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Association of time on outcome after intravenous thrombolysis in the elderly in a telestroke network

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Abstract

Background: Recent studies showed that the safety and benefit of early intravenous (IV) thrombolysis on favourable outcomes in acute ischemic stroke are also seen in the elderly. Furthermore, it has shown that age increases times for pre- and in-hospital procedures. We aimed to assess the applicability of these findings to telestroke.

Methods: We retrospectively analysed 542 of 1659 screened consecutive stroke patients treated with IV thrombolysis in our telestroke network in East-Saxony, Germany from 2007 to 2012. Outcome data were symptomatic intracranial hemorrhage (sICH) by ECASS-2-criteria, survival at discharge and favourable outcome, defined as a modified Rankin scale (mRS) of 0–2 at discharge.

Results: Thirty-three percent of patients were older than 80 years (elderly). Being elderly was associated with higher risk of sICH ($p = 0.003$), less favourable outcomes ($p = 0.02$) and higher mortality ($p = 0.01$). Using logistic regression analysis, earlier onset-to-treatment time was associated with favourable outcomes in not elderly patients (adjusted odds ratio (OR) 1.18; 95% CI 1.03–1.34; $p = 0.01$), and tended to be associated with favourable outcomes (adjusted OR 1.13; 95% CI 0.92–1.38; $p = 0.25$) and less sICH (adjusted OR 0.88; 95% CI 0.76–1.03; $p = 0.11$) in elderly patients. Age caused no significant differences in onset-to-door-time ($p = 0.25$), door-to-treatment-time ($p = 0.06$) or onset-to-treatment-time ($p = 0.29$).

Conclusion: Treatment time seems to be critical for favourable outcome after acute ischemic stroke in the elderly. Age is not associated with longer delivery times for thrombolysis in telestroke.

Keywords

Telemedicine, thrombolysis, ischemic stroke, acute stroke therapy, epidemiology, stroke facilities

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Introduction

Although stroke is more common in old age, elderly patients were excluded or underrepresented in the majority of acute revascularization studies. Therefore, in the European Union and several other countries intravenous (IV) thrombolysis is restricted to patients <80 years. Despite patients >80 years of age having a lower probability of gaining functional outcome and a higher mortality rate due to higher stroke severity, concurrent medical problems, prestroke disability, and less-aggressive management there is still a benefit for those patients to be treated within 3.5 hours and even within 4.5 hours of stroke onset.[1–3]

The quality of treatment, complication rates, and short and long term outcomes are similar for acute stroke patients treated with IV tissue plasminogen activator (tPA) via a telemedicine consultation at local hospitals and those treated in specialized stroke centres.[4–13]

We sought to assess the safety and benefits of early thrombolysis in the elderly (>80) within a telestroke network. Moreover, we wanted to evaluate whether age is associated with longer delivery and treatment times in a telestroke network compared to younger patients (<80 years) since IV thrombolysis is not administered routinely to elderly patients with acute ischemic stroke in rural settings. An observational study found that age affected increasing times for pre- and in-hospital procedures.[14]

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Methods

Stroke Eastern Saxony Network

The Stroke Eastern Saxony Network (SOS-NET) was established as a telemedical stroke network by the Dresden University Stroke Center (DUSC) in 2007 and provides stroke care for 14 smaller community hospitals. Stroke neurologists from the DUSC are available 24/7. Teleconsultations consisted of the patient history, a structured clinical assessment using the National Institutes of Health Stroke Scale (NIHSS) score and a standardized evaluation of the transferred CT scans using the Alberta Stroke Program Early CT Score (ASPECTS).[6,7]

Patients

We performed a retrospective cohort study. We included all consecutive SOS-NET patients who had clinically suspected acute ischemic stroke and received IV thrombolysis after telemedical consultation during a five year period (07/2007 to 07/2012). Patients with primary diagnoses other than clinical suspected acute ischemic stroke (e.g. primary intracerebral hemorrhage (ICH), intracranial tumour, epileptic seizure, transient ischemic attack, and psychological disorders) were excluded from the study. We also excluded patients who did not receive IV thrombolysis after initial recommendation by the stroke neurologist and patients with missing documentation of the outcome measures.

