Racial differences in the association of NT-proBNP with risk of incident heart failure in REGARDS

Nirav Patel, … , Emily B. Levitan, Pankaj Arora


BACKGROUND. Black individuals have lower natriuretic peptide levels and greater risk of heart failure (HF) than white individuals. Higher N-terminal-pro-B-type natriuretic peptide (NT-proBNP) is associated with increased risk of incident HF, but little information is available in black individuals. We examined race-specific differences in 1) the association of NT-proBNP with incident HF and 2) the predictive ability of NT-proBNP for incident HF across body mass index (BMI) and estimated glomerular filtration rate (eGFR) categories.

METHODS. In a prospective case-cohort study, baseline NT-proBNP was measured among 687 participants with incident HF and 2,923 (weighted 20,075) non-case randomly selected participants. Multivariable Cox proportional hazard modeling was used to assess the objectives of our study. Global Wald Chi-square score estimated from multivariable Cox models was used to assess predictive ability of NT-proBNP across BMI and eGFR categories.

RESULTS. In the multivariable model, a doubling of NT-proBNP concentration was associated with greater risk of incident HF among white individuals [hazard ratio (HR): 1.73; 95% CI: 1.55–1.94] than black individuals (HR: 1.51; 95% CI: 1.34–1.70); \( P_{interaction} \) by race = 0.024. Higher NT-proBNP was the strongest predictor of incident HF across all BMI and eGFR categories […]

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Abstract

Background
Black individuals have lower natriuretic peptide levels and greater risk of heart failure (HF) than white individuals. Higher N-terminal-pro-B-type natriuretic peptide (NT-proBNP) is associated with increased risk of incident HF, but little information is available in black individuals. We examined race-specific differences in 1) the association of NT-proBNP with incident HF and 2) the predictive ability of NT-proBNP for incident HF across body mass index (BMI) and estimated glomerular filtration rate (eGFR) categories.

Methods
In a prospective case-cohort study, baseline NT-proBNP was measured among 687 participants with incident HF and 2,923 (weighted 20,075) non-case randomly selected participants. Multivariable Cox proportional hazard modeling was used to assess the objectives of our study. Global Wald Chi-square score estimated from multivariable Cox models was used to assess predictive ability of NT-proBNP across BMI and eGFR categories.

Results
In the multivariable model, a doubling of NT-proBNP concentration was associated with greater risk of incident HF among white individuals [hazard ratio (HR): 1.73; 95%CI: 1.55-1.94] than black individuals (HR: 1.51; 95%CI: 1.34-1.70); Pinteraction by race=0.024. Higher NT-proBNP was the strongest predictor of incident HF across all BMI and eGFR categories among white individuals. By contrast, among black individuals with obesity (BMI ≥30kg/m²) or eGFR <60mL/min/1.73 m², the predictive ability of NT-proBNP for incident HF was attenuated.

Conclusions
The magnitude of the association of higher NT-proBNP with incident HF risk was greater among white individuals than black individuals. The diminished ability of NT-proBNP to predict the risk of HF in black population with obesity or impaired kidney function highlights the need of further investigations.
Introduction

Natriuretic peptides (NPs) are hormones produced by the heart. Hemodynamic challenges such as pressure overload seen in hypertension and volume overload seen in heart failure (HF) are associated with higher circulating NP levels. The role of NPs in the diagnosis and prognosis of HF has been well established. Additionally, population-based studies have concluded that NPs can predict the risk of cardiovascular disease including incident HF. However, the information on racial differences in the relationship between N-terminal-pro B-Type NP (NT-proBNP) levels and incident HF is small. Study of racial differences in magnitude of association of NP levels with incident HF is of particular relevance since we and others recently described that black individuals have significantly lower NP levels as compared with white individuals.

In addition to race, increasing age, sex, obesity, and impaired renal function affect circulating NP levels. Prior studies have reported that the association between NP levels and incident HF differed by body mass index (BMI) and estimated glomerular filtration rate (eGFR) categories. However, little is known about the relationship of NP levels and incident HF across BMI and eGFR categories among black individuals, a key racial group at risk for HF. The REasons for Geographic And Racial Differences in Stroke (REGARDS) study offers a unique opportunity to examine race-specific risk associated with NT-proBNP for incident HF, including in subgroups who are obese or with impaired renal function in a large, bi-racial population of the United States adults.
We aimed to examine 1) the differences in the relationship of NT-proBNP levels and incident HF by race, and 2) whether the risk of incident HF predicted by NT-proBNP levels across BMI and eGFR categories differed by race.
Results

Study Participants

Of the 4,415 randomly selected participants, we excluded individuals with missing NT-proBNP (n=254), suspect or missing information on HF status (n=598), missing or BMI less than 18.5 kg/m\(^2\) (n=70) (i.e., due to fewer participants and possible confounding with other BMI categories). We additionally excluded individuals with missing information of other covariates (n=446) (Figure 1). There were 124 incident HF cases identified among randomly selected participants. After applying similar exclusion criteria, we excluded 249 individuals from the 812 incident HF cases (Figure 1). These exclusions resulted in including 687 cases of incident HF during follow-up and 2,923 participants in the cohort random sample in the study (Figure 1).

