hour after onset, using a pooled analysis of 2 prospective prehospital and in-hospital registries in Berlin/Germany.[4]

Methods of patient inclusion and documentation in the 2 registries were described elsewhere[4] (URL: http://www.clinicaltrials.gov. Unique identifier: NCT02358772). Briefly, all patients admitted through emergency medical services who received IVT between February 5, 2011, and March 5, 2015, were included in the registries. The prehospital registry included patients thrombolysed in an MSU and admitted to the nearest stroke unit thereafter. Intra-arterial treatment was optional in patients with occlusion of proximal intracranial arteries in both cohorts. The in-hospital registry comprised patients receiving IVT at Charité-Universitätsmedizin, Campus Benjamin Franklin. We excluded patients with nonstroke diagnosis, IVT without known exact (witnessed) time of onset, denial/withdrawal of informed consent for follow-up, missing 3-month follow-up, or incomplete documentation of data used in the multivariable analyses.

For the pooled analyses of time-to-treatment effects, we included all ischemic stroke patients who received IVT within 4.5 hours. We compared results of the first two 60-minute OTT intervals with OTT of 121 to 270 minutes as reference. The primary outcome was survival without disability (modified Rankin Scale [mRS] score ≤1 at 3 months after ischemic stroke). The primary study population did not include patients who had previously lived with need of assistance because only patients without prestroke disability can realistically achieve an outcome of mRS score ≤1. Secondary outcomes were survival without severe disability (mRS score ≤3) and mortality at 3 months (also assessed in the entire study population, including patients with prestroke need of assistance). These outcomes were assessed by certified mRS raters through standardized telephone interview or based on information from Berlin registration offices.

Outcomes were adjusted in multivariable regression for demographics, comorbidities, intra-arterial treatment, and stroke severity according to the National Institutes of Health Stroke Scale as a continuous variable (Table). Because of the low 3-month mortality, we had to restrict the covariables in this regression analysis to age, continuous National Institutes of Health Stroke Scale, and time intervals. A 2-sided significance level of α=0.05 was applied with IBM SPSS Statistics version 22.

The Charité-Universitätsmedizin Berlin ethics committee approved the study (registration EA4/061/14).

Correspondence to: Heinrich J. Audebert, MD, Department of Neurology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany. E-mail heinrich.audebert@charite.de

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Table. Adjusted Analyses for Modified Rankin Scale Score ≤1 and Mortality at 3 Months (Multivariable Logistic Regression, Inclusion Model)

	OR (95% CI), mRS Score ≤1 (n=625)	*P* Value	OR (95% CI), mRS Score ≤3 (n=625)	*P* Value	OR (95% CI), Mortality Within 90 d (n=625)	*P* Value
Nagelkerke R^2	0.21		0.34		0.30	
AUC (95% CI)	0.74 (0.70–0.77)		0.84 (0.80–0.87)		0.86 (0.81–0.91)	
Age (per SD of age, per 12 y)	0.86 (0.72–1.03)	0.11	0.45 (0.34–0.60)	<0.001	2.07 (1.42–3.02)	<0.001
Female	0.74 (0.52–1.05)	0.09	1.10 (0.70–1.75)	0.67		
Atrial fibrillation	0.71 (0.48–1.05)	0.09	0.80 (0.50–1.30)	0.37		
Diabetes mellitus	0.69 (0.45–1.05)	0.09	0.96 (0.56–1.66)	0.89		
NIHSS as continuous variable	0.89 (0.89–0.92)	<0.001	0.86 (0.83–0.90)	<0.001	1.19 (1.13–1.26)	<0.001
Intra-arterial treatment	0.60 (0.31–1.16)	0.13	0.34 (0.17–0.66)	0.001	1.84 (0.82–4.13)	0.14
Start of treatment within 0–60 min	1.87 (1.12–3.11)	0.02	3.01 (1.48–6.13)	0.002	0.26 (0.10–0.69)	0.01
Start of treatment within 61–120 min	1.06 (0.71–1.58)	0.76	1.38 (0.81–2.33)	0.23	0.42 (0.20–0.90)	0.03
Start of treatment within 121–270 min	1 (Reference)		1 (Reference)		1 (Reference)	

The Nagelkerke R^2 is the coefficient of determination, proportion of variance in dependent variables that is explained by variance in independent variables of the logistic regression models. AUC indicates area under the curve of the regression model derived from receiver-operating characteristic analysis; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

In all, 625 patients fulfilled the prespecified inclusion criteria of the primary study population. The majority of patients treated within 60 minutes from onset were treated on an MSU (111 of 133 patients, 84%). Of 259 patients, 111 (43%) treated on MSU received IVT within 60 minutes compared with 22 of 366 patients (6%) treated in the hospital. In addition, 300 patients received IVT within 61 to 120 minutes and 192 within 121 to 270 minutes.

After adjustment for covariables, the odds ratios (ORs) for mRS score ≤1 and ≤3 were increased whereas ORs for mortality were decreased with earlier treatment (Table). Compared with OTT ≥121 minutes (reference), ORs for mRS score ≤1 were 1.86 (95% confidence interval [CI], 1.12–3.11; *P*=0.02) for 0 to 60 minutes and 1.06 (95% CI, 0.71–1.58; *P*=0.76) for 61 to 120 minutes.

Similar results were seen in adjusted analyses of the entire study cohort (n=799), including patients with prestroke need of assistance. For mRS score ≤3, ORs were 2.80 (95% CI, 1.51–5.19; *P*=0.001) for patients treated within 60 minutes and 1.14 (95% CI, 0.73–1.78; *P*=0.56) for patients treated within 61 to 120 minutes, whereas ORs for mortality were 0.28 (95% CI, 0.13–0.62; *P*=0.002) and 0.56 (95% CI, 0.33–0.96, *P*=0.03), respectively.

Shorter OTT, especially OTT ≤60 minutes, was associated with reduced mortality and increased probabilities for favorable outcome (mRS score ≤1) and survival without severe disability (mRS score ≤3). This is the first study providing estimates of a better 3-month functional outcome in patients treated with IVT in the golden hour after onset. The results are in line with findings from randomized controlled trials,[1] registries,[2] and a post hoc analysis of the PHANTOM-S (Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke) prehospital stroke thrombolysis study.[3] Investigators of the GWTG (Get With The Guidelines)–Stroke program have recently published an analysis comparing short-term outcomes of patients treated within 60 minutes or later and found increased odds of golden-hour IVT for in-hospital survival, ambulatory status at discharge, and discharge home.[5] However, functional outcome at 3 months was not available in that study, similar to the previous PHANTOM-S prehospital stroke thrombolysis study.

Limitations of the study include (1) the fact that to date an MSU is available only in a few areas worldwide; (2) mRS assessment by certified raters who were not blinded to the mode of prehospital care and IVT application; (3) different times of National Institutes of Health Stroke Scale assessment after stroke onset, with possible worsening or improvement of symptoms during the natural course of hyperacute stroke; (4) the relatively small sample size compared with the pooled randomized controlled trials[2] and large registries[5]; and (5) the fact that registry-based comparisons cannot adjust for nonobserved or nondocumented confounders.

Thrombolysis within the first hour after acute ischemic stroke onset was associated with improved functional outcome and survival at 3 months compared with thrombolysis >2 hours after ischemia. These findings suggest that prehospital thrombolysis is an efficient approach in

acute ischemic stroke treatment but need confirmation in controlled trials.

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AFFILIATIONS

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FOOTNOTES

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