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NT-proBNP as a Mediator of the Racial Difference in Incident Atrial Fibrillation and Heart Failure

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Background—Blacks harbor more cardiovascular risk factors than whites, but experience less atrial fibrillation (AF). Conversely, whites may have a lower risk of heart failure (CHF). N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are higher in whites, predict incident AF, and have diuretic effects in the setting of increased ventricular diastolic pressures, potentially providing a unifying explanation for these racial differences.

Methods and Results—We used data from the CHS (Cardiovascular Health Study) to determine the degree to which baseline NT-proBNP levels mediate the relationships between race and incident AF and CHF by comparing beta estimates between models with and without NT-proBNP. The ARIC (Atherosclerosis Risk in Communities) study was used to assess reproducibility. Among 4731 CHS (770 black) and 12 418 ARIC (3091 black) participants, there were 1277 and 1253 incident AF events, respectively. Whites had higher baseline NT-proBNP (CHS: 40% higher than blacks; 95% CI, 29–53; ARIC: 39% higher; 95% CI, 33–46) and had a greater risk of incident AF compared with blacks (CHS: adjusted hazard ratio, 1.60; 95% CI, 1.31–1.93; ARIC: hazard ratio, 1.93; 95% CI, 1.57–2.27). NT-proBNP levels explained a significant proportion of the racial difference in AF risk (CHS: 36.2%; 95% CI, 23.2–69.2%; ARIC: 24.6%; 95% CI, 14.8–39.6%). Contrary to our hypothesis, given an increased risk of CHF among whites in CHS (adjusted hazard ratio, 1.20; 95% CI, 1.05–1.47) and the absence of a significant association between race and CHF in ARIC (adjusted hazard ratio, 1.07; 95% CI, 0.94–1.23), CHF-related mediation analyses were not performed.

Conclusions—A substantial portion of the relationship between race and AF was statistically explained by baseline NT-proBNP levels. No consistent relationship between race and CHF was observed. (J Am Heart Assoc. 2019;8:e010868. DOI: 10.1161/JAHA.118.010868.)

Key Words: atrial fibrillation arrhythmia • congestive heart failure • mechanisms • mediation • natriuretic peptide • NT-proBNP

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States and the leading cause of embolic stroke.1,2 Hypertension and congestive heart failure (CHF) are 2 of the most important risk factors for development of AF.3,4 However, despite the finding that these and other AF risk factors are more common in blacks,5–11 whites have a greater risk for AF12–15 as do American blacks with greater European ancestry.16 The pathophysiology underlying this paradox is unknown. Similarly, in some populations, blacks also have a substantially higher risk for...
CHF than whites, but the mechanism underlying this difference is not completely understood.

Of interest, AF is associated with higher ANP (atrial natriuretic peptide) levels. Evidence that genetic aberrations in the ANP gene are associated with AF raises the question as to whether abnormalities in ANP expression may cause AF (rather than reflect an atrial myopathy secondary to AF). Furthermore, serum levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide) have been closely correlated with ANP, and are known to have diuretic effects that might relieve volume overload in the setting of CHF. Recent evidence demonstrates that NT-proBNP levels are lower in blacks. Therefore, it is plausible that NT-proBNP levels might mediate the discordant race-AF and race-CHF associations. Specifying the higher baseline level of natriuretic peptides in whites may have a direct atrial effect that increases AF susceptibility. We hypothesized that higher levels of NT-proBNP at baseline in the absence of elevated pressures, by the diuretic action of this protein, may also render whites less prone to CHF.

Understanding these relationships might help to elucidate the mechanisms underlying both of these important diseases and may point to specific prediction strategies and novel treatment approaches informed by racial background.

We sought to quantify the racial differences in incident AF and CHF, and then determine the degree to which NT-proBNP levels may mediate the racial differences between blacks and whites in incident AF and CHF.

Methods

Using the CHS (Cardiovascular Health Study) and then subsequently the ARIC (Atherosclerosis Risk in Communities) Study population as an independent replication cohort, we measured the degree to which NT-proBNP level at baseline may explain the differential relationship between race and incident AF and CHF in prospective, population-based cohort studies. The authors will make the methods (codes for the statistical analysis) available to any researcher for purposes of reproducing the results. The data belong to CHS and ARIC, and the authors therefore do not have the authority to share the study data with investigators outside the University of California, San Francisco (San Francisco, CA); however, investigators can submit an application to obtain the data directly from the CHS or the ARIC Study using their established processes.

