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Editorial

Race/ethnicity and plasma NT-proBNP in black and white individuals: How it matters

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Population studies from the United States have established that African ancestry is accompanied by a higher cardiovascular risk, translating in a higher incidence of heart failure (HF) and greater 5-year mortality [1]. This may be, in part, due to more prevalent clinical risk factors for HF/death among Blacks, such as higher rates of hypertension, diabetes mellitus, and obesity and also more frequent genetic predisposition toward earlier and more severe cardiovascular disease.

Notably, ethnic differences in natriuretic peptides (NP), i.e. the established tools for diagnosis and prognostic stratification, which may be present have not been extensively evaluated. This is not insignificant, since NPs promote natriuresis, diuresis, and vasodilation and relative NP deficiency experimentally may lead to myocardial hypertrophy and fibrosis and higher blood pressure, clear risk factors for clinical HF [2]. Studies on 4 general population cohorts (the Atherosclerosis Risk in Communities - ARIC – Study [3], the Dallas Heart Study [4], the Multi-Ethnic Study of Atherosclerosis – MESA [5], and the REasons for Geographic And Racial Differences in Stroke – REGARDS [6]) consistently found that black people show lower NP concentrations. Such relative NP deficiency has thus been considered as a potential contributor to the higher prevalence of hypertension and diabetes among blacks, and may be related to genetic polymorphisms affecting NP expression or processing, such as variants in the *NPPB* gene or the protease corin [4]. Other possible reasons remain elusive, as all studies performed extensive adjustment for factors potentially impacting on NP levels [3–6]. Reassuringly, though ethnic differences may exist in NP concentrations, data have repeatedly shown that N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations are similarly useful for the diagnosis of acute HF in dyspneic subjects and predictive of outcome, regardless of race [7].

In this issue of the Journal, Patel et al. address the issue of ethnic differences in the general population from another perspective, by evaluating the shape of the relationship between NT-proBNP and several variables potentially affecting NP levels [6]. The Authors performed a sub-analysis of the REGARDS study, which enrolled a total of 30,239 black and white individuals from 2003 to 2007 and aimed to investigate racial and geographic differences in stroke among adults aged 45 years or more, self-identifying as non-Hispanic white or black. NT-proBNP was measured in a sample of 4106 individuals (55% female and 41% black). After adjusting for multiple potential confounders, including HF, sex, atrial fibrillation, left ventricular hypertrophy, and diabetes, NT-proBNP displayed a linear increase with age in both black and white individuals, and was 30% higher among women. By contrast, NT-proBNP displayed an almost linear decrease from <20 kg/m^2 to over 50 kg/m^2 BMI in whites, and a U-shaped relationship in blacks, decreasing from <20 kg/m^2 to around 30 kg/m^2, then increasing again in obese individuals. U-shaped curves were observed for NT-proBNP as a function of eGFR, especially in blacks. Finally, NT-proBNP were similarly predictive of outcome in black and white subjects [6].

The Authors should be congratulated for their effort to clarify how NT-proBNP varies based on age, BMI and renal function in black individuals from the general population, which is the necessary prerequisite to correctly interpret NP levels in these subjects. Since obesity affects 38% of men and 57% of women in the US, the shape of the relationship between BMI and NT-proBNP seems particularly relevant. Some caution is advisable before concluding that obese and normal weight black subjects have similar NT-proBNP concentrations, which would represent an exception to the inverse relationship between BMI and NP levels in the general population. Since opposite findings from the Jackson Heart Study have been reported [8], further analyses on other large-scale multiethnic cohorts seem advisable. After elucidating the correlates of circulating NP in blacks and whites, the underlying mechanisms should be explored through dedicated, mechanistic studies.

Lastly, in the present era of neprilysin inhibition—which leads to a pharmacologic rise in NP concentrations—it must be asked whether neprilysin inhibition might be more beneficial in those with relative

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NP deficiency. Given the extremely limited enrollment of black patients into HF clinical trials (e.g. 5.1% in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure - PARADIGM-HF - trial) [9], a much greater attention to ethnic differences in the response to treatment is mandatory. The upcoming Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) study [10], focused on effects of sacubitril/valsartan on ventricular remodeling and symptoms will enroll substantially more Blacks, and provide an opportunity to further examine this question.

Conflict of interest

None.

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