Table 1 depicts the baseline characteristics of REGARDS participants in the non-case cohort random sample by race. The proportion of females were higher among black participants as compared with white participants (61.6% vs. 49.9%, p<0.001) (Table 1). Higher proportion of black individuals were the current smokers, while higher proportion of white individuals were the current alcohol users (Table 1). Black individuals were more likely to have higher BMI, systolic blood pressure, hypertension, diabetes, left ventricular hypertrophy as compared with white individuals. On contrary, white individuals were more likely to have dyslipidemia, aspirin use, and coronary artery disease compared with black individuals (Table 1). The median eGFR was significantly higher among black participants as compared with white participants [94 (IQR: 77-108) vs. 85 (74-95), p<0.001] (Table 1). White participants were more likely to live in more advantaged neighborhood compared with black participants [median Z score (IQR); 1.0 (-2.2, 5.5) vs. -2.8 (-5.1, 0.0), p<0.001] (Table 1). The baseline characteristics of participants in the
non-case cohort random sample by tertiles of NT-proBNP as well as participants who developed HF (n=687) were presented as Supplemental Table 1 and 2, respectively.

**NT-proBNP Levels and Incident Heart Failure**

The risk of HF rose sharply across tertiles of baseline NT-proBNP (Table 2). Specifically, the multivariable-adjusted HR for incident HF in the 2<sup>nd</sup> and 3<sup>rd</sup>, compared to the 1<sup>st</sup> tertile were 1.77 [95% confidence interval (CI): 1.29-2.43], and 6.28 (95% CI: 4.51-8.73), respectively (Table 2). In an unadjusted model, each doubling of NT-proBNP was associated with 86% greater risk of incident HF (HR: 1.86; 95% CI: 1.71 – 2.03) (Table 2). Results were mildly attenuated in the age, sex, and race adjusted model (HR: 1.69; 95% CI: 1.56 – 1.84), and the fully adjusted model (HR: 1.63; 95% CI: 1.50 – 1.76). The relationship between NT-proBNP with incident HF was significantly modified by race in the fully adjusted model ($P_{interaction} = 0.024$). Therefore, we further examined the models stratified by race (Table 3). Among 687 incident HF cases, 302 were classified as HFrEF and 247 as HFrEF. In fully adjusted model, we did not observe any effect modification between NT-proBNP and incident HFrEF or HFpEF by race ($P_{interaction} = 0.10$).

The magnitude of the association between NT-proBNP levels and incident HF was greater in white individuals (HR per doubling of NT-proBNP: 2.09; 95% CI: 1.85 – 2.37) than in black individuals (HR: 1.69; 95% CI: 1.52 – 1.89) in the unadjusted model (Table 3). In the multivariable model, the pattern was the same (HR: 1.73; 95% CI: 1.55 – 1.94) than in black individuals (HR: 1.51; 95% CI: 1.34 – 1.70) (Table 3). Among white individuals, the multivariable-adjusted HR for incident HF in the 2<sup>nd</sup> and 3<sup>rd</sup>, compared with 1<sup>st</sup> tertile were 1.51 (95% CI: 0.95-2.41) and 5.82 (95% CI: 3.59-9.42), respectively (Table 3). Compared with 1<sup>st</sup>
tertile, the multivariable-adjusted HR for incident HF in 2nd and 3rd tertiles were 2.24 (95% CI: 1.44-3.50) and 6.99 (95% CI: 4.34-11.3) among black individuals (Table 3).

**NT-proBNP Levels and Incident Heart Failure by BMI and eGFR Categories**

Among white participants, the risk of HF per doubling of NT-proBNP was similar across BMI and eGFR categories (P_{interaction} > 0.1) (Table 4). However, among black individuals, we observed significant interactions between NT-proBNP and BMI (P_{interaction} = 0.08) and eGFR (P_{interaction} < 0.001) categories (Table 4). We further assessed the risk of HF per doubling of NT-proBNP among white and black individuals with obesity (BMI ≥ 30 kg/m²) or renal dysfunction (eGFR < 60 ml/min/1.73 m²). In multivariable adjusted models, we observed that the relationship between NT-proBNP and incident HF was significantly modified by race in both obese (P_{interaction} = 0.016) and renal dysfunction sub-groups (P_{interaction} = 0.007). The level of significance for the aforementioned interaction terms remained significant (p<0.1) after adjusting for multiple testing using bonferroni method. Among individuals with obesity, the magnitude of the association between NT-proBNP and incident HF was greater in white participants (HR: 2.03; 95% CI: 1.73-2.38) than black participants (HR: 1.28; 95% CI: 1.08-1.53). Similarly among individuals with renal dysfunction, the effect size of the relationship between NT-proBNP and incident HF was greater in white participants (HR: 1.78; 95% CI: 1.46-2.17) as compared with black participants (HR: 1.35; 95% CI: 1.17-1.55) (Table 4).

