Heart Failure Prevention Is the Best Option To Stem High Costs and Disease Burden
Research for More Effective Heart Failure Treatment Is Needed

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In this issue of Circulation: Cardiovascular Quality and Outcomes, Okin and colleagues1 report on the incidence of heart failure in a cohort of patients with hypertension enrolled in the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. This study, an international randomized trial, demonstrated that losartan, when compared with atenolol, provided superior reduction of events in high-risk patients with hypertension and no history of heart failure before enrollment.2 Over a 5-year follow-up period, the incidence of heart failure in blacks was 7%, significantly higher than the 3.1% incidence rate found in nonblack patients. This difference persisted even when appropriately adjusted for differences such as the heavier risk factor burden, younger age, sex, renal disease, diabetes mellitus, randomized treatment, incident myocardial infarction, in-treatment QRS duration, strain and left ventricular hypertrophy as measured by ECG, and diastolic and systolic pressure. Additionally, an echocardiographic substudy demonstrated adverse differences in left ventricular structure and performance after 2 years of antihypertensive therapy in blacks compared to nonblacks.

These findings are consistent with several previous reports detailing heart failure differences in blacks, who, when receiving their diagnosis of heart failure, are younger; have greater risk factor burden; are more overweight; and are more likely to have diabetes, renal disease, less coronary disease, and higher heart failure-related hospitalization and death rates than whites.3,4 Unique in this report is that the cohort is entirely high-risk patients with hypertension. The small numbers of black participants (497) compared with white participants (8199), and thus, small numbers of new heart failure cases in blacks, is an important recognized limitation.

The definition of heart failure relied on predefined hospital-based criteria and confirmatory evidence of heart failure as a cause of death. Blacks more often have impaired medical access, and thus may be less likely to be in a hospital to have their heart failure identified. These factors suggest that the observed heart failure incidence may be low in the study by Okin et al,1 and therefore, the observed black versus nonblack disparity may be underestimated by the analyses. The findings of an accelerated rate of ventricular structural change and dysfunction despite treatment and adjustments for risks suggest unrecognized and unique or common disease mechanisms in black patients with hypertension. Okin et al offer compelling evidence for 2 separate but complementary imperatives: (1) Aggressive programs to prevent heart failure are needed, and (2) a robust research agenda should include investigations of the accelerated myocardial dysfunction observed in some black patients with hypertension.

First, the urgent need for effective prevention of heart failure could not be clearer. As suggested by Okin et al,1 heart failure is more common and deadly in black patients with hypertension.3,5,6 Aggressive prevention in high-risk (and all at-risk) patients is imperative. In fact, current reviews of heart failure therapy acknowledge that the greatest opportunity to reduce the high healthcare costs, morbidity, and mortality is heart failure prevention.7,8 By far, treatment of hypertension is the most effective strategy for preventing heart failure. Each 5-mm Hg reduction in systolic blood pressure reduces the overall risk of heart failure by 24%.8 Treatment of conventional cardiovascular disease (CVD) risk factors, including smoking, physical inactivity, being overweight, dyslipidemia, and diabetes mellitus, provides added risk reduction. Antihypertensive regimens are effective in reaching and maintaining target blood pressure with few side effects and good long-term adherence.9 Unfortunately, despite continued improved awareness of the risks of hypertension and the benefits of blood pressure control by treatments to maintain target blood pressure ≤140/90 mm Hg in reducing risk of complications, current rates of blood pressure control are unacceptable, with <50% of treated patients reaching target blood pressure.10 It is alarming that, despite having disproportionate end-organ damage at every stage of hypertension, control rates for black patients with hypertension are below the average, with 35.3% of men and 45.3% of women achieving target blood pressure.5,10 Similarly, despite high awareness of the risks and benefits of control of other conventional cardiovascular risk factors, which are highly prevalent and can be managed by lifestyle or drug treatments that are effective and well tolerated with excellent long-term
adherence, blacks are consistently undertreated and experience disproportionate disease burden. A National Heart, Lung, and Blood Institute-initiated program to improve hypertension control rates in blacks supports several community-based projects and offers multiple strategies.\textsuperscript{11} The results of this program are not yet reported. Aggressive programs to prevent CVD, and thus heart failure, by controlling conventional cardiovascular risk factors, especially hypertension, will decrease burden of disease for all patients at risk.\textsuperscript{12} Prevention programs that target high-risk blacks are urgently needed.

