Race-Based Therapeutics

Clyde W. Yancy, MD

Corresponding author
Clyde W. Yancy, MD
3500 Gaston Avenue, Suite H-030, Dallas, TX 75246, USA.
E-mail: clydey@baylorhealth.edu

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The issue of race in medicine is problematic. Race is not a physiologic grouping, and all persons of a given race do not necessarily share the same clinical phenotype or genetic substrate. Despite clear signals that certain risk factors and diseases vary as a function of race, translating those differences into race-based therapeutics has been awkward and has done little to change the natural history of cardiovascular disease as it affects special populations. Among the varied special populations, the African American population appears to have the most significant and adverse variances for cardiovascular disease as well as worrisome signals that drug responsiveness varies. Recent guideline statements have now acknowledged certain treatment options that are most appropriate for African Americans with cardiovascular disease, especially hypertension and heart failure. As more physiologic markers of disease and drug responsiveness become available, the need for racial designations in medicine may lessen, and therapies can be optimized for all patients without regard to race or ethnicity.

Introduction

The issue of race is both a paralyzing and polarizing factor in American society. Akin to society in general, the practice of medicine is not immune to the awkward environment that race creates. The use of race in medicine must be done so with care, as references to race may only serve to further polarize and disadvantage those already at greatest risk. The suggestion that self-identified race imparts any physiologic significance is a controversial concept, if not a frankly errant thought process. Race alone determining the natural history of disease or responsiveness to medical therapy is similarly debatable. Race has no identified genetic basis but rather is an acknowledgement of similar socialization patterns and shared cultural experiences.

Nevertheless, epidemiologic surveys have consistently identified clusters of risk factors and a constellation of disease profiles that are aligned along racial designations. Several racial groups appear to be disproportionately affected by these maldistributed risk factors and diseases. These special populations include African Americans, Hispanic Americans, Asians and Pacific Islanders, and Native Americans.

Of these groups, African Americans experience the highest rates of mortality from heart disease, a rate that is 1.6 times that of Caucasians [1]. The average annual death rate due to heart disease expressed as deaths per 100,000 in the 45- to 64-year-old age range is 404 for African Americans, 219 for Caucasian Americans, 188 for Native Americans, 143 for Hispanic Americans, and 90 for Asians and Pacific Islanders. For the 65- to 74-year-old age range, the corresponding numbers are 1278 for African Americans, 871 for Caucasians, 650 for Native Americans, 614 for Hispanic Americans, and 443 for Asians and Pacific Islanders [2].

The prevalence of coronary heart disease is higher in African Americans, with prevalence rates of 7.1% and 9.0% for men and women, respectively, compared with 6.9% and 5.4% for Caucasian men and women. Death rates per 100,000 due to coronary heart disease are 272 and 193 for African American men and women, compared with 249 and 153 for Caucasian men and women [2]. Death rates from stroke are also higher in African Americans. Compared with Caucasians, young African Americans have a threefold increased risk of ischemic stroke and a fourfold increased risk of stroke-related death. The prevalence of coronary heart disease in Mexican Americans is 7.2% and 6.8% for men and women. The prevalence rates of myocardial infarction are 4.1% and 1.9% for Mexican-American men and women, compared with 5.2% and 2.0% for Caucasian men and women and 4.3% and 3.3% for African American men and women experiencing a myocardial infarction. Death rates are similar for Hispanic Americans and Caucasians [2].

The disease burden borne by special populations is considerable, and despite the awkwardness of using race as a treatment variable, unique attention must be focused on these special populations. Based on the foregoing data, the population with the greatest evidence of a disproportionate disease burden and disproportionate distribution of risk factors is the African American population. The remainder of this discussion regarding race-based therapeutics focuses on this cohort.

The Disproportionate Impact of Hypertensive Cardiovascular Disease in African Americans

The intensive treatment of hypertension to target levels in African American patients is of extreme importance. Hypertension in African Americans develops earlier in life and tends to be more severe, increasing the risk for hypertension-related complications, including an increased risk of nonfatal stroke (RR, 1.3), fatal stroke (RR, 1.8), heart disease death (RR, 1.5), and end-stage kidney disease (RR, 4.2) [3•]. Hypertension is also strikingly associated with left ventricular dysfunction leading to heart failure in African Americans, accounting for approximately 30% to 60% of cases of heart failure [4].