Clinical data were prospectively collected with SOS-NET quality assurance forms, which were completed by the affiliated hospitals according to the German Stroke Registries Study Group guidelines including occurrence of symptomatic intracerebral hemorrhage (sICH) and modified Rankin scale (mRS) score at discharge.[15] Missing data and additional data with clinical relevance (blood pressure before IV thrombolysis, baseline glucose levels, time of symptom onset and time of IV thrombolysis) were retrospectively derived from in-patient records or were imputed using available data.

This study was approved by the Dresden University of Technology ethics committee (EK293082011).

Outcome measures

The clinical outcome measure was sICH on follow-up images defined by the European cooperative acute stroke study II (ECASS-II) criteria (hemorrhagic transformation of infarction causing a neurological deterioration with an increase of NIHSS score by more than three points) as documented in quality assurance forms.[16] Follow-up images were performed within 48 hours of thrombolysis. Fatal sICH were defined as sICH resulting in mRS score of 6 at discharge. An additional outcome measure was favourable functional outcome at discharge defined as modified mRS scores of 0–2 as well as survival at discharge.

Statistical analysis

Measures of central tendency and measures of variability were used according to standard descriptive statistics. We imputed 38 missing values for onset-to-needle-time and 44 missing values for systolic blood pressure with the median values of the available data. Fifty-six missing values for baseline glucose levels were imputed with the mean value of the available data.

We used a chi-squared test to demonstrate the association between the dichotomized age and the outcome measures. We finally developed multivariable regression models to test whether there are clinical predictors for the association between dichotomized age and the outcome measures. The model development was based upon the step-wise manual elimination of variables using bivariate analysis. For the final parsimonious model, we included only variables that were relevant *a priori* (baseline systolic blood pressure and glucose levels, baseline NIHSS score and categorical (30 minute periods) onset-to-treatment time) and were predictive of the outcome in bivariate analysis ($p < 0.2$).

The scatter plot of the frequency of favourable outcome and onset-to-treatment time (categorical, 30 minutes periods) was completed with a logarithmic trend line because the rate of change in frequencies of favourable functional outcome decreased quickly and then levelled out. We calculated *R*-squared value (coefficient of determination). For the benefit of early thrombolysis we performed a meta-analysis with the results from logistic regression analysis stratified by age and created a forest plot using the step-by-step guide developed by Neyeloff et al.[17]

Statistical analysis was performed using Microsoft Excel.

Results

Patient population

Among 3172 teleconsultations which were performed from 07/2007 to 07/2012, 1513 patients had non-ischemic diagnoses. Among 1659 patients with clinically suspected ischemic stroke, stroke neurologists recommended IV thrombolysis in 688 patients (41.5%) and 657 patients (39.6%) finally received IV thrombolysis.

Of the 657 patients who received IV thrombolytics, we excluded 115 patients as the outcome measures (sICH, mRS) were not documented in the quality assurance forms or the in-patients records. We therefore included 542 patients with complete clinical data into the analysis (Figure 1). The clinical baseline characteristics are summarized in Table 1.

The thrombolysis rate of the elderly patients was higher than those of the younger patients (180/454 patients (39.6%) vs. 362/1205 patients (30%); p-value <0.01).

Thirty-three of 542 patients (6.1%) suffered sICH. Overall, at discharge, 179 patients (33%) had a favourable

