Thrombolysis in stroke patients aged 80 years and older: Swiss survey of IV thrombolysis

S. T. Engelter, M. Reichhart, L. Sekoranja, et al.

Neurology 2005;65;1795; Published online before print October 12, 2005;
DOI 10.1212/01.wnl.0000183702.04080.27

HIGH LIGHT
CME

Thrombolysis in stroke patients aged 80 years and older: Swiss survey of IV thrombolysis

Abstract—This databank-based, multicenter study compared all stroke patients with IV tissue plasminogen activator aged ≥80 years (n = 38) and those <80 years old (n = 287). Three-month mortality was higher in older patients. Favorable outcome (modified Rankin scale ≤1) and intracranial hemorrhage (asymptomatic/symptomatic/fatal) were similarly frequent in both groups. Logistic regression showed that stroke severity, time to thrombolysis, glucose level, and history of coronary heart disease independently predicted outcome, whereas age did not.

NEUROLOGY 2005;65:1795–1798

S.T. Engelter, MD; M. Reichhart, MD; L. Sekoranja, MD; D. Georgiadis, MD; A. Baumann, MD; B. Weder, MD; F. Müller, MD; R. Lüthy, MD; M. Arnold, MD; P. Michel, MD; H.P. Mattle, MD; B. Tettenborn, MD; H.J. Hungerbühler, MD; R.W. Baumgartner, MD; R. Sztajzel, MD; J. Bogousslavsky, MD; and P.A. Lyrer, MD

Very elderly stroke patients were either excluded or underrepresented in the randomized controlled trials (RCT) of IV recombinant tissue plasminogen activator (rtPA).[1,2] In rtPA cohorts, advancing age is associated with increased in-hospital mortality[3] and higher risk of intracranial hemorrhage (ICH). However, older stroke patients are less likely to recover than younger ones also without rtPA treatment.[4] Until new RCT results are available, data from cohort studies may be useful to guide clinicians in their decision whether IV rtPA should be used in individual stroke patients ≥80 years old.

Methods. In a Swiss databank-based, multicenter cohort study, all rtPA-treated stroke patients ≥80 years old were compared with their younger counterparts. Outcome measures were favorable (modified Rankin scale [mRS] ≤1) vs poor outcome (mRS ≥2), death (all causes) and ICH (asymptomatic/symptomatic/fatal by the National Institute of Neurological Disorders and Stroke [NINDS] trial definition).[1] Furthermore, we assessed the importance of the variable age. All participating centers (five university, four community hospitals) used rtPA according to the NINDS protocol with minor modifications. All but one center excluded patients with early CT infarcts signs greater than one-third of the middle cerebral artery (MCA) territory. Patients with either mild (NIH Stroke Scale Score [NIHSS] <6 or one center <4) or severe impairment (NIHSS >20 or one center >25) were excluded. Neither center applied an upper age limit for rtPA treatment, because in Switzerland rtPA is licensed for stroke without age restrictions. For very elderly patients, no additional criteria for rtPA use were present. Each center's treating stroke physician decided whether an individual stroke patient ≥80 years of age should receive rtPA. Eight of nine centers thrombolyzed at least one patient ≥80 years old.

All centers' rtPA data were collected in a standardized way between April 1998 and March 2003. Consensus was reached to obtain baseline and outcome variables according to specified definitions or classifications as outlined in the supplemental Methods section (available on the *Neurology* Web site at www.neurology.org). After data pooling, comparisons between both age groups were done using t-test, Mann-Whitney *U* test, Fisher's Exact Test, and Bonferroni corrections for multiple testing where appropriate. The importance of the variable age was estimated with univariate analyses of variables potentially predicting outcome.[5] All variables with $p < 0.2$ in univariate analyses[5] were entered into stepwise logistic regression analysis.

Results. *Study population.* Among 325 rtPA-treated patients, 38 (12%) were ≥80 years old and 287 (88%) patients were <80 years old. In the younger group, two-thirds (193/287) were male. In the older group, only 37% (14/38) were men ($p < 0.001$). Systolic blood pressure was higher, and cardioembolic stroke etiology and atrial fibrillation were more frequent among older than among younger patients ($p < 0.001$; table 1).

