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Racial Differences in Plasma Levels of N-Terminal Pro–B-Type Natriuretic Peptide and Outcomes

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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IMPORTANCE Recent studies have suggested that the natriuretic peptide system may be endogenously suppressed in black individuals who are free of prevalent cardiovascular disease. Whether natriuretic peptide levels contribute to racial disparities in clinical outcomes is unknown.

OBJECTIVE To examine racial differences in N-terminal pro–B-type natriuretic peptide (NTproBNP) levels and their association with all-cause mortality and cause-specific mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.

DESIGN, SETTING, AND PARTICIPANTS Baseline NTproBNP levels were measured in a randomly selected sample of 4415 REGARDS study participants. Those with prevalent cardiovascular disease and renal dysfunction were excluded. From July 1, 2003, to September 12, 2007, among the remaining 1998 individuals, racial differences in NTproBNP levels were estimated, and the percentage difference in NTproBNP levels by race was meta-analyzed and compared with published results on participants free of prevalent cardiovascular disease from the Dallas Heart Study and Atherosclerosis Risk in Communities study, using random effects modeling. The association of NTproBNP levels, race, all-cause mortality, and cause-specific mortality in the REGARDS study was studied using appropriate modeling techniques. Data analysis was conducted from July 1, 2003, to March 31, 2016.

MAIN OUTCOMES AND MEASURES Racial differences in NTproBNP levels and association with all-cause mortality and cause-specific mortality.

RESULTS Among the 1998 participants studied (972 women and 1026 men; median age, 63 years [interquartile range, 54-72 years]), median NTproBNP levels in black individuals were significantly lower than those in white individuals (46 pg/mL [interquartile range, 23-91] vs 60 pg/mL [interquartile range, 33-106]; $P < .001$). With multivariable adjustment, NTproBNP levels were up to 27% lower in black individuals as compared with white individuals (β, −0.32; 95% CI, −0.40 to −0.24; $P < .001$) in the REGARDS study. In meta-analysis of the 3 cohorts, NTproBNP levels were 35% lower in black individuals than white individuals. Among the REGARDS study participants, for every 1-SD higher log NTproBNP, there was a 31% increased risk of death in the multivariable-adjusted model (hazard ratio, 1.31; 95% CI, 1.11-1.54). This increase was driven primarily by association of NTproBNP with cardiovascular mortality (hazard ratio, 1.69; 95% CI, 1.19-2.41). No interaction between race and NTproBNP levels was observed with all-cause mortality and cause-specific mortality.

CONCLUSIONS AND RELEVANCE Plasma NTproBNP levels are significantly lower in black individuals as compared with white individuals in the REGARDS study and in pooled results from the REGARDS study, Dallas Heart Study, and Atherosclerosis Risk in Communities study. Higher NTproBNP levels were associated with higher incidence of all-cause mortality and cardiovascular mortality in healthy black and white individuals, and this association did not differ by race.

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Natriuretic peptides (NPs) are diuretic and vasodilatory hormones synthesized from the heart in response to increased myocardial wall stress.[1] A previous study reported that an NP deficiency state exists in obesity[2] and in individuals with common genetic variants.[3] Whether there are differences in NP levels by race is not well understood. Prior studies reported no differences in NP levels by race.[4,5] However, 2 recent population studies suggested that black individuals have lower N-terminal pro-B-type NP (NTproBNP) levels as compared with white individuals.[6,7] These data are potentially important in that an endogenously suppressed NTproBNP system could contribute to a higher risk of hypertension and heart failure in black individuals as compared with white individuals.

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study[8] offers a unique opportunity to characterize plasma NTproBNP levels according to race in a large study of participants free of cardiovascular and kidney disease. We sought to examine the hypothesis in these healthy individuals that plasma NTproBNP levels would be lower in black individuals as compared with white individuals. In addition, we tested whether racial differences in NP levels are associated with dissimilar rates of all-cause mortality, CV mortality, non-CV mortality, and incident hypertension in black and white participants in the REGARDS study.

Key Points

Question Does primary natriuretic peptide deficiency exist in black individuals?

Findings In this cohort study, N-terminal pro–B-type natriuretic peptide levels were 27% lower in black individuals as compared with white individuals, tested in a stratified random subgroup from a national cohort; these findings were consistent when meta-analyzed with other population-based cohorts. There was a robust association of natriuretic peptide levels with all-cause mortality driven by cardiovascular mortality in individuals free of prevalent cardiovascular and renal disease that did not differ by race.

