

## LESSER RESPONSE TO ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR THERAPY IN BLACK AS COMPARED WITH WHITE PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

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### ABSTRACT

**Background** Black patients with heart failure have a poorer prognosis than white patients, a difference that has not been adequately explained. Whether racial differences in the response to drug treatment contribute to differences in outcome is unclear. To address this issue, we pooled and analyzed data from the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials, two large, randomized trials comparing enalapril with placebo in patients with left ventricular dysfunction.

**Methods** We used a matched-cohort design in which up to four white patients were matched with each black patient according to trial, treatment assignment, sex, left ventricular ejection fraction, and age. A total of 1196 white patients (580 from the prevention trial and 616 from the treatment trial) were matched with 800 black patients (404 from the prevention trial and 396 from the treatment trial). The average duration of follow-up was 35 months in the prevention trial and 33 months in the treatment trial.

**Results** The black patients and the matched white patients had similar demographic and clinical characteristics, but the black patients had higher rates of death from any cause (12.2 vs. 9.7 per 100 person-years) and of hospitalization for heart failure (13.2 vs. 7.7 per 100 person-years). Despite similar doses of drug in the two groups, enalapril therapy, as compared with placebo, was associated with a 44 percent reduction (95 percent confidence interval, 27 to 57 percent) in the risk of hospitalization for heart failure among the white patients ( $P < 0.001$ ) but with no significant reduction among black patients ( $P = 0.74$ ). At one year, enalapril therapy was associated with significant reductions from base line in systolic blood pressure (by a mean [ $\pm$ SD] of  $5.0 \pm 17.1$  mm Hg) and diastolic blood pressure ( $3.6 \pm 10.6$  mm Hg) among the white patients, but not among the black patients. No significant change in the risk of death was observed in association with enalapril therapy in either group.

**Conclusions** Enalapril therapy is associated with a significant reduction in the risk of hospitalization for heart failure among white patients with left ventricular dysfunction, but not among similar black patients. This finding underscores the need for additional research on the efficacy of therapies for heart failure in black patients. (N Engl J Med 2001;344:1351-7.)

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**L**ARGE-SCALE trials of therapy for heart failure over the past decade have shown improvements in outcome with angiotensin-converting-enzyme (ACE) inhibitors and beta-blockers.<sup>1-7</sup> In the Studies of Left Ventricular Dysfunction (SOLVD), two concurrent trials evaluating the efficacy of enalapril in patients with left ventricular systolic dysfunction, enalapril was associated with a 16 percent reduction in the risk of death from any cause among patients with symptoms<sup>6</sup> and a 20 percent reduction in the risk of death from any cause or hospitalization for heart failure among patients without symptoms.<sup>7</sup> These results and the results of other studies<sup>1-5</sup> led to the recommendation that all patients who have heart failure accompanied by a low ejection fraction and who can tolerate ACE inhibitors and beta-blockers should be treated with both agents.<sup>8,9</sup>

However, data from the second Vasodilator-Heart Failure Trial (V-HeFT II) indicated that although enalapril therapy, as compared with treatment with a combination of hydralazine and isosorbide dinitrate, was associated with a significant reduction in the risk of death from any cause among white patients, no such benefit was observed among black patients.<sup>10</sup> Furthermore, in the Beta-Blocker Evaluation of Survival Trial it was found that white, but not black, patients with heart failure appear to benefit from the beta-blocker bucindolol,<sup>11</sup> suggesting that there may be racial differences in therapeutic response. A critical impediment to the analysis of racial differences in therapeutic response is the underrepresentation of black patients in trials of therapy for heart failure. In V-HeFT I and II,<sup>2,12</sup> 27 percent of the patients were black, and in SOLVD,<sup>6,7</sup> 12 percent were black. In other trials, the proportion of black patients was considerably smaller,<sup>1-5</sup> in part because of the inclusion of patients from large numbers of European centers.

