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# Outcomes by Gender in the African-American Heart Failure Trial

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**OBJECTIVES** Previous trials testing isosorbide dinitrate/hydralazine (I/H) were performed in all-male study cohorts, and thus the efficacy of I/H in women was unknown; 40% of the A-HeFT (African-American Heart Failure Trial) cohort were women. We therefore compared outcomes by gender and treatment.

**BACKGROUND** Fixed-dose combined I/H significantly reduced mortality and heart failure hospitalizations and improved quality of life in 1,050 black patients with heart failure treated with background neurohormonal blockade. Previous trials testing I/H were done in all-male study cohorts, and thus the efficacy of I/H in women was unknown.

**METHODS** Baseline characteristics and medications were compared between men and women by I/H and placebo treatment. Survival, time to first heart failure hospitalization, change in quality of life, and event-free survival were compared by gender and treatment.

**RESULTS** At baseline, women had lower hemoglobin and creatinine levels; less renal insufficiency; and higher body mass indexes, diabetes prevalence, and systolic blood pressures; but worse quality of life scores. All-cause mortality was lower in women than in men treated with I/H but without significant treatment interaction by gender. The primary composite score, which weighted mortality, first heart failure hospitalization, and change in quality of life at 6 months, was similarly improved by I/H in men and women. First heart failure hospitalization and event-free survival (time to death or first heart failure hospitalization) were similarly improved in both genders.

**CONCLUSIONS** Fixed-dose I/H improved heart failure outcomes in both men and women in A-HeFT. The I/H significantly improved the primary composite score and event-free survival as well as reduced the risk of first heart failure hospitalizations similarly in both genders. The I/H had a slightly greater mortality benefit in women, but without a significant treatment interaction by gender. (J Am Coll Cardiol 2006;48:2263–7) © 2006 by the American College of Cardiology Foundation

Women make up 50% of the population of heart failure patients; however, they are significantly under-represented in heart failure clinical trials (1–3), with still greater under-representation of ethnically diverse women. The hypothesis that isosorbide dinitrate/hydralazine (I/H) improved outcomes in African American patients was generated by reanalysis of the all-male V-HeFT (Vasodilator Heart Failure Trial)-I and -II trials (4–6); thus, the effects of gender on response to I/H was unknown. The A-HeFT (African-American Heart Failure Trial) (7) confirmed the benefit of I/H in black heart failure patients. Importantly, 40% of the A-HeFT cohort (n = 420) were women (1,2); therefore, this analysis of outcomes by gender in A-HeFT provides unique insight into the effect of gender on response to nitric oxide enhancing therapy for heart failure.

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## METHODS

**Study design.** The A-HeFT study design, patient characteristics, end point definitions, complete methodology, and main outcomes have been previously published (7). The A-HeFT was a randomized, placebo-controlled, double-blind trial in self-identified African American patients with class III or IV heart failure receiving background neurohormonal inhibition.

After eligibility was confirmed, patients were randomized to receive either a fixed-dose combination of I/H (20 mg/37.5 mg, respectively) or a placebo, added to background therapy, initiated at 1 tablet 3 times daily and titrated up to 2 tablets 3 times daily over an 18-month follow-up.

The primary efficacy end point for the trial was a composite score weighting all-cause mortality, first hospitalization for heart failure, and change in quality of life at 6 months (7).

**Statistical analysis.** Analyses were based on the intention-to-treat principle. Survival, time to either death or first hospitalization for heart failure (event-free survival), and time to first hospitalization for heart failure were compared by Kaplan-Meier survival analysis methods with the log-

**Abbreviations and Acronyms**

A-HeFT = African-American Heart Failure Trial
CI = confidence interval
HR = hazard ratio
I/H = isosorbide dinitrate/hydralazine

rank test. Additional descriptive statistics calculated for patient characteristics were displayed as counts (and percentages). Baseline characteristics and cause-specific mortality were compared among groups within gender using either a 2-sample *t* test or Fisher exact test. Comparison between gender and treatment interaction by gender were performed using 2-way analysis of variance. Analysis of composite scores with categorical variables was performed with PROC LOGISTIC software (version 8.2, SAS Institute, Cary, North Carolina).

