

**BiDil® (Isosorbide Dinitrate and  
Hydralazine Hydrochloride) Tablets**

NDA 20-727

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Cardiovascular and Renal Drugs Advisory Committee

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## 1.0 Synopsis

This document summarizes the clinical data presented in New Drug Application # 20-727 for BiDil® (isosorbide dinitrate and hydralazine hydrochloride) Tablets, in which NitroMed requests approval for its use to treat black patients with heart failure. This NDA is based on three clinical trials; V-HeFT I, V-HeFT II and A-HeFT. The previous sponsor of this NDA, Medco Research, submitted the overall results for V-HeFT I and V-HeFT II in the original NDA and received a not approvable letter in 1997 requesting additional clinical research. NitroMed subsequently acquired the NDA and determined in consultation with heart failure experts and FDA that the clinical trial most likely to yield a positive outcome was a trial in black patients with heart failure. This briefing document describes the scientific rationale and regulatory history of BiDil® and presents the data from the three trials that form the basis of the NDA.

Heart failure, a serious, progressive and debilitating condition, presents a particular burden in the black community. Black patients suffer disproportionately from heart failure, are diagnosed at younger ages and appear to respond less well to currently approved therapies. In spite of the introduction of generally effective heart failure treatments, e.g., angiotensin-converting enzyme (ACE) inhibitors and beta blockers, a need for additional, more effective treatments for black patients remains for the following reasons:

- The current number of black patients diagnosed with heart failure in the United States of America is 725,000 and it is expected to grow to 900,000 by the end of the decade. Mortality rates for heart failure remain high and patients living with heart failure suffer from incapacitating symptoms and repeated hospitalizations.
- Current treatments for black patients with heart failure are insufficient. Published data suggest that ACE inhibitors may be less effective in black patients, and may cause higher rates of angioedema in this population. Beta blockers have generally not been tested in a meaningful number of black patients with heart failure; in addition, when used in the treatment of hypertension, beta blockers have a known attenuation of effectiveness in black patients.

Given the need for additional therapies for heart failure, three studies have evaluated the safety and efficacy of the combination of isosorbide dinitrate and hydralazine hydrochloride (ISDN/HYD; proposed trade name BiDil®) in this condition. The first study, the first Vasodilator Heart Failure Trial (V-HeFT I) evaluated the safety and efficacy of ISDN/HYD against placebo, added to standard therapy, in the treatment of heart failure. At the time this study was conducted, the standard of therapy for the treatment of heart failure was digitalis glycosides and diuretics. The second Vasodilator Heart Failure Trial (V-HeFT II) tested the ISDN/HYD combination against enalapril, added to standard therapy; standard therapy was again generally digitalis glycosides and diuretics. Initial results from these two trials were suggestive of a benefit in heart failure patients of all races but the dataset was not adequate to gain FDA approval.

Retrospective reanalyses of the results from V-HeFT I and II generated the hypothesis that the observed benefit of the ISDN/HYD combination occurred primarily in black patients. This finding was consistent with a growing body of scientific literature suggesting that ethnic groups

might respond differently to certain treatments. Particularly in the cardiovascular area, differential responses to treatments for hypertension and heart failure have been observed and documented.

The principal investigator of V-HeFT I and V-HeFT II, Dr. Jay Cohn, and the current sponsor of the BiDil® NDA, NitroMed, approached FDA with these reanalyses in 1999 and 2000 and together developed a clinical plan to test the hypothesis. The discussions with FDA resulted in a letter to NitroMed in 2001 stating that “[g]iven the subset finding and the overall trend toward a survival effect in V-HeFT I, we believe a single, clearly positive study in a black CHF population would be a basis for approval of BiDil for the treatment of heart failure in blacks.” That trial, the African American Heart Failure Trial (A-HeFT), provides the largest body of evidence on BiDil® in black patients with heart failure, and strongly confirms and extends the results of V-HeFT I and II in black patients with heart failure. Taken as a whole, the results from these three trials support approval of BiDil® to treat heart failure in black patients.

As described in detail in this document, the three trials supporting approval of BiDil® used a variety of endpoints, and were compared to a different standard of therapy in each case. However, V-HeFT I, V-HeFT II and A-HeFT show consistency in their overall key findings.

- Black patients with heart failure treated with ISDN/HYD experience a meaningful reduction in relative risk of mortality.
  - In A-HeFT when BiDil® was compared to placebo, black patients demonstrated a 43% reduction in relative risk of mortality ( $p=0.012$ ).
  - In V-HeFT I retrospective analysis showed that black patients demonstrated a 47% reduction in risk of mortality relative to placebo ( $p=0.04$ ).
  - In V-HeFT II, ISDN/HYD did not demonstrate a significant reduction in risk in mortality in all patients when compared to the active drug enalapril. However, retrospective analysis demonstrated that the hazard ratio for the mortality results in black patients in the two treatment arms was approximately 1, suggesting that BiDil was as effective as enalapril in this patient population.

In all three studies both ISDN/HYD and the comparator were added to standard heart failure therapy. When V-HeFT I and V-HeFT II were performed, standard therapy was digitalis glycosides and diuretics; during A-HeFT, standard therapies generally included ACE inhibitors/angiotensin receptor blockers, beta blockers, and/or aldosterone antagonists along with digitalis glycosides and diuretics.

These mortality results therefore demonstrate that BiDil® has a positive effect on survival over the heart failure spectrum and across a wide range of symptoms and background medications.

- Black patients with heart failure treated with ISDN/HYD experience a meaningful reduction in hospitalizations for heart failure.
  - In A-HeFT, patients in the BiDil® group demonstrated a 39% decrease in relative risk of first hospitalization for heart failure (relative to placebo). The mean

number of hospitalizations for heart failure per patient and mean the number of days hospitalized for heart failure as a percentage of days on study were both statistically decreased in the BiDil® group relative to placebo.

- In V-HeFT I in black patients, at the end of the first year, the cumulative heart failure hospitalization rate was 17.2% in placebo patients but only 6.3% in ISDN/HYD patients as determined by retrospective analysis.
- In V-HeFT II in black patients, at the end of the first year, the cumulative heart failure hospitalization rate was 5.0% in ISDN/HYD patients versus 13.1% in enalapril patients as determined by retrospective analysis.

The concordance of these findings in patients over the heart failure spectrum supports the conclusion that BiDil® reduces the risk of hospitalization for heart failure in black patients across a wide range of symptoms and background medications.

- Black patients with heart failure treated with ISDN/HYD experience an improvement in quality of life.
  - An improvement in quality of life was observed in both A-HeFT and V-HeFT II as measured by patient questionnaires. (A quality of life patient questionnaire was not used when V-HeFT I was performed.) The improvement in quality of life produced in A-HeFT by BiDil® in black male and female patients with moderate-to-severe heart failure generally treated with ACE inhibitors/ARBs, beta blockers and/or aldosterone antagonists as well as digitalis glycosides and diuretics was concordant with the improvement in quality of life seen in V-HeFT II with a combination of ISDN/HYD in black men with mild-to-severe heart failure generally receiving only digitalis glycosides and diuretics.

The concordance of these findings in patients over the heart failure spectrum supports the conclusion that BiDil® improves the symptoms of heart failure that impair quality of life in black patients across a wide range of symptoms and background medications.

- The results of these three studies demonstrate that the combination of isosorbide dinitrate and hydralazine is safe and generally well tolerated as treatment for heart failure. The most common adverse events observed among patients receiving the ISDN/HYD combination in all three studies were headache, dizziness and other vasodilator-type reactions.

Based on the results of the V-HeFT I, V-HeFT II and A-HeFT clinical studies, NitroMed proposes the following indication for the fixed-dose combination BiDil® (isosorbide dinitrate and hydralazine hydrochloride) Tablets:

BiDil® is indicated for the treatment of heart failure in black patients. BiDil® has been shown to reduce the risk of mortality from any cause, to reduce the risk of heart failure hospitalization and to improve quality of life.

## 2.0 Introduction

### 2.1 Public Health Impact of Heart Failure in Black Patients

Heart failure afflicts nearly 5 million patients in the United States and is responsible for considerable disability and loss of life. Heart failure is a particularly important public health concern in African Americans (also referred to as black persons). Approximately 3% of all black persons have heart failure, and it is estimated that 25-30% of all patients with heart failure in the United States are black.<sup>1,2</sup>

Several studies suggest that the black population may be disproportionately affected by heart failure, as compared with the non-black population.<sup>3</sup> At the time of diagnosis, black patients frequently are younger, have more advanced left ventricular impairment, and more advanced clinical symptoms than non-black patients.<sup>4-7</sup> Some reports suggest that once the diagnosis of heart failure is made, black patients frequently receive less than optimal care, and this may lead to a higher risk of hospitalization and a higher risk of death.<sup>8-14</sup>

### 2.2 Current Treatment Strategies in Black Patients with Heart Failure

To make matters more complicated, the optimal treatment of heart failure in black patients with the disease has not been clearly defined. Black patients are frequently under-represented in large-scale clinical trials, particularly those carried out primarily or exclusively outside of the United States.<sup>15</sup> Even in trials conducted in this country, the number of black patients in each trial has generally been so small that estimates of the magnitude of treatment responses in this subgroup have been very imprecise. This has led to considerable uncertainty about the benefit to risk relation in black patients of many widely-used treatment strategies. For example,