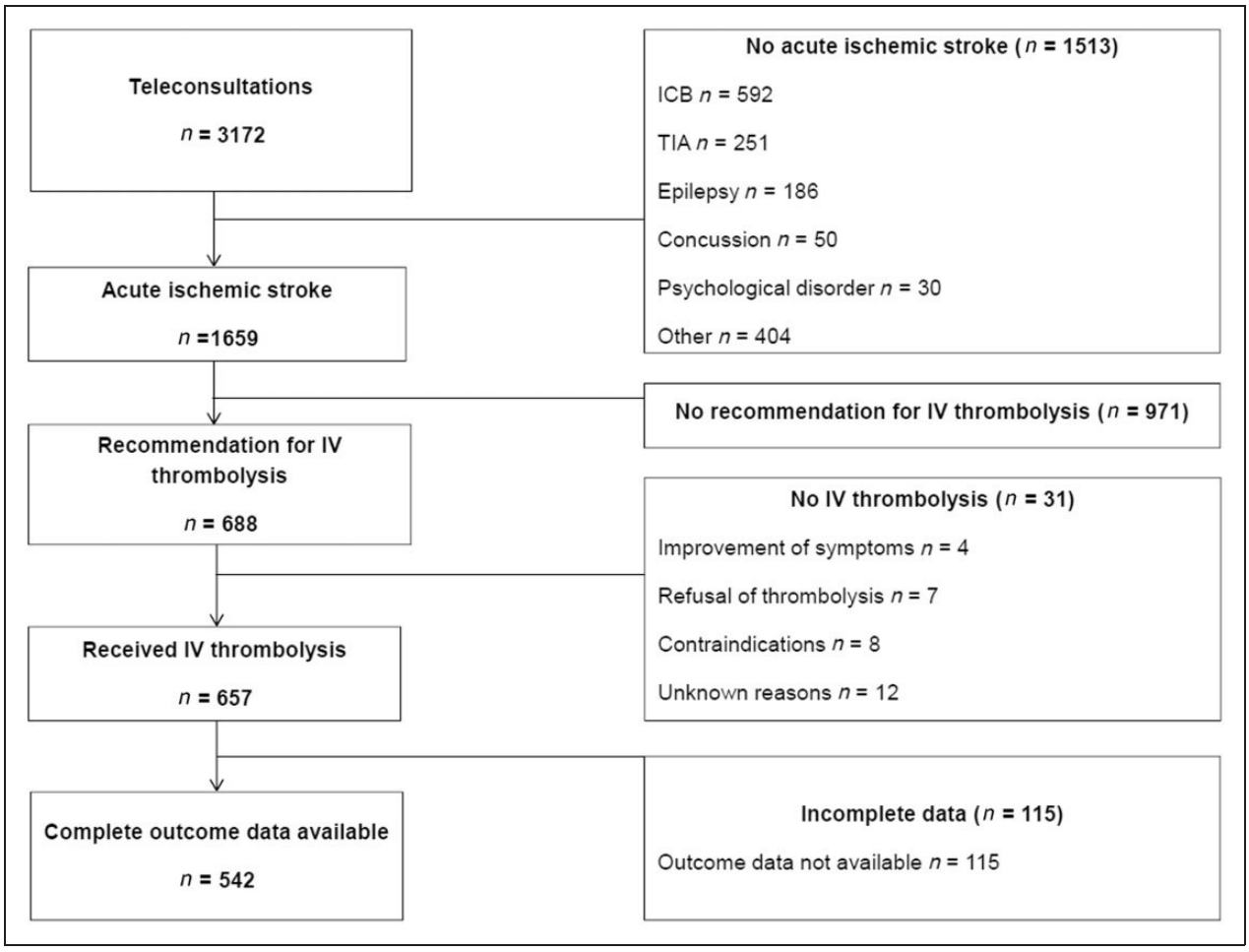

Figure 1. Flowchart of study population.
IV: intravenous; ICB: Intracranial Bleed; TIA: Transitoric Ischemic Attack.

Table 1. Clinical baseline characteristics.

