The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 11, 2004 VOL. 351 NO. 20

Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

Anne L. Taylor, M.D., Susan Ziesche, R.N., Clyde Yancy, M.D., Peter Carson, M.D., Ralph D'Agostino, Jr., Ph.D., Keith Ferdinand, M.D., Malcolm Taylor, M.D., Kirkwood Adams, M.D., Michael Sabolinski, M.D., Manuel Worcel, M.D., and Jay N. Cohn, M.D., for the African-American Heart Failure Trial Investigators*

ABSTRACT

BACKGROUND

We examined whether a fixed dose of both isosorbide dinitrate and hydralazine provides additional benefit in blacks with advanced heart failure, a subgroup previously noted to have a favorable response to this therapy.

METHODS

A total of 1050 black patients who had New York Heart Association class III or IV heart failure with dilated ventricles were randomly assigned to receive a fixed dose of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for heart failure. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and change in the quality of life.

RESULTS

The study was terminated early owing to a significantly higher mortality rate in the placebo group than in the group given isosorbide dinitrate plus hydralazine (10.2 percent vs. 6.2 percent, P=0.02). The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group (−0.1±1.9 vs. −0.5±2.0, P=0.01; range of possible values, −6 to +2), as were its individual components (43 percent reduction in the rate of death from any cause [hazard ratio, 0.57; P=0.01] 33 percent relative reduction in the rate of first hospitalization for heart failure [16.4 percent vs. 22.4 percent, P=0.001], and an improvement in the quality of life [change in score, −5.6±20.6 vs. −2.7±21.2, with lower scores indicating better quality of life; P=0.02; range of possible values, 0 to 105]).

CONCLUSIONS

The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure including neurohormonal blockers is efficacious and increases survival among black patients with advanced heart failure.

From the University of Minnesota (A.L.T., J.N.C.) and Minneapolis Veterans Affairs Hospital (S.Z.) — both in Minneapolis; University of Texas Southwestern Medical Center, Dallas (C.Y.); Veterans Affairs Medical Center, Washington, D.C. (P.C.); Wake Forest University, School of Medicine, Winston-Salem, N.C. (R.D.); Heartbeats Life Center and Xavier University, New Orleans (K.F.); Jackson Cardiology Associates, Jackson, Miss. (M.T.); Association of Black Cardiologists, Atlanta (M.T.); University of North Carolina, Chapel Hill (K.A.); and NitroMed, Lexington, Mass. (M.S., M.W.). Address reprint requests to Dr. Anne Taylor at the Department of Medicine/Cardiology, University of Minnesota Medical School, 420 Delaware St. SE, MMC 293, Minneapolis, MN 55455, or at taylo135@umn.edu.

*Participants in the African-American Heart Failure Trial (A-HeFT) are listed in the Appendix.

N Engl J Med 2004;351:2049-57.

Neurohormonal inhibitors alone or in combination slow the progression of left ventricular dysfunction, retarding the structural remodeling of the left ventricle that characterizes chronic heart failure and reducing the rates of death and complications among patients with heart failure.[1-10] Endothelial dysfunction, impaired bioavailability of nitric oxide, and increased oxidant stress also occur in patients with congestive heart failure and contribute to the remodeling process in experimental and clinical models of heart failure.[11-27] Augmentation of nitric oxide may therefore be an alternative or supplemental approach to slow or reverse progressive heart failure. The first Vasodilator Heart Failure Trial (V-HeFT I)[6] demonstrated the benefit of combining the nitric oxide donor isosorbide dinitrate with the antioxidant hydralazine in patients with mild-to-severe heart failure; however, the potential long-term benefit of this therapy in patients treated with neurohormonal inhibitors has not been evaluated.

Differences exist in the prevalence and causation of congestive heart failure and in the associated morbidity and mortality, consistent with population-based variations in the mechanisms of heart failure.[28-30] Studies have suggested that persons who identify themselves as black may have, on average, a less active renin–angiotensin system[29,31] and a lower bioavailability of nitric oxide than those self-identified as white.[32-37] Retrospective analyses of the databases of previous heart-failure trials[38,39] strongly suggested that black patients have a clinically significant response to a combination of isosorbide dinitrate and hydralazine. On the basis of these observations, we evaluated the efficacy of a fixed dose of isosorbide dinitrate plus hydralazine in black patients who had New York Heart Association (NYHA) class III or IV heart failure with dilated ventricles and who were receiving background therapy that included neurohormonal blockers.