A previous analysis of data from SOLVD identified a poorer outcome in black patients than in white patients.<sup>13</sup> Black patients were 28 percent more likely to die from any cause and 37 percent more likely to

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die from any cause or to be hospitalized for heart failure than white patients, a finding that was independent of important prognostic and socioeconomic factors. However, the relatively small number of black patients and the prominent differences between their baseline characteristics and those of the white patients prevented reliable evaluation of differences in the response to enalapril in terms of mortality. Nonetheless, a possible difference in the response to enalapril in terms of the risk of death from any cause or hospitalization for heart failure was observed after adjustment for important prognostic variables ( $P=0.08$ ). This observation formed the rationale for the present analysis of participants in SOLVD. In this analysis, procedures for matching<sup>14</sup> were used to identify a population of similar white patients in whom the response to enalapril could be more reliably compared with that in the black patients.

## METHODS

### Patients

Patients 21 to 80 years of age who had a left ventricular ejection fraction of 0.35 or less, as measured by echocardiography, radionuclide angiography, or contrast angiography, were eligible for enrollment in SOLVD.<sup>6,7</sup> Enrollment began in June 1986, and enrollment was completed in March 1989 in the case of the treatment trial and May 1990 in the case of the prevention trial. Patients with a recent history of myocardial infarction (within the preceding 30 days), clinically significant valvular heart disease, or a serious coexisting illness were excluded.<sup>6,7</sup> All 6797 participants underwent a detailed base-line evaluation at the time of enrollment. Patients were enrolled in the prevention trial if they had no symptoms of heart failure requiring treatment and were enrolled in the treatment trial if they had symptomatic disease. There were 4228 patients in the prevention trial and 2569 patients in the treatment trial; most of the patients in the treatment trial had New York Heart Association (NYHA) functional class II or III symptoms. Patients were randomly assigned to receive up to 20 mg of enalapril or placebo daily and then were followed for a mean ( $\pm$ SD) of  $35 \pm 14$  months in the prevention trial and  $33 \pm 15$  months in the treatment trial.<sup>6,7</sup> The protocol was approved by the institutional review boards of the participating centers, and written informed consent to participate in the trials was obtained from all patients.

### Classification of Race

Data on race and ethnic background were obtained from the SOLVD eligibility form, on which participants identified themselves as American Indian, Asian, black, white, Hispanic, or "other." Participants who identified themselves as black or white constituted the comparison groups for this analysis. A total of 800 participants (404 [50.5 percent] in the prevention trial and 396 [49.5 percent] in the treatment trial) categorized themselves as black. Another 5719 participants categorized themselves as white and thus were eligible to be matched with one of the 800 black participants.

### Matching

Because of the difficulty in ascertaining whether racial differences in outcomes are attributable to race or to other factors,<sup>10,13</sup> patients were matched according to important prognostic variables so as to allow a precise evaluation of the response to enalapril in black patients as compared with white patients. A maximum of four white patients were matched with each black patient to increase statistical power.<sup>14</sup> Patients were matched according to the trial (participation in the prevention trial or in the treatment trial), exact value of the left ventricular ejection fraction, randomly assigned

therapy (enalapril or placebo), sex, and age (<60, 60 to 67, or >67 years). Matching was performed in an automated fashion, independently of outcome, with Stata software (release 6.0, Stata, College Station, Tex.).

### Variables

Age, blood pressure, and left ventricular ejection fraction were assessed as continuous variables. The randomly assigned therapy (enalapril or placebo) as well as sex, the presence or absence of financial distress during the 12 months before enrollment in SOLVD, and the cause of left ventricular dysfunction (ischemic or other) were assessed as dichotomous variables, as were other base-line characteristics, including the use of medications at base line. Indicator variables were used in the evaluation of NYHA functional class (class II vs. class I, and class III or IV vs. class I) and the highest level of education (high school vs. elementary, and college or higher vs. elementary).

