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Stroke. 2005;36:720-723; originally published online February 24, 2005;

doi: 10.1161/01.STR.0000158917.59233.b7

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Incidence and Short-Term Prognosis of Transient Ischemic Attack in a Population-Based Study

Dawn Kleindorfer, MD; Peter Panagos, MD; Arthur Pancioli, MD; Jane Khoury, MS; Brett Kissela, MD; Daniel Woo, MD; Alexander Schneider, MD; Kathleen Alwell, RN; Edward Jauch, MD; Rosie Miller, RN; Charles Moomaw, PhD; Rakesh Shukla, PhD; Joseph P. Broderick, MD

Background and Purpose—Transient ischemic attacks (TIAs) have been shown to be a strong predictor of subsequent stroke and death. We present the incidence and short-term prognosis of TIA within a large population with a significant proportion of minorities with out-of-hospital TIA.

Methods—TIA cases were identified between July 1, 1993 and June 30, 1994 from the Greater Cincinnati/Northern Kentucky population of 1.3 million inhabitants by previously published surveillance methods, including inpatient and out-of-hospital events. Incidence rates were adjusted to the 1990 population, and life-table analyses were used for prognosis.

Results—The overall race, age, and gender-adjusted incidence rate for TIA within our population was 83 per 100 000, with age, race, and gender adjusted to the 1990 US population. Blacks and men had significantly higher rates of TIA than whites and women. Risk of stroke after TIA was 14.6% at 3 months, and risk of TIA/stroke/death was 25.2%. Age, race, and sex were not associated with recurrent TIA or subsequent stroke in our population, but age was associated with mortality.

Conclusions—Using our incidence rates for TIA in blacks and whites, we conservatively estimate that \approx 240 000 TIAs occurred in 2002 in the United States. Our incidence rate of TIA is slightly higher than previously reported, which may be related to the inclusion of blacks and out-of-hospital events. There are racial and gender-related differences in the incidence of TIA. We found a striking risk of adverse events after TIA; however, there were no racial or gender differences predicting these events. Further study is warranted in interventions to prevent these adverse events after TIA. (*Stroke*. 2005;36:720-724.)

Key Words: cerebral ischemia ■ cerebral ischemia, transient ■ epidemiology ■ prognosis

Transient ischemic attacks (TIAs) have been found to be a strong predictor of subsequent stroke and death. Johnston et al found that in 1707 patients with TIA diagnosed in the emergency departments of a large Northern California health maintenance organization, the 90-day stroke risk was 10.5% after TIA.¹ Hill et al found that the risk of stroke after TIA in Canada was 9.5% at 90 days, and 14.5% at 1 year.² However, both of these studies were performed without physician confirmation, excluded out-of-hospital events, and were not within a population of similar socioeconomic characteristics of the overall US population.

The population of Rochester, Minnesota has provided the only population-based data addressing temporal trends in TIA incidence in the United States over the past 50 years.^{3,4,5} However, blacks represent only 1% of the Rochester population as compared with 13% for the United States.^{5,6} Although there are many other studies describing TIA in the literature, few have required cases to be physician-reviewed

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or have been performed within a population with significant minority populations.⁷⁻¹⁴

The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) is a large US population-based metropolitan study of stroke/TIA incidence rates and outcomes.¹⁵ This population is estimated to be 1.3 million residents, with similar percentage of blacks and similar socioeconomic demographics to the United States in general. We present incidence rates of TIA and short-term outcomes after TIA drawn from our large, biracial population of 1.3 million, including inpatient and out-of-hospital events. These data are useful in identifying subpopulations at additional risk and will allow for a more focused public health approach for preventive strategies.

Subjects and Methods

The methodology of the greater Cincinnati/northern Kentucky Stroke Study (GCNKSS) has been previously described.¹⁵ The study

Received September 7, 2004; final revision received December 13, 2004; accepted December 21, 2004.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000158917.59233.b7

population for the GCNKSS is defined as all residents of the greater Cincinnati metropolitan 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 surrounding counties seek care at these hospitals, only residents of the 5 study area counties as determined by zip code of residence are included as cases. Previous studies have documented that residents of the 5 counties who have a stroke exclusively seek care at these 19 hospitals rather than more distant hospitals in the outlying region.⁶ This population is estimated to be 1.3 million residents, with similar percentage of blacks, and similar socioeconomic demographics to the United States in general. This study was approved by the institutional review board at all participating hospitals.

