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ARE RACIAL DIFFERENCES IN ANTIHYPERTENSIVE RESPONSIVENESS REFLECTED IN USAGE AFTER STROKE?

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Abstract

Objective—To evaluate whether differential antihypertensive responsiveness in Blacks is reflected in discharge antihypertensive prescription patterns among patients hospitalized with an ischemic cerebrovascular event.

Methods—We analyzed use of discharge antihypertensive medications among patients hospitalized with an ischemic cerebrovascular event in the California Acute Stroke Prototype Registry (CASPR), examining rates in Black patients compared to all other races combined. Generalized estimating equations were used to identify factors independently associated with receipt of any antihypertensive medication overall and with use of specific types of antihypertensives.

Results—Data were collected on 794 consecutive patients treated at 11 hospitals. No significant differences were observed between rates of antihypertensive use in Black patients (74%) when compared to all others (69%), either for overall use or for any specific category of antihypertensive, although there was a trend toward more frequent use of diuretics in Black patients ($p=0.12$). Results were similar when analysis was limited to those with a history of hypertension.

Conclusions—In spite of a known differential response to antihypertensives in Blacks, we found no differences in discharge antihypertensive prescription patterns in hospitalized Black TIA and ischemic stroke patients compared to other races.

Keywords

hypertension; prevention; African American; stroke; transient ischemic attack

INTRODUCTION

Black individuals disproportionately shoulder the burden of stroke.¹ As a result, calls have been made for more stroke studies that take into account ethnic variations in treatment and outcomes.^{2, 3} An example of an ethnic treatment variation, which has been well known for over two decades, is the differential response of Blacks to antihypertensive treatment. Indeed, high blood pressure is notoriously difficult to control in Black patients.⁴ However, it has been

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shown that among Black patients pharmacological treatment of hypertension is most consistently achieved through diuretics and calcium-channel blockers, whilst beta-blockers, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) tend to be less effective at lowering blood pressure, possibly due to the low renin state in these patients.^{5–12}

Recently, the impact of this differential effect on achieving target blood pressure goals has been proven to influence vascular outcomes. In a large head-to-head antihypertensive trial, the diuretic treatment was associated with greater reductions in blood pressure: at five years, the average decline blood pressure among Black patients was 4.1 mmHg on a diuretic and 0.6 mmHg on an ACEI while no significant difference in response between agents was demonstrated among non-Blacks.^{13, 14} Consistent with this, the subsequent stroke risk among Blacks was lower with the diuretic than with the ACEI.^{14, 15} Taking this into consideration, guidelines by the Canadian Hypertension Society advise against the use of ACEIs as first line monotherapy in black patients.¹⁶ In another head-to-head antihypertensive trial, ARB treatment was associated with a trend towards greater vascular risk in Black subjects compared to beta blocker treatment, while in non-Black individuals the ARB conferred greater vascular protection than the beta blocker.^{17, 18}

Hypertension remains a potent yet modifiable risk factor for recurrent stroke,¹⁹ and the use of antihypertensive treatment has been shown to reduce this risk substantially, even among stroke survivors with relatively normal blood pressures.²⁰ In this study, we aimed to evaluate the influence of recent clinical trial evidence and widely known data about the differential efficacy of various antihypertensives in Blacks, on current clinical practice in Black persons discharged from the hospital following a TIA or ischemic stroke.

METHODS

Data from the California Acute Stroke Prototype Registry (CASPR) were analyzed. CASPR collected data prospectively on acute stroke care, in individuals with a diagnosis of suspected stroke or TIA, in 11 hospitals in five major population regions of California from November 1, 2002 through January 31, 2003, and from November 1, 2003 through January 31, 2004. CASPR hospitals comprised four university hospitals, four community hospitals, two county hospitals, and one health maintenance organization hospital. CASPR's study methods have been previously described.²¹ Human subjects review boards at each participating center approved CASPR.