The ranking in the percentage contribution of NT-proBNP for HF risk was examined to assess the predictive ability of NT-proBNP for incident HF across BMI and eGFR categories by race (Figures 2 and 3 across BMI and Figures 4 across eGFR categories by race). In these assessment, a higher rank (i.e., greater percentage contribution in global Wald Chi-square score)
means the variable is a stronger predictor than variables with lower ranks. In multivariable-adjusted Cox models among white individuals, higher NT-proBNP was the strongest predictor of incident HF across BMI (Figure 2, Panel A, B and C) and eGFR categories (Figure 4, Panel A and B) as compared with other covariates. However, the strength of the association between NT-proBNP levels and incident HF was variable across BMI and eGFR categories among black individuals. Higher NT-proBNP was the strongest predictor of incident HF only among lean and overweight black individuals (Figure 3, Panel A and B) as well as black individuals with eGFR ≥60 mL/min/1.73 m² (Figure 4, Panel C). Among black individuals with obesity (BMI ≥30 kg/m²), current smoking and increasing age were the strongest predictors of incident HF followed by NT-proBNP levels (Figure 3, Panel C). Higher NT-proBNP was the second strongest predictor behind dyslipidemia among black individuals with eGFR <60 mL/min/1.73 m² (Figure 4, Panel D). Furthermore, the incremental value of NT-proBNP levels when added to other covariates was small among black individuals with obesity (BMI ≥30 kg/m²; C-Statistics from 0.75 to 0.76) and eGFR <60 mL/min/1.73 m² (C-Statistics from 0.69 to 0.70) as assessed by Harrell’s C-statistic.
Discussion

In this population-based study of REGARDS participants, higher NT-proBNP was strongly associated with incident HF independent of sociodemographic and clinical risk factors. The magnitude of the relationship of NT-proBNP levels with incident HF was greater in white individuals than black individuals (Figure 5). Further, the magnitude of association between NT-proBNP and incident HF was preserved across BMI and eGFR categories among white individuals. However, among black individuals, an attenuation in the magnitude of the relationship between NT-proBNP and incident HF with increasing BMI and decreasing renal function was observed. The relative importance of NT-proBNP levels was lower among black individuals with obesity or impaired renal function compared with other covariates (i.e., an attenuated Wald score rank and a marginal 0.01 increment in C-statistics), suggesting that NT-proBNP loses predictive ability for incident HF in the setting of obesity or kidney disease in black individuals (Figure 5).

The role of NT-proBNP as a biomarker in diagnosis and prognosis of HF has been well established. Hemodynamic challenges such as pressure or volume overload typically stimulate NP secretion, representing the response arm (i.e., a consequence of cardiovascular disease) of the NP system. The finding that higher NT-proBNP levels were associated with higher risk of incident HF suggests that higher baseline NT-proBNP levels are reflective of subclinical cardiac dysfunction that subsequently manifests itself as overt HF. The relationship of NT-proBNP with incident HF has been previously reported in the Atherosclerosis Risk in Communities (ARIC)(8), Multiethnic Study of Atherosclerosis (MESA),(7) and other population-based studies. Our HR estimated for the relationship of NT-proBNP with incident HF were concordant with the previous studies. We observed that the association of
higher NT-proBNP levels with incident HF differed by race, i.e., greater magnitude in HRs among white than black individuals. Albeit, the absolute difference in the HRs for incident HF by race was small. These findings may partially be explained by the differences in the NT-proBNP levels between white and black individuals.(10-13) Black individuals have lower NT-proBNP levels than white individuals.(10-13) We speculate that black individuals, when exposed to increased wall stress such as pressure and volume overload, may not able to mount an appropriate NP response as compared with white individuals. Therefore, the differences in the slope of NP release when exposed to a trigger may explain some of the observed differences in the strength of the relationship of NT-proBNP with incident HF by race. The ARIC and MESA investigators also assessed the association of NT-proBNP with incident HF by race.(7,8) The authors of the ARIC study did observe differences in the magnitude of the association of NT-proBNP with incident HF by race.(8) However, possibly due to the limited number of black individuals (~26%), ARIC study investigators did not observe a significant interaction by race.(8) Similar to the ARIC study,(8) investigators from MESA did not observe any modification of NT-proBNP levels with incident HF by race, again possibly due to the limited number of black participants (~24%).(7) Ours is the first study to report a significant interaction by race in the association of NT-proBNP levels with incident HF. This may be due to the fact that our study is a case-cohort study design and included a large proportion of black individuals. Additionally, the difference between our findings compared with other cohorts could be due to the changing paradigm of cardiovascular disease risk factors (i.e., decreasing prevalence of ischemic heart disease and increasing prevalence of hypertension and diabetes). This further underscores the significance of assessing the relationship of NT-proBNP with incident HF by race in contemporary cohorts such as REGARDS. A recent population-based study has
suggested that black race is associated with lower lifetime risk in development of HFpEF but not with HFrEF as compared with other races. However, we did not observe any modification in the relationship between NT-proBNP and incident HF sub-groups by race, which may be due to limited power to detect this interaction.