### End Points

Deaths from any cause and hospitalizations for heart failure were prospectively recorded for all the participants. The causes of death were evaluated in a blinded fashion and categorized by the investigators at each center as worsening heart failure (with or without arrhythmia), arrhythmia without preceding heart failure, another cardiovascular cause, or a noncardiovascular cause. For the present analysis, deaths due to pump failure included those classified as due to worsening heart failure (with or without arrhythmia), and deaths due to arrhythmia included those attributed to an arrhythmia without worsening heart failure. Since the composite end point of death from any cause or hospitalization for heart failure is considered a valid and robust indicator of therapeutic efficacy in patients with heart failure,<sup>7,15</sup> it and its components were used as the primary end points in this analysis.

### Statistical Analysis

Characteristics assessed as continuous variables are presented as means  $\pm$ SD. Pairwise comparisons were made with use of the chi-square test or t-test. Overall incidence rates were compared by means of the log-rank test. Estimates of the association of enalapril with outcome were assessed with the use of Cox proportional-hazards analysis.<sup>16</sup> Additional Cox models, which included age, educational level, presence or absence of financial distress, NYHA functional class, cause of left ventricular dysfunction, presence or absence of a history of hypertension, presence or absence of a history of diabetes, and use or nonuse of beta-blockers at base line, were used to assess the independent association of enalapril therapy with outcome. The presence of a statistical interaction was assessed in a Cox model that included the racial category, randomly assigned treatment, and a multiplicative interaction term (for the interaction between treatment and race). Estimates of relative risks and 95 percent confidence intervals were obtained from the Cox models. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

## RESULTS

### Matching

A total of 1196 white patients, 580 (48.5 percent) of whom were enrolled in the SOLVD prevention trial and 616 (51.5 percent) of whom were enrolled in the SOLVD treatment trial, were matched with the 800 black patients (404 [50.5 percent] and 396 [49.5 percent], respectively). The proportion of black patients and matched white patients was similar in the two trials ( $P=0.38$ ). There were 1, 2, 3, or 4 matched white patients for each of 579, 72, 67, and 68 black patients, respectively; the remaining 14 black patients could not be matched.

**Characteristics**

In line with previously described differences between the overall populations of black and white patients in SOLVD,<sup>13</sup> the black patients in the analysis were slightly younger, on average, than the matched white patients and had higher mean diastolic blood pressures. Black patients were also more likely to report having had financial distress in the 12 months before enrollment and were less likely to have attended college than the matched white patients. There were also differences between the black and matched white patients with respect to medical history and medication use at base line (Table 1). The matched white patients had base-line characteristics and degrees of illness that were more similar to those of the black patients than did the overall group of white patients. Specifically, the

proportion of women, the proportion in each NYHA functional class, and the mean left ventricular ejection fraction were similar in the black patients and the matched white patients but not in the black patients and the overall group of white patients (Table 1).

The mean final dose of study drug was similar in the black patients and the matched white patients ( $14.5 \pm 6.8$  and  $15.0 \pm 6.9$  mg per day, respectively;  $P=0.25$ ). In 389 of the 800 black patients (48.6 percent) and 750 of the 1196 matched white patients (62.7 percent), blood-pressure measurements were available at base line and one year after the initiation of therapy. At one year, black patients randomly assigned to receive enalapril did not have significant reductions from base line in either systolic blood pressure (a decline of  $1.7 \pm 20.3$  mm Hg,  $P=0.25$ ) or diastolic blood