Recruitment, characterization, and outcome ascertainment in the CHS and ARIC have been previously published. Each cohort’s research protocol was approved by its respective institutional review board, and all participants provided written informed consent. The specific methods of the CHS and ARIC are summarized below. Criteria for baseline ascertainment of hypertension, coronary heart disease, CHF, and diabetes mellitus for each cohort are described in Table S1.

Cardiovascular Health Study

CHS is a prospective, community-based cohort study designed to follow patients aged ≥65 years to assess cardiovascular risk factors and outcomes, the methods for which have previously been described. AF and CHF ascertainment was complete through 2008, during which time medical records were obtained for all hospitalizations. Prevalent AF was identified from the baseline ECG, and incident AF was identified from study visit ECGs and hospital discharge diagnoses. Incident CHF was identified through self-report, hospital diagnosis codes, and in-and outpatient medical records adjudicated by the CHS Cardiac Events Subcommittee.

Levels of NT-proBNP were measured from blood samples taken at study entry. Methods were the same for both the main cohort (1989–1990) and in the additional cohort of black participants (1992–1993). Serum was initially frozen and stored at −70°C to −80°C until testing, which occurred between 2007 and 2008. All testing was performed in a lab certified by the Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists. A US Food and Drug Administration–approved immunoassay was used for NT-proBNP measurement on an Elecsys 2010 instrument (Roche Diagnostics, Indianapolis, IN). The coefficient of variation for the NT-proBNP assay was 2% to 5% during the testing period, and the analytical measurement range for NT-proBNP was 5 to 35 000 pg/mL. The core laboratory reported data to the central data repository and was blinded to patient outcomes.

ARIC Study

The ARIC Study is a prospective study of 15 792 primarily white and black middle-aged participants recruited from 4
RESULTS

CHS Participants and NT-proBNP by Race

Of the 5888 participants in CHS, 4731 were included in the analyses after exclusions. Participant characteristics at baseline are shown in Table 1. On average, blacks had lower income and less education than whites. Blacks had more hypertension and diabetes mellitus at baseline, were more likely to have smoked, and consumed less alcohol at baseline. Whites exhibited a higher baseline NT-proBNP than blacks (Table 1), and after log transformation and multivariable adjustment, whites had a 40% higher NT-proBNP than blacks (95% CI, 29–53; P<0.001; unadjusted, 29%; 95% CI, 19–41; P<0.001; Figure 1).

ARIC Participants and NT-proBNP by Race

After exclusion, 12,418 ARIC participants were included in these analyses. Their characteristics are shown in Table 1. In ARIC, blacks were, on average, younger than whites, a greater proportion were female, and blacks had less education and lower annual income. Black participants had a higher body mass index, on average, and a higher prevalence of baseline hypertension, diabetes mellitus, and left ventricular hypertrophy. Whites had more coronary artery disease at baseline and were more likely to have ever smoked or consumed alcohol. Whites had higher NT-proBNP at baseline than blacks (Table 1) and, with log transformation and multivariable adjustment, 39% higher baseline NT-proBNP than blacks, on average (95% CI, 33–46; P<0.001; unadjusted, 55% higher NT-proBNP than blacks, on average; 95% CI, 54–56; P<0.001; Figure 1).

AF in the CHS

CHS participants were followed for a mean of 11.8 years in the AF analysis, accumulating 1277 incident AF events. Whites had a greater risk of incident AF both before (hazard ratio [HR], 1.32; 95% CI, 1.12–1.58; P<0.001) and after multivariable adjustment (HR, 1.60; 95% CI, 1.31–1.93; P<0.001; Figure 2). Furthermore, each doubling of NT-proBNP increased the risk of incident AF by 46% (95% CI, 40–52; P<0.001) after adjusting for age, sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, left ventricular hypertrophy, chronic kidney disease, ever smoking, drinks per week, education, and income.

Mediation analysis demonstrated that the percent of racial differences in AF risk statistically explained by NT-proBNP was ≈36% (Table 2).

AF in the ARIC

Follow-up for a mean of 18.2 years yielded 1253 incident AF events. As in CHS, whites in ARIC had a greater risk of...
incident AF (unadjusted HR, 1.53; 95% CI, 1.32–1.77; \( P < 0.001 \); adjusted HR, 1.93; 95% CI, 1.57–2.27; \( P < 0.001 \); Figure 2). After adjustment, a doubling of baseline NT-proBNP was associated with an increased risk of incident AF by over 50% (adjusted, 56%; 95% CI, 50–63%; \( P < 0.001 \); unadjusted, 62%; 95% CI, 56–68; \( P < 0.001 \)).