Outcome. After 3 months, 32% (12/38) of the elderly vs 12% (35/287) of the younger patients had died ($p < 0.01$). The rate of ICH (asymptomatic/symptomatic/fatal) did not differ significantly between older (14%/13%/5%) and younger (9%/8%/3%) patients. Favorable outcome occurred in 29% of the elderly and in 37% of the younger patients

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the December 13 issue to find the title link for this article.

This article was previously published in electronic format as an Expedited E-Pub on October 12, 2005, at www.neurology.org.

From the Stroke Units and Neurological Clinics/Departments of Neurology, University Hospital Basel (Drs. Engelter and Lyrer), University Hospital Lausanne (Drs. Reichhart, Michel, and Bogousslavsky), University Hospital Bern (Drs. Arnold and Mattle), University Hospital Geneva (Drs. Sekoranja and Sztajzel), University Hospital Zurich (Drs. Georgiadis and Baumgartner), Cantonal Hospital Aarau (Drs. Baumann and Hungerbühler), Cantonal Hospital St. Gallen (Drs. Weder and Tettenborn), Cantonal Hospital Thurgau Muensterlingen (Dr. Müller), and Department of Internal Medicine, Triemli Hospital Zurich (Dr. Lüthy), Switzerland.

Disclosure: The authors report no conflicts of interest.

Received March 18, 2005. Accepted in final form August 17, 2005.

Address correspondence and reprint requests to Dr. S.T. Engelter, Neurological Clinic and Stroke Unit, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland; e-mail: sengelter@uhbs.ch

Editorial, see page 1690

Table 1 *Clinical characteristics of recombinant tissue plasminogen activator-treated stroke patients ≥80 vs <80 years old*

Clinical characteristics	Patients ≥80 y	Patients <80 y	*p* Value
n	38	287	
Demographic data			
Age			
Mean, y ± SD	84 ± 3.1	63 ± 12.4	
Median (range)	84 (80–92)	14 (23–79)	
Male sex, n (%)	14 (37)	193 (67)	<0.001
Independence prior to stroke, %	95	98	
Stroke severity			
NIHSS, mean ± SD	14.1 ± 5.4	13.5 ± 5.2	0.56
Median (range)	14 (5–23)	14 (2–35)	
Laboratory findings prior to lysis, mean ± SD			
Platelet count/1,000/ccm	245.3 ± 90.4	240.7 ± 68.3	0.78
International normalized ratio	1.07 ± 0.19	1.01 ± 0.09	0.12
Glucose level, mmol/L	7.3 ± 1.6	7.5 ± 5.6	0.81
C-reactive protein, mmol/L	8.7 ± 11.0	12.5 ± 23.0	0.46
Vital signs prior to lysis, mean ± SD			
Systolic blood pressure, mm Hg	171 ± 24.5	153 ± 24.6	<0.001
Diastolic blood pressure, mm Hg	96 ± 16.5	89 ± 15.6	0.11
Temperature, ºC	36.7 ± 0.8	36.6 ± 0.7	0.51
Time to lysis, minutes, mean ± SD	155 ± 35.5	158 ± 35.3	0.60
Cardioembolic stroke etiology, %	79	33	<0.001*
Prior use of antithrombotics,† %	53	32	0.16*
Protocol violations, all causes,† %	8	22	0.43*
Vascular risk factors, %			
Hypertension	69	54	0.08
Atrial fibrillation	72	19	<0.001*
Smoking (current)†	11	39	0.26*
Hypercholesterolemia	36	34	0.88
Diabetes mellitus	18	15	0.80
Coronary heart disease	31	22	0.20
Prior stroke	17	8	0.11

Missing data are excluded from analysis.

* After Bonferroni correction.

† Prior use of antithrombotic agents was more frequent, whereas protocol violations and smoking were less common among elderly patients. However, after Bonferroni correction for multiple testing, these differences were no longer significant.

($p > 0.1$). Among patients who survived 3 months, the rate of favorable outcome was 42% (11/26) for older and 43% (107/252) for younger patients (table 2).

Importance of the variable age. Univariate analyses showed that age as dichotomized categorical variable (≥80 vs <80 years) did not predict outcome. Age as continuous variable, NIHSS, time to lysis, glucose level, history of coronary heart disease, hypertension, and atrial fibrillation were factors predicting poor outcome (table 3). Stepwise logistic regression clarified that after controlling for other variables, age as continuous variable has no more prognostic importance (table 3).

