Intravenous Thrombolysis in Unknown-Onset Stroke

Results From the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry

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Background and Purpose—Stroke patients with unknown onset (UKO) are excluded from thrombolytic therapy. We aim to study the safety and efficacy of intravenous alteplase in ischemic stroke patients with UKO of symptoms compared with those treated within 4.5 hours in a large cohort.

Methods—Data were analyzed from 47 237 patients with acute ischemic stroke receiving intravenous tissue-type plasminogen activator in hospitals participating in the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry between 2010 and 2014. Two groups were defined: (1) patients with UKO (n=502) and (2) patients treated within 4.5 hours of stroke onset (n=44 875). Outcome measures were symptomatic intracerebral hemorrhage per Safe Implementation of Treatment in Stroke on the 22 to 36 hours post-treatment neuroimaging and mortality and functional outcome assessed by the modified Rankin Scale at 3 months.

Results—Patients in UKO group were significantly older, had more severe stroke at baseline, and longer door-to-needle times than patients in the ≤4.5 hours group. Logistic regression showed similar risk of symptomatic intracerebral hemorrhage (adjusted odds ratio, 1.09; 95% confidence interval, 0.44–2.67) and no significant differences in functional independency (modified Rankin Scale score of 0–2; adjusted odds ratio, 0.79; 95% confidence interval, 0.56–1.10), but higher mortality (adjusted odds ratio, 1.58; 95% confidence interval, 1.04–2.41) in the UKO group compared with the ≤4.5 hours group. Patients treated within 4.5 hours showed reduced disability over the entire range of modified Rankin Scale compared with the UKO group (common adjusted odds ratio, 1.29; 95% confidence interval, 1.01–1.65).

Conclusions—Our data suggest no excess risk of symptomatic intracerebral hemorrhage but increased mortality and reduced favorable outcome in patients with UKO stroke compared with patients treated within the approved time window. **(*Stroke*. 2017;48:720-725. DOI: 10.1161/STROKEAHA.116.014889.)**

Key Words: alteplase ■ cerebral hemorrhage ■ neuroimaging ■ prognosis ■ safety ■ stroke

Patients waking-up with symptoms of stroke or in whom no witness is available and time from last time the patient was seen normal is >4.5 hours represent a specific subgroup of stroke patients. Unknown onset (UKO) of stroke is quite frequent and affecting ≈≤25% of acute stroke patients.[1,2]

Given that the exact time point of symptom onset is unknown but may exceed 4.5 hours, this large group of patients is excluded from thrombolysis according to the approval criteria and guideline recommendations.[2,3] Nevertheless, there is evidence showing that incidence of early morning strokes rises with around 50% compared with the nightly incidence,[4] suggesting that many wake-up strokes occur close to awakening, and thus, patients might be within the approved time window of thrombolysis when presenting to the emergency department.

Because of the lack of any evidence-based treatment recommendation for this subgroup of stroke patients, there are a growing number of case series that report on thrombolysis given based on imaging findings in patients with UKO time of stroke.[5–10] Not only the results of these studies, but also a recently published meta-analysis from nonrandomized clinical studies[11] showed the feasibility of imaging-guided

Received July 26, 2016; final revision received December 14, 2016; accepted December 16, 2016.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.014889/-/DC1.

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thrombolysis in ischemic stroke patients with unknown time of symptom onset, no excess in symptomatic intracerebral hemorrhage (SICH), while outcome seemed similar when compared with those treated within 4.5 hours of symptoms onset.

The present work aims to study whether the safety and functional outcomes of intravenous thrombolysis in stroke patients with UKO are comparable to patients treated within the approved time window (4.5 hours from symptom onset) and also to identify factors associated with poor alteplase response in stroke patients with UKO. The study was performed with data obtained from patients recorded in the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR).[12,13]

Methods

Patients

All patients with confirmed baseline and treatment data recorded in the SITS-ISTR over a 5-year period (2010–2014) were considered for the study. Patients who, in addition to intravenous alteplase (Actilyse; Boehringer Ingelheim, Germany), were treated with endovascular techniques (n=394) were excluded from the analysis. Final sample included 47 237 patients. These were enrolled in 564 centers in 46 countries, 95% in European hospitals.

