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Influence of Blood Pressure on the Effectiveness of a Fixed-Dose Combination of Isosorbide Dinitrate and Hydralazine in the African-American Heart Failure Trial

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Objectives This study sought to assess the effect of baseline systolic blood pressure (SBP) and changes in SBP on the effectiveness of treatment with fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) in patients with heart failure (HF).

Background Low SBP is a risk factor for adverse outcomes in patients with HF. However, FDC I/H lowered SBP in the A-HeFT (African-American Heart Failure Trial) and yet prolonged survival. Whether blood pressure (BP) lowering is critical to the efficacy of FDC I/H and whether a low BP limits its effectiveness is unclear.

Methods The effects of FDC I/H on SBP and on mortality and hospitalization were compared in patients with a low or high baseline SBP using multivariable Cox regression models. The interaction between the effect of treatment and baseline SBP was examined.

Results Mean ± SD baseline SBP in all of the patients was 126 ± 18 mm Hg. Patients with baseline SBP equal to or below the median (126 mm Hg) had features of more severe HF. Baseline SBP equal to or below the median was an independent risk factor for death (hazard ratio [HR] 2.09; 95% confidence interval [CI] 1.02 to 4.29) or first hospitalization for HF (HR 1.66; 95% CI 1.18 to 2.34). The FDC I/H treatment reduced BP in patients with SBP above the median but not in patients with SBP below 126 mm Hg. The FDC I/H treatment was associated with a similar decrease in mortality or hospitalization for HF in patients with SBP below the median and above the median. The effects of FDC I/H on mortality alone were also similar.

Conclusions In A-HeFT, patients with lower SBP had a greater risk but a similar relative benefit from the use of FDC I/H as those with higher SBP. The FDC I/H treatment did not reduce SBP in patients with low SBP. An asymptomatic low SBP should not be considered a contraindication to use of FDC I/H in patients with HF. (J Am Coll Cardiol 2007;49:32–9) © 2007 by the American College of Cardiology Foundation

High blood pressure increases the risk of death in the general population (1), and the benefits of reducing blood pressure on risks of major cardiovascular events are well established (2–4). In patients with heart failure (HF), however, low blood pressure is a manifestation of a low cardiac output and is associated with an increase in mortality (5–7). Indeed, vasodilator drugs that increase cardiac output may further reduce blood pressure in some but not all patients (8). In the V-HeFT (Vasodilator Heart Failure Trial) study, the vasodilator combination of isosorbide dinitrate and hydralazine added to background therapy with digoxin and diuretics did not significantly lower blood pressure but improved survival

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(9). Furthermore, prazosin, an alpha-adrenergic receptor blocker, lowered blood pressure but did not improve survival (9). In the recently reported A-HeFT (African-American Heart Failure Trial) study, the fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) therapy resulted in a modest blood pressure reduction and profound reduction in mortality and morbidity when added to background therapy that included angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), and/or beta-blockers (10). The benefits of FDC I/H and other antihypertensive regimens on outcome has been attributed to the blood pressure lowering effect (11,12) and not to any specific direct action of the drugs on vascular and cardiac structure and function.

However, concerns about the hypotensive effects of medications with vasodilator actions often limit their use in patients with HF, especially in those with a low pretreatment blood pressure. Indeed, some physicians hesitate to prescribe these drugs to avoid reducing blood pressure further. Whether FDC I/H worsens hypotension, particularly in patients with low pretreatment blood pressure, and whether an initial low systolic blood pressure (SBP) or decrease in blood pressure related to the use of FDC I/H limits its effectiveness in patients with HF has not been evaluated.

The purpose of this investigation was to analyze the effects of baseline blood pressure and changes in blood pressure on the effectiveness of treatment with FDC I/H on morbidity and mortality in the A-HeFT study. First, we confirmed that a lower baseline SBP was independently associated with increased risk of morbidity and mortality. Then the interaction between the effects of treatment and baseline SBP controlling for several other known prognostic variables was examined. Changes in SBP with FDC I/H or placebo were related to subsequent morbidity and mortality. Finally, to determine whether adjusting for any potentially deleterious decreases in blood pressure would enhance the apparent beneficial effects of FDC I/H, we examined how controlling for changes in SBP affected the beneficial effect of treatment on morbidity and mortality.