Comparing models with and without NT-proBNP included, differences in baseline NT-proBNP statistically explained nearly 25% of the increase in incident AF among whites (Table 2).

### CHF in CHS

Participants were followed for a mean of 10.9 years, with 1354 incident CHF events. Before adjustment, white race was associated with lower incidence of CHF (HR, 0.87; 95% CI, 0.75–1.01; \( P = 0.07 \)). After adjustment, contrary to what had been hypothesized, there was an increased risk of incident CHF with white race (HR, 1.20; 95% CI, 1.05–1.47; \( P = 0.01 \); Figure 2). Sequential addition of each covariate into the unadjusted model was performed, and the increased risk of CHF in whites after adjustment could not be attributed to any single variable alone; however, diabetes mellitus, hypertension, and income exhibited the largest effects (Table S2). Furthermore, in the CHS cohort as a whole, there was an increased risk of CHF with doubling of baseline NT-proBNP (45% increased risk; 95% CI, 41–52; \( P < 0.001 \); adjusted, 34% increased risk; 95% CI, 29–40; \( P < 0.001 \))—again, contrary to our hypothesis that higher baseline NT-proBNP in the absence of clinical AF or CHF would have a protective association with CHF. Because there was no increased risk of incident CHF with black race after adjustment, a mediation analysis was not performed.

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**Table 1. Baseline Participant Characteristics by Race in CHS and ARIC**

<table>
<thead>
<tr>
<th></th>
<th>CHS (n=4731)</th>
<th>ARIC (n=12 418)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black (n=770)</td>
<td>White (n=3961)</td>
</tr>
<tr>
<td></td>
<td>Black (n=3091)</td>
<td>White (n=9327)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>72.6 (5.6)</td>
<td>72.4 (5.4)</td>
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<tr>
<td>Male, n (%)</td>
<td>281 (37)</td>
<td>1559 (39)</td>
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<tr>
<td></td>
<td>1055 (37)</td>
<td>4275 (46)</td>
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<tr>
<td>Annual income, n (%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>&lt;$12 000</td>
<td>365 (51)</td>
<td>781 (20)</td>
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<tr>
<td>≥$12 000</td>
<td>357 (49)</td>
<td>2926 (80)</td>
</tr>
<tr>
<td></td>
<td>8406 (94)</td>
<td></td>
</tr>
<tr>
<td>Education, n (%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤ High school†</td>
<td>531 (70)</td>
<td>2511 (64)</td>
</tr>
<tr>
<td>≥ Some college</td>
<td>228 (30)</td>
<td>1438 (36)</td>
</tr>
<tr>
<td>NT-proBNP level, median (Q1, Q3), pg/mL</td>
<td>88.0 (43.2, 183.3)</td>
<td>113.6 (60.0, 215.0)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>28.5 (5.5)</td>
<td>26.2 (4.4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>564 (73)</td>
<td>2167 (55)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>176 (23)</td>
<td>531 (13)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>126 (16)</td>
<td>605 (15)</td>
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<tr>
<td>Left ventricular hypertrophy, n (%)‡</td>
<td>226 (29)</td>
<td>622 (16)</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>113 (15)</td>
<td>540 (14)</td>
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<tr>
<td>Creatinine, mean (SD), mg/dL</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>122 (16)</td>
<td>439 (11)</td>
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<tr>
<td>Alcoholic drinks/week, median (Q1, Q3)</td>
<td>0 (0, 0.25)</td>
<td>0.02 (0, 1.27)</td>
</tr>
<tr>
<td>Ever drinker, n (%)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Incident atrial fibrillation, n (%)</td>
<td>146 (19)</td>
<td>1131 (29)</td>
</tr>
<tr>
<td>Incident heart failure, n (%)</td>
<td>215 (28)</td>
<td>1139 (29)</td>
</tr>
</tbody>
</table>

NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; Q1, Q3, first and third quartiles; CHS, Cardiovascular Health Study; ARIC, Atherosclerosis Risk in Communities Study.


†Includes some or graduation from vocational school.