Hypertension independently increases the risk of cardiovascular events: as blood pressure (BP) increases, the risks of heart failure, myocardial infarction, and stroke also increase. Conversely, antihypertensive therapy is associated with a 35% to 40% reduction in stroke, a 20% to 25% reduction in myocardial infarction, and a more than 50% reduction in heart failure [5]. These observations represent a strong imperative for therapy, but hypertension remains undertreated. Data from the NHANES, 1988 to 1991, demonstrate that less than 25% of patients with hypertension had their BP controlled; this percentage increased in 2000 to approximately 31%. In addition, less than 50% of patients with hypertension and diabetes were being controlled to a BP less than 140/90 mm Hg, and only 25% of those patients achieved goal BP reductions to less than 130/85 mm Hg [6].

Race-Based Therapeutics: Hypertension

Treatment guidelines

Effective management of hypertension involves lowering BP to a target goal instead of merely lowering BP, and physicians should use this measure to gauge the effectiveness of therapy. Reducing BP to less than 140/90 mm Hg, although adequate for the general population, is inadequate for patients with diabetes or renal disease or for African Americans. These patients should have a target goal of 130/80 mm Hg or lower, and some clinicians even suggest targets as low as 120/80 mm Hg [5]. In the management of hypertension, increased risk necessitates a greater imperative to reach lower target BP goals.

The seventh report from the JNC VII recategorized hypertension. These new guidelines simplified the categorization and lowered the initial threshold of hypertension. Individuals with BP previously considered normal (120 to 129/80 to 84 mm Hg) and borderline (130 to 139/85 to 89 mm Hg) in JNC VI are now classified to have prehypertension. Patients with BP 140 to 159/90 to 99 mm Hg are still classified to have stage 1 hypertension, but those with a BP of 160/100 mm Hg are now considered to have stage 2 hypertension. In addition, epidemiologic evidence suggests that systolic BP is a more important risk factor than diastolic BP, resulting in the recommendation that practitioners focus on treating systolic BP to target levels, particularly in persons less than 50 years of age [5,7].

JNC VII digressed further from the traditional stepped care approach by acknowledging that certain compelling indications warranted combination or multidrug regimens, typically with agents shown to affect the specific concomitant illness [5]. Given the burden of hypertension and the incidence of end-organ disease, African American race may represent a compelling indication, warranting a lower threshold for considering multidrug or combination regimens.

Pharmacologic management of hypertension in African Americans

The chief objective of therapy for the high-risk African American patient is achieving and maintaining a target BP goal. Evidence shows that even slightly elevated BP, either diastolic or systolic, significantly increases the risk of morbidity and mortality. In the UKPDS, patients with diabetes randomized to therapy to achieve tight BP control (144/82 mm Hg) had a significantly lower incidence of heart failure (56% risk reduction; $P = 0.0043$) and nonfatal stroke (44% risk reduction; $P = 0.013$) than those who achieved less stringent BP control (154/87 mm Hg) [8].

Although all antihypertensive agents lower BP in African Americans, and simple regimens appear to work best at reducing cardiovascular outcomes, certain drug classes may have unique cardioprotective effects that would be beneficial in the higher risk hypertensive patient. Clinical evidence suggests that angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and β-blockers may offer benefits beyond simply lowering BP in patients with certain comorbid cardiovascular or metabolic conditions.

Monotherapy with a thiazide diuretic is the preferred strategy for any uncomplicated hypertensive patient, regardless of race. However, monotherapy with other agents and drug classes may be more or less effective as a function of race. In the ALLHAT, which included more than 10,000 African Americans, ACE inhibitors were less effective than either a thiazide-type diuretic or a calcium channel blocker. African American patients randomized to an ACE inhibitor had a 40% greater risk of stroke, a 32% greater risk of heart failure, and a 19% greater risk of cardiovascular disease (CVD) than those randomized to a diuretic. However, the interracial differences in BP lowering observed with these drugs disappeared when they were combined with a diuretic [9]. This observation from ALLHAT should carry over into the clinical domain.

The JNC VII guidelines recommend that most patients receive first-line therapy with thiazide diuretics, but the majority of patients will require greater than or equal to two antihypertensive agents to achieve adequate BP control [5]. In the AASK, an average of three antihypertensive agents was needed to achieve target BP goals (mean arterial pressure, 102 to 107 or < 92 mm Hg) [10]. Combination therapy may be used in most patients, may

Table 1. A summary of treatment recommendations from the ISHIB hypertension guidelines

Uncomplicated hypertension: goal BP* reduction < 140/90 mm Hg	
BP < 155/100 mm Hg	Use monotherapy†; start with a thiazide diuretic.‡ If uncontrolled, then add a second agent, increase dosage or intensify lifestyle changes.‡
BP > 155/100 mm Hg	Use combination therapy.‡§ If uncontrolled, then add a third agent, increase dosage of the other agents or intensify lifestyle changes.‡
Complicated hypertension: goal BP* reduction < 130/80 mm Hg (especially with diabetes or nondiabetic renal disease and proteinuria)	
BP < 145/90 mm Hg	Use monotherapy† or combination therapy using a RAS blocker.‡§ If uncontrolled, then add a second agent from a different class or increase dosage.‡
BP > 145/90 mm Hg	Use combination therapy with a RAS blocker.‡§ If uncontrolled, then increase dosage or add a third agent from a different class.‡