- In a large-scale heart failure trial with an angiotensin-converting enzyme (ACE) inhibitor that enrolled black patients (Studies of Left Ventricular Dysfunction; SOLVD trial), black patients responded less favorably to ACE inhibition than non-black patients.<sup>16</sup> In this trial, enalapril reduced mortality similarly in black and non-black patients, but reduced the risk of hospitalization less effectively in black than non-black patients. This finding was consistent with the attenuation of responsiveness to ACE inhibitors in black patients when these drugs are used for the treatment of hypertension.<sup>17</sup> Furthermore, not only may ACE inhibitors be less effective in black patients, but they are known to cause potentially life-threatening angioedema more frequently in black patients than in non-black patients.<sup>18</sup>
- In a large trial with a beta blocker carried out in the United States (BEST trial), black patients responded less favorably to beta-blockade than non-black patients.<sup>19</sup> In this trial, bucindolol reduced the risk of death in non-black patients but increased the risk of death in black patients. This finding was consistent with the attenuation of effectiveness of beta blockers in black patients when these drugs are used for the treatment of hypertension.<sup>20</sup> Although a trial with carvedilol showed benefits with the drug in black patients with heart failure,<sup>21</sup> carvedilol may exert pharmacological effects beyond beta-blockade that may contribute to its efficacy in heart failure.<sup>22</sup> The efficacy of other beta blockers (metoprolol and bisoprolol) in black persons with heart failure remains uncertain, since trials with these agents failed to enroll meaningful number of black patients.<sup>23,24</sup>

- Aldosterone antagonists have recently emerged as a treatment for heart failure, but the trials carried out with eplerenone in early-stage post-infarction heart failure and with spironolactone in late-stage patients with severe heart failure failed to enroll meaningful numbers of black patients.<sup>25,26</sup> Although eplerenone has been reported to be equally effective in reducing blood pressure in black and non-black patients with hypertension,<sup>27</sup> black patients have been reported to be resistant to the potassium-sparing properties of aldosterone antagonists.<sup>28</sup> This is noteworthy because the potassium sparing actions of aldosterone antagonists may contribute importantly to their survival effects in heart failure.<sup>29</sup>

Therefore, the available data from large-scale trials have created considerable uncertainty about the efficacy and safety in black patients of most of the therapeutic interventions that have been shown in non-black patients to modify the course of the disease. Individual reports have raised concerns about diminished efficacy and/or safety, and the current level of uncertainty is heightened by the fact that some of the clinical trials that have led to the approval of key drugs for heart failure were carried out in Europe and did not have an opportunity to enroll large numbers of black patients. As a result, physicians are uncertain about the treatment of heart failure in black persons.

### 2.3 Pathophysiology of Heart Failure in Black Patients

The current level of uncertainty about the management of heart failure in black patients is heightened by recent evidence that the pathophysiology of heart failure in black patients may differ from that in non-black patients.

When compared with non-black patients, black patients demonstrate a markedly reduced ability of peripheral blood vessels to dilate in response to endogenous stimuli of nitric oxide.<sup>30-33</sup> This defect appears to be related in part to an increased frequency in black persons of polymorphisms in the genes that regulate both the synthesis of nitric oxide and the production of oxygen free radicals capable of degrading nitric oxide.<sup>34-36</sup> As a result, black patients show decreased responsiveness to drugs that stimulate endothelium-dependent vasodilation (e.g., methacholine) and enhanced responsiveness to drugs that increase the delivery of nitric oxide to peripheral blood vessels (e.g., arginine).<sup>32,37,38</sup>

The reduced vasodilator responsiveness seen in black patients may explain the high prevalence of hypertension in this racial group. Hypertension afflicts black patients far more than white patients<sup>39</sup> and has unique characteristics, i.e., hypertension is typically characterized by salt sensitivity and reduced production of nitric oxide in black patients whereas it is characterized by the activation of neurohormonal systems (the renin-angiotensin system and the sympathetic nervous system) in white patients.<sup>40,41</sup> Both characteristics may help to explain why hypertension in black patients is commonly associated with end-organ consequences (e.g., left ventricular hypertrophy)<sup>42</sup> and responds less readily to treatment with neurohormonal antagonists [ACE inhibitors, angiotensin receptor blockers (ARBs) and beta-adrenergic blockers].<sup>17,22</sup>

The deficiency of nitric oxide seen in black patients may not only increase the predisposition of black persons to hypertension, but also to the development of heart failure.<sup>43,44</sup> Whereas the most common risk factor for heart failure in non-black patients is coronary artery disease, the most common risk factor for heart failure in black persons is hypertension — even in the absence of a

defined ischemic event.<sup>43-45</sup> Furthermore, independent of race, heart failure is characterized by both defects in nitric-oxide-mediated vasodilation and enhanced superoxide-mediated nitric oxide destruction,<sup>46-50</sup> and the presence of defects in nitric oxide-mediated vasodilation identifies patients who are most likely to experience worsening heart failure, cardiac transplantation or death.<sup>51,52</sup> The high prevalence of deficient nitric oxide-mediated vasodilation in black patients may explain in part why heart failure develops disproportionately in black patients and why, once developed, heart failure progresses more rapidly in black than in non-black patients.<sup>4-14</sup>

These observations support the hypothesis that a vascular deficiency of nitric oxide may contribute meaningfully to the development and progression of heart failure and suggests that pharmacological amelioration of this deficiency (by the administration of a nitric oxide donor, an anti-oxidant that prevents the degradation of nitric oxide, or both<sup>53-57</sup>) may exert clinical benefits, particularly in patients most likely to be deficient.<sup>37</sup>

## 2.4 Effect of Isosorbide Dinitrate and Hydralazine on Vascular Nitric Oxide

When the concept of using isosorbide dinitrate and hydralazine (ISDN/HYD) together for the treatment of heart failure was first introduced in the late 1970s, the combination was believed to produce its clinical benefits by exerting complementary effects to relax both peripheral arteries and veins and thereby improve cardiac performance. This mechanism of action was supported by the following observations:

- The oral administration of isosorbide dinitrate to patients with heart failure produced short- and long-term decreases in right and left ventricular filling pressures at rest and during exercise with minimal change in blood pressure or heart rate. These effects were accompanied by little change in blood flow to the limbs and kidneys.<sup>62,67-72</sup> Doses of 10 mg or less produced little hemodynamic effect, but sustained effects were seen with 20-40 mg, given TID or QID.<sup>68,73</sup> Small placebo-controlled trials of isosorbide dinitrate alone failed to demonstrate between-group improvement in symptoms or exercise tolerance in patients with heart failure, possibly because of the inadequate size of the studies or the limitation of monotherapy with isosorbide dinitrate.<sup>71, 74-75</sup>
- The oral administration of hydralazine to patients with heart failure produced short- and long-term increases in cardiac output and stroke volume at rest and during exercise with minimal change in blood pressure or heart rate. These effects were accompanied by an improvement in blood flow to the limbs and kidneys.<sup>58-63</sup> Doses of 50 mg or less produced little hemodynamic effect, but sustained effects were seen with 300 mg daily, given as 100 mg TID or 75 mg QID.<sup>58,59,64</sup> Two placebo-controlled trials using low doses (150-200 mg daily) of hydralazine alone failed to demonstrate improvement in symptoms or exercise tolerance in patients with heart failure,<sup>65,66</sup> possibly because of the inadequate doses used, the small size of the studies or the limitations of monotherapy with hydralazine.
- The oral administration of ISDN/HYD together in patients with heart failure produced short- and long-term increases in cardiac output and decreases in cardiac filling pressures at rest and during exercise with minimal change in blood pressure or heart rate. When used in doses of 160 mg daily of isosorbide dinitrate and 300 mg daily of hydralazine, the complementary effects of the two drugs produced a hemodynamic response comparable both qualitatively and quantitatively to that produced by intravenous nitroprusside.<sup>76-79</sup>

In addition to these complementary hemodynamic effects, several studies have also suggested that isosorbide dinitrate and hydralazine may exert complementary biochemical effects that could underlie or contribute importantly to their hemodynamic actions. Isosorbide dinitrate exerts vasodilator effects by acting as a nitric oxide donor within blood vessels.<sup>80</sup> However, the hemodynamic actions of nitrate therapy are frequently lost during repeated administration of the drug (“nitrate tolerance”),<sup>81-83</sup> and this has limited the utility of the drug as monotherapy. Several studies have postulated that oxidative stress contributes importantly to the development of nitrate tolerance.<sup>84-87</sup> It is therefore noteworthy that — in addition to its vasodilator effects — hydralazine exerts anti-oxidant effects<sup>88,89</sup> and its co-administration with isosorbide dinitrate can prevent the development of nitrate tolerance.<sup>90-93</sup>

## 2.5 Regulatory Background of BiDil® (Isosorbide Dinitrate and Hydralazine Hydrochloride)

BiDil® is a fixed-dose combination of two active ingredients, isosorbide dinitrate (ISDN) and hydralazine hydrochloride (HYD). Isosorbide dinitrate was approved in 1961 to treat angina, and hydralazine was first approved in 1952 to treat hypertension. Neither of the approved labels describes the use of the agent for the treatment of heart failure, either alone or in combination and the combination of ISDN/HYD has not been approved for any indication.

In the 1980s the combination of ISDN/HYD to treat heart failure was evaluated in two trials sponsored by the Department of Veterans Affairs (V-HeFT I and V-HeFT II). These studies were licensed by Medco Research (currently King Pharmaceuticals) and an NDA was developed and filed in 1996 for the proposed use of BiDil® (a fixed-dose combination of ISDN/HYD) for the treatment of heart failure in patients who could not tolerate treatment with an angiotensin-converting enzyme inhibitor. BiDil® was assigned NDA number 20-727.

The Division of Cardiovascular and Renal Drugs convened a meeting of its Advisory Committee to consider the BiDil® NDA in February 1997. The Advisory Committee recommended against the approval of BiDil® for the proposed indication. A not approvable letter was issued in July 1997 stating that additional clinical data would be required. Medco Research opted not to pursue the development of BiDil®.

Based on a growing body of data suggesting that ethnic groups might differ in their mechanisms of disease and their response to treatment, Dr. Jay Cohn, the principal investigator for V-HeFT I and II, conducted additional retrospective analyses of the studies and observed that the black patients in V-HeFT I had remarkably better responses to ISDN/HYD than white patients.<sup>94</sup> In light of these new analyses, Dr. Cohn approached NitroMed, a company dedicated to research and development of nitric oxide enhancing technologies, to pursue the development of BiDil®. In 1999, NitroMed became the official sponsor of the BiDil® NDA.

