Greater Cincinnati/Northern Kentucky Stroke Study
Volume of First-Ever Ischemic Stroke Among Blacks in a Population-Based Study

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Background and Purpose—The volume of ischemic stroke on CT scans has been studied in a standardized fashion in acute stroke therapy trials with median volumes between 10.5 to 55 cm³. The volume of first-ever ischemic stroke in the population is not known.

Methods—The first phase of the population-based Greater Cincinnati/Northern Kentucky Stroke Study identified all ischemic strokes occurring in blacks in the greater Cincinnati region between January and June of 1993. The patients in this phase of the study who had a first-ever ischemic clinical stroke were identified, and the volume of ischemic stroke was measured.

Results—There were 257 verified clinical cases of ischemic stroke, of which 181 had a first-ever ischemic infarct. Imaging was available for 150 of these patients, and 79 had an infarct on the CT or MRI study that was definitely or possibly related to the clinical symptoms. For these patients, volumetric measurements were performed by means of the modified ellipsoid method. The median volume of first-ever ischemic stroke for the 79 patients was 2.5 cm³ (interquartile range, 0.5 to 8.8 cm³). There was a significant relation between location of lesion and infarct size (P<0.001) and between volume and mechanism of stroke (P=0.001).

Conclusions—The volume of first-ever ischemic stroke among blacks in our population-based study is smaller than has been previously reported in acute stroke therapy trials. The large proportion of small, mild strokes in blacks may be an important reason for the low percentage of patients who meet the inclusion criteria for tissue plasminogen activator. Further study is necessary to see if these results are generalizable to a multiracial population. (Stroke. 2001;32:1285-1290.)

Key Words: blacks ■ cerebral infarction ■ population ■ stroke, ischemic

The volume of stroke seen on imaging has been correlated with severity of symptoms, clinical outcome, and time to presentation. The volume of stroke on CT scans has been studied in a standardized fashion in acute stroke clinical trials with median volumes between 10.5 and 55 cm³. These volumes may be larger than the true volume of first stroke in the general population because the patients included in these trials presented to hospitals sooner and in general have more severe symptoms consistent with large strokes. Milder strokes in these trials are often excluded from enrollment. Our hypothesis was that stroke volume in a population-based study would be smaller than in acute stroke studies. If the true volume of ischemic stroke is smaller and associated with milder symptoms and/or later arrival to the hospital, this may explain why many stroke patients are not candidates for treatment with tissue plasminogen activator (TPA).

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Only one community-based study has measured volume of cerebral infarct. A Swedish study measured stroke size in all patients admitted to the neurology service at their hospital and reported mean volumes of 34 cm³. One previous study found race to be an independent and significant predictor of the location of infarcts after controlling for variation in the prevalence of risk factors. The first phase of the population-based Greater Cincinnati/Northern Kentucky Stroke Study sought to identify all strokes occurring in blacks in the greater Cincinnati region between January and June of 1993. Data from this phase of the study have already determined that stroke incidence rates among blacks are 288 per 100 000 after adjustment for age and sex, which is a rate greater than that seen among a predominantly

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Stroke is available at http://www.strokeaha.org
white population in Rochester, Minnesota. The patients in this phase of the study who had a first-ever ischemic clinical stroke were identified, and the volume of stroke was measured.

Our objective was to determine the volume and location of infarcts in blacks for comparison with current available literature regarding the volume of first-ever ischemic infarct. We specifically were testing the hypothesis that blacks might have smaller strokes than whites.

**Subjects and Methods**

The study population is defined as all black residents of the Greater Cincinnati/Northern Kentucky region, which includes 2 southern Ohio counties and 3 contiguous Northern Kentucky counties that abut the Ohio River. Included in this area are 19 hospitals. Although residents of nearby counties seek care at the 19 hospitals, only residents of the 5 study area counties are included as cases.

The screening of cases has been described elsewhere. Briefly, study nurses reviewed the medical records of all patients with ICD-9 codes 430 to 438 as primary or secondary discharge diagnoses from the 19 acute-care hospitals in the study region. The study nurses also reviewed all autopsy cases in which stroke was listed as the primary or secondary cause of death. Patients were identified as being from the study area based on their zip code. Last, death certificates that listed stroke as a primary or secondary cause of death were obtained from the Ohio and Kentucky Departments of Vital Statistics for the residents of the 5 study counties.