	Not elderly (⩽80 years)	Elderly (>80 years)	*P*-value
Total, *n*	362	180	
Female, *n* (%)	165 (45.6)	126 (70.0)	
Age, years, median (IQR) [mean; SD]	72 (5) [69,2; 9,9]	84 (5) [84,6; 3,3]	
NIHSS score, median (IQR)	11 (11)	14 (10)	<0.01
Systolic blood pressure, mmHg, median (IQR)	155 (5)	155 (14)	0.16
Glucose level, mmol/l, mean (SD)	7.57 (2.32)	7.52 (2.43)	0.84*
Onset-to-door-time, minutes, median (IQR)	65 (65)	73 (37.75)	0.02*
Door-to-needle-time, minutes, median (IQR)	70 (38.5)	73 (37.75)	0.47*
Onset-to-needle-time, minutes, median (IQR)	145 (41.25)	145 (47)	0.34*
Cardiovascular risk factors			
Hypertension, *n* (%)	312 (86.2)	163 (90.6)	0.15°
Hyperlipidaemia, *n* (%)	205 (56.6)	75 (41.7)	<0.01°
Diabetes, *n* (%)	172 (47.5)	77 (42.8)	0.30°
Atrial fibrillation, *n* (%)	144 (39.8)	110 (61.1)	<0.01°
Carotid stenosis, *n* (%)	63 (17.4)	25 (13.9)	0.30°
Previous stroke, *n* (%)	68 (18.8)	41 (22.8)	0.27°

P values are Mann–Whitney *U* test, student's *t*-test* (2-tailed) or chi-squared test°.
NIHSS: National Institute of Health Stroke Scale; IQR: interquartile range; mmHg: millimeters of mercury; mmol/l: millimoles per liter.