The SITS-ISTR is an ongoing, prospective, academic-driven, multinational registry for centers using thrombolysis for the treatment of acute ischemic stroke. The methodology of the SITS-ISTR, including procedures for data collection and management, patient identification, and verification of source data, has been previously described.[12,13] Consecutive case reporting is a basic commitment for participating in the SITS-ISTR. We collected baseline and demographic characteristics, stroke severity per the standard 11-item, 42-point National Institutes of Health Stroke Scale (NIHSS), time from hospital arrival to alteplase bolus (door-to-needle time), risk factors, medication history, and imaging data on admission and post-thrombolysis (22–36 hours), NIHSS at 2 hours, 24 hours, 7 days, and modified Rankin Scale (mRS) at 3 months.

In 2010, the checkbox time of stroke onset, unknown, was implemented in the SITS-ISTR. The sample of the project consists of patients included in the database after that moment.

We defined 2 groups: (1) stroke patients with UKO n=502 and (2) patients treated with intravenous thrombolysis within 4.5 hours of stroke onset n=44 875. Patients treated after 4.5 hours of stroke onset (n=1402) and those who were not identified as unknown in the checkbox and in which the time of symptoms onset was missing (n=458) were excluded from the analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval and patient consent for participation in the SITS-ISTR were obtained in countries that required this; other countries approved the register for anonymized audit. The SITS International Coordination Office monitored the SITS-ISTR data online and checked individual patient data regularly to identify errors or inconsistencies.

Outcome Measurements

The following definitions of cerebral hemorrhages were used:

1. SICH per SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study): parenchymal hematoma type 2 or remote parenchymal hematoma type 2 on imaging 22 to 36 hours after treatment, or earlier if scanned because of clinical deterioration, combined with a neurological deterioration of ≥4 NIHSS points or leading to death within 24 hours.
2. SICH per ECASS II (European Cooperative Acute Stroke Study II): any ICH on any post-thrombolysis imaging scan and increase of ≥4 NIHSS points or leading to death, within 7 days.
3. SICH per National Institute of Neurological Diseases and Stroke: any ICH on any post-thrombolysis imaging scan and any clinical deterioration in NIHSS or death within 7 days.

Rate of mortality and functional outcome per the mRS were evaluated at 3 months. Functional independency was defined as mRS score of 0 to 2 and poor functional outcome as functional dependency (mRS score of 3–5) or death (mRS score of 6). All assessments of imaging studies and neurological and functional status were done according to the routine clinical practice at centers participating in the SITS-ISTR. Survival status is normally done by hospital follow-up records, supported either by consulting official population registers (if available) or through contact with the patient's general practitioner. Nevertheless, the procedure for collection of mortality data at 3 months is not recorded in the registry and a large registry like SITS; it is not possible to guarantee the completeness of the registry.

Statistical Analysis

We performed descriptive univariate analysis for baseline clinical, demographic, and imaging data, as well as outcomes comparing patients treated within 4.5 hours of stroke onset and patients with UKO of symptoms. Statistical significance for intergroup differences was assessed by the χ^2 test for categorical variables and the ANOVA test and Kruskal–Wallis test for continuous variables. Logistic regression was used to study the adjusted probability of SICH, functional independency, and mortality between groups. The effect of treatment in the group of stroke patients with UKO compared with those treated within 4.5 hours on clinical outcome was also analyzed by a common odds ratio over any cut-point of the mRS estimated with an ordinal logistic regression (shift analysis). Baseline variables with significant differences in univariate analysis ($P<0.05$) were included in both multivariate analyses.

Taking into consideration only the subgroup of stroke patients with UKO, we explored potential predictors of poor functional outcome (mRS score of ≥3) using a logistic regression model with adjustment for variables with significant differences in univariate analysis ($P<0.05$). To check for potential reporting bias, we compared baseline variables between patients with missing outcome data and patients with available outcome data at 3 months. A multivariate sensitivity analysis of predictors of functional dependency was performed imputing the worst possible prognosis (mRS score of 6) in patients with missing outcome data at 3 months.