NitroMed and Dr. Cohn met with FDA in 1999 and 2000 to explore further development of BiDil® for the treatment of heart failure in black patients. After these discussions and review the V-HeFT reanalyses and supporting documentation, FDA issued a letter in March 2001 stating that “[g]iven the subset finding and the overall trend toward a survival effect in VHeFT I, we believe a single, clearly positive study in a CHF population would be a basis for approval of

BiDil® for the treatment of heart failure in blacks.” In May 2001, NitroMed launched the African American Heart Failure Trial (A-HeFT).

In July 2004, A-HeFT was stopped following a unanimous recommendation of its Data and Safety Monitoring Board (DSMB) and Steering Committee. This recommendation was based on the observation of a 43% reduction in relative risk of mortality in patients treated with BiDil® relative to placebo.

The complete response (or NDA amendment) to the original 1997 not approvable letter including the A-HeFT study report was submitted to the FDA in December 2004. The PDUFA date is June 23, 2005.

The indication being pursued by NitroMed is for the “treatment of heart failure in black patients. BiDil® has been shown to reduce the risk of mortality from any cause, to reduce the risk of heart failure hospitalization and to improve quality of life.”

### 3.0 Large-Scale Controlled Clinical Trials with Isosorbide Dinitrate and Hydralazine

Three large-scale multicenter controlled clinical trials have been carried out to evaluate the efficacy of a combination of isosorbide dinitrate and hydralazine (ISDN/HYD) in patients with heart failure: the first Vasodilator Heart Failure Trial (V-HeFT I); the second Vasodilator Heart Failure Trial (V-HeFT II); and the African American Heart Failure Trial (A-HeFT). Their primary characteristics are summarized in Table 1.

Table 1. Characteristics of Major Trials with Isosorbide Dinitrate and Hydralazine in Heart Failure

	<b>V-HeFT I</b>	<b>V-HeFT II</b>	<b>A-HeFT</b>
<b>Sponsor</b>	Veterans Affairs	Veterans Affairs	NitroMed
<b>Number of Patients</b>	642	804	1050
<b>Gender</b>	Men	Men	Men & women
<b>Race</b>	All races	All races	African Americans
<b>Drugs Studied</b>	Placebo ISDN/HYD Prazosin	Enalapril ISDN/HYD	Placebo ISDN/HYD
<b>Target Doses of ISDN/HYD</b>	ISDN 40 mg QID HYD 75 mg QID	ISDN 40 mg QID HYD 75 mg QID	ISDN 40 mg TID HYD 75 mg TID
<b>ISDN/HYD</b>	As individual products	As individual products	As fixed-dose combination tablet (BiDil®)
<b>Severity of Heart Failure</b>	Mild-to-severe	Mild-to-severe	Moderate-to-severe
<b>Background Therapy for Heart Failure</b>	Digoxin Diuretics	Digoxin Diuretics	Digoxin Diuretics ACE inhibitors/ARBs Beta blockers Aldosterone antagonists

## 4.0 Trials with Isosorbide Dinitrate and Hydralazine Administered as Individual Drugs

Two controlled trials have evaluated the efficacy and safety of a combination of isosorbide dinitrate and hydralazine (ISDN/HYD) in heart failure as individual agents: (1) the first Vasodilator Heart Failure Trial (V-HeFT I) and (2) the second Vasodilator Heart Failure Trial (V-HeFT II). These trials were carried out by the Department of Veterans Affairs in the 1980's and early 1990's.

### 4.1 Vasodilator Heart Failure Trial I (V-HeFT I)

#### 4.1.1 Study Overview

The first Vasodilator Heart Failure Trial (V-HeFT I) was a multicenter, randomized, double-blind, parallel group, placebo controlled trial conducted at 11 sites in the United States under the auspices of the Department of Veterans Affairs.

V-HeFT I was the first trial ever carried out to evaluate the effect of orally administered treatment on the survival of patients with chronic heart failure. Initiated in 1980, V-HeFT I was designed to test the hypothesis that peripheral vasoconstriction not only contributes to hemodynamic derangement and symptoms in heart failure but also leads to progressive deterioration of left ventricular function and premature death. The trial evaluated two different vasodilator regimens: a combination of ISDN/HYD, and monotherapy with prazosin. Both treatments had been shown to exert balanced vasodilator effects on systemic arteries and veins in a manner similar to that seen with an intravenous infusion of nitroprusside.

V-HeFT I enrolled men who had heart failure associated with impaired or preserved ejection fraction, and who were generally taking only digitalis glycosides and diuretics.

#### 4.1.2 Study Organization

The Executive Committee was the management and decision-making body for the operational aspects of the conduct of the study. It also monitored the performance of participating sites. The members of the Committee were:

- Jay Cohn, M.D., Minneapolis VA Hospital (chair)
- Donald Archibald, M.Phil., West Haven VA Hospital (biostatistician)
- Ross Fletcher, M.D., Washington DC VA Hospital
- Joseph Franciosa, M.D., Little Rock VA Hospital
- Gary Francis, M.D., Minneapolis VA Hospital
- Clair Haakenson, R.Ph., Albuquerque VA Hospital (research pharmacist)
- Pravin Shah, M.D., West Los Angeles VA Hospital
- Susan Ziesche, R.N., Minneapolis VA Hospital

A Data and Safety Monitoring Board composed of clinicians who did not participate in the trial, periodically reviewed study results and evaluated the treatments for excess events. The members of the DSMB were:

Richard Gorlin, M.D., Mount Sinai School of Medicine (chair)  
Yick-Kwong Chan, Ph.D., West Haven VA Hospital  
Leon Goldberg, M.D., Ph.D., University of Chicago  
Genell Kantterud, Ph.D., Maryland Research Institute  
William Parmley, M.D., University of California  
David Shand, M.D., West Haven VA Hospital

### 4.1.3 Study Population

#### 4.1.3.1 Inclusion Criteria

- Men, 18 to 75 years old.
- Heart failure as evidenced by reduced exercise tolerance for at least 3 months. Reduced exercise tolerance was defined as maximal oxygen consumption  $< 25$  mL/kg/min during graded bicycle ergometry testing.
- Persistent symptoms despite treatment with digitalis glycosides and diuretics.
- Cardiothoracic ratio on chest x-ray  $\geq 0.55$ , or an echocardiographic left ventricular internal dimension  $> 2.7$  cm/m<sup>2</sup>, or a radionuclide or contrast left ventricular ejection fraction  $< 0.45$ .

#### 4.1.3.2 Exclusion Criteria

- Myocardial infarction or cardiac surgery within 3 months.
- Hypertrophic cardiomyopathy or hemodynamically significant aortic or mitral valve or pericardial disease.
- Patients with hypertension requiring antihypertensive drugs other than diuretics.
- Angina pectoris severe enough to require long-acting nitrates or frequent administration of sublingual nitroglycerin (more than 4 tablets per week).
- Chronic treatment with a beta-blocking drug, calcium channel blockers, or vasodilators other than occasional sublingual nitroglycerin.
- History of systemic lupus erythematosus or history of intolerance to isosorbide dinitrate, hydralazine or prazosin.
- Chronic lung disease sufficient to limit exercise tolerance.
- Severe intrinsic renal disease or primary hepatic disease.
- Hematocrit  $< 30\%$ .
- Disease that was expected to limit survival within 2 years.

#### 4.1.4 Study Plan

After each patient was screened, he entered a baseline period of two weeks' duration to establish optimal therapy with a digitalis glycoside and a diuretic and to allow any nonstudy drugs to be discontinued. Patients fulfilling all inclusion criteria and none of the exclusion criteria were randomized to one of three treatment groups: placebo, prazosin or the combination of ISND/HYD. Randomization was stratified by the presence or absence of clinically suspected

coronary artery disease. Randomization was carried out within each stratification group at each center in blocks of 7, with 3 patients assigned to placebo and 2 patients assigned to each of the active drug regimens. This ratio was used because it allowed nearly optimal power for comparisons between the two active treatments and for a possible comparison between both active treatments combined and placebo.

Following randomization, patients were instructed to take 1 tablet QID and 1 capsule QID. The tablet contained ISDN 20 mg or placebo. The capsule contained HYD 37.5 mg, prazosin 2.5 mg or placebo. After 2 weeks, if tolerated, the patients were uptitrated to 2 tablets QID and 2 capsules QID. The target doses for the study were 160 mg/day of ISDN and 300 mg/day of HYD, or 20 mg/day of prazosin.

If the study medications were not tolerated, the patient could reduce the dose of one or both of the study drugs. The goal was to achieve the highest tolerated dose of the study medication, and the doses of other medications could be adjusted as clinically indicated.

Following randomization, each patient was to be seen as an outpatient every 2 weeks until two successive visits revealed stability, and then every 1-3 months for the duration of the trial. Chest x-ray, M-mode echocardiography, Holter monitoring, physician assessment of quality of life, radionuclide imaging for assessment of left ventricular ejection fraction, and maximum exercise testing were performed at baseline, at 2 and 6 months, and every 6 months thereafter.

#### 4.1.5 Study Assessments

The study protocol described several major and several minor endpoints. However, the study was envisioned primarily as a mortality study, and mortality was the only variable that was used to determine the sample size of the trial.

##### 4.1.5.1 Major Endpoints

- All-cause mortality during the entire study period
- All-cause mortality at 2 years
- Number and duration of cardiovascular hospitalizations
- Maximum oxygen consumption during peak exercise
- Maximum treadmill exercise time on a graded test
- Duration of exercise on submaximal test

##### 4.1.5.2 Minor Endpoints

- Heart size by M-mode echocardiography
- Left ventricular function by M-mode echocardiography
- Heart size and pulmonary congestion by chest x-ray
- Ejection fraction by radionuclide ventriculography
- Arrhythmias assessed by Holter monitoring
- Patient and investigator global assessment of improvement

### 4.1.5.3 Safety Assessments

Safety assessments consisted of monitoring and recording all treatment-emergent adverse events and serious adverse events, the performance of physical examinations (which included the measurement of vital signs at every visit), and laboratory evaluations.