*Preferable BP goal for patients with renal disease with proteinuria > 1 g per 24 h is < 125/75 mm Hg.
†Initiate monotherapy at the recommended starting dose with an agent from any of the following classes: diuretics, β-blockers, CCBs, ACE inhibitors, or ARBs.
‡Consider specific clinical indications when selecting agents.
§To achieve BP goals more expeditiously, initiate low-dose combination therapy with any of the following combinations: β-blocker/diuretic, ACE inhibitor/diuretic, ACE inhibitor/CCB, or ARB/diuretic.
ACE—angiotensin-converting enzyme; ARB—angiotensin II receptor blockers; BP—blood pressure; CCB—calcium channel blockers; ISHIB—International Society on Hypertension in Blacks; RAS—renin-angiotensin system.
(*Data from* Douglas et al. [12].)

have synergistic effects that improve BP control, may improve medication compliance, and may reduce the risk of dose-related adverse effects [5,11]. While calcium channel blockers and diuretics have been shown to be the most effective therapies for lowering BP in the African American patient, the patient at high risk for CVD should also be considered for therapy with cardioprotective agents, such as ACE inhibitors, ARBs, and β-blockers that have been shown to provide greater protection against end-organ damage. This protection is the ultimate rationale for their inclusion in antihypertensive therapy. However, combination therapy should be initiated at a lower BP threshold in the African American hypertensive patient than in the Caucasian hypertensive patient. The recently published ISHIB guidelines should serve as the guideline for therapy of African American hypertensive patients [12]. Table 1 provides a summary of treatment recommendations from the ISHIB hypertension guidelines.

The Disproportionate Impact of Heart Failure in African Americans

Despite significant advances in therapy, heart failure remains a disease state associated with significant morbidity and mortality. At the age of 40, the estimated lifetime risk of developing heart failure is as high as 40%, depending on the presence of uncontrolled hypertension or other morbid cardiovascular conditions [3•]. The deleterious effects of an activated neurohormonal system in response to left ventricular dysfunction have proven to be responsible for disease progression, and treatment strategies to counteract these actions (eg, ACE inhibitors and β-blockers) are now associated with notable reductions in systolic heart failure hospitalizations and improvement in overall survival [13]. However, a fundamental question arises: do all patient populations benefit similarly from the advances noted in systolic heart failure management?

African Americans continue to have a disproportionately higher prevalence of heart failure when compared with Caucasians [13,14]. Systolic heart failure in African Americans is less likely to correlate with a burden of coronary artery disease but is more likely to be associated with younger age and the presence of hypertension [15]. The etiology of left ventricular dysfunction leading to systolic heart failure differs in African Americans, and the responsiveness to medical therapies may differ as well.

Effects of drug therapy in African Americans with heart failure are difficult to interpret. A major obstacle prohibiting the interpretation and evaluation of heart failure therapy in African Americans is the inadequate representation of African Americans in clinical trials. Data pertaining to drug effect and outcome of heart failure in African Americans have unfortunately been based on post hoc analyses, which fail to have sufficient power to detect meaningful endpoints within this group. The evidence for most systolic heart failure drug therapy in African Americans is speculative at best. Even so, no data suggest that evidence-based therapies are ineffective; treatment of heart failure in African Americans should follow guideline-based care. In other words, no evidence to date suggests that such a management plan is not equally beneficial for African Americans as it would be in all other patients [13,15].

Of all of the proven adjunctive treatment regimens that have been evaluated for evidence of efficacy in patients with systolic heart failure, the vasodilators have emerged with the strongest signal of benefit for African

Americans. Through post hoc analyses of the earlier vasodilator trials, a hypothesis-generating concept led to the landmark A-HeFT, which demonstrated a striking benefit of isosorbide dinitrate with hydralazine (ISDN/HYD) as combination therapy in African Americans with systolic heart failure [16•].