Results

Baseline Characteristics

Mean age of the overall study population was 69.7±13.0, and 24 838 (54.7%) were men. Of the 45 377 patients, 699/44 074 (1.6%) experienced previous stroke ≤3 months before admission, and 4876/44 668 (10.9%) had a history of stroke >3 months before admission. Baseline stroke severity as measured by the NIHSS was 11 (6–17), and median door-to-needle time was 66 minutes (45–93 minutes).

Baseline characteristics of the studied groups are shown in Table 1. Stroke patients with UKO were 2 years older (median) and had a 1 point higher median baseline NIHSS scores than the known ≤4.5 hours stroke group. Prealteplase systolic blood pressure and serum glucose levels were higher, and door-to-needle time was 6 minutes longer among patients with UKO stroke compared with those treated within 4.5 hours. No other significant differences were found with respect to other vascular risk factors or pretreatment with antiplatelet or anticoagulant drugs.

Magnetic resonance was used as the initial imaging modality in 3.6% of overall cases with higher proportion in stroke

Table 1. Baseline Characteristics According to the 2 Groups Defined (Alteplase in ≤4.5 Hours From Symptoms Onset and Alteplase in Unknown Onset of Symptoms)

	<4.5 h (n=44 875)		Unknown Onset (n=502)		
	n/Total	Median (IQR) or %	n/Total	Median (IQR) or %	*P* Value
Age, y	44 815	72 (62–79)	502	74 (65–82)	0.001
Sex (male)	24 583/44 875	54.8%	255/502	50.8%	0.07
Baseline mRS	42 393	0 (0–0)	453	0 (0–1)	0.003
Previous disability (mRS score of >2)	2365/42 393	5.6%	31/453	6.8%	0.24
DTN time, min	42 900/44 785	66 (45–93)	392/502	72 (50–103)	<0.001
Hypertension	29 461/44 310	66.5%	348/496	70.2%	0.08
Diabetes mellitus	8237/44 349	18.6%	101/496	20.4%	0.30
Hyperlipidemia	13 214/43 449	30.4%	159/487	32.6%	0.28
Smoker, current	7510/42 415	17.7%	78/462	19.6%	0.64
Atrial fibrillation	9818/44 217	22.2%	121/492	24.6%	0.20
Stroke, within 3 mo	691/43 583	1.6%	8/491	1.6%	0.38
Stroke, n within 3 mo	4830/44 178	10.9%	46/490	9.4%	0.93
Congestive heart failure	3733/44 056	8.5%	43/489	8.8%	0.16
Oral anticoagulants	1433/37 106	3.9%	10/433	2.3%	0.08
Aspirin	14 514/44 096	32.9%	171/473	36.2%	0.13
Clopidogrel	2579/44 229	5.8%	35/477	7.3%	0.16
NIHSS baseline score	43 954	11 (6–17)	480	12 (7–18)	<0.001
BPsys prealteplase	43 682	150 (137–169)	444	155 (140–170)	0.04
BPdia prealteplase	43 491	80 (73–90)	442	85 (73–90)	0.10
Glucose, mmol/L	40 761	6.60 (5.70–8.00)	432	6.81 (5.80–8.60)	0.008
MR at baseline	1458/44 875	3.2%	79/502	15.7%	<0.001
Infarct in baseline CT	7488/43 228	17.3%	171/486	35.2%	<0.001
Hyperdense artery sign in baseline CT	9475/42 190	22.5%	131/424	30.9%	<0.001

Bpdia indicates diastolic blood pressure; BPsys, systolic blood pressure; CT, computed tomography; DTN, door-to-needle; IQR, interquartile range; MR, magnetic resonance; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

patients with UKO (15.7%) than in those treated within 4.5 hours (3.2%). In patients with available computed tomographic (CT) scan at baseline, frequency of early infarct signs was 2-fold higher (35.2% versus 17.3%) in stroke patients with UKO. Hyperdense artery sign was also more frequent in UKO group than in the group of known onset stroke (30.9% versus 22.5%).

Outcome Parameters

Figure illustrates the distribution of mRS scores at 3 months, and Table 2 shows the results of SICH, functional independency, and mortality in the 2 study groups.

In the logistic regression analysis, there was not an increased probability of having SICH or functional independency in the UKO stroke group compared with the ≤4.5 group after adjustment for covariates. Nevertheless, mortality was significantly higher in the UKO group (Table 2).

