ORIGINAL RESEARCH

# Practice Patterns for Acute Ischemic Stroke Workup: A Longitudinal Population-Based Study

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***Background*—**We examined practice patterns of inpatient testing to identify stroke etiologies and treatable risk factors for acute ischemic stroke recurrence.

***Methods and Results*—**We identified stroke cases and related diagnostic testing from four 1-year study periods (July 1993 to June 1994, 1999, 2005, and 2010) of the Greater Cincinnati/Northern Kentucky Stroke Study. Patients aged ≥18 years were included. We focused on evaluation of extracranial arteries for carotid stenosis and assessment of atrial fibrillation because randomized controlled trials supported treatment of these conditions for stroke prevention across all 4 study periods. In each study period, we also recorded stroke etiology, as determined by diagnostic testing and physician adjudication. An increasing proportion of stroke patients received assessment of both extracranial arteries and the heart over time (50%, 58%, 74%, and 78% in the 1993–1994, 1999, 2005, and 2010 periods, respectively; $P<0.0001$ for trend), with the most dramatic individual increases in echocardiography (57%, 63%, 77%, and 83%, respectively). Concurrently, we observed a decrease in strokes of unknown etiology (47%, 48%, 41%, and 38%, respectively; $P<0.0001$ for trend). We also found a significant increase in strokes of other known causes (32%, 25%, 45% and 59%, respectively; $P<0.0001$ for trend).

***Conclusions*—**Stroke workup for treatable causes of stroke are being used more frequently over time, and this is associated with a decrease in cryptogenic strokes. Future study of whether better determination of treatable stroke etiologies translates to a decrease in stroke recurrence at the population level will be essential. **(*J Am Heart Assoc*. 2017;6:e005097. DOI: 10.1161/JAHA.116.005097.)**

**Key Words:** acute stroke • evidence-based medicine • population



As much as 25% of annual ischemic strokes are recurrent events.[1] Establishing stroke etiology is the cornerstone to identifying treatable conditions that may reduce this risk. Cryptogenic strokes occur at a yearly rate of at least 35%.[2] Clearly, absence of the etiology of a stroke precludes any targeted and thoughtful secondary prevention strategies; therefore, cryptogenic strokes represent a barrier to reducing stroke recurrence.

In the 1990s, with the publication of the NASCET (North American Symptomatic Carotid Endarterectomy)[3] and SPAF (Stroke Prevention in Atrial Fibrillation)[4] trials, treatment of carotid stenosis ≥70% with carotid endarterectomy and anticoagulation for nonvalvular atrial fibrillation (AF) became evidence-based interventions. Importantly, these interventions were specifically targeted at a particular stroke etiology. Consequently, assessment of the extracranial arteries for high-grade stenosis and the heart for thrombi or evidence of AF (eg, an enlarged left atrium) became essential.[5]

In the current study, we hypothesized that more rigorous use of appropriate investigative modalities to determine stroke etiology would be associated with a decrease in strokes of unknown etiology (cryptogenic strokes) over time. Given that symptomatic carotid stenosis and AF are treatable and that their treatment is known to improve outcomes, it is essential to identify them during diagnostic testing.

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/6/e005097/DC1/embed/inline-supplementary-material-1.pdf

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## Clinical Perspective

### What Is New?

- The inpatient evaluation of acute ischemic stroke has changed over time in our population.
- From 1993 to 2010, there has been an increase in diagnostic modalities aimed at assessing extracranial carotid disease, cardioembolism, and small vessel disease.
- Concurrently, we observed a decrease in the frequency of cryptogenic stroke (from 47% to 38%).

### What Are the Clinical Implications?

- More frequent identification of stroke etiology is essential for discovery and successful implementation of secondary prevention strategies.

## Methods

We reviewed stroke-related diagnostic testing for first-ever hospitalized ischemic strokes among residents of the Greater Cincinnati/Northern Kentucky (GCNK) 5-county region of 1.3 million people during four 1-year study periods (July 1993 to June 1994 and calendar years 1999, 2005, and 2010). In the region, 19 hospitals were active in 1993–1994, 18 in 1999, 17 in 2005, and 16 in 2010, including a broad range of hospital types, ranging from small community hospitals to large academic medical centers. This study was approved by the institutional review boards of all participating hospitals for each study period; given the observational nature of the study, the requirement for informed consent was exempted.