Meaning Black race is a natriuretic peptide deficiency state; the prognostic value of natriuretic peptide levels in a population-based cohort is similar in black and white individuals.

Methods

Assembly of Cohort

The REGARDS study is a national population-based cohort study evaluating racial and geographic disparities in stroke in US adults 45 years of age or older.[8] Participants were excluded from the REGARDS study if they self-identified as Hispanic white individuals or Hispanic black individuals. Details of the study design were described previously.[8] The demographic, socioeconomic, and medical information along with verbal informed consent was obtained by computer-assisted telephone interview, which was followed by an in-home visit at which written informed consent, blood pressure (BP), anthropomorphic measures, blood samples, electrocardiogram results, and medication inventory were obtained.[8] The University of Alabama at Birmingham, University of Vermont, Wake Forest University School of Medicine, University of Arkansas for Medical Sciences, University of Cincinnati, and Indiana University Institutional Review Boards approved the study protocol.

A stratified random cohort of 4415 participants was selected for NTproBNP measurement. Stratification factors included age, sex, and race. These participants underwent NTproBNP measurements using stored samples from baseline. Fasting baseline blood samples were drawn and stored using standardized methods.[9] N-terminal pro-B-type NP was measured in the random cohort sample using an electrochemiluminescence immunoassay (Roche Elecsys 2010; Roche Diagnostics; coefficient of variation, <5%).

To address our hypothesis of NP suppression by race, we excluded 2417 participants for the following reasons: missing NTproBNP levels (n = 283), prevalent CV disease (n = 1327; defined as individuals with coronary artery disease [including coronary artery bypass grafting, percutaneous coronary interventions, self-reported myocardial infarction, or presence of myocardial infarction on electrocardiogram results as defined by the Minnesota code[10]], stroke, transient ischemic attack, atrial fibrillation, peripheral vascular disease, and aortic aneurysm), heart failure (n = 608), or estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 (n = 199).[11] We conducted our analysis among the remaining 1998 participants from July 1, 2003, to September 12, 2007.

Measurements and Definitions

Hypertension was defined as systolic BP of 140 mm Hg or more and diastolic BP of 90 mm Hg or more or self-reported hypertension with use of antihypertensive medications. Diabetes was defined by self-report with use of oral antidiabetic medications or insulin, fasting glucose more than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555), or nonfasting glucose more than 200 mg/dL. Hyperlipidemia was defined by total cholesterol of 240 mg/dL or more (to convert to millimoles per liter, multiply by 0.0259), low-density lipoprotein cholesterol of 160 mg/dL or more (to convert to millimoles per liter, multiply by 0.0259), high-density lipoprotein cholesterol of 40 mg/dL or less (to convert to millimoles per liter, multiply by 0.0259), or self-reported use of antihyperlipidemic medications. Aspirin use was self-reported. Atrial fibrillation was defined by self-report or from presence on electrocardiogram. Baseline stroke and transient ischemic attack were defined by self-report. Heart failure was defined as presence of orthopnea or paroxysmal nocturnal dyspnea or NTproBNP levels greater than 300 pg/mL.[12] Smoking, alcohol use, exercise, educational level, and income status were self-reported. Peripheral vascular disease and history of aortic aneurysm repair were self-reported. Renal dysfunction was defined as estimated glomerular filtration rate less than 60 mL/min/1.73 m^2.[11]

All-Cause Mortality, Cause-Specific Mortality, and BP Measures

After the baseline examination for the REGARDS study, routine semiannual interviews were conducted. If it was not possible to reach participants, mortality was assessed through contact with proxies. The date of death was corroborated through death certificates or the national death index, as described previously.[13] Our analyses in this article are based on deaths that occurred through March 2016.

In the REGARDS study, cause of death was adjudicated by a committee of physicians using information from death certificates, hospital records, and interviews with proxies. These centrally adjudicated CV and non-CV mortality characterizations were used for our analyses.[13] Briefly, CV mortality was defined as death from any of the following adjudicated events: myocardial infarction, stroke, sudden death, heart failure, pulmonary embolism, noncardiac CV disease, and other cardiac causes of death. Any other deaths apart were considered as non-CV deaths.