Ordinal regression analysis showed reduced disability over the entire range of the mRS in patients treated within the approved time window compared with stroke patients with UKO (common adjusted odds ratio, 1.29; 95% confidence interval, 1.01–1.65) after adjustment for the same covariates.

In the whole sample, poor outcome (mRS score of 3–6) was more frequent in patients with early infarct signs (54% versus 41.2%; $P<0.001$) and in patient with hyperdense artery sign (62% versus 38%; $P<0.001$) compared with patients without early infarct and hyperdense artery sign, respectively. Early infarct signs (73/111, 65.8% versus 2970/5458, 54%; $P=0.017$) were associated with poor outcome (mRS score of 3–6) in the UKO group compared with the ≤4.5 hours group but not hyperdense artery sign (67/100, 67% versus 4454/7188, 62%; $P=0.303$).

Predictors of Poor Functional Outcome in Stroke Patients With UKO

Among stroke patients with UKO (n=502), 3-month outcome was available in 359 patients (168 functionally independent, 111 with functionally dependent, and 80 death). Table I in the online-only Data Supplement shows baseline characteristics of stroke patients with UKO according to the outcome availability at 3 months.

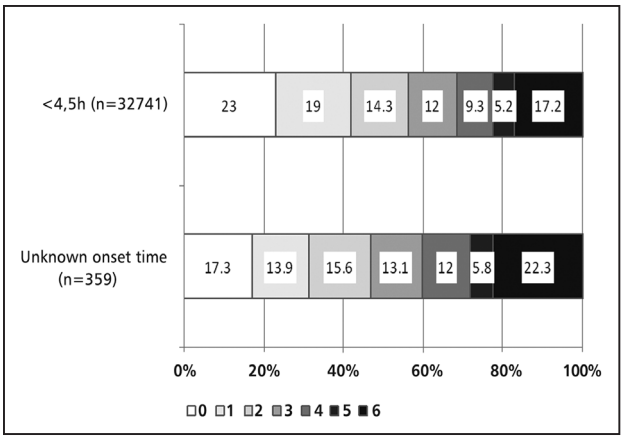

Figure. Distribution of modified Rankin Scale score at 90 d according to study groups (<4.5 h and unknown onset).

Patients with poor functional outcome (functionally dependent or death) at 3 months were 8 years older (median), had 10% higher rates of baseline disability, and were more frequently treated with aspirin before stroke; moreover, stroke severity as measured per NIHSS score was 8 points, and glucose levels at baseline were higher than in patients with functional independency. On neuroimaging variables, the presence of infarct signs and hyperdense artery sign in baseline CT scan was more frequent in the group of patients with poor outcome compared with those with functionally independent (Table II in the online-only Data Supplement). Multivariate analysis identified advanced age, worse NIHSS at baseline, higher prebolus glucose levels, and infarct signs in baseline CT as variables independently associated with poor functional outcome at 3 months after adjustment for previous mRS, hyperdense middle cerebral artery, and for other covariates (Table 3). A sensitivity analysis imputing the worst possible prognosis at 3 months (mRS score of 6) for patients with missing data obtained the same predictors of poor functional outcome.

Discussion

This is the largest observational study of ischemic stroke patients with UKO of symptoms and treated with intravenous alteplase in whom intravenous thrombolysis is currently off-label. We compared this subset of patients to those treated within the approved time window. Our main findings are that in stroke patients with UKO treated with systemic thrombolysis, the occurrence of SICH was comparable to patients treated within 4.5 hours of symptoms onset, but mortality and functional disability over the entire range of the mRS were higher.

Previous reports have shown that most patients with unknown time of symptoms onset without large infarct volume on baseline neuroimaging likely suffer the stroke shortly before awareness[14] or have good collateral blood flow.[15] Our results confirm that there is a higher likelihood of poor outcomes when there are early infarct signs in baseline CT, but not when there is a hyperdense artery sign when comparing patients with UKO to those treated within 4.5 hours.