METHODS

STUDY DESIGN

The African-American Heart Failure Trial (A-HeFT) was a randomized, placebo-controlled, double-blind trial with patients recruited at 161 centers in the United States. The study protocol was reviewed and approved by the institutional review board at each site. All patients gave written informed consent. Site monitoring, data collection, and data management were performed by Medifacts International, a clinical research organization. Data analysis was performed by independent statisticians and by Virtu Stat. The study sponsor was NitroMed. Independent committees adjudicated all primary and secondary end points, reviewed data on safety, and oversaw the two prespecified interim analyses, which were performed solely to assess the adequacy of the sample size. The manuscript was prepared by the authors and reviewed by the steering committee and the sponsor. The study design has been described previously.[40,41]

INCLUSION AND EXCLUSION CRITERIA

Patients 18 years of age or older, self-identified as black (defined as of African descent), who had had NYHA class III or IV heart failure for at least three months were eligible for screening. Patients were required to have been receiving standard therapy for heart failure, as determined to be appropriate by their physicians; such therapy included angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, beta-blockers for at least three months before randomization, digoxin, spironolactone, and diuretics. Patients also had to have evidence of left ventricular dysfunction within the six months preceding randomization in the form of a resting left ventricular ejection fraction of no more than 35 percent or a resting left ventricular ejection fraction of less than 45 percent with a left ventricular internal end-diastolic diameter of more than 2.9 cm per square meter of body-surface area or more than 6.5 cm on the basis of echocardiography.

Women were excluded if they were pregnant, nursing, or of childbearing age and not using an effective method of contraception. The following were also reasons for exclusion: an acute myocardial infarction, acute coronary syndrome, or stroke within the preceding three months; cardiac surgery or percutaneous coronary intervention within the preceding three months or the likelihood of a requirement for such procedures during the study period; the presence of clinically significant valvular heart disease, hypertrophic or restrictive cardiomyopathy, active myocarditis, or uncontrolled hypertension; a history of cardiac arrest or life-threatening arrhythmias within the preceding three months (unless they had been treated with an implantable defibrillator); treatment with parenteral inotropic agents within one month before randomization; a potential need for cardiac transplantation; the presence of symptomatic hypotension; the presence of an illness other than heart failure that was likely to result

in death within the study period; an inability to complete the quality-of-life questionnaire; and contraindications to the use of nitrate or hydralazine therapy.

RANDOMIZATION PROCEDURE

Randomization was performed centrally by Medifacts International, with stratification according to the use or nonuse of beta-blockers as background therapy. Blocks of 4 patients per stratum were used, with each site allowed to randomize up to 6 blocks of patients (24 patients) in the non–beta-blocker group and up to 10 blocks (40 patients) in the beta-blocker group.

Eligible patients were required to be receiving stable doses of therapy for heart failure and to have had a variation in body weight of less than 2.5 percent in the two weeks before randomization. At randomization, baseline evaluations included echocardiography, a metabolic profile, measurement of B-type natriuretic peptide and hemoglobin levels, and a quality-of-life questionnaire. After stratification according to the use or nonuse of beta-blockers as background therapy, patients were randomly assigned to receive a fixed-dose combination of isosorbide dinitrate plus hydralazine or to receive placebo, each in addition to background therapy. The initial dose was one tablet containing either placebo alone or 37.5 mg of hydralazine hydrochloride and 20 mg of isosorbide dinitrate three times daily. The dose was increased to two tablets three times daily, for a total daily dose of 225 mg of hydralazine hydrochloride and 120 mg of isosorbide dinitrate. An increase in the dose was dependent on the absence of drug-induced side effects as judged by the investigator. Patients were followed for up to 18 months, with assessment of the left ventricular ejection fraction, left ventricular internal diastolic dimension, left ventricular wall thickness, and level of B-type natriuretic peptide at 6 months and assessment of the quality of life every 3 months. Patients were interviewed by telephone monthly and returned for follow-up visits every three months.

OUTCOME MEASURES

The primary efficacy end point for the trial was a composite score made up of weighted values for death from any cause, a first hospitalization for heart failure during the 18-month follow-up period, and change in the quality of life at 6 months. The quality of life was assessed by means of the Minnesota Living with Heart Failure questionnaire, a 21-question self-administered instrument in which scores can range from 0 to 5 for each question, and higher scores indicate a poorer quality of life.[42] The composite scoring system is shown in Table 1.

Secondary end points included individual components of the primary composite score, death from cardiovascular causes, the total number of hospitalizations for heart failure, the total number of hospitalizations for any reason, the total number of days of hospitalization, the overall quality of life throughout the trial, the number of unscheduled emergency room and office or clinic visits, the change in B-type natriuretic peptide level at six months, a newly recognized need for cardiac transplantation, and a change in the left ventricular ejection fraction, the left ventricular internal diastolic dimension, and the left ventricular wall thickness at six months. Data on patients who underwent cardiac transplantation during the trial were censored at the time of transplantation.

STATISTICAL ANALYSIS

Estimates of the sample size needed for the study to detect significant differences in the primary composite end point were based on data from V-HeFT I and II. Since the composite measure used in this trial had not been evaluated in previous trials, two interim analyses were prespecified in the protocol to permit an assessment of the adequacy of the sample size without knowledge of efficacy. The specific techniques for assessing the adequacy of the sample size were based on methods described by Cui et al.[43] The data and safety monitoring board met four times during the trial and conducted the prespecified interim analyses. The initial estimate that 800 patients (400 per group) were needed for the

Table 1. Scoring System for the Primary Composite End Point.

