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Title Racial Differences in Low Natriuretic Peptide Levels: Implications for Heart Failure Clinical Trials

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Racial Differences in Low Natriuretic Peptide Levels: Implications for Heart Failure Clinical Trials

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An abstract of
A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research
2023

Abstract

Racial Differences in Low Natriuretic Peptide Levels: Implications for Heart Failure Clinical Trials

By Apoorva Gangavelli BS

Background: Some patients with heart failure (HF) have low natriuretic peptide (NP) levels. It is unclear whether these populations are disproportionately excluded from participation in randomized clinical trials (RCT) with inclusion requirements for elevated NPs. We investigated factors associated with unexpectedly low NP levels in a cohort of patients hospitalized with HF, and the implications on racial diversity in a prototype HF RCT.

Methods: We created a retrospective cohort of 31,704 patients (age 72 ± 16 years, 49% female, 52% Black) hospitalized with HF from 2010-2020 with B-type natriuretic peptide (BNP) measurements. Factors associated with unexpectedly low BNP levels (<50 pg/ml) were identified using multivariable logistic regression models. We simulated patient eligibility for a prototype HF trial using specific inclusion and exclusion criteria, and varying BNP cut-offs.

Results: Unexpectedly low BNP levels were observed in 8.9% of the cohort. Factors associated with unexpectedly low BNP levels included HFpEF (aOR 3.76, 95% CI 3.36-4.20), obesity (aOR 1.96, 95% CI 1.73 – 2.21), self-identification as Black (aOR 1.53, 95% CI 1.36 – 1.71), and male gender (aOR 1.45, 95% CI 1.31-1.60). Applying limited inclusion and exclusion criteria from PARAGLIDE-HF and adding BNP criteria ≥ 35, ≥ 50, ≥ 67, ≥ 100 and ≥ 150 pg/ml decreased the proportion of Black patients (44.6.0%, 43.7%*, 43.4%*, 43.3%*, and 43.3%*, respectively) eligible for RCT participation (* p≤0.01).

Conclusions: Nearly 10% of patients hospitalized with HF have unexpectedly low BNP levels. Simulating inclusion into a prototype HF RCT demonstrated that requiring increasingly elevated NP levels disproportionately excluded Black patients.

Racial Differences in Low Natriuretic Peptide Levels: Implications for Heart Failure Clinical Trials

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INTRODUCTION

Heart failure (HF) affects over 6 million Americans, and is the most common cause of cardiovascular hospitalization in adults over the age of 65.[1] Accordingly, there has been a steady increase over the past decade in the number of randomized clinical trials (RCTs) aiming to expand pharmacologic options available to treat HF. Improving the diversity and representativeness of HF RCTs is a priority, as patients who are from racial and ethnic minority groups are underrepresented as subjects in RCTs even though they bear a disproportionate burden of HF. For example, a recent analysis demonstrated that the enrollment of Black patients in industry-sponsored HF trials decreased from 8% in 2001-2004 to 5% in 2013-2016.[2]

Trial specific factors, including strict inclusion and exclusion criteria, may create barriers to enrolling representative patient populations. Natriuretic peptides (NPs) are recommended in HF to confirm the diagnosis, as well as to assess the effect of treatment and to predict clinical outcomes.[3] The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) experience confirmed that significant differences in risk of clinical events occur when allowing optional enrollment through either NP levels or history of HF hospitalization.[4] Contemporary HF RCTs increasingly use NPs as inclusion criteria to enhance diagnostic accuracy and to enrich for clinical events, however there currently is no standard practice for what thresholds of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT pro-BNP) should guide entry into trials.[5] Moreover, NPs do not perform equally well in all clinical settings. Numerous causes of relative NP deficiency are recognized, including obesity, African ancestry, genetic polymorphisms, insulin resistance, and others.[6] Similarly, patients with HF with preserved ejection fraction (HFpEF) have lower NP levels than patients with HF with reduced ejection fraction (HFrEF). A prior study confirmed unexpectedly low BNP levels (<50 pg/ml) in a significant portion of patients hospitalized for HF, confirming that many patients at high risk for clinical events may be excluded from RCT participation based on NP deficiency syndrome.[7] As such, current expert consensus suggests that trialists consider lowering the enrollment threshold of BNP and NT-proBNP by at

least 20% to 30% for special populations (e.g. Black patients, obese patients) to avoid exclusion from clinical trials, however these criteria have not been widely tested in clinical populations.[5]

Improving the racial and ethnic diversity of patients who participate in RCTs is a critical need, since patients from underrepresented groups are at increased risk for adverse clinical outcomes. Black patients, for example, have the highest risk of incident and prevalent HF, as well as the highest risk of death and hospitalizations [8], but data demonstrating whether Black patients are disproportionately excluded from HF clinical trials due to existing inclusion criteria for elevated NPs or other criteria are limited. There is also some suggestion that modification of NP cutoff values based on race or ethnicity may be more relevant in prevention studies than trials of patients with acute or chronic HF, since patients with manifest HF often have higher NP concentrations than those at risk for HF.[5] In the current analysis, we investigate 1) demographic and clinical factors associated with unexpectedly low BNP levels in a diverse cohort of patients hospitalized with HF, and 2) implications of varying BNP cut-offs on the inclusion of Black patients into prototype HF randomized trials.

METHODS

Data source. We utilized the Emory Healthcare Clinical Data Warehouse, according to previously published methods.[9] The Data Warehouse is a data repository that integrates standardized patient-level data from the electronic medical records (EMR) across the Emory Healthcare system, the largest and most comprehensive hospital system in Atlanta, Georgia. Available data within the Emory Healthcare Clinical Data Warehouse includes both inpatient and outpatient visit data, provider information, diagnoses and procedures, clinical laboratory results, clinician documentation, pharmacy, and emergency department utilization. For this analysis, we examined data from Emory University Hospital (EUH) and EUH Midtown (EUHM) since they are staffed primarily by Emory clinicians and housestaff, and are each equipped with their own large general medicine, general cardiology, and advanced HF services. Because of the sensitive nature of the data collected for this study, requests to access a subset of the data from

qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author. This study was approved by the Emory Institutional Review Board.