‡By electrocardiographic criteria.
Study participants were followed for a mean of 18.8 years, accumulating 1783 incident CHF diagnoses. In an unadjusted Cox proportional hazard model, white race was associated with a lower incidence of CHF (HR, 0.66; 95% CI, 0.59–0.73; \( P < 0.001 \); Figure 2). This association disappeared with adjustment, resulting in no association between race and incident CHF (HR, 1.07; 95% CI, 0.94–1.23; \( P = 0.32 \)). Covariates were individually added to the unadjusted model, and the addition of income alone eliminated the statistical racial difference in incident CHF (Table S3). No other single variable alone eliminated statistical significance in the model. Similar to the finding in CHS, there was in increased risk of CHF with doubling of baseline NT-proBNP (unadjusted increased risk, 62%; 95% CI, 56–68; \( P < 0.001 \); adjusted, 58%; 95% CI, 51–64; \( P < 0.001 \)). Because there was no association of race with incident CHF in ARIC, a mediation analysis for NT-proBNP was not performed.

**Discussion**

Utilizing baseline NT-proBNP levels before the diagnoses of AF or CHF, we found that higher NT-proBNP statistically explained a significant proportion of the racial difference noted in incident AF in 2 large, community-based studies. However, contrary to our hypothesis, higher baseline NT-proBNP levels in the absence of clinical AF or CHF were not protective against incident CHF in either CHS or ARIC after taking potential confounders into account, and there was no disparate racial association with incident CHF.

**NT-proBNP and AF**

The paradoxical racial association with AF in various populations has been a point of interest in the literature. The cardiac risk factors for AF have been well defined in multiple population studies and have similarly been shown to be more common in blacks than whites. Despite this, whites experience a greater risk of AF, as do blacks with a greater proportion of European ancestry.

A potential explanation for this paradox—that, despite fewer independent risk factors for AF, whites have a higher risk for AF than blacks—may be mechanistically related to natriuretic peptides, higher levels of which have been associated with incident AF and circulating levels of which are higher in whites than blacks. Presence of AF has been associated with higher natriuretic peptides both acutely and chronically, and natriuretic peptide levels have been shown to decrease after cardioversion of AF, illustrating that AF itself may increase natriuretic peptide levels. However, because higher levels of baseline natriuretic peptide predict incident AF, the relationship likely goes “both ways.” More-elevated levels of natriuretic peptide have been associated with atrial dysfunction, atrial fibrosis, and a shorter atrial effective refractory period, all characteristics known to enhance the probability of AF and even mechanistically serve as a cause. In fact, in a case of familial AF, a mutation in the gene expressing ANP was mechanistically linked to the AF phenotype. In the current study, despite substantial differences in absolute baseline NT-proBNP levels between the CHS and ARIC (likely related to the differences in age between the cohorts), the relationships between every doubling of NT-proBNP levels and increased risk of AF were remarkably similar.

Consistent with our current findings, whites have previously been shown to exhibit higher levels of natriuretic peptide levels than blacks, and the difference does not

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**CHF in ARIC**

**Figure 1.** (A) Baseline NT-proBNP levels and (B) adjusted relative relationship between NT-proBNP level in whites versus blacks, on average, in the Cardiovascular Health Study and Atherosclerosis Risk in Communities study. (A) \( P < 0.001 \) blacks vs. whites in both cohorts. (B) \( P < 0.001 \) percent difference in baseline NT-proBNP in both cohorts. *Adjustment in the model was made for age, gender, body mass index, hypertension, diabetes, coronary artery disease, left ventricular hypertrophy, chronic kidney disease, ever smoker, drinks per week, education, and income. †Adjustment in the model was made for age, gender, body mass index, hypertension, diabetes, coronary artery disease, left ventricular hypertrophy, creatinine, ever smoker, ever drinker, education, and income.

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appear to be related to more heart failure or volume overload. Therefore, there is presumably some genetic predisposition to releasing more NT-proBNP independent of myocardial stretch or left ventricular end-diastolic pressure. Similarly, whites have a higher risk of AF compared with blacks unrelated to more-established cardiovascular risk factors, and blacks with more European ancestry (determined by genotyping) have a higher risk of AF, suggesting that the race-AF relationship is likely genetically mediated. Our current mediation analysis is consistent with the notion that propensity to have a higher NT-proBNP level at baseline may explain some of the differential risk of AF by race. This itself, in turn, raises the question as to whether natriuretic peptides may have a direct causal relationship with AF.