Incident hypertension was determined in participants free from the diagnosis of hypertension at the baseline visit. Longitudinal BP progression was assessed as change in systolic and diastolic BP at the second visit from the baseline visit. Description of incident hypertension ascertainment and longitudinal changes in BP along with details of the second visit are described in the eAppendix in the Supplement.

Statistical Analysis

Statistical analysis was conducted from July 1, 2003, to March 31, 2016, using STATA, version 14.0 MP (StataCorp LP). Differences in baseline characteristics among black and white individuals were compared using χ^2 tests for categorical variables and the Mann-Whitney test for continuous variables. Cumulative distribution curves of NTproBNP levels by race were constructed to assess racial differences. Associations of NTproBNP with race were evaluated by linear regression models, including unadjusted, age- and sex-adjusted, and multivariable models. Natural log-transformed NTproBNP was the dependent variable for all models. Covariates in multivariable models were included if they were known to clinically affect NTproBNP levels or were included in previous studies.[6,7] These variables included age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), systolic BP, antihypertensive medications, aspirin use, hyperlipidemia, income, smoking, exercise, and estimated glomerular filtration rate. White race was chosen as a reference, and the percentage difference with 95% CI was calculated using the formula: $(e^{\beta} - 1) \times 100$ (where β is the beta coefficient from linear regression). Appropriate modeling techniques were used to estimate the association of natural log-transformed NTproBNP levels and race with outcomes described above. The details of these analyses are described in the eAppendix in the Supplement.

Meta-analysis With Other Cohort Studies

Our literature search revealed 2 studies assessing racial differences in NTproBNP using the identical NTproBNP assay, the Dallas Heart Study (DHS)[6] and Atherosclerosis Risk in Communities (ARIC) study.[7] The β estimates for log-transformed NTproBNP levels in multivariable models (adjusted for similar factors across 3 cohorts) were meta-analyzed using random effects modeling. The details of these analyses are described in the eAppendix in the Supplement.

Results

Our assembled cohort included 1998 participants with median age of 63 years (interquartile range [IQR], 54-72 years). A total of 981 participants (49.1%) were black, 972 (48.6%) were female, and 694 (34.7%) were obese (body mass index ≥30). The median NTproBNP level was 53 pg/mL (IQR, 28-97 pg/mL). **Table 1** shows baseline characteristics by race. Black participants had higher median systolic BP than white participants (129 vs 121 mm Hg; $P < .001$) as well as a higher rate of antihypertensive drug use (547 of 981 [55.8%] vs 338 of 1017 [33.2%]). Black participants were more likely than white participants to have diabetes (236 of 981 [24.1%] vs 115 of 1017 [11.3%]; $P < .001$), had higher body mass index (29 vs 27; $P < .001$), and were more likely to be current smokers (165 of 981 [16.8%] vs 115 of 1017 [11.3%]; $P < .001$). White participants were more likely than black participants to be current alcohol drinkers (647 of 1017 [63.6%] vs 440 of 981 [44.9%]; $P < .001$).

Table 1. Baseline Characteristics in REGARDS Study Cohort Participants

Characteristic	Patients, No. (%)[a]		
	Black Participants (n = 981)	White Participants (n = 1017)	*P* Value
Age, median (IQR), y	64 (54-72)	62 (54-72)	.14
Female sex	485 (49.4)	487 (47.9)	.49
Educational level, college graduate	277 (28.2)	476 (46.8)	<.001
Income >$75 000	114 (11.6)	250 (24.6)	<.001
Lifestyle habits			
Current smoker	165 (16.8)	115 (11.3)	<.001
Current alcohol use	440 (44.9)	647 (63.6)	<.001
Exercise >4 times/wk	281 (28.6)	343 (33.8)	.02
BMI, median (IQR)	29 (26-33)	27 (24-31)	<.001
SBP, median (IQR), mm Hg	129 (119-140)	121 (113-132)	<.001
Medication use			
Aspirin	268 (27.3)	367 (36.1)	<.001
Antihypertensive	547 (55.8)	338 (33.2)	<.001
Diabetes	236 (24.1)	115 (11.3)	<.001
Hyperlipidemia	466 (47.5)	547 (53.8)	.004
NTproBNP, median (IQR), pg/mL	46 (23-91)	60 (33-106)	<.001
Log NTproBNP, median (IQR)	3.8 (3.1-4.5)	4.1 (3.5-4.7)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; NTproBNP, N-terminal pro–B-type natriuretic peptide; REGARDS, Reasons for Geographic and Racial Differences in Stroke; SBP, systolic blood pressure.

