Research Report

Eligibility for Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke
A Population-Based Study

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Background and Purpose—Acute ischemic stroke patients are infrequently treated with recombinant tissue plasminogen activator (rtPA). We present unique population-based data regarding the eligibility of ischemic stroke patients for rtPA treatment.

Methods—All ischemic strokes presenting to an emergency department (ED) within a biracial population of 1.3 million were identified. The patient was considered eligible for rtPA on the basis of exclusion criteria from the National Institute of Neurological Disorders and Stroke rtPA trial.

Results—Of 2308 ischemic strokes, 1849 presented to an ED. Only 22% of all ischemic strokes in the population arrived in the ED in <3 hours from symptom onset; of these, 209 (51%) were ineligible for rtPA on the basis of mild stroke severity, medical and surgical history, or blood tests.

Conclusions—In our population in 1993 to 1994, 8% of all ischemic stroke patients presented to an ED within 3 hours and met other eligibility criteria for rtPA. Even if time were not an exclusion for rtPA, only 29% of all ischemic strokes in our population would have otherwise been eligible for rtPA. (Stroke. 2004;35:e27-e29.)

Key Words: eligibility determination ■ emergency treatment ■ stroke, acute ■ stroke, ischemic ■ tissue plasminogen activator

Acute ischemic stroke patients are infrequently treated with recombinant tissue plasminogen activator (rtPA), despite its proven effectiveness for reducing morbidity after stroke. For example, in the Greater Cincinnati/Northern Kentucky (GCNK) population, the percentage of ischemic stroke patients receiving rtPA is only 3% to 4% and did not change between 1993 to 1994 and 1999, despite Food and Drug Administration approval of rtPA. Similarly, the Paul Coverdell National Acute Stroke registry reported that only 4% of all ischemic stroke patients received rtPA in 2001. The reasons underlying the low frequency of rtPA use remain unclear.

We present unique population-based data regarding the eligibility of ischemic stroke patients for rtPA treatment within a major metropolitan population of 1.3 million with a proportion of blacks and socioeconomic demographics similar to those of the US population.

Materials and Methods
The unique methodology of the GCNK stroke study has been previously described. This study was approved by the institutional review board at all participating hospitals. The methods involved collection of all strokes in the study population between July 1, 1993, and June 30, 1994. Study nurses reviewed the medical records of all inpatients with primary or secondary stroke-related International Classification of Diseases, ninth revision, discharge diagnoses (codes 430 through 438) from the 19 acute-care hospitals in the study region.

In addition to ascertaining inpatient strokes using the methodology described above, we also ascertained strokes not found by inpatient monitoring by screening all visits to 18 of the hospital’s emergency departments (EDs; Cincinnati Children’s Hospital was excluded), 5 county coroner’s offices, 16 public health clinics, and 14 hospital-based outpatient clinics and family practice centers. In addition, monitoring was performed using a random sample of 50 of 878 primary care physicians’ offices and 25 of 193 nursing homes in the greater Cincinnati metropolitan area. Events found by out-of-hospital monitoring were checked against inpatient records to prevent double counting.

Once potential cases were identified, the study nurse reviewed the medical record and abstracted detailed information regarding the event in question. Specifically, information was collected on possible inclusion and exclusion criteria used in rtPA treatment decisions. An estimated retrospective National Institutes of Health Stroke Scale Score (NIHSSS) was obtained from review of the physician examination as documented in the ED evaluation. This estimation of the NIHSSS was validated by a comparison with a total of 183 charts that had a true NIHSSS documented (as performed by an NIHSSS...
trained physician), with a correlation coefficient of 0.83 ($P<0.0001$); this correlation also held true for milder strokes, with $r=0.76$ for NIHSSS $<5$ (data not shown). For this analysis, we included only those patients who were judged by the study physician to have had a new ischemic stroke.

Patients were considered eligible for rtPA if they arrived in an ED in the study region and met the inclusion criteria as published by the National Institute of Neurological Disorders and Stroke (NINDS) study group: arrival within 3 hours of symptom onset; moderate to severe stroke with estimated NIHSSS $\geq 5$; serum glucose $>50$ mg/dL or $<400$ mg/dL; international normalized ratio $<1.5$; partial thromboplastin time $<40$ seconds; platelet count $>100\ 000$/mm$^3$; no history of ischemic stroke within 3 months; no history of brain tumor or intracranial hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage; no seizure at onset of symptoms; and systolic blood pressure $<180$ mm Hg and diastolic blood pressure $<110$ mm Hg. Major surgery at a noncompressible site within 30 days was the original exclusion criteria from the NINDS study. However, only recent coronary bypass grafting or carotid endarterectomy information was collected at the time of the chart abstraction; therefore, we cannot comment on the exclusion of patients for rtPA because of other major surgical procedures.

Bivariate analyses were performed using $\chi^2$ or Fisher’s exact test as appropriate to compare rates in the ED population versus those within the 3-hour window. Spearman’s rank correlation was used to compare the estimated NIHSSS with the full score. Data were managed and analyzed with SAS version 8.2 (SAS Institute).