Methods

Study design and patient selection. The details of the A-HeFT study have been published previously (10). Briefly, the A-HeFT study was a randomized, placebo-controlled, double blind trial in self-identified black patients recruited at 169 centers in the U.S. The trial evaluated the efficacy of FDC I/H versus placebo in 1,050 patients with New York Heart Association functional class III to IV HF. Patients 18 years and older with a left ventricular ejection fraction (LVEF) ≤35% or LVEF <45% with a left ventricular internal diastolic diameter >2.9 cm/m^2 of body surface area or >6.5 cm by echocardiography within the 6 months preceding randomization were eligible for screening. Exclusion criteria included uncontrolled hypertension defined as an SBP persistently >160 mm Hg or diastolic blood pressure >95 mm Hg. The protocol did not specify a minimum required SBP at baseline; however, patients with symptomatic hypotension were excluded. Randomization to either a fixed-dose combination of FDC I/H or a placebo added to background therapy was stratified according to use of a beta-blocker in background therapy. Therapy was initiated at 1 tablet containing either placebo or 20 mg isosorbide dinitrate and 37.5 mg hydralazine hydrochloride 3 times daily. Up-titration of the dose to 2 tablets 3 times daily (120/225 mg of FDC I/H daily) was scheduled after 3 to 5 days, depending on tolerability as assessed by telephone. The first follow-up visit was scheduled for 3 months, and follow-up continued at 3-month intervals for up to 18 months. At baseline and at each follow-up visit, a single measurement of blood pressure was recorded in the supine position using the cuff method.

Abbreviations and Acronyms

ACE-I = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker
CI = confidence interval
FDC I/H = fixed-dose combination of isosorbide dinitrate and hydralazine
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
SBP = systolic blood pressure

The primary efficacy end point for the trial was a novel composite score weighting all-cause mortality, first hospitalization for HF, and change in the effect of HF on quality of life as measured by the Minnesota Living With Heart Failure questionnaire at 6 months (10).

Data analysis. Baseline variables were compared using the 2-sample *t* test for quantitative variables and Fisher exact test for categorical variables. Time-to-events in various groups were described by Kaplan-Meier curves. Cox proportional hazards regression models were used to assess the association between time to death from any cause and baseline SBP, changes in SBP during the first 3 months of follow-up, and treatment with FDC I/H. Baseline SBPs were initially grouped into quartiles to examine whether baseline SBP was linearly related to the mortality and hospitalization hazards, and to examine the effects of FDC I/H on SBP. The quartile analysis indicated that the relationships between baseline SBP and hazards were not linear. We did not attempt to fit nonlinear models of SBP as a continuous variable. Subsequent tests for interactions between the effects of FDC I/H and baseline SBP and effect modification by changes in SBP used the median baseline SBP to group patients. Median groupings were used to enhance statistical power and also because the effects of SBP were similar in the 2 quartiles below the median and in the 2 quartiles above the median. Analyses were repeated using time to first hospitalization for HF or death as the dependent variable. All of the regression models included baseline age, body mass index, heart rate, serum sodium, creatinine, uric acid, hemoglobin, logarithm of the brain natriuretic peptide concentration (measured in 649 of the 1,050 subjects), LVEF, Minnesota Living With Heart Failure questionnaire score, presence of ischemic heart disease, diabetes mellitus or atrial

fibrillation, and use of an ACE-I or ARB, beta-adrenergic receptor blocker, spironolactone, or diuretics as covariates. The SBPs in the 2 treatment groups were compared at each time point using a 2-sample *t* test. SAS statistical software (version 8.2, SAS Institute Inc., Cary, North Carolina) was used for all analyses. A p value <0.05 was considered significant without adjustment for making multiple comparisons for this secondary analysis of data from a clinical trial.