Population-based studies have suggested that obese individuals have lower circulating NP levels as compared with lean individuals, while impaired renal function is associated with higher circulating NP levels. The association between circulating NP levels and incident HF differed by BMI and renal function categories in other studies. However, none of the prior studies have observed that the association between NP levels and incident HF across BMI and eGFR categories differed by race. Investigators from the ARIC study observed a blunting in the relationship of NT-proBNP levels with incident HF among individuals with obesity as compared with individuals with normal weight in overall population. Similar to the ARIC study, we observed an attenuation in the association between NT-proBNP levels and incident HF. However, this attenuation was only observed among black individuals but not in white individuals in our cohort. The differences between our findings and those of the ARIC study may be likely due to the differences in the proportion of black individuals and characterization of incident HF. The MESA study investigators observed a diminished relationship of NT-proBNP levels with incident HF among individuals with impaired renal function. We also observed a weakening in the relationship of the NT-proBNP levels with incident HF albeit among black individuals.

We observed that NT-proBNP remained a strong predictor of incident HF across BMI and eGFR categories among white individuals, but not in black individuals with obesity and impaired renal function. This observed weaker predictive ability of NT-proBNP with incident
HF in these subgroups may be explained by the non-linear relationship of NT-proBNP with BMI and eGFR among black individuals. (19,28-30) We recently observed a U-shaped relationship between NT-proBNP levels and BMI among black individuals. (31) As black race and obesity both are associated with relatively low NP levels, one can speculate that black individuals with obesity may be particularly susceptible in their inability to produce an appropriate NP response leading to its weaker predictive ability for future risk of HF. Similarly, we observed a greater increase in NT-proBNP levels among black participants with eGFR < 60 ml/min/1.73m² as compared with white participants. (31) The aforementioned finding, as well as a weaker predicative ability of NT-proBNP in black individuals with impaired renal function, highlights a need for future investigations examining race-specific thresholds for NT-proBNP levels among individuals with impaired renal function.

Public Health Implications

Our finding that NT-proBNP levels had a weaker association with incident HF in black individuals likely has significant clinical implications. NT-proBNP levels have been used as an entry/eligibility criteria in multiple recently conducted clinical trials. (32-34) Since black race is associated with relatively low NP levels, this may be a reason behind the marked underrepresentation of black individuals in the clinical trials where recruitment was based on NP levels. (32-34) Our finding of the decrease in the predictive ability of NT-proBNP in black individuals with severe obesity and impaired renal function may suggest that race-specific cut-off values (i.e., upper limit for normal NP levels) for the diagnosis of HF and the use of NT-proBNP to drive enrollment in clinical trials may be necessary. Currently, the guidelines only provide age-stratified NT-proBNP cut-off values for the diagnosis and prognosis of HF. (5,35) Our findings suggest that to improve the accuracy of risk prediction models using NT-proBNP
levels for incident HF, we need to account for other factors that can affect NP levels, such as race, BMI, and eGFR, may be warranted.

**Limitations**

There are some limitations of our study. Prior studies have shown that NP levels have genetic basis.\(^{(11,13)}\) Self-reported characterization of race was used instead of genetic ancestry information markers in this study. The results of the current study cannot be generalized to other racial or ethnic groups as the REGARDS study only included non-Hispanic white and black individuals. We used medication-based criteria to identify the presence of suspected HF at baseline instead of clinical diagnosis, which likely overestimated the prevalence of baseline HF. Residual confounding due to unmeasured confounders is always possible, in spite of our inclusion of many of the factors that are known to affect NP levels. Finally, we used baseline NT-proBNP levels rather than serial measurements, which precludes study of race-specific trajectories of NT-proBNP in relation to incident HF.
**Conclusions**

In conclusion, we confirmed that NT-proBNP levels are associated with incident HF in a large biracial population-based study. The relationship of NT-proBNP levels with incident HF differed by race, showing a greater magnitude among white than black individuals. The risk of HF predicted by NT-proBNP levels was preserved across BMI and eGFR categories among white individuals. However, the predictive ability of NT-proBNP for incident HF was diminished with obesity and impaired renal function among black individuals. Besides age, important factors such as race, BMI, and eGFR should be considered while assessing and interpreting risk prediction models using NT-proBNP levels for incident HF.
Methods

Study Population

The REGARDS study was designed to investigate racial and geographic differences in stroke mortality. It recruited non-Hispanic white individuals and black individuals aged 45 years or more from the contiguous United States from 2003 to 2007. Detailed information on the study design including inclusion-exclusion criteria and the recruitment process have been published. A computer-assisted telephone interview followed by an in-home visit were performed to collect information on demographic, socioeconomic, anthropometric, medical history, and medications. Blood and urine were also sampled during the in-home visit, and stored in a central laboratory.

