Outcomes of Thrombolysis for Acute Ischemic Stroke in Octogenarians Versus Nonagenarians

Farrah J. Mateen, MD; Alastair M. Buchan, MD; Michael D. Hill, MD; on behalf of the CASES Investigators

**Background and Purpose**—Little is reported on the outcomes of nonagenarians who are treated with intravenous tissue plasminogen activator for acute ischemic stroke. It is uncertain whether nonagenarians have higher mortality and worse functional outcomes than octogenarians.

**Methods**—All patients who were ≥80 years of age were extracted from the Canadian Activase for Stroke Effectiveness Study national registry, a 60-center Canadian acute ischemic stroke treatment network. Patients were divided into 2 groups: those who were 80 to 89 years of age (octogenarians) and those who were 90 to 99 years of age (nonagenarians), and compared by baseline clinical, demographic, treatment, and outcome-related measures.

**Results**—Twenty-eight nonagenarians and 242 octogenarians were treated with intravenous tissue plasminogen activator for acute ischemic stroke over the 2.5-year observation period. Nonagenarians and octogenarians did not differ on any of the baseline clinical or demographic variables. Both groups were predominantly female (77% nonagenarians and 61% octogenarians), hypertensive (54% and 60%), and predominantly had severe strokes (National Institutes of Health Stroke Scale score >15; 58% and 52%). The rate of symptomatic intracerebral hemorrhage (7% nonagenarians versus 4% octogenarians; \( P=0.359 \)), 90-day mortality (52% versus 33%; \( P=0.087 \)), and 30-day favorable functional outcomes (modified Rankin score ≤1) 30% versus 26%; \( P=0.647 \) showed no statistically significant difference when comparing the 2 age groups.

**Conclusions**—There is no significant difference in 90-day mortality, 30-day functional outcome, or rate of symptomatic intracerebral hemorrhage between nonagenarians and octogenarians treated with intravenous tissue plasminogen activator when comparing populations of similar baseline risk. 

**Key Words:** acute ischemic stroke • oldest old • nonagenarian • tissue plasminogen activator • thrombolysis

By 2050, there will be an estimated 56.9 million nonagenarians worldwide, an 800% increase compared with today.1 Although the majority of all stroke deaths occur after 80 years old,2 this age group comprises only 0.5% of subjects in clinical trials of thrombolysis for acute ischemic stroke (AIS).3 Recent studies to redress the persistent under-reporting of treatment outcomes in the elderly have focused on octogenarians. It remains unclear whether nonagenarians experience the same treatment outcomes after intravenous tissue plasminogen activator (IV-tPA) when compared with their younger octogenarian counterparts. We present the outcomes of nonagenarians compared with octogenarians after IV-tPA for AIS from a multicenter, nationwide stroke registry.

**Methods**

The Canadian Activase for Stroke Effectiveness Study (CASES) is a national, observational, prospective stroke registry of 1135 patients treated with IV-tPA for AIS. CASES involved 60 Canadian centers in both metropolitan and community settings over 2.5 years, from 1999 to 2001. The methods and results of the complete, age-aggregated, cohort have been reported.4-6

Patients ≥80 years of age were identified from the CASES registry and divided into 2 categories: octogenarians (80 to 89.99 years of age) and nonagenarians (90 to 99.99 years of age). Baseline demographic and clinical variables included presence of comorbidities and stroke risk factors, baseline functional status (as assessed by modified Rankin scale [mRS] score), and history of previous stroke. Treatment-associated variables included National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECTS), time to thrombolysis, Oxfordshire Community Stroke Project stroke subtype, treatment in a high-versus low-volume stroke center, and evidence of IV-tPA protocol violations at the time of administration. Final outcome was assessed by 30-day mRS scores and 90-day case fatality. A “good” functional outcome was defined as a 30-day mRS score of ≤1.

Data analysis was performed using basic descriptive statistics, 95% CIs, and relative risk ratios using exact methods. Level of significance was predetermined at \( \alpha=0.05 \), and all hypothesis tests were performed using 2-tailed tests.

**Results**

Twenty-eight nonagenarians (6 men; median age 91; range 90 to 97) were identified in the CASES database, representing 2.5% of all AISs registered in CASES. Median baseline NIHSS score among nonagenarians was 17 (range 8 to 26), with 25% of
nonagenarians having a baseline NIHSS score of 0.9% to 23.5%) experienced a symptomatic intracerebral hemorrhage after IV-tPA and died within 90 days.

Follow-up was available on 27 of 28 (96%) nonagenarians at 90 days after thrombolysis. Patients who had an mRS score of 1 were more likely to have had a lower NIHSS score at presentation (median 13.5 versus 20.5; \( P=0.022 \)). The median duration of post–IV-tPA hospital stay among nonagenarians was 12.5 days (interquartile range 34).

Octogenarians comprised 21% of CASES registry patients. Symptomatic intracerebral hemorrhage occurred in 4.1% (95% CI, 2.0 to 7.5%) and was fatal in 9 of the 10 cases. When comparing octogenarians and nonagenarians on all measured demographic, clinical, and treatment outcome-related variables, there was no significant difference between the 2 age groups (Table 1). There was no evidence that nonagenarians of similar comorbidity and risk fared worse than octogenarians. There were 2 symptomatic hemorrhages in the nonagenarian group. Both were treated within 180 minutes, had baseline ASPECTS of 7 and 9, and baseline NIHSS of 9 and 25. Overall, the rates of symptomatic intracerebral hemorrhage, 90-day mortality, and 30-day favorable functional outcomes did not significantly differ between the groups (Table 2; Figure).