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

CHARACTERISTIC	BLACK PATIENTS (N=800)	MATCHED WHITE PATIENTS (N=1196)	ALL WHITE PATIENTS (N=5719)
Duration of follow-up — mo	32±15	33±14	34±14†
Age — yr	57±11	59±10‡	60±10†
Female sex — no. (%)	212 (26)	349 (29)	721 (13)†
Maximal educational level — no. (%)§			
Elementary school	168 (28)	166 (17)†	821 (19)†
High school	346 (58)	565 (59)	2348 (54)
College or higher	87 (14)	232 (24)	1187 (27)
Financial distress in past year — no. (%)¶	202 (37)	217 (24)†	931 (23)†
NYHA functional class — no. (%)			
I	312 (39)	461 (39)	2675 (47)†
II	364 (46)	537 (45)	2381 (42)
III	121 (15)	187 (16)	622 (11)
IV	3 (<1)	11 (<1)	38 (<1)
Blood pressure — mm Hg			
Systolic	126±19	124±17	125±17
Diastolic	80±11	77±10†	77±10†
Left ventricular ejection fraction	0.26±0.07	0.25±0.07	0.27±0.06†
Random assignment to enalapril — no. (%)	405 (51)	586 (49)	2844 (50)
Medical history — no. (%)			
Ischemic heart disease	433 (54)	929 (78)†	4766 (83)†
Hypertension	496 (62)	417 (35)†	2034 (36)†
Diabetes	228 (28)	235 (20)†	992 (17)†
Atrial fibrillation	45 (6)	98 (8)†	372 (7)
Medication use — no. (%)			
Aspirin	210 (26)	533 (45)†	2817 (49)†
Beta-blockers	77 (10)	178 (15)‡	1094 (19)†
Digoxin	298 (37)	510 (43)	1874 (33)†
Diuretics	525 (66)	612 (51)†	2247 (39)†
Antiarrhythmic agents	98 (12)	244 (20)†	1078 (19)†

\*Plus-minus values are means ±SD. Because of rounding, not all percentages total 100. NYHA denotes New York Heart Association.

† $P < 0.01$  for the comparison with the black patients.

‡ $P < 0.001$  for the comparison with the black patients.

§Data were available for 601 of the black patients, 963 of the matched white patients, and 4356 of all the white patients.

¶Data were available for 543 of the black patients, 894 of the matched white patients, and 4054 of all the white patients.

||Data were available for 5716 of all the white patients.

pressure (a decline of  $0.5 \pm 17.8$  mm Hg,  $P=0.58$ ). In contrast, the matched white patients randomly assigned to enalapril had significant reductions in both systolic blood pressure (a decline of  $5.0 \pm 17.1$  mm Hg,  $P<0.001$ ) and diastolic blood pressure (a decline of  $3.6 \pm 10.6$  mm Hg,  $P<0.001$ ) during this period. Among those randomly assigned to placebo, both black patients and matched white patients had significant increases in systolic blood pressure ( $3.0 \pm 19.8$  mm Hg [ $P=0.04$ ] and  $2.4 \pm 15.7$  mm Hg [ $P=0.002$ ], respectively) but no significant changes in diastolic blood pressure (increases of  $0.6 \pm 11.9$  mm Hg [ $P=0.48$ ] and  $0.1 \pm 10.7$  mm Hg [ $P=0.92$ ], respectively) at one year as compared with base line.

### Outcomes

Overall, most deaths were categorized as having a cardiac cause (Table 2). The rate of death was higher among the black patients than among the matched white patients; this difference was largely attributable to the difference between the groups in the rate of death due to progressive pump failure. Rates of hospitalization for heart failure were also higher among the black patients than among the matched white patients. Rates of death due to arrhythmia, other cardiac causes, and noncardiac causes were similar in the two groups.

Among the patients randomly assigned to enalapril, black patients had 7.9 more hospitalizations per 100 person-years of follow-up (95 percent confidence interval, 5.3 to 10.6) than matched white patients ( $P<0.001$  by Fisher's exact test) (Fig. 1). In contrast, black patients and matched white patients randomly assigned to placebo had similar rates of hospitalization for heart failure (2.8 more hospitalizations per 100 patient-years [95 percent confidence interval, 0.1 fewer to 10.6 more] among black patients;  $P=0.06$  by Fisher's exact test). Mortality was similar among the black patients and the matched white patients regardless of treatment assignment (Fig. 1).