Study Population. The study cohort consisted of adults ages 18-80 years hospitalized with HF at EUH and EUHM from January 1st, 2010 to December 31st, 2020 based on ICD-9 and -10 codes, who had BNP concentrations measured at admission. Since patients can be hospitalized for HF multiple times, patients' sociodemographic characteristics, comorbidities, ejection fraction (EF), laboratory values, and hospital characteristics (e.g. discharging specialty and length of stay) were assigned based on values present during the patient's first hospitalization within the study period. As the number of Asian (n= 330, 2.2%) and Hispanic (n= 431, 2.8%) patients hospitalized for HF during the study period were too low to draw meaningful conclusions, they were excluded from the present analysis.

Clinical Covariates. We considered a prespecified list of covariates extracted from the EMR at the time of admission during the index AHF hospital encounter, including sociodemographic characteristics (age, race-ethnicity, gender, insurance status), HF type (HFpEF, HFrEF, HFmrEF, other), medical comorbidities (hypertension, diabetes mellitus, chronic kidney disease [CKD], coronary artery disease [CAD], atrial fibrillation, chronic obstructive pulmonary disease [COPD], peripheral vascular disease, and cerebrovascular accident/transient ischemic attack [CVA/TIA]), body mass index (BMI), vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate), laboratory values (serum sodium, creatinine, estimated glomerular filtration rate [eGFR], blood urea nitrogen [BUN], hemoglobin, BNP, and troponin [TNI]), year of index hospitalization, discharging specialty (cardiovascular, hospitalist/internal medicine, other), hospital location (EUH versus EUHM), and guideline-directed medical therapy (GDMT). The Charlson comorbidity index was derived as a summary measure of the medical comorbid conditions.[10] In an effort to adjust for the social construct of race-ethnicity, we used the Social Deprivation Index (SDI), which summarizes 7 socio-demographic measures taken from the US Census American Community Survey.[11] To assign each patient an SDI value, patient addresses were

geocoded to street level accuracy using the US Census Bureau's geocoder. SDI scores range from 1 to 100, with a higher score indicating greater census tract deprivation.

Statistical Analysis. Patient characteristics, including demographics, medical comorbidities, and laboratory values are presented according to racial group at the time of the index hospitalization for AHF. Data are presented as mean (SD) for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, or N (%) for categorical variables as appropriate. Similar to prior studies, we defined an unexpectedly low BNP level as any measurement <50 pg/ml.[7] Factors associated with unexpectedly low BNP were identified using multivariable logistic regression models. Covariates included in the multivariable regression were identified using a backwards selection method, with the final model adjusted for age, gender, race, BMI, HF type, creatinine, atrial fibrillation, and SDI. The amount of missing data present can be found in Table 1.

In order to examine the impact of BNP levels on enrollment into a prototype acute HF RCT, we utilized the inclusion and exclusion criteria from the A Multicenter, Randomized, Double-blind, Double-dummy, Parallel Group, Active Controlled Study to Evaluate the Effect of Sacubitril/Valsartan (LCZ696) Versus Valsartan on Changes in NT-proBNP, Safety, and Tolerability in HFpEF Patients With a WHF Event (HFpEF Decompensation) Who Have Been Stabilized and Initiated at the Time of or Within 30 Days Post-decompensation (PARAGLIDE-HF) trial.[12] We utilized the PARAGLIDE-HF eligibility criteria that could be readily extracted from the EMR, including patients aged 40 years or older with EF greater than 40% within the previous 6 months, and excluded those with hemoglobin <10 g/dL, BMI >50 kg/m2, systolic blood pressure <100 mm Hg, eGFR <20 mL/min/1.73 m^2, and serum potassium >5.3 mEq/L. Subsequently, patients were further excluded for increasing concentrations of BNP according to the following definitions: ≥35 pg/mL based on the universal definition of HF in an ambulatory setting [3]; ≥50 pg/mL based on the definition of an unexpectedly low BNP level used in Bachmann et al. [7]; ≥67 pg/mL based on the suggestion to lower RCT enrollment thresholds for NP by at least 20-30% for Black patients to avoid exclusion from clinical trials[5]; ≥100 pg/mL based on the universal definition of HF in an

acute setting; ≥150 pg/mL based on the inclusion criteria used in the PARAGLIDE-HF trial.[13] The change in the proportion of Black patients was compared after each additional exclusion criteria using McNemar's chi-squared test. Restricted cubic splines models with 3 knots were constructed to display the association between log-transformed, standardized BNP concentrations as a continuous variable and the incidence of rehospitalization over the study period for the overall cohort and stratified by racial group, as well as the trial-eligible cohort and stratified by racial group. Comparisons by racial group were conducted by using an ANOVA model to compare the two restricted cubic splines. Models are adjusted for age, gender, race, BMI, HF classification, insurance, and comorbidities (hypertension, atrial fibrillation, coronary artery disease, chronic kidney disease, and diabetes),

All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc.), and RStudio version 1.3.1073 (The Comprehensive R Archive Network: https://cran.r-project.org). A two-sided P-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics. Baseline characteristics of the 31,704 patients included in the analytic cohort are shown in **Table 1**. Compared to non-Black patients, Black patients were younger, more likely to be female, had higher blood pressure, and were less likely to discharged from a primary cardiology service. Of the entire cohort, 2669 (8.9%) had a BNP <50 pg/mL, and 5372 (18.0%) had BNP <100 pg/mL on admission for acute HF. Black patients were more likely than non-Black patients to have a BNP <50 pg/mL (10.9% vs. 6.6%, p<0.01) and <100 pg/mL (20.0% vs. 15.6%, p<0.01).