### 4.1.6 Statistical Plan and Analyses

#### 4.1.6.1 Sample Size Determination and Interim Monitoring Plan

The study protocol projected a sample size of 720 patients (308 in the placebo group and 206 in each of the vasodilator regimens) in order to provide 84% power to detect a difference in survival curves if either vasodilator treatment reduced the annual mortality rate by 33% compared with the placebo group, assuming a dropout rate of 6% per year.

The Data and Safety Monitoring Board met at 6 month intervals throughout the study. The Committee used an O'Brien-Fleming boundary to guide decision-making during four interim analyses. The Committee made no decision to recommend modification of the course of the study.

#### 4.1.6.2 Statistical Analyses

##### Mortality

Survival curves were compared among the three treatment groups using the log-rank test, and differences between the survival curve of each drug regimen vs that of placebo were analyzed using a protocol-specified one-sided  $\alpha=0.025$  (or two-sided  $\alpha=0.05$ ).

##### Non-Fatal Measures of Efficacy

Mean changes from baseline in exercise duration and capacity, left ventricular ejection fraction, heart size and quality of life assessments were calculated for each variable for those patients with data available at each study visit. [Such an approach does not account for the differences in survival between treatment groups.] The observed treatment difference was evaluated for significance using two-sample t-tests.

### 4.1.7 Results

#### 4.1.7.1 Baseline Characteristics

A total of 642 patients were randomized to treatment with placebo (n=273), ISDN/HYD (n=186), and prazosin (n=183).

The patients enrolled in V-HeFT I were middle-aged men, of whom approximately 27-29% were black in each group (see Table 2). The most common cause of heart failure was coronary artery disease. The mean left ventricular ejection fraction was approximately 30%, and the mean oxygen consumption was approximately 15 mL/kg/min. The groups were well-matched for baseline characteristics.

Table 2. Baseline Demographic and Clinical Characteristics; V-HeFT I

	<b>Placebo n=273</b>	<b>ISDN/HYD n=186</b>	<b>Prazosin n=183</b>
<b>Demographic features</b>			
Age (years; mean)	58.5	58.5	58.3
Race (n, %)			
White	192 (70.3%)	132 (71.4%)	NA
Black	79 (28.9%)	49 (26.5%)	NA
Other	2 (0.7%)	4 (2.2%)	NA
<b>Cardiovascular history (n,%)</b>			
Coronary artery disease	129 (47.3%)	86 (46.2%)	86 (46.2%)
Alcohol excess	104 (38.1%)	80 (43.0%)	80 (43.0%)
Hypertension	118 (43.2%)	74 (39.8%)	74 (39.8%)
Diabetes	67 (24.5%)	32 (17.2%)	32 (17.2%)
<b>Drug therapy (prior 6 mos; n, %)</b>			
Vasodilators	99 (36.3%)	78 (41.9%)	78 (41.9%)
Antiarrhythmics	73 (26.7%)	53 (28.5%)	53 (28.5%)
Sublingual nitroglycerin	53 (19.4%)	39 (21.0%)	39 (21.0%)
Anticoagulants	48 (17.6%)	34 (18.3%)	34 (18.3%)
<b>Clinical data (mean)</b>			
Symptom score <sup>a</sup>	5.6	5.6	5.6
Left ventricular ejection fraction (%)	30.4	30.4	30.3
Maximal O <sub>2</sub> consumption (mL/kg/min)	15.0	14.5	14.4
Cardiothoracic ratio (%)	53.0	52.8	52.8
Exercise duration (min)	9.8	9.7	9.7

<sup>a</sup> Sum of scores for dyspnea, fatigue, orthopnea, and paroxysmal nocturnal dyspnea; each symptom was scored as 1 = none, 2 = moderate, and 3 = severe. Maximum possible score was 12.

#### 4.1.7.2 Patient Disposition and Exposure to Study Medication

The first of 642 patients was enrolled in May 1980, the last patient was enrolled in June 1985 and the study was completed in December 1985.

Six months after randomization, target doses of the study medications were prescribed in 83% of the patients in the placebo group, 75% of the prazosin group, and 55% of those in the ISDN/HYD group. The average prescribed doses were: 18.6 mg daily for prazosin, 136 mg daily for ISDN and 270 mg daily for HYD. More than 85% of the prescribed dosage (tablets or capsules) was taken in each group.

The mean follow-up period was 2.3 years (range: 6 months to 5.7 years). Vital status was determined at the end of the study in all but four patients: two in the placebo group, one in the prazosin group and one in the ISDN/HYD group.

#### 4.1.7.3 Efficacy Results

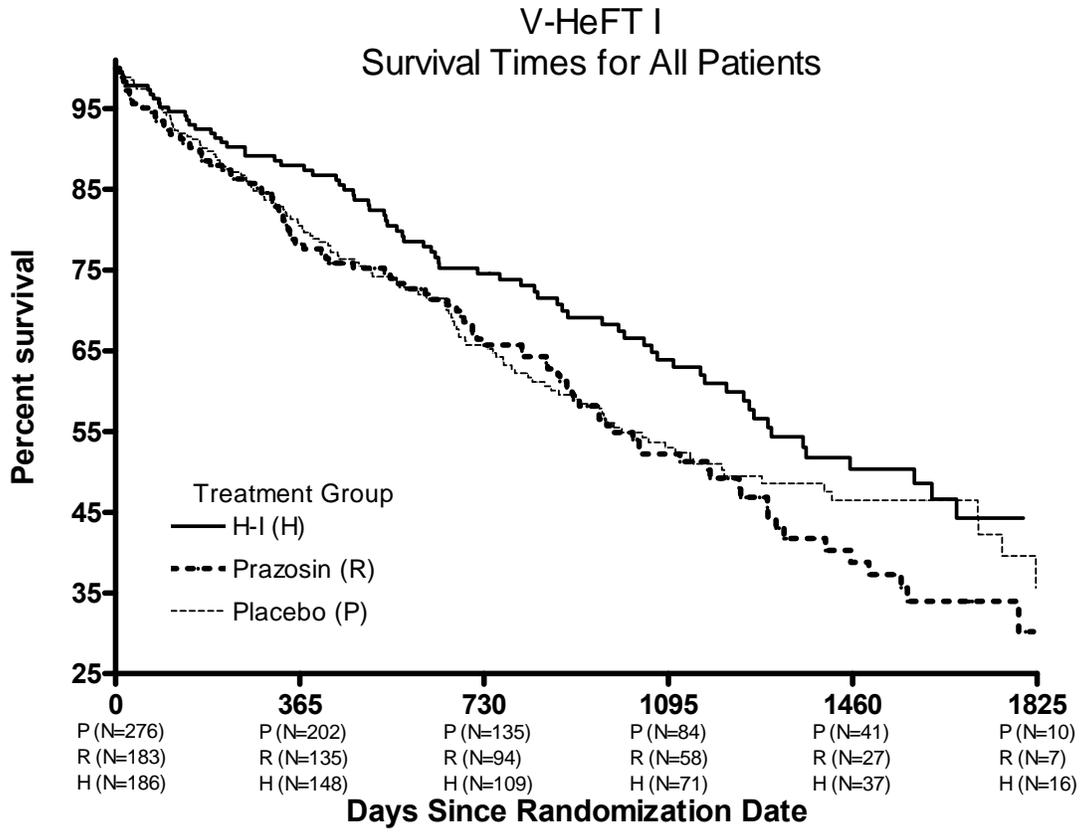
##### 4.1.7.3.1 Overall Mortality

By intention to treat, during the follow-up period there were 120 deaths from all causes in the placebo group (44.0%), compared with 72 deaths in the ISDN/HYD group (38.7%) and 91 deaths in the prazosin group (49.7%). The log-rank p-value for the comparison of ISDN/HYD vs placebo was 0.093; the p-value for the comparison of prazosin and placebo was 0.441 (Table 3, Figure 1).

Table 3. Effects on All-Cause Mortality; V-HeFT I

<b>Treatment</b>	<b>Placebo (N, %)</b>	<b>Drug (N, %)</b>	<b>Hazard ratio (95% CI)</b>	<b>Log-rank p-value</b>
ISDN/HYD	120 (44.0%)	72 (38.7%)	0.78 (0.58, 1.04)	0.093
Prazosin	120 (44.0%)	91 (49.7%)	1.11 (0.85, 1.46)	0.441

Figure 1. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality; V-HeFT I



At the protocol specified endpoint of 2 years, the cumulative mortality rate was 34.3% in the placebo group and 25.6% in the ISDN/HYD group. By the log-rank test, the p-value for this comparison of placebo and ISDN/HYD was 0.053. At 2 years, the mortality rates in the prazosin group were similar to those in the placebo group.

#### 4.1.7.3.2 Retrospective Subgroup Analysis of Mortality

A reduction in the risk of death approximating that seen in the overall trial as a whole was generally seen across nearly all of the subgroups examined (Figure 2). However, the most striking effect was seen in black patients who experienced a 47% reduction in relative risk (hazard ratio = 0.53; p=0.04); the magnitude of the mortality benefit in black patients was nearly four times the magnitude of mortality benefit seen in white patients, who experienced only a 12% reduction in relative risk (hazard ratio = 0.88; p=0.47); interaction p=0.15 (Figures 3, 4). The survival effect in black patients treated with ISDN/HYD was significant even though black patients represented one of the smallest subgroups and comprised only 30% of the patients in the trial.