Results

Patient characteristics. The mean ± SD of the SBP at baseline was 126 ± 18 mm Hg (n = 1,050). Baseline characteristics of patients with SBP above and below the median value of 126 mm Hg are subgrouped by treatment and compared in Table 1. Patients with SBP equal to or below the median had features of more severe HF with lower LVEF, higher LV internal diameters in diastole, higher prevalence of atrial fibrillation, and poorer quality of life than those with an SBP above the median. Patients with a lower SBP were also more likely to be male and to be treated with diuretics, digoxin, and spironolactone, and less likely to receive calcium channel blockers. Patients with a higher SBP were more likely to have their HF attributed to hypertension.

Above the median, baseline mean SBPs averaged 141 ± 11 mm Hg and 141 ± 10 mm Hg in the FDC I/H and placebo treatment groups, respectively. Most other patient characteristics were also similar in these FDC I/H and placebo groups, although the percentage of male patients was higher and

Table 1 Baseline Characteristics by Median SBP and Treatment Group (n = 1,050)

	SBP ≤126 mm Hg (n = 537)		SBP >126 mm Hg (n = 513)	
	FDC I/H (n = 256)	Placebo (n = 281)	FDC I/H (n = 262)	Placebo (n = 251)
Demographics				
Age (yrs)	55 ± 12	55 ± 13	58 ± 13	59 ± 13
Male (%)	61	67	51	60*
Blood pressure (mm Hg)				
Systolic	113 ± 10	111 ± 10*	141 ± 11	141 ± 10
Diastolic	73 ± 9	70 ± 9†	82 ± 9	82 ± 9
Mean	86 ± 8	84 ± 8†	102 ± 8	101 ± 8
Heart rate (beats/min)	74 ± 13	73 ± 11	74 ± 12	73 ± 11
Cause of heart failure (%)				
Ischemic heart disease	24	22	22	24
Hypertensive	32	30	48	46
Idiopathic	29	34	20	21
Valvular	4	3	1	3
Other	11	11	8	7
NYHA functional class (%)				
III	96	95	98	95
IV	4	5	2	5
Qualifying LVIDD (cm)	6.62 ± 0.91	6.69 ± 0.97	6.31 ± 0.83	6.31 ± 0.87
Qualifying LVEF (%)	23.4 ± 7.3	22.5 ± 6.9	25.3 ± 6.5	25.7 ± 6.7
Diabetes mellitus (%)	40	31*	50	44
Atrial fibrillation (%)	17	20	14	16
MLHFQ score	55 ± 24	54 ± 25	47 ± 26	47 ± 26
LnBNP (pg/ml)	4.80 ± 1.52	5.05 ± 1.43	4.85 ± 1.39	4.91 ± 1.40
Body mass index (kg/m^2)	32 ± 8	32 ± 8	31 ± 8	32 ± 9
Serum sodium (mEq/l)	139 ± 3	139 ± 3	140 ± 3	140 ± 3
Serum creatinine (mg/dl)	1.24 ± 1.2	1.32 ± 1.2	1.23 ± 1.1	1.23 ± 1.1
Uric acid (mg/dl)	8.8 ± 2.3	8.7 ± 2.7*	7.9 ± 2.1	7.8 ± 2.3
Hemoglobin (g/dl)	13.3 ± 1.6	13.3 ± 1.8	13.3 ± 1.7	13.2 ± 2.0
Baseline medications (%)				
Diuretic	91	96*	91	89
ACE-I or ARB	93	93	91	93
Beta-blocker	84	80	83	84
Digoxin	61	66	56	55
Spironolactone	48	45	32	30
Calcium channel blocker	14	12	28	28

Values are mean ± SD. *p < 0.05. †p < 0.01.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; FDC I/H = fixed-dose combination of isosorbide dinitrate and hydralazine; LnBNP = log brain natriuretic peptide; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic diameter; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association; SBP = systolic blood pressure.