Patients aged ≥18 years were included. The methods of the GCNK Stroke Study have been reported previously.[6] Briefly, the GCNK Stroke Study involved ascertainment of all stroke events that occurred in the population during the 4 study periods. In 1993–1994, research nurses screened the medical records of all inpatients with primary or secondary stroke-related *International Classification of Diseases, 9th Revision* (ICD-9) discharge diagnoses 430 to 438 from the acute care hospitals in the study region. In 1999, 2005, and 2010, the ICD-9 codes 430 to 436 were used because of low yield from codes 437 and 438 in 1993–1994. In addition, strokes not found by inpatient screening were ascertained by monitoring all stroke-related visits to hospital emergency departments, public health clinics, hospital-based outpatient clinics, and family practice centers. Patients for whom stroke was listed as the primary or secondary cause of death by the county coroners' offices were also included.

The seminal SPAF and NASCET studies, which supported assessment of the heart and extracranial vessels, were published by 1991. Therefore, we defined a *complete workup* as a combination of (1) echocardiography or history of AF (which already suggests a cardioembolic source and may not necessitate echocardiogram) and (2) evaluation of extracranial arteries by carotid ultrasound, magnetic resonance angiogram (MRA), or digital subtraction angiography. We utilized a hierarchy of etiology to assign a "final" cause of stroke that gave highest priority to the most distal cause.

Specifically, we recorded testing aimed at determination of the following stroke etiologies: (1) large vessel atherothrombosis (by carotid ultrasound or MRA), with the goal of determining those who would benefit from carotid endarterectomy or stenting; (2) cardioembolism (by ECG, echocardiogram, or history of AF). Notably, we did not include patent foramen ovale as cardioembolic unless a peripheral source was found such as a deep vein thrombosis; (3) small vessel atherosclerosis (by computed tomography or magnetic resonance imaging [MRI]). We requested films and measured infarcts when relevant for diagnosing a small vessel etiology which required infarcts of <1.5 cm in diameter, and size was not available in the radiological report. Of note, computed tomography angiogram was performed infrequently in the early study periods, and we did not abstract data on whether those studies included head, neck, or both; therefore, this information was not included in the temporal trends table. Similarly, we did not abstract data on prolonged outpatient cardiac rhythm monitoring until the most recent study period.

## Statistics

The data were managed and analyzed with SAS version 9.3 (SAS Institute, Cary, NC). Only first-ever ischemic stroke cases evaluated in an emergency department were used for this analysis. The same clinical definition of ischemic stroke was used in each time period (ie, acute onset of focal neurological signs consistent with a cerebrovascular lesion and a negative noncontrast head computed tomography for intracranial hemorrhage). Analysis of the demographic variables involved assessment of change over time. For the continuous variables age and systolic blood pressure, year was treated as an interval variable (4 time points) in the general linear model. For National Institutes of Health Stroke Scale (NIHSS) score, there were only 2 time points, and due to the distribution of the score, a Wilcoxon rank sum test was used to examine the difference between 2005 and 2010. For the remaining categorical variables, the Cochran-Armitage test for trend was used, with $P<0.05$ considered statistically significant; this 2-tailed $P$ value was calculated from the $Z$ distribution. For examination of the stroke etiology, a Bonferroni correction was used for evaluation of the critical value for the outcome variables.

## Results

The baseline patient characteristics are shown in Table 1. The numbers of patients were 1458, 1455, 1403, and 1475 in

**Table 1.** Patient Demographics by Study Period

| | 1993–1994 (n=1458) | 1999 (n=1455) | 2005 (n=1403) | 2010 (n=1475) | *P* Value (for Time Trend) |
|---|---|---|---|---|---|
| Age, mean±SD | 72.4±12.7 | 72.1±13.6 | 69.1±15.1 | 69.0±15.3 | <0.001 |
| Female, n (%) | 826 (56.6) | 806 (55.4) | 780 (55.6) | 820 (55.6) | 0.60 |
| Black, n (%) | 256 (17.6) | 257 (17.7) | 305 (21.7) | 300 (20.3) | 0.006 |
| Baseline NIHSS, median | Not recorded | Not recorded | 3 (2–7) | 3 (1–6) | <0.0001 |
| Baseline SBP, mean±SD | 164.3±50.9 | 164.0±46.2 | 158.4±31.9 | 158.3±31.1 | <0.0001 |
| CAD, n (%) | 250 (17.2) | 456 (31.3) | 403 (28.7) | 459 (31.1) | <0.0001 |
| CHF, n (%) | 241 (16.5) | 233 (16.0) | 218 (15.5) | 253 (17.2) | 0.78 |
| Hypertension, n (%) | 875 (60.0) | 977 (67.2) | 1052 (75.0) | 1166 (79.0) | <0.0001 |
| Current smoker, n (%) | 313 (21.5) | 331 (22.8) | 359 (25.6) | 418 (28.3) | <0.0001 |
| Prior TIA, n (%) | 193 (13.2) | 152 (10.4) | 211 (15.0) | 197 (13.4) | 0.20 |

CAD indicates coronary artery disease; CHF, congestive heart failure; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TIA, transient ischemic attack.