Race-Based Therapeutics: Heart Failure

ACE inhibitors

Activation of the renin-angiotensin-aldosterone system is a hallmark of heart failure and correspondingly a target of therapy. ACE inhibitors, by blocking activation of this system, reduce BP and slow the progression of heart failure. The seminal heart failure trials establishing the benefit of ACE inhibitors had few African Americans, but the SOLVD was among the first to separately describe the African American cohort. The SOLVD investigators suggested that heart failure outcomes might differ as a function of race [14,17]. A post hoc analysis of the primary trial results demonstrated that mortality from heart failure was higher in African Americans, with a 1.8-fold increase for African American men and a striking 2.4-fold increase for African American women [14]. These data persisted even after adjusting for educational level and measures of financial stress, which are both crude but quantifiable measures of socioeconomic status. A subsequent reanalysis that adjusted for the degree of left ventricular dysfunction and for trial participation (ie, SOLVD Prevention or SOLVD Treatment trial) yielded no differences in mortality but showed a significantly higher risk (44%) for hospitalization in the African American patients, compared with Caucasian patients ($P = 0.005$) [17]. A suggested clinical explanation for this apparent lower responsiveness to the ACE inhibitor enalapril was the lack of a BP-lowering response at the doses used in the trial in African Americans, compared with that of others. These observations would be consistent with a broad statement that ACE inhibitors are less effective, but not absent in effect, in African Americans.

The randomized placebo-controlled HOPE studied the effect of 5 years of treatment with ramipril in patients with evidence of vascular disease or diabetes plus one additional risk factor. The primary end point was a composite of cardiovascular mortality, myocardial infarction, and stroke. Despite only small BP differences by the study end (136/76 mm Hg compared with 139/77 mm Hg for ramipril and placebo, respectively), patients receiving ramipril had a 22% reduced risk of the primary end point ($P < 0.001$), with significant reductions in the risk of cardiovascular mortality, myocardial infarction, stroke, and especially heart failure [18]. Unfortunately, the number of African Americans in HOPE was insufficient to allow extrapolation of these results to the higher-risk African American patient.

ARBs

Recent trial evidence has shown that ARBs, which inhibit the action of angiotensin II by blocking its angiotensin II type 1 receptors, are clearly appropriate in ACE-intolerant patients and represent a reasonable a priori alternative to the use of ACE inhibitors for heart failure, especially given another appropriate indication to be on an ARB (eg, hypertensive heart disease, especially with renal insufficiency). The issue regarding responsiveness to angiotensin-receptor antagonists (ARBs) in African Americans with heart failure is unclear, as unpublished data from the Val-HeFT [19] suggested that African Americans randomized to the ARB did not demonstrate the same degree of efficacy as the overall patient population (Personal communication, Cohn). The data referable to African Americans are similarly lacking in the CHARM investigations of the role of candesartan in heart failure [20]. Even in one of the largest hypertension trial testing ARBs, the VALUE trial, only 4% of subjects were African American [21]. An ARB may be a good candidate as a primary or adjunctive agent in the African American patient with heart failure or high-risk hypertension, but this recommendation is based on little race-specific data regarding the use of ARBs.

β-Blockers

Conflicting data points have also emerged from the clinical trial experience with β-blockers. A recent RAND Corporation (Santa Monica, CA) meta-analysis incorporated data reported by race from the major published β-blocker trials in heart failure [22]. Whereas the aggregate benefit of β-blockers for the Caucasian population was a 31% reduction in mortality, the apparent benefit of β-blockers in African Americans was only 3%.

These unfavorable data are heavily influenced by the negative outcomes from the BEST [23]. Within this trial that evaluated the effect of bucindolol on survival in patients with advanced heart failure, no apparent benefit was realized in the African American cohort, but a benefit was seen in the Caucasian cohort. However, the magnitude of that benefit was approximately 50% less than that typically seen in prior trials with β-blockers. Subsequent data have since emerged to confirm that bucindolol has partial intrinsic sympathomimetic activity and, as such, represents an unfavorable β-blocking agent for heart failure [24]. Nevertheless, an apparent difference in the benefit of β-blocker therapy in African Americans compared with Caucasians raised the concern that African Americans with heart failure exhibit lesser responsiveness to β-blockers.

The experience with carvedilol has been quite different and varies substantially from the observations seen with bucindolol. In both the US Carvedilol Heart Failure Trials program and the COPERNICUS, retrospective analyses by ethnicity showed statistically significant benefits with carvedilol [25,26]. The US Carvedilol Heart Failure Trials program demonstrated that the combination of carvedilol and an ACE inhibitor yielded similar outcomes in both

African Americans and non-African Americans [25]. For both groups, the reduction in the progression of heart failure, defined as death due to heart failure, hospitalization for heart failure, or worsening symptoms requiring augmented medical therapy, was greater than 50%. These benefits were supported by observations of similar improvements in measures of left ventricular function and similar hemodynamic effects on heart rate and BP [25]. Thus, therapy with the combination of ACE inhibitors and carvedilol was demonstrated to be effective in African American patients. Whether these benefits are limited to carvedilol remains unclear. Data from the MERIT-HF are inconclusive, because too few African Americans were included in this trial of nearly 4000 people [27].