**Figure 2.** Cumulative incidence of (A) atrial fibrillation and (B) heart failure in the Cardiovascular Health Study and Atherosclerosis Risk in Communities Study, by race. *Adjustment in the model was made for age, sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, left ventricular hypertrophy, chronic kidney disease, ever smoker, drinks per week, education, and income. †Adjustment in the model was made for age, sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, left ventricular hypertrophy, creatinine, ever smoker, ever drinker, education, and income.

### NT-proBNP and CHF

In designing the present study, we had hypothesized that higher levels of baseline NT-proBNP, while potentially increasing risk of AF for whites, may also mediate the differential racial association with CHF observed in some populations. The general theory is that a higher NT-proBNP level, on average, would help maintain diuresis and therefore help to mitigate volume overload. In fact, we observed no increased risk of CHF in blacks versus whites after adjustment in either CHS or ARIC, and so the extent to which baseline NT-proBNP may mediate the differential association was rendered moot in statistical analyses. Indeed, although whites had greater risk for CHF in CHS, there was no such association with CHF in ARIC.
These observations themselves demonstrate that the apparent racial propensity to differential NT-proBNP levels does not translate into consistent differences in CHF incidence. It is possible that the higher prevalence of CHF risk factors among blacks is counterbalanced by a protective effect of NT-proBNP, resulting in a net equivalence of incident CHF.

Our findings regarding race and CHF are also consistent with previous literature. In the MESA (Multiethnic Study of Atherosclerosis), Bahrami et al concluded that blacks have more incident CHF than whites; however, after adjustment for hypertension and/or diabetes mellitus, that difference was attenuated. Interestingly, data from the CARDIA (Coronary Artery Risk Development in Young Adults) study clearly showed that young blacks were at a substantially higher risk than whites for CHF, more consistent with our findings in ARIC (a younger population than that of CHS), where, after adjustment, risk for CHF in whites and blacks was statistically equivalent. This may suggest that there is an important interaction between age and race that is relevant to CHF pathophysiology.

This study had several limitations. CHS and ARIC rely on intake questionnaires for prevalence of diseases at baseline, although review of medical records and surveys of treating physicians were performed at baseline to identify prevalent cardiovascular disease in CHS. The current study lacked echocardiography data or other direct measurements of filling pressures to determine potential underlying mechanistic relationships to baseline NT-proBNP levels. Self-report of baseline comorbidities may limit the sensitivity and specificity of disease prevalence at baseline, particularly with AF, which cannot necessarily be refuted by ECG. The effects of the bias this creates cannot be determined, but nonetheless the sensitivity and specificity of the presence of diagnoses at baseline is likely similar between the predictor groups in this study and therefore may not affect comparative results. Although NT-proBNP was measured in blood samples at study entry, and those with prevalent AF or CHF were excluded from the study, there may have been occult AF or presence of certain comorbidities at baseline, such as undetected hypertension, that may have increased baseline NT-proBNP measurements and similarly increased the risk of AF and CHF in those patients. However, although this may have biased the analysis toward an increased risk of AF and/or CHF in patients with higher NT-proBNP, it would not appear to affect or explain the results of the mediation analysis. Follow-up in both CHS and ARIC included multiple visits, review of intervening medical records, and serial ECGs; however, it remains possible that some AF remained undetected. Nonetheless, more-sensitive monitoring should generally affect the incidence of AF similarly in both whites and blacks, but again should not affect the mediation analysis. Whereas the statistical model of the study is meant to address the possible role NT-proBNP may play in mediation of the differential relationship between race and AF, the statistical model is merely suggestive and not definitive of mediation or a causal relationship. Also, there may be unmeasured confounders not captured by data available in CHS and ARIC, although both of these cohorts include robust lifestyle and demographic information, and all relevant covariates were included in multivariable models. Finally, because this is an observational study, the relationships described should be interpreted as associations, and no conclusions regarding causality can be made.
Conclusion
A substantial portion of the strong and paradoxical relationship between white race and AF was explained by higher baseline NT-proBNP levels in both a middle-aged and older adult population. Conversely, despite the higher NT-proBNP levels in whites, no consistent relationship between race and CHF was observed between the 2 cohorts. Given previous literature demonstrating an atrial remodeling effect of natriuretic peptides, these data draw attention to whether natriuretic peptides may have a direct causal effect on AF, suggesting that targeting such pathways to prevent or treat AF may prove fruitful.

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Disclosures
None.

References