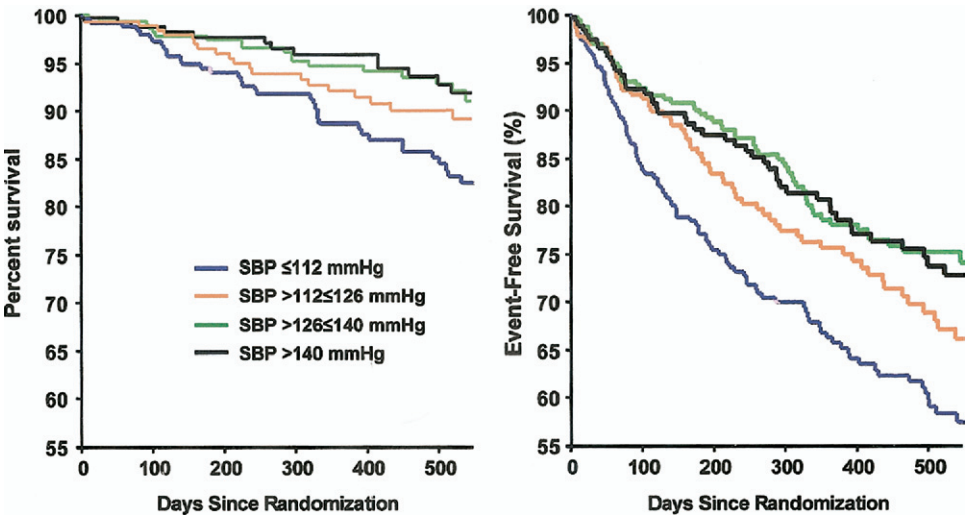

Figure 1 **Effect of Baseline SBP on Mortality and Morbidity**

Kaplan-Meier curves for mortality **(left)** and for mortality or the first hospitalization for heart failure **(right)**, by quartiles of baseline systolic blood pressure (SBP).

diabetes mellitus tended to be less prevalent in the placebo group. The mean SBP in patients below the median were 113 ± 10 mm Hg and 111 ± 10 mm Hg ($p < 0.05$) in the FDC I/H and placebo treatment groups, respectively. Use of a diuretic was less prevalent, and diabetes mellitus was more prevalent in this FDC I/H group compared with the placebo group.

Baseline SBP related to morbidity and mortality. Unadjusted time-to-event curves within quartiles of baseline SBP are shown in Figure 1. The risk of mortality alone and mortality or first hospitalization for HF were similar in the 2 upper quartiles and increased in the lower quartiles. The unequal spacing between the curves representing quartiles of SBP suggests that SBP is not linearly related to the risk (hazard) of death or hospitalization for HF. Adjusted hazard ratios (HRs) for morbidity and mortality for groups defined by baseline SBP are shown in Table 2. The adjusted risks of mortality and mortality or the first hospitalization for HF in the quartile with a baseline SBP above 140 mm Hg were not significantly different from the reference quartile with SBP ranging from over 126 to 140 mm Hg. However, the risk of hospitalization for HF or death was significantly greater in the quartile with SBP ≤112 mm Hg and in the quartile with SBP >112 mm Hg to 126 mm Hg. The mortality risk was also significantly greater when the baseline SBP was ≤112 mm Hg compared with the reference quartile (SBP >126 and ≤140 mm Hg), and the risk tended to be higher in the quartile with SBP ranging from 112 to 126 mm Hg. Collapsing quartiles above and below the median to increase precision, patients with a baseline SBP below the median of 126 mm Hg had a significantly increased risk of death (HR 2.09, 95% confidence interval [CI] 1.02 to 4.29) and risk of death or first hospitalization for HF (HR 1.66, 95% CI 1.18 to 2.34) compared with those with an SBP above 126 mm Hg. Thus, a lower baseline SBP was an independent risk factor for morbidity and mortality.

