Population-Based Analysis of the Impact of Expanding the Time Window for Acute Stroke Treatment

Jennifer Juhl Majersik, MD; Melinda A. Smith, DPH; Darin B. Zahuranec, MD; Brisa N. Sánchez, PhD; Lewis B. Morgenstern, MD

Background and Purpose—Currently, a major focus on expanding acute ischemic stroke treatment opportunities centers on the development of drugs and devices with longer time windows for use. We sought to determine the time intervals within which stroke patients present to establish whether time window expansion will translate into more treatment.

Methods—Data were derived from the Brain Attack Surveillance in Corpus Christi project, a population-based stroke surveillance study in an urban, southeast Texas county. This community does not contain an academic medical center, thus providing a “real-world” setting to capture patient arrival times. Onset time was recorded from the chart according to a prespecified methodology.

Results—From January 2000 to June 2005, 2347 patients with acute ischemic stroke were validated. The mean age was 71 years, and 53% were female. Thirty-one percent presented within 3 hours of symptom onset; 13% between 3 and 6 hours; and 15% between 6 and 12 hours. Forty-one percent presented beyond 12 hours from symptom onset. Nearly half of patients with moderate and severe strokes presented in the 0- to 3-hour time window, whereas only 28% of mildly affected patients presented early.

Conclusions—This population-based study provides estimates of time to presentation in a representative community without tertiary referral bias. These data are useful for planning acute stroke therapy interventions and suggest that in addition to developing therapies with expanded time windows, research resources should also be devoted to reducing hospital presentation delays.

Key Words: cerebrovascular accident ■ epidemiology ■ health services research

The efficacy of acute stroke therapies is critically dependent on their time of initiation since stroke onset.1 The only therapy currently approved by the US Food and Drug Administration of proven benefit for stroke, intravenous recombinant tissue-type plasminogen activator (rt-PA), must be given within 3 hours of stroke onset.2 However, <5% of acute ischemic stroke patients in the United States receive rt-PA primarily due to delay in hospital presentation.3 To increase the proportion of stroke patients who receive acute treatment, efforts are ongoing to try to expand the time window for reperfusion therapy beyond 3 hours. These efforts include the development of novel thrombolytic agents,4 mechanical thrombectomy,5 and the use of advanced imaging techniques to select patients who might benefit from rt-PA after 3 hours.6 However, stroke patient arrival times in communities without academic centers are unknown. The aim of this study was to define the “real-world” experience of acute stroke arrival times by using a population-based study in a community without an academic medical center to avoid referral bias.

Subjects and Methods
The data for this study were derived from the Brain Attack Surveillance in Corpus Christi (BASIC) project, a population-based surveillance study of stroke in an urban community in southeast Texas. The nearest academic medical centers are ~150 miles away in San Antonio and Houston. This geographic isolation allows for complete capture of cerebrovascular events in the community.

Detailed BASIC methodology has been previously published.7 In brief, cases of potential stroke and transient ischemic attack 45 years and older are captured by active and passive surveillance of the Emergency Departments and inpatient services of local hospitals. Cases are ascertained actively by trained abstractors by manually searching visit and admissions logs for a set of previously validated screening diagnostic codes.8 Through chart review, abstractors then verify whether cases are “potential stroke.” Passive surveillance uses the International Classification of Diseases, ninth revision, code searches for stroke hospital discharges.9 Board-certified neurologists use source documentation to validate each potential stroke case as stroke or nonstroke based on published international criteria.10 An initial National Institutes of Health Stroke Scale (NIHSS) score is retrospectively abstracted from the chart for all patients according to a previously validated approach.11 Race/ethnicity was determined by abstraction of the medical record, as we have previously demonstrated excellent agreement between self-reported and medical record race/ethnicity in this community.7

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Table 1. Demographic Variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean)</td>
<td>71</td>
</tr>
<tr>
<td>Female</td>
<td>1237 (53)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>984 (42)</td>
</tr>
<tr>
<td>MA</td>
<td>1204 (51)</td>
</tr>
<tr>
<td>Other</td>
<td>159 (7)</td>
</tr>
<tr>
<td>Health insurance coverage</td>
<td>2213 (95)</td>
</tr>
<tr>
<td>NIHSS, median (interquartile range)</td>
<td>4 (2–7)</td>
</tr>
<tr>
<td>Previous stroke/transient ischemic attack</td>
<td>1433 (61)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>942 (40)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>521 (22)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>287 (12)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>759 (32)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>942 (40)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>423 (18)</td>
</tr>
</tbody>
</table>

*Unless specified otherwise.

