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## CLINICAL AND POPULATION SCIENCES

# Intravenous Thrombolysis in Patients With Ischemic Stroke Aged $\geq 90$ Years: A Cohort Study From the TRISP Collaboration

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**BACKGROUND:** The probability to receive intravenous thrombolysis (IVT) for treatment of acute ischemic stroke declines with increasing age and is consequently the lowest in very elderly patients. Safety concerns likely influence individual IVT treatment decisions. Using data from a large IVT registry, we aimed to provide more evidence on safety of IVT in the very elderly.

**METHODS:** In this prospective multicenter study from the TRISP (Thrombolysis in Ischemic Stroke Patients) registry, we compared patients  $\geq 90$  years with those  $< 90$  years using symptomatic intracranial hemorrhage (ECASS [European Cooperative Acute Stroke Study]-II criteria), death, and poor functional outcome in survivors (modified Rankin Scale score 3–5 for patients with prestroke modified Rankin Scale score  $\leq 2$  and modified Rankin Scale score 4–5 for patients prestroke modified Rankin Scale score  $\geq 3$ ) at 3 months as outcomes. We calculated adjusted odds ratio with 95% CI using logistic regression models.

**RESULTS:** Of 16974 eligible patients, 976 (5.7%) were  $\geq 90$  years. Patients  $\geq 90$  years had higher median National Institutes of Health Stroke Scale on admission (12 versus 8) and were more often dependent prior to the index stroke (prestroke modified Rankin Scale score of  $\geq 3$ ; 45.2% versus 7.4%). Occurrence of symptomatic intracranial hemorrhage (5.7% versus 4.4%, odds ratio<sub>adjusted</sub> 1.14 [0.83–1.57]) did not differ significantly between both groups. However, the probability of death (odds ratio<sub>adjusted</sub> 3.77 [3.14–4.53]) and poor functional outcome (odds ratio<sub>adjusted</sub> 2.63 [2.13–3.25]) was higher in patients aged  $\geq 90$  years. Results for the sample of centenarians (n=21) were similar.

**CONCLUSIONS:** The probability of symptomatic intracranial hemorrhage after IVT in very elderly patients with stroke did not exceed that of their younger counterparts. The higher probability of death and poor functional outcome during follow-up in the very elderly seems not to be related to IVT treatment. Very high age itself should not be a reason to withhold IVT.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** aged ■ intracranial hemorrhage ■ ischemic stroke ■ registries ■ survivors

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## Nonstandard Abbreviations and Acronyms

<b>ECASS</b>	European Cooperative Acute Stroke Study
<b>IQR</b>	interquartile range
<b>IST-3</b>	Third International Stroke
<b>IVT</b>	intravenous thrombolysis
<b>mRS</b>	modified Rankin Scale
<b>NIHSS</b>	National Institutes of Health Stroke Scale
<b>sICH</b>	symptomatic intracranial hemorrhage
<b>TRISP</b>	Thrombolysis in Ischemic Stroke Patients

The probability of treatment with intravenous thrombolysis (IVT) in patients with acute ischemic stroke is decreasing with increasing age and is consequently the lowest in patients aged  $\geq 90$  years.<sup>1</sup> Furthermore, advanced age was a main reason to refrain from IVT treatment in otherwise eligible patients with stroke.<sup>2</sup> The restraint from IVT treatment in patients  $\geq 90$  years is likely due to limited availability of data on safety and efficacy of IVT in this age group.

The IST-3 trial (Third International Stroke) and 2 meta-analyses of randomized controlled IVT trials provided data for patients  $>80$  years but did not analyze the age group of patients  $\geq 90$  years separately.<sup>3–5</sup> Previous observational studies focused on outcomes of IVT in patients  $\geq 90$  years.<sup>6,7</sup> However, the small sample sizes, exclusion of patients with prestroke disability or lack of adjustment for prestroke disability were relevant limitations of these studies.<sup>6,7</sup>

Comparison of clinical outcome between IVT-treated patients with stroke and non-IVT-treated controls of different age groups was performed in 2 further studies.<sup>1,8</sup> Although IVT treatment was associated with better clinical outcome in one study, it was not in the other.<sup>1,8</sup> Neither of these studies provided information on the frequency of symptomatic intracranial hemorrhages (sICH).