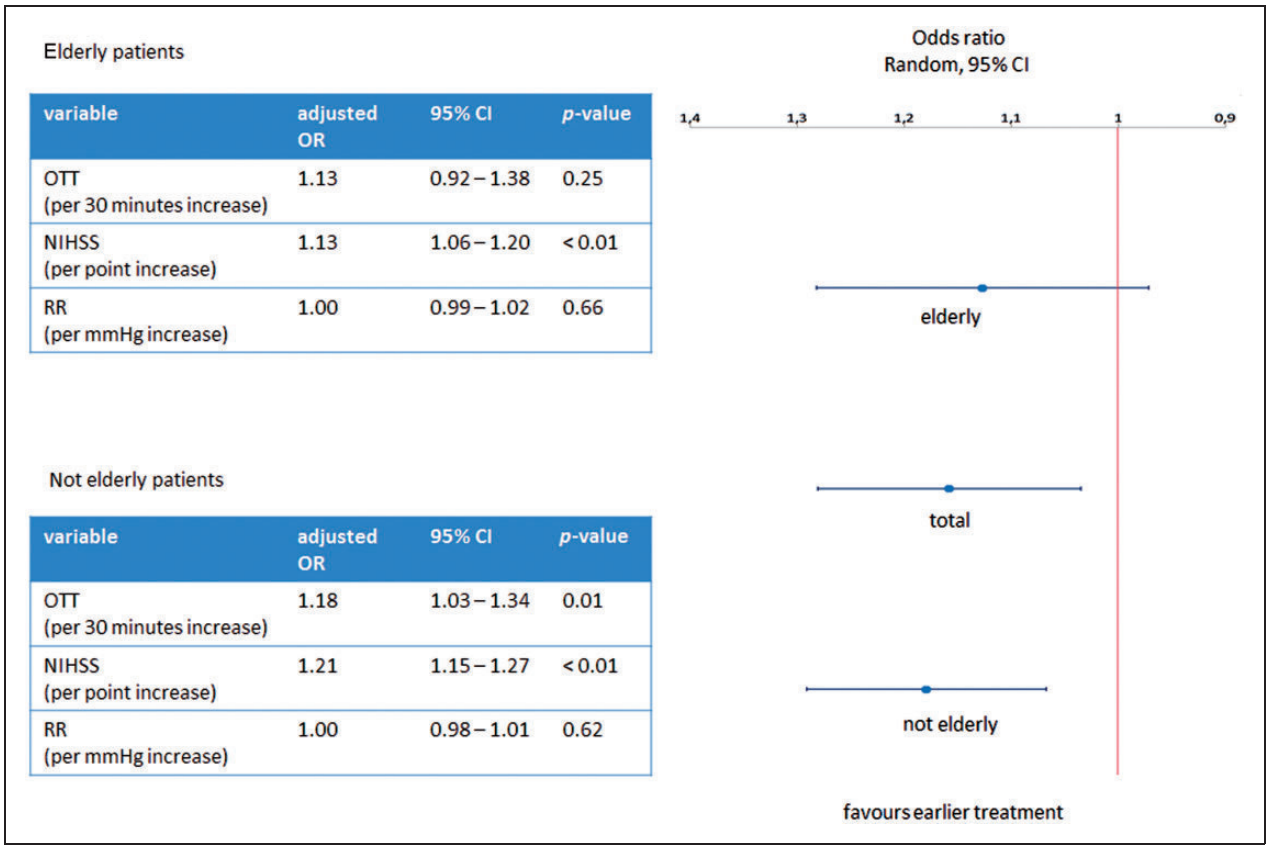

Figure 2. Forest plot of odds ratio for functional outcome depending on onset-to-treatment time, by age.
Derived from a logistic regression analysis stratified by age, which enabled separate estimation of odds ratio after adjustment for two other baseline characteristics (NIHSS, baseline blood pressure).
NIHSS: National Institute of Health Stroke Scale; OTT: Onset-to-Treatment Time; RR: Riva-Rocci; mmHg: millimeter of mercury.

functional outcome (mRS scores 0–2), 262 patients (48.3%) had an unfavourable functional outcome (mRS scores 3–5) and 101 (18.6%) patients had died.

The final clinical diagnoses were cerebral ischemic events in 539 patients (99.4%) and stroke mimics in three patients (0.6%). None of the patients with stroke mimics had sICH.

Elderly and non-elderly patient had significantly different stroke baseline severity (median 14 interquartile range (IQR) 10) vs. median 11 (IQR 11); p-value <0.01), rate of hyperlipidemia (75/180 patients (41.7%) vs. 205/362 patients (56.6%); p-value <0.01) and atrial fibrillation (110/180 patients (61.1%) vs. 144/362 (39.8%); p-value <0.01).

Association of age and outcome measures

The sICH rate was higher in the elderly (19/180 patients (10.6%) vs. 14/362 patients (3.9%), respectively; p-value = 0.003). Being elderly was also associated with lower frequency of favourable functional outcome (47/180 patients (26.1%) vs. 132/362 patients (36.5%); p-value = 0.02) and lower survival rate at discharge (136/180 patients (75.6%) vs. 305/362 patients (84.3%); p-value = 0.01) compared to their younger counterparts. In logistic regression analysis adjusted for NIHSS and baseline blood pressure, elderly patients were 2.6 times more likely to suffer sICH (adjusted OR 2.58; 95% confidence interval (CI) 1.25–5.33; p-value = 0.01). The frequency of fatal sICH was similar in both the elderly and not elderly relative to the sICH occurrences in each group (12/19 patients (63.2%) vs. 9/14 patients (64.3%); p-value = 0.95).

Effect of treatment delay

The majority of elderly and non-elderly patients were treated within 180 minutes (142/180 patients (78.9%) vs. 292/362 patients (80.7%); p-value = 0.63).

Using logistic regression analysis, earlier onset-to-treatment (per 30 minute increase) tended to be associated with favourable outcome (adjusted OR 1.13; 95% CI 0.92–1.38; $p = 0.25$) in elderly patients. Detailed results and the forest plot are displayed in Figure 2.

The logarithmic trend lines (Figure 3) fitted for the plotted frequency of favourable outcome and onset-to-treatment time were similar but showed a stronger decrease for elderly patients ($y = -0.106 \ln(x) + 0.7436$; R-squared value = 0.24) compared to not elderly patients ($y = -0.083 \ln(x) + 0.8145$; R-squared value = 0.23).

Additionally, elderly patients tended to have fewer sICH when treated earlier (adjusted OR 0.88; 95% CI 0.76–1.03; $p = 0.11$).