Time of hospital arrival was the earliest time documented in the medical record. Time of stroke onset was noted by the abstractors for each patient as the last time when the patient was known to be normal. All times of onset were then categorized during abstraction into <3 hours, 3 to 6 hours, >6 to 12 hours, >12 to 24 hours, and >24 hours. When specific onset time was not recorded, a previously published standardized estimation method was used. Symptom onset described in the chart as “morning” was recorded as 9AM, in the “afternoon” as 3PM, in the “evening” as 9PM, and at “night” as midnight. If the patient awoke with symptoms, the last time he or she was known to be awake and normal was recorded. If the patient awoke during the night and had been seen to be normal, then that time was used as the last observed normal time. However, if the patient had not been observed to be normal during the night and the bedtime was unknown, 11 PM the prior night was recorded. In addition, when the chart contained a reference to a time frame, this was used to estimate arrival time. For example, if the symptoms started “at lunch” and the patient presented to the hospital at 12:30 PM, the abstrator would record presentation as being <3 hours. If no reference to time of onset was listed in the medical record, time was recorded as “unknown.”

χ² tests were used to examine the distribution of presentation times in relation to categories of stroke severity, race/ethnicity (Mexican-American [MA] or non-Hispanic white [NHW]), and presentation from a nursing home. For this article, cases from January 1, 2000, to June 7, 2005, with validated completed ischemic stroke and presentation to a hospital or Emergency Department, were included. In-hospital strokes were excluded. This project was approved by the institutional review boards at the Nueces County hospital system and the University of Michigan.

Results

During the study period, 23 594 subjects were screened by active and passive surveillance for potential stroke. There were 4365 validated cerebrovascular events, including ischemic stroke, transient ischemic attack, intracerebral hemorrhage, and subarachnoid hemorrhage. Of this total, 2347 patients had a validated ischemic stroke. Demographics are shown in Table 1. There was no onset time available for 4% of patients.

Time to presentation is shown in Table 2. In this population, the largest proportion of patients (31%) presented within 3 hours of symptom onset compared with the other time intervals. Of all patients presenting within 3 hours, 4% (31) received intravenous rt-PA. In this urban, nonacademic setting, intra-arterial thrombolytic therapy was unavailable during the time period studied.

Time to presentation was associated with initial stroke severity, with patients with more severe strokes presenting earlier (χ²=89.29, df=10, P<0.001; Table 3). Race/ethnicity (MA versus NHW) was also associated with time to presentation (χ²=12.24, df=5, P=0.032). However, the relative differences between time intervals were quite small, and there was no specific pattern across the 5 time windows when the 2 race/ethnic groups were compared (Table 4). Presentation from a nursing home versus other residence was associated with time to presentation (χ²=49.17, df=5, P<0.001); however, no difference between these 2 groups was seen in the first 6 hours of presentation (χ²=0.068, df=1, P>0.05; Table 2).

Discussion

This population-based study suggests a relatively small percentage gain in the number of patients eligible for acute therapy by increasing the therapeutic time window from 3 to 6 hours. Indeed, more acute stroke patients arrive at the hospital in the first 3 hours than in the next 9 hours combined. However, if this population is representative of the US stroke population, the additional 13% of patients potentially eligible for therapy between 3 and 6 hours translates to roughly 80 000 patients in the United States, a real public health benefit. To more effectively treat the maximal number of patients, future research should focus not only on expanding the time window but also on decreasing presentation delays in acute stroke, with a specific focus on the social, cognitive, and emotional factors contributing to delays. New interventions must do more than just teach stroke symptoms, as this knowledge alone is insufficient to motivate patients to call 911 after stroke. Previous studies have demonstrated that community interventions can be effective in reducing the time to presentation, resulting in measurable and sustained improvements in stroke care.

Our rate of early presentation (<6 hours) is among the highest reported when compared with studies that used similar definitions of time to presentation (Table 5). This may be a reflection of our study population being cared for solely in community hospitals without academic centers, which has been shown in 1 study to result in shorter times to presenta-
tion.\textsuperscript{16} Not included in Table 5 are studies that have used noncomparable definitions of time to presentation,\textsuperscript{16–19} which often report a higher percentage of early-presenting patients. For example, inclusion of patients with intracerebral hemorrhage\textsuperscript{16} shortens the average time to presentation,\textsuperscript{20} whereas exclusion of patients with “unknown” times to onset\textsuperscript{16–17,19} overreports the percentage of patients presenting early. Studies of patient and family reaction times usually define time to presentation as delay from the first notice of symptoms,\textsuperscript{17,18} rather than when the patient was last known to be well, which again shortens the reported time to presentation.