Discussion

Old age may preclude eligible patients from receiving IV-tPA, either because official recommendations are not clearly supportive of IV-tPA treatment in the elderly, or case-by-case exclusion occurs outside of recognized treatment protocols. Current regulations in Europe forbid use of IV-tPA in patients >80 years of age. Nonagenarians may be especially vulnerable to subjective judgments of the benefit after IV-tPA, given their extreme age. In this large national registry, we detected no difference in functional outcomes or survival after IV-tPA for AIS between nonagenarians and octogenarians of similar comorbidities and risk factors. A large number of both octogenarians and nonagenarians treated with IV-tPA were functionally independent at 30 days, including 30% of octogenarians and 26% of nonagenarians.

Mortality rates in AIS are high in those >80 years of age, with or without treatment with IV-tPA. The 90-day mortality in nonagenarians after IV-tPA for AIS reaches 50%. If you consider an mRS score of 4 to 6 as poor outcome, >60% of patients do poorly. This may be primarily because of the higher baseline stroke severity seen in the oldest old. Yet no report, including the original post hoc analysis of generalizability of efficacy of IV-tPA for acute stroke, has found a reason to subselect patients solely on the basis of age. In fact, good outcomes after thrombolysis for patients >75 years of age may even exceed those found in younger patients.

It is unclear whether very advanced age poses a special risk of symptomatic intracerebral hemorrhage after IV-tPA for AIS.

### Table 1. Baseline Characteristics of Octogenarians Versus Nonagenarians Treated With IV-tPA for AIS in CASES

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Age 80–89 Years (n=242)</th>
<th>Age ≥90 Years (n=28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>93/240 (39%)</td>
<td>6/26 (23%)</td>
<td>0.135</td>
</tr>
<tr>
<td>Ethnic group (Caucasian)</td>
<td>208/216 (96%)</td>
<td>23/25 (92%)</td>
<td>0.278</td>
</tr>
<tr>
<td>Historical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke or transient ischemic attack</td>
<td>60/226 (27%)</td>
<td>7/26 (27%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>135/226 (60%)</td>
<td>14/26 (54%)</td>
<td>0.674</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>83/226 (37%)</td>
<td>11/26 (42%)</td>
<td>0.669</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30/226 (13%)</td>
<td>1/26 (4%)</td>
<td>0.219</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>22/226 (10%)</td>
<td>2/26 (8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>67/226 (30%)</td>
<td>8/26 (31%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>23/226 (10%)</td>
<td>5/26 (19%)</td>
<td>0.184</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>11/226 (5%)</td>
<td>2/26 (8%)</td>
<td>0.630</td>
</tr>
<tr>
<td>Dementia</td>
<td>10/226 (4%)</td>
<td>2/26 (8%)</td>
<td>0.357</td>
</tr>
<tr>
<td>History of cancer</td>
<td>28/226 (12%)</td>
<td>2/26 (8%)</td>
<td>0.750</td>
</tr>
</tbody>
</table>

### Table 2. Clinical Outcomes of Nonagenarians Versus Octogenarians After IV-tPA for AIS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age 80–89 (%) (n=242)</th>
<th>Age 90–99 (%) (n=28)</th>
<th>Relative Risk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day mRS score ≤1</td>
<td>26% CI 95 20%–32% (61/239)</td>
<td>30% CI 95 13%–50% (8/27)</td>
<td>1.2 (0.6–2.2)</td>
<td>0.647</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
<td>4% CI 95 2%–7% (10/242)</td>
<td>7% CI 95 1%–24% (2/28)</td>
<td>1.7 (0.4–7.5)</td>
<td>0.359</td>
</tr>
<tr>
<td>90-Day Mortality</td>
<td>33% CI 95 27%–40% (80/239)</td>
<td>52% CI 95 32%–71% (14/27)</td>
<td>1.5 (1.0–2.3)</td>
<td>0.087</td>
</tr>
</tbody>
</table>
This study suggests that nonagenarians are at no increased risk of symptomatic intracerebral hemorrhage compared with octogenarians, although in both age groups, symptomatic intracerebral hemorrhage was almost uniformly fatal. The aging process of the cerebral vessels, in terms of atherosclerosis, amyloid angiopathy, and friability, may be more important than a patient’s exact chronological age in such cases.

This study has limitations. The study is a post hoc analysis of a registry; selection bias is an important limitation to the data set. Given the large number of treating centers, the decision to administer IV-tPA was made by multiple different treating physicians. If nonagenarians were more carefully selected than octogenarians for administration of IV-tPA, the findings of this study would not generalize to all nonagenarians. Age may influence the use of diagnostic resources, and it is unknown whether nonagenarians or their families are more likely to decline thrombolytic treatment when they are eligible. By measuring functional outcome on an absolute mRS score, patients who had baseline moderate disability and did not worsen may have been overlooked as “favorable functional outcomes” in both age groups in this study. In addition, we recognize that the sample size is small, and it remains possible that our conclusions represent a type 2 error.

The analysis of CASES supports the concept that treating nonagenarians presenting with AIS with IV-tPA can result in favorable outcomes in nearly a third of patients. However, death and poor outcome rates are high because stroke is commonly the final illness in this age group; recognizing this fact and adjusting family expectations accordingly is important. Functional independence, even among nonagenarians, will become increasingly important in neurological care in the coming decades, particularly for women who do and will represent the majority of the world’s increasingly “graying” population. These data provide empirical observation that we hope will stimulate further research into this group of patients.

Disclosures

None.

References

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