Journal of the Neurological Sciences 365 (2016) 203–206

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Association of black race with recurrent stroke risk

Jong-Ho Park [a], Bruce Ovbiagele [b,*]

[a] Department of Neurology, Seonam University Myongji Hospital, Goyang, South Korea
[b] Department of Neurology, Medical University of South Carolina, Charleston, SC, USA

ARTICLE INFO

Article history:
Received 14 January 2016
Received in revised form 11 March 2016
Accepted 8 April 2016
Available online 13 April 2016

Keywords:
Race
Black
Secondary prevention
Stroke
Disparities
Recurrent

ABSTRACT

Background: The significantly higher risk of primary stroke in Black vs. Whites is very well established. However, very few studies have specifically examined the presence of this racial disparity in recurrent stroke risk.
Methods: We conducted an analysis of a clinical trial dataset comprising 3470 recent non-cardioembolic stroke patients aged ≥35 years and followed for 2 years. Subjects were categorized by race into Whites and Blacks. Cox regression analysis was used to evaluate the associations between Black (vs. White) and ischemic stroke (primary outcome); and stroke/coronary heart disease (CHD)/vascular death as major vascular events (secondary outcome) with and without adjustment for comorbid conditions associated with stroke.
Results: Among participants (2925 Whites and 545 Blacks), a total of 287 (8.3%) incident stroke and 582 (16.8%) major vascular events occurred. Compared with Whites, Blacks had higher frequencies of prior stroke, hypertension, diabetes mellitus, and smoking; but were younger with lower prevalence of CHD. Frequency of stroke was higher in Blacks vs. Whites (11.4% vs. 7.7%; $P = 0.004$), but there was no difference in major vascular events (16.9% vs. 16.8%). Compared with Whites, Blacks experienced a significantly higher risk of recurrent stroke (HR 1.58; 95% CI, 1.19–2.09), but the stroke risk was not significant after multivariable adjustment (1.13; 0.81–1.59).
Conclusion: Blacks are ~60% more likely to experience a recurrent stroke within 2 years than their Whites, but this risk is likely mediated via stroke risk factors. These results underscore a need to optimize and sustain risk factor control in Black stroke populations.

1. Introduction

Several population-based studies have shown that people of Black race are at significantly higher risk of a first-time stroke compared to people of White race [1,2]. However, there is a relative paucity of studies that have specifically examined whether this racial disparity exists for recurrent stroke risk. A single hospital study of 299 patients (110 black and 132 white) found an unadjusted relative risk of stroke recurrence for blacks relative to white to 2.0 (95% CI: 0.9–4.4) [3], and another single site study (135 Whites and 177 Blacks) demonstrated that Whites had a higher risk of stroke recurrence than Blacks [4]. Data covering bigger numbers of participants and more sites are needed to better determine the nature of secondary stroke risk among Blacks vs. Whites, and assess potential mitigating factors. The objective of this study was to compare the risk of recurrent stroke in Black vs. White patients with a recent ischemic stroke.

2. Methods

2.1. Database

We reviewed data from the Vitamin Intervention for Stroke Prevention (VISP) trial [5]. VISP study was a multicenter, double blind, randomized controlled clinical trial performed at 56 centers across the United States, Canada, and Scotland. The study enrolled 3680 patients aged ≥35 years to determine whether high doses of multivitamin (folic acid, pyridoxine, and cobalamin) given to lower total homocysteine levels would reduce the risk of recurrent stroke and major vascular events in patients with a recent (<120 days) non-cardioembolic stroke [5]. In VISP trial, high-dose vitamin therapy had no effect on the outcome measures of stroke, composite of vascular events, or death [5]. Details of methods and main results of the trial have been reported previously. Demographic, physical, neurological examination including stroke scales, medication use assessment, and laboratory data collected at randomization, with subsequent information obtained at follow-up visits of 1, 6, 12, 18, and 24 months. Physicians were instructed to provide best available background medical and surgical management to prevent recurrent stroke, which included risk factor control education

* Corresponding author at: Department of Neurology, Medical University of South Carolina, 96 Jonathan Lucas St. CSB 301 • MSC 606, Charleston, SC 29425-6160, USA.
E-mail address: Ovibes@musc.edu (B. Ovbiagele).

http://dx.doi.org/10.1016/j.jns.2016.04.012
0022-510X/

and, usually, administration of aspirin, 325 mg/d [5]. For each patient, presence of hypertension and diabetes were documented not only by history, but also if newly diagnosed at the first visit. We reviewed data on medication use, which was collected at every 6-month interval follow-up visit. We utilized secondary prevention drug information including antihypertensive, antithrombotic (antiplatelet or anticoagulant), and lipid-lowering therapy (statin mostly) that was provided at the last follow-up visit, because the number and type of such medications can vary during the post-discharge follow-up setting [6] and our preliminary evaluation indicated that several hundred patients had their baseline prescriptions modified to include more therapeutic drug classes at the time of their 2nd or 3rd (and further) follow-up visits. Last follow-up visit was defined as the last documented study encounter that preceded either a vascular outcome event or end of the trial. Furthermore, we retrieved information on mini-mental state examination (MMSE) score, since cognitive impairment has been implicated as a potential predictor for stroke risk [7]. Study subjects were categorized into White race and Black race. The trial was approved by the ethics committee or institutional review board at each national or local site, and all participants provided written informed consent before enrolment [5].