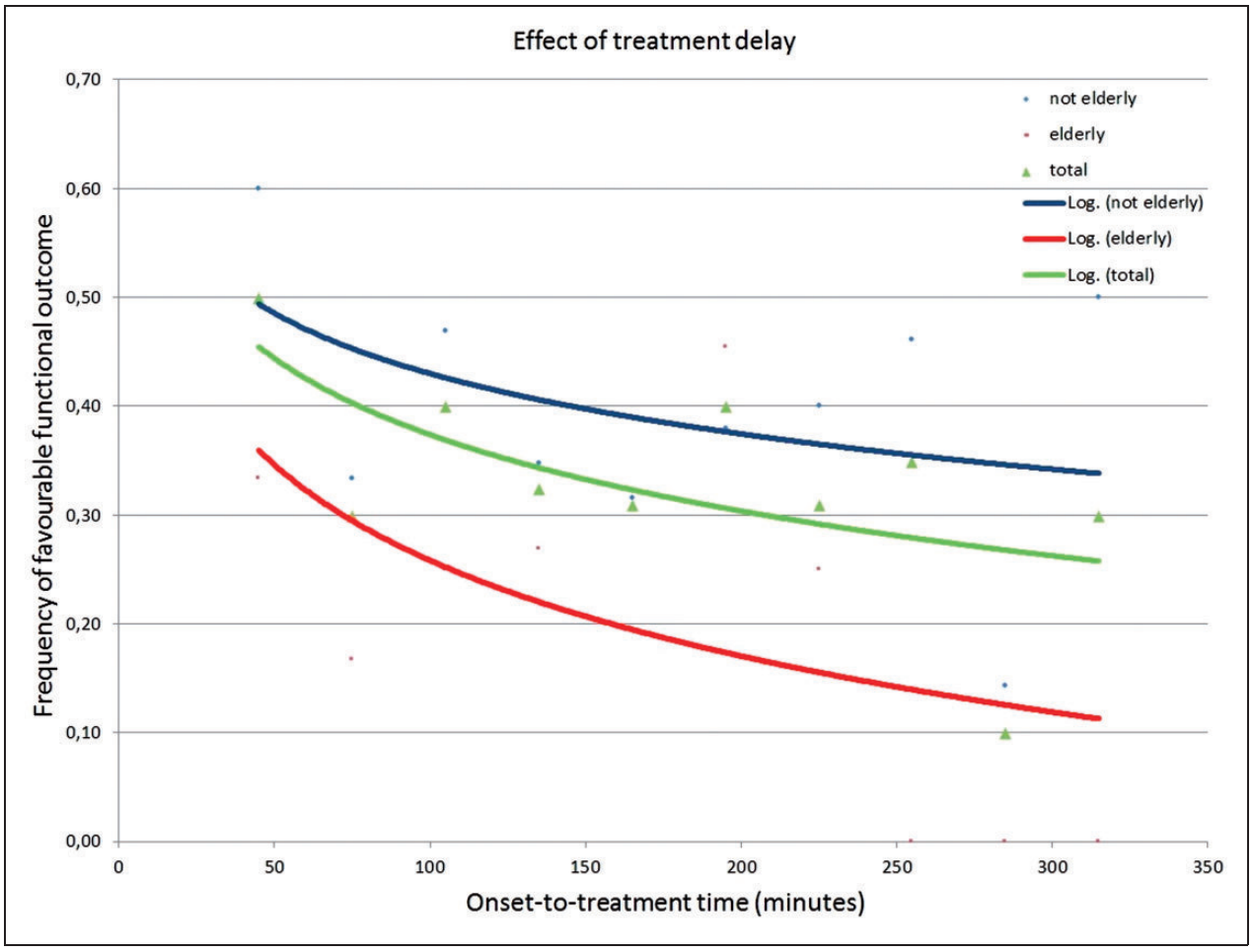

Figure 3. Effect of treatment delay.
Scatter plot of frequency of favourable outcome per categorical onset-to-treatment time (30 minute periods). Blue dots are for not elderly patients, red dots are for elderly patients. Logarithmic trend lines indicate lines of best fit.

There was no significant difference in either onset-to-door-time (p-value = 0.25), door-to-treatment-time (p-value = 0.06) or onset-to-treatment-time (p-value = 0.29) between elderly and not elderly patients.