[a] Data are presented as number (percentage) of patients and were compared using the χ^2 test unless otherwise indicated. Continuous variables were compared using the Mann-Whitney test.

NTproBNP and Race

The median NTproBNP level in black participants was significantly lower than in white participants (46 pg/mL [IQR, 23-91] vs 60 pg/mL [IQR, 33-106]; $P < .001$) (Table 1). The cumulative distribution plots of NTproBNP levels by race showed that NTproBNP levels were lower in black participants as compared with white participants (eFigure 1 in the Supplement). The adjusted absolute differences in log NTproBNP levels by race are shown in **Table 2**. In the unadjusted model, NTproBNP levels were 21% lower in black participants. After adjusting for age and sex, the NTproBNP levels were 23% lower in black participants, and were 27% lower in the fully adjusted model (Table 2). To assess the use of thiazide or loop diuretics as a possible residual confounder contributing to the observed racial differences in NTproBNP levels, we conducted the above analyses in

Table 2. Racial Differences in Plasma NTproBNP Levels in Multivariable Linear Regression Models[a]

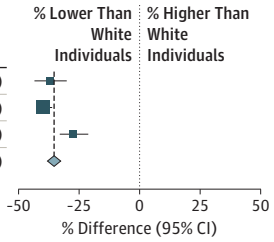
Model	White Participants	Black Participants, β (95% CI)	% Lower Than White Participants	*P* Value
Unadjusted	Reference	−0.24 (−0.32 to −0.17)	−21	<.001
Adjusted for age and sex	Reference	−0.26 (−0.33 to −0.20)	−23	<.001
Adjusted for age, sex, income, college education, exercise, smoking, alcohol, body mass index, systolic blood pressure, antihypertensive medications, aspirin use, hyperlipidemia, diabetes, and eGFR	Reference	−0.32 (−0.40 to −0.24)	−27	<.001

Abbreviations: eGFR, estimated glomerular filtration rate; NTproBNP, N-terminal pro–B-type natriuretic peptide.

[a] Multivariable linear regression models using natural log-transformed NTproBNP as the dependent variable and race as the independent variable were used. Values shown are β coefficient (95% CI), which are on the log NTproBNP scale. Percentage lower than white participants is the estimated percentage difference in NTproBNP levels in black vs white participants, which was calculated by using the formula $(e^{\beta} - 1) \times 100$, assuming all other variables in the model remained constant.

Figure 1. Estimated Percentage Difference in N-Terminal Pro–B-Type Natriuretic Peptide (NTproBNP) Levels in Black vs White Individuals

Source	No. of Participants	Median NTproBNP, pg/mL: Black Participants	Median NTproBNP, pg/mL: White Participants	% Lower Than White Participants (95% CI)
DHS[6]	2575	24	32	-36.87 (-43.45 to -30.23)
ARIC[7]	9137	43	68	-39.95 (-42.88 to -36.24)
REGARDS[8]	1998	46	60	-27.39 (-32.97 to -21.34)
Overall percentage lower than white participants				-34.95 (-42.31 to -26.66)



A random-effects model was used to derive pooled estimates for percentage difference in black vs white individuals from multivariable models in the ARIC (Atherosclerosis Risk in Communities) study, Dallas Heart Study (DHS), and Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. The vertical dotted line represents white individuals as a reference for NTproBNP levels. The vertical dashed line represents pooled NTproBNP levels in black individuals. Pooled estimates from different cohorts and the 95% CIs are represented by the blue diamond.

1515 participants not taking any diuretic medications and found comparable racial differences in NTproBNP levels as in the study cohort of 1998 individuals (eTables 1 and 2 in the Supplement).