The aim of this study was to provide additional evidence on the safety of IVT in the fast-growing population of patients with stroke aged  $\geq 90$  years using data from large multicenter prospective IVT collaboration.

## METHODS

### Ethics Statement and Data Sharing Policy

The study was approved by the ethics committee in Basel, Switzerland. The requirement for additional local ethical approval differed between participating centers and was obtained if required. Anonymized data will be shared by request from any qualified investigator. This manuscript conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline and checklist.<sup>9</sup>

For this cohort study, we used prospectively collected data from the TRISP (Thrombolysis in Ischemic Stroke Patients) registry which has been previously described.<sup>10</sup> Twenty TRISP centers participated in this study (Table S1). Data collection was done locally in each stroke center using a standardized form with predefined parameters.<sup>11</sup> Data of the local registries were pooled and analyzed at the stroke center, Basel. Parameters of interest for the present study were age, sex, National Institutes of Health Stroke Scale (NIHSS) score,<sup>12</sup> blood pressure before IVT treatment, onset-to-treatment time, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula, glucose levels, vascular risk factors according to predefined criteria,<sup>13</sup> and prior treatment with antithrombotic agents (antiplatelet agents or anticoagulants). Primary functional outcome parameters were death and the modified Rankin Scale (mRS) score at 3 months assessed either by outpatient visits or telephone calls with patients or relatives. Poor functional outcome was defined by an mRS score of 3 to 5 for patients who were independent before the index stroke (prestroke mRS score of  $\leq 2$ ) and by an mRS score of 4 to 5 for patients who were dependent before the index stroke (prestroke mRS of  $\geq 3$ ) as it has been done in prior research.<sup>14</sup> As safety outcome, we defined the occurrence of sICH using the ECASS (European Cooperative Acute Stroke Study)-II criteria where sICH is defined as an intracranial hemorrhage associated with a clinical deterioration causing an increase in the NIHSS score of  $\geq 4$  points.<sup>15</sup> Intracranial hemorrhage was monitored by follow-up computed tomography or magnetic resonance imaging as described in prior research.<sup>16</sup>

Early functional improvement was a secondary functional outcome parameter. It was defined by any decrease in the NIHSS score after 24 hours compared with the baseline NIHSS score. Because the NIHSS score after 24 hours was not routinely collected in all participating TRISP centers, early functional improvement was investigated in a subgroup only.

Included data were collected up to June 30, 2020 (Table S1). All patients with missing data on (1) age, (2) 3-month mRS, and (3) sICH were excluded.

## STATISTICAL ANALYSES

Statistical analyses were performed with SPSS Statistics version 25 (IBM).

We investigated associations between age and outcome measures using age as a categorical variable distinguishing age  $\geq 90$  and age  $<90$  years. Age  $<90$  years served as reference group.

Continuous data were summarized as median and interquartile range (IQR). We used  $\chi^2$ -test and Fisher exact test for categorical variables where appropriate and the Mann-Whitney  $U$  test for continuous variables. The association between age and each outcome was estimated by calculating odds ratios (OR) with 95% CI, using binary logistic regression models. All variables with  $P < 0.05$  in the univariate analyses were included in the multivariable analyses. To avoid overfitting, the maximum number of potential confounders in the final model was restricted to one-tenth of the number of outcome events.

Post hoc, we calculated predictive margins from the multivariate generalized linear models, conditioned on age groups summarized per decade.

## RESULTS

From a total of 17 964 IVT-treated patients, data were eligible for analysis in 16 974 patients. Age was available in all patients. Reasons for exclusion were missing data on 3-month mRS (n=745; 4.15%) and missing data on sICH (n=245; 1.36%; Figure S1). Of the 16 974 included patients, 976 (5.7%) were aged ≥90 years and 15 998 (94.3%) were aged <90 years. Twenty-one patients were ≥100 years.