Other subgroups in which there was a trend for ISDN/HYD to reduce the risk of mortality were:

- Younger patients [age  $\leq$  59 years; 33% reduction in risk when compared with 9% reduction in risk in older patients]
- Diabetic patients [25% reduction in risk when compared with 5% reduction in risk in non-diabetics]
- Lower systolic blood pressure [ $\leq$  118 mm Hg; 26% reduction in risk when compared with 14% reduction in risk in patients with higher systolic blood pressure]
- Ejection fraction < 40% [25% reduction in risk when compared with 17% reduction in risk in patients with preserved ejection fractions]

Figure 2. Hazard Ratios and 95% Confidence Intervals for Effect of ISDN/HYD on All-Cause Mortality in Subgroups; V-HeFT I

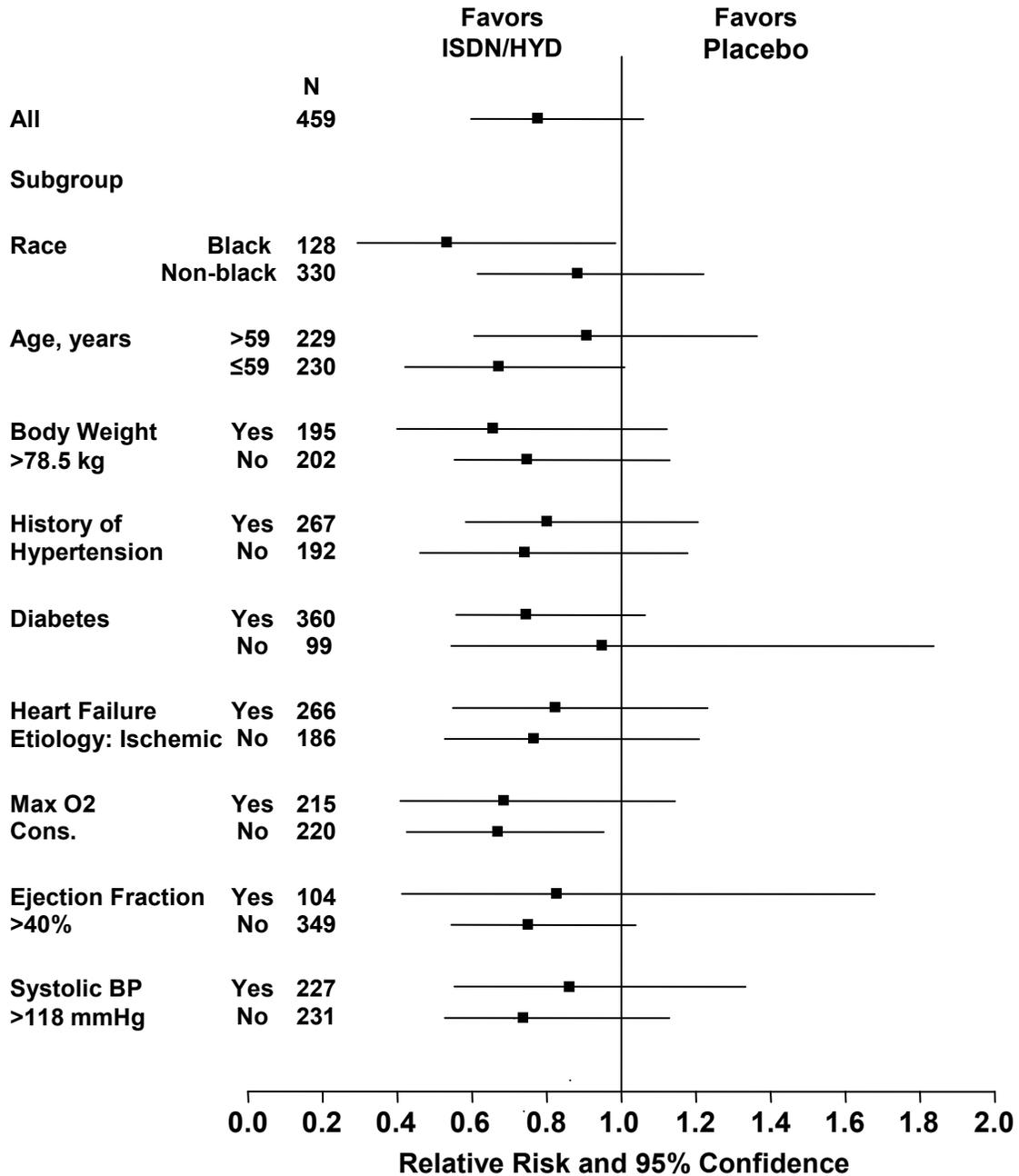


Figure 3. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in Black Patients; V-HeFT I

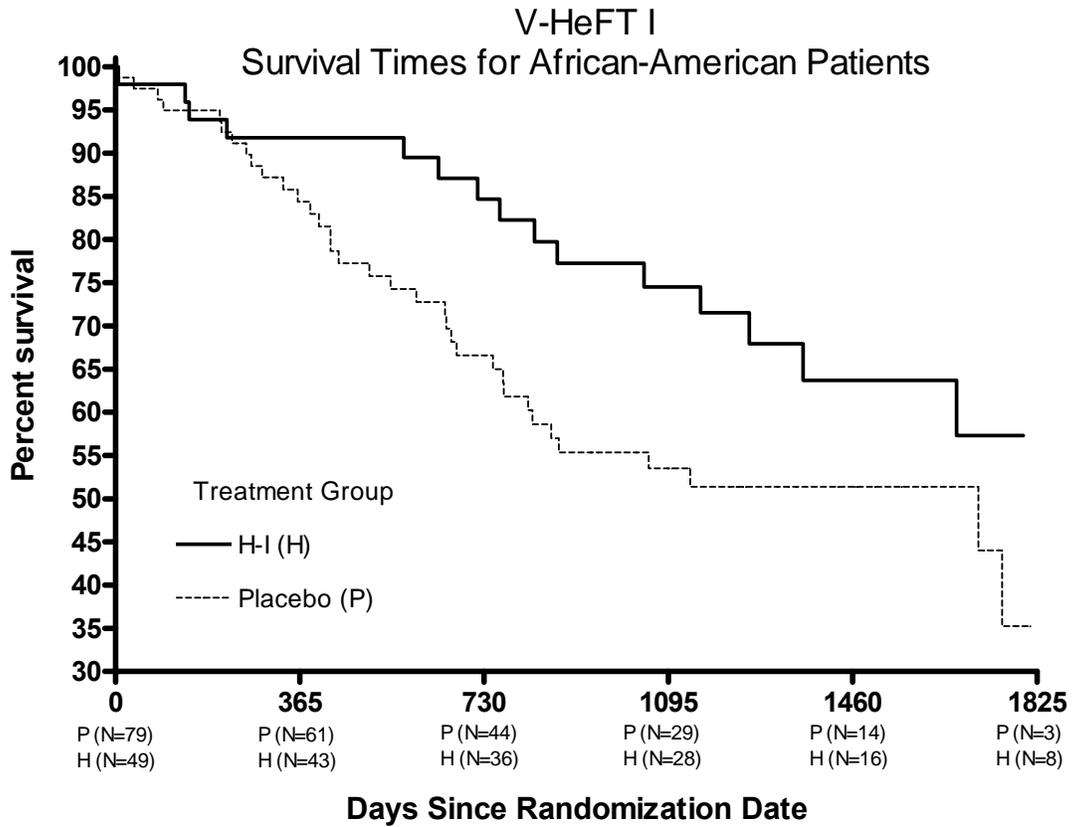
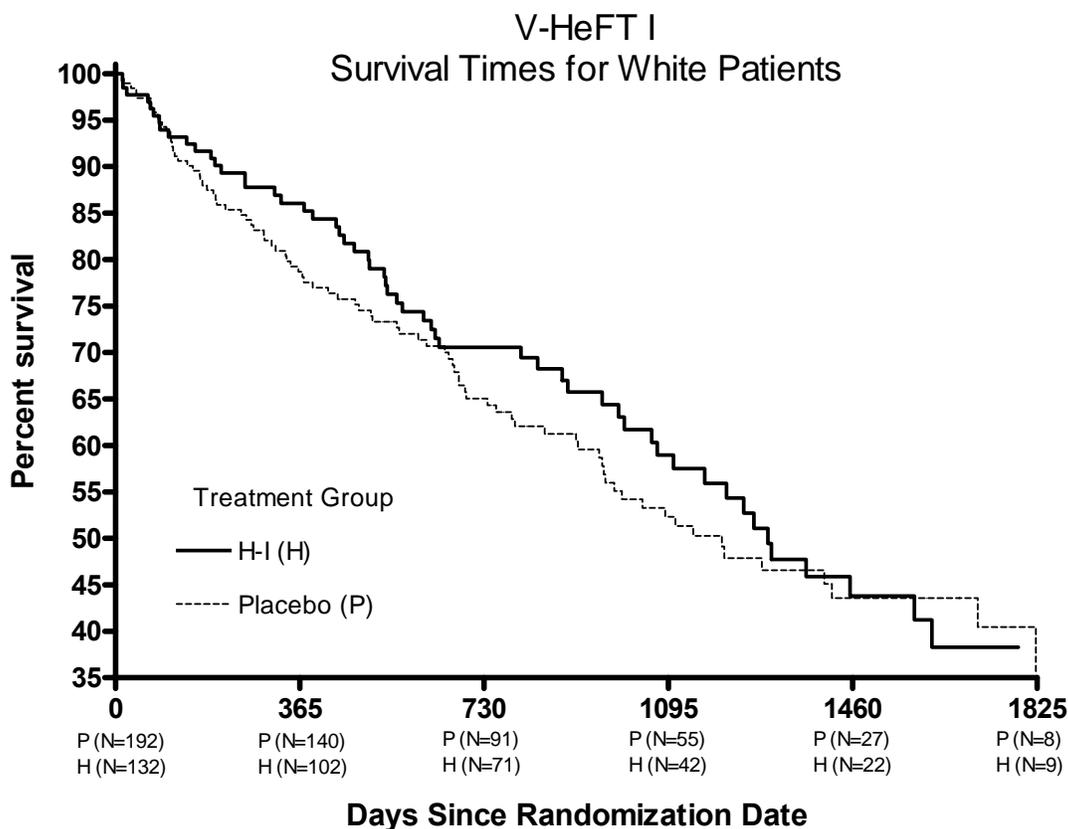


Figure 4. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in White Patients; V-HeFT I



#### 4.1.7.3.3 Hospitalizations

Although the occurrence of hospitalization was recorded in the trial at each visit, the dates of hospitalization were not recorded and the causes of hospitalization were not centrally adjudicated. Nevertheless, each investigative site provided an assessment of the cause of each hospitalization, and in general, the occurrence of hospitalization during the study was recorded at the patient’s next regularly scheduled visit. Assuming that a hospitalization occurred at the time it was recorded (rather than when it actually occurred), it is possible to construct time-to-event analyses of the occurrence of hospitalization for heart failure – recognizing that a hospitalization may have actually occurred at any time between scheduled visits.