Effect of baseline SBP on effectiveness of treatment. Overall, FDC I/H caused a 43% reduction in all-cause mortality (HR 0.57, 95% CI 0.37 to 0.89) and a 37%

Table 2 **Adjusted Hazard Ratios (95% Confidence Interval) for Morbidity and Mortality for Patients Grouped by Baseline Systolic Blood Pressure**

Systolic Blood Pressure (mm Hg)	Number of Patients	Mortality	Mortality or First Heart Failure Hospitalization
Quartiles			
≤112	179	2.59 (1.03–6.51)*	1.90 (1.23–2.94)†
>112 and <126	139	1.71 (0.60–4.89)	1.64 (1.03–2.63)*
>126 and ≤140	179	Reference group	Reference group
>140	129	1.12 (0.36–3.46)	1.19 (0.70–2.03)
Median			
≤126	318	2.09 (1.02–4.29)*	1.66 (1.18–2.34)†
>126	308	Reference group	Reference group

See Data Analysis section for list of covariates in the Cox regression model (n = 626 with all covariates). *$p < 0.05$. †$p < 0.01$.

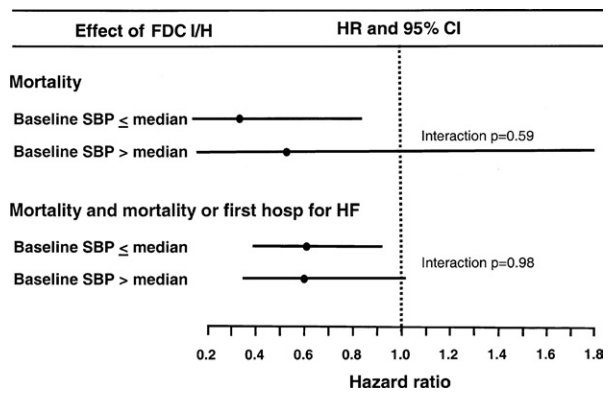

Figure 2 **Effect of FDC I/H Treatment on Mortality and Morbidity by Median Baseline SBP**

Effectiveness of fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) treatment on mortality and morbidity in patients above or below the median baseline systolic blood pressure (SBP) shown as point estimates of the hazard ratios (HR) with 95% confidence intervals (CI). HF = heart failure.

reduction in mortality or first hospitalization for HF (HR 0.63, 95% CI 0.49 to 0.81) (10). When baseline SBP and other covariates were included in a Cox regression model, the effects of FDC I/H on mortality or morbidity were not different in patients with a baseline SBP below or above the median of 126 mm Hg (Fig. 2). The FDC I/H treatment was associated with a 67% decrease in mortality in patients with an SBP below the median (HR 0.33, 95% CI 0.13 to 0.85) and a 48% decrease in mortality in patients with an SBP above the median (HR 0.52, 95% CI 0.15 to 1.80) (interaction p = 0.59). Similarly, the effects of FDC I/H on mortality or first hospitalization for HF in patients with SBP below the median (HR 0.61, 95% CI 0.39 to 0.92) and above the median (HR 0.60, 95% CI 0.35 to 1.02) did not differ (interaction p = 0.98) (Fig. 2).

Effect of treatment on SBP. Overall, treatment with FDC I/H caused a significant decrease in blood pressure throughout the trial (Fig. 3). The reduction in SBP was evident at the 3-month visit, averaging 3.2 mm Hg compared with placebo ($p < 0.001$) and remained stable over time. The change in SBP with FDC I/H by quartiles of baseline SBP is shown in Table 3 and Figure 4. Compared with placebo, treatment with FDC I/H did not lower SBP in the lower 2 quartiles (≤112 and >112 and ≤126 mm Hg). In fact, the mean SBP increased in both groups, as one might expect with regression to the mean. Because the use of vasodilators might be most problematic for patients with an extremely low SBP, we also compared the response to FDC I/H (mean SBP = 95 mm Hg; n = 31) versus placebo (mean SBP = 95 mm Hg; n = 48) in the 79 patients whose baseline SBP was ≤100 mm Hg and found similar increases in SBP (Fig. 4, bottom panel). A decrease in SBP was seen in the patients in the 2 higher quartiles, and FDC I/H caused a greater decrease in SBP than placebo at the 3-month visit.