Once cases were identified, the study nurse abstracted the medical record to gather information regarding stroke symptoms and physical examination findings, past medical and surgical history, medication use before stroke, social history and habits, prehospital evaluation, vital signs and emergency room evaluation, neurological evaluation, diagnostic test results (including laboratory testing, electrocardiographic and cardiac testing, neuroimaging of any type, and so forth), treatments, outcome, type of insurance, and current address (the address identified which census tract to consult for population demographic information). If the time of symptom onset was not known, it was estimated by the study nurse or defined in a standardized fashion; for example, if the patient awoke with symptoms, time of onset was listed as 03:59. The study nurse abstracted this information onto a laptop computer and then made a determination as to whether a stroke or TIA had occurred. All borderline cases were included.

Abstracted information and all available neuroimaging were then reviewed by a study neurologist who made a final determination as to whether the patient would be defined as a case. For each case, all available imaging studies were evaluated. MRI volumes were preferentially used if the patient had both an MRI and a CT scan. All lesions >0.5 cm were characterized, as was the magnitude of periventricular white matter changes. The volume of each stroke was calculated from the CT or MRI films by means of the modified ellipsoid method.

Lesions were characterized into categories based on location: brain stem, cerebellum, cortical, subcortical, combined cortical and subcortical, or watershed. Brain stem lesions were those that involved the midbrain,pons, or medulla. Cerebellum lesions were those that involved the cerebellar hemispheres or peduncles. Cortical lesions were those that involved primarily the cerebral cortex in the frontal, temporal, parietal, or occipital lobes. Subcortical lesions were those that involved the basal ganglia, internal capsule, corona radiata, centrum semiovale, or periventricular region and did not involve the cerebral cortex. Combined lesions were those that involved both cortical and subcortical locations. Watershed lesions were those that involved arterial border zones, such as in the frontal lobe (between the middle cerebral and anterior cerebral arteries) or in the parietal lobe (between the middle cerebral and posterior cerebral arteries). On the basis of the imaging characteristics, the physician attempted to determine the “age” of each lesion. Lesions were classified as either 0 to 30 days or >30 days of age. Lesions were judged to be >30 days if there was no surrounding edema, if the infarct margins were distinct, and there was compensatory dilatation of the lateral ventricle on the side of the infarct.

The physician then decided if the location of the lesion could explain the patient’s clinical symptoms. The physician was asked to determine if the symptoms were definitely, probably, or not related to the lesion seen on imaging.

The most likely classification/cause of stroke was assigned on the basis of the history of symptoms and physical findings and results of testing. The classifications used have been described elsewhere and are adapted from the Classification of Cerebrovascular Diseases III, 1989, and from the epidemiologic studies of stroke in Rochester, Minnesota.

**Inclusions/Exclusions**

There were 257 verified clinical cases of ischemic stroke identified between January and June of 1993, of which 181 had a first infarct (70 had a history of stroke; in 5 patients it was unknown if a prior stroke had occurred; and 1 patient had 2 strokes during the study period but was only counted once). Two of the 181 were also excluded because of a history of intracerebral hemorrhage. Of the 179 eligible patients, 150 had imaging available for review (Figure). Of the 150 patients with imaging available, 71 were excluded from the present analysis (61 had no visible/measurable infarct on admission or subsequent imaging and 10 had lesions that did not explain the clinical symptoms). The remaining 79 patients had an infarct that was definitely or possibly related to the clinical symptoms (Figure). These 79 patients are the basis for the subsequent volume analyses.

In 19 of the 150 patients with available imaging, one lesion possibly or definitely explained the clinical symptoms, but a prior infarct was also seen that appeared older than 30 days. The symptomatic infarct was included in the present volume analysis. The older lesions in these 19 patients plus the 10 patients with lesions that did not explain the clinical symptoms were classified as clinically “silent” cerebral infarctions. These patients are the subjects of a previous report. Patient characteristics were compared between included and excluded cases by means of χ2 analyses. Lesion volumes were measured by the formula [Length (l)×depth (d)× height (h)]/2, and reported as medians (interquartile range). Lesion volumes from this study were compared with lesion volumes of black patients in the placebo group of the NINDS rt-PA trial. Analysis of volume by location and by mechanism was performed with a Kruskall-Wallis test. Last, the small population (n=28) who had both MRI and CT scans were described, and the number of appropriate lesions discovered with each imaging modality was compared by means of χ2 analysis.