We expect that the times to presentation in Corpus Christi, Tex, were stable during the study period, as there have been no community-wide stroke educational efforts during the BASIC study. Although we have been involved in previous community stroke education efforts,\textsuperscript{21} those programs were conducted in Texas counties >400 miles from Corpus Christi and thus had no impact on the patient population in this study. The Kids Identifying and Defeating Stroke project aimed to teach Corpus Christi middle school children about stroke symptoms and the need to call 911 when stroke symptoms were witnessed. The educational intervention was conducted from February 2004 to the fall of 2005, thus overlapping with the final 18 months of this study period. However, that educational effort has affected only \approx150 middle school children. Thus, we expect that any effect on time to presentation in the adult community would be minimal.

This study found a significant association between ethnicity and time to presentation, but there was no consistent pattern in the differences. These data are thought provoking and warrant further study. Differences in presentation times by presentation from nursing home or other residence were restricted to the later time windows (>6 hours) and did not show a trend toward consistent delay in presentation in nursing home patients.

A limitation of this study is that we did not record which patients had an exact time of onset listed in the chart versus those in whom onset time was estimated. Thus, we do not know whether our estimation method introduced bias into the results. In addition, times to presentation were recorded only in large blocks, ie, <3 hours, 3 to 6 hours, >6 to 12 hours, 12 to 24 hours, and >24 hours. Because 60 minutes are needed by many facilities to evaluate an acute ischemic stroke patient before administering therapy\textsuperscript{22} (and only 30 minutes by well-organized facilities), a more refined delineation of arrival times into individual-hour blocks (0 to 1 hours, 1 to 2 hours, etc) would provide a better estimation of the proportion of patients eligible for early therapies. Furthermore, the NIHSS score was retrospectively calculated from the chart. Although this has been validated and shown to be well correlated with prospectively obtained NIHSS scores,\textsuperscript{11} our relatively high proportion of mild stroke cases suggests there may be an overall underestimation of stroke severity. Finally, time to presentation is only 1 component necessary to determine eligibility for acute stroke therapies; additional patient factors are required to determine the appropriateness of a specific therapy, such as thrombolysis.

Several distinct advantages of this study are its population-based design, large sample size, and absence of an academic medical center suggesting a real-world setting. In addition, a large percentage of initially inexact times to presentation were found to have some indication of onset time in the chart. For these cases, abstractors were able to estimate a presentation time window, resulting in an overall low rate of indeterminable time to presentation.

This study examined the most salient factor related to acute ischemic stroke treatment and revealed that time window expansion will yield a small but important number of patients eligible for therapy. The study also suggests that in addition to developing therapies with expanded time windows, research resources should also be devoted to reducing hospital presentation delays.

\section*{Table 3. Time to Presentation by Initial Stroke Severity}

<table>
<thead>
<tr>
<th>Admission NIHSS Score</th>
<th>0–3 h</th>
<th>&gt;3–6 h</th>
<th>&gt;6–12 h</th>
<th>&gt;12–24 h</th>
<th>&gt;24 h</th>
<th>Unknown Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, 0–7 (n=1884)</td>
<td>526 (28)</td>
<td>247 (13)</td>
<td>282 (15)</td>
<td>252 (13)</td>
<td>515 (27)</td>
<td>61 (3)</td>
</tr>
<tr>
<td>Moderate, 8–15 (n=268)</td>
<td>118 (44)</td>
<td>36 (13)</td>
<td>38 (14)</td>
<td>18 (7)</td>
<td>40 (15)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Severe, &gt;15 (n=196)</td>
<td>92 (47)</td>
<td>25 (13)</td>
<td>29 (15)</td>
<td>21 (11)</td>
<td>18 (9)</td>
<td>11 (6)</td>
</tr>
</tbody>
</table>

Values are n (%).