As shown in Figures 5, 6, and 7, time to event analysis for the occurrence of a heart failure hospitalization suggest the following:

- For the first two years of the study (the duration for which a meaningful proportion of the randomized patients were followed), the risk of hospitalization for heart failure was lower in the ISDN/HYD group than in the placebo group. At the end of one year, the cumulative heart failure hospitalization rate was 17.1% in placebo patients but only 9.2% in ISDN/HYD patients.

- The difference in favor of ISDN/HYD during the first two years of the study was greater in black patients. In black patients at the end of one year, the cumulative heart failure hospitalization rate was 17.2% in placebo patients but only 6.3% in ISDN/HYD patients. In white patients at the end of one year, the cumulative heart failure hospitalization rate was 17.3% in placebo patients but only 10.8% in ISDN/HYD patients.

These data on hospitalizations for heart failure raise the possibility of a race-by-treatment interaction which parallels that observed for survival.

Figure 5. Kaplan-Meier Time to First Heart Failure Hospitalization – All Patients; V-HeFT I

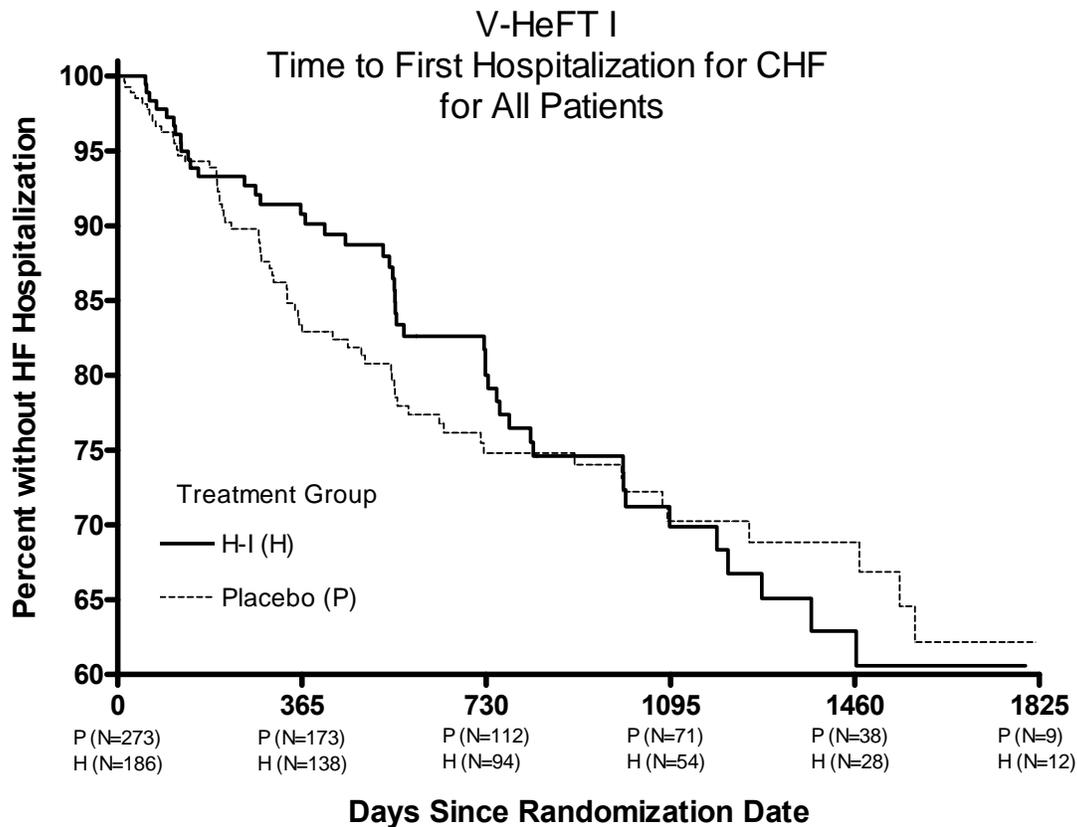


Figure 6. Kaplan-Meier Time to First Heart Failure Hospitalization – Black Patients; V-HeFT I

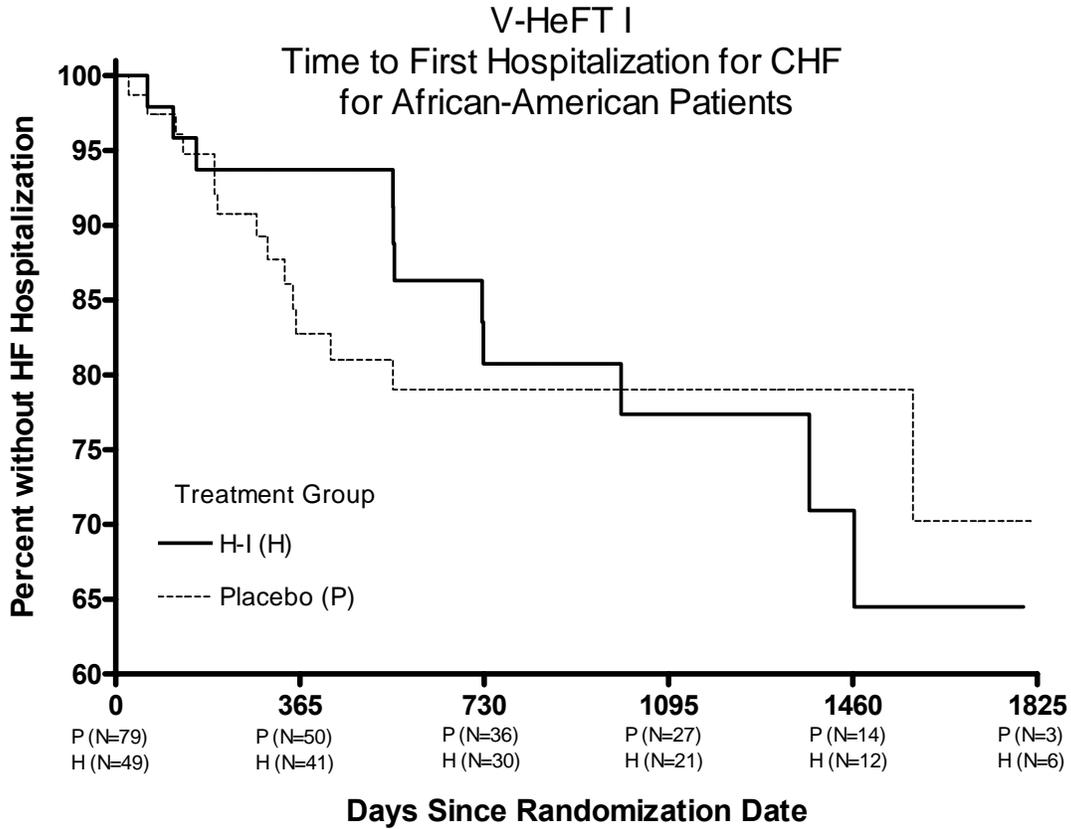
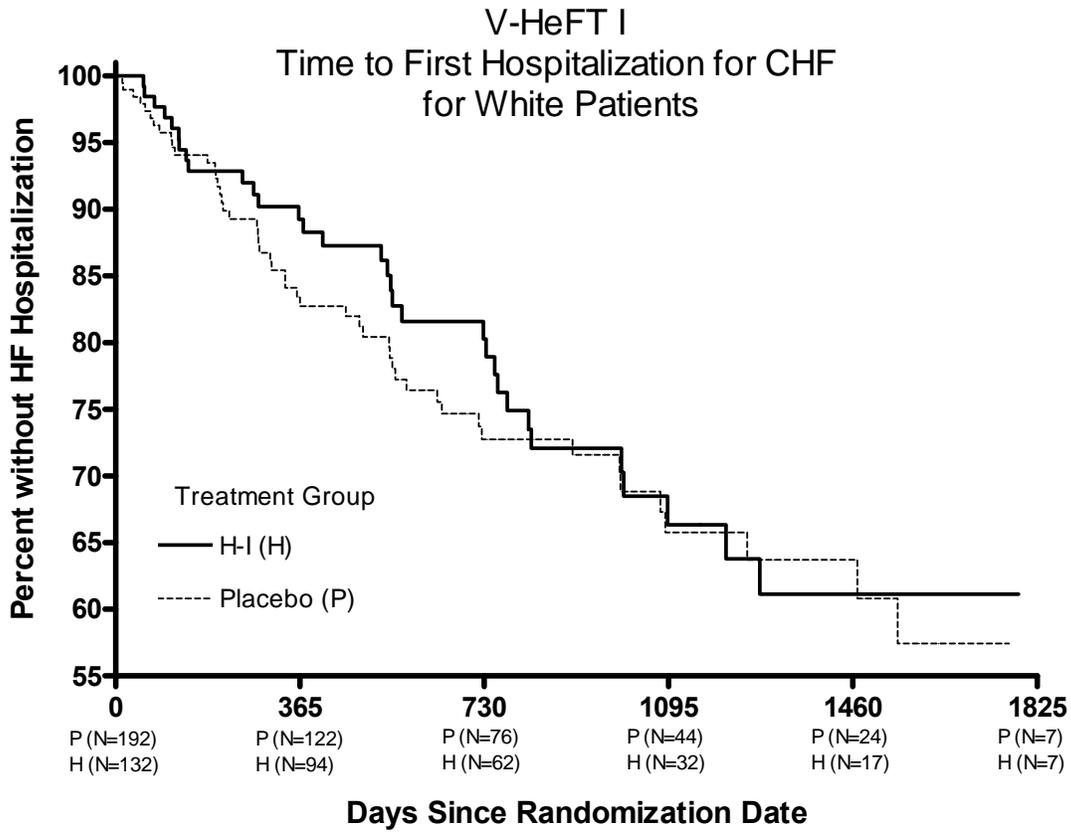


Figure 7. Kaplan-Meier Time to First Heart Failure Hospitalization – White Patients; V-HeFT I



#### 4.1.7.3.4 Maximum Oxygen Consumption at Peak Exercise

For the first 2 years, exercise capacity (as assessed by the mean change from baseline in maximum oxygen consumption at peak exercise) was greater in the ISDN/HYD group than in the placebo group (Table 4). The difference in the response to treatment between the two groups was approximately 0.5 mL/kg/min at all time points, but was not statistically significant at any time point.