1993–1994, 1999, 2005, and 2010, respectively. Across the study periods, there was a decrease in mean age (72.4 years in 1993–1994 versus 69.0 years in 2010; $P<0.001$), an increase in the proportion of black participants (17.6% versus 20.3%; $P=0.006$), and a small decrease in baseline systolic blood pressure (164.3 versus 158.3 mm Hg; $P<0.0001$). There were increases in the proportion of patients with coronary artery disease (17.2% versus 31.1%), hypertension (60.0% versus 79.0%), and current smoking (21.5% versus 28.3%; $P<0.0001$ for each trend). In 2005 and 2010, respectively, 5% and 6% of patients had NIHSS >20.

Across the 4 study periods, we observed a significant increase in stroke patients that had both cardiac and extracranial artery assessments (ie, our definition of a complete workup); in 2010, 78% of patients had complete assessments compared with 74% in 2005, 58% in 1999, and 50% in 1993–1994 (Table 2). The largest increase was seen in cardiac assessment with echocardiography, from 57% in 1993–1994 to 83% in 2010. Unfortunately, we did not have data regarding prolonged cardiac rhythm monitoring in the earlier study periods, given that this modality is relatively new. We also performed MRIs and MRAs more frequently (18% and 8%, respectively) in 1993–1994 compared with 2010 (74% and 47%, respectively). Moreover, there was an increase in the assessment of lipids, as shown by either a history of hyperlipidemia or testing of lipids during hospitalization (from 51% in 1993–1994 to 86% in 2010, $P<0.0001$ for trend). Even in the 2 most recent study periods (2005 and 2010), there continued to be an increasing proportion of patients who received a complete workup (Table S1).

Across study periods, the number of strokes classified as *undetermined* was reduced from 46% in 1993–1994 to 38% in 2010 ($P<0.0001$ for trend; Table 3). In the 2 most recent study periods, there was a smaller proportion of undetermined strokes from 2005 to 2010; however, this difference did not reach statistical significance (Table S2).

## Discussion

In our study, there was an increase over time in diagnostic tests aimed at identification of strokes attributable to large vessel disease (primarily through the increased use of MRA), cardioembolism (through more frequent echocardiograms), and small vessel disease (through more rigorous brain imaging and assessment of lipids). Concurrently, we observed a decrease in the frequency of cryptogenic stroke (from 47% to 38%).

Although there was an increase in the frequency of MRAs, we did not find a change in the number of large vessel strokes. An explanation is that MRAs were being done for reasons other than assessment of extracranial carotid stenosis. In these cases, there would have been a low pretest suspicion of significant carotid disease. With the increase in MRIs, we identified more strokes caused by small vessel disease. This increase in small vessel disease may also be related to having more evidence that strokes were not due to large vessel disease because there was also an increase in cardiac assessment and more frequent identification of cardioembolic strokes over time. The sharp increase in the proportion of patients with a diagnosis of hyperlipidemia most likely reflects better understanding of cardiovascular event risk factors or more frequent diagnosis, as opposed to a significant increase in the true prevalence. Alternatively, there may have been increased adherence to clinical quality measures. Indeed, the first major randomized controlled trial for cholesterol reduction in secondary stroke prevention was SPARCL, published in 2006. SPARCL demonstrated a 5-year absolute risk reduction of 2.2% in participants treated with 80 mg of atorvastatin, with even greater benefit in the