Meta-analysis of Other Cohort Studies

We included the REGARDS study, the DHS, and the ARIC study for this analysis. The number of participants without prevalent CV disease in the REGARDS study was 1998, in the DHS was 2575, and in the ARIC study was 9137. There were 981 black participants (49.1%) in the REGARDS study, 1606 of 2575 (62.4%) in the DHS, and 1973 of 9137 (21.6%) in the ARIC study. The median NTproBNP levels in black participants were 46 pg/mL (IQR, 23-91 pg/mL) in the REGARDS study, 24 pg/mL (IQR, 10-52 pg/mL) in the DHS, and 43 pg/mL (IQR, 18-88 pg/mL) in the ARIC study. The participants in the REGARDS study were oldest, with a median age of 63 years (IQR, 54-72 years), followed by the ARIC study, in which the median age was 61 years (IQR, 57-67 years), and the DHS, in which the median age was 44 years (IQR, 36-52 years). In all 3 cohorts, NTproBNP levels in black participants were significantly lower than in white participants. The highest multivariable-adjusted percentage difference by race was observed in the ARIC study (40% lower in black participants), whereas the lowest multivariable-adjusted percentage difference was observed in the REGARDS study (27% lower in black participants) as compared with white participants (**Figure 1**). Pooling cohorts, multivariable-adjusted NTproBNP was 35% lower in black vs white participants (I^2 = 86%; *P* < .001) (Figure 1).

Mortality, Incident Hypertension, and Longitudinal Changes in BP in REGARDS Study Participants

In the 1998 REGARDS study participants, a total of 279 individuals (155 black participants and 124 white participants) died during a median follow-up period of 8.4 years (IQR, 6.9-10.7 years). In unadjusted models, for every 1-SD increment in log NTproBNP levels, there was an 87% increase in the risk of death for the overall population (hazard ratio [HR], 1.87; 95% CI, 1.64-2.13; *P* < .001). Results were similar in the age-, sex-, and race-adjusted model (HR, 1.43; 95% CI, 1.24-1.66; *P* < .001) and the multivariable model (HR, 1.31; 95% CI, 1.11-1.54; *P* = .001) (**Table 3**). This increase was driven by the association of NTproBNP with CV mortality (multivariable model: HR, 1.69; 95% CI, 1.19-2.41; *P* = .004) (Table 3). We did not observe an association between NTproBNP levels and non-CV mortality (multivariable model: HR, 1.20; 95% CI, 1.00-1.46; *P* = .06) (Table 3).

A total of 978 participants were normotensive at baseline. Of these 978, 529 participants had their hypertension status ascertained at the second in-home visit. Among those participants, 187 (35.3%) developed hypertension. We did not observe any association between NTproBNP levels and incident hypertension or progression of systolic or diastolic BP (eTables 3, 4, and 5 in the Supplement).

Effect of Race on Association Between NTproBNP and Mortality, Incident Hypertension, and BP Progression

The association of NTproBNP with incidence of all-cause mortality, CV mortality, and non-CV mortality using restricted cubic splines, stratified by race, are shown in **Figure 2**. After multivari-

able adjustment for established risk factors, there were no significant differences in incident rates of all-cause mortality (likelihood ratio [LR] χ^2 = 0.30; P = .96), CV mortality (LR χ^2 = 3.23; P = .36), and non-CV mortality (LR χ^2 = 1.78; P = .62) in black participants as compared with white participants. In addition, there was no interaction between race and NTproBNP levels on all-cause mortality (LR χ^2 = 0.23; P = .89), CV mortality (LR χ^2 = 2.76; P = .25), and non-CV mortality (LR χ^2 = 1.78; P = .41).

We also did not observe any difference in the risk of incident hypertension in black vs white participants in the multivariable-adjusted model (odds ratio, 0.93; 95% CI, 0.70-1.23; P = .61) or an interaction between race and NTproBNP on the risk of incident hypertension in the multivariable logistic regression model (odds ratio, 1.10; 95% CI, 0.69-1.77; P = .68). The association of NTproBNP levels with longitudinal change in systolic and diastolic BP stratified by race are shown in eFigures 2 and 3 in the Supplement. There was no association or racial interaction between NTproBNP and change in systolic or diastolic BP.

Table 3. Association of a 1-SD Increment of Natural Log of Baseline Plasma NTproBNP Levels With Mortality

Model	Hazard Ratio (95% CI)	*P* Value
All-cause mortality[a]		
Unadjusted	1.87 (1.64-2.13)	<.001
Adjusted for age, sex, and race	1.43 (1.24-1.66)	<.001
Multivariable model[b]	1.31 (1.11-1.54)	.001
Cardiovascular mortality[a]		
Unadjusted	2.01 (1.50-2.09)	<.001
Adjusted for age, sex, and race	1.82 (1.32-2.25)	<.001
Multivariable model[b]	1.69 (1.19-2.41)	.004
Non-CV mortality[a]		
Unadjusted	1.77 (1.52-2.05)	<.001
Adjusted for age, sex, and race	1.32 (1.11-1.55)	.001
Multivariable model[b]	1.20 (1.00-1.46)	.06

Abbreviation: NTproBNP, N-terminal pro–B-type natriuretic peptide.