End Point	Score
Death (at any time during the trial)	–3
Survival to end of trial	0
First hospitalization for heart failure (adjudicated)	–1
No hospitalization	0
Change in quality of life at 6 mo (or at last measurement if earlier than 6 mo)	
Improvement by ≥10 units	+2
Improvement by 5–9 units	+1
Change by <5 units	0
Worsening by 5–9 units	–1
Worsening by ≥10 units	–2
Possible score	–6 to +2

study to have sufficient statistical power (P<0.02) was modified to 1100 patients (550 per group) in March 2003 on the basis of the prespecified interim analyses.

The primary efficacy comparison included all participants who had undergone randomization (intention-to-treat analysis). When data were missing, the worst-case score for that component of the composite end point was used in the primary analysis. The composite end point was compared between the groups with the use of a two-sample t-test.

The three individual components of the composite end point — death from any cause, first hospitalization for heart failure, and a change in the quality of life — were examined separately in secondary analyses. For the analysis of death from any cause, we used standard Kaplan–Meier survival methods with the log-rank test. These analyses included all randomized patients. We compared the incidence rates of death and of a first hospitalization for heart failure between groups using Fisher's exact test. We compared the change in the quality of life between groups using a two-sample t-test for the difference in scores (on the basis of the data obtained at six months or, when unavailable, data from the three-month assessment carried forward).

Additional descriptive statistics were estimated for patients' characteristics and reported as the mean (±SD) or the total number (and percentage). Adverse events were also compared between groups with the use of chi-square tests.

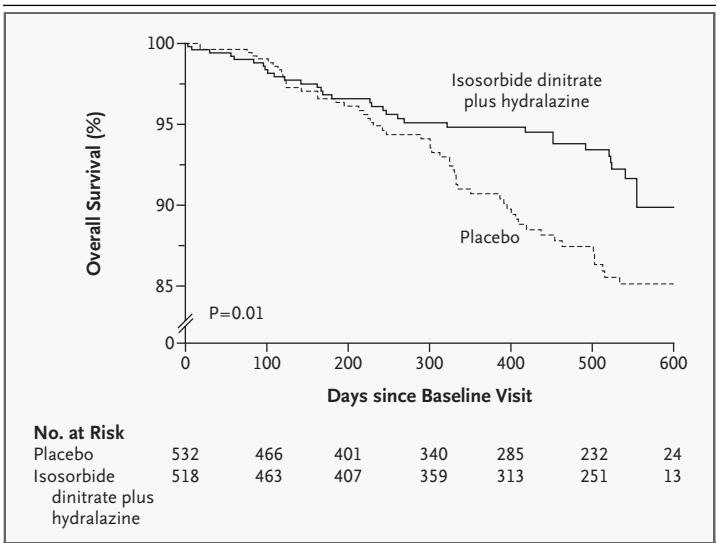

Figure 1. Kaplan–Meier Estimates of Overall Survival.

RESULTS

Randomization was initiated on June 12, 2001, and the study was terminated on July 19, 2004, on the recommendation of the independent data and safety monitoring board after 1050 of the planned 1100 patients had undergone randomization — 518 to receive isosorbide dinitrate plus hydralazine and 532 to receive placebo. No patients were lost to follow-up.

The decision to stop the trial was based on the Lan–DeMets sequential-boundaries calculation.[44] The trial was halted owing to a significantly higher mortality rate in the placebo group than in the group given isosorbide dinitrate plus hydralazine. At the time the trial was halted, 54 patients had died in the placebo group (10.2 percent) and 32 patients had died in the combination-therapy group (6.2 percent). There was a significant 43 percent improvement in survival (hazard ratio, 0.57; P=0.01 by the log-rank test). The mean duration of follow-up was 10 months (range, 0 to 18). The Kaplan–Meier survival analysis (Fig. 1) demonstrates that survival differences emerged at approximately 180 days and widened progressively thereafter (P=0.01 by the log-rank test).

The baseline clinical characteristics of the patients are shown in Table 2. At the termination of the trial, the primary composite score was −0.1±1.9 in the group given isosorbide dinitrate plus hydralazine, as compared with −0.5±2.0 in the placebo group (P=0.01), thus demonstrating a significant beneficial effect of nitric oxide–enhancing therapy (Table 3). In addition to the reduction in the rate of death from any cause, the other individual components of the primary composite score were also significantly improved by treatment with isosorbide dinitrate and hydralazine (Table 3). The rate of first hospitalizations for heart failure was reduced by 33 percent, as compared with that in the placebo group (16.4 percent vs. 24.4 percent; 85 patients vs. 130 patients; P=0.001). The quality-of-life scores also improved more in the group given isosorbide dinitrate plus hydralazine than in the placebo group (−5.6±20.6 vs. −2.7±21.2, P=0.02).