Factors associated with unexpectedly low BNP concentrations. Table 2 shows the demographic and clinical factors associated with BNP <50 pg/ml in patients hospitalized with HF. Compared to the overall cohort, patients with low BNP were younger (p<0.001), with a larger proportion of Black individuals (p<0.001), and a larger proportion of with overweight or obesity (p<0.001). On multivariable analysis (**Figure 1**), factors associated with unexpectedly low BNP levels included HFpEF (adjusted odds ratio

[aOR] 3.76, 95% confidence interval [CI] 3.36-4.20), overweight (aOR 1.21, 95% CI 1.04 – 1.40) and obesity (aOR 1.96, 95% CI 1.73 – 2.21), self-identification as Black (aOR 1.53, 95% CI 1.36 – 1.71), and male gender (aOR 1.45, 95% CI 1.31-1.60).

Effect of increasing BNP thresholds on the inclusion of Black patients into a prototype HF RCT. To examine the impact of BNP levels on enrollment into a prototype HF RCT, we applied the clinical inclusion and exclusion criteria from PARAGLIDE-HF. We first applied EF $\geq$ 40% and age $\geq$ 40 as initial inclusion criteria (**Figure 2**), reducing the cohort size to n=18,033 , and the proportion of Black patients from 52.1% to 51.2% (p=.057). Applying additional exclusion criteria related to hemoglobin, BMI, systolic blood pressure, eGFR, and serum potassium values further reduced the proportion of Black patients from 51.2% to 46.5% (p<0.001). Among these clinical criteria, the greatest proportion of Black patients was lost due to the requirement for eGFR $\geq$20 mL/min/1.73 m^2. After applying the clinical inclusion and exclusion criteria from PARAGLIDE-HF, 6077 patients were eligible for trial participation, of which 2823 (46.5%) were Black. Adding increasingly stringent thresholds for BNP of ≥35, ≥50, ≥67, ≥100, and ≥150 pg/ml further decreased the overall cohort size (n=5474, 5159, 4843, 4352 and 3761), and further reduced the proportion of eligible Black patients (44.6%, 43.7%*, 43.4%*, 43.3%*, and 43.3%*, respectively) (*p<0.01).

Association of BNP with risk of rehospitalization. During a median follow-up period of 4.0 (interquartile range 1.77-6.39) years, the rate of rehospitalization was 1.87 admissions/year among the entire study cohort, with a higher rate of rehospitalization for Black patients compared to non-Black patients (1.91 admissions/year vs 1.81 admissions/year, p=.008). Among the entire study cohort, the risk of rehospitalization during the follow-up period increased with increasing BNP values (**Figure 3A**). Among the overall cohort, the risk of rehospitalization across increasing BNP values differed by racial group (**Figure 3B**, p=0.0002 for race*BNP interaction). Among the clinical trial eligible cohort, risk of rehospitalization during the study period also increased with increasing BNP values (**Figure 3C**). There were no differences in risk of rehospitalization during the follow-up period by racial group in the trial-eligible cohort (**Figure 3D**) with no significant interaction(p=0.8).

DISCUSSION

This analysis has four main findings: 1) in a real-world cohort of patients hospitalized with HF, 8.9% had unexpectedly low BNP concentrations (i.e. <50 pg/mL), 2) demographic and clinical characteristics, including self-identification as Black, HFpEF, obesity, and male gender, are associated with unexpectedly low BNP concentrations, 3) simulating inclusion into a prototype acute HFpEF RCT demonstrated that restrictive clinical criteria and requiring increasingly elevated BNP concentrations disproportionately excluded Black patients, and 4) clinical event rates are similarly high in patients excluded from trial participation as those who meet RCT inclusion criteria, particularly among those patients who self-identify as Black. These findings have important implications in prioritizing diversity in HF clinical trials.

It is well known that various demographic and clinical factors affect NP levels. A prior post-hoc analysis of the TOPCAT trial evaluated the prognostic significance of NPs across six key subgroups of the enrolled participants with HFpEF.[4] The investigators found lower NP levels among younger, Black, and obese individuals, and those with better renal function. Of note, however, TOPCAT required either a previous HF hospitalization within 12 months or elevated NP concentration (BNP ≥100 ng/L or NT-proBNP ≥360 ng/L) within 60 days of enrollment. Thus, this analysis is demonstrative of clinical event rates in a population of patients who have already met criteria for enrollment in a RCT. More recently, Bachmann et al. examined the prevalence of unexpectedly low NP levels in a real-world cohort of patients hospitalized with HF, and similar to our analysis, demonstrated that obesity and HFpEF were the strongest predictors of BNP <50 pg/ml.[7]

As our cohort contained a significantly larger proportion of Black patients compared to many prior analyses, we also demonstrate that Black patients are more likely to have low BNP levels. Prior studies have documented that Black and Hispanic individuals at risk for HF have lower levels of NP than other racial and ethnic groups.[14,15] A relative deficiency of NP may be associated with a phenotype

characterized by increased risk for hypertension, insulin resistance, salt and fluid retention, left ventricular hypertrophy, and subsequent HF.[16] Although patients with prevalent HF typically have elevated levels of NP, a prior analysis of the PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for HF) study also demonstrated a relative deficiency of NP among Black and Hispanic patients with HFrEF compared to their White counterparts.[17] Our cohort included patients hospitalized for both HFrEF and HFpEF, but still confirms lower BNP levels among Black patients regardless of HF classification. Prior analyses in patients at risk for HF document that increasing proportion of African ancestry is associated with lower NP levels among patients who self-identify as Black race or Hispanic ethnicity, while increasing proportion of European ancestry is associated with higher NP levels.[15] Moreover, limited adjustment for factors associated with the social determinants of health (e.g. income, education) did not attenuate the association of Black race with NP levels in prior studies.[14] We utilized the SDI in our analysis as a metric that incorporates multiple factors associated with the social construct of race-ethnicity and the social determinants of health. Furthermore, confounders such as obesity are associated with low NP levels, but are also more common in Black patients, in part, due to high levels of social deprivation. While SDI levels were higher in Black patients in our cohort, additional adjustment for the SDI did not attenuate the association of Black race with unexpectedly low BNP levels.

