Effect of sex on outcome after recurrent stroke in African Americans
Results from the African-American Antiplatelet Stroke Prevention Study (AAASPS)

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Running Title: Effect of Sex on Stroke Outcome in Blacks

Abstract

Background: Sex-related disparities in stroke have been previously reported. However, the influence of sex on the outcome of recurrent stroke in blacks is less clear. Our objective is to investigate the effect of sex on the outcome of recurrent non-fatal stroke in the African American Antiplatelet Stroke Prevention Study (AAASPS)

Methods: The AAASPS is a double-blind, randomized, controlled trial of recurrent stroke. Participants -967 black women and 842 black men- with non-cardioembolic ischemic stroke were assigned to receive ticlopidine or aspirin and followed for up to two years. The NIH Stroke Scale (NIHSS), modified Barthel score (mBS), and the Glasgow Outcome Scale (GOS) were determined at enrollment, at pre-specified times thereafter and at the time of recurrent stroke. Survival analysis was used to test for a significant difference in the time to recurrent stroke between women and men.

Results: Of the total 1,809 subjects enrolled in AAASPS, 186 subjects (89 women and 97 men) suffered recurrent non-fatal stroke. At enrollment, the NIHSS (2.87 for women and 3.00 for men; p=0.73), the mBS (18.26 for women and 18.52 for men; p=0.47) and the GOS (1.49 for women and 1.51 for men; p=0.86) were not significantly different. In follow-up and at the time of stroke recurrence, the NIHSS, mBS, and GOS were similar for both groups, except for the mBS at the 6-month visit, which was lower in women (18.49) than in men (19.37) (p=0.02). In the survival analysis, no significant difference in the time to recurrent stroke was found between women and men (p=0.69).

Conclusions: Although sex-related stroke disparities have been reported, in the AAASPS cohort outcomes for recurrent non-fatal non-cardioembolic ischemic stroke for women

were not significantly different than for men. Differences in study populations and methodologies may explain discrepancies in results from the various studies.

Key Words

African Americans

Ischemic stroke

Advances in Stroke

Database

Gender

Sex

Introduction

The occurrence of sex-related disparities in stroke has been reported. Some studies have shown that male sex is a predictor of stroke mortality, whereas other studies have found higher mortality rates among women.[1-4] These differences by sex may be more accentuated for certain racial groups or specific stroke subtypes.[3, 5] For example, the female-to-male death risk ratio is 0.94 for ischemic stroke, 0.82 for intracerebral hemorrhage, and 1.58 for subarachnoid hemorrhage.[3] Our objective is to investigate the effect of sex on outcome of patients with recurrent non-fatal stroke in the African American Antiplatelet Stroke Prevention Study (AAASPS).

Methods

Study population

A description of the design and methods of AAASPS has been reported previously.[6] AAASPS is a multicenter, double-blind, randomized, controlled clinical trial of recurrent stroke prevention sponsored by the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH). Participants were recruited from 62 hospitals in the United States between December 12, 1995 and October 1, 2001. Randomized subjects were 1,809 black women (n=967) and men (n=842) who had a recent (within a 90-day time window) non-cardioembolic ischemic stroke. Subjects were assigned to receive either ticlopidine 250 mg two times per day or aspirin 325 mg two times per day and followed for up to two years. Participants were examined at baseline, every 2 weeks during the first 3 months, at 6, 10, 12, 16 and 24 months, and at the time of an outcome event. The primary end point was the composite of recurrent stroke,

myocardial infarction, and vascular death. The NIH Stroke Scale (NIHSS) was determined at baseline, 12 and 24 months, and at the termination visit. The 20-point modified Barthel score (mBS) and the Glasgow Outcome Scale (GOS) (1=death, 2=persistent vegetative state, 3=severe disability, 4=moderate disability, and 5=good recovery) were determined at baseline, 6, 12, and 24 months, and at the time of an outcome event. All sites had to receive formal approval from their institutional review boards before initiation of enrollment.