The composite end point was based on data on 1050 patients (the intention-to-treat population). A total of 742 patients filled out the quality-of-life questionnaire at six months. For all other patients, either an earlier post-baseline quality-of-life score was used or, if no such score was available, the patient received the worst possible score for the

change in the quality of life (−2) as part of the composite end point.

The target dose was achieved in 68.0 percent of the patients in the group given isosorbide dinitrate plus hydralazine, as compared with 88.9 percent of the patients in the placebo group (P<0.001). The mean number of tablets per day was 3.8±2.5 in the group given isosorbide dinitrate plus hydralazine and 4.7±2.2 in the placebo group (P<0.001).

Combination therapy had a slight but significant blood-pressure–lowering effect at six months, decreasing systolic blood pressure by a mean of 1.9 mm Hg, as compared with an increase of 1.2 mm Hg in the placebo group (P=0.02), and decreasing diastolic blood pressure by a mean of 2.4 mm Hg, as compared with an increase of 0.8 mm Hg in the placebo group (P<0.001). There was no significant change in the heart rate between the two groups.

Adverse events are shown in Table 4. Symptoms of headache and dizziness were significantly more frequent in the group given isosorbide dinitrate plus hydralazine, whereas exacerbations of congestive heart failure (both moderate and severe) were significantly more frequent in the placebo group.

DISCUSSION

We confirmed the findings in V-HeFT I of the efficacy and survival advantage of a combination of isosorbide dinitrate plus hydralazine added to standard background therapy in patients with moderate-to-severe heart failure. The trial population was limited to patients who identified themselves as black, a subgroup that had had a particularly favorable response to this therapy in retrospective analyses.[6,38]

The 43 percent reduction in the mortality rate in the group given isosorbide dinitrate plus hydralazine occurred among patients who were well treated with a background regimen of neurohormonal-inhibitor drugs. Thus, the reduction in mortality is consistent with the existence of an alternative mechanism controlling the progression of heart failure. A similar reduction in mortality was previously reported among blacks with NYHA class II, III, or IV heart failure in V-HeFT I who were receiving only diuretics and digitalis rather than neurohormonal-inhibiting agents.[6,38] These results suggest that a fixed-dose combination of isosorbide dinitrate plus hydralazine may benefit patients in a manner that is independent of background therapy.

Growing evidence supports the concept that nitric oxide protects against myocardial and vascular

Table 2. Baseline Characteristics.*

Characteristic	Isosorbide Dinitrate plus Hydralazine (N=518)	Placebo (N=532)
Age (yr)	56.7±12.7	56.9±13.3
Male sex (% of patients)	55.8†	63.9
Weight (kg)	92.5±21.4	94.1±25.5
Primary cause of heart failure (% of patients)		
Ischemic heart disease	23.4	22.7
Hypertension	40.0	37.4
Idiopathic	24.5	27.6
Valvular cause	2.5	3.2
Other	9.7	9.0
NYHA class (% of patients)‡		
I	0	0
II	0.2	0
III	96.7	94.7
IV	3.1	5.3
Diabetes (% of patients)	44.8§	37.0
Renal insufficiency (% of patients)	16.2	18.2
Atrial fibrillation (% of patients)	15.0	18.0
Cardiac resynchronization therapy (% of patients)	2.0	2.1
Implantable cardiac defibrillator (% of patients)	16.6	17.3
Ejection fraction (%)‡	23.9±7.3	24.2±7.5
LVIDD (cm)‡	6.5±0.9	6.5±1.0
Blood pressure (mm Hg)		
Systolic	127.2±17.4	125.3±18.1
Diastolic	77.6±10.3¶	75.6±10.5
Minnesota Living with Heart Failure Questionnaire score (range, 0 to 105)	50.9±24.9¶	50.7±25.5
Medications for heart failure (% of patients)		
Diuretic	88.0	91.5
ACE inhibitor	69.4	69.5
ARB	17.2	16.5
Beta-blocker	74.1	73.5
Carvedilol	55.2	55.8
Digoxin	58.5	60.7
Spironolactone	40.2	37.6

* Plus–minus values are means ±SD. NYHA denotes New York Heart Association, LVIDD left ventricular internal diastolic dimension, ACE angiotensin-converting enzyme, and ARB angiotensin-receptor blocker. Because of rounding, percentages may not total 100.
† P=0.008 for the comparison with the placebo group.
‡ Data were obtained at screening.
§ P=0.01 for the comparison with the placebo group.
¶ P=0.002 for the comparison with the placebo group.

Table 3. End Points.*

End Point	Isosorbide Dinitrate plus Hydralazine (N=518)	Placebo (N=532)	P Value
Primary composite score†	−0.1±1.9	−0.5±2.0	0.01
Components of the primary composite score			
Death from any cause — no. (%)	32 (6.2)	54(10.2)	0.02
First hospitalization for heart failure — no. (%)	85 (16.4)	130 (24.4)	0.001
Change in quality-of-life score at 6 mo‡	−5.6±20.6	−2.7±21.2	0.02

* Plus–minus values are means ±SD.
† Scores can range from −6 to 2, with higher scores indicating a better outcome.
‡ Lower scores indicate a better quality of life.