## RESULTS

Baseline characteristics are shown in Table 1. Differences by gender but not treatment group assignment were observed in the following parameters: compared with men, women had slightly lower baseline hemoglobin and creatinine levels, as well as a lower prevalence of renal insufficiency and atrial fibrillation. Women had slightly higher body mass index, diabetes prevalence, and systolic blood pressure. Screening

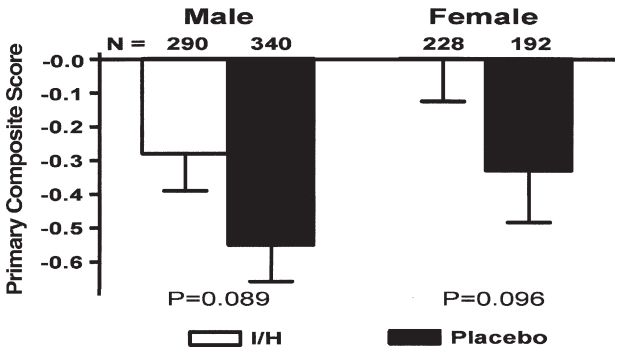


**Figure 1.** Primary composite score by gender and treatment groups. The entire group (men plus women) treated with isosorbide dinitrate/hydralazine (I/H) had a significantly improved the composite score ($p = 0.016$) compared with the entire group (men plus women) in the placebo arm. Women as a group had better composite scores than men ($p = 0.049$); however, there was no gender-by-treatment interaction ($p = 0.806$).

**Table 1.** Baseline Characteristics of Male and Female Patients by Treatment Groups (n = 1,050)

| Characteristics | Male (n = 630) | | Female (n = 420) | |
|---|---|---|---|---|
| | I/H (n = 290) | Placebo (n = 340) | I/H (n = 228) | Placebo (n = 192) |
| Age (yrs) | 56.6 ± 12.8 | 56.9 ± 12.7 | 56.9 ± 13.4 | 56.7 ± 14.3 |
| Weight (kg)* | 95.7 ± 24.8 | 97.5 ± 26.0 | 88.4 ± 23.4 | 88.0 ± 23.3 |
| Primary cause of heart failure (% of patients) | | | | |
| Ischemic heart disease | 28.3 | 23.8 | 17.1 | 20.8 |
| Hypertension | 37.2 | 39.1 | 43.4 | 34.4 |
| Idiopathic | 23.8 | 25.3 | 25.4 | 31.8 |
| Valvular cause | 2.8 | 3.2 | 2.2 | 3.1 |
| Other | 7.9 | 8.5 | 11.8 | 9.9 |
| NYHA functional class (% of patients) | | | | |
| II + III† | 96.6 | 93.2 | 97.4 | 97.4 |
| IV | 3.4 | 6.8 | 2.6 | 2.6 |
| Diabetes mellitus (%)* | 38.6 | 35.6 | 52.6 | 39.6 |
| Renal insufficiency (%)* | 20.0 | 21.1 | 11.4 | 12.5 |
| Creatinine (mg/dl)* | 1.4 ± 0.57 | 1.4 ± 0.49 | 1.1 ± 0.44 | 1.1 ± 0.38 |
| Atrial fibrillation (%)‡ | 17.9 | 19.4 | 12.3 | 14.6 |
| Ejection fraction (%)* | 23.2 ± 7.1 | 23.2 ± 7.6 | 24.8 ± 7.6 | 25.8 ± 7.0 |
| LVIDD/BSA ($cm/m^2$) | 3.16 ± 0.54 | 3.10 ± 0.53 | 3.16 ± 0.56 | 3.21 ± 0.64 |
| BMI* | 30.7 ± 7.8 | 31.3 ± 7.8 | 32.8 ± 8.3 | 33.2 ± 8.8 |
| Hemoglobin (g/dl)* | 13.8 ± 1.6 | 13.7 ± 1.8 | 12.7 ± 1.6 | 12.3 ± 1.8 |
| Blood pressure (mm Hg) | | | | |
| Systolic‡ | 125.8 ± 17.4 | 124.5 ± 17.7 | 129.0 ± 17.3 | 126.8 ± 18.6 |
| Diastolic | 77.2 ± 10.7 | 75.9 ± 10.7 | 78.1 ± 9.7 | 75.0 ± 10.2 |
| MLHF QoL score* | 48.4 ± 24.6 | 49.7 ± 25.1 | 54.1 ± 25.0 | 52.6 ± 26.2 |
| Baseline medications (%) | | | | |
| Diuretic | 92.8 | 91.5 | 89.5 | 95.3 |
| ACE inhibitor or ARB | 93.4 | 93.8 | 90.8 | 91.7 |
| Beta-blockers | 84.5 | 82.6 | 82.9 | 81.3 |
| Digoxin | 60.7 | 60.9 | 56.1 | 60.9 |
| Spironolactone | 38.6 | 38.5 | 42.1 | 36.5 |

Plus-minus values represent mean ± SD. Lower quality of life scores indicate better quality of life. There were no significant gender-by-treatment interactions in baseline characteristics. *$p < 0.01$ comparing men with women. †New York Heart Association (NYHA) functional class II represented only 1% of the A-HeFT patient population. ‡$p < 0.05$ comparing men with women.