**Results**

**Volumes**

The demographic characteristics of the 79 patients with measurable first-ever ischemic clinical cerebral infarct are presented in Table 1. In comparison with the 71 patients...
without measurable infarct, there were no differences in age, sex, history of TIA, hypertension, diabetes, hyperlipidemia, myocardial infarction, angina, congestive heart failure, atrial fibrillation, smoking, or hyperlipidemia. The 71 patients without measurable infarct had a significantly earlier median time of imaging (11.4 hours) versus those who had measurable infarcts (26.8 hours, \( P=0.04 \)). The 79 patients with measurable infarcts were more likely to have had an MRI scan (\( P=0.007 \)). The median volume of first-ever ischemic stroke for the 79 patients was 20.1 cm\(^3\) (interquartile range, 0.5 to 8.8 cm\(^3\)). For comparison with other studies, mean volume was also calculated. The mean volume of first-ever ischemic stroke for the 79 patients was 20.1 ± 56.3 cm\(^3\) (standard deviation) (Table 2).

The median volumes by location of infarct are presented in Table 3. There was a significant relation between location of lesion and infarct size (\( P<0.001 \)). Median volumes for each mechanism of stroke are also displayed in Table 3. There was a significant association between volume and mechanism of stroke (\( P<0.001 \)). Median volumes for each mechanism of stroke are shown in Table 3.

### Table 1. Demographics and Imaging Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Included (n=79)</th>
<th>Excluded (n=71)</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 80 y</td>
<td>40 (50.6%)</td>
<td>36 (50.7%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Male</td>
<td>45 (57.0%)</td>
<td>45 (66.4%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (69.4%)</td>
<td>43 (69.4%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>10 (12.7%)</td>
<td>7 (11.2%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27 (37.5%)</td>
<td>20 (32.8%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prior myocardial infarct</td>
<td>12 (16.7%)</td>
<td>10 (17.2%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8 (10.1%)</td>
<td>13 (18.3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Prior atrial fibrillation</td>
<td>6 (7.6%)</td>
<td>5 (7.0%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Tobacco use (ever)</td>
<td>33 (50.8%)</td>
<td>26 (43.3%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (12.3%)</td>
<td>7 (12.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Time of imaging, h</td>
<td>26.8 (5.8–61.4)</td>
<td>11.4 (3.9–34.5)</td>
<td>0.0397</td>
</tr>
</tbody>
</table>

### Table 2. Median Infarct Volume in Blacks

<table>
<thead>
<tr>
<th>Location</th>
<th>Median Volume</th>
<th>Interquartile Range</th>
<th>Mean (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cincinnati</td>
<td>2.5</td>
<td>0.5, 8.8</td>
<td>20.1 (56.3)</td>
</tr>
<tr>
<td>NINDS trial (24 h)</td>
<td>10.6</td>
<td>0.5, 72.2</td>
<td>48.8</td>
</tr>
<tr>
<td>NINDS trial (7–10 d)</td>
<td>18.3</td>
<td>2.1, 70.0</td>
<td>52.3</td>
</tr>
</tbody>
</table>

NINDS trial volumes reported are from 24-hour and 7- to 10-day CT scans of placebo group blacks (courtesy of John Marler, Mei Lu, and the NINDS t-PA Study Group). Standard deviations are shown where available.

### Imaging

Of the 150 cases with imaging available for review, CT scan alone was performed in 119 patients (79.3%), MRI scan alone in 5 patients (3.3%), and both CT and MRI in 28 patients (18.6%). Regarding timing of the scans, 75 CT scans (63%) were performed in the first 24 hours after symptom onset versus 44 (37%) performed >24 hours after onset. Only 5 (16.1%) MRIs were performed in the first 24 hours versus 26 (83.9%) done >24 hours after symptom onset. With \( \chi^2 \) analysis, MRI scans were performed significantly later (\( P=0.001 \)).

In the patients who had both MRI and CT, the median time to CT was 11.1 hours versus 50.7 hours to MRI. The median difference in time between CT and MRI in these patients was 32.16 hours. MRI was more likely to have a lesion that was possibly or definitely related to the clinical symptoms than was CT (\( P<0.001 \)).

### Discussion

The volume of first-ever ischemic stroke reported here (median volume of 2.5 cm\(^3\), mean volume of 20.1 cm\(^3\)) is smaller than has been previously reported in acute stroke therapy trials and is similar to that seen in the one available population-based study. The volume reported in stroke therapy trials would be expected to be larger than the size of first stroke in the population because of selection bias. Our data and data from the only other available community-based study suggest that most strokes are mild. This may be an important reason for the low percentage of strokes that are treated with TPA.