The study was based on the population included in SITS-ISTR registry over a 5-year period. Patients with unknown stroke symptom onset represent only a small proportion (≈1%) of the total sample, which contrasts to the reported frequency of unknown time of symptoms onset in ≤25% of stroke patients.[1,2] This reflects the off-label situation of thrombolysis in stroke patients with UKO, where intravenous alteplase is only given in carefully selected individual cases.

Stroke patients with UKO had higher frequency of poor baseline prognostic factors such as higher NIHSS, older age, longer door-to-needle time, hyperdense artery sign, and early ischemic changes in baseline CT. These findings are in line with the fact that the off-label treatment with thrombolysis in stroke patients with UKO is rather considered in more severely affected stroke patients but not in mildly affected ones.

Multivariate analysis did not confirm the results of the univariate analysis on rate of functional dependency when adjusting for potential confounders. But, when the multivariate analysis was performed behind any cutoff point of the mRS, treatment in the approved <4.5 hours window was associated with a significant shift toward better outcomes across the entire spectrum of disability.

Clinical and radiological factors independently associated with higher dependency rates at 3 months in stroke patients with UKO in our study (age, NIHSS, glucose at baseline, and infarct in baseline CT) are similar to those described in studies with stroke patients with known time of symptoms onset.[16,17]

The higher proportion of patients selected with multimodal imaging in UKO group compared with within 4.5 hours

Table 2. Outcome Parameters in Patients Treated With Alteplase in ≤4.5 Hours From Symptoms Onset and in Those With Unknown Onset of Symptoms

	Onset ≤4.5 h (n=44 875)		Unknown Onset (n=502)			OR (95% CI)	
Outcome Measure	n/total	%	n/total	%	*P* Value	Unadjusted	Adjusted*
SICH (SITS-MOST)	694/43 104	1.6	13/474	2.7	0.052	1.72 (0.98–3.00)	1.09 (0.44–2.67)
SICH (ECASS)	1808/42 861	4.2	29/465	6.2	0.032	1.51 (1.03–2.20)	1.18 (0.66–2.14)
SICH (NINDS)	2659/42 991	6.2	42/466	9	0.012	1.50 (1.09–2.06)	1.17 (0.72–1.92)
Mortality, 3 mo	5644/33 454	16.9	80/364	22	0.010	1.38 (1.08–1.78)	1.58 (1.04–2.41)
Functional independency, 3 mo	18 416/32 741	56.2	168/359	46.8	<0.001	0.68 (0.55–0.84)	0.79 (0.56–1.10)

Crude and adjusted ORs in unknown onset of symptoms group compared with the ≤4.5 h group. CI indicates confidence interval; ECASS, European Cooperative Acute Stroke Study; NINDS, National Institute of Neurological Diseases and Stroke; OR, odds ratio; SICH, symptomatic intracerebral hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Adjusted for age, previous modified Rankin scale, door-to-needle time, baseline systolic blood pressure and glucose levels, magnetic resonance at baseline, hyperdense artery sign and infarct in baseline computed tomography, and National Institutes of Health Stroke Scale score prebolus.

Table 3. Adjusted OR for Functional Dependency or Death (mRS Score of ≥3) Predictors in Stroke Patients with Unknown Time of Symptoms Onset

	OR (95% CI)
Age, by 10 y increase	1.20 (1.13–1.28)
Baseline NIHSS, by 1 point increase	1.20 (1.13–1.28)
Baseline glucose, by mmol/L increase	1.26 (1.09–1.14)
Infarct in baseline CT (yes/no)	4.30 (1.71–10.80)

Adjusted for age, previous mRS, DTN time, baseline systolic BP and glucose levels, MR at baseline, hyperdense artery sign and infarct signs in baseline CT and NIHSS score before alteplase. OR>1 means higher probability of functional dependency or death (mRS score of ≥3). BP indicates blood pressure; CI, confidence interval; CT, computed tomography; DTN, door-to-needle; MR, magnetic resonance; mRS, modified Rankin Scale; NIHSS, National Institutes Health Stroke Scale; and OR, odds ratio.

group might explain similar rates of SICH in both groups. Retrospective studies of stroke patients with unknown time of symptom onset treated with intravenous alteplase using magnetic resonance imaging as surrogate marker of lesion age or perfusion CT and multimodal magnetic resonance imaging to identify tissue at risk have reported lower rate of SICH and higher frequency of good functional outcome when compared with those of treated patients selected by noncontrast CT.[18]