A-HeFT = African-American Heart Failure Trial; ARB = angiotensin receptor blocker; ACE = angiotensin-converting enzyme; BMI = body mass index; BSA = body surface area; I/H = isosorbide dinitrate/hydralazine; LVIDD = left ventricular internal diameter in diastole; MLHF QoL score = Minnesota Living With Heart Failure Quality of Life score.

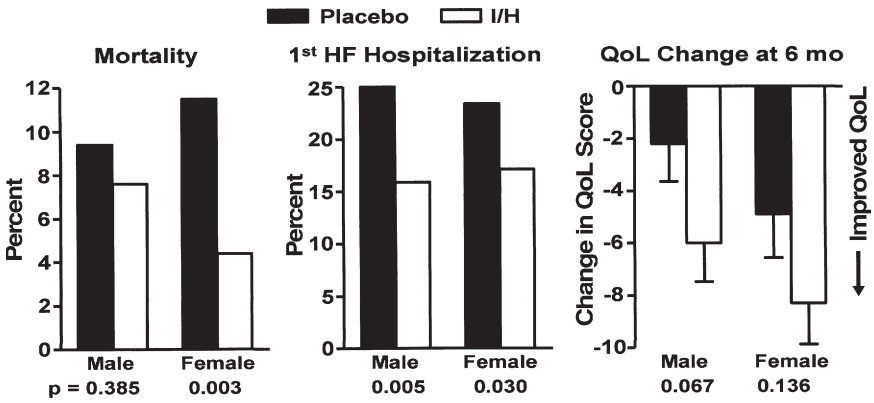


**Figure 2.** Components of the primary composite score by gender and treatment groups. The p values compare isosorbide dinitrate/hydralazine (I/H) with placebo in each group. Mortality was reduced by I/H in both men and women, with a slightly greater effect in women. First heart failure hospitalization was similarly reduced in both men and women, whereas change in quality of life (QoL) was improved in both genders without gender-by-treatment interaction.

ejection fraction was slightly lower in men than women; however, left ventricular internal diameter in diastole normalized to body surface area did not differ between the genders. Baseline quality of life scores were slightly worse in women compared with men. Analysis of the interaction between gender and treatment group assignment showed no differences in baseline characteristics.

The baseline primary composite score end point in the total group of women was significantly better than that in the total group of men ($p = 0.049$). Both genders had a response to fixed-dose combined I/H with similar magnitude of improvement over placebo in the primary composite score (Fig. 1). Components of the primary composite score (death, first heart failure hospitalization, and change in quality of life at 6 months) are shown in Figure 2. Mortality was reduced in both genders, but seemed to be reduced to a greater degree in women. First hospitalization for heart failure was significantly and similarly reduced in both genders. Change in quality of life was improved by treatment in both genders but did not reach the level of significance, likely because of the decrease in sample size by subgroup analysis.

Survival by gender and treatment groups is shown in Figure 3. Survival was better in women in the I/H arm compared with women in the placebo arm (hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.16 to 0.71, $p = 0.003$), whereas for men the difference between treatment and placebo arms was directionally similar, but of lesser magnitude (HR 0.79, 95% CI 0.46 to 1.35, $p = 0.385$). However, there was no significant difference by gender ($p = 0.303$) or treatment interaction by gender ($p = 0.470$). Figure 4 shows that the improvement in time to first heart failure hospitalization in the I/H arm was nearly identical for both genders (HR men 0.60, 95% CI 0.42 to 0.89, $p = 0.005$; HR women 0.62, 95% CI 0.41 to 0.96, $p = 0.03$). Similarly, event-free survival (time to death or first hospitalization for heart failure) (Figure 5) improved in both men and women in the I/H group (HR men 0.67, 95% CI 0.49 to 0.92, $p = 0.013$; HR women 0.58, 95% CI 0.39 to 0.86, $p = 0.007$).