Study nurses screened the medical records of all inpatients with primary or secondary stroke-related *International Classification of Diseases, 9th Edition* discharge diagnoses (430 to 438, 747.81, 674.0, 325) from the 19 acute-care hospitals in the study region for the study period of July 1, 1993 to June 30, 1994. We also ascertained strokes not found by inpatient monitoring; this was performed by monitoring all visits to 18 of the hospital's emergency departments (excluded Cincinnati Children's Hospital), 5 county coroner's offices, 16 public health clinics, and 14 hospital-based outpatient clinics and family practice centers. In addition, cases were ascertained using a random sample generated by our statistician of 50 of 878 primary care physicians' offices and 25 of 193 nursing homes in the greater Cincinnati metropolitan area. This random sample was generated from a list of all physician's offices and nursing homes in the area, drawn from the local yellow pages and from the local Academy of Physicians listing of all physicians in the area. All events found by out-of-hospital monitoring were checked against inpatient records to prevent double counting.

To qualify as a case, a patient must have met the criteria for 1 of the 5e stroke categories adapted from the Classification for Cerebrovascular Diseases III and from epidemiological studies of stroke in Rochester, Minnesota.^{3,6,16} Specifically, the definition of TIA was focal acute neurological signs and symptoms that lasted <24 hours. The onset of symptoms must have occurred within the study time period of July 1, 1993 to June 30, 1994. A qualifying TIA may have been a first-ever TIA or a recurrent TIA after a previous event occurring outside of the study time period. All recurrent TIAs after the first event during the study period were not counted for incidence.

Once potential cases were identified, the study nurse gathered information regarding stroke symptoms, physical examination findings, past medical/surgical history, vital signs and emergency room evaluation, neurological evaluation, diagnostic test results treatments, and outcome. Classification of race/ethnicity was as self-reported in the medical administrative record. The study nurse abstracted all information and then made a determination as to whether a stroke or TIA had occurred. All borderline or possible cases were abstracted for physician review.

A study physician reviewed every possible case, and all available neuroimaging studies to determine whether a stroke or TIA had occurred. The physician assigned stroke/TIA category and mechanism to each event based on all available information, using definitions listed and previously reported.⁶ Agreement between nurse abstractors and physicians for TIA case/not a case was 93% ($\kappa=0.84$).

The numerator for incidence rate calculation was the number of incidence cases confirmed by physician review. The denominator was based on linear extrapolations of county populations in race, sex, and age subcategories for the years 1993 to 1994 as published by the US Census Bureau (www.census.gov). Given our out-of-hospital ascertainment sampling scheme, the number of physician-confirmed outpatient cases was weighted to estimate the total number of out-of-hospital events in the study population. In this manner, events ascertained in the physician offices and nursing homes were multiplied \approx 18-fold and 8-fold (878/50 and 193/25), respectively. Weighting of out-of-hospital events was only performed for calculations of incidence rates, not for outcome event rates. The at-risk population for 1993 to 1994 included 197 541 blacks and 1 114 092 whites. Age-, race-, and gender-specific rates were also determined.

TABLE 1. Incidence Rates of TIA (Per 100 000)

	TIA Incidence Rate (95% CI)*	P Value
Male	101.4 (92.4, 110.4)	<0.0001 vs female
Female	69.8 (64.0, 75.8)	
Black	98.0 (82.1, 113.9)	0.025 vs White
White	81.3 (76.0, 86.6)	
Total	82.9 (77.9, 88.0)	

*Adjusted for age, and race or gender as appropriate, and standardized to the 1990 US population.

Race-specific adjusted rates were adjusted to the 1990 US Population. We followed standard procedures for adjustments of incidence rates, which accounts for potential interactions between race, age, and gender by simultaneously adjusting for demographic characteristics. The 95% confidence intervals for the incidence rates were calculated assuming a Poisson distribution.

The estimated total number of TIA events for the US were calculated for the year 2002 using the following technique: using the published census population for 2002 (<http://www.census.gov>), the rates were projected to 2002 and adjusted to the 2002 population. Hispanic and other minority populations were assumed to have similar rates of TIA as whites.