Although the use of elevated NPs as inclusion criteria in clinical trials allows for enrichment of clinical events, it is also necessary to ensure these criteria don't create a barrier to enhancing the diversity of RCT populations. In TOPCAT, patients enrolled based on a history of previous HF hospitalization had lower event rates and no benefit from spironolactone when compared to patients enrolled based on elevated NP levels, raising concern for misdiagnosis of HF.[18] However, prior post-hoc analyses of both TOPCAT and the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) have shown higher rates of hospitalization among Black patients compared to patients of other races and ethnicities, irrespective of NP levels at entry.[4,19] We simulated the impact on inclusion in a prototype acute HF RCT by using varying thresholds of BNP, and demonstrated that Black

patients are excluded from participation due to clinical criteria (particularly eGFR values) and are further excluded as NP eligibility thresholds increase, even though overall rates of hospitalization during the follow-up period were higher for Black vs. non-Black patients. Furthermore, the higher prevalence of obesity among Black patients with HF may further increase the risk for unexpectedly low NP levels. Given that class II or greater obesity is often an exclusion criteria in HFpEF RCTs, the exclusion of patients who lack elevated NP levels and who are obese may impose a particular selection against eligibility of Black individuals. Current expert consensus recommends lowering the threshold of BNP and NT-proBNP by 20% to 30% for Black patients, as well as other characteristics that increase the risk for NP deficiency (e.g. obese patients). Our analysis suggests that even a 20-30% lowering would still disproportionately exclude Black patients, as compared to inclusion based on a prior HF hospitalization, for which all patients in our cohort would meet criteria.

Several limitations of our study must be noted. Our study is retrospective and is limited by the availability of data typically collected in an EMR. Self-identified race and ethnicity correlate with both genetic ancestry as well as the social construct of race-ethnicity, neither of which can be fully accounted for by variables readily available in the EMR. Although we attempted to adjust for the social construct of race and ethnicity by including the limited information available on social determinants of health such as insurance status and the SDI, other variables are not accounted for (e.g. income, educational attainment, etc). Similarly, other racial and ethnic groups (e.g. Hispanic and Asian patients) did not comprise a large enough proportion of our patient cohort to draw meaningful conclusions, so they were not analyzed individually. Furthermore, rehospitalizations that occurred at institutions outside of Emory were not captured for patients in our cohort. Lastly, we chose to use limited inclusion and exclusion criteria from the PARAGLIDE-HF clinical trial as an exemplar, however other RCTs have used different cut-offs for NP levels.

In conclusion, this study demonstrates that increasing BNP thresholds for HF trials may disproportionately exclude Black patients. In order to improve the diversity and representative enrollment

of patients in HF trials, clinical trialists should reconsider NP thresholds for inclusion, or consider alternative criteria such as recent history of HF hospitalization.

ACKNOWLEDGMENTS

AG is supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Numbers UL1TR002378 and TL1TR002382.
KP is supported by the Stimulating Access to Research in Residency of the National Institutes of Health under Award Number R38AI140299. AAM is supported by AHRQ (HS026081), the Woodruff Foundation, the Association of Black Cardiologists, and the American Heart Association.

CONFLICTS OF INTEREST

AAM reports consulting fees from Abbott, Acorai, BI Lilly, Cytokinetics, Edwards Lifesciences, Ionis and Merck.

REFERENCES:

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics 2022 Update: A Report From the American Heart Association. Circulation 2022;145(8):e153-e639. DOI: doi:10.1161/CIR.0000000000001052.
2. Tahhan AS, Vaduganathan M, Greene SJ, et al. Enrollment of Older Patients, Women, and Racial and Ethnic Minorities in Contemporary Heart Failure Clinical Trials: A Systematic Review. JAMA Cardiology 2018;3(10):1011-1019. DOI: 10.1001/jamacardio.2018.2559.
3. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail 2021 (In eng). DOI: 10.1016/j.cardfail.2021.01.022.
4. Myhre PL, Vaduganathan M, Claggett BL, et al. Association of Natriuretic Peptides With Cardiovascular Prognosis in Heart Failure With Preserved Ejection Fraction: Secondary Analysis of the TOPCAT Randomized Clinical Trial. JAMA Cardiology 2018;3(10):1000-1005. DOI: 10.1001/jamacardio.2018.2568.
5. Ibrahim NE, Burnett JC, Jr., Butler J, et al. Natriuretic Peptides as Inclusion Criteria in Clinical Trials: A JACC: Heart Failure Position Paper. JACC Heart Fail 2020;8(5):347-358. (In eng). DOI: 10.1016/j.jchf.2019.12.010.
6. Shah SJ. BNP: Biomarker Not Perfect in heart failure with preserved ejection fraction. European Heart Journal 2022. DOI: 10.1093/eurheartj/ehac121.
7. Bachmann KN, Gupta DK, Xu M, et al. Unexpectedly Low Natriuretic Peptide Levels in Patients With Heart Failure. JACC: Heart Failure 2021;9(3):192-200. DOI: doi:10.1016/j.jchf.2020.10.008.