More evidence is emerging that β-blockers may have a role in preventing arrhythmias. The use of β-blockers as antiarrhythmic agents should be not overlooked in the African American population. Sudden death may be more common in young African Americans, and β-blockers are one of the few therapies that have been shown to reduce the incidence of sudden death [28,29]. Arrhythmias and sudden death are common after a myocardial infarction and in the setting of heart failure. A blinded post hoc analysis of arrhythmic events identified from the adverse events database of the placebo-controlled CAPRICORN trial showed that carvedilol had a markedly beneficial effect on arrhythmias when added to an ACE inhibitor [30]. A similar analysis of the MERIT HF data in class II heart failure confirmed a nearly 50% reduction in the risk of sudden cardiac death in patients on long-acting metoprolol succinate [27].

Overall, the practitioner should not be hesitant in prescribing evidence-based β-blocker therapy to African Americans with heart failure. As an example, in the community-based COHERE, carvedilol treatment had similar results in reducing hospitalizations, heart failure, and death in African American and Caucasian patients [31]. http://www.acc.org/qualityandscience/clinical/guidelines/failure/indexupdate101705_pkt.pdf provides a synopsis of evidence-based therapy for heart failure [13].

Vasodilator Therapy in Heart Failure

Prior to 1980, the effects of vasodilator therapy on heart failure were not well understood. The V-HeFT I was the first double-blind randomized controlled trial to examine the benefit of vasodilator therapy in heart failure [32]. The initial hypothesis addressed abnormal loading conditions in heart failure that were presumed to be responsible for hemodynamic compromise and further progression of symptoms in patients with heart failure. The choice of ISDN/HYD was based on the ability of this combination to reduce preload (venodilation) and afterload (arterial dilation), similar to the effects seen with nitroprusside [33]. The V-HeFT I study enrolled 642 men, of whom 180 (28%) were African American. All participants received ISDN/HYD combination (n = 186), prazosin (n = 183), or placebo (n = 273). The average dose of ISDN/HYD combination was 136 mg and 270 mg, respectively. Approximately 55% of the ISDN/HYD group achieved the maximum dose (160 mg of ISDN and 300 mg of HYD). The mean period of follow-up was 2.3 years. At 1 year, a 38% reduction in mortality was observed for the patients receiving ISDN/HYD, compared with placebo (12.1% vs. 19.5%, respectively). At the end of the prespecified time point of 2 years, a 25% reduction in mortality was observed (25.6% for the ISDN/HYD group, compared with 34.3% for the placebo group; $P < 0.028$). The prazosin group had a mortality rate that was similar to the placebo group. At the end of the trial, the overall cumulative mortality reduction for the ISDN/HYD group was of borderline statistical significance ($P = \sim 0.05$) [32].

After the results of the V-HeFT I, the effects of the ISDN/HYD combination therapy were further evaluated in the V-HeFT II against an ACE inhibitor, enalapril [34]. The V-HeFT II trial enrolled 804 patients and compared the use of ISDN/HYD (maximum dose 160 mg and 300 mg, respectively, divided into four daily doses) with enalapril (maximum dose 20 mg daily). At the prespecified endpoint of 2 years, enalapril reduced mortality 28% more than the ISDN/HYD therapy. Although death from worsening heart failure did not differ between the groups, a significant reduction in sudden cardiac death with enalapril was observed, compared with the ISDN/HYD group. The results from this study suggested that enalapril was superior to ISDN/HYD therapy for improving survival in patients with mild to moderate heart failure [34].

Racial Differences in Response to Vasodilator Therapy: Lessons from V-HeFT I and II

As the studies of vasodilator therapies in heart failure developed, a specific signal of differentiation between African Americans and Caucasians appeared. A post hoc analysis of V-HeFT I and II revealed a striking difference in outcomes in African Americans who were administered ISDN/HYD therapy [35]. In V-HeFT I, a 47% reduction in mortality for African Americans receiving ISDN/HYD combination was observed, compared with African American patients in the placebo group (9.7% vs. 17.3%, respectively; $P = 0.04$). When the use of ISDN/HYD was compared with enalapril in African American patients from V-HeFT II, no significant difference in mortality was found (12.9% vs. 12.8%, P = not significant). However, the Caucasian patients had a 26% reduction in mortality with the use of enalapril when compared with the Caucasian patients receiving ISDN/HYD therapy (11% vs. 14.9% respectively, $P = 0.02$) [35]. The reasons for these findings of differential response in V-HeFT I and II were not well understood at the time. Several baseline differences in the African American patients were observed when compared with their Caucasian counterparts.