The primary exposure in this study was plasma NT-proBNP level. As described previously, NT-proBNP measurement was performed using an automated electrochemiluminescence immunoassay (Roche Elecsys 2010) in baseline plasma samples. The intra- and inter-assay coefficients of variation were less than 2% and 5%, respectively.

Outcome of Interest

The outcome of interest was incident HF hospitalization. Study participants were followed up every 6 months via telephone to detect hospitalizations. Each suspected heart disease hospitalization was adjudicated by two clinicians by assessing medical records. Any disagreement between two adjudicators was resolved by discussion among the team members. Adjudication of a HF hospitalization was based on clinical signs and symptoms, laboratory studies (including B-type NP or NT-proBNP), and assessment of left ventricular
function. An assessment of left ventricular function was based on echocardiography which was performed during the hospitalization and reported in the medical records. Based on the results of echocardiography, HF was sub-classified into 1) HF with reduced ejection fraction (EF) with left ventricular EF <40%; 2) HF with preserved EF with left ventricular EF >50%; 3) HF with mid-range EF (40-50%); and 4) undetermined category. HF assessment included screening for the following signs and symptoms: abnormal jugular vein distension, pulmonary rales, cardiomegaly, central venous pressure >16 mmHg, hepatomegaly, pleural effusion, heart rate >120/minute, and ≥ 4.5-kilogram weight loss in 5 days with diuresis, paroxysmal nocturnal dyspnea, orthopnea, nocturnal cough, exertional dyspnea.

Case-Cohort Study

A case-cohort study design was utilized. This approach provides an unbiased estimate of the relative hazard of an outcome(s) without requiring measurement of biomarkers in all participants and without compromising the power of large cohort studies. Cases included all participants who developed an incident HF during follow-up through December 31st, 2015. After excluding participants with suspected HF at baseline, participants who experienced an adjudicated hospitalization for HF during follow-up from baseline through December 31, 2015 were included as cases (Figure 1). Suspected HF was determined by the use of HF-related medications at the baseline visit i.e., digoxin in the absence of atrial fibrillation, carvedilol, spironolactone, hydralazine + isosorbide mononitrate/dinitrate, loop diuretics or taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker + beta-blocker in the absence of hypertension. This approach had >99% negative predictive value for excluding prior HF hospitalization compared to Medicare claims.
The cohort random sample (comparison group) was selected using stratified sampling to ensure sufficient representation of high-risk groups. All participants with at least one follow-up contact (n=29,653) were categorized into 20 strata based on age (45-54, 55-64, 65-74, 75-84, ≥85 years), race (black or white), and sex (male or female). In each stratum, participants were randomly selected to fulfill the desired distribution: 50% black, 50% white, 50% female, 50% male, 20% age 45-54, 20% age 55-64, 25% age 65-74, 25% age 75-84, and 10% age ≥85. For the purpose of this analysis we excluded individuals with prevalent HF in the cohort random sample.

**Covariates of Interest**

Baseline characteristics such as age, sex, race, smoking status, alcohol use, and exercise were self-reported. BMI was measured during the in-home visit as weight in kilograms divided by height in meters squared. We divided the study participants into lean (i.e., BMI ≥18.5 to <25 kg/m²), overweight (i.e., BMI ≥25 to <30 kg/m²) and obese (i.e., BMI ≥30 kg/m²) categories. The average of two blood pressure measurements taken 5 minutes apart was used to assess systolic blood pressure. Hypertension was considered present if systolic blood pressure was ≥140 mm Hg, diastolic blood pressure was ≥90 mm Hg, or if the participant reported current use of anti-hypertensive medication. Aspirin use was self-reported. Diabetes was defined as self-reported current use of oral diabetes medications or insulin, or fasting glucose ≥126 mg/dl (or non-fasting glucose ≥200 mg/dl among those who did not fast). Dyslipidemia was defined as total cholesterol ≥240 mg/dl, low-density lipoprotein cholesterol ≥160 mg/dl, high-density cholesterol ≤40 mg/dl, or self-reported medication use for cholesterol. History of stroke or transient ischemic attack was self-reported. Atrial fibrillation was defined by self-report or from the presence of atrial fibrillation on the electrocardiogram obtained at the in-home visit. History
of coronary artery disease was considered present if the participant reported a past myocardial infarction, coronary bypass grafting, angioplasty, or coronary stenting; or had evidence of myocardial infarction on the electrocardiogram at baseline. A history of peripheral vascular disease was considered present if the participant reported a leg amputation or any surgery to fix the arteries in the legs. The presence of left ventricular hypertrophy was determined using Sokolow-Lyon voltage criteria.(42,43) Geocoded addresses were used to calculate neighborhood socioeconomic status (nSES) among REGARDS participants using the United States Census data.(44) The nSES score was calculated based on six variables as described previously.(44,45) The nSES score was summarized based on a Z score (ranging from -11.8 to 29.0, with higher scores meaning higher nSES, i.e., most advantaged neighborhood) using the aforementioned variables.(45) The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate GFR,(46) and was categorized as eGFR as ≥60 mL/min/1.73 m² or <60 mL/min/1.73 m².