8. Nayak A, Hicks AJ, Morris AA. Understanding the Complexity of Heart Failure Risk and Treatment in Black Patients. Circ Heart Fail 2020;13(8):e007264. (In eng). DOI: 10.1161/circheartfailure.120.007264.

9. Patel SA, Krasnow M, Long K, Shirey T, Dickert N, Morris AA. Excess 30-Day Heart Failure Readmissions and Mortality in Black Patients Increases with Neighborhood Deprivation. Circ Heart Fail 2020;13(12):e007947. (In eng). DOI: 10.1161/circheartfailure.120.007947.

10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases 1987;40(5):373-383. DOI: 10.1016/0021-9681(87)90171-8.

11. Butler DC, Petterson S, Phillips RL, Bazemore AW. Measures of social deprivation that predict health care access and need within a rational area of primary care service delivery. Health services research 2013;48(2 Pt 1):539-59. (In eng). DOI: 10.1111/j.1475-6773.2012.01449.x.

12. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine 2019;381(17):1609-1620. DOI: 10.1056/NEJMoa1908655.

13. Changes in NT-proBNP, Safety, and Tolerability in HFpEF Patients With a WHF Event (HFpEF Decompensation) Who Have Been Stabilized and Initiated at the Time of or Within 30 Days Post-decompensation (PARAGLIDE-HF). https://clinicaltrials.gov/ct2/show/NCT03988634. Accessed June 28, 2022.

14. Gupta DK, de Lemos JA, Ayers CR, Berry JD, Wang TJ. Racial Differences in Natriuretic Peptide Levels: The Dallas Heart Study. JACC: Heart Failure 2015;3(7):513-519. DOI: https://doi.org/10.1016/j.jchf.2015.02.008.

15. Gupta DK, Daniels LB, Cheng S, et al. Differences in Natriuretic Peptide Levels by Race/Ethnicity (From the Multi-Ethnic Study of Atherosclerosis). The American Journal of Cardiology 2017;120(6):1008-1015. DOI: https://doi.org/10.1016/j.amjcard.2017.06.030.

16. Wang TJ. Natriuretic Peptide Deficiency—When There Is Too Little of a Good Thing. JAMA Cardiology 2018;3(1):7-9. DOI: 10.1001/jamacardio.2017.4208.

17. Ibrahim NE, Piña IL, Camacho A, et al. Racial and Ethnic Differences in Biomarkers, Health Status, and Cardiac Remodeling in Patients With Heart Failure With Reduced Ejection Fraction Treated With Sacubitril/Valsartan. Circ Heart Fail 2020;13(11):e007829. (In eng). DOI: 10.1161/circheartfailure.120.007829.

18. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370(15):1383-92. DOI: 10.1056/NEJMoa1313731.

19. Pahuja M, Leifer ES, Clarke J-RD, et al. Assessing race and ethnicity differences in outcomes based on GDMT and target NT-proBNP in patients with heart failure with reduced ejection fraction: An analysis of the GUIDE-IT study. Progress in Cardiovascular Diseases 2022;71:79-85. DOI: https://doi.org/10.1016/j.pcad.2022.04.010.

TABLE AND FIGURE LEGEND

Table 1. Baseline characteristics at time of index hospitalization by racial group.

Table 2. Characteristics of patients hospitalized with HF with BNP <50 pg/ml and <100 pg/mL

Figure 1. Multivariable predictors of unexpectedly low BNP in patients hospitalized with HF.

Figure 2. Effects of increasing BNP cut-offs on inclusion of Black patients into a prototype HF randomized clinical trial. **Central Illustration.**

Figure 3. Association between BNP levels and incidence of rehospitalization during the study period.

Table 1. Baseline characteristics at time of index hospitalization by racial group.

	Overall (N=31704)	**Black (N=16515)**	**Non-Black (N= 15189)**	**P-value**
Age, years	71.6 ± 16.1	68.4 ± 15.9	75.1 ± 15.6	<0.001
Women	15532 (49.0)	8805 (53.3%)	6727 (44.3%)	<0.001
Insurance • Private • Medicare • Medicaid • Other/not recorded	 5723 (18.1) 21313 (67.2) 2749 (8.7) 1919 (6.1)	 2897 (17.5) 10400 (63.0) 1979 (12.0) 1239 (7.5)	 2826 (18.6) 10913 (71.8) 770 (5.1) 680 (4.5)	<0.001
HF Classification[†] • HFrEF • HFmrEF • HFpEF	 6953 (21.9) 3445 (10.9) 16041 (50.6)	 3804 (23.0) 1844 (11.2) 8230 (49.8)	 3149 (20.7) 1601 (10.5) 7811 (51.4)	<0.001
Hypertension	20250 (63.9)	11101 (67.2)	9149 (60.2)	<0.001
Coronary Artery Disease	14769 (46.6)	6250 (37.8)	8519 (56.1)	<0.001
Chronic Kidney Disease	13001 (41.0)	7819 (47.3)	5182 (34.1)	<0.001
Diabetes Mellitus	11579 (36.5)	6479 (39.2)	5100 (33.6)	<0.001
Atrial Fibrillation	10523 (33.2)	3988 (24.1)	6535 (43.0)	<0.001
Chronic Pulmonary Disease	9596 (30.3)	4878 (29.5)	4718 (31.1)	0.003
Systolic Blood Pressure, mm Hg	137.0 (117.0-160.0)	142.0 (119.0-169.)	133.0 (115.0-152.0)	<0.001
Diastolic Blood Pressure, mm Hg	76 (65-88)	80 (68-93)	72 (63-82)	<0.001
BMI, kg/m^2	28.4 (23.8-34.4)	29.4 (24.4-36.1)	27.4 (23.4-32.6)	<0.001
Creatinine, mg/dL	1.2 (0.9-1.7)	1.2 (0.9-2.2)	1.0 (0.8-1.4)	<0.001
eGFR, ml/min/1.73m^2	59 (35-71)	53 (26-71)	66 (44-71)	<0.001
Blood urea nitrogen, mg/dL	21 (14-33)	21.5 (14-35)	20 (14-30)	<0.001
Hemoglobin, g/dL	10.3 (8.9-12.0)	10.3 (8.8-12.0)	10.4 (9.1-12.1)	0.287
HbA1c, %	5.9 (5.4-6.9)	6.1 (5.5-7.1)	5.8 (5.4-6.6)	<0.001
Sodium, mEg/L	138 (135-140)	138 (135-140)	137 (135-140)	<0.001
BNP, pg/mL	398 (148-944)	406 (134-1031)	383 (159-846)	<0.001