When patients were grouped by the median SBP at baseline, the mean SBP increased at 3 months in the group with SBP below the median in both treatment groups, although the SBP tended to increase less in the FDC I/H group than the placebo group (1.5 vs. 4.1 mm Hg, p = 0.06). In contrast, SBP decreased after 3 months in patients with a baseline SBP above the median, with a significantly greater decrease in the FDC I/H versus the placebo group (−7.9 vs. −2.3 mm Hg, p = 0.002). Interestingly, the daily dose of the FDC I/H received by the patients in the groups above or below the median baseline SBP was the same (4.4 ± 2.1 tablets vs. 4.4 ± 2.0 tablets).

At the 3-month visit, dizziness was reported more frequently in the FDC I/H group (24.6%) than in the placebo group (8.9%, $p < 0.001$). Reports of postural hypotension were infrequent (≤0.6%) in both groups. Syncope occurred slightly more frequently in the FDC I/H group (2% vs. 1% for placebo, p = 0.14). During the first 3 months, study medication was permanently discontinued in 2 subjects in each group because of symptomatic hypotension, and only 1 of these subjects (FDC I/H group) had a baseline SBP ≤100 mm Hg. No subjects permanently discontinued study medication because of renal dysfunction or acute renal failure during the first 3 months. Of the patients who permanently discontinued study medications for any reason, only 5%

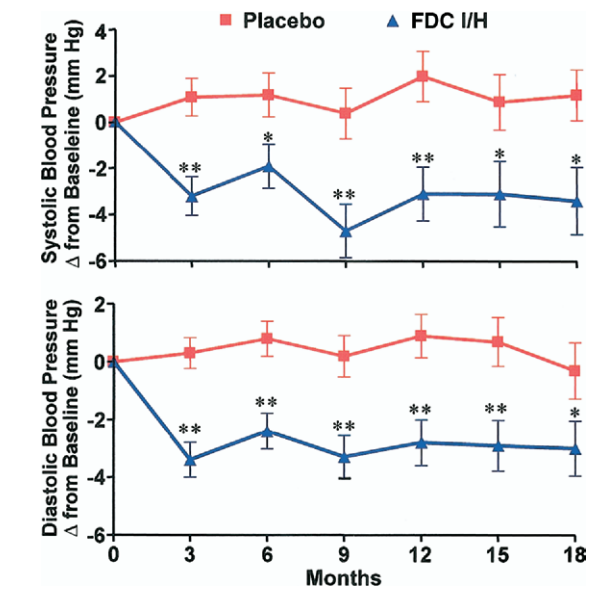

Figure 3 **Time Course of Mean SBP and DBP Change in the Placebo and FDC I/H Groups**

Note that blood pressure decreased in the active treatment group soon after starting treatment, with no further change in blood pressure over time. The p values compare changes between treatment groups: *$p < 0.05$; **$p < 0.01$. DBP = diastolic blood pressure; FDC I/H = fixed-dose combination of isosorbide dinitrate and hydralazine; SBP = systolic blood pressure.

Table 3 Effects of FDC I/H Versus Placebo on SBP After Three Months by Quartiles of Baseline SBP

	Quartiles of Baseline SBP (mm Hg)							
	≤112		>112 and ≤126		>126 and ≤140		>140	
	FDC I/H	Placebo	FDC I/H	Placebo	FDC I/H	Placebo	FDC I/H	Placebo
Number of patients	122	157	133	121	156	136	106	113
Mean SBP	105 ± 7	104 ± 7	120 ± 3	120 ± 3	134 ± 4	133 ± 4	151 ± 10	151 ± 8
Mean change	4.8	5.9	−1.6	1.6	−5.6†	0.2	−11.2*	−5.3

*$p < 0.05$. †$p < 0.01$, FDC I/H versus placebo.
Abbreviations as in Table 1.

had a baseline SBP ≤100 mm Hg. There were 6 deaths and 31 hospitalizations for HF in the FDC I/H group and 5 deaths and 51 hospitalizations for HF in the placebo group during the first 3 months.

Changes in SBP related to morbidity and mortality. Controlling for baseline SBP and other covariates and ignoring assigned treatment, change in SBP from baseline to 3 months in the group with baseline SBP above the median was positively associated with an increase in mortality (HR 1.04, 95% CI 1.00 to 1.08, $p < 0.05$) but not in combined morbidity and mortality (HR 1.0, 95% CI 0.99 to 1.02). Changes in SBP in the group with baseline SBP below the median were not associated with mortality (HR 0.99, 95% CI 0.96 to 1.02) or morbidity (HR 1.0, 95% CI 0.99 to 1.02).