[a] Cox proportional hazards regression model was used (proportional hazards assumption was not violated in any of the models).

[b] Multivariable model adjusted for age, sex, race, income, college education, exercise, smoking, alcohol, body mass index, systolic blood pressure, antihypertensive medications, aspirin use, hyperlipidemia, diabetes, and estimated glomerular filtration rate.

Discussion

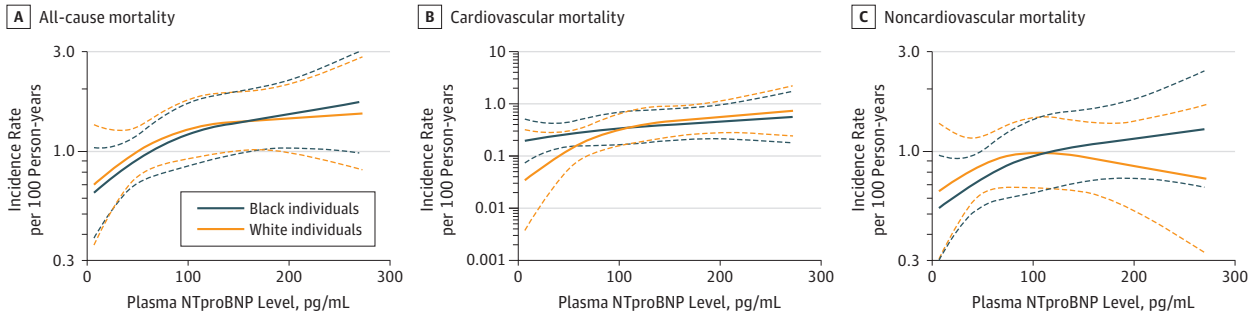
In our well-characterized random cohort of participants from the REGARDS study, black participants had significantly lower plasma NTproBNP levels than white participants. This difference was significant after adjusting for multiple clinically relevant factors and remained consistent when meta-analyzed with other large population-based cohorts. Furthermore, we observed that baseline NTproBNP levels were associated with the risk of future all-cause and CV mortality. These associations were not modified by race. Last, we did not observe any association between NTproBNP levels and incident hypertension or BP progression in our subgroup analyses. However, these analyses were conducted in a subgroup of our population and were not adequately powered to detect small differences in incident hypertension and BP progression.

N-terminal pro-B-type NP is produced in response to stretch on cardiomyocytes owing to effects of hemodynamic challenges on the heart and the NP system.[14,15] We noted that percentage differences in NTproBNP levels in black participants became more pronounced (Table 2) after adjusting for known biological and clinical variables (eg, age, sex, body mass index, and hypertension) that change NP levels.[16-19] This observation, along with the genetic basis (ie, detection of increasing NTproBNP levels with increasing percentage of European ancestry in the ARIC study[7]), puts forward the hypothesis that black individuals have an NP deficiency state that is unexplained. In addition, common genetic variants associated with hypertension and altered NP processing activity in *Corin*, an enzyme responsible for NP processing, occur almost exclusively in black individuals.[20,21] Finally, black individuals have a higher prevalence of CV disease[22]; therefore, intuitively they should have higher NTproBNP levels than white individuals, suggesting possible nonhemodynamic mechanisms (eg, decreased production) as a cause for lower NTproBNP levels in black individuals. Taken collectively, the findings of paradoxically low NP levels suggest the likelihood of a primary deficiency among black individuals.

Two recent studies by Gupta et al[6,7] reported racial differences in NTproBNP levels in the DHS[6] and ARIC study cohorts.[7] The direction of results from our study is in concordance with the findings from these 2 studies. We observed an adjusted difference of 27% lower NTproBNP levels in black participants as compared with white participants, whereas in DHS and the ARIC study this difference was up to 40%. However, there are several differences worth mentioning. Although participants in our study were older, we had equal representation of black and white participants. Moreover, we used additional stringent criteria compared with previous studies to exclude participants with prevalent CV disease. We excluded participants with peripheral vascular disease, aortic aneurysm repair, estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, which the earlier studies[6,7] did not. To our knowledge, ours is the first study to summarize the percentage difference in black vs white individuals in participants free of prevalent CV disease across 3 different cohorts, which lends more generalizability to our results. Our findings suggest that NTproBNP levels are lower in black vs white individuals, which makes the argument for reporting race-specific NTproBNP values in individuals free of prevalent CV and renal disease. This finding is particularly relevant since American College of Cardiology and American Heart Association guidelines[23] provide cutoff values of NTproBNP levels that are not stratified by race to rule out heart failure in ambulatory patients.