Descriptive and comparative statistical analyses were performed using SAS version 8.1 (SAS Institute). Kaplan–Meier life-table analysis was used to assess the length of time to the adverse events and the event rate at discrete time points. Cox regression was used to assess the effect of age, race, and gender on the chance of a subsequent event after the index TIA.

All strokes and TIAs occurring after the index TIA in the study period should have been captured, unless the patient moved outside the study area, or if the patient never sought medical attention for their symptoms, both of which could result in an underestimation of stroke risk. An additional 2 months of screening beyond the 18-month study period was performed to ensure inclusion of stroke patients who had the onset of TIA within the study year but were discharged after the study period had ended. All cases of TIA in our database were cross-matched with vital statistic data from the states of Ohio and Kentucky, as well as the US Social Security Death Index database to determine survival.

Results

During the study period, a total of 1023 TIA events occurred among 927 patients (first-ever or recurrent). For the 927 subjects with a TIA event, the mean age at the first event in the study period was 70.4 (SD, 12.6) years. Blacks comprised 15.2% of the patients and other races were 0.4%; 496 patients (53.5%) were female, 81.9% presented at the emergency department, and 78.7% of these were admitted to the hospital. The overall annual age- and sex-adjusted incidence rate, adjusted to the 2000 population, for a single TIA during the study period in our population was 83 per 100 000 (95% confidence interval, 78–88).

Blacks had a significantly higher overall incidence of TIA when compared with whites, and men had a significantly higher overall incidence of TIA when compared with women. (Table 1). When subdivided by race and gender, the age-adjusted incidence was somewhat higher in black males than white males, although the difference was not statistically significant. The age-adjusted rate was significantly lower for white females than for all other race/gender groups. (Table 2) The highest incidence of TIA of any group was seen in the

TABLE 2. Age-Specific Incidence Rates of TIA Per 100 000 by Race and Gender

Age Range, y	TIA Incidence Rates			
	White Male	White Female	Black Male	Black Female
<35	1.0 (0.0–2.2)	1.8 (0.2–3.3)	1.7 (0.0–5.2)	3.2 (0.0–7.8)
35–44	4.6 (0.1–9.0)	12.3 (5.0–19.6)	16.0 (0.0–38.3)	12.7 (0.0–30.2)
45–54	82.2 (59.2–105.2)	73.3 (52.3–94.2)	129.8 (49.4–210.3)	30.2 (0.0–64.3)
55–64	155.4 (118.7–192.1)	96.3 (69.0–123.5)	205.7 (89.3–322.1)	249.0 (139.9–358.2)
65–74	468.5 (395.7–541.3)	246.6 (201.1–292.1)	338.2 (172.5–503.9)	330.2 (192.2–468.3)
75–84	750.4 (620.9–879.9)	521.1 (441.8–600.4)	612.8 (279.7–945.9)	647.9 (393.9–901.9)
85+	718.5 (457.0–980.0)	589.3 (455.0, 723.5)	1557.9 (478.3–2637.5)	847.8 (346.8, 1348.8)
Overall Adjusted Rates (95% CI)	100.6 (91.1, 110.1)	67.6* (61.4, 73.9)	107.2 (79.8, 134.7)	92.6 (72.9, 112.4)

*White females overall rate less than all others $P < 0.05$.

extremely elderly black men, at 1558 events per 100 000. The incidence of TIA increased exponentially with age, regardless of race or gender.

Median follow-up for patients in the study population was 122 days (25th to 75th percentile, 30 to 232 days). This follow-up time excludes follow-up for death, because this was achieved separately and complete 1-year follow-up was attained. The median time between the index TIA and a recurrent event was 12 days for TIA (25th to 75th percentiles, 2 to 3 days), 12 days for stroke (25th to 75th percentiles, 3 to 48 days), and 11 days for either TIA or stroke (25th to 75th, 2 to 38 days).

Within 6 months of the index TIA, 144 patients had an ischemic stroke, 80 experienced a recurrent TIA, and 77 died. Table 3 depicts the actuarial risks of recurrent TIA, stroke, and death at discrete time points during the first 6 months after the index TIA. The short-term outcome measured at 2 days was 2.4% for recurrent TIA and 3.9% for ischemic stroke after a TIA. The mortality rate at 1 year after TIA was 12.3%.