For these analyses, we included all patients with a discharge diagnosis of ischemic stroke or TIA who were admitted during either time period. We identified the rates of use of different classes of medication, categorizing antihypertensives into the following groups: Beta adrenergic blocking agents, calcium channel blockers, ACEIs, ARBs, diuretics, and "other" antihypertensives, including centrally acting adrenergics, peripherally acting antiadrenergics, and vasodilators. Furthermore, we assessed the utilization patterns of antihypertensive medication in Black patients vs. all others, both in terms of overall use (based on clinical trial evidence indicating benefit of antihypertensive treatment in stroke patients regardless of blood pressure level),²⁰ and in prescription of different classes of medication. We then examined the subgroup of Black patients for treatment that contained either a diuretic or calcium channel blocker. CASPR antihypertensive treatment regimens that included a diuretic or calcium channel blocker were evaluated because of clinical trial evidence, systematic reviews, and statements in the US national hypertension guidelines noting greater blood pressure reducing efficacy and fewer side effects in Blacks compared to non-Blacks, who receive this regimen.^{5, 12, 13, 15, 17, 22} Furthermore, several studies have shown that when combined with a

diuretic or calcium channel blocker, there are no racial differences in the blood pressure lowering effects of beta blockers, ARBs and ACEIs.^{6, 23, 24}

Statistical analysis

The chi-square test for homogeneity was used to evaluate whether or not the hospitals were homogeneous with respect to the proportion of patients treated with antihypertensive medications. Because a significant difference in treatment rates was observed, generalized estimating equations (GEE) were used for univariate and multivariate analyses in order to account for both within-hospital and between-hospital variances. Variables significant at the $\alpha = 0.05$ level in univariate analysis were included in multivariate analysis. SAS (version 8e, SAS Institute, Cary, NC) was used for all statistical analysis.

RESULTS

Overall, 794 patients were diagnosed with either ischemic stroke or TIA at the 11 CASPR hospitals, of whom 77 (9.7%) were Black. Blacks and non-Blacks were similar in terms of gender, diagnosis, ambulation status at discharge, and proportion discharged home (Table 1). Black patients were younger, less likely to have a history of atrial fibrillation, more likely to have a history of diabetes, and almost twice as likely to report a history of smoking.

There was a non-significant trend ($p=0.12$) towards a higher utilization of a diuretic-based regimen in Black patients (31%) vs. others (22%) (Table 2). Only 31 (40%) of Black patients received treatment that contained either a diuretic or calcium channel blocker. Among Black patients, gender was significantly associated with receiving diuretic or calcium channel blocker-based (DB/CCBB) treatment, with men less likely to receive this treatment than women (OR 0.46, 95% CI 0.24–0.89, $p=0.02$). Patients with a history of diabetes were only about half as likely to receive DB/CCBB treatment (OR 0.49, 95% CI 0.29–0.83, $p=0.0008$) as those without diabetes (Table 3). Both of these variables remained significant in multivariate analysis (results not shown).

In a separate analysis of Black vs. non-Black subjects with a history of hypertension, we found no significant differences in overall discharge antihypertensive prescription use (87.9% vs. 83.3%, $p=0.36$). Similarly, among those with a history of hypertension, no significant differences were noted between Blacks vs. others in the discharge prescription of the pre-specified categories of antihypertensive medications (results not shown). Only 45% of Black patients with a history of hypertension received DB/CCBB treatment. Of the 46 patients who received treatment other than DB/CCBB therapy, 20 (26% of all Black patients) received no antihypertensive whatsoever at discharge.

In analysis of patients who got ACEIs (the most prescribed class of antihypertensives), 18% had CAD (vs. 17% of those who didn't receive ACEI, $p=0.55$), and 36% had diabetes (vs. 19% of those who didn't receive ACEI, $p<0.0001$). Of patients who got beta-blockers, 23% had CAD (vs. 15% of those who didn't receive beta-blockers, $p=0.003$), while 33% had diabetes (vs. 23% of those who didn't receive beta-blockers, $p=0.003$). There were no significant differences in Blacks vs. non-Blacks, with respect to prevalence of CAD and diabetes among patients receiving beta-blockers or ACEIs.

Among the 31 Black patients taking two or more antihypertensives, the most common combination regimen was combined treatment with ACEIs and beta-blockers, which was employed in 7 patients (22.6%).