**Table 2.** In-Hospital Ischemic Stroke Workup by Study Period

| Diagnostic Test | 1993–1994 (n=1458) | 1999 (n=1455) | 2005 (n=1403) | 2010 (n=1475) | *P* for Time Trend |
|---|---|---|---|---|---|
| Standard tests, n (%) | | | | | |
| Complete workup* | 722 (50) | 837 (58) | 1036 (74) | 1144 (78) | <0.0001 |
| Cardiac assessment | 917 (63) | 1007 (69) | 1140 (81) | 1293 (88) | <0.0001 |
| ECG | 1329 (91) | 1358 (93) | 1344 (96) | 1451 (98) | |
| Telemetry | Not recorded | Not recorded | Not recorded | 1342 (91) | |
| History of AF | 218 (15) | 211 (14) | 204 (15) | 323 (22) | |
| Echocardiogram | 837 (57) | 917 (63) | 1085 (77) | 1224 (83) | |
| Extracranial arteries assessed† | 982 (67) | 1065 (73) | 1185 (84) | 1252 (85) | <0.0001 |
| Carotid ultrasound | 926 (64) | 924 (64) | 830 (59) | 900 (61) | |
| MRA | 118 (8) | 224 (15) | 684 (49) | 698 (47) | |
| Digital subtraction angiogram | 61 (4) | 70 (5) | 45 (3) | 35 (2) | |
| Carotid ultrasound and MRA | 82 (6) | 108 (7) | 339 (24) | 355 (24) | |
| Carotid ultrasound only | 809 (55) | 787 (54) | 482 (34) | 543 (37) | |
| MRA only | 36 (2) | 107 (7) | 330 (24) | 328 (22) | |
| Brain imaging | 1378 (94.5) | 1444 (99.2) | 1401 (99.9) | 1474 (99.9) | <0.0001 |
| CT of head | 1365 (94) | 1427 (98) | 1378 (98) | 1441 (98) | |
| MRI of brain | 259 (18) | 441 (30) | 932 (66) | 1096 (74) | |
| Risk factor screening, n (%) | | | | | |
| Lipids assessed | 749 (51) | 594 (41) | 982 (70) | 1264 (86) | <0.0001 |
| History of hyperlipidemia | 131 (9) | 294 (20) | 498 (36) | 737 (50) | |
| Lipid levels | 702 (48) | 384 (26) | 759 (54) | 1024 (69) | |
| Statin on admission | 37 (3) | 197 (14) | 390 (28) | 528 (36) | <0.0001 |
| Statin on discharge | Not recorded | Not recorded | 605 (43) | 850 (58) | <0.0001 |
| Diabetes mellitus assessed | Not recorded | Not recorded | 993 (71) | 1275 (86) | <0.0001 |
| History of diabetes mellitus | 398 (27) | 437 (30) | 441 (31) | 484 (33) | |
| Hemoglobin $A_{1c}$ | Not recorded | Not recorded | 269 (19) | 526 (36) | |
| Fasting glucose | Not recorded | Not recorded | 741 (53) | 1177 (80) | |

AF indicates atrial fibrillation; CT, computed tomography; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging.
*Complete workup was considered to be assessment of extracranial carotids and history of atrial fibrillation or echocardiography.
†Defined as having at least 1 of the following: carotid ultrasound, MRA, or digital subtraction angiogram.



subgroup with low-density lipoprotein <70 mg/dL.[7] We also observed an increase in the use of statins over our study periods that may be related to the increased diagnosis of hyperlipidemia.

It is important to mention several limitations of the current study. First, our study represents a Midwestern population of 1.3 million. It is unclear whether our practice patterns, patient demographics, and health care system characteristics are generalizable to other regions, although we know, based on census data, that our region is representative of the United States with regard to median age, percentage of black persons, median household income, and percentage of the population below the poverty level (Table 4). Second, with respect to detection of paroxysmal AF, it is known that transthoracic echocardiogram and a single ECG are not sensitive.[8] A limitation of our study is that we did not have data on the frequency of telemetry use on the inpatient stroke unit for all study periods or on discharge with Holter or 30-day event monitors. Transthoracic echocardiogram use, however, would evaluate for focal wall motion abnormalities, intracardiac shunts, thrombi, or valvular abnormalities, all of which could lead to cardioembolism. Third, the median NIHSS score from the 2005 and 2010 study periods was 3, indicating that the majority of strokes were mild. It is possible that more testing is done for mild strokes because their etiologies are less apparent and because the patients may be eligible for more risk-reduction treatments such as anticoagulation and carotid endarterectomy. Unfortunately, we do not have