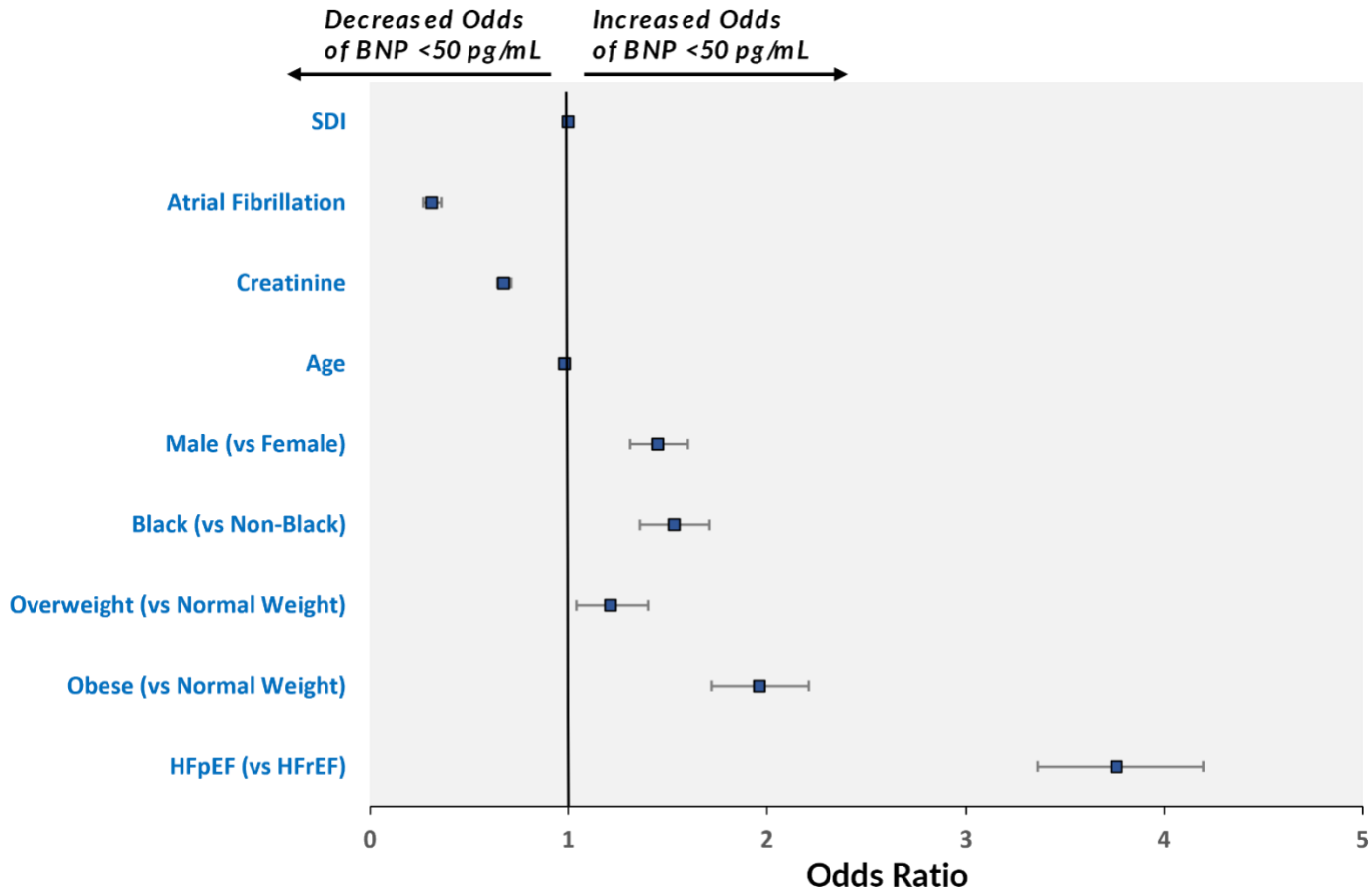
BNP < 50 pg/mL	2669 (8.9)	1795 (10.9)	874 (6.6)	<0.001
BNP <100 pg/mL	5372 (18.0)	3299 (20.0)	2073 (15.6)	<0.001
Troponin I, pg/mL	0.05 (0.02-0.23)	0.05 (0.02-0.16)	0.06 (0.02-0.36)	<0.001
Discharging Specialty • Cardiovascular • Internal Medicine • Other	 13127 (23.7) 20354 (36.7) 21933 (39.6)	 4892 (18.0) 13293 (49.0) 8971 (33.0	 7302 (29.6) 6150 (24.9) 11244 (45.4)	<0.001
Medical Therapy‡ • ACE • ARB • ARNI • Beta-blocker • MRA	 7253 (22.9) 2599 (8.2) 250 (0.8) 15762 (49.7) 3008 (9.5)	 4259 (25.8) 1516 (9.2%) 152 (0.9) 8637 (52.3) 1700 (10.3)	 2994 (19.7) 1083 (7.1) 98 (0.6) 7125 (46.9) 1308 (8.6)	<0.001
Length of stays, days	6 (3-11)	6 (2-10)	6 (3-11)	<0.001

Values are mean ± standard deviation, median (interquartile range), or N (%).
†Total of 5265 (16.6%) patients with missing ejection fraction values.
‡Total of 6111 (19.3%) patients with missing medication data.