Discussion

Telemedical thrombolysis itself seems to be safe, with an overall sICH rate in our study (6.1%) which was similar to other stroke thrombolysis trials.[18] In our study 10.6% of elderly patients suffered sICH, whereas other studies reported sICH rates ranging from 2.4% to 13%, comparable or higher than their younger counterparts.[19,20] With every 30 minutes saved in onset-to-treatment time, elderly people are 0.88 times less likely to suffer sICH.

However, the higher bleeding rate may not be responsible for the higher mortality rate in elderly patients since the frequency of fatal sICH was similar in both groups. Death in acute stroke patients is mostly caused by pneumonia and other complications of stroke. Greater stroke severity, increased prestroke dependency, and frequency of atrial fibrillation and heart failure are factors that contribute to the increased mortality in those older than 80 years.[21]

Our data indicate that the benefit of early thrombolysis in elderly patients on functional outcome also applies to telestroke networks. Although the association between onset-to-treatment time and favourable outcome was not significant, the odds ratio was similar to the one calculated for not elderly patients. The findings might be relevant to facilitate thrombolysis rates in neurologically underserved areas, especially since the predicted ageing of our population will lead to roughly 400 million persons worldwide aged 80 years or over in the year 2050.[22] Regional stroke care systems should accelerate treatment as much as possible.

A previous observational study reported delayed treatment times for patients aged 80 years and over.[14] In our study, however, the majority of patients, both elderly and not elderly, were treated within less than 180 minutes from stroke onset. There was no significant difference in treatment times for pre- and in-hospital procedures for elderly and not elderly patients. This finding might be a result of the continuous cooperation between hospitals within a telestroke network and could be also relevant for the

organization of regional stroke care in neurologically underserved areas.

The thrombolysis rate was even higher for elderly patients compared to their younger counterparts. This might due to a selection bias in the community hospitals. Physicians tended to present younger patients despite a time window >4.5 hours and with minimal stroke severity whereas elderly patients were more often presented when thrombolysis seemed likely, thus leading to more frequent recommendation of thrombolysis in the elderly. The increased stroke severity in the elderly could be a result of the high rate of atrial fibrillation causing proximal stenosis of the cerebral arteries with greater infarct volume in the elderly. We have no data about whether atrial fibrillation was known before hospitalization and patients were insufficiently anticoagulated or if the diagnosis was newly made.

The number of stroke mimics in our population was smaller than in other stroke thrombolysis studies; none of the three patients with stroke mimics suffered sICH.[23,24] Although the number was very small, thrombolysis in stroke mimics seems also to be safe in telestroke care. The affiliated hospitals do not have neurology service coverage and their experience and expertise with neurological disorders is limited. We therefore suspect that the low number of stroke mimics stems from an inability of extensive neurological workup (electromyogram, electroencephalogram, MRI, spinal tap, etc.) and a tendency to stay with the initial diagnosis given by the teleconsultant.

Our study is limited by its retrospective design and the data imputation. We had to exclude 17.5% of the thrombolysed patients from our analysis due to missing outcome data. This could have introduced a selection bias into our analysis by either excluding many favourable or unfavourable outcomes that remained unknown to us. Furthermore, we only had documented mRS scores at discharge, but it has been shown that these have a high predictive value for functional outcome at three months poststroke.[25] Although prestroke disability and concurrent medical problems influence the functional outcome in elderly patients as well, we could not account for those factors in our statistical analysis since no according data were available. We had a low coefficient of determination (R-squared value 0.23 and 0.24, respectively) when using a logarithmic trend line to show the benefit of earlier thrombolysis in our scatter plot. Our sample size was smaller compared to previous studies, which caused highly variable frequencies of favourable outcome for the categorical onset-to-treatment time, thus resulting in a low representativeness of the trend line.[3]

Conclusion

Shorter time and younger age is associated with favourable outcome after telestroke mediated thrombolysis. However, even in the elderly, time seems to be critical for favourable outcome. Age is not associated with longer delivery times for thrombolysis in a telestroke network in rural areas.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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