### Baseline Characteristics

The median age of patients ≥90 years was 92 years, compared with 72 years for patients aged <90 years. In the elderly group, patients were more often female and more often disabled before the index stroke. They had higher NIHSS, blood pressure, glucose, and creatinine levels on admission, and more often cardiovascular risk factors compared with patients aged <90 years. The median time from symptom onset to treatment did not differ significantly between both groups (Table 1).

### Patients Aged ≥90 Years Versus <90 Years

Outcome events occurred more frequent in patients aged ≥90 years than in the reference group (sICH: 5.7% versus 4.4%; mortality: 38.1% versus 12.9%; poor functional outcome: 51.4% versus 27.9%). Figure 1 shows the distribution of mRS after 3 months for both age groups. After adjustment for potential confounders (adjusted for NIHSS on admission, glucose on admission, systolic blood pressure on admission, and use of prior antithrombotics), the probability for sICH did not differ significantly (OR<sub>adjusted</sub> 1.14 [0.83–1.57]) between both age groups. The probability of death (OR<sub>adjusted</sub> 3.77 [3.14–4.53]) and poor functional outcome (OR<sub>adjusted</sub> 2.63 [2.13–3.25]) remained significantly higher in patients aged ≥90 years in the adjusted analyses (Tables 2 and 3).

### Patients Aged ≥100 Years Versus <100 Years

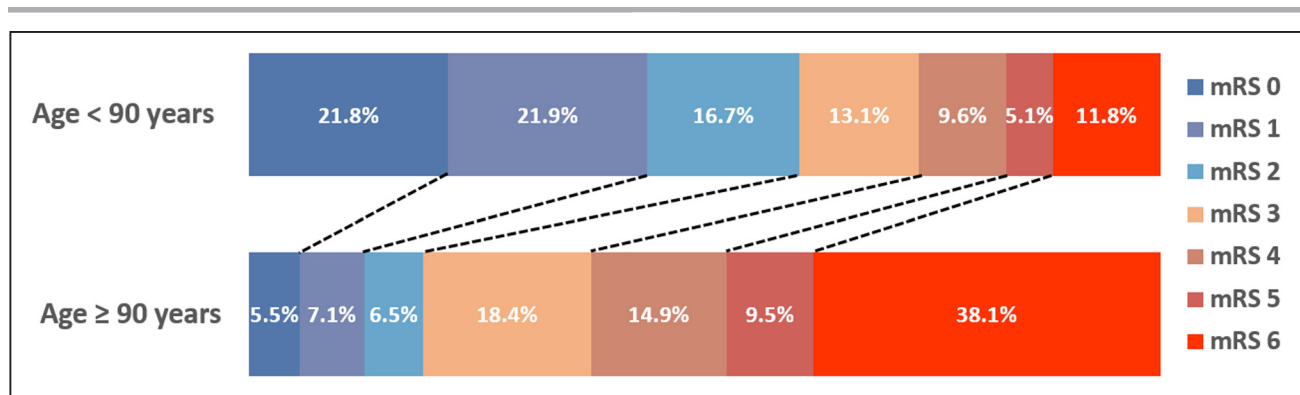
For the small group of patients ≥100 years, Figure S2 shows the distribution of mRS at 3 months patients aged <100 years and ≥ 100 years. The odds for sICH (OR<sub>adjusted</sub> 0.89 [0.12–6.67]) did not differ significantly compared with patients aged <100 years. But the probability of death (OR<sub>adjusted</sub> 5.02 [2.00–12.60]) was higher (Table 2 and 3). Age ≥100 years was not significantly

**Table 1. Clinical Characteristics and Frequency of Outcome Events of IVT-Treated Patients With Stroke Depending on Age Groups**