Our study has some limitations. First, its observational design and retrospective analysis. Second, given that the selection criteria to treat stroke patients with UKO with intravenous alteplase are neither defined nor registered in the SITS-ISTR, we cannot rule out that included patients were those with the most favorable benefit/risk ratio. Third, in 26% and 27.5%, 3-month follow-up data for survival status and outcome are lacking. However, a sensitivity analysis imputing the worst possible prognosis at 3 months for patients with missing data obtained the same results. Fourth, SITS-ISTR lacks the option to register whether UKO stroke is wake-up strokes or unwitnessed strokes and to register last time the patient was seen normal or the time when symptoms were discovered.

There are several ongoing randomized controlled trials (RCTs) of intravenous thrombolysis in patients with unknown stroke onset: 3 with alteplase at the standard dose versus placebo (ECASS-4, EXTEND [Extending the Time for Thrombolysis in Emergency Neurological Deficits], WAKE-UP [Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke]), 1 with alteplase at the dose of 0.6 mg/kg versus placebo (THAWS [Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg]), and 1 with tenecteplase at the dose of 0.4 mg/Kg (NORTEST [Study of Tenecteplase Versus Alteplase for Thrombolysis (Clot Dissolving) in Acute Ischemic Stroke]) versus alteplase at the standard dose. The results of the MR WITNESS trial (A Study of Intravenous Thrombolysis With Alteplase in MRI-Selected Patients) were recently presented at the International Stroke Conference 2016. This trial was an open-label, Phase II, single-arm, and multicenter safety study of intravenous alteplase in magnetic resonance imaging–selected patients. Eighty patients were included showing that intravenous alteplase is safe and feasible in selected patients treated within 4.5 hours after symptom discovery with response rates similar to other studies treating patients in a 3- to 4.5-hour window from last time seen well.

Endovascular treatment may also likely be an effective option in stroke patients with unknown time of symptom's onset with large artery occlusion because it is in stroke patients with known time of symptom's onset.[19–23] However, this indication is not supported by any data from RCT yet. Two RCTs of endovascular treatment compared with standard of care are now ongoing (DAWN [Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes] and POSITIVE [Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy]).

In conclusion, our study with a large cohort of stroke patients with UKO treated with intravenous alteplase suggests that the treatment in this group of patients is associated with higher mortality and poor functional outcome compared with treatment in the approved time window. Variables associated with poor outcome in this subgroup of patients are similar to those that have been described in known onset stroke patients. We cannot recommend routine treatment with intravenous alteplase in stroke patients with unknown time of symptom's onset, and we strongly recommend physicians to enroll these patients in the ongoing RCTs which results will provide definitive answer.

Disclosures

Dr Ahmed holds the position of vice chairman and senior researcher in SITS International, which receives unrestricted grant from Boehringer Ingelheim for the SITS-ISTR and SITS-MOST. The other authors report no conflicts.

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Intravenous Thrombolysis in Unknown-Onset Stroke: Results From the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry

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Stroke. 2017;48:720-725; originally published online February 7, 2017;
doi: 10.1161/STROKEAHA.116.014889
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTARY ONLINE APPENDIX

Intravenous thrombolysis in unknown-onset stroke. Results from the SITS-ISTR registry.

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Table I. Baseline characteristics of stroke patients with unknown time of symptoms onset according to outcome availability at three months.