Table 4. Adverse Events.*

Adverse Event	Isosorbide Dinitrate plus Hydralazine	Placebo	P Value
	percent		
Exacerbations of CHF	8.7	12.8	0.04
Severe exacerbation of CHF	3.1	7.0	0.005
Headache	47.5	19.2	<0.001
Dizziness	29.3	12.3	<0.001

* CHF denotes congestive heart failure.

remodeling.[11,22-27,45-47] The combination of isosorbide dinitrate and hydralazine may serve as a nitric oxide donor, with hydralazine conferring protection against the degradation of nitric oxide induced by oxidative stress.[48-52] Thus, data from A-HeFT support, but do not prove, the existence of a protective role of nitric oxide even in the presence of neurohormonal blockade.

We used two strategies to demonstrate the efficacy of isosorbide dinitrate plus hydralazine as therapy for heart failure in a moderate-sized cohort. First, we designed the trial to include only patients self-identified as black, since previous data suggested that such patients had increased responsiveness to this therapy.[6,38] Second, we used a composite score, composed of weighted values for death from any cause, a first adjudicated hospitalization for heart failure, and change in the quality of life, as the primary end point. We hypothesized that including in the primary end point data relevant to all important outcomes of chronic disease would enhance the statistical power of the study to detect efficacy in a moderate-sized cohort.[53] The significant benefit of isosorbide dinitrate plus hydralazine demonstrated by the differences in the composite score (−0.1±1.9, as compared with −0.5±2.0 in the placebo group; P=0.01) provides support for the use of such an end point in future trials.

Nitric oxide regulates cardiovascular processes including myocardial hypertrophy, remodeling, and substrate use, as well as vascular function, inflammation, and thrombosis.[11,22-27,45-47] Substantial evidence exists that endothelial dysfunction and impaired bioavailability of nitric oxide occur in both ischemic and nonischemic models of heart failure and contribute to the pathophysiology of congestive heart failure.[12-19,21] Studies of murine models of heart failure — mice deficient in endothelial nitric oxide synthase and mice overexpressing nitric oxide synthase — have demonstrated the role of nitric oxide in preserving left ventricular performance, inhibiting myocardial remodeling, and improving survival.[23,24,27,46] Nitric oxide has also been shown to regulate the use of myocardial substrate[47] and mitochondrial respiration.[25] In clinical models of heart failure, basal cardiac release of nitric oxide is decreased,[54] sensitivity to inhibition of nitric oxide synthase is increased,[55] nitric oxide–mediated processes are impaired,[12,13,18] and oxidative stress is increased.[14,15,17,19,20]

Our choice of a study cohort of patients identifying themselves as black is based on observations of differences in prevalence, risk profiles, causation, disease severity, outcomes, and response to therapy between black patients and white patients with heart failure.[28-30] Retrospective analyses according to race in V-HeFT I, V-HeFT II, and the Studies of Left Ventricular Dysfunction have shown significant differences between blacks and whites in the response to pharmacotherapy for heart failure.[30,38,39] In a novel experimental system, Kalinowski et al.[37] found that, as compared with endothelial cells from healthy white women, endothelial cells from healthy black women had diminished bioavailability of nitric oxide as a result of increased oxidative stress. Data suggesting that endothelial function and bioavailability of nitric oxide may be less robust in blacks than in whites[32-37] lend credibility to the hypothesis that the balance of mechanisms leading to the progression of heart failure may vary with geographic origin.

The combination of isosorbide dinitrate and hydralazine was used as a vasodilator in V-HeFT I because of its balanced effect on arteriolar dilation and venodilation. Once the physiologic role of nitric oxide was elucidated, it became apparent that isosorbide dinitrate exerts its vasodilatory effect by donating nitric oxide or forming related compounds.[48,56] Concomitant administration of hydralazine prolongs the vasodilatory effects of isosorbide dinitrate in experimental and clinical models.[19,49-52] Munzel et al.[51] have shown that hydralazine is an effective antioxidant, inhibiting the generation of nitric oxide–inactivating reactive oxygen species by inhibiting vascular NADH and NADPH oxidases. Similarly, other antioxidants have been shown to reduce the mitochondrial production of reactive oxygen species.[57] Thus, hydralazine, by reducing oxidative stress, may enhance the effects of nitric oxide derived from nitric oxide donors as well as from endogenous sources. This study, however, does not establish that these mechanisms explain the clinical benefit of isosorbide dinitrate plus hydralazine in heart failure.