Table 4. Changes in Maximal Oxygen Consumption Relative to Baseline; V-HeFT I

	Placebo	ISDN/HYD	p-value*
<b>Baseline</b>	n=259	n=176	
Mean (SD)	14.9 (3.9)	14.7 (3.9)	
<b>Week 8</b>	n=221	n=151	
Mean (SD)	15.4 (4.4)	15.5 (4.3)	
Mean change (SD)	+0.2 (3.0)	+0.7 (2.8)	p=0.125
<b>Week 28</b>	n=193	n=136	
Mean (SD)	15.4 (4.0)	15.3 (4.8)	
Mean change (SD)	+0.1 (2.9)	+0.4 (3.8)	p=0.472
<b>Year 1</b>	n=155	n=113	
Mean (SD)	15.0 (4.0)	15.4 (4.1)	
Mean change (SD)	-0.2 (3.7)	+0.6 (3.0)	p=0.056
<b>Year 1.5</b>	n=111	n=95	
Mean (SD)	15.1 (4.2)	15.3 (4.4)	
Mean change (SD)	-0.2 (3.3)	+0.2 (3.8)	p=0.341
<b>Year 2</b>	n=99	n=73	
Mean (SD)	15.3 (4.2)	15.3 (3.4)	
Mean change (SD)	-0.4 (3.5)	+0.2 (3.1)	p=0.270

\* p-values refer to between-group comparisons vs placebo

Of note, the placebo-corrected increase in maximum oxygen consumption was generally larger in black patients than non-black patients (e.g., +1.64 mL/kg/min in black patients vs +0.84 mL/kg/min in non-black patients at one year).

When compared with placebo, prazosin had no effect on maximum oxygen consumption at any time in the study.

#### 4.1.7.3.5 Left Ventricular Ejection Fraction

At all time points during the first 2 years of the study, mean change from baseline in left ventricular ejection fraction was significantly greater in the ISDN/HYD group than in the placebo group ( $p < 0.03$ ; Table 5).

Table 5. Changes in Left Ventricular Ejection Fraction (% Units); V-HeFT I

	<b>Placebo</b>	<b>ISDN/HYD</b>	<b>p-value*</b>
<b>Baseline</b>	n=252	n=176	
Mean (SD)	30.4 (13.5)	30.3 (12.9)	
<b>Week 8</b>	n=230	n=143	
Mean (SD)	30.7 (13.8)	32.9 (14.4)	
Mean change (SD)	+0.4 (6.2)	+2.9 (7.3)	p=0.0004
<b>Week 28</b>	n=199	n=141	
Mean (SD)	30.6 (14.0)	34.2 (15.0)	
Mean change (SD)	+0.1 (7.4)	+3.7 (9.2)	p=0.0001
<b>Year 1</b>	n=166	n=124	
Mean (SD)	31.6 (15.0)	35.5 (15.6)	
Mean change (SD)	+0.3 (9.2)	+4.6 (10.0)	p=0.0002
<b>Year 1.5</b>	n=128	n=101	
Mean (SD)	30.5 (15.1)	33.2 (16.1)	
Mean change (SD)	-1.3 (8.7)	+2.0 (10.1)	p=0.0093
<b>Year 2</b>	n=107	n=85	
Mean (SD)	31.9 (15.9)	34.6 (17.2)	
Mean change (SD)	-1.2 (8.5)	+2.0 (10.3)	p=0.0261

\* p-values refer to between-group comparisons vs placebo

Of note, the placebo-corrected increase in left ventricular ejection fraction with ISDN/HYD was larger in non-black patients than black patients (+0.07 vs +0.01 units) at 1 year, but the race-by-treatment interaction was not significant ( $p=0.23$ ).

When compared with placebo, prazosin had no effect on left ventricular ejection fraction at any time during the study.

#### 4.1.7.3.6 Other Endpoints

The duration of tolerable exercise was greater in the ISDN/HYD group than in the placebo and prazosin groups at each time point during the first 2.5 years of the study. Slight mean increases from baseline were observed in the ISDN/HYD group, compared with slight mean decreases in the placebo group. However, none of the between-group differences was significant at any time point.

The cardiothoracic ratio assessed by chest x-ray was smaller in the ISDN/HYD group than in the placebo or prazosin groups early in the study. Compared with slight mean increases from baseline in the placebo group, the ISDN/HYD group experienced slight mean decreases from baseline in cardiothoracic ratio after 8 weeks (+0.1% placebo vs. -0.7% ISDN/HYD,  $p=0.046$ ) and after 28 weeks (+0.1% placebo vs. -0.7% ISDN/HYD,  $p=0.063$ ).

#### 4.1.7.4 Safety Results

##### 4.1.7.4.1 Adverse events regardless of relationship to study drug

Table 6 lists the number of patients who reported various adverse events. At each visit, investigators questioned the patients using a preprinted list of adverse events known to be associated with use of isosorbide dinitrate, hydralazine or prazosin; adverse events not on the preprinted list were recorded under “other.” A listing of specific “other” events is not available. Safety data for prazosin are not included in this briefing document.

Adverse events related to systemic vasodilation (headache, dizziness, flushing) or reflecting gastrointestinal distress (nausea, vomiting, diarrhea and abdominal pain) were more frequent in ISDN/HYD-treated than placebo-treated patients.

Table 6. Patients with Adverse Events; V-HeFT I

Preferred Term	Placebo N=273		ISDN/HYD N=186	
	n	(%)	n	(%)
Headache	139	(50.9)	139	(74.7)
Dizziness	163	(59.7)	131	(70.4)
Arthralgias	158	(57.9)	118	(63.4)
“Other”	135	(49.5)	114	(61.3)
Palpitation	120	(44.0)	104	(55.9)
Nausea or vomiting	123	(45.1)	97	(52.2)
Ischemic chest pain	113	(41.4)	91	(48.9)
Diarrhea	106	(38.8)	87	(46.8)
Abdominal pain	95	(34.8)	84	(45.2)
Flushing	83	(30.4)	81	(43.6)
Rash	104	(38.1)	80	(43.0)
Fever	72	(26.4)	62	(33.3)
Syncope	65	(23.8)	49	(26.3)

Of these adverse events, about 30% were rated severe as assessed by the investigator. The proportion of patients who experienced one or more severe adverse events was higher in the ISDN/HYD group than in the placebo group (41.4% vs 20.5%). The most frequent severe adverse events were headache (3.3% placebo vs. 27.4% ISDN/HYD), dizziness (7.3% placebo vs. 12.9% ISDN/HYD), “other” (5.9% placebo vs. 6.5% ISDN/HYD), arthralgias (3.3% placebo vs. 5.4% ISDN/HYD), and nausea or vomiting (2.6% placebo vs. 5.4% ISDN/HYD).

#### 4.1.7.4.2 Adverse events leading to permanent withdrawal of study drug

A patient was considered to have discontinued ISDN/HYD prematurely if he permanently discontinued both study medications prior to study end. A higher proportion of ISDN/HYD patients discontinued the study drugs prematurely because of adverse events (5.9% vs 1.1% on placebo). Adverse events leading to discontinuation of study medication included dizziness/syncope (0.7% placebo vs. 3.8% ISDN/HYD), headache (0.0% placebo vs. 3.2% ISDN/HYD), “other” (0.7% placebo vs. 2.7% ISDN/HYD), disorientation (0.0% placebo vs. 1.1% ISDN/HYD), arthralgia (0.0% placebo vs. 0.5% ISDN/HYD), and nausea (0.0% placebo vs. 0.5% ISDN/HYD).

#### 4.1.7.4.3 Other safety topics

##### Vital signs

Neither systolic nor diastolic blood pressures were lower in the ISDN/HYD group when compared with the placebo group. When compared with placebo, both systolic and diastolic blood pressures were significantly lower in the prazosin group at 8 weeks but not at one year. Heart rates were also similar across the three treatment groups for the duration of the study.

##### Lupus syndrome

Arthralgias were considered severe and possibly or probably related to the study medication in 7 patients (6 in the ISDN/HYD group and 1 in the placebo group). A total of 12 patients (10 ISDN/HYD and 2 placebo) were discontinued from the study due to arthralgia. In 5 patients (3 ISDN/HYD and 2 placebo), arthralgias were associated with a significant increase ( $\geq 1:160$ ) in ANA titer; this increase was sustained ( $\geq 2$  consecutive assessments excluding baseline) in 1 patient in the placebo group and 3 patients in the ISDN/HYD group. In addition, two ISDN/HYD patients were diagnosed with lupus-like syndrome based on symptoms and immunologic (ANA titer and LE prep) assessments.

##### Clinical laboratory evaluations

No clinically relevant mean changes in values for clinical laboratory tests were seen during the study.

#### 4.1.8 Summary and Conclusions for V-HeFT I

The findings of the first Vasodilator Heart Failure Trial (V-HeFT I) support the following conclusions:

- The long-term administration of a combination of ISDN/HYD to middle-aged men with mild-to-severe heart failure treated with digitalis glycosides and diuretics was associated with a 22% reduction in the relative risk of death. The p-value equaled 0.093 (protocol-specified log-rank test).
- In a retrospective analysis a reduction in the risk of death similar to that seen in the overall trial was seen across nearly all of the subgroups examined. The most striking effect was seen in black patients who experienced a 47% reduction in relative risk, as compared with white patients who experienced only a 12% reduction in relative risk, interaction  $p=0.15$ . The survival effect in black patients with ISDN/HYD was statistically significant in its own right ( $p=0.04$ ), even though black patients were one of the smallest subgroups and comprised only 30% of the patients in the trial.