Statistical methods

The baseline demographic and risk-factor characteristics of women and men were compared using appropriate statistical tests. The occurrence of congestive heart failure, valvular disease, atrial fibrillation, history of cardiac surgery, thoracic or abdominal aortic surgery, carotid endarterectomy, epilepsy, and leg claudication among sexes was analyzed by using the Fisher's exact test. All the other variables measured (Table 1) were analyzed by using the χ^2 test and the Student's *t* test. NIHSS, mBS, and GOS were analyzed by using the Student's *t* test. A Cox proportional hazards model was used to test for a significant difference in the time to recurrent stroke between women and men.

Results

Of the total 1,809 subjects enrolled in AAASPS, 186 subjects (89 women and 97 men) suffered recurrent non-fatal stroke. The baseline characteristics of each group are shown in Table 1. The mean time from stroke entry to enrollment was 45 days. The mean body mass index and the prevalence of hypertension, diabetes mellitus, hypercholesterolemia

and angina pectoris were higher in women. Conversely, history of past or current smoking was more common in men than in women. The frequency of other risk factors including socioeconomic status, leg claudication, sedentary lifestyle, and family history of stroke did not differ among men and women (Table 1). The occurrence of different stroke subtypes, defined as large vessel atherothrombotic, lacunar, and other causes of stroke, was similar in women and men.

At enrollment, the NIHSS, mBS, and GOS were not significantly different between groups indicating that both had a comparable degree of neurological impairment, disability and dependency after the entry stroke (Table 2). Furthermore, the number of women and men with no or minimal disability (GOS of 1; 55.1% women and 54.6% men; p=0.95), or moderate or severe disability (GOS of 2, 3 or 4; 44.9% women and 45.4% men; p=0.95) was not statistically different.

In the follow up period, the NIHSS, mBS, and GOS were similar between both groups, except for the mBS measured at the 6-month visit which was lower in women (18.25) than in men (19.39) (Table 2). The NIHSS, mBS, and GOS determined at enrollment, at pre-specified times, and at the time of recurrent stroke were not statistically different among groups after adjusting for hypertension, diabetes mellitus, hypercholesterolemia, angina pectoris and body mass index greater than 30.

During the 24-month follow-up period, the average NIHSS was 8.59±4.30 for women and 9.17±4.97 for men (p= 0.61), and the mean mBS was 17.69±4.17 for women and 17.66±4.95 for men (p=0.98).

At the time of recurrent stroke, the NIHSS, mBS and GOS were similar between women and men (Table 2) as were the proportion of women and men with no or minimal

disability (GOS of 5; 30.7% women and 39.7% men; p=0.21), or moderate or severe disability (GOS 2, 3 or 4; 59.1% women and 55.2% men; p=0.60).

In the survival analysis, there was no significant difference in the time to recurrent stroke between women and men after controlling for age and treatment (p=0.69) (Figure).

Discussion

Our results show that the time to recurrent stroke and the overall outcome (GOS), neurological deficit (NIHSS) and activities of daily living (mBS) after recurrent ischemic stroke in African-American women were not significantly different than for men.

Sex-related disparities in stroke-related outcomes have been previously reported with women showing worse outcomes than men.[3, 7] For example, Qureshi et al reported that African-American women had the lowest 1-year survival rate after stroke (63%), followed by white women (73%), African American men (75%), and white men (79%).[5] Excess in mortality in African-American women was more pronounced in young- and middle-aged subjects. In AAASPS, we have shown previously that blacks had relatively poor rates of awareness, treatment and control of hypertension, hypercholesterolemia and diabetes mellitus.[8] Furthermore, in AAASPS women had a higher frequency of hypertension, diabetes mellitus, lack of leisure exercise, and obesity than men. We hypothesized, therefore, that these factors might increase the risk of women having more severe stroke and worse overall outcomes.[9] This was not shown to be the case, however, based on the current analysis.