\section*{Table 4. Time to Presentation by Race/Ethnicity}

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>0–3 h</th>
<th>&gt;3–6 h</th>
<th>&gt;6–12 h</th>
<th>&gt;12–24 h</th>
<th>&gt;24 h</th>
<th>Unknown Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHW (n=984)</td>
<td>335 (34)</td>
<td>120 (12)</td>
<td>146 (15)</td>
<td>134 (14)</td>
<td>211 (21)</td>
<td>38 (4)</td>
</tr>
<tr>
<td>MA (n=1204)</td>
<td>360 (30)</td>
<td>175 (15)</td>
<td>175 (15)</td>
<td>138 (11)</td>
<td>314 (26)</td>
<td>42 (3)</td>
</tr>
</tbody>
</table>

Values are n (%).
\[ \chi^2=12.243, df=5, P=0.032. \]
Table 5. Comparable Studies of Time to Presentation

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study Population</th>
<th>N</th>
<th>Median NIHSS Score</th>
<th>Time to Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>Southeast Texas</td>
<td>Population based</td>
<td>2347</td>
<td>4</td>
<td>0–3 h 13% 3–6 h 27% 6–24 h 24% &gt;24 h 4%</td>
</tr>
<tr>
<td>Owe et al, 2006</td>
<td>Bergen, Norway</td>
<td>3 selected hospitals</td>
<td>88</td>
<td>4</td>
<td>0–3 h 23% 3–6 h 8% 6–24 h 69%* &gt;24 h 4%</td>
</tr>
<tr>
<td>CASPR, 2005</td>
<td>California</td>
<td>11 selected hospitals, including 3 academic centers</td>
<td>374</td>
<td>7</td>
<td>0–3 h 24% 3–6 h 6% 6–24 h 40% &gt;24 h 30%*</td>
</tr>
<tr>
<td>Qureshi et al, 2005</td>
<td>Western New York</td>
<td>11 selected hospitals, including 8 academic centers</td>
<td>1590</td>
<td>3–5</td>
<td>0–3 h 21% 3–6 h 11% 6–24 h 19% &gt;24 h 26%</td>
</tr>
<tr>
<td>Kleindorfer et al, 2004</td>
<td>Ohio/Kentucky</td>
<td>Population based, including 1 academic center</td>
<td>1849</td>
<td>NR</td>
<td>0–3 h 22% 3–6 h 5% 6–24 h 51% &gt;24 h 22%</td>
</tr>
<tr>
<td>Kothari et al, 1999</td>
<td>Ohio/Kentucky</td>
<td>4 selected hospitals, including 1 academic center</td>
<td>151</td>
<td>NR</td>
<td>0–3 h 30% 3–6 h 10% 6–24 h 21% &gt;24 h 18%</td>
</tr>
<tr>
<td>Azzimondi et al, 1997</td>
<td>Bologna, Italy</td>
<td>Single teaching hospital</td>
<td>204</td>
<td>NR</td>
<td>0–3 h 40% 3–6 h 12% 6–24 h 31% &gt;24 h 9%</td>
</tr>
</tbody>
</table>

NR indicates not reported.
*Includes patients with “overnight onset.”

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Disclosures
None.

References


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In the article “Population-Based Analysis of the Impact of Expanding the Time Window for Acute Stroke Treatment” by Majersik et al., the authors recently discovered that some of their estimates of delay to hospital arrival were not recorded accurately by their field abstractors. The authors would like to emphasize that none of the analyses are affected by this small reporting error and that the central message of the article is completely unchanged. The small changes affect Table 2. Please see below for the corrected version of Table 2. The authors believe that the few percent differences shown below are within the natural error margins of population-based research, but wish to make readers aware of the accurate numbers. The authors regret this error.

The corrected version can be viewed online at http://stroke.ahajournals.org.

Table 2. Time to Presentation

<table>
<thead>
<tr>
<th></th>
<th>0–3 h</th>
<th>&gt;3–6 h</th>
<th>&gt;6–12 h</th>
<th>&gt;12–24 h</th>
<th>&gt;24 h</th>
<th>Unknown Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=2347)</td>
<td>638 (27)</td>
<td>304 (13)</td>
<td>381 (16)</td>
<td>309 (13)</td>
<td>570 (24)</td>
<td>145 (6)</td>
</tr>
<tr>
<td>Patients admitted from a nursing home (n=164)</td>
<td>40 (24)</td>
<td>23 (14)</td>
<td>44 (27)</td>
<td>14 (9)</td>
<td>16 (10)</td>
<td>27 (16)</td>
</tr>
</tbody>
</table>

Values are n (%).