	Age ≥90 y	Age <90 y	Age <90 y vs Age ≥90 y	Age ≥100 y	Age <100 y vs age ≥100 y
	n=976	n=15998	P value	n=21	P value
Age, y, median (IQR)	92 (91–94)	72 (61–79)	<0.001	101 (100–101)	<0.001
Men, n (%)	262 (26.8)	9007 (56.3)	<0.001	1 (4.8)	<0.001
Stroke severity, NIHSS, median (IQR)	12 (7–18)	8 (5–14)	<0.001	12 (9–19)	0.005
Independent before stroke (pre-mRS score 0–2), n (%)	489 (54.8)	12997 (92.6)	<0.001	10 (47.6)	<0.001
Onset-to-treatment time, min, median (IQR)	145 (105–202)	145 (105–195)	0.615	125 (108–249)	0.672
Systolic blood pressure, mm Hg, median (IQR)	159 (140–176)	155 (140–171)	0.002	149 (138–165)	0.255
Glucose on admission, mmol/L, median (IQR)	6.8 (5.8–8.1)	6.6 (5.7–7.9)	0.015	6.6 (6.1–7.5)	0.774
Creatinine on admission, μmol/L, median (IQR)	92 (72–114)	80 (68–97)	<0.001	81 (56–107)	0.745
Atrial fibrillation, n (%)	403 (50.0)	3577 (24.8)	<0.001	5 (33.3)	0.810
Hypertension, n (%)	794 (81.4)	10862 (68.0)	<0.001	15 (71.4)	0.796
Current (or stopped <2 y) smoking, n (%)	13 (1.4)	3281 (22.4)	<0.001	0 (0)	0.024
Hypercholesterolemia, n (%)	346 (35.7)	7187 (45.1)	<0.001	2 (9.5)	0.001
Diabetes, n (%)	143 (14.7)	3112 (19.5)	<0.001	1 (4.8)	0.092
Coronary artery disease, n (%)	193 (19.9)	2876 (18.0)	0.148	1 (4.8)	0.111
Prior ischemic stroke, n (%)	185 (19.0)	2356 (14.8)	<0.001	2 (9.5)	0.530
Prior antithrombotics, any, n (%)	429 (59.2)	6316 (43.8)	<0.001	7 (43.8)	0.951
sICH (ECASS-2 criteria), n (%)	56 (5.7)	696 (4.4)	0.041	1 (4.8)	0.941
Death, n (%)	372 (38.1)	1711 (12.9)	<0.001	10 (47.6)	<0.001
Poor functional outcome, n (%)*	303 (51.4)	3860 (27.9)	<0.001	5 (54.5)	0.225

ECASS indicates European Cooperative Acute Stroke Study; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracerebral hemorrhage (ECASS II definition).

\*Poor functional outcome=mRS score 3–5 for patients with prestroke mRS score ≤2 and mRS score 4–5 for patients with prestroke mRS score >2.



**Figure 1.** Distribution of modified Rankin Scale (mRS) in percent at 3 mo in intravenous thrombolysis–treated patients with stroke aged <90 y and ≥90 y.

associated with poor functional outcome ( $OR_{\text{adjusted}} 1.62$  [0.49–5.72]).

### Subgroup Analysis: Early Functional Improvement After IVT

Data on the NIHSS score after 24 hours were available in 12 017 (70.8%) patients. Any improvement in the NIHSS score after 24 hours compared with the baseline NIHSS score was less frequent in patients aged ≥90 years (60.9% versus 67.9%). After adjustment for potential confounders, the probability of early functional improvement did not differ significantly between patients aged ≥90 years and patients aged <90 years ( $OR_{\text{adjusted}} 0.85$  [0.70–1.04]; Table S2).

### Post Hoc Analysis: Outcomes Stratified by Age by Decade

The rate for poor functional outcome and mortality increased with each decade when calculating predictive margins from the multivariate generalized models in Table 3. The rate for sICH increased with each decade until the age group of 70 to 79 years and then remained stable for the age groups 80 to 89 and ≥90 years (Figure 2).

## DISCUSSION

This study showed the following key results for the association between high age and outcomes in patients with acute ischemic stroke treated with IVT: (1) The probability of sICH after IVT in the very elderly (age ≥90 years) did not exceed that of their younger counterparts. (2) The probability of death and poor functional outcome within 3 months after IVT treatment was higher in patients aged ≥90 years.