African Americans have been shown to have a higher incidence of intracranial stenotic arterial disease.[10, 11] A subgroup analysis of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study showed that women with intracranial stenosis had a higher risk for recurrent ischemic stroke and for the combined end point of stroke or vascular death than men.[12] Also, previous studies have suggested that women may receive a different level of diagnostic evaluation and medical care for stroke than men. For example, standard diagnostic tests may be obtained less often in women with stroke, [13-15] and elderly women may be less likely to receive antiplatelet therapy, but are only equally as likely to receive warfarin despite having a higher rate of atrial fibrillation than men.[2] Furthermore, although women may benefit more than men from receiving recombinant-tissue plasminogen activator, [15, 16] women with stroke symptoms maybe less likely to be admitted to the hospital within a 3-hour time window when intravenous thrombolitics may be given.[17]

Contrary to the aforementioned reports, we did not find sex-related disparities in recurrent stroke outcome. This might be explained at least in part by differences in study populations and designs. For example, Qureshi et al studied a biracial population with acute ischemic stroke presenting within 3 hours of onset of symptoms with about 40% of them having a suspected cardioembolic etiology.[5] AAASPS enrolled only patients with non-cardioembolic stroke limiting our results to these specific ischemic stroke mechanisms. Recently, in a retrospective study Reid et al showed that women were less likely to be discharged home and to have better outcome after stroke than men.[7] This study, however, had a high proportion of elderly patients (median age 77 for women and

70 for men) and included hemorrhagic and ischemic strokes.[7] Furthermore, the proportion of patients aged ≥80 years was significantly higher in women (40%) than in men (18%). In contradistinction, AAASPS patients were younger and included only persons with non-cardioembolic ischemic stroke.

Some studies investigated sex-related differences in outcome after stroke using mortality as the main end point.[2, 5, 12] We used scales of neurological deficits, activities of daily living, and global outcome to estimate the stroke burden in recurrent stroke survivors. These might be better estimates of the public health burden of this condition as degree of disability and dependency are directly related to higher direct (e.g. inpatient care, rehabilitation, follow-up care) and indirect (e.g., long-term disability, lost years of productivity) costs of stroke.[18, 19]

Finally, all of the patients enrolled in AAASPS were treated with antithrombotics (either ticlopidine or aspirin), and the number of diagnostic tests ordered such as carotid duplex and echocardiography did not differ among women and men in the study (data not shown but available on request). Therefore, it is unlikely that there was a bias in terms of treatment or level of evaluation in one group or the other in AAASPS.

Our study has several limitations. Based on AAASPS eligibility criteria we studied primarily non-cardioembolic ischemic stroke patients in a clinical trial setting. Therefore, our findings may not be generalizeable to the African-American community at large or other racial or ethnic groups. Furthermore, the mean time from stroke entry to enrollment was 45 days raising the possibility of a survival bias as more impaired patients may have

died or were non-eligible or less interested in enrolling in the study selecting out for a less neurologically-impaired patient. The overall drop-out rate in AAASPS was generally higher than in other stroke prevention trials. This was expected to occur based on the study of a previously underserved population and could be attributed to lower socioeconomic status of some of the subjects, distrust of the medical system which has been shown to occur in the African-American community, and other possible factors such as access to medical care, social isolation, and less previous involvement in clinical trials.[6]

In conclusion, our results suggest that black women and men have similar outcomes after recurrent non-fatal non-cardioembolic stroke based on assessment of neurological deficits, activities of daily living, and global outcome despite having different cardiovascular risk factor profiles at baseline.

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Itemized list of the number of tables and number and types of figures included in the manuscript.