2.2. Outcome measure

The primary outcome for this analysis was time to recurrent ischemic stroke. Secondary outcome was time to the first stroke, coronary heart disease (CHD) including myocardial infarction, coronary revascularization, cardiac resuscitation, and fatal CHD, or vascular death as major vascular events. Recurrent stroke was diagnosed only with evidence of sudden onset of focal neurologic deficit lasting at least 24 h accompanied by an increased National Institutes of Health Stroke Scale (NIHSS) score in an area that was previously normal [5]. When the sudden onset of symptoms lasting at least 24 h was not accompanied by an increased NIHSS score in an area that was previously normal, then recurrent stroke was diagnosed using cranial CT or MRI evidence of new infarction consistent with the clinical presentation [5].

2.3. Statistical analysis

Data are summarized as mean ± standard deviation (SD) or number of subjects (percentage), as appropriate. Comparisons across the groups were examined using the χ^2 test for categorical variables and Student *t*-test for continuous variables. Whites were the control group for purposes of comparison. Baseline demographic and clinical covariates were preselected based on previous studies of factors that influence vascular events after ischemic stroke. Cox proportional hazard regression analyses were performed to estimate the risk of outcome events during 2 years after adjusting for baseline covariates (age, sex, systolic blood pressure, hypertension, diabetes mellitus, smoking, stroke severity, history of stroke (before VISP qualifying stroke), history of CHD, history of congestive heart failure (CHF), history of carotid endarterectomy, history of alcohol use, body mass index (BMI), serum levels of triglycerides, high-density lipoprotein cholesterol (HDL-C) and creatinine, mini-mental state examination (MMSE) score, antihypertensive medication, antithrombotic therapy, and lipid modifier use; all $P < 0.10$). Participants not having outcome events were censored at last follow-up examination, or last visit. Participants lost to follow-up during the course of the study were included in the Cox model until the last contact. Results are given by hazard ratio (HR) and its 95% confidence interval (CI). All analyses were conducted using IBM SPSS Version 22.0 (IBM Corp., Armonk, NY) and a probability value of <0.05 was considered statistically significant.

3. Results

3.1. Subjects characteristics by race

Of 3680 participants in the trial, 210 non-White and non-Black persons were excluded from the final analysis, yielding a total of 3470 (94.3%) subjects. Among 3470 participants, mean age was 66.5 ± 10.8 years, 62.5% were men, and 15.7% were Black. Baseline demographic and clinical characteristics between white and black races are provided in Table 1. Compared with Whites, Blacks had higher systolic blood pressure, higher BMI, higher serum levels of HDL-C and creatinine, higher National Institutes of Health Stroke Scale (NIHSS) score, higher frequencies of male, hypertension, diabetes mellitus, smoker and antihypertensive medication, higher histories of prior stroke and CHF, whereas age, serum triglycerides levels, MMSE score, frequencies of male, history of CHD, carotid endarterectomy and alcohol use, antithrombotic and lipid-lowering medication were lower.

3.2. Comparison of vascular outcomes between whites and blacks

During 2-years of follow-up, a total of 287 (8.3%) incident stroke and 582 (16.8%) major vascular events were recorded. Results of the unadjusted and adjusted associations between Blacks (vs Whites) and vascular events appear in Table 2. Occurrence of stroke was higher in Blacks vs Whites (11.4% vs 7.7%; $P = 0.004$), whereas that of major vascular events was not (16.9% vs 16.8%). When referenced to white group, Blacks were significantly linked to risk of recurrent stroke (HR 1.58; 95% CI, 1.19–2.09), but not of major vascular events (HR 1.07; 95% CI, 0.86–1.34). The adjusted HR for stroke for Blacks was however, attenuated and non-significant after multivariable

Table 1
Baseline characteristics of study patients between Whites and Blacks.