**Table 3.** Etiology Determined by Diagnostic Testing and Physician Adjudication

| Etiology | 1993–1994 (n=1458) | 1999 (n=1455) | 2005 (n=1403) | 2010 (n=1475) | *P* Value* |
|---|---|---|---|---|---|
| Small vessel | 240 (17) | 216 (15) | 278 (20) | 264 (18) | 0.04 |
| Cardioembolic | 321 (22) | 301 (21) | 300 (21) | 404 (27) | 0.0006 |
| Large vessel | 187 (13) | 209 (14) | 199 (14) | 186 (13) | 0.82 |
| Other known cause (all) | 32 (2.2) | 25 (1.7) | 45 (3.2) | 59 (4.0) | 0.0003 |
| Other known cause (not iatrogenic) | 20 (2.2) | 21 (1.7) | 41 (3.2) | 55 (4.0) | <0.0001 |
| Iatrogenic/periprocedural | 12 (0.82) | 4 (0.27) | 4 (0.29) | 4 (0.27) | 0.09 |
| Dissections | 2 (0.14) | 7 (0.48) | 16 (1.14) | 18 (1.22) | 0.0004 |
| Undetermined | 678 (47) | 704 (48) | 581 (41) | 562 (38) | <0.0001 |

Data are shown as n (%).
*Only those significant at the 0.01 level are considered statistically significant (Bonferroni correction).

information about the median NIHSS scores from the 2 earlier time points to formally consider whether milder strokes are associated with an increase in testing. It should also be noted that we might have underestimated the frequency of essential diagnostic testing. Some tests may have occurred in an outpatient setting, and others may have had appropriately limited workup because of terminal stroke or comorbidities that limit subsequent secondary prevention therapies (eg, anticoagulation or carotid endarterectomy). Nevertheless, given that only 5% and 6% of patients had NIHSS >20 in 2005 and 2010, respectively, it is unlikely that a significant number of patients had testing limited because of terminal strokes. Similarly, we do not have information regarding initiation or adherence to risk-reduction treatments; therefore, we do not have sufficient data to make any direct associations.

Annual recurrent stroke rates seen in clinical trials have decreased over the past 50 years by ≈3.5%.[9] A recent meta-analysis found that increasing use of antiplatelet drugs and antihypertensive medications was associated with this decline,[8] although a causal relationship clearly cannot be determined. It may also be speculated that carotid endarterectomy and anticoagulation have reduced recurrent strokes in patients with high-grade carotid stenosis and AF, respectively. Furthermore, because there was more rigorous testing, there were fewer cryptogenic strokes in the current study. Because our definition of complete workup included a known history of certain stroke risk factors, this change could be due to better premorbid medical care.

Three main criteria have historically been used in assigning the cause of stroke as cryptogenic.[10] First are cases in which no apparent cause can be determined despite an appropriate evaluation. Second are others that may have no obvious etiology, but the workup was not thorough. Finally, some patients have ≥2 likely causes; therefore, 1 etiology cannot be assigned. In our study, we assigned the final cause as the most distal. A patient with AF and ipsilateral carotid stenosis, for example, would be labeled as *carotid stenosis*. Nonetheless, we found that 38% of strokes still had no identifiable etiology despite appropriate workup; others have reported similar numbers.[2] Of note, MRIs were not obtained for all patients to assist in determining etiology, perhaps because MRI is not well established to change outcome. At the least, these findings underscore the need to maximize investigations that lead to evidence-based stroke risk reduction. In the future, it will be important to determine whether rigorous workups translate into reduction of recurrent strokes at the population level.

**Table 4.** GCNK Vs US Population (2010 Census)

| Demographic | GCNK | United States |
|---|---|---|
| Size | 1 368 604 | 308 700 000 |
| Median age, y | 34 | 37 |
| Black, % | 16.3 | 13.1 |
| White, % | 79.8 | 78.1 |
| Median household income | $53 178 | $52 762 |
| Below poverty, % | 13.5 | 14.3 |
| High school graduate, % | 87.9 | 85.4 |

GCNK indicates Greater Cincinnati/Northern Kentucky.

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## Disclosures

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# SUPPLEMENTAL MATERIAL

**Table S1.** In-Hospital Ischemic Stroke Workup, 2005 and 2010 Study Periods

| Diagnostic Test | 2005<br>N=1403 | 2010<br>N=1475 | p-value |
|---|---|---|---|
| Complete Workup | 1036 (74%) | 1144 (78%) | 0.02 |
| Cardiac Assessment | 1140 (81%) | 1293 (88%) | <0.0001 |
| Extracranial Arteries Assessed | 1185 (84%) | 1252 (85%) | 0.75 |

**Table S2.** Etiology Determined by Diagnostic Testing and Physician Adjudication, 2005 and 2010 Study Periods

| Etiology | 2005<br>N=1403 | 2010<br>N=1475 | p |
|---|---|---|---|
| Undetermined | 581 (41%) | 562 (38%) | 0.07 |

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