Our trial represents a departure from the recent approach to the design of cardiovascular trials. Rather than studying a large heterogeneous population, we examined a specific population in whom efficacy was more likely to be established. A heterogeneous population may have substantial variations in genetic and environmental factors that influence disease progression and the response to therapy. Since subgroups of the trial cohort are rarely large enough for statistical analyses of the heterogeneity of an effect, the standard thinking is that the overall response to therapy should be accepted as a mandate for the use of that therapy in all subgroups in the trial. Recent insights into mechanistic variability, however, lend credence to the concept that the average effects in heterogeneous populations may obscure therapeutic efficacy in some subgroups and the lack of such efficacy in others.

Our finding of the efficacy of isosorbide dinitrate plus hydralazine in black patients provides strong evidence that this therapy can slow the progression of heart failure. A future strategy would be to identify genotypic and phenotypic characteristics that would transcend racial or ethnic categories to identify a population with heart failure in which there is an increased likelihood of a favorable response to such therapy.

Supported by NitroMed.

Dr. Cohn was the inventor on two patents (6,784,177 and 6,465,463) for the use of combinations of hydralazine compounds and isosorbide dinitrate or isosorbide mononitrate in heart failure. In return for equity and potential future royalties, NitroMed licensed from him the patent for mortality reduction of the drug combination in heart failure. NitroMed subsequently applied for a patent for use in black patients. Dr. Anne Taylor, Ms. Ziesche, and Dr. Adams have received research support from NitroMed. Dr. Yancy has received consulting and lecture fees from the company. Drs. Sabolinski and Worcel are employees of the company, in which they and Ms. Ziesche own equity. Dr. Anne Taylor reports having served as a consultant to Wyeth–Ayerst and Bristol-Myers Squibb. Dr. Yancy reports having received consulting and lecture fees from GlaxoSmithKline, Scios, and Medtronic. Dr. Carson reports having received consulting fees from and having served on paid advisory boards for Bristol-Myers Squibb, Pfizer, NitroMed, AstraZeneca, GlaxoSmithKline, Guidant, and Myogen and having received lecture fees from AstraZeneca, Bristol-Myers Squibb/Sanofi, and Novartis. Dr. D'Agostino reports having received consulting fees from Target Health and having been the independent statistician who performed the analysis for the study and who was paid by Target Health, which billed NitroMed. Dr. Ferdinand reports having received consulting fees from Pfizer and AstraZeneca and lecture fees from Pfizer, AstraZeneca, and Merck. Dr. Malcolm Taylor reports having received consulting fees from Pfizer and GlaxoSmithKline and lecture fees from GlaxoSmithKline and AstraZeneca. Dr. Cohn reports having received consulting fees and an advisory-board membership from NitroMed, Novartis, Amgen, and Medtronics; equity ownership and stock options from Hypertension Diagnostics; and research support from Novartis.

We are indebted to the Association of Black Cardiologists, whose partnership facilitated the conduct of the trial, and to Ms. Kristine Olson for her assistance in the preparation of the manuscript.

APPENDIX

The A-HeFT included the following: **Steering Committee —** A.L. Taylor (chair), K. Adams, P. Carson, J.N. Cohn, K. Ferdinand, E. Ofili, A. Olukotun, M. Taylor, C. Yancy, and S. Ziesche; **Data and Safety Monitoring Committee —** D. DeMets (chair), R. Grimm, P. Ouyang, J.T. Wright, Jr., R. D'Agostino, Jr., and M. Walkup (independent statisticians); **Independent Adjudication Committee —** P. Carson, A.B. Miller, J. Lindenfeld, C. O'Connor, F. Tristani, J. Ghali, and I. Anand; **Participating Investigators —** J. Adams, K. Adams, T. Addai, A. Amanullah, I. Anand, J. Anderson, J. Babb, L.Bass, A. Bazzi, H. Benipal, S.K. Bennett, W. Bennett, M. Berk, R. Berry, H. Bhatia, A. Bouchard, J. Boutros, S. Broadwater, C.S. Brown, K. Brown, K. Burnham, J. Butler, L. Campos, D. Chapman, D. Chomsky, F. Cobb, R. Cooke, C. Corder, K.M. Coy, L. Crawford, G. Crossley, C. Curry, K.G. Curry, B. Czerska, P.H. D'Amato, K.N. Dave, V. Dave, J. Dean, R. Delgado, S. Desai, A. Deswal, W. Drummond, M. Dunlap, L.C. Egbujiobi, U. El Kayam, J. Farahi, R. Fei, K. Ferdinand, Gary Fishbein, S.J. Fitzmorris, J. Flack, M. Garg, R. Gelzer-Bell, J. Ghali, S. Goldsmith, S. Gottleib, I. Gradus-Pizlo, B. Grant-Anderson, B.A. Graves, M. Greenberg, D. Gupta, E. Hamilton, S. Hankins, J. Hargrove, B.L. Harris, R. Harrison, K. Hebert, K. Taylor, A. Herioux, J. Hernandez, M. Hess, J.T. Heywood, G. Hillard, C. Hunter, S.W. Hutchins, H.M. Ibrahim, D. Ike, C.S. Ince, Jr., C. Israel, J. Joseph, A. Kaneshige, S. Katz, A. Khan, S. Khan, M. Klapholz, D. Knox, M. Krolick, M. Kukin, A. Kumar, K. Kutoloski, B. Lachterman, R. Lang, D. Lewis, R. Lewis, I. Lieber, C.F. Lovell, J. Tift Mann, O. Maytin, F. McGrew, M. McIvor, H. Meilman, G. Mikdadi, A. Miller, C.K. Moore, D. Moraes, T.E. Motley, Sr., M. Nallasivan, A. Niederman, A. Oduwole, E. Ofili, J. Olowoyeye, L. O'Meallie, A. Onwukwe, S. Patel, D. Pauly, D. Pearce, G. Perry, D. Phillips, I. Pina, R. Player. D.S. Primack, L.M. Prisant, M. Ptacin, J.A. Puma, J. Quartner, M.I. Rana, L. Reiss, H. Ribner, R. Rigmaiden, J.G. Rogers, J. Rozanski, M. Rubinstein, A. Saenz,