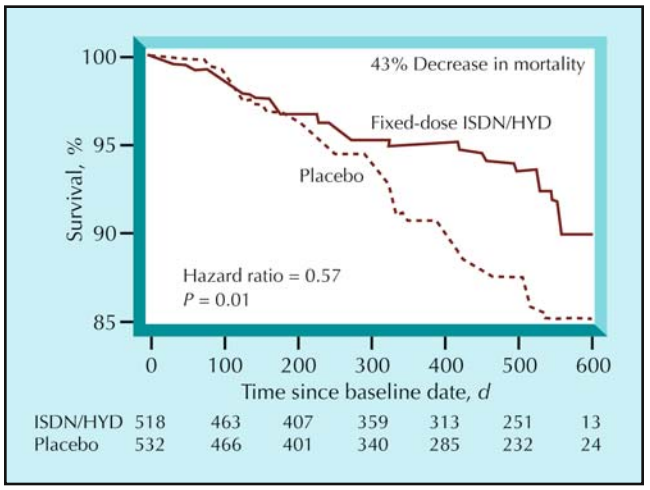

Figure 1. A-HeFT: overall survival. Although mortality was not a primary endpoint of A-HeFT, this prespecified component of the primary composite endpoint was markedly positive, with an additional 43% reduction in the risk of death over placebo. Note that the risk of death on background therapy of ACE inhibitor/ARB and β-blocker therapy was as predicted, and the benefit of ISDN/HYD is clearly adjunctive and substantial. A-HeFT—African American Heart Failure Trial; ACE—angiotensin-converting enzyme; ARB—angiotensin II receptor blockers; ISDN/HYD—isosorbide dinitrate plus hydralazine.

African American patients were younger, had less CAD, and had a significantly higher incidence of hypertension (V-HeFT II only). Interestingly, the Caucasian patients had higher plasma norepinephrine when compared with the African American patients, although no difference in renin activity between groups was found. Patients with uncontrolled hypertension or hypertension requiring more than diuretic therapy were excluded from both V-HeFT I and II. An antihypertensive effect cannot be presumed to be the rationale for the enhanced responsiveness seen with combined vasodilator therapy.

The A-HeFT

These observations of unique responsiveness to combined vasodilator therapy in African Americans with heart failure were confirmed in the A-HeFT [16•]. In this randomized, double-blind, placebo-controlled trial of 1040 African American patients with class III HF, the adjunctive use of a fixed dose combination of ISDN/HYD (BiDil; NitroMed Inc., Lexington, MA) resulted in significant improvement of a composite endpoint that consisted of total mortality, heart failure hospitalizations, and quality of life. Each component of the composite was favorably and statistically improved and included the following: a 43% additional reduction in mortality on top of ACE inhibitor and β-blocker therapy, a substantial reduction in the time to first hospitalization, and a significant improvement in measures of quality of life (Fig. 1). As seen in other trials, the African American cohort with heart failure was noted to have a lesser likelihood of ischemic heart disease as a cause of left ventricular dysfunction, a much greater association of hypertension and heart failure, a higher mean body weight, higher BP, and younger age. The most frequent side effect was headache, but this required cessation of therapy in less than 10% of patients. The study ended prematurely due to the presence of a significant benefit on protocol therapy, but the magnitude of the survival advantage is consistent with that seen in the prior vasodilator trials and seen yet again in the recently reported African American Heart Failure Extended Access Trial [36]. Within the A-HeFT, the annual mortality rate due to heart failure in patients with New York Heart Association class III was approximately 6%, the lowest yet seen for this disease severity. Thus, the favorable effects of combined vasodilator therapy are felt to be reproducible and significant.

Nitric Oxide Homeostasis: A New Mechanism of Disease and a New Therapeutic Target

The effects of nitric oxide (NO) and its relationship to endothelial function in African Americans represent an attractive hypothesis to explain this apparent unique responsiveness seen in African Americans. Previous studies evaluating the response of innate vasodilatory stimuli on forearm arterial resistance suggested differential effects between African Americans and Caucasians [37]. Cardillo et al. [38] evaluated the racial differences in NO-mediated vasodilation on forearm arterial resistance in relation to mental stress on normal patients. Mental stress, in the form of serial seven subtractions, was used as a standard measure to increase forearm blood flow. The increase in forearm blood flow was easily demonstrated in the Caucasian subjects but not in the African American subjects. Use of a NO-synthesis inhibitor NG-monomethyl-L-arginine (L-NMMA) infusion significantly reduced forearm blood flow in Caucasian patients, whereas the forearm blood flow in African American patients was unaffected. Results of this study suggested impaired NO-related vasodilatory action of endothelial and smooth muscle cell function in African Americans, a finding that implicates endothelial dysfunction in this group of patients [38].