The median and mean volumes in our epidemiologic study were smaller than those seen in the 24-hour CT scans of the 87 black patients in the placebo group of the NINDS t-PA (personal communication, John Marler, Table 2). Our median volume is also smaller than the median volume of 28.0 cm\(^3\) reported in the RANITAS trial (39.2% blacks) and the mean volume of 33 cm\(^3\) reported in an acute stroke trial of naloxone\(^9\) (percentage of blacks not reported). Our volumes are also smaller than those reported for subacute stroke as measured on CT (mean volume of 55±16 cm\(^3\)) in patients identified in the outpatient setting >2 weeks after their stroke.\(^7\)

The only other community-based study is from Lund, Sweden,\(^10\) which had similar methods for case ascertainment. Both studies may have incomplete case ascertainment if there were errors in diagnosis codes (ie, strokes were not coded appropriately). The Swedish population is largely white and thus differs from the population described in this study. Stroke volumes from the Swedish study were subgrouped by affected circulation rather than anatomic location or presumed mechanism and were reported in mean values rather than medians.

To allow comparison to the Swedish study, however, we display mean volumes (Table 2). Our mean volume was 20.1 cm\(^3\), which appears smaller than the Swedish mean volume. Their technique of volume measurement was Length (l)×Depth (d)×Height (h), which overestimates the volume of stroke, whereas our technique was \( 1\times d \times h / 2 \). Therefore, to compare mean volumes, we divided their numbers by 2. After
this correction, their mean volumes were 17.1 cm³ on CT scans obtained in the first 15 days after stroke and 13.8 cm³ on MRI scans obtained 16 to 180 days after stroke. This suggests similar stroke volumes in both populations.

Our study excluded patients without appropriate lesions on imaging, which in many cases was due to imaging performed shortly after the onset of symptoms when lesions are not yet present on CT. This is evidenced by the shorter median time to imaging in the excluded patients versus those who were included in this analysis. It is possible that patients with earlier presentation and imaging would ultimately have larger strokes, more similar in size to those seen in the therapy trials.

Our methods are similar to and based on other well-designed epidemiological studies. However, our study may be criticized for the large number of clinical cases without an appropriate lesion on imaging. We found appropriate lesions in 79 of 150 (52.7%). This may be related to timing (early scans may be negative) or sensitivity of imaging (CT may miss small lesions or lesions in the posterior fossa and brain stem). Nonetheless, our numbers are not dissimilar to those reported in the Swedish population-based study. On CT scans performed in the first 48 hours after onset, 38 of 81 (47%) had an appropriate lesion identified. Later CT scans and MRI scans identified symptomatic lesions with a frequency >70%.

### TABLE 3. Infarct Volumes by Location/Mechanism of Stroke

<table>
<thead>
<tr>
<th>Location of infarct</th>
<th>n (%)</th>
<th>Median Volume, cm³ (Interquartile Range)</th>
<th>Mean Volume, cm³ (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>2 (2.5%)</td>
<td>0.1 (0.1, 0.1)</td>
<td>0.1 (0)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>32 (40.5%)</td>
<td>0.6 (0.3, 1.6)</td>
<td>1.5 (3.0)</td>
</tr>
<tr>
<td>Cortical</td>
<td>19 (21.5%)</td>
<td>3.8 (1.9, 8.8)</td>
<td>7.4 (13.6)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>4 (5.1%)</td>
<td>3.9 (0.5, 33.8)</td>
<td>17.1 (29.1)</td>
</tr>
<tr>
<td>Watershed</td>
<td>8 (10.1%)</td>
<td>4.0 (1.9, 7.0)</td>
<td>4.5 (3.6)</td>
</tr>
<tr>
<td>Both subcortical and cortical</td>
<td>14 (17.7%)</td>
<td>38.4 (16.0, 114.0)</td>
<td>79.9 (108.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>n (%)</th>
<th>Median Volume, cm³ (Interquartile Range)</th>
<th>Mean Volume, cm³ (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small vessel</td>
<td>22 (27.8%)</td>
<td>0.5 (0.1, 0.8)</td>
<td>0.6 (0.8)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>20 (25.3%)</td>
<td>5.1 (2.8, 30)</td>
<td>25.8 (50.3)</td>
</tr>
<tr>
<td>Large vessel</td>
<td>3 (3.8%)</td>
<td>8.8 (0.7, 8.8)</td>
<td>6.1 (4.6)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (11.4%)</td>
<td>1.9 (0.4, 9.0)</td>
<td>16.3 (36.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (31.7%)</td>
<td>3.6 (1.3, 11.7)</td>
<td>36.4 (85.8)</td>
</tr>
</tbody>
</table>