	Whites (n = 2925)	Blacks (n = 545)	*P*
Age, years	67.3 ± 10.6	62.2 ± 10.9	<0.001
Systolic blood pressure, mm Hg	140.4 ± 18.6	143.7 ± 19.0	<0.001
BMI, kg/m^2	28.0 ± 5.5	29.9 ± 6.7	<0.001
Total cholesterol, mg/dL	202.1 ± 45.9	200.1 ± 46.1	0.358
LDL-C, mg/dL	121.8 ± 39.4	123.6 ± 40.2	0.349
Triglycerides, mg/dL	179.8 ± 166.6	143.2 ± 91.0	<0.001
HDL-C, mg/dL	45.3 ± 15.7	46.9 ± 14.2	0.034
Creatinine, mg/dL	1.11 ± 0.60	1.19 ± 0.56	0.004
Homocystein, μmol/L	14.1 ± 6.1	14.5 ± 5.2	0.148
Baseline MMSE score	27.1 ± 3.2	25.9 ± 3.6	<0.001
Male	1871 (64.0)	299 (54.9)	<0.001
Hypertension	2418 (82.7)	502 (92.1)	<0.001
Diabetes mellitus	788 (26.9)	218 (40.0)	<0.001
Smoker	445 (15.2)	146 (26.8)	<0.001
Qualifying stroke NIHSS			<0.001
0	1064 (36.4)	122 (22.4)	
1–4	1653 (56.5)	356 (65.3)	
≥5	208 (7.1)	67 (12.3)	
History			
Prior stroke[a]	639 (21.9)	175 (32.1)	<0.001
Coronary heart disease[b]	789 (27.0)	116 (21.3)	0.005
Congestive heart failure	143 (4.9)	42 (7.7)	0.008
Carotid endarterectomy	236 (8.1)	10 (1.8)	<0.001
Alcohol use	1804 (63.0)	227 (44.0)	<0.001
Medication			
Antihypertensive	2346 (80.2)	472 (86.6)	<0.001
Antithrombotic	2754 (94.2)	490 (89.9)	<0.001
Lipid-lowering	1648 (56.3)	237 (43.5)	<0.001
High-dose B vitamin	1473 (50.4)	259 (47.5)	0.224

Values provided are number (%) or mean ± SD, as appropriate, otherwise stated. BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MMSE, mini-mental state examination; NIHSS, National Institutes of Health Stroke Scale.

[a] Before VISP qualifying stroke.

[b] Defined as history of myocardial infarction, angina, coronary angioplasty/stenting, or coronary artery bypass graft surgery.

Table 2
Multivariate risk adjusted effect of racial disparity (Black vs White) during 2-year risk of vascular outcomes after a recent stroke.

Vascular outcome	White	Black	Unadjusted	Multivariable[a]	*P*
	n = 2925	n = 545	HR (95% CI)	HR (95% CI)	
	Events, n (%)				
Stroke	225 (7.7)	62 (11.4)[†]	1.58 (1.19–2.09)[‡]	1.13 (0.81–1.59)	0.479
Stroke/CHD/vascular death	490 (16.8)	92 (16.9)	1.07 (0.86–1.34)	0.87 (0.67–1.14)	0.312

[a] Adjusted for age, sex, systolic blood pressure, hypertension, diabetes mellitus, smoking, stroke severity, history of prior stroke, history of coronary heart disease, history of congestive heart failure, history of carotid endarterectomy, history of alcohol use, body mass index, serum levels of triglycerides, high-density lipoprotein cholesterol and creatinine, mini-mental state examination score, antihypertensive medication, antithrombotic therapy, and lipid modifier use.
[†] $P = 0.004$.
[‡] $P = 0.002$. CHD indicates coronary heart disease; HR, hazard ratio; CI, confidence interval.

adjustment (1.13; 95% CI, 0.81–1.59). Adjusted HRs of covariates included in the multivariable-adjusted model for stroke and major vascular events are provided in Supplementary Table I. History of stroke was significantly associated with increased risk of both stroke and major vascular events, whilst lipid modifier therapy was independently linked to lesser risk of both vascular outcomes.

When study subjects were divided into low-dose (n = 1738) and high-dose B vitamin (n = 1732) groups, the adjusted HR for stroke for Blacks in each group was not dissimilar to that in overall VISP patients (1.10; 95% CI, 0.67–1.80 for low-dose group, 1.11; 95% CI, 0.69–1.79 for high-dose group, and 1.13; 95% CI, 0.81–1.59 for overall patients) (please see Supplementary Table II and III).

4. Discussion

We observed that Black patients after a recent ischemic stroke were more likely to experience a recurrent stroke by 1.6 fold (vs. Whites) within 2 years, although this disparity disappeared after multivariable adjustment. Key vascular risk factors like previous stroke history (i.e. before the VISP-qualifying stroke), hypertension, diabetes mellitus, smoking, and high BMI were more prevalent in Blacks compared with Whites and likely contributed to the significantly higher risk of recurrent stroke seen in the unadjusted analysis.