Current IVT guidelines recommend IVT for patients with ischemic stroke who are >80 years old.<sup>17</sup> However, this recommendation is not based on evidence from any studies focusing on IVT in very elderly patients (ie,

≥90 years). Furthermore, data from cohort studies suggested that higher age is still an important reason for withholding IVT in daily routine.<sup>1,2</sup> In line, the proportion of patients aged ≥90 years among all IVT-treated patients with stroke was small in 2 large observational studies (0.6% and 3.8%).<sup>1,8</sup> However, patients aged ≥90 years account for ≈18% of overall ischemic strokes in population-based studies.<sup>18</sup> In our study  $n=976$  patients aged ≥90 years were treated with IVT representing 5.7% of all IVT-treated patients with stroke in the TRISP collaboration. As expected, patients ≥90 years had more severe strokes, more often relevant prestroke disability and were more likely to have cardiovascular risk factors compared with patients <90 years. Consequently, patients ≥90 years died more often during follow-up and had poorer functional outcomes even after adjustment for potential confounders.

However, although widely accepted risk factors for sICH were more frequent in the very elderly (ie, higher age, higher severity of stroke, serum glucose levels, prestroke mRS score, systolic blood pressure on admission and history of hypertension, ischemic heart disease, atrial fibrillation, renal impairment, and treatment with antiplatelets before stroke), the probability of sICH after IVT did not differ significantly between patients ≥90 and <90 years in our study.<sup>19</sup> However, when analyzing the age-dependent probability for sICH by decade, the probability increased up to 70 to 79 years and plateaued for higher age, which might reflect a ceiling effect of sICH after the age of 70 in our cohort (Figure 2).

Previously, 2 observational studies focused on safety of IVT in nonagenarians with relatively small sample sizes ( $n=122$  and  $n=43$ , respectively) of patients aged ≥90 years.<sup>6,7</sup> In one study, the frequency of sICH in IVT-treated nonagenarians was not significantly different from a nonthrombolized control group of nonagenarian patients with stroke (5.9% versus 4.9%).<sup>6</sup> In the other study, the frequency of sICH in IVT-treated nonagenarians was higher (13.3% versus 5.9%) compared to IVT-treated patients with stroke aged 80 to 9 years.<sup>7</sup> Therefore, authors

**Table 2. Univariate Analysis of Clinical Characteristics (Odds Ratio With 95% CI) in IVT Patients**

Putative predicting variables	sICH	Death	Poor functional outcome*
Sex (female)	1.08 (0.93–1.25); <i>P</i> =0.303	1.38 (1.27–1.51); <i>P</i> <0.001	1.49 (1.39–1.60); <i>P</i> <0.001
NIHSS (each point)	1.07 (1.06–1.08); <i>P</i> <0.001	1.15 (1.14–1.16); <i>P</i> <0.001	1.16 (1.15–1.16); <i>P</i> <0.001
Systolic blood pressure (each mmHg)	1.002 (1.00–1.004); <i>P</i> =0.014	1.00 (0.99–1.002); <i>P</i> =0.698	1.001 (1.000–1.002); <i>P</i> =0.188
Creatinine (each μmol/L)	1.002 (1.00–1.003); <i>P</i> =0.043	1.006 (1.005–1.007); <i>P</i> <0.001	1.001 (1.000–1.002); <i>P</i> =0.012
Glucose (each mmol/L)	1.07 (1.05–1.10); <i>P</i> <0.001	1.10 (1.08–1.11); <i>P</i> <0.001	1.07 (1.06–1.09); <i>P</i> <0.001
Atrial fibrillation	1.51 (1.28–1.78); <i>P</i> <0.001	2.15 (1.95–2.36); <i>P</i> <0.001	1.84 (1.69–2.00); <i>P</i> <0.001
Hypertension	1.38 (1.16–1.63); <i>P</i> <0.001	1.57 (1.42–1.74); <i>P</i> <0.001	1.50 (1.38–1.62); <i>P</i> <0.001
Current (or stopped <2y) smoking	0.57 (0.45–0.71); <i>P</i> <0.001	0.48 (0.41–0.55); <i>P</i> <0.001	0.68 (0.62–0.75); <i>P</i> <0.001
Hypercholesterolemia	1.03 (0.89–1.19); <i>P</i> =0.736	0.83 (0.76–0.91); <i>P</i> <0.001	0.91 (0.85–0.98); <i>P</i> =0.010
Diabetes	1.39 (1.17–1.65); <i>P</i> <0.001	1.55 (1.40–1.72); <i>P</i> <0.001	1.47 (1.35–1.61); <i>P</i> <0.001
Coronary artery disease	1.32 (1.11–1.58); <i>P</i> =0.002	1.81 (1.63–2.00); <i>P</i> <0.001	1.16 (1.06–1.28); <i>P</i> =0.002
Prior ischemic stroke	1.19 (0.98–1.44); <i>P</i> =0.088	1.56 (1.40–1.75); <i>P</i> <0.001	1.24 (1.12–1.37); <i>P</i> <0.001
Prior antithrombotics	1.60 (1.38–1.87); <i>P</i> <0.001	1.97 (1.79–2.17); <i>P</i> <0.001	1.31 (1.21–1.41); <i>P</i> <0.001
Age, ≥90 y vs <90 y	1.34 (1.01–1.77); <i>P</i> =0.042	4.60 (4.01–5.28); <i>P</i> <0.001	2.73 (2.31–3.22); <i>P</i> <0.001
Age, ≥100 y vs <100 y	1.08 (0.15–8.05); <i>P</i> =0.941	2.52 (2.52–13.99); <i>P</i> <0.001	2.05 (0.63–6.73); <i>P</i> =0.235