More recent data evaluating the use of methacholine, a parasympathetic agonist, in patients with hypertension also demonstrated less vasodilatory response of forearm blood flow in African American patients, compared with Caucasian patients [37]. These results echoed the previous findings suggesting impaired endothelial vasomotor function in African American patients. Even in healthy individuals, provocative data suggest reduction in endothelium-derived NO bioavailability in African Americans, compared with Caucasians [39]. Moreover, these data are accompanied by findings that suggest increased oxidative stress (ie, increased production of superoxide and peroxynitrite), further increasing the likelihood of endothelial impairment in African Americans.

Extrapolation of these findings may implicate the effects of reduced NO bioavailability on myocyte function. NO is generated by the NO synthases (NOS) neuronal NOS, inducible NOS, and endothelial NOS (eNOS), which convert L-arginine to L-citrulline in the presence of molecular oxygen, nicotinamide-adeninine dinucleotide phosphate, calmodulin, and other cofactors [40]. Dysfunctional endothelium hinders the production and bioavailability of NO, which increases the production of reactive oxygen species and oxidative stress. Reduced concentrations of NO cosubstrates, such as L-arginine, promote inactivation of eNOS and one electron reduction of O_2 to O_2^-, also known as superoxide. Increased production of O_2^- further increases oxidative stress by reacting with available NO to form peroxynitrite [41,42]. Production of peroxynitrite is associated with proapoptotic effects, possibly contributing to increased ventricular remodeling and impairment of systolic function. NO is also responsible for antihypertrophic effects, primarily mediated by cGMP-dependent protein kinases [43]. Overexpression of eNOS has been demonstrated to reduce myocyte hypertrophy after myocardial infarction in animal models, suggesting greater antihypertrophic effects with increased production of physiologic levels of NO [44]. Total eNOS protein appears to be increased in African Americans, but biologically active NO production is lacking [42]. Reduced NO bioavailability may alter myocyte function and increase cardiac hypertrophy. However, these concepts are controversial, as higher or "supernormal" levels of NO, which are perhaps related to inducible NOS activation, appear to induce caspase activation, DNA fragmentation, and cell death [43]. This is a thought-provoking hypothesis, as the majority of evidence suggests that a relative NO deficiency is present in African Americans, possibly contributing to the burden of CVD. The use of ISDN/HYD therapy may indeed replete NO in this group, possibly altering steady state NO balance without causing the deleterious cellular effects [41].

These preliminary data suggest impairment in NO production as well as endothelial dysfunction and a proapoptotic milieu in African Americans serve as potential mechanisms for several vascular complications, including endothelial damage, hypertension-related complications, concentric left ventricular hypertrophy, and possibly the progression of left ventricular dysfunction due to hypertension in the absence of ischemic heart disease. The foregoing hypotheses will require careful testing before these mechanisms can be deemed definitive.

The Emerging Role of Pharmacogenomics

The data supporting the use of combined vasodilator therapy in heart failure represent the first race-specific recommended therapies approved by the US Food and Drug Administration. However, the uptake of this therapy has been slow, in part because of its race-specific implications. Recently, data have become available from the A-HeFT trial that begin to define a genetic substrate that responds to therapy. Race may simply represent a clinical phenotype that serves as a crude surrogate for several more physiologic factors, among which might be an at-risk clinical genotype and genetic profile that either determines the progression of disease or predicts responsiveness to therapy.

Aldosterone production is closely related to the function of aldosterone synthase. An identified single nucleotide polymorphism of aldosterone synthase at CYP 11B2-344 has been associated with better outcomes with a TT substitution and less favorable outcomes with a CC substitution. The TT allele was overrepresented in the A-HeFT population and, when present, was associated with a favorable response to ISDN/HYD. If the CC allele or the heterozygote was present, no association of response to ISDN/HYD was demonstrable [45•].

Additional genetic markers under active investigation include single nucleotide polymorphisms of NOS, angiotensin converting enzyme, and adrenergic receptors, especially the β-1 and α receptors. Table 2 provides a list of described and potential genetic markers of heart failure in African Americans.