### Association of Enalapril with Outcome

The risk of hospitalization for heart failure differed significantly between the black patients and the matched white patients assigned to therapy with enalapril ( $P=0.005$ ). A 44 percent reduction (95 percent confidence interval, 27 to 57 percent) in the risk of hospitalization for heart failure was observed with enalapril as compared with placebo among the matched white patients but not among the black patients (Table 3). The reduction associated with enalapril in the risk of hospitalization for heart failure was similar in the matched white patients enrolled in the prevention trial (47 percent; 95 percent confidence interval, 10 to 69 percent) and those enrolled in the treatment trial (45 percent; 95 percent confidence interval, 26 to 60 percent). Differences between the black patients and the matched white patients in the

**TABLE 2. OUTCOMES AMONG BLACK PATIENTS AS COMPARED WITH MATCHED WHITE PATIENTS.**

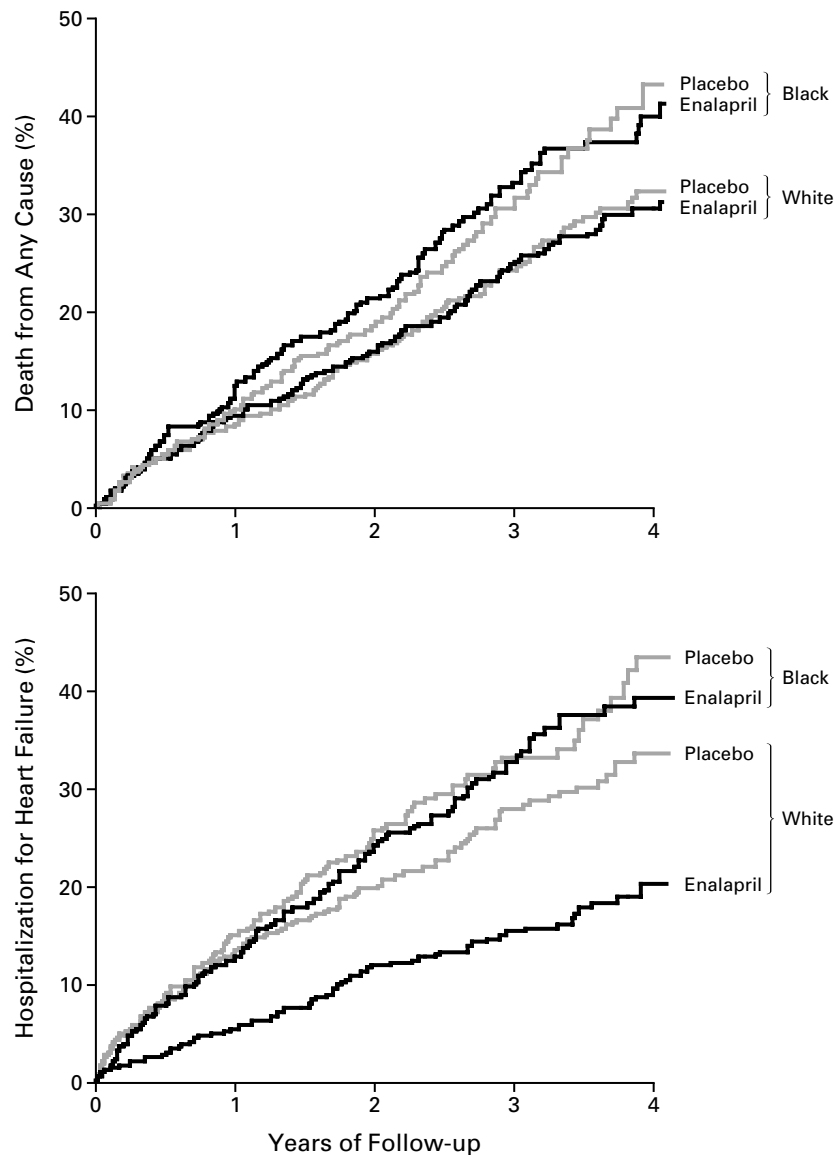
OUTCOME	BLACK PATIENTS (N=800)		MATCHED WHITE PATIENTS (N=1196)	
	NO.	INCIDENCE PER 100 PERSON-YR	NO.	INCIDENCE PER 100 PERSON-YR
Death from any cause	256	12.2	311	9.7*
Death due to specific causes				
Pump failure	117	5.6	126	3.9*
Sudden arrhythmia	53	2.5	94	2.9
Other cardiac cause	59	2.8	60	2.0
Noncardiac cause	27	1.3	31	1.0
Hospitalization for heart failure	238	13.2	226	7.7*