Our findings of a greater burden of vascular risk factors among Blacks compared to Whites are in accord with findings from several previously published population-based studies. For instance, a higher risk ratio of first-ever stroke in Blacks, especially among younger adults compared with their White counterparts, was seen in a population-based study [8]. In REGARDS (REasons for Geographic and Racial Differences in Stroke) study [9], Blacks were more aware of their hypertension than Whites, but among those treated hypertension was less likely to be controlled, which is in line with findings from our study that the frequency of antihypertensive prescription was higher, but systolic blood pressure was higher in Blacks compared with Whites. Data from the National Health and Nutrition Examination Survey (NHANES 1988 to 2006) showed that the prevalence of diabetes mellitus was higher among Blacks than among Whites [10]. Since Blacks had higher prevalence of hypertension, systolic blood pressure, diabetes mellitus, smoking, and left ventricular hypertrophy, their Framingham Stroke Risk Score was higher and had less history of CHD in REGARDS study [11]. Of note in our study, White patients were older, with a higher prevalence of CHD and lower serum HDL-C levels, findings which are consistent with the previous studies indicating that those risk factors are related to stroke in Whites [12,13]. The lack of a difference between Blacks and Whites in our composite secondary outcome, even when unadjusted, was probably due to the greater burden of CHD at baseline in Whites vs. Blacks.

There are several possible reasons for the non-significant difference in stroke outcomes by race. First, since these analyses were based on a clinical trial cohort, study subjects may have been generally more likely to comply with medical instructions. As such, the attention that comes from all the various timepoint assessments in a research study may remind patients to take better care of themselves and allow clinicians to promptly identify or address future problems. Second, motivation to comply with medical instructions after a stroke would presumably be greater after rather than before a stroke occurs. Finally, the follow-up period of two years in VISP may have been too short to see a racial difference by stroke endpoint.

Given the higher prevalence of major vascular risk factors in Blacks vs. Whites in this study, which when adjusted for, eliminated the higher risk of recurrent strokes in Blacks, it is conceivable that better long term control of these vascular risk factors in recent Black stroke patients, may bridge the racial gap in secondary stroke outcomes. Indeed, we showed that lipid modifier use (statin mostly) played a significant role for lowering risk of recurrent stroke, the finding of which conforms with a previous study [14] that statin was found to significantly reduce the risk of recurrent stroke. Also, analysis of data in the Get With The Guidelines–Stroke program, which comprises a network of US hospitals interested in improving the quality of stroke care, showed that hospitalized Black patients with stroke received fewer in-hospital evidence-based care processes than White patients, but participation in the program over a 5-year period improved care quality for Blacks and Whites [15]. Strategies to enhance and sustain the utility of evidence-based stroke prevention care processes in the post-discharge/outpatient setting, and especially designed to address Black stroke patients, may be needed to definitively narrow the racial disparity in recurrent stroke occurrence.

This study has limitations. First, VISP trial was conducted over a decade ago, given that strategies for secondary stroke prevention become gradually updated. This is a retrospective sub-study, not a defined population-based cohort, thus our findings may not necessarily be representative of Black-White disparities in recurrent stroke risk encountered in routine practice. However, the disparities in demographic and clinical features between Blacks and Whites in our study were highly comparable to published population based studies of primary stroke, and given challenges recruiting Black subjects into clinical trials (<16%), we suspect our study probably underestimates the racial disparity in recurrent stroke risk in the real world. Second, VISP populations comprise individuals from the United States, Canada, and Scotland thus the possibility that genetic, environmental, or cultural heterogeneities between countries and differences between races could affect the null outcomes in this study cannot be excluded. Finally, since the VISP dataset did not provide subtypes of index and recurrent strokes, we were unable to correlate them with stroke outcomes, which could have shed more light on the possible contributions of underlying burden on the association of index stroke with recurrent events. In spite of the aforementioned limitations, our study was strengthened by the prospective nature of data collection in VISP, rigorous trial procedures, multiple sites, and a fairly large sample size [5].

In conclusion, in this analysis of large, multicenter data, we found that Black patients with a recent ischemic stroke had ~60% higher risk of recurrent stroke compared to their White counterparts. However, this difference was explained by a substantially greater baseline vascular risk factor burden in the Black patients. These results suggest

that special care for better risk factor control after a stroke in Black patients may close this gap in racial stroke outcomes. Given that there has been a gradual increase in the use of lipid modifiers over the last decade period (2003 − 2012) [16], additional data especially from large population based studies are needed to confirm or disconfirm these results.

Sources of funding

Dr. Ovbiagele is supported by Awards NS079179 and NS094033 from the National Institute of Neurological Disorders and Stroke.

Disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2016.04.012.

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