Statistical Analyses

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). Within the cohort random sample, baseline characteristics were calculated using weights to account for the stratified sampling design by tertiles of NT-proBNP.

Cox proportional hazards models for case-cohort studies were used to estimate the association of NT-proBNP (modeled as a continuous variable and in tertiles) with incident HF.(40) For the continuous models, we employed log base 2-transformed NT-proBNP in order to calculate the hazard ratio (HR) for incident HF per doubling of NT-proBNP level. In the analyses with NT-proBNP modeled in tertiles, participants with the lowest tertile were chosen as
a reference group. We constructed unadjusted models; followed by age, race, and sex-adjusted models; and then multivariable-adjusted models to assess the relationship of NT-proBNP with incident HF. The covariates included in the multivariable models were selected based on previous studies demonstrating their association with NT-proBNP levels: (10-13, 47-49) age, race, sex, nSES, tobacco usage, physical activity, alcohol use, BMI, systolic blood pressure, use of antihypertensive medications, aspirin use, dyslipidemia, diabetes mellitus, history of stroke or transient ischemic attack, atrial fibrillation, peripheral vascular disease, history of coronary artery disease, left ventricular hypertrophy, and eGFR. In the multivariable models using NT-proBNP levels as a continuous variable, we further examined for effect modification by race by using a multiplicative interaction term (i.e., race * log$_2$ NT-proBNP).

The relationship between log$_2$ NT-proBNP and incident HF across BMI and eGFR categories by race were also examined using multivariable Cox proportional hazard models. The following covariates were included in the multivariable models: age, sex, nSES, lifestyle habits (tobacco usage, physical activity), alcohol use, BMI (when eGFR is exposure), systolic blood pressure, use of antihypertensive medications, aspirin use, dyslipidemia, diabetes mellitus, history of stroke or transient ischemic attack, atrial fibrillation, peripheral vascular disease, history of coronary artery disease, left ventricular hypertrophy, and eGFR (when BMI is exposure). Multiplicative interaction terms (i.e., BMI * log$_2$ NT-proBNP and eGFR * log$_2$ NT-proBNP) were used to assess any modification in the association of NT-proBNP with incident HF by BMI and levels of kidney function within each race.

The predictive ability of NT-proBNP and other covariates for incident HF in each BMI and eGFR category by race was further assessed using Wald test statistics. (50) The relative importance of NT-proBNP and other covariates for predicting incident HF across BMI and
eGFR categories with corrected degrees of freedom allocated to each covariate were depicted by ranking the percentage contribution of the variable-specific Wald test out of the global Wald Chi-square score (i.e., Wald statistics).(51) Ranking of the percentage contribution of $\log_2$ NT-proBNP and other variables in the final model was calculated using the following formula: (the Chi-square score of the predictor variable/the global Chi-square score)*100. If an attenuation in the ranking of the percentage contribution of NT-proBNP compared with other variables was detected within any of the BMI and eGFR categories, the incremental value of NT-proBNP levels for incident HF was evaluated with Harrell’s C-statistic for that model.(52,53) First, we ran a Cox regression model with all the covariates except $\log_2$ NT-proBNP and noted the C-statistic. Then we added $\log_2$ NT-proBNP and reran the Cox models. The difference in C-statistics between these two models was calculated. The level of statistical significance was set at $p<0.05$ and all p-values were two-tailed. A p-value of $<0.1$ was considered significant for interactions.

Study Approval

All participants provided written informed consent and the institutional review boards from each participating center approved the REGARDS study protocol.
Author Contributions

Drs. Patel and Pankaj Arora had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Patel, Garima Arora, Pankaj Arora.

Acquisition, analysis, or interpretation of data: Patel, Cushman, Gutierrez, Levitan, Garima Arora, Pankaj Arora.

Drafting of the manuscript: Patel, Cushman, Gutierrez, Garima Arora, Pankaj Arora.

Critical revision of the manuscript for important intellectual content: Patel, Cushman, Gutierrez, Howard, Safford, Muntner, Durant, Prabhu, Levitan, Garima Arora, Pankaj Arora.

Statistical analysis: Patel, Pankaj Arora.

Obtained funding: Pankaj Arora.

Administrative, technical, or material support: Cushman, Gutierrez, Howard, Safford, Muntner, Durant, Prabhu, Levitan, Garima Arora, Pankaj Arora.

Supervision: Cushman, Gutierrez, Howard, Safford, Muntner, Durant, Prabhu, Levitan, Garima Arora, Pankaj Arora.
**Acknowledgments:** We thank investigators, staff, and participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study for their valuable contributions.

A full list of investigators and institutions can be found at [http://www.regardsstudy.org](http://www.regardsstudy.org).
References


42. Antikainen R et al. The determinants of left ventricular hypertrophy defined by Sokolow-Lyon criteria in untreated hypertensive patients. J Hum Hypertens 2003;17:159-164.

43. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 1949;37:161-186.