Table 2. Characteristics of patients hospitalized with HF with BNP <50 pg/ml and <100 pg/mL

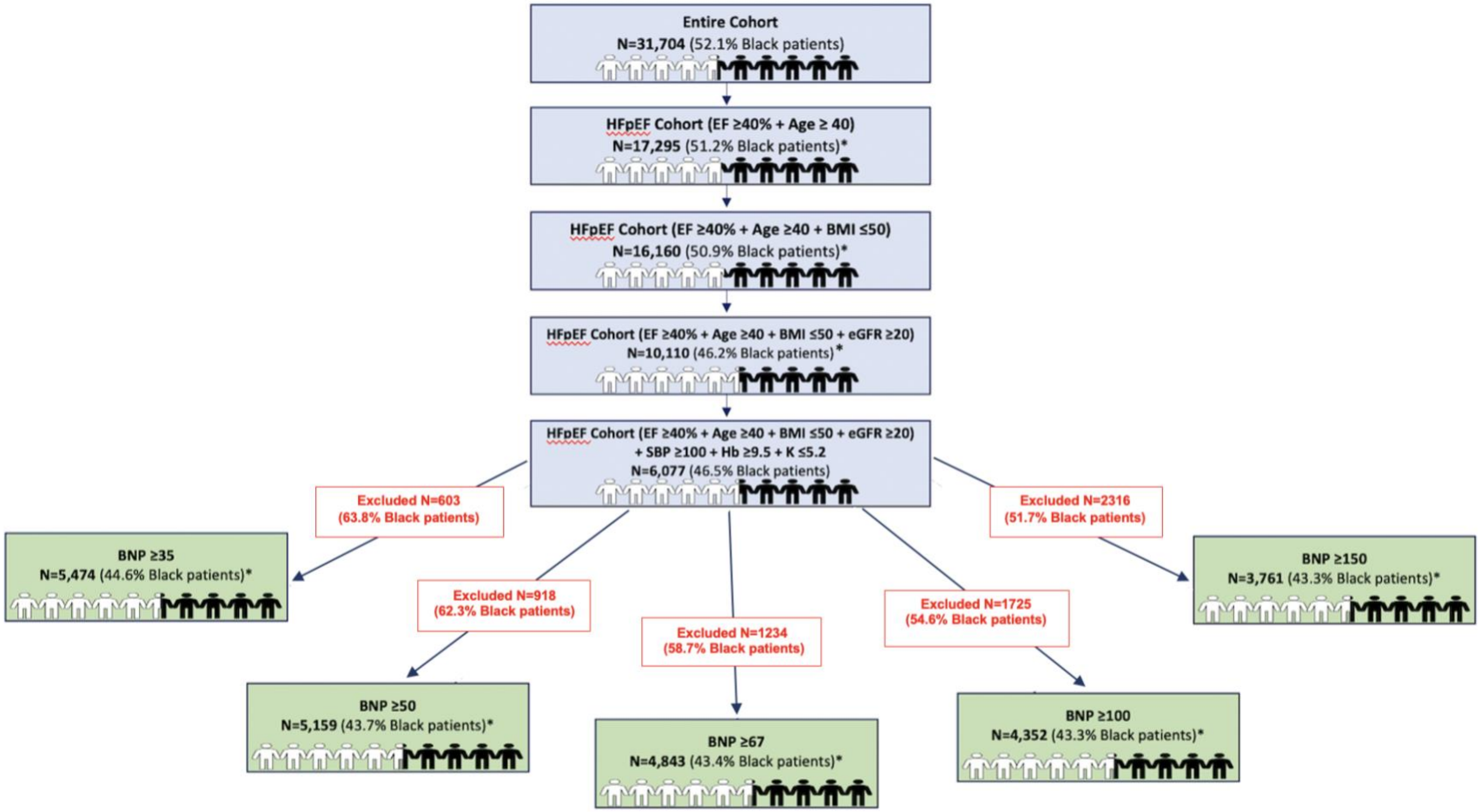
	Overall (N=31704)	**BNP <50 pg/ml (N=2791)**	**BNP <100 pg/ml (N=5372)**
Age, years	71.6 ± 16.1	64.4 ± 15.5	66.8 ± 15.8
Black	16515 (52.1)	1795 (64.3)	3299 (58.7)
Women	15532 (49.0)	1425 (51.1)	2847 (50.6)
HF Classification			
• HFrEF	6953 (21.9)	173 (6.2)	458 (8.1)
• HFmrEF	3445 (10.9)	175 (6.3)	368 (6.5)
• HFpEF	16041 (50.6)	1905 (68.3)	3716 (66.1)
Hypertension	20250 (63.9)	1904 (68.2)	3799 (67.5)
Coronary Artery Disease	14769 (46.6)	940 (33.7)	2103 (37.4)
Chronic Kidney Disease	13001 (41.0)	638 (22.9)	1407 (25.0)
Diabetes Mellitus	11579 (36.5)	1608 (38.3)	2159 (38.4)
Atrial Fibrillation	10523 (33.2)	334 (12.0)	949 (16.9)
Systolic Blood Pressure, mm Hg	137 (117-160)	137 (120-158)	137 (119-159)
Diastolic Blood Pressure, mm Hg	76 (65-88)	77 (67-87)	76 (65-88)
BMI, kg/m^2	28.4 (23.8-34.4)	32.0 (26.0-39.5)	28.4 (23.8-34.4)
Creatinine, mg/dL	1.2 (0.9-1.7)	1.0 (0.8-1.3)	1.0 (0.8-1.3)
eGFR, ml/min/1.73m2	57 (35-71)	71 (53-72)	71 (50-71)
Hemoglobin, g/dL	10.5 (9.0-12.2)	11.1 (9.5-12.7)	10.9 (9.4-12.5)
Values are mean ± standard deviation, median (interquartile range), or N (%).			