ECASS indicates European Cooperative Acute Stroke Study; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracerebral hemorrhage (ECASS II definition).

\*Poor functional outcome=modified Rankin Scale score 3–5 for patients with prestroke mRS score ≤2 and modified Rankin Scale score 4–5 for patients with prestroke mRS score >2.

recommended a careful selection for IVT treatment in very old patients with stroke. Another study focusing on short-term outcomes of patients with stroke ≥90 years treated with IVT found higher rates of mortality and poor outcome while the risk for sICH was not significantly different. However, outcome was defined by discharge destination and independent ambulatory status without a formal 3 months follow-up mRS score. In addition, only patients treated with IVT within 2 hours from stroke onset were included likely making this study more susceptible to selection bias.<sup>20</sup>

Our study revealed robust evidence that high age itself should not be a reason to withhold IVT. In addition, in our study, the probability of early functional improvement after IVT did not differ significantly between patients aged <90 years and ≥90 years. Therefore, it is likely that the higher probability of mortality and poor functional outcome at 3 months is not directly related to the treatment with IVT but rather driven by age-related confounders (eg, frequency of comorbidities, likelihood

of discharge to inpatient neurorehabilitation, or frequency of best supportive care).

Our study has the following strengths: (1) the large sample size (n=16974, 976 IVT-treated patients ≥90 years) which allowed adjusting for confounding variables, (2) only 5.5% of IVT-treated patients with stroke had to be excluded.

This study has limitations: (1) the TRISP collaboration is not monitored and does not provide data on patients not treated with IVT. Thus, we were not able to calculate the treatment effect of IVT stratified to age categories. (2) We cannot rule out that some patients were excluded from IVT because of unmeasured reasons, for example, preexisting cognitive impairment and dementia, which are associated with poorer functional outcome after ischemic stroke, independently of confounding factors.<sup>21</sup> (3) We were not able to provide information about the underlying cause of death during the 3-month follow-up. (4) We were not able to calculate the biological age according to recently published algorithms.<sup>22</sup>

**Table 3. Multivariable Analysis of Outcomes (Odds Adjusted for Variables With *P*<0.05 in the Univariable Analysis)**

Putative predicting variables	sICH	Death	Poor functional outcome*
Age, ≥90 y vs <90 y	1.14 (0.83–1.57)†; <i>P</i> =0.427	3.77 (3.14–4.53)‡; <i>P</i> <0.001	2.63 (2.13–3.25)‡; <i>P</i> <0.001
Age, ≥100 y vs <100 y	0.89 (0.12–6.69)§; <i>P</i> =0.910	5.02 (2.00–12.60)§; <i>P</i> =0.001	1.62 (0.49–5.72)§; <i>P</i> =0.455

