

to benefit from ICD therapy appears to be oversimplified. The mean left ventricular ejection fraction at six weeks was approximately 0.30, which was one of the inclusion criteria in the Multicenter Automatic Defibrillator Implantation Trial II.<sup>2</sup>

Dr. Micheletta and colleagues are correct in emphasizing the importance of early aldosterone blockade. In our trial, only a minority of patients were receiving this medication at baseline. It is important to note, however, that the decisive trial on the benefits of early aldosterone antagonism after myocardial infarction was published in 2003, approximately nine years after our trial was designed.<sup>3</sup>

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## Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

**TO THE EDITOR:** Taylor et al. (Nov. 11 issue)<sup>1</sup> show that isosorbide dinitrate plus hydralazine increased survival in a group of black patients with heart failure. The authors state that a retrospective analysis of the Vasodilator Heart Failure Trial (VHeFT) studies<sup>2</sup> identified black patients with heart failure as the group benefiting from this therapy.

Black patients in the V-HeFT cohorts had a lower prevalence of a history of coronary artery disease and a higher prevalence of a history of hypertension than did white patients (Table 1). These differences indicate proportional differences in the causes of heart failure in the subgroups of black patients and white patients — findings that are consistent with those of other trials.<sup>3,4</sup> According to the report by Taylor et al. on the African-American Heart Failure Trial (A-HeFT),<sup>1</sup> nonischemic causes of heart failure also predominated in their cohort of all black patients.

Differences in the causes of heart failure might have better guided the design of a trial evaluating treatment with isosorbide dinitrate plus hydralazine. These characteristics are more biologically relevant than race. It is clinically more practical for physicians to identify a history of hypertension or coronary artery disease instead of asking if the patient is black. There is a large population of non-

**Table 1. Prevalence of a History of Hypertension or Coronary Artery Disease (CAD) in Black Patients and White Patients in the Vasodilator Heart Failure Trials (V-HeFT I and II).\***

Study	Black Patients	White Patients
V-HeFT I		
Total no.	180	480
Hypertension (%)	46.6	37.3
CAD (%)	20.8	53.2
V-HeFT II		
Total no.	215	574
Hypertension (%)	64.9	41.5
CAD (%)	28.4	61.6

\* The data are from Carson et al.<sup>2</sup>

black patients with heart failure from hypertension or other causes who may not benefit if this therapy is approved by the Food and Drug Administration for black patients only.

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**TO THE EDITOR:** There is evidence that hypertensive cardiomyopathy is associated with certain clinical characteristics, including an increased body-mass index, black race, and female sex.<sup>1</sup> Accordingly, approximately 40 percent of patients in A-HeFT were thought to have a cardiomyopathy resulting solely from hypertension. Despite the moderate size of the cohort, it would be interesting to contrast the primary outcome in patients who were predominantly hypertensive with that in patients with ischemic heart failure. Could the increased prevalence of hypertensive cardiomyopathy in the black population explain the results of A-HeFT? If so, this might be just the transcendent phenotype the authors are looking for.

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1. Dunlap SH, Sueta CA, Tomasko L, Adams KF Jr. Association of body mass, gender and race with heart failure primarily due to hypertension. *J Am Coll Cardiol* 1999;34:1602-8.

**TO THE EDITOR:** In the A-HeFT trial, isosorbide dinitrate and hydralazine were added to “standard therapy,” as determined by the patients’ own physicians. The mean baseline blood pressure of 127/78 mm Hg, however, suggests that the study population had inadequate afterload reduction and suboptimal blood-pressure control. Although it is apparently normal, this blood pressure is relatively high in patients with class III or IV heart failure and an average ejection fraction of 24 percent. In addition, Taylor et al. do not report on the baseline use of calcium-channel blockers, such as amlodipine, which has been used safely in patients with chronic severe heart failure<sup>1</sup> and may be particularly beneficial in treating hypertension in black patients. Thus, the benefits of isosorbide dinitrate and hydralazine in the A-HeFT trial may primarily reflect

improved blood-pressure control in an undertreated population.

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1. Packer M, O’Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107-14.