Figure 1. Multivariable predictors of unexpectedly low BNP in patients hospitalized with HF.



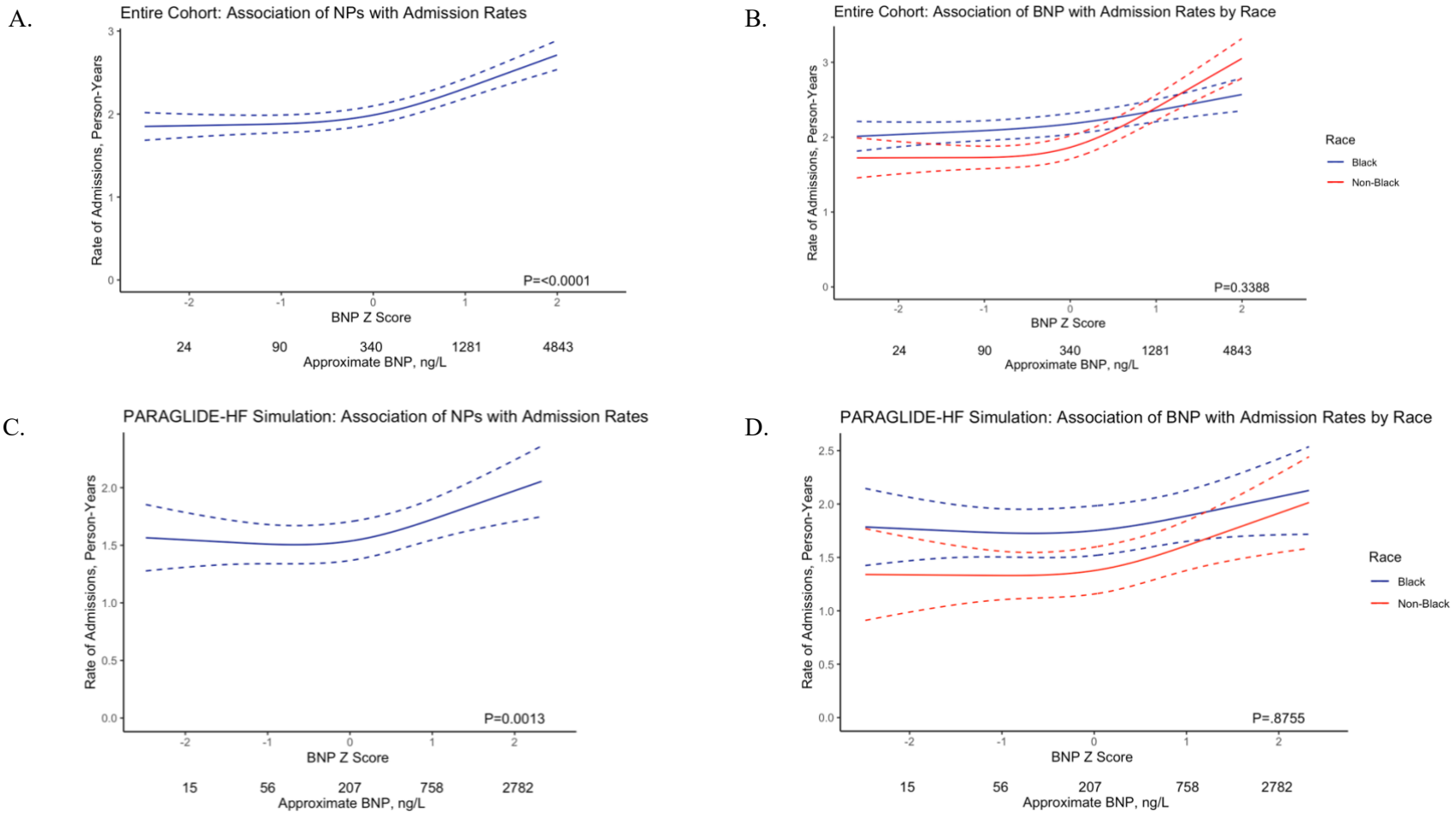
In multivariable logistic regression analyses, the strongest predictors of having BNP levels <50 pg/ml in the setting of HF hospitalization were HFpEF, higher BMI, followed by younger age, and lower creatinine ($p < 0.001$ for all).

Figure 2. Effects of increasing BNP cut-offs on inclusion of Black patients into a prototype HF randomized clinical trial.



After applying the clinical inclusion and exclusion criteria from PARAGLIDE-HF, 6077 patients were eligible for trial participation, of which 2823 (46.5%) were Black. Adding a criteria of BNP ≥35, ≥50 ≥67, ≥100 and ≥150 pg/ml further decreased the overall cohort size (n=5474, 5159, 4843, 4352 and 3761), as well as the proportion of Black patients (44.6%, 43.7%*, 43.4%*, 43.3%*, and 43.3%, respectively) eligible (* $p<0.01$)

Figure 3. Association between BNP levels and incidence of rehospitalization during the study period.



Restricted cubic splines models with 3 knots were constructed to display the association between log-transformed, standardized BNP concentrations as a continuous variable and the incidence of the rehospitalization over the study period for the overall cohort (A) and stratified by race (B), as well as the trial-eligible cohort (C), and stratified by race (D). The dotted lines reflect the 95% confidence intervals.