DISCUSSION

We found that antihypertensive prescription patterns in Black patients with TIA or ischemic stroke discharged from representative hospitals in California reflect neither the well known differential response to antihypertensives in Blacks, nor findings from recent head-to-head antihypertensive clinical trials, which have suggested increased vascular risk for Blacks when treated with specific antihypertensive regimens.^{13, 17} Underscoring the importance of these findings and consistent with previous studies,^{2, 4, 25} Blacks in the CASPR cohort had a worse vascular risk factor profile, and were younger than their other racial counterparts.

In this study we noted that ACEIs were the most prescribed class of antihypertensives in both Black and non-Black groups. Several factors may explain this high use of ACEIs. Firstly, several studies have shown a benefit for ACEIs with regard to vascular risk reduction among hypertensive patients and those with high-risk vascular conditions,^{26, 27} and current guidelines have not universally recognized the possible greater benefit with other agents such as diuretics for stroke prevention in Blacks. Therefore, some clinicians might argue that ACEIs remain preferred agents after stroke in Blacks. However, it has to be pointed out that in the aforementioned ACEI efficacy studies, Blacks constituted a very small proportion of the study populations.

Another possible reason for the high ACEI use could have been a desire by the treating physicians to limit end organ damage. Perhaps this why we found that Blacks in our study who had diabetes were only half as likely to receive a diuretic/calcium channel blocker-based regimen as those without diabetes. Diabetic non-Blacks in our study were also more likely to receive an ACEI at discharge. It is true that modulators of the renin-angiotensin system such as ACEIs and ARBs, have been shown to provide protection against end-organ damage,²⁸ but treatment to goal blood pressure is an essential first step towards optimal target-organ protection.²⁹ In addition, the ALLHAT trial revealed no advantage of ACEIs or ARBs in preventing hard clinical endpoints over diuretics (in fact the diuretic-based treatment resulted in the lowest risk of heart failure) in high risk hypertensive patients,¹⁵ or in patients with diabetes or insulin resistance.²⁹ As such, the Seventh Joint National Committee on Hypertension (JNC-7) recommends a diuretic-based regimen for the majority of hypertensive patients regardless of race.¹³ Finally, the high utilization of ACEI may have reflected a cautionary approach by the physicians to initiate a “milder” antihypertensive agent in the setting a recent ischemic cerebrovascular event.

Supporting a role for modulators of the renin-angiotensin system in stroke prevention, a recent trial showed an ARB to be more effective than a calcium channel blocker in reducing vascular morbidity and mortality in hypertensive stroke patients despite the same level of blood pressure control in both treatment groups.³⁰ However, it is not clear what percentage of trial enrollees were Black.

We found that Black men in our study were significantly less likely than Black women both to receive any antihypertensive and to receive optimal treatment. It is not immediately obvious why this is, but it could conceivably reflect a higher pre-morbid utilization of antihypertensives among the Black women.

Our study has limitations. Firstly, even though data on history of hypertension was collected in CASPR subjects, we did not collect data on the premorbid use of antihypertensive agents or on actual blood pressure measurements during hospitalization. However, blood pressure measurements within several days of an ischemic stroke often do not reflect a patient’s baseline values,³¹ and the vast majority of stroke patients will benefit from treatment with antihypertensives regardless of their baseline blood pressure.²⁰ Secondly, we are limited by a paucity of information on the potential contraindications or adverse reactions that might have

prevented the use of certain antihypertensive medication regimens. Lastly, we have no information on initiation of antihypertensive medications after discharge, and some clinicians may have delayed treatment to reduce risk of exacerbating the initial ischemic insult. However, our study was focused on racial prescription patterns among those *actually* discharged on antihypertensive medications following stroke, for who it would appear that exacerbating the initial ischemic stroke, was not an overriding concern in administering such treatment.

In conclusion, a timely and profiled treatment approach that incorporates the widely known differential response and potential for greater vascular risk in Black ischemic stroke and TIA patients exposed to certain antihypertensive regimens is not currently employed, and may be one step in a process geared at reducing the huge burden that secondary stroke exacts on these individuals.