Effects of treatment adjusted for change in SBP. Controlling for baseline covariates, the effect of FDC I/H on the risk of death in patients with an SBP above the median was not greatly enhanced when the change in SBP (a decrease on average) was added to the regression model (HR 0.52, 95% CI 0.15 to 1.80 vs. HR 0.49, 95% CI 0.13 to 1.80). Similarly, the risk of death in patients with an SBP below the median was not affected when the change in SBP (an increase on average) was added to the regression model (HR 0.33, 95% CI 0.13 to 0.86 vs. HR 0.33, 95% CI 0.13 to 0.87). Likewise, the effects of FDC I/H on time to first hospitalization or death also were not altered substantially when the 3-month change in SBP was added to the regression model for patients above the median baseline SBP (HR 0.60, 95% CI 0.35 to 1.02 vs. HR 0.55, 95% CI 0.32 to 0.95) or below the median SBP (HR 0.60, 95% CI 0.39 to 0.92 vs. HR 0.58, 95% CI 0.38 to 0.90). These data suggest that the effect of FDC I/H on blood pressure did not influence its effectiveness in reducing mortality or morbidity, irrespective of whether the baseline SBP was low or high.

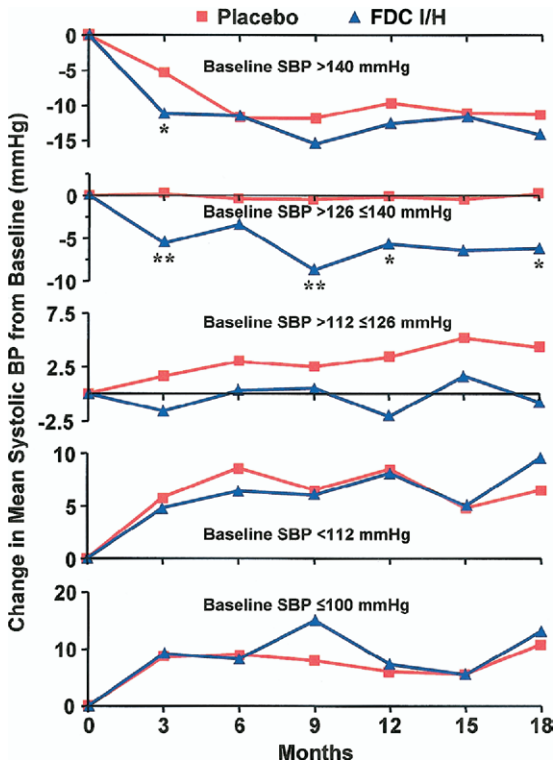

Figure 4 Change in Mean SBP in Baseline SBP Quartiles and in Baseline SBP ≤100 mm Hg

In the fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) group, blood pressure (BP) decreased in the 2 highest systolic blood pressure (SBP) quartiles and increased in the lowest SBP quartile and in subjects with baseline systolic BP ≤100 mm Hg, but did not change in the second lowest SBP quartile. There were 79 subjects with baseline systolic BP ≤100 mm Hg (mean SBP in FDC I/H group 95.0 ± 5.0 mm Hg, n = 31, and in placebo group 95 ± 5.4 mm Hg, n = 48). The p values compare changes between treatment groups: *$p < 0.05$; **$p < 0.01$.

Discussion

This report confirms that low SBP is independently associated with an increase in the risk of hospitalization and mortality in patients with moderate to severe HF, probably because low blood pressure in this setting is a manifestation of a low cardiac output. The increased risk was observed in patients with an SBP below the median of 126 mm Hg, and the risk tended to increase in a nonlinear manner. The beneficial effects of FDC I/H compared with placebo for reducing mortality and hospitalization for HF or mortality were similar in patients with a baseline SBP above or below 126 mm Hg. Interestingly, FDC I/H did not reduce SBP in patients with the lowest pretreatment values, including the quartile with an SBP <112 mm Hg, or even the subgroup with an SBP ≤100 mm Hg. In patients with a baseline SBP >126 mm Hg, FDC I/H did reduce the blood pressure more than placebo, as expected. However, changes in SBP during the first

3 months of treatment with FDC I/H did not influence its effectiveness.