Cox regression analysis was performed to determine if there was an association between potential risk factors and recurrent TIA, subsequent stroke, or death. Age, race, and sex were not associated with recurrent TIA or subsequent stroke in our population. We did, however, find a strong association between increasing age and increasing risk of death, a 79% (95% confidence interval, 40% to 126%) increase for each 10-year increase in age. Race and sex did not affect the rate of death in the TIA patients. We were unable to evaluate the effect of the concomitant medical conditions because this information was not available on the majority of those patients discharged from the emergency department.

TABLE 3. Short-Term Prognosis After a TIA: GCNK 93–94

Recurrence	TIA, %	Infarct, %	Combined (Infarct/TIA), %	Death, %	Combined (Infarct/TIA/Death), %
2 d	2.4	3.9	6.2	0.0	6.2
7 d	3.9	7.0	10.9	0.6	11.4
1 mo	6.9	11.2	17.8	3.2	19.8
2 mo	7.8	13.3	20.5	4.4	22.8
3 mo	8.6	14.6	22.5	5.2	25.2
6 mo	9.5	17.3	25.8	8.3	29.9

Discussion

In our large, biracial population, we found the incidence of a single TIA to be 83 per 100 000, with age, race, and gender adjusted to the 1990 US population, which is much higher than reported in other countries and slightly higher than the incidence reported from the all-white, affluent population of Olmstead County, Minnesota.⁵ The difference in rates may be caused to in part by the inclusion of blacks and out-of-hospital TIAs within our population; however, our age- and gender-adjusted rate for whites is still higher at 80 per 100 000. Comparisons to other incidence rates must be made with caution, however, because we included both first-ever and recurrent events that occurred during the study period in the denominator, whereas many other studies only evaluate first-ever events.

We also found a striking risk of adverse events after TIA. The overall 6-month ischemic stroke rate was 17%, with >65% occurring within 30 days of the initial TIA, with an extremely high rate of stroke or TIA seen within 2 days, at 6%.

The short-term rate of stroke or recurrent TIA was 26% during the 6 months after a TIA. Subsequent TIA or stroke was not related to age, race, or gender of the patients presenting with TIA, although age was significantly related to mortality. A previous publication by Johnston et al had found that age older than 65 was predictive of stroke after TIA. It is not immediately clear why our data differ on this point, unless it is related to differences in the patient populations.

The issue of racial disparity in TIA incidence has not been clearly examined in the literature to date. We found that the incidence of inpatient and out-of-hospital TIA among blacks was 1.4-times greater than the overall age- and sex-adjusted incidence rate of TIA among the white population. These data are similar to the 1.5-times increase in overall black stroke risk burden previously reported in our population.¹⁵ Previous studies of TIA in Rochester, Minnesota, Oxfordshire, England, and Estonia, Russia had small proportions of blacks within their populations and an advantage of our study is a direct comparison of incidence rate of TIA among blacks compared with whites within the same population.^{7,12} We are unable to address the incidence of TIA in other minorities, such as Asian or Hispanic populations, because they comprise <2% of our population.

Our group has previously reported that the increased incidence of stroke in blacks is driven by a large difference in the younger age groups, in that blacks younger than age 55 have 5-times the risk of similarly aged whites.¹⁵ However, with TIA, the incidence is increased in blacks in most age groups, with the extreme differences occurring in elderly black men and women. However, this extreme effect could be because of the small denominators in this age group.

Our rate of stroke after TIA within 90 days (14.6%) is very similar to other rates previously reported. Our study's slightly higher rates may be related to the inclusion of the uninsured, a larger proportion of minority populations at higher risk and/or out-of-hospital ascertained TIA.

Despite being population-based, there are some important limitations to our study. First, cases were identified retrospectively from inspection of medical records, and there is always a risk of incomplete case ascertainment. However, prospective monitoring of an entire population is not feasible. Our use of passive surveillance of emergency rooms, nursing homes, physician offices, and clinics may reduce the chances of incomplete ascertainment. However, the random sampling of offices, nursing homes, etc, assumes a uniform distribution of TIAs by region; of course, this may not be the case, particularly because differences by race may impact the assumption of uniformity. In addition, any incidence study that relies on medical contact for counting of events risks missing events that were not recognized by the general public as needing medical attention. All of these considerations mean that several counter-balancing biases may influence the final incidence rate of TIA that we observed.