The association of elevated NP levels with adverse outcomes in apparently healthy white individuals was established by the work done by Wang and colleagues.[24] These findings were replicated in multiple studies in the general population,[25-27] although most of the studies included predominantly white participants. This association of increasing NP levels with increasing mortality has been thought to be owing to the presence of subclinical CV disease, which exists even in apparently healthy individuals. The association of NTproBNP levels with higher risk

Figure 2. Incident Mortality Rates per 100 Person-years of Follow-up in Black and White Participants



A, Incident rates of all-cause mortality per 100 person-years (test for equality, $P = .96$; test for interaction, $P = .89$). B, Incident rates of cardiovascular mortality per 100 person-years (test for equality, $P = .36$; test for interaction, $P = .25$). C, Incident rates of noncardiovascular mortality per 100 person-years (test for equality, $P = .62$; test for interaction, $P = .41$). Rates were adjusted for age, sex, income, college education, exercise, smoking, alcohol, body mass index, systolic blood pressure, antihypertensive medications, aspirin use, hyperlipidemia, diabetes, and estimated glomerular filtration rate. The solid blue line represents black individuals, and the solid orange line represents white individuals. Dashed lines represent 95% CIs.

of CV risk and mortality has been described among black individuals with hypertensive kidney disease.[28] To our knowledge, there are no studies testing the association of NTproBNP levels and mortality by race in apparently healthy individuals. To our knowledge, our study is the first to report an increasing risk of all-cause mortality and CV mortality with increasing NTproBNP levels, and that this association was not modified by race in individuals free of prevalent CV and kidney disease. This finding suggests that higher NTproBNP levels are associated with similar increases in the risk of all-cause mortality in black and white individuals even though black individuals on average have lower NTproBNP levels than white individuals. This finding highlights the importance of the fact that studying the effects of NP deficiency (eg, black race) using population cohorts as a model system can be challenging owing to the involvement of the NP axis in a feedback loop.

Lower levels of NTproBNP may contribute to an excess burden of CV outcomes such as heart failure and other CV events seen in black individuals. This notion is supported by genetic association studies where common genetic variants associated with an approximately 20% decrease in NP levels are associated with an approximately 15% increase in the risk of systolic BP, diastolic BP, and hypertension.[29] To summarize, we believe that NP deficiency (in black individuals) may be associated with development of CV disease, whereas association of elevated NP levels with mortality reflects the consequence of subclinical CV disease in apparently healthy individuals. This association highlights our inability to provide mechanistic insights using an epidemiologic cohort as a model system. Overall, our findings are of public health and clinical importance as NP deficiency seen in black individuals may be contributing to racial disparities in the burden of CV disease. Additional studies are required to establish and confirm the role of the NP system in the development of CV disease.

Strengths and Limitations

Our study was a well-characterized cohort of black and white individuals with a standardized collection of data at baseline and careful documentation of mortality. Despite this, study limitations require consideration. Race was self-identified, instead of using genetic ancestry information markers, which may have resulted in misclassification. We did not have direct noninvasive assessment of left ventricular size and/or function. However, to overcome this limitation, we excluded all participants with orthopnea, paroxysmal nocturnal dyspnea, or NTproBNP levels greater than 300 pg/mL. Small sample size and lack of time to event date for incident hypertension limits our ability to determine any effects that hypertension had on mortality. We adjusted for all the known factors that can affect NP levels but there still remains the issue of unidentified confounders. Last, our conclusion that the endogenous NP system is suppressed in black individuals as compared with white individuals is based primarily on studying differences in plasma NTproBNP levels. Other NPs including mature B-type NP, N-terminal-pro-atrial type NP, and mature atrial NP were not measured in the REGARDS study.

Conclusions

We have established lower NTproBNP levels in black vs white adults in our population cohort that was free of prevalent CV and renal disease. Similar associations were observed in other cohorts. Endogenous suppression of the NP system in black individuals did not affect the association between NTproBNP levels and all-cause or cause-specific mortality, which needs to be confirmed in other cohorts.

ARTICLE INFORMATION

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