### Table 1. Baseline characteristics in non-case random cohort participants stratified by race from REGARDS. Weighted back to original cohort overall.

<table>
<thead>
<tr>
<th></th>
<th>White Individuals</th>
<th>Black Individuals</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted Frequency</td>
<td>11,872</td>
<td>8,203</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>64 (58 - 71)</td>
<td>63 (56 - 69)</td>
<td>0.10</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5,919 (49.9)</td>
<td>5,056 (61.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Lifestyle habits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>1,386 (11.7)</td>
<td>1,373 (16.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current Alcohol use, n (%)</td>
<td>7,271 (61.2)</td>
<td>3,495 (42.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise &gt;4 times a week, n (%)</td>
<td>4,065 (34.2)</td>
<td>2,261 (27.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (24 - 31)</td>
<td>29 (26 - 34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>122 (115 - 134)</td>
<td>129 (119 - 140)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>5,625 (47.4)</td>
<td>2,845 (34.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive, n (%)</td>
<td>5,593 (47.1)</td>
<td>5,760 (70.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1,550 (13.1)</td>
<td>2,061 (25.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>7,153 (60.3)</td>
<td>4,294 (52.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of Stroke or TIA, n (%)</td>
<td>939 (7.9)</td>
<td>795 (9.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>History of Atrial Fibrillation, n (%)</td>
<td>966 (8.1)</td>
<td>548 (6.7)</td>
<td>0.20</td>
</tr>
<tr>
<td>Coronary Artery Disease, n (%)</td>
<td>1,767 (14.9)</td>
<td>916 (11.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Peripheral Vascular Disease, n (%)</td>
<td>167 (1.4)</td>
<td>119 (1.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy, n (%)</td>
<td>717 (6.0)</td>
<td>1,019 (12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nSES</td>
<td>1.0 (-2.2, 5.5)</td>
<td>-2.8 (-5.1, 0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NTproBNP, pg/ml</td>
<td>71 (38 - 137)</td>
<td>52 (25 - 109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>85 (74 – 95)</td>
<td>94 (77 - 108)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are shown as median and interquartile range and categorical variables are shown as n (%).

Abbreviations: BMI, indicates body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; nSES: neighborhood socioeconomic status at census block level; PVD, peripheral vascular disease; REGARDS, REasons for Geographic And Racial Differences in Stroke Study; SBP, indicates systolic blood pressure; and TIA, Transient ischemic attack.
Table 2. Hazard ratio of incident heart failure by tertiles and per doubling of plasma N-terminal pro B-type natriuretic peptide (NT-proBNP)

<table>
<thead>
<tr>
<th>Model</th>
<th>Tertile 1 (&lt;42 pg/mL)</th>
<th>Tertile 2 (42-105 pg/mL)</th>
<th>Tertile 3 (&gt;105 pg/mL)</th>
<th>Per Doubling of NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, No.</td>
<td>81</td>
<td>165</td>
<td>441</td>
<td>687</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>Reference</td>
<td>2.21 (1.65-2.96)</td>
<td>14.0 (10.6-18.5)</td>
<td>1.86 (1.71-2.03)</td>
</tr>
<tr>
<td>Age, sex, and race</td>
<td>Reference</td>
<td>2.02 (1.50-2.72)</td>
<td>9.44 (6.98-12.8)</td>
<td>1.69 (1.56-1.84)</td>
</tr>
<tr>
<td>Multivariable Model</td>
<td>Reference</td>
<td>1.77 (1.29-2.43)</td>
<td>6.28 (4.51-8.73)</td>
<td>1.63 (1.50-1.76)</td>
</tr>
</tbody>
</table>

Multivariable Cox regression model including age, sex, race, exercise, smoking, alcohol, body mass index, systolic blood pressure, antihypertensive medication, aspirin use, dyslipidemia, diabetes, estimated glomerular filtration rate, history of stroke, history of transient ischemic attack, atrial fibrillation, peripheral vascular disease, history of coronary artery disease, left ventricular hypertrophy, and neighborhood socioeconomic status at census block level.
### Table 3. Racial differences in the relationship of baseline plasma NT-proBNP with incident heart failure (by tertiles and per doubling of NT-proBNP levels)

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% Confidence interval)</th>
<th>NTproBNP levels</th>
<th>Per Doubling of NTproBNP Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tertile 1 (&lt;42 pg/mL)</td>
<td>Tertile 2 (42-105 pg/mL)</td>
</tr>
<tr>
<td><strong>White Individuals</strong></td>
<td></td>
<td>Events, No.</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Black Individuals</strong></td>
<td></td>
<td>Events, No.</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Abbreviation: HR, hazard ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Multivariable Cox regression model including age, sex, exercise, smoking, alcohol, body mass index, systolic blood pressure, antihypertensive medication, aspirin use, dyslipidemia, diabetes, estimated glomerular filtration rate, history of stroke or transient ischemic attack, atrial fibrillation, peripheral vascular disease history of coronary artery disease, left ventricular hypertrophy, and neighborhood socioeconomic status at census block level.

p=0.024 for interaction in the association of NT-proBNP with incident heart failure by race.
Table 4. Racial differences in the relationship of baseline plasma NT-proBNP with incident heart failure stratified by body mass index and estimated glomerular filtration rate.