Race-Based Therapeutics: Treatment Disparities

The burden of hypertension (and probably diabetes) coupled with poor treatment practices for African American patients leave this population at great risk for CVD. The African American population remains severely undertreated, despite guideline recommendations. According to recent NHANES data, although approximately 60% of both African Americans and Caucasians were being treated for hypertension, only 45% of African Americans had their BP under control, compared with 56% of Caucasian. These small numbers of adequately treated patients leave most of the population vulnerable to poor BP control and subsequent cardiovascular risk. While the NHANES population was only 19% African American, it is likely representative [6]. The disproportionate impact of CVD on African Americans may in part be due to genetic factors, and environmental risks, socioeconomic variances, and treatment differences are undeniable. However, the African American population is treated less aggressively for CVD [46]. New guidelines for providing care to and educational tools for African American patients may be required, as well as a heightened awareness of the risks related to hypertension and the early markers of target-organ disease. When overt CVD is established, relevant guidelines and treatment options specific for the African American patient should be followed (Table 3). This is especially relevant in the treatment of heart failure, where the use of combined vasodilator therapy as adjunctive therapy for symptomatic heart failure is minimal at best.

Table 2. Described and potential genetic markers of heart failure in African Americans

Genetic polymorphism	Clinical implications
β-1 adrenergic receptor; Gly389	Subsensitive β-1 receptor; decreased affinity for agonist and less cAMP generation.
β-1 adrenergic receptor; Arg389/α 2C Del322-325 receptor	Presence of both polymorphisms is associated with increased risk for heart failure in African Americans; RR = 10.11 when both are present.
eNOS - Glu298Glu	Subsensitive NO system; possibly associated with better responsiveness to ISDN/HYD.
Aldosterone synthase [CYP11B2-344TT allele]	Possibly associated with excessive fibrosis; associated with better responsiveness to ISDN/HYD.
TGF-β 1, codon 25	40% higher TGF-β 1 levels; possibly associated with higher endothelin levels and more fibrosis.
G Protein 825-T allele	Marker of low renin HTN, LVH, and stroke.

eNOS—endothelial nitric oxide syntase; HTN—hypertension; HYD—hydralazine; ISDN—isosorbide dinitrate; LVH—left ventricular hypertrophy; NO—nitric oxide; TGF—transforming growth factor.
(*Data from* McNamara et al. [45•], Turner et al. [47], Suthanthiran et al. [48], Mason et al. [49], Small et al. [50], McNamara [51], and McNamara et al. [52,53].)

Table 3. Combination hydralazine nitrate recommendations*

I, IIa, IIb, III	Recommendations
IIa, A	Addition is reasonable in patients with reduced LVEF who are already taking an ACEI and β-blocker for symptomatic HF and who have persistent symptoms.
IIa, A	Addition to standard medical regimen for HF, including ACEIs and β-blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested.
IIb, C	Might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency.

*Changes from 2001 guidelines.
ACEI—angiotensin-converting enzyme inhibitor; ARB—angiotensin receptor blocker; HF—heart failure; LVEF—left ventricular ejection fraction; NYHA—New York Heart Association.
(*Data from* Hunt et al. [13].)

Conclusions

In accordance with focusing on novel treatment approaches, more research is needed to better understand the context of race in medicine and to preferably remove its presence from any dialogue regarding health or disease, to be replaced by a more physiologic profile that accurately determines risk and assesses responsiveness to medical therapies. These more physiologic determinants of the excess in CVD burden or the important psychosocial and socioeconomic factors that contribute to this disease burden need further clarification.

In the meantime, a new paradigm for the treatment of African American patients at risk for CVD is necessary. This new paradigm needs to include a comprehensive patient assessment for treatment that includes race, family history, and concomitant conditions in addition to earlier treatment with appropriate agents. Physicians should be familiar with antihypertensive agents and should employ them more frequently. In the future, gene-environment interactions may be important to take into account when deciding on therapy. Most importantly, physicians and care providers should rigorously adhere to a guideline-driven evidence-based approach in the care of African Americans with CVD, and where race-specific recommendations or therapies are suggested, these approaches should not be dismissed.

Clinical Trial Acronyms

A-HeFT—African American Heart Failure Trial; AASK—African American Study of Kidney Disease; ALLHAT—Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BEST—Beta-Blocker Evaluation of Survival Trial; CAPRICORN—Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CHARM—Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Trials; COHERE—Coreg (GlaxoSmithKline, London, United Kingdom) Heart Failure Registry; COPERNICUS—Carvedilol Prospective Randomized Cumulative Survival Trial; HOPE—Heart Outcomes Prevention Evaluation; ISHIB—International Society on Hypertension in Blacks; JNC VII—Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; MERIT-HF—Metoprolol CR/XL Randomised Intervention Trial in Heart Failure;

NHANES—National Health and Nutrition Examination Survey; SOLVD—Studies of Left Ventricular Dysfunction; UKPDS—United Kingdom Prospective Diabetes Study; V-HeFT—Veterans Administration Cooperation Study; Val-HeFT—Valsartan in Heart Failure Trial; VALUE—Valsartan Antihypertensive Long-term Use Evaluation.

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