\* $P<0.01$  for the comparison with the black patients by the log-rank test.

effect of enalapril on the risk of hospitalization for heart failure were not significantly different when patients were stratified according to the presence or absence of a history of hypertension or a history of diabetes or according to the cause of left ventricular dysfunction. Similar results were observed after adjustment for these and other potentially confounding variables, including educational level and the presence or absence of financial distress (Table 3). No significant alteration in mortality was observed in association with enalapril therapy in either group. Although quantitative differences in the risk of the combined end point (death from any cause or hospitalization for heart failure) were observed between the black patients and the matched white patients according to treatment assignment, there was no significant interaction between treatment and race.

### Overall Population of White Patients

Enalapril was associated with a 40 percent reduction (95 percent confidence interval, 32 to 47 percent) in the risk of hospitalization for heart failure in the overall population of 5719 white patients before statistical adjustment and a 46 percent reduction (95 percent confidence interval, 37 to 53 percent) after adjustment for age, sex, educational level, presence or absence of financial distress, left ventricular ejection fraction, NYHA functional class, cause of left ventricular dysfunction, presence or absence of a history of hypertension, presence or absence of a history of diabetes, and use or nonuse of beta-blockers at base line. Enalapril was also associated with a significant reduction of 11 percent (95 percent confidence interval, 1 to 20 percent) in the risk of death from any cause before adjustment and with a 14 percent reduction (95 percent confidence interval, 3 to 24 percent) in the risk of death from any cause after mul-



**Figure 1.** Rates of Death from Any Cause (Top Panel) and of Hospitalization for Heart Failure (Bottom Panel) among Black Patients and Matched White Patients Randomly Assigned to Enalapril or Placebo.

The rate of hospitalization for heart failure among black patients assigned to enalapril was significantly higher than that among matched white patients assigned to enalapril ( $P < 0.001$  by Fisher's exact test). Mortality was similar among black patients and matched white patients, regardless of treatment.

tivariate adjustment in the overall group of white patients.

### DISCUSSION

Enalapril therapy is associated with a significant reduction in the risk of hospitalization for heart failure in white patients with left ventricular dysfunction, but with no significant alteration in this outcome among similar black patients. Despite similar doses

of the study drug, black patients randomly assigned to enalapril had no significant reduction in systolic or diastolic blood pressure, whereas white patients had significant reductions in both systolic and diastolic blood pressure. No significant change in the risk of death was observed in association with enalapril among either the black or the matched white patients.

The results of V-HeFT II raised the possibility of a racial difference in the response to ACE inhibitors

**TABLE 3.** OUTCOMES AMONG BLACK AND MATCHED WHITE PATIENTS ASSIGNED TO ENALAPRIL THERAPY AS COMPARED WITH PLACEBO.

OUTCOME	RELATIVE RISK (95% CI)*		P VALUE FOR INTERACTION†
	UNADJUSTED	ADJUSTED‡	
Hospitalization for heart failure			0.005
Black patients	0.96 (0.74–1.24)	0.86 (0.64–1.16)	
Matched white patients	0.56 (0.43–0.73)§	0.51 (0.37–0.70)§	
Death from any cause			0.68
Black patients	0.89 (0.69–1.13)	0.85 (0.64–1.14)	
Matched white patients	0.95 (0.76–1.18)	0.92 (0.72–1.17)	

\*CI denotes confidence interval.

†P values are for the interaction between treatment and race with respect to the specified end point.

‡The model was adjusted for age, New York Heart Association functional class, educational level, presence or absence of financial distress in preceding 12 months, cause of left ventricular dysfunction, presence or absence of a history of hypertension, presence or absence of a history of diabetes, and use or nonuse of beta-blockers at base line.