<table>
<thead>
<tr>
<th>BMI categories</th>
<th>White Individuals</th>
<th>Black Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, No.</td>
<td>Hazard Ratio (95% CI)*</td>
</tr>
<tr>
<td>Normal (18.5 to 25.0 kg/m²)</td>
<td>108</td>
<td>1.83 (1.55-2.17)#</td>
</tr>
<tr>
<td>Overweight (25.0 to 29.9 kg/m²)</td>
<td>178</td>
<td>1.81 (1.61-2.03)#</td>
</tr>
<tr>
<td>Obese (more than 30.0 kg/m²)</td>
<td>126</td>
<td>2.03 (1.73-2.38)#</td>
</tr>
<tr>
<td>eGFR categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 (mL/min/1.73 m²)</td>
<td>299</td>
<td>1.78 (1.55-2.05)#</td>
</tr>
<tr>
<td>&lt;60 (mL/min/1.73 m²)</td>
<td>113</td>
<td>1.78 (1.46-2.17)#</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

*HR per doubling (log base 2) of NT-proBNP

Multivariable cox regression model including log base 2 plasma NT-proBNP levels as independent variable including age, exercise, smoking, alcohol, BMI (when eGFR categories is the exposure), systolic blood pressure, antihypertensive medication, aspirin use, dyslipidemia, diabetes, eGFR (when BMI categories is the exposure), history of stroke, history of transient ischemic attack, atrial fibrillation, peripheral vascular disease, history of coronary artery disease, left ventricular hypertrophy, and neighborhood socioeconomic status at census block level.

*p=0.005; #p<0.001.

p=0.85 and p=0.21 for interaction in the association of NT-proBNP with incident heart failure by BMI and eGFR categories among white individuals, respectively.

p=0.08 and p<0.001 for interaction in the association of NT-proBNP with incident heart failure by BMI and eGFR categories among black individuals, respectively.
Figure 1. Flow diagram describing the selection of participants for the case-cohort study.

*Covariates include age, race, sex, neighbourhood socioeconomic status, tobacco usage, physical activity, alcohol use, systolic blood pressure, use of antihypertensive medications, aspirin use, dyslipidemia, diabetes mellitus, history of stroke or transient ischemic attack, atrial fibrillation, peripheral vascular disease, history of coronary artery disease, left ventricular hypertrophy, and estimated glomerular filtration rate.
Figure 2. The association between plasma NT-proBNP levels and other factors with incident heart failure across BMI (Panel A, B and C) categories among white individuals. (Lean Panel A; BMI 18.5-24.9 kg/m², Overweight Panel B; BMI 25-29.9 kg/m², Obese Panel C; BMI ≥ 30 kg/m²). The panels display the factors (y-axis) and their percentage contribution in global Wald Chi-square score from multivariable adjusted Cox model. BMI: body mass index; GFR: glomerular filtration rate; LVH: left ventricular hypertrophy; NT-proBNP: N-terminal-pro-B-Type natriuretic peptide; nSES: neighborhood socioeconomic status at census block level; PVD: peripheral vascular disease; TIA: Transient ischemic attack.
Figure 3. The association between plasma NT-proBNP levels and other factors with incident heart failure across BMI (Panel A, B and C) categories among black individuals. (Lean Panel A; BMI 18.5-24.9 kg/m², Overweight Panel B; BMI 25-29.9 kg/m², Obese Panel C; BMI ≥ 30 kg/m²).

The panels display the factors (y-axis) and their percentage contribution in global Wald Chi-square score from multivariable adjusted Cox model. BMI: body mass index; GFR: glomerular filtration rate; LVH: left ventricular hypertrophy; NT-proBNP: N-terminal-pro-B-Type natriuretic peptide; nSES: neighborhood socioeconomic status at census block level; PVD: peripheral vascular disease; TIA: Transient ischemic attack.
Figure 4. The association between plasma NT-proBNP levels and other factors with incident heart failure across eGFR categories among white (Panel A and B) and black (Panel C and D) individuals. (Panel A: eGFR ≥60 ml/min/1.73m², Panel B: eGFR <60 ml/min/1.73m² among white individuals; Panel C: eGFR ≥60 ml/min/1.73m², Panel D: eGFR <60 ml/min/1.73m² among black individuals). The panels display the factors (y-axis) and their percentage contribution in global Wald Chi-square score from multivariable adjusted Cox model. BMI: body mass index; GFR: glomerular filtration rate; LVH: left ventricular hypertrophy; nSES: neighborhood socioeconomic status at census block level; PVD: peripheral vascular disease; TIA: Transient ischemic attack.
Figure 5. Natriuretic Peptides, Race, and Incident Heart Failure.
NT-proBNP: N-terminal-pro-B-Type natriuretic peptide.