L. Salciccioli, F. Sam, G.T. Schuyler, E. Schwarz, C.L. Scott, M. Shah, K. Sheikh, V. Singh, A.L. Smith, R. Smith, J.C. Sobolski, A. Soffer, R. Soucier, A. Stern, J. Tallaj, W.R. Taylor, U. Thadani, G. Torre, R.A. Townsend, P. Underwood, A. Van Bakel, L. Wagoner, J. Wallia, M. Walsh, A.L. Warner, R. Workman, and C. Yancy.

REFERENCES

1. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316:1429-35.
2. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327:669-77.
3. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344:1651-8.
4. Effect of metoprolol CF/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353:2001-7.
5. Dries DL, Strong MH, Cooper RS, Drazner MH. Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. J Am Coll Cardiol 2002;40:311-7. [Erratum, J Am Coll Cardiol 2002;40:1019.]
6. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547-52.
7. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.
8. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
9. Yancy CW, Fowler MB, Colucci WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med 2001;344:1358-65.
10. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001; 344:1659-67.
11. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840-4.
12. Drexler H, Hayoz D, Munzel T, et al. Endothelial function in chronic congestive heart failure. Am J Cardiol 1992;69:1596-601.
13. Wang J, Seyedi N, Xu XB, Wolin MS, Hintze TH. Defective endothelium mediated control of coronary circulation in conscious dogs after heart failure. Am J Physiol 1994; 266:H670-H680.
14. Sharma R, Davidoff MN. Oxidative stress and endothelial dysfunction in heart failure. Congest Heart Fail 2002;8:165-72.
15. Diaz-Velez CR, Garcia-Castineiras S, Mendoza-Ramos E, Hernandez-Lopez E. Increased malondialdehyde peripheral blood of patients with congestive heart failure. Am Heart J 1996;131:146-52.
16. Keith M, Geranmayegan A, Sole MJ, et al. Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol 1998;31:1352-6.
17. Belch JJ, Bridges AB, Scott N, Chopra M. Oxygen free radicals and congestive heart failure. Br Heart J 1991;65:245-8.
18. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium dependent vasodilation is attenuated in patients with heart failure. Circulation 1991;84:1589-96.
19. Munzel T, Harrison DG. Increased superoxide in heart failure: a biochemical baroreflex gone awry. Circulation 1999;100: 216-8.
20. Gryglewski RJ, Palmer RM, Moncada S. Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor. Nature 1986;320:454-6.
21. Dixon LJ, Morgan DR, Hughes SM, et al. Functional consequences of endothelial nitric oxide synthase uncoupling in congestive cardiac failure. Circulation 2003;107:1725-8.
22. Prabhu SD. Nitric oxide protects against pathological ventricular remodeling: reconsideration of the role of NO in the failing heart. Circ Res 2004;94:1155-7.
23. Janssens S, Pokreisz P, Schoonjans L, et al. Cardiomyocyte-specific overexpression of nitric oxide synthase 3 improves left ventricular performance and reduces compensatory hypertrophy after myocardial infarction. Circ Res 2004;94:1256-62.
24. Scherrer-Crosbie M, Ullrich R, Bloch KD, et al. Endothelial nitric oxide synthase limits left ventricular remodeling after myocardial infarction in mice. Circulation 2001; 104:1286-91.
25. Loke KE, Laycock SK, Mital S, et al. Nitric oxide modulates mitochondrial respiration in failing human heart. Circulation 1999;100:1291-7.
26. Drexler H. Nitric oxide synthases in the failing human heart: a double-edged sword. Circulation 1999;99:2972-5.
27. Jones SP, Greer JJM, van Haperen R, Duncker DJ, de Crom R, Lefer DJ. Endothelial nitric oxide synthase overexpression attenuates congestive heart failure in mice. Proc Natl Acad Sci U S A 2003;100:4891-6.
28. Yancy CW. Does race matter in heart failure? Am Heart J 2003;146:203-6.
29. *Idem*. Heart failure in African Americans: a cardiovascular enigma. J Card Fail 2000;6:183-6.
30. Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. N Engl J Med 1999;340:609-16. [Erratum, N Engl J Med 1999;341:298.]
31. Gillum RF. Pathophysiology of hypertension in blacks and whites: a review of the basis of racial blood pressure differences. Hypertension 1979;1:468-75.
32. Cardillo C, Kilcoyne CM, Cannon RO III, Panza JA. Racial differences in nitric oxide-mediated vasodilator response to mental stress in the forearm circulation. Hypertension 1998;31:1235-9.
33. Stein CM, Lang CC, Nelson R, Brown M, Wood AJ. Vasodilation in black Americans: attenuated nitric oxide-mediated responses. Clin Pharmacol Ther 1997;62:436-43.
34. Hinderliter AL, Sager AR, Sherwood A, Light KC, Girdler SS, Willis PW IV. Ethnic differences in forearm vasodilator capacity. Am J Cardiol 1996;78:208-11.
35. Kahn D, Duff SJ, Tomasian D, et al. Effects of black race on forearm resistance vessel function. Hypertension 2002;40:195-201.
36. Houghton JL, Smith VE, Strogatz DS, Henches NL, Breisblatt WM, Carr AA. Effect of African-American race and hypertensive left ventricular hypertrophy on coronary vascular reactivity and endothelial function. Hypertension 1997;29:706-14.
37. Kalinowski L, Dobrucki I, Malinski T. Race-specific differences in endothelial function: predisposition of African Americans to vascular disease. Circulation 2004; 109:2511-7.
38. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. J Card Fail 1999;5:178-87.
39. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting–enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med 2001;344:1351-7.
40. Franciosa JA, Taylor AL, Cohn JN, et al. African-American Heart Failure Trial (A-HeFT): rationale, design, and methodology. J Card Fail 2002;8:128-35.
41. Taylor AL. The African-American Heart Failure Trial (A-HeFT): rationale and methodology. J Card Fail 2003;9:Suppl:S216-S219. [Erratum, J Card Fail 2003;9:481.]
42. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability

and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Am Heart J 1992;124:1017-25.
43. Cui L, Hung HMJ, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999;55:853-7.
44. Lan KKG, Reboussin DM, DeMets DL. Information and informational fractions for design and sequential monitoring of clinical trials. Comm Stat Theory Methods 1994;23:403-20.
45. Harrison DG. Cellular and molecular mechanisms of endothelial cell dysfunction. J Clin Invest 1997;100:2153-7.
46. Liu YH, Xu J, Yang XP, Yang F, Shesely E, Carretero OA. Effect of ACE inhibitors and angiotensin II type 1 receptor antagonists on endothelial NO synthase knockout mice with heart failure. Hypertension 2002;39:375-81.
47. Recchia FA, Osorio JC, Chandler MP, et al. Reduced synthesis of NO causes marked alterations in myocardial substrate metabolism in conscious dogs. Am J Physiol Endocrinol Metab 2002;282:E197-E206.
48. Ignarro LJ, Napoli C, Loscalzo J. Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview. Circ Res 2002;90:21-8.
49. Bauer JA, Fung HL. Concurrent hydralazine administration prevents nitroglycerin-induced hemodynamic tolerance in experimental heart failure. Circulation 1991;84:35-9.
50. Gogia H, Mehra A, Parikh S, et al. Prevention of tolerance to hemodynamic effects of nitrates with concomitant use of hydralazine in patients with chronic heart failure. J Am Coll Cardiol 1995;26:1575-80.
51. Munzel T, Kurz S, Rajagopalan S, et al. Hydralazine prevents nitroglycerine tolerance by inhibiting activation of a membrane-bound NADH oxidase: a new action for an old drug. J Clin Invest 1996;98:1465-70.
52. McVeigh GE, Hamilton P, Wilson M, et al. Platelet nitric oxide and superoxide release during the development of nitrate tolerance: effect of supplemental ascorbate. Circulation 2002;106:208-13.
53. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. J Card Fail 2001;7:176-82.
54. Mohri M, Egashira K, Tagawa T, et al. Basal release of nitric oxide is decreased in the coronary circulation in patients with heart failure. Hypertension 1997;30:50-6.
55. Hare JM, Givertz MM, Creager MA, Colucci WS. Increased sensitivity to nitric oxide synthase inhibition in patients with heart failure: potentiation of beta-adrenergic inotropic responsiveness. Circulation 1998;97:161-6.
56. Chen Z, Zhang J, Stamler JS. Identification of the enzymatic mechanism of nitroglycerin bioactivation. Proc Natl Acad Sci U S A 2002;99:8306-11.
57. Sydow K, Daiber A, Oelze M, et al. Central role of mitochondrial aldehyde dehydrogenase and reactive oxygen species in nitroglycerin tolerance and cross-tolerance. J Clin Invest 2004;113:482-9.