## Results

During the study period of July 1993 to June 1994, a total of 2308 patients were determined to have had ischemic infarcts within our population. Of these, 1849 (80%) presented to an ED (the Figure). Of the ED-presenting strokes, 727 (39%) had documentation of exact stroke onset times, 713 (39%) had estimated stroke onset times, and 409 (22%) had unknown stroke onset times. Only 670 (36%) of all ischemic stroke patients presenting to an ED had clearly documented times of symptom onset and ED arrival in the medical record. In our population, 406 ischemic stroke patients (22%) presented to an ED arrived in $<3$ hours from symptom onset; 19%, in $<2$ hours. Five percent of patients arrived in the 3- to 6-hour window. Of the 406 patients who arrived within 3 hours, 209 (51%) were ineligible for rtPA on the basis of mild stroke severity, medical and surgical history, or blood tests (the Table). Of the 197 remaining eligible patients, 39 had extreme hypertension in the ED. Nineteen of these patients received some sort of antihypertensive therapy in the ED, but posttreatment blood pressure measurements were not collected, so we considered these 19 patients ineligible to receive rtPA for the purpose of this analysis.

The potential reasons for ineligibility between those patients who arrived within 3 hours and those presenting to an ED $>3$ hours after symptom onset were remarkably similar (the Table). More severe strokes and strokes with seizure at onset were significantly more likely to present within the 3-hour time window. However, only 29% of all ischemic strokes in our population would have been eligible for rtPA if time were not an exclusion (ie, if time is removed as an exclusion from our analysis).

## Discussion

The most important exclusion for rtPA in our population was time to presentation. Only 22% of ischemic stroke patients who presented to an ED came in within 3 hours. This is similar to the findings of Barber et al$^4$ in Canada, who found that 27% of ischemic stroke patients arrived within 3 hours. Important potential reasons responsible for the delay in
presentation to the ED include poor public knowledge of stroke signs and available treatments and delays in emergency transport. After delay in arrival at the EDs, the next most important exclusion for rtPA use in our population was mild stroke severity as measured by an estimated NIHSSS obtained from chart review.

To the best of our knowledge, our data provide the first description of eligibility of acute ischemic stroke patients for rtPA within a population that is generalizable to the United States. The strength of this study is the population-based methodology, with strokes from a variety of settings in the denominator, including inpatient, outpatient, academic, and community medical centers. Studies reporting eligibility from single centers or those including only hospitalized stroke are subject to referral bias. The limitations of this study are the retrospective nature of the study and possible incomplete case ascertainment. In addition, incomplete documentation, especially of the times in question, was very prevalent. However, this poor documentation of times reflects the practice within the population, and although it is clearly an area that needs to be addressed to improve the quality of care given to acute stroke patients, there is no other way to obtain eligibility data from an entire population.

From our data, we conservatively estimate that in 1993 to 1994, \( \approx 8\% \) of ischemic stroke patients presenting to an ED, or 6.4% of all ischemic stroke patients, were eligible for rtPA. In addition, only 29% of all stroke patients were eligible for rtPA regardless of time to presentation, a novel finding that has not been reported previously. Future analysis of the GCNK population during 1999 will examine whether these patterns of eligibility have improved as a result of the public awareness initiatives that have occurred since approval of tPA for acute stroke.

Acknowledgment

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References


Non–Time-Related Exclusions for rtPA in Acute Ischemic Stroke Patients

<table>
<thead>
<tr>
<th>Exclusion</th>
<th>Patients Presenting to ED &lt;3 Hours (n=406), n (%)</th>
<th>Patients Presenting to ED &gt;3 Hours or Unknown Times (n=1443), n (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSSS &lt;5</td>
<td>174 (43)</td>
<td>781 (54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extreme hypertension</td>
<td>39 (10)</td>
<td>156 (11)</td>
<td>0.473</td>
</tr>
<tr>
<td>Seizure at onset</td>
<td>28 (7)</td>
<td>56 (4)</td>
<td>0.010</td>
</tr>
<tr>
<td>INR &gt;1.5</td>
<td>11 (3)</td>
<td>40 (3)</td>
<td>0.938</td>
</tr>
<tr>
<td>PTT &gt;40 s</td>
<td>9 (2)</td>
<td>48 (3)</td>
<td>0.249</td>
</tr>
<tr>
<td>Platelet &lt;100 000/mm(^3)</td>
<td>3 (1)</td>
<td>54 (4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Glucose &gt;400 mg/dL</td>
<td>8 (2)</td>
<td>31 (2)</td>
<td>0.819</td>
</tr>
<tr>
<td>Glucose &lt;50 mg/dL</td>
<td>4 (1)</td>
<td>40 (3)</td>
<td>0.041</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent ischemic stroke (&lt;3 mo)</td>
<td>5 (1)</td>
<td>31 (2)</td>
<td>0.310</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>0</td>
<td>7 (0.5)</td>
<td>0.359</td>
</tr>
<tr>
<td>AVM</td>
<td>0</td>
<td>2 (0.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>1 (0.3)</td>
<td>5 (0.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>ICH, SAH, IVH</td>
<td>2 (0.5)</td>
<td>11 (0.8)</td>
<td>0.745</td>
</tr>
<tr>
<td>Recent CAGG (&lt;30 d)</td>
<td>2 (0.5)</td>
<td>7 (0.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Recent CEA (&lt;30 d)</td>
<td>1 (0.3)</td>
<td>4 (0.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Total eligible remaining</td>
<td>155 (38)</td>
<td>390 (27)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; PTT, partial thromboplastin time; AVM, arteriovenous malformation; ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; CAGG, coronary artery bypass grafting; and CEA, carotid endarterectomy.
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