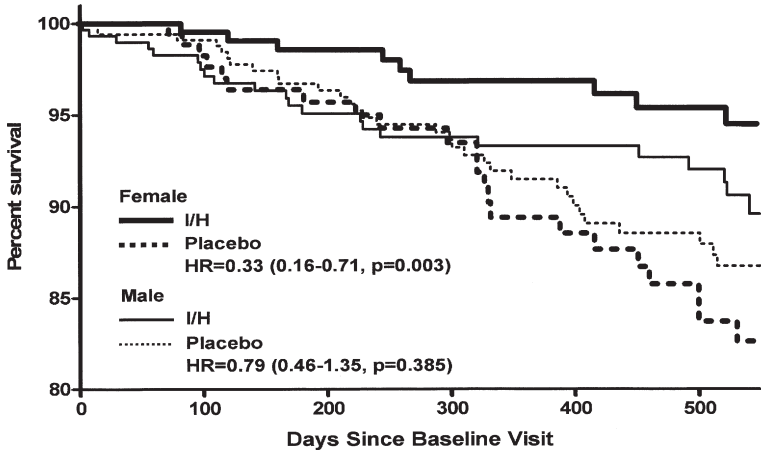


**Figure 3.** Kaplan-Meier curves for survival by gender and treatment groups. HR = hazard ratio; I/H = isosorbide dinitrate/hydralazine.

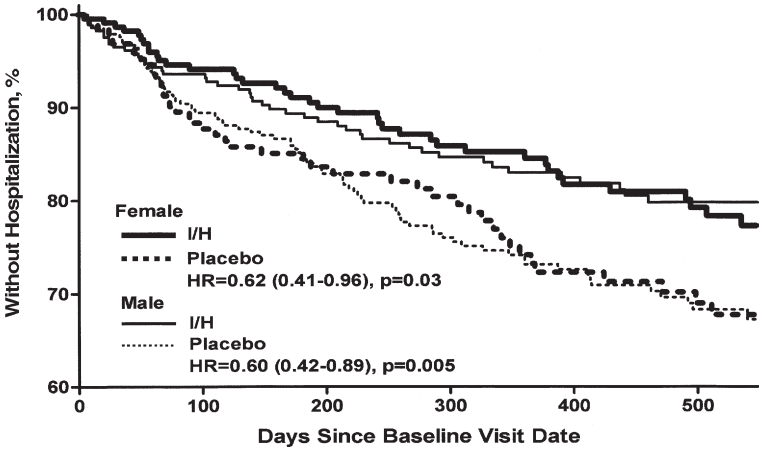


**Figure 4.** Kaplan-Meier curves for first hospitalization for heart failure by gender and treatment groups. Abbreviations as in Figure 3.

Mortality from any cause was low and without gender-by-treatment interaction (Table 2). Women had significantly lower total mortality in the I/H arm, whereas men had a directionally similar trend.

The most common I/H associated adverse events (headache, dizziness) as well as placebo-associated headaches were more common in women than men, whereas hypotension frequency was similar in men and women.

## DISCUSSION

The unique features of the A-HeFT study (7) included the focus on a single ethnic group for whom retrospective data suggested an increased responsiveness to fixed dose I/H, an exploration of the novel mechanistic approach of nitric oxide enhancement for heart failure therapy, and the inclusion of the largest percentage of women (40%), as well as the largest absolute number of African American women (n = 420), in a heart failure trial. Importantly, the V-HeFT I and II trials, which provided the hypothesis-generating data for the A-HeFT study, included only men (4–6). Thus, there were no clinical trial data examining the effect of I/H on heart failure outcomes in women.

The results of these analyses comparing heart failure outcomes in men and women in the A-HeFT cohort show that fixed-dose combined I/H improved heart failure outcomes in both men and women. There were no gender differences between men and women in the benefit of I/H on the primary composite score, time to first heart failure hospitalization, and event-free survival. The I/H seemed to have a more pronounced mortality benefit in women, but there was no significant treatment interaction by gender; thus it is possible that this finding might be attributable to chance because of the low number of deaths in the study.

Assessment of the impact of gender and/or race on response to heart failure treatment has been hampered by the low numbers of women and ethnic minorities in randomized clinical trials (1–3,8). Post-hoc and meta-analyses have therefore been performed to provide insights into the impact of these 2 variables, with the recognition that small sample size and different study designs impose limitations to interpretation (9).

