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EDITORIAL

Moving Beyond Self-Reported Race in Our Understanding of Cardiovascular Medicine

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When the US Food and Drug Administration first approved sacubitril-valsartan for patients with chronic systolic heart failure (HF) in 2015, it had been a full 10 years since the last oral therapy approved for HF (hydralazine–isosorbide dinitrate). Sacubitril-valsartan, an angiotensin receptor neprilysin inhibitor (ARNI) combination drug, was heralded as "disruptive" and "a paradigm shift" for patients with HF. However, of the 8442 global participants randomized, only 5.1% (428 total patients) were Black race and 22% were women, mirroring the historical low enrollment of non-White, nonmale participants in clinical trials.[1] Inevitable questions were raised of whether efficacy seen in the trial population would extend to those less well represented. Investigators followed up with 3 trials with US-only populations (PROVE-HF [Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure], PIONEER-HF [Comparison of Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode], and LIFE [LCZ696 in Hospitalized Advanced Heart Failure] trials), and at least 2 with specifically prespecified analyses to evaluate any impact of race. The PIONEER-HF trial, a randomized trial of hospitalized patients with acute HF, enrolled 36% Black patients (316 of 881 patients)[2]; the PROVE-HF trial, an open-label biomarker and ventricular remodeling study, enrolled 22.7% Black patients (178 of 782 patients)[3]; and the LIFE trial, a randomized trial of patients with advanced HF, enrolled 38% Black patients (127 of 335 patients).[4] None showed differential ARNI outcomes influenced by race and ethnicity.[2–4]

See Article by Chapman et al.

This same question has also been investigated in observational data. For example, investigators from the Mayo Clinic evaluated ARNI prescription association with clinical outcomes in US administrative claims data from 2015 to 2018. They found lower hazard of all-cause mortality or all-cause hospitalization with sacubitril-valsartan among White patients but not Black patients, where Black patients represented 21% of their 7893 patient pairs sample.[5] Those authors championed their data as inclusive of "more than 7 times the number of Black patients in PARADIGM-HF and 10 times the number enrolled in PIONEER-HF" and called for "more thorough investigation into potential racial differences in treatment effect and biological mechanisms mediating these differences."[5]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Chapman et al approach an analogous question with data from the CHAMP-HF (Change the Management of Patients With Heart Failure) registry, a prospective, observational cohort of outpatients in the United States with chronic HF with reduced ejection fraction.[6] The authors evaluated ARNI initiation by race and ethnicity with associated changes in health status and clinical outcomes. To minimize bias, the authors used propensity score methods to match 758 ARNI starts with non-ARNI patient pairs. When additional imbalances remain after propensity matching, the covariate values were further adjusted in

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subsequent modeling. The authors conclude that race and ethnicity did not alter the association between ARNI initiation and outcomes, including changes in health status.

The method is sound and elegantly described by the experienced statistical team, and limitations of the database population are well described by the authors. Some key considerations to highlight are that this analysis only evaluated new initiation of ARNI after enrollment in the registry, thus limiting selection bias from factors even less well captured by registry data collection. Patients were also matched by covariates in a time-dependent manner, to account for temporal variation related to participation in a clinical registry.

Sample size still plagues the analysis, however. The 758 matched pairs only represent about 30% of patients in the CHAMP-HF registry (because only 758 patients were newly initiated on ARNI during the time of the registry). In addition, careful readers will note Black patients represented only 17% (131 of 758 pairs) of the analysis population, which is both smaller proportionally and numerically than PIONEER-HF and PROVE-HF trials.[2,3]

Chapman et al deftly supplement the corpus of clinical trial evidence suggesting ARNI effects are not significantly modified by race and ethnicity. Certainly, considering race is a critical facet because Black patients face disproportionate rates of HF hospitalizations as well as HF mortality, and ignoring it will undermine our ability to detect and reduce factors related to health disparities.[7] Nevertheless, we in cardiovascular medicine must actively avoid the trap in assuming that disease incidence or therapeutic response is rooted in “racial” differences. The fact is race is a social construct not based in biology. The human genome project has shown us there is more genetic variation within one so-called race cohort than between 2 such “races.” And in the pursuit of more “personalized” medicine, self-reported race has no basis in the genetic code and serves as a poor substitute for genomic identification. Even in the 1970s, 34% of census respondents changed their self-reported ethnic or racial identity within 2 years.[8] And in the 2020 census, >33 million Americans self-identified as more than one race, and 5.8 million identified as Black and another race group. The larger question is whether anyone truly believes in a clinical question of "with [holding ARNI] on the basis of race/ethnicity alone" (as the authors write)? And if so, will this article change their minds?

ARTICLE INFORMATION

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Dr Luo reports consulting from AstraZeneca and Pfizer. She has also recently (within 3 years) collaborated with Adrian Hernandez and Gregg Fonarow, two authors of the related article by Chapman et al published in *JAHA*.

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