**TO THE EDITOR:** Taylor et al. chose as their primary end point a composite score, referencing Packer.<sup>1</sup> Unfortunately, Packer explicitly rejects their composite score, stating “The clinical composite score does not attempt to combine efficacy of unequal weight, that is, it does not try to combine death (a major weight) and a change in symptoms (minor weight) into a single score.”<sup>1</sup> Taylor et al. use a composite score but do not explain how they developed their scoring system and its components, which include death (a score of –3), the first hospitalization for heart failure (–1), and a worsening of the quality of life by 10 or more units, as measured by the Minnesota Living with Heart Failure questionnaire (–2). They were fortunate that each component of the composite score by itself was statistically significant. The comment by Taylor et al. that this study provides support for the use of such an end point in future trials is an overreach. The authors do not explain how they developed power expectations for their study other than to say that once they did, they used interim analyses to correct their original expectations, citing Cui et al.<sup>2</sup> to justify the interim adjustment.

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2. Cui L, Hung HMJ, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics* 1999;55:853-7.

**TO THE EDITOR:** In their study of isosorbide dinitrate and hydralazine in black patients with heart failure, Taylor et al. do not record lupus-like syndrome as a reported adverse event. Drug-induced lupus is a relatively common side effect of hydralazine use, with a reported incidence of up to 20 percent.<sup>1,2</sup> There is also evidence that lupus-like syndrome occurs more frequently at doses of 200 mg

or more daily<sup>1,2</sup>; Taylor et al. used a total daily dose of 225 mg. Recent experience with spironolactone showed that the initial enthusiasm for using a new therapy in heart failure can have potentially fatal, and avoidable, side effects in patients.<sup>3</sup> Clinicians should counsel patients appropriately about the potential side effect of hydralazine-induced lupus and monitor them for this disorder, especially until its incidence in patients who are treated with the regimen suggested by Taylor et al. is better characterized.

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**THE AUTHORS REPLY:** Drs. Moran and Cooper and Dr. Fitzgibbons suggest that the hypertensive phenotype might be a better distinguishing feature than race to predict a response to isosorbide dinitrate plus hydralazine. This is a reasonable hypothesis, but preliminary subgroup analysis of the A-HeFT data suggests that the response to this combination drug was similar in patients with ischemic heart disease and those without. Thus, it is unlikely that the hypertensive phenotype alone will serve as an adequate identifier of a favorable response.

Dr. Chow suggests that the mechanism of the efficacy of treatment with isosorbide dinitrate plus hydralazine may be attributable only to blood-pressure reduction. Although vasodilation to reduce left-ventricular workload certainly may contribute to the beneficial effect of isosorbide dinitrate plus hydralazine, previous trials have shown that this is unlikely to be the only factor in improved survival. Prazosin lowered blood pressure more than isosorbide dinitrate and hydralazine did in V-HeFT I, but only the nitrate-hydralazine combination reduced mortality.<sup>1</sup> Felodipine in V-HeFT III<sup>2</sup> and amlodipine in the Prospective Randomized Amlodipine Survival Evaluation<sup>3</sup> lowered blood pres-

sure but did not improve survival. Therefore, it is unlikely that reduced pressure load was the only factor in the improvement in outcome in heart failure.

Dr. Bellin expresses concern about our composite score. We believe it is appropriate and rational to mix mortality, hospitalization, and quality-of-life outcomes, since all are important variables in the management of a chronic disease. The scoring system is arbitrary but weights variables by seriousness. Thus, death received the worst score, and hospitalizations and quality of life received lesser scores. Power calculations were facilitated by applying this new composite score to the original V-HeFT database. The statistical model allowed for an interim analysis to assess the adequacy of the power calculation. This is described in our report.

Dr. Eisenberger expresses concern about hydralazine-induced lupus. We performed antibody studies in all patients in the first V-HeFT.<sup>1</sup> To our surprise and relief, we found no excess of lupus in the treatment group as compared with the placebo group in any of the V-HeFT studies. We did not measure antibodies in A-HeFT, but only one patient in the cohort of 1050 was described by his physician as having symptoms that suggested a lupus-like syndrome. The incidence in these two cohorts of patients with heart failure was extraordinarily low. Thus, 225 mg daily of hydralazine apparently has not induced a measurable occurrence of lupus in what is now more than 1000 patients. We do agree with Dr. Eisenberger that appropriate monitoring for this potential side effect is quite reasonable.

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