	Missing outcome (n=143)		**Available outcome (n=359)**		
	No/total	Median (IQR) or %	No/total	Median (IQR) or %	p Value
Age, y	143/143	72 [61-81]	359/359	74 [65-82]	0.200
Gender (male)	70/143	49%	185/359	51.5%	0.602
Baseline mRS	109/143	0 [0-1]	344/359	0 [0-1]	0.818
Previous disability (mRS>2)	8/109	7.3%	23/344	6.7%	0.814
DTN time (minutes)	117/143	75 [50-105]	275/359	72 [50-101]	0.754
Hypertension	92/139	66.2%	256/357	71.7%	0.227
Diabetes mellitus	33/140	23.6%	68/356	19.1%	0.266
Hyperlipidemia	40/134	29.9%	119/353	33.7%	0.417
Smoker, current	29/131	22.1%	49/331	14.8%	0.058
Atrial fibrillation	33/139	23.7%	88/353	24.9%	0.783
Stroke (within 3m)	1/138	0.7%	7/353	2%	0.322
Stroke (no within 3m)	10/137	7.3%	36/353	10.2%	0.323
Congestive heart failure	12/138	8.7%	31/351	8.8%	0.962
Oral anticoagulants	3/127	2.4%	7/316	2.2%	0.925
Aspirin	39/134	29.1%	132/339	38.9%	0.045
Clopidogrel	7/134	5.2%	28/343	8.2%	0.268
NIHSS baseline score	133/143	11 [7-18]	347/359	13 [8-18]	0.208
BPsys pre-alteplase	128/143	150 [139-170]	316/359	157 [140-170]	0.587
BPdia pre-alteplase	128/143	81 [74-90]	314/359	85 [73-90]	0.813
Glucose (mmol/L)	120/143	7.10 [5.89-8.75]	312/359	6.72 [5.80-8.59]	0.453
MR at baseline	17/143	11.9%	62/359	17.3%	0.135
Infarct in baseline CT	60/137	43.8%	111/349	31.8%	0.013
Hyperdense artery sign in baseline CT	31/116	26.7%	100/308	32.5%	0.254

Abbreviations: mRS= modified Rankin Scale; DTN= door to needle; NIHSS= NIH Stroke Scale; BPdia= diastolic blood pressure; BPsys= systolic blood pressure; MR= magnetic resonance; CT= computed tomography.

Table II. Baseline characteristics of stroke patients with unknown time of symptoms onset according to functional independency at three months (Yes: mRS 0-2, No: mRS 3-6).

	Functional independency (mRS 0-2)				
	Yes (n=168)		No (n=191)		
	No/total	Median (IQR) or %	No/total	Median (IQR) or %	p Value
Age, y	168/168	70 [58-78]	191/191	78 [69-84]	<0.001
Gender (male)	93/168	55.4%	92/191	49.7%	0.174
Baseline mRS	167/168	0 [0-0]	177/191	0 [0-1]	0.001
Previous disability (mRS>2)	3/167	1.8%	20/177	11.3%	<0.001
DTN time (minutes)	137/168	75 [51-110]	138/191	70 [48-96]	0.315
Hypertension	114/168	67.9%	142/189	75.1%	0.128
Diabetes mellitus	27/167	16.2%	41/189	21.7%	0.186
Hyperlipidemia	53/165	34.5%	62/188	33%	0.765
Smoker, current	32/162	19.8%	17/169	10.1%	0.013
Atrial fibrillation	36/168	21.4%	52/185	28.1%	0.147
Stroke (within 3m)	1/168	0.6%	6/185	3.2%	0.075
Stroke (no within 3m)	18/168	10.7%	18/185	9.7%	0.760
Congestive heart failure	12/167	7.2%	19/184	10.3%	0.300
Oral anticoagulants	3/153	2%	4/163	2.5%	0.766
Aspirin	54/165	32.7%	78/174	44.8%	0.022
Clopidogrel	15/167	9%	13/176	7.4%	0.590
NIHSS baseline score	167/168	9 [6-14]	180/191	17 [12-21]	<0.001
BPsys pre-alteplase	141/168	157 [139-170]	149/191	158 [140-171]	0.475
BPdia pre-alteplase	141/168	85 [73-90]	149/191	85 [71-94]	0.691
Glucose (mmol/L)	141/168	6.50 [5.75-7.94]	149/191	7.06 [5.92-9.00]	0.047
MR at baseline	32/168	19%	30/191	15.7%	0.403
Infarct in baseline CT	38/165	23%	73/184	29.7%	0.001
Hyperdense artery sign in baseline CT	33/147	22.4%	67/161	41.6%	<0.001

Abbreviations: mRS= modified Rankin Scale; DTN= door to needle; NIHSS= NIH Stroke Scale; BPdia= diastolic blood pressure; BPsys= systolic blood pressure; MR= magnetic resonance; CT= computed tomography.