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Table 1
Demographic and Clinical Characteristics by Race

Characteristic	Black Patients (n=77) N(%)	All Other Races (n=717) N(%)	P-Value *
Age, quartiles			<0.0001
< 60 years	37(48.0)	161(22.0)	
60–73 years	21(27.0)	167(23.0)	
73–82 years	10(13.0)	180(25.0)	
> 82 years	9(12.0)	209(29.0)	
Gender			0.94
Female	41(53.0)	385(54.0)	
Male	36(47.0)	332(46.0)	
Discharge diagnosis			0.16
TIA	12(15.6)	162(22.6)	
Ischemic stroke	65(84.0)	555(77.4)	
Independent ambulation **	43(55.8)	366(51.1)	0.42
Discharged home	50(64.9)	457(63.7)	0.64
History of:			
Stroke/TIA	35(45.5)	252(35.2)	0.07
MI	5(6.5)	64(8.9)	0.47
CAD	11(14.3)	126(17.6)	0.47
Afib	6(7.8)	124(17.3)	0.03
CHF	13(16.9)	75(10.5)	0.09
Hypertension	58(75.3)	479(66.8)	0.13
Dyslipidemia	23(29.9)	227(31.7)	0.75
Diabetes	27(35.1)	178(24.8)	0.05
Smoking	31(40.3)	139(19.4)	<0.0001
Dementia	3(3.9)	46(6.4)	0.38

* All p-values calculated using chi-squared test

** As assessed at discharge

MI=myocardial infarction; CAD=coronary artery disease;

Afib=atrial fibrillation; CHF=congestive heart failure

Table 2

Class of Antihypertensive[*]	Total n	Black Patients (n=77) n	(%)	UnivariateOR(95% CI) **	P value
ACEI [†]	318	31	9.7	1.10(0.65, 1.85)	0.73
Beta-blocker	236	25	10.6	1.23(0.64, 2.34)	0.54
Calcium channel-blocker	96	11	11.5	1.14(0.55, 2.36)	0.72
Diuretic	180	24	13.3	1.61(0.88, 2.94)	0.12
ARB [‡]	24	4	16.7	1.27(0.25, 6.51)	0.77
Other	64	6	9.4	0.98(0.41, 2.35)	0.97

* Each class of antihypertensive was used as an outcome, with Black vs. other race as a predictor

** All analyses were performed using GEE. O.R. calculates Black race as a predictor of receipt of a given agent, compared to all other races combined.

[†] ACEI=angiotensin converting enzyme inhibitor

[‡] ARB=angiotensin receptor blocker

Table 3
Use of Antihypertensive Medications in Black Patients (n=77)

Characteristic	Any Antihypertensive N (%)	O.R.	95% C.I.	P-Value	DB/CCBB Treatment N (%)	O.R.	95% CI	P-Value
Age		1.03	(1.00, 1.06)	0.08		1.00	(0.97, 1.03)	0.87
Gender								
Female	34(82.9)		ref.		20(48.8)		ref.	
Male	23(63.9)	0.37	(0.15, 0.91)	0.03	11(30.6)	0.46	(0.24, 0.89)	0.02
History of:								
Stroke/TIA	28(80.0)	1.80	(0.68, 4.74)	0.23	15(42.9)	1.23	(0.53, 2.82)	0.63
MI	5(100.0)		N/A ^{**}		3(60.0)	2.37	(0.39, 14.4)	0.35
CAD	11(100.0)		N/A ^{**}		6(54.6)	1.97	(0.70, 5.50)	0.20
Afib	5(83.3)	1.83	(0.18, 18.9)	0.61	3(50.0)	1.56	(0.44, 5.57)	0.50
CHF	11(84.6)	2.21	(0.51, 9.52)	0.29	9(69.0)	4.42	(1.25, 15.7)	0.02
Dyslipidemia	19(82.6)	2.01	(0.74, 5.48)	0.17	11(47.8)	1.55	(0.75, 3.20)	0.23
Diabetes	23(85.2)	2.69	(1.29, 5.62)	0.01	8(29.6)	0.49	(0.29, 0.83)	0.008
Smoking	22(71.0)	0.75	(0.19, 2.94)	0.68	13(41.9)	1.12	(0.30, 4.19)	0.86
Dementia	2(66.7)	0.69	(0.06, 7.98)	0.77	1(33.3)	0.73	(0.06, 8.83)	0.80

DB/CCBB=diuretic based/calcium channel-blocker based treatment

^{**} All patients in this group received an antihypertensive medication

MI=myocardial infarction; CAD=coronary artery disease;

Afib=atrial fibrillation; CHF=congestive heart failure