Diagnostic accuracy of TIA may be another limitation of our study. For instance, with the advent of magnetic resonance imaging technologies that are becoming more and more widespread, the specificity of diagnosis of TIA may improve for hospitalized cases and the overall sensitivity may change as well.^{18–20} In addition, because the time period of the study was only 1 year, it is possible that our projections of recurrent events beyond the study period are conservative, although analyses over each 6-month block of study period showed remarkable consistency in event rates. Finally, the data we present are from 1993 to 1994, and as such the medications, imaging, and medical management of TIA may have changed in the interim.

We provide a first-ever, to our knowledge, comparison of incidence rates of TIA between blacks and whites in a large biracial population. Using our incidence rates for TIA in blacks and whites, we conservatively estimate that $\approx 240\,000$ TIAs occurred in 2002 in the United States. This estimate is based on incidence rates of TIA among whites and blacks from our population. Hispanic and Asian and other ethnic and racial minorities may have different incidence rates of TIA, which may further modify the estimate.¹⁷ The proportion of TIAs that occur on an outpatient basis suggests that studies of TIA, whether epidemiologic or treatment-based, should include outpatient settings. The causes of the increased incidence rate of TIA among blacks compared with whites require further study.

TIA is a high-risk event for stroke and death, and making prompt recognition and accurate diagnosis a challenging but

incredibly important task. We did not find any association between age, race, and gender on the risk of subsequent stroke or TIA after TIA. Further study is needed regarding interventions to prevent these short-term adverse outcomes in TIA patients.

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Editorial Comment

Transient Ischemic Attacks Are Emergencies

A series of recent studies—with the one by Kleindorfer et al¹ being a particularly good one—demonstrate that transient ischemic attacks (TIAs) are far from benign, especially in the short-term. Most recent studies report risk of stroke >10% in the 90 days after a TIA,^{2–5} as demonstrated here. These event rates are higher than those reported in older studies, likely because previous studies missed strokes that occurred during the first few days after a TIA, when the risk is particularly high.

The short-term event rates after TIA are generally higher than those reported from most studies of stroke after an initial ischemic stroke, indicating that TIA is a particularly unstable condition. One possible explanation is that the initial recovery identifies tissue still at risk.⁶ For example, if a ruptured plaque is responsible for the event, it remains thrombogenic after TIA, thereby generating a high risk of further ischemia. If the ruptured plaque initially produces a stroke rather than a TIA, it is less likely that the plaque will produce further symptoms: The adjacent vessel may remain occluded or the distal tissue may already be infarcted and not affected by further hypoperfusion or embolus.

A leisurely outpatient evaluation for TIA seems inappropriate in light of this instability. The risk of stroke in the first 48 hours after a TIA is ≈5%.² This is actually greater than the risk of myocardial infarction in patients presenting with acute chest pain,⁷ and emergent evaluation of chest pain is standard of care.

One argument for not recommending an emergent evaluation after TIA has been that there is nothing to do to prevent a subsequent stroke. Although there are no completed large-scale trials of emergent therapies for TIA, most proven agents for secondary prophylaxis are expected to be effective in the short-term.⁸ Also, the risk of stroke after TIA is particularly high in those with carotid stenosis.⁴ The benefits of therapy are greater if endarterectomy is performed sooner after the initial ischemic event and complications are no more frequent,^{9,10} so carotid imaging should be performed immediately and endarterectomy should follow without delay in appropriate candidates. Finally, close monitoring of those presenting with an acute TIA should provide a greater opportunity to use tissue plasminogen activator in those with stroke afterward.¹¹ Although emergent evaluation, treatment, and monitoring are expensive, the high short-term risk and

substantial cost of stroke are likely to justify very aggressive care.

Every stroke after a TIA is a failure. Sometimes it is a failure of clinicians to use proven therapies. More frequently, it is a failure of researchers to establish effective proven therapies for TIA. We all have more work to do in this area; the opportunity is just too great.

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