§P<0.001 for the comparison between treatment with enalapril and treatment with placebo.

because enalapril, as compared with a combination of hydralazine and isosorbide dinitrate, was associated with a reduction in mortality among white patients but not among black patients.<sup>10</sup> Interpretation of this observation is complicated by the fact that in V-HeFT I, the combination of hydralazine and isosorbide dinitrate had a benefit predominantly in black patients.<sup>10</sup> Thus, the difference in response between black and white patients in V-HeFT II may be attributable to a better response to enalapril among the white patients, a better response to hydralazine and isosorbide dinitrate among the black patients, or a combination of these factors.

In V-HeFT II, enalapril produced a sustained reduction in blood pressure in the white patients but not in the black patients,<sup>10</sup> providing evidence that some of the difference in benefit may be due to a difference in the response to ACE-inhibitor therapy. The present analysis of data from SOLVD supports this hypothesis. In addition, in the recently completed Beta-Blocker Evaluation of Survival Trial, it was found that patients with heart failure who were white, but not those who were black, had evidence of benefit from beta-blocker therapy.<sup>11</sup> These trials have raised the troubling possibility that black patients with heart failure may not benefit from commonly used doses of currently recommended therapies to the same extent as white patients.

A lesser response to ACE inhibitors in black patients as compared with white patients is not surprising, given previous clinical and experimental evidence. Black patients with hypertension have been shown to have smaller reductions in blood pressure, on average, than white patients given similar doses of ACE inhibitors<sup>17</sup> and beta-blockers.<sup>18</sup> This difference in re-

sponse has previously been attributed to lower plasma renin activity in black patients.<sup>19,20</sup> Although the renin mechanism may contribute to responsiveness to ACE inhibitors, renin activity has not served as a useful marker of the long-term effects of ACE-inhibitor therapy in either patients with hypertension<sup>21-23</sup> or those with heart failure.<sup>24</sup> Recent evidence suggests that the long-term benefits of ACE inhibition may be related to factors other than a reduction in circulating angiotensin.<sup>25</sup> ACE inhibition results in increased kinin activity, which may exert favorable long-term effects on the heart through endogenous nitric oxide release.<sup>26</sup> The bioactivity of endogenous nitric oxide is known to be lower in blacks than in whites, perhaps because of higher oxidative stress in blacks.<sup>27,28</sup> Thus, a difference in the response to ACE inhibitors between black and white patients may be related to mechanisms other than differences in plasma renin activity.

In the present analysis, we matched white patients with black patients according to important prognostic factors. However, the groups differed in other respects. The black patients were slightly younger, were more likely to report financial distress, were less educated, were more likely to have left ventricular dysfunction that was not related to ischemia, and were more likely to have a history of hypertension or diabetes than the matched white patients. Although multivariate statistical modeling was used, the groups may have differed in other respects as well, and no degree of statistical adjustment can ensure complete comparability. It is also possible that the findings may have resulted from differences between the groups in compliance, diet, medical follow-up, or access to care. However, rates of hospitalization for heart failure were similar among the black and matched white

patients who were randomly assigned to receive placebo, suggesting that a diminished response to enalapril contributed to the poorer outcome in the black patients. It is also possible that the dose of enalapril studied (maximum, 20 mg daily) was insufficient to alter the outcome in black participants. Finally, it must be recognized that racial categorization is only a surrogate marker for genetic or other factors responsible for individual responses to therapy. Indeed, racial intermixing makes genetic distinctions problematic, and any identified differences will certainly not apply to all the members of each stratified group.

This analysis, combined with other recent data from clinical trials, suggests that the overall population of black patients with heart failure may be underserved by current therapeutic recommendations. The fact that large-scale trials of therapy for heart failure have been performed in preponderantly white populations has limited the ability of the medical community to assess the efficacy of current therapies in black patients. Thus, clinical trials in black patients that are designed prospectively to evaluate therapeutic responses appear to be warranted. Nonetheless, on the basis of available physiological, pharmacologic, and clinical data, it seems appropriate to consider current therapeutic recommendations as applying to white patients but not necessarily to black patients. The observation in V-HeFT I that the combination of isosorbide dinitrate and hydralazine, a nitric oxide donor, exerted a greater benefit in black patients than in white patients<sup>12</sup> further emphasizes the idea that therapeutic recommendations may need to be tailored according to racial background.

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