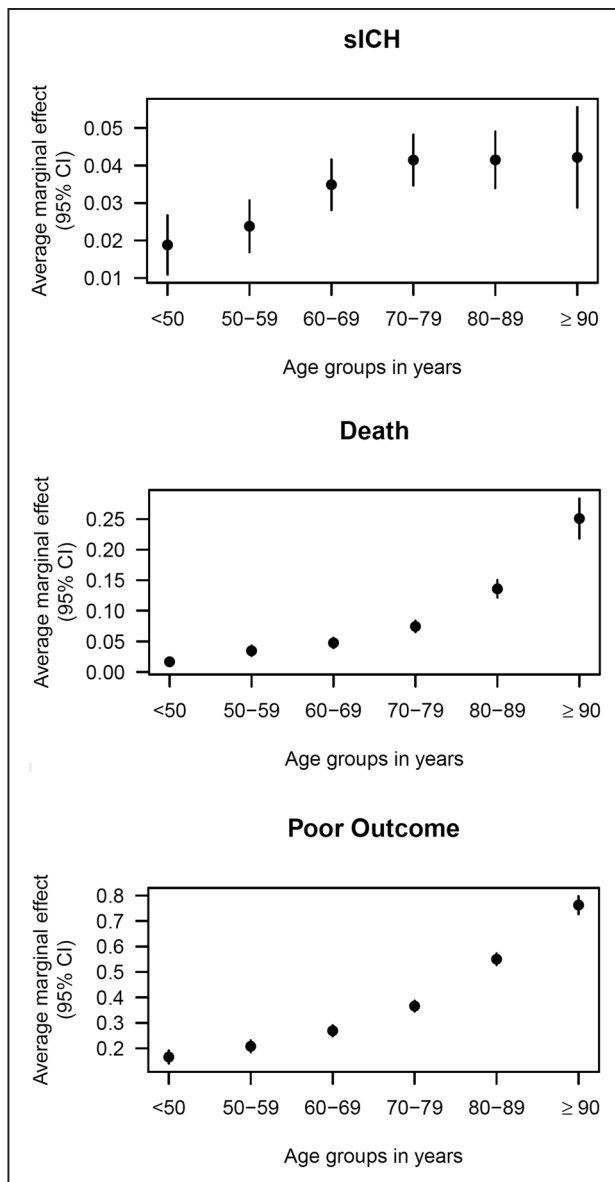
Odds ratio (95% CI); *P* value. ECASS indicates European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracerebral hemorrhage (ECASS II definition).

\*Poor functional outcome=modified Rankin Scale score of 3–5 for patients with prestroke mRS score ≤2 and modified Rankin Scale score 4–5 for patients with prestroke mRS score of >2.

†Adjusted for NIHSS on admission, glucose on admission, systolic blood pressure on admission, prior antithrombotics.

‡Adjusted for NIHSS on admission, glucose on admission, systolic blood pressure on admission, creatinine on admission, diabetes, hypercholesterolemia, current smoking, coronary artery disease, and prior ischemic stroke.

§Adjusted for NIHSS on admission.



**Figure 2. Predictive margins calculated from multivariate generalized linear models conditioned on age group summarized per decade.**

Death: Mortality at 3 mo poor outcome: independent before index stroke; modified Rankin Scale (mRS) score of 3–5 at months; dependent before index stroke: mRS score of 4–5 at 3 months. sICH indicates symptomatic intracranial hemorrhage.

In conclusion, expectedly IVT-treated patients with stroke aged  $\geq 90$  years have a higher probability of poor functional outcome and death compared with younger patients. However, the observation that the risk of sICH did not differ between the age groups may indicate that IVT should not be withheld for the fear of intracranial bleeding in the very elderly patients with stroke.

## ARTICLE INFORMATION

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### Supplemental Material

Tables S1–S2  
 Figures S1–S2  
 STROBE checklist

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