Table 1: Baseline Characteristics of the AAASPS Patients by Sex

Table 2: Outcome Scores in subjects with recurrent stroke

Figure: Time to recurrent stroke in women and men

Table 1. Baseline Characteristics of the AAASPS Patients by Sex

	Women (n=89)	**Men (n=97)**	***p*-value***
Demographics	Mean (s.d)	Mean (s.d)	
Age	62.8 (9.8)	60.6 (10.8)	0.14
Body mass index	31.7 (7.2)	28.7 (5.8)	0.0034
Treatment group (aspirin)	40 (44.9)	44 (45.4)	0.95
Education	n (%)	n (%)	
< high school	57 (64.0)	76 (78.3)	0.03
> high school	29 (32.6)	21 (21.7)	0.09
unknown	3 (3.4)	0 (0.0)	0.11**
Household Income	n (%)	n (%)	
< $14,999	39 (43.8)	42 (43.3)	0.94
> $14,999	30 (33.7)	36 (37.1)	0.63
unknown	20 (22.5)	19 (19.6)	0.63
Risk Factors	n (%)	n (%)	
Hypertension	84 (94.4)	82 (84.5)	0.03
Diabetes mellitus	54 (60.7)	43 (44.3)	0.03
Cardiovascular			
Hypercholesterolemia	39 (49.4)	27 (31.8)	0.02
Angina pectoris	16 (18.0)	8 (8.3)	0.05
Myocardial infarction	10 (11.4)	11 (11.6)	0.96
Congestive heart failure	2 (2.3)	5 (5.2)	0.45**
Valvular heart disease	3 (3.4)	0 (0.0)	0.11**
Atrial fibrillation	2 (2.3)	2 (2.1)	1.00**
Surgery			
Cardiac	3 (3.4)	5 (5.2)	0.72**
Thoracic or abdominal aortic	3 (3.4)	1 (1.0)	0.35**
Peripheral arterial vascular	2 (2.3)	2 (2.1)	1.00**
Carotid endarterectomy	0 (0.0)	0 (0.0)	-
Other			
Chronic lung disease	6 (6.7)	6 (6.2)	0.88
Epilepsy or seizures	0 (0.0)	4 (4.1)	0.12**
Leg claudication	5 (5.6)	3 (3.1)	0.48**
Family history			
Stroke	43 (55.1)	42 (47.2)	0.31
Myocardial infarction	28 (36.4)	32 (36.0)	0.96
Hypercholesterolemia	17 (31.5)	13 (22.0)	0.26
Life style			
Cigarette smoking (past or current)	45 (50.6)	78 (80.4)	<0.0001
No exercise	59 (67.1)	52 (54.2)	0.07
Alcohol use within 24h of stroke	8 (9.1)	14 (15.1)	0.22
Entry Stroke Subtype	n (%)	n (%)	***p*-value***
Large vessel atherothrombotic	23 (25.8)	18 (18.6)	0.23
Small vessel (lacunar)	53 (59.6)	70 (72.2)	0.07
Other etiology or unknown	13 (14.6)	9 (9.3)	0.26

* Based on χ^2 test and the Student's *t* test

** Based on Fisher exact test

Table 2. Outcome Scores in subjects with recurrent stroke (Means)

	NIHSS			mBS			GOS		
	Female	Male	*p*-value*	Female	Male	*p*-value*	Female	Male	*p*-value*
Baseline	2.86 (89)	3.00 (96)	0.73	18.26 (89)	18.52 (96)	0.44	1.49 (89)	1.51 (96)	0.86
6 months	NA	NA	-	18.49 (63)	19.37 (63)	0.02	1.44 (63)	1.35 (63)	0.34
12 months	7.53 (43)	7.78 (53)	0.74	18.26 (43)	18.36 (53)	0.89	1.40 (43)	1.45 (53)	0.65
24 months	8.59 (32)	9.17 (35)	0.61	17.69 (32)	17.66 (35)	0.98	1.66 (32)	1.60 (35)	0.74
Termination	11.83 (89)	10.48 (96)	0.09	14.72 (80)	15.85 (92)	0.23	1.95 (81)	1.83 (92)	0.33

* p-value calculated using χ^2 and the Student's *t* test. Number of patients shown in parentheses.

Legend to Figure

Figure. Time to recurrent stroke in women (dotted line, n=89) and men (solid line, n=97)