Discussion. This Swiss multicenter databank-based study showed the following findings: stroke patients ≥80 years receiving rtPA bear a higher mortality risk than younger patients; the likelihood of favorable outcome and the risk for symptomatic ICH were similar in both groups; and age was not an independent predictor of outcome.

Nearly one-third of IV rtPA-treated stroke pa-

Table 2 *Three-month outcome of recombinant tissue plasminogen activator-treated stroke patients ≥80 vs <80 years old*

Outcome variables after 3 mo	Patients ≥80 y	Patients <80 y	*p* Value
n	38	287	
Death from all causes, n (%)	12 (32)	35 (12)	0.005
Favorable outcome, n (%)*			
Among all patients	11 (29)	107 (37)	0.37
Among survivors	11/26 (42)	107/252 (43)	0.99
Intracranial hemorrhage, n (%)			
All	10 (26)	49 (17)	0.18
Symptomatic†	5 (13)	24 (8)	0.36
Fatal‡	2 (5)	9 (3)	0.62
Asymptomatic	5 (13)	25 (9)	0.37

* Modified Rankin scale ≤1.

† Symptomatic intracranial hemorrhage was defined as any CT/MRI-documented hemorrhage that was temporally related to any deterioration in the patient's clinical condition.[1]

‡ Fatal hemorrhage was defined as any symptomatic intracranial hemorrhage leading to death.

Table 3 *Variables predicting poor outcome after 3 months by univariate analyses*

Univariate analyses variables	Favorable outcome	Poor outcome	*p* Value
n	118	207	
Demographic data			
Mean age, y ± SD	62 ± 14.6	67 ± 12.4	0.001
Male, %	41	34	0.23
Stroke severity,* mean NIHSS ± SD	11.2 ± 5.3	14.9 ± 4.7	<0.001
Laboratory findings prior to lysis, mean ± SD			
Glucose level, mmol/L	6.5 ± 1.7	7.4 ± 2.6	0.001
C-reactive protein, mmol/L	8.9 ± 18.0	13.8 ± 23.9	0.08
Vital signs prior to lysis, mean ± SD			
Systolic blood pressure, mm Hg	153 ± 26.3	156 ± 24.7	0.4
Diastolic blood pressure, mm Hg	90 ± 16.2	89 ± 15.2	0.9
Temperature, ºC	36.7 ± 0.8	36.5 ± 0.7	0.2
Time to lysis, minutes, mean ± SD	152 ± 38.8	160 ± 32.9	0.04
Protocol violations, all causes, %	19	21	0.6
Time to lysis >3 h, %	9	12	
Blood pressure >185/110 mm Hg, %	9	8	
Other	1	1	
Cardioembolic stroke etiology, %	36	40	0.6
Antithrombotics prior to lysis, %	27	38	0.09
Vascular risk factors, %			
Hypertension	46	61	0.015
Atrial fibrillation	16	31	0.008
Smoking (current)	34	24	0.08
Hypercholesterolemia	38	34	0.5
Diabetes mellitus	14	16	0.7
Coronary heart disease	14	28	0.006
Prior stroke	8	9	0.8
Stepwise regression analyses of variables predicting poor outcome†	***p* Value**	**Odds ratio**	**95% CI**
NIH Stroke Scale score (each point)	<0.001	1.16	1.09–1.24
History of coronary heart disease	0.002	3.52	1.55–8.22
Glucose level, mmol/L	0.002	1.29	1.07–1.55
Time to thrombolysis (each 10 min)	0.006	1.14	1.04–1.25
Age (each y)	0.17		

Favorable outcome is defined as modified Rankin scale score ≤1. All other scores including 6 (i.e., death) indicate poor outcome. Missing data are excluded from analysis.