The second imperative—to identify novel mechanisms of heart failure in black patients with hypertension—is also important. Blacks have the highest prevalence of hypertension in the United States, and black patients with heart failure have more hypertension and less coronary disease.\textsuperscript{13} Among otherwise similar patients with hypertension, why should some black patients have an accelerated progression of myocardial dysfunction and heart failure? Investigations of potential alternate disease pathways may offer new insight or strategies for antihypertensive and myocardial protective therapeutic targets.

Elucidating mechanisms of heart failure is the Holy Grail for many established and emerging basic and clinical investigators. Racial differences in response to drug treatment have gained interest in treating heart failure. Some well-documented examples include response to diuretics, \textit{\beta}-adrenergic blockade, and angiotensin-converting enzyme (ACE) inhibitors, and all have been evaluated with the hope of identifying mechanisms for observed differences and how these might affect patient management.\textsuperscript{14} Pharmacogenomics is an emerging field of high interest and may provide an opportunity for tailoring pharmacological intervention to individual or population characteristics in the treatment of heart failure.\textsuperscript{15} Indeed, the differential changes in left ventricular structure and function observed in black LIFE participants, which cannot be accounted for by known differences in risk factors, might be explained by genetic variation in disease mechanisms. This finding should spark further investigation. However, the context of race for elucidating disease mechanisms has proven problematic. Using self-identified race is imprecise and not biological. Most studies that suggest racial differences have been based on retrospective analyses.\textsuperscript{16}

Racial differences in response to vasodilator therapy were noted in the first Vasodilator Heart Failure Trial (V-HeFT), in which isosorbide dinitrate and hydralazine improved survival in patients with heart failure compared with placebo.\textsuperscript{17} A retrospective analysis of V-HeFT demonstrated a beneficial signal in blacks compared to whites. Subsequently, in V-HeFT II, blacks demonstrated greater benefit from isosorbide dinitrate and hydralazine than from an ACE inhibitor, whereas whites had a greater improvement with an ACE inhibitor compared to isosorbide dinitrate and hydralazine. There was no placebo comparison in V-HeFT II.\textsuperscript{18} The V-HeFT trials led to the landmark African-American Heart Failure Trial (A-HeFT). A-HeFT demonstrated a 43\% reduction of mortality in self-identified African American participants with class III/IV heart failure by adding a fixed-dose combination isosorbide dinitrate and hydralazine to guideline medical treatment and led to the first-ever approval by the Food and Drug Administration of a heart failure therapy in a specific racial subset.\textsuperscript{19} However, few eligible patients receive this therapy.

Blacks experience a disproportionate burden of CVD. Since the 1986 Department of Health and Human Services Secretary’s report on black and minority health,\textsuperscript{20} documenting and combating CVD in blacks and other minority populations has been a priority in federally supported research, health education outreach, demonstration and prevention projects, and research programs aimed at reducing health disparities. Consistent with overall cardiovascular trends, death rates from heart disease have steadily declined since the 1960s in all US populations, including blacks. Despite these improvements, blacks continue to have excess CVD morbidity and mortality compared with whites, including higher death rates for hypertension, coronary heart disease, stroke, and congenital heart disease.\textsuperscript{10} For example, the overall death rate from CVD in 2007 was 251.2 per 100 000 patients, whereas the rate for black men was 405.9 per 100 000 patients, and for black women, 286.1 per 100 000 patients.\textsuperscript{10} CVD is the leading cause of a death for all US populations, so even small differences in disease risk and outcomes exact a large burden of disability and death. Reducing health disparities remains a challenge not only because of incomplete knowledge, but also because we have not fully applied what we already know.

The implications of racial differences have become an albatross for the patient and provider. The biological significance of race is correctly suspect because race is a social construct, a proxy for socioeconomic and environmental factors, and without a common gene pool. Historically, race and ethnicity have been exploited, even in medicine, to promote or provide a rationale for unjust practices.\textsuperscript{21} Providers often are not comfortable discussing race with their patients. Black patients, having appropriately learned to question the notion of “separate but equal,” are reluctant to accept treatments marketed for blacks, regardless of the strength of the science. Public health officials, investigators, providers, and patients cannot afford to be ambivalent about identification and aggressive treatment of high-risk profiles, including evaluation of the role of race. Discomfort, lack of trust, and suspicion are regrettable and will keep us mired in past failures. Aggressive heart failure prevention programs can begin immediately and will quickly save lives and reduce healthcare costs. A robust research agenda, including investigation of the influence of race on disease manifestations and treatment, will require more time to improve therapeutic options. Even though it may be difficult, meeting the public health imperative to reduce disability and death in blacks is both feasible and correct.

Disclosures

None.

References


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