We believe these findings have important implications for clinicians treating patients with moderate to severe HF, particularly those with low initial SBP. The observation that blood pressure did not decrease in the group with low initial SBP, despite the use of the same dose of FDC I/H as in patients with high SBP, challenges the belief that vasodilators are deleterious in patients with low SBP. In fact, the data suggest that vasodilator therapy can usually be well tolerated by patients with severe HF, and that low blood pressure should not preclude a trial of these agents, which seem to offer a benefit to all patients. Admittedly, there were too few patients in this clinical trial with an SBP below 100 mm Hg to be assured that most would tolerate FDC I/H and not have deleterious effects caused by a decrease in blood pressure. Because patients with a low initial SBP have greater risk and the relative risk reduction with the use of FDC I/H was similar regardless of SBP, patients with a low SBP would be expected to derive the greatest absolute benefit from this treatment.

Although this study was not designed to address the reasons that FDC I/H did not lower blood pressure in patients with a low pretreatment SBP, an appreciation of the basic hemodynamics abnormalities in HF may help explain these observations. In the failing heart, a low stroke volume threatens the arterial blood pressure and leads to a baroreceptor-mediated activation of several neurohormones that help to preserve blood pressure by increasing arterial impedance (13). The increase in impedance is, however, deleterious to the failing heart, and further reduces the stroke volume, worsening hypotension. Vasodilators such as sodium nitroprusside reverse the functional abnormalities acutely by improving stroke volume and may increase blood pressure (7). Thus, the vasodilator effects of FDC I/H probably lowered arterial impedance of patients with the lowest SBP, who would be expected to have the highest impedance, and increased cardiac output. Furthermore, over a 6-month period, use of FDC I/H was also associated with a favorable effect on LV remodeling with a significant increase in LVEF (14), similar to the effect of other vasodilators such as ACE-I and ARBs (15,16). Thus, the dual effects of lowering impedance and improving LV structural remodeling might have contributed to the lack of deleterious effects of FDC I/H on hemodynamics and subsequently to improved morbidity and mortality.

The decrease in blood pressure observed in the overall A-HeFT study population in response to FDC I/H was strikingly different than the experience in the V-HeFT study, in which blood pressure was not reduced by the drug combination. Because in the V-HeFT study the drug was administered in the absence of background neurohormone-inhibiting therapy, it is likely that the blood pressure reduction in the A-HeFT study resulted from the inhibiting effect of the background therapy on reflex vasoconstriction and cardiac stimulation. The difference might also be due to different drug formulations used in the 2 studies. The mortality reduction in the A-HeFT study (10) and in the retrospective analysis of a small number of black subjects in the V-HeFT study (17) further suggests that blood pressure reduction is not a prerequisite for the favorable effect of the fixed-dose drug combination. Indeed, this analysis suggests that deceases in SBP observed in patients with a baseline SBP over 126 mm Hg might be deleterious, although they did not influence the beneficial effects of FDC I/H.

In conclusion, the results of this study suggest that patients with a low SBP can benefit from FDC I/H therapy without an inordinate risk of deleterious hypotension. These patients derive a similar benefit from FDC I/H therapy as those with normal or high pretreatment blood pressures. Patients with low blood pressure are at the highest risk, and therefore are at the greatest need for aggressive therapy. Judicious use of FDC I/H in such patients is likely to produce an even greater absolute benefit than in those with higher blood pressures. However, the data were not sufficient to determine whether these findings generalize to patients with an SBP well below 100 mm Hg. Regardless, blood pressure reduction is neither an independent contributor to nor does it counteract the favorable effects of FDC I/H on hospitalization and mortality, and it cannot be used as a surrogate for efficacy.

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