* NIH Stroke Scale score prior to thrombolysis.
† All variables with $p < 0.2$ in univariate analysis were included.

tients aged ≥ 80 years compared to only one of eight of the younger counterparts had died within 3 months. For younger patients, the mortality rate of the current study (12%) was lower than that of the 3-hour cohorts of the ECASS trial (27%)[6] and the ATLANTIS trial (17%),[7] respectively, which both had excluded patients above age 80 years. For patients ≥80 years, the current study recorded virtually the same mortality rate (32%) as a recent case series on the same age group (33%).[8] Thus, the case fatality of rtPA-treated stroke patients is higher in patients aged ≥80 years than in younger ones. However, the same is true for elderly stroke patients without rtPA treatment and a case fatality of 45% vs 21%.[9]

Despite higher mortality, 3 of 10 patients aged ≥80 years had a favorable 3-month outcome, which is more than in one series (20%)[8] but less compared to another study (37%).[10] Differences in baseline variables or length of follow-up may account for the wide range between the aforementioned studies.

Among survivors, the rate of favorable outcome was virtually the same for older (42%) and younger patients (43%).

The frequency of symptomatic ICH among rtPA-treated patients ≥80 years old (13%) was higher in our study than reported by others (3% to 10%),[10,8] whereas fatal ICHs were similarly frequent in all three studies (3% to 5%). Differences in the definition of symptomatic ICH (ECASS vs NINDS criteria) may explain these discrepancies. More importantly, the risk of ICH (asymptomatic/symptomatic/fatal) was similar in both patient groups, although the elder patients exhibit features that predispose to hemorrhagic transformation including higher systolic blood pressure and cardioembolic stroke etiology.

Advancing age was not an independent predictor of poor outcome; neither as dichotomized categorical variable (≥80 vs < 80 years) nor as continuous variable. Independent predictors of poor outcome were stroke severity, time to thrombolysis, glucose level and history of coronary heart disease. One point on the NIHSS had the same prognostic importance as 10 minutes treatment delay.

As strength, our rtPA study combined a comparative analysis of older vs younger stroke patients with the evaluation of the predictive importance of the variable age among several variables potentially predicting outcome.

Our study has the following limitations. First, our registry applied exclusion criteria, which were not used in the NINDS trial,[1] including early CT-infarct signs greater than one-third of the MCA territory and NIHSS limits. This approach limits the comparability with the NINDS data concerning outcome. However, as these criteria are effective for both age groups, the comparisons between older and younger patients are unlikely to be jeopardized.

Second, we applied the NINDS definition for symptomatic ICH.[1] Because even mild hemorrhagic transformation in progressive infarction accounts for symptomatic ICH, the NINDS definition bears the risk to overstate the rate of symptomatic ICH. In turn, our approach enables the comparability with NINDS data on hemorrhages.

Third, 12% of our rtPA-treated stroke patients were ≥80 years old, although this age group is reported to account for 30% of strokes.[9] This discrepancy suggests a selection bias. Despite the absence of specific exclusion criteria for patients ≥80 years of age, it is possible that unwillingly only those with the best prestroke health received rtPA. The NINDS trial with 13% (42/333)[1,2] and the US rtPA Stroke Survey with 16% (30/189)[10] reported similarly low proportions for very elderly patients.

Fourth, our results must not be interpreted as proof of efficacy of rtPA among stroke patients aged ≥80 years, because we did no RCT.

Acknowledgment

The authors thank Susanna Papa for language assistance and Andreas Schötzau for statistical advice.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–1587.
2. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2003;3:CD000213.
3. Heuschmann PU, Kolominsky-Rabas PL, Roether J, et al. Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. JAMA 2004;292:1831–1838.
4. Kammersgaard LP, Jorgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS. Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. Age Ageing 2004;33:149–154.
5. Demchuk AM, Tanne D, Hill MD, et al. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology 2001;57:474–480.
6. Steiner T, Bluhmki E, Kaste M, et al. The ECASS 3-hour cohort. Secondary analysis of ECASS data by time stratification. ECASS Study Group European Cooperative Acute Stroke Study Cerebrovasc Dis 1998;8:198–203.
7. Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. Stroke 2002;33:493–495.
8. Simon JE, Sandler DL, Pexman JHW, Hill MD, Buchan AM. Is intravenous recombinant tissue plasminogen activator (rt-PA) safe for use in patients over 80 years old with acute ischaemic stroke? The Calgary experience. Age Ageing 2004;33:143–149.
9. Di Carlo A, Lamassa M, Pracucci G, et al. Stroke in the very old: clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. Stroke 1999;30:2313–2319.
10. Tanne D, Gorman MJ, Bates VE, et al. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older : the tPA stroke survey experience. Stroke 2000;31:370–375.