Our study is unique in that the study population included only blacks. We have previously reported a higher incidence rate of stroke in blacks compared with the predominantly white population of Rochester, Minnesota. The increased incidence rate was distributed over multiple stroke subtypes, with highest incidence rates in "unknown," then small-vessel, then cardioembolic stroke mechanisms. Examination of Table 3 shows that median volumes were small for all defined mechanisms of stroke. Unless black race confers lesion-limiting neuroprotective effects, this disparity suggests that stroke subtype diagnosis, with the methods we used, underestimated the occurrence of small-vessel stroke. Our previous work indicated that hypertension and diabetes were the risk factors with highest attributable risk in this population. Both of these systemic diseases affect small vessels. Our results may not be generalizable to all black populations or to the multiracial population as a whole and must be independently confirmed.

### Conclusions

The volume of cerebral infarction among blacks in our population-based study is smaller than volumes reported in acute stroke therapy trials. Most strokes in the black population are small, with mild symptoms. If this is true for the general population, small infarct size (and mild neurological defects) may be an important reason for the low percentage of patients who present in time or qualify for treatment with TPA.

### Acknowledgments

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### References


The authors present a study indicating that at least since 1993, low-volume ischemic strokes in black Americans at greater risk for small-vessel intracranial vascular disease may indeed be an important cause for the delay in presentations for acute stroke therapy. Studies at present suggest the average presentation of stroke patients to acute therapy is 22 hours. As this and other studies cited in this study suggest, most strokes at initial presentation are mild, particularly in high-risk populations such as blacks. Thus, the study underscores the need to stimulate early awareness of risk factors and stroke warning signs for more disabling stroke. A previous unattended stroke and particularly stroke therapy delayed by low infarct volume and, hence, symptomatology for those high-risk black Americans is thus addressed. The importance of this study should not be dictated by the limitations of possible miscoding in the use of discharge death diagnosis codes as the method used for case ascertainment. It is also obvious that the study results cannot be generalized to all blacks or to multiracial populations as a whole. Rather, ongoing, current, and biracial Cincinnati/Northern Kentucky population comparative studies are warranted. Such current studies, using present techniques, should support these findings and urge the rapid transport of so-called minor strokes and TIA’s to appropriate acute stroke therapy. Thus, not only will such small numbers of patients presenting in the required “therapeutic window” for tPA be increased, but also such patients can gain more appropriate access to basic stroke care. Such will allow the goals of the American Heart/American Stroke Association and the federal government Healthy People 2010 be realized to reduce those at risk for stroke, such as black Americans.

One must question the arbitrary assigned designation of 3:59 AM as the onset of stroke in patients awakening during the night or morning arousal with the signs and symptoms of stroke. While such designation overestimates and also underestimates the time of onset in some strokes, one might assume that the errors would likely occur with equal frequency in either direction, thereby theoretically canceling each other out without introducing bias. Yet with the risk of hemorrhagic strokes high in blacks who bear an increased burden of hypertension, an error in time of stroke onset for the use of tPA could prove critical.

Therefore, one must conclude from this study that further investigation into the relationship of stroke size and its impact on rapid access to stroke therapy must be pursued. Such studies should be performed using present and developing imaging studies in multicultural populations and locations. Coding validations are important if discharge/death diagnosis codes are methods for case ascertainment. The use of an arbitrary assigned time of onset, particularly in small infarcts...
in black populations at risk for hypertension when tPA is used, needs to be reexamined.

However, it is through ongoing studies such as pursued so effectively by these authors that the AHA and its newly formed division, the American Stroke Association, can pursue its goal of reducing stroke and those at risk for stroke by 25% by the year 2010. Of more immediate impetus, the study will help to achieve the goal of moving from 3% to 5% present levels of patients presenting to the “therapeutic window” to a desired 20% by the year 2003, as set by the AHA/ASA goals. Such will particularly benefit black Americans, who assume such an excess burden for stroke.

References
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