Differences by gender and race in the impact of risk factors, clinical features, outcomes, and response to treat-

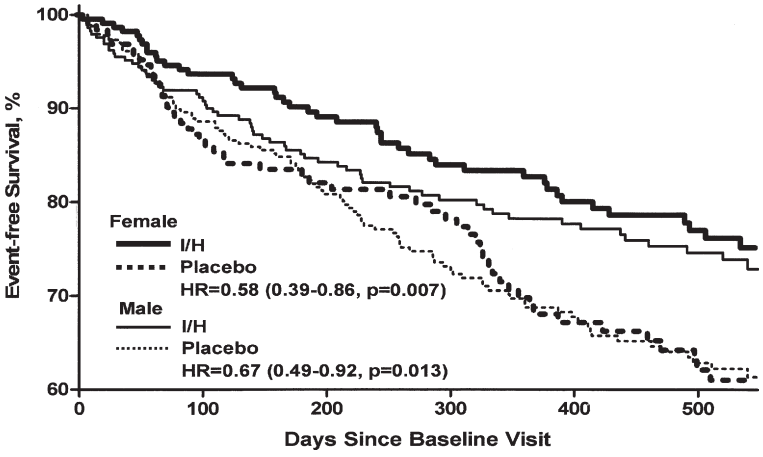


**Figure 5.** Kaplan-Meier curves for event-free survival (time to either death or heart failure hospitalization) by gender and treatment groups. Abbreviations as in Figure 3.

**Table 2.** Cause-Specific Mortality by Gender and Treatment Groups

| | Cause-Specific Mortality | | | | | |
|---|---|---|---|---|---|---|
| | Male | | | Female | | |
| | I/H (n = 290) | Placebo (n = 340) | p Value | I/H (n = 228) | Placebo (n = 192) | p Value |
| Total deaths | 22 | 32 | 0.48 | 10 | 22 | 0.009 |
| CV deaths | 18 | 28 | 0.36 | 8 | 17 | 0.023 |
| SCD | 14 | 17 | 1.0 | 3 | 7 | 0.197 |
| Pump failure | 3 | 8 | 0.24 | 1 | 8 | 0.013 |
| MI | 0 | 1 | 1.0 | 0 | 1 | 0.45 |
| CVA | 1 | 2 | 1.0 | 3 | 1 | 0.63 |
| Non-CV deaths | 4 | 4 | 1.0 | 2 | 5 | 0.25 |

Numbers indicate events. Men versus women, p = 0.049. Gender-by-treatment interaction, p = 0.806. I/H treatment versus placebo, p = 0.016. p values compare treatment with I/H to placebo.

CV = cardiovascular; CVA = cerebrovascular accident; I/H = isosorbide dinitrate/hydralazine; MI = myocardial infarction; SCD = sudden cardiac death.

ment (1,3,6,8–11) have been documented in patients with heart failure. Thus, diabetes increases the risk of heart failure to a much greater extent in women than men (3), and women with heart failure experience greater functional impairment as well as poorer quality of life than men (3). Comparisons of men and women with nonischemic cardiomyopathies show significantly better survival in women; however, both genders with ischemic cardiomyopathies have equally poor outcomes. Comorbidities such as renal insufficiency, anemia, and diabetes have all been shown to adversely impact heart failure outcomes (3). In the A-HeFT cohort, there were differences between men and women in baseline clinical characteristics, but no consistent pattern that would predict a differential response to I/H by gender.

Importantly, in contrast with what has been reported in the literature (3), there were no gender differences in baseline medications and there were no gender-by-treatment assignment group interactions. Patients in both arms of the trial were equally well treated with background neurohormonal blockade. Thus, the very significant improvement in survival in this cohort strongly suggests alternative or additional mechanisms of progression of heart failure that are responsive to fixed-dose combined I/H.

These studies emphasize the importance of inclusion of adequate numbers of subpopulations (whether defined by gender or ethnicity) to probe for differences in drug responsiveness (12). It was especially important to include an adequate sample of women in the A-HeFT trial because the original observation of enhanced efficacy of I/H in African Americans was made in all-male cohorts (4–6). This analysis of outcomes in 420 African American women with low ejection fractions and dilated left ventricles shows improved morbidity and mortality in both genders and provides strong evidence for the use of fixed-dose I/H in African American men and women.

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