- Further retrospective examination of subgroup effects suggested other subgroups might also respond well (with respect to survival) to the ISDN/HYD combination. These subgroups included: ejection fraction < 40% [25% reduction in risk when compared with 17% reduction in risk in patients with preserved ejection fractions]; younger patients [age  $\leq$  59 years; 33% reduction in risk when compared with 9% reduction in risk in older patients]; diabetic patients [25% reduction in risk when compared with 5% reduction in risk in non-diabetics]; lower systolic blood pressure [ $\leq$  118 mm Hg; 26% reduction in risk when compared with 14% reduction in risk in patients with higher systolic blood pressures].
- For the first two years of the study (the duration for which a meaningful proportion of the randomized patients were followed), the risk of hospitalization for heart failure was lower in the ISDN/HYD group than in the placebo group. A treatment effect in black patients contributed importantly to the overall differences.
- Although maximal exercise capacity was not significantly increased by the combination of ISDN/HYD in the overall trial, the magnitude of the functional improvement in black patients (who had an increase of 1.64 mL/kg/min) was greater than that seen in white patients (who had an increase of 0.84 mL/kg/min). This observation suggested that future trials might appropriately seek to confirm the efficacy of ISDN/HYD, using an endpoint that measures the effects of the drug on both clinical status and survival.
- The long-term administration of a combination of ISDN/HYD was associated with a consistent and meaningful improvement in left ventricular ejection fraction (about 3-4 units). Demonstration of the persistence of this effect for 2 years suggests that hemodynamic tolerance did not develop to this combination of ISDN/HYD during the course of long-term treatment of patients with heart failure.
- The long-term administration of prazosin, another drug with arterial and venous vasodilating effects, did not demonstrate favorable effects on survival, ejection fraction or exercise capacity. This finding suggests that the mechanisms by which drugs exert their vasodilator effects appear to be relevant in determining their efficacy in the treatment of heart failure.
- The long-term administration of a combination of ISDN/HYD was associated with headache, dizziness and other vasodilator-type reactions.
- A meaningful proportion of patients failed to achieve target doses of both ISDN and HYD. Clinical benefits were seen despite the use of lower-than-target doses, suggesting that future trials might appropriately target lower doses of ISDN/HYD.

In conclusion, the findings of V-HeFT I suggested that the combination of isosorbide dinitrate and hydralazine was likely to have favorable effects on survival and functional status when used in the treatment of heart failure and that the subgroup of black patients might be particularly sensitive to these benefits.

## 4.2 Vasodilator Heart Failure Trial II (V-HeFT II)

### 4.2.1 Study Overview

The second Vasodilator Heart Failure Trial (V-HeFT II) was a multicenter, randomized, double-blind, parallel group, active controlled trial conducted at 13 sites in the United States under the auspices of the Department of Veterans Affairs, which compared the vasodilator combination of ISDN/HYD and the angiotensin-converting enzyme inhibitor enalapril.

The intent in V-HeFT II was to compare two different drug treatments that had been shown in separate trials to reduce the risk of death in patients with chronic heart failure: (1) ISDN/HYD, which had favorable effects on survival in V-HeFT I; and (2) enalapril, which had favorable effects on survival in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). Both drug regimens were known to produce hemodynamic benefits by exerting dilating effects on systemic blood vessels, but it was unclear whether the distinctly different mechanisms by which the treatments exerted vasodilator effects might result in distinctly different patterns of clinical benefit.

As was the case of V-HeFT I, V-HeFT II enrolled men who generally had class II-IV symptoms, had heart failure associated with both impaired and preserved ejection fraction, and were generally taking only digitalis glycosides and diuretics. The entry criteria, design and endpoints of V-HeFT II closely paralleled those of V-HeFT I.

### 4.2.2 Study Organization

The Executive Committee was the management and decision-making body for the operational aspects of the conduct of the study. The members of the Committee were:

- Jay Cohn, M.D., Minneapolis VA Hospital (chair)
- Donald Archibald, M.Phil., West Haven VA Hospital (biostatistician)
- Frederick Cobb, M.D., Durham VA Hospital
- Ross Fletcher, M.D., Washington DC VA Hospital
- Gary Francis, M.D., Minneapolis VA Hospital
- Clair Haakenson, R.Ph., Albuquerque VA Hospital (research pharmacist)
- Gary Johnson, MS., West Haven VA Hospital (biostatistician)
- Pravin Shah, M.D., West Los Angeles VA Hospital
- Maylene Wong, M.D., West Los Angeles VA Hospital
- Susan Ziesche, R.N., Minneapolis VA Hospital

A Data and Safety Monitoring Board; composed of clinicians who did not participate in the trial periodically reviewed study results and evaluated the treatments for excess events. The members of the DSMB were:

Richard Gorlin, M.D., Mount Sinai School of Medicine (chair)  
Dorothea Collins, M.S., West Haven VA Hospital  
Leon Goldberg, M.D., Ph.D., University of Chicago  
Genell Kantterud, PhD, Maryland Research Institute, Baltimore  
John Oates, M.D., Vanderbilt University  
William Parmley, M.D., University of California San Francisco

## 4.2.3 Study Population

### 4.2.3.1 Inclusion Criteria

- Men, 18 to 75 years old.
- Heart failure as evidenced by reduced exercise tolerance for at least 3 months. Reduced exercise tolerance was defined as maximal oxygen consumption  $< 25$  mL/kg/min during graded bicycle ergometry testing
- Persistent symptoms despite digitalis glycosides and diuretics.
- Cardiothoracic ratio on chest x-ray  $\geq 0.55$ , or an echocardiographic left ventricular internal dimension  $> 2.7$  cm/m<sup>2</sup>, or a radionuclide or contrast left ventricular ejection fraction  $< 0.45$ .

### 4.2.3.2 Exclusion Criteria

- Myocardial infarction or cardiac surgery within 3 months.
- Hypertrophic cardiomyopathy or hemodynamically significant aortic or mitral valve or pericardial disease.
- Patients with hypertension requiring antihypertensive drugs other than diuretics.
- Angina pectoris severe enough to require long-acting nitrates or frequent administration of sublingual nitroglycerin (more than 4 tablets per week).
- Chronic treatment with a beta-blocking drug, calcium channel blockers, or vasodilators other than occasional sublingual nitroglycerin.
- History of systemic lupus erythematosus or history of intolerance to isosorbide dinitrate, hydralazine or enalapril.
- Chronic lung disease sufficient to limit exercise tolerance.
- Severe intrinsic renal disease or primary hepatic disease.
- Hematocrit  $< 30\%$ .
- Disease that was expected to limit survival within 2 years.

It should be noted that 129 patients who had completed V-HeFT I in either the placebo or prazosin treatment group and who met the eligibility criteria for V-HeFT II, were randomized into V-HeFT II.

## 4.2.4 Study Plan

After each patient was screened, he entered a baseline period of four weeks' duration to establish optimal therapy with a digitalis glycoside and a diuretic and to allow any nonstudy drugs to be discontinued. Patients fulfilling all inclusion criteria and none of the exclusion criteria were randomized to either enalapril or a combination of ISDN/HYD. Randomization was stratified by center using a permuted block size of 6.

Each randomized patient received three bottles of medications: the first containing enalapril 5 mg or matching placebo, the second containing hydralazine 37.5 mg or matching placebo, and the third containing isosorbide dinitrate 40 mg or matching placebo. The patients began treatment by taking one tablet BID from the first bottle, one tablet QID from the second bottle and one-half tablet QID from the third bottle. After 2 weeks, if tolerated, the dose of each medication was to be doubled so that the target daily treatment consisted of either enalapril 10 mg BID, or ISDN 40 mg QID plus HYD 75 mg QID. If the study medications were not tolerated, the patient could reduce the dose of one or both of the study drugs. The goal was to achieve the highest tolerated dose of the study medication up to the target dose, and the doses of other medications could be adjusted as clinically indicated.

Following randomization, each patient was to be seen as an outpatient every 2 weeks until two successive visits revealed stability, and then every 1-3 months for the duration of the trial. Chest x-ray, Holter monitoring, quality of life assessment, radionuclide imaging for assessment of left ventricular ejection fraction, maximum exercise testing and plasma norepinephrine were assessed at baseline, at 3 and 6 months, and every 6 months thereafter.

## 4.2.5 Study Assessments

As in the case of V-HeFT I, the study protocol for V-HeFT II described several major and several minor endpoints. However, the study was envisioned primarily as a mortality study, and mortality was the only variable that was used to determine the sample size of the trial.

### 4.2.5.1 Major Endpoints

- All-cause mortality during the entire study period
- All-cause mortality at 2 years
- Number and duration of cardiovascular hospitalizations
- Maximum oxygen consumption during peak exercise
- Oxygen consumption at anaerobic threshold
- Maximum treadmill exercise time on a graded test
- Quality of life assessed by the Heart Condition Assessment Questionnaires

#### 4.2.5.2 Minor Endpoints

- Heart size and pulmonary congestion by chest x-ray
- Ejection fraction by radionuclide ventriculography
- Arrhythmias assessed by Holter monitoring
- Plasma norepinephrine

#### 4.2.5.3 Safety Assessments

Safety assessments consisted of monitoring and recording all treatment-emergent adverse events and serious adverse events, the performance of physical examinations (which included the measurement of vital signs at every visit), and laboratory evaluations.

#### 4.2.6 Statistical Plan and Analyses

##### 4.2.6.1 Sample Size Determination and Interim Monitoring Plan

The study protocol projected a sample size of 952 patients in order to provide 87% power to detect a 30% difference in survival, assuming a mortality rate with ISDN/HYD similar to that observed with ISDN/HYD in V-HeFT I ( $\alpha=0.05$ ).

The Data and Safety Monitoring Board met at 6 month intervals throughout the study and used an O'Brien-Fleming boundary to guide decision-making during four interim analyses. The Committee made no decision to recommend modification of the course of the study.

##### 4.2.6.2 Statistical Analyses

###### Mortality

Differences in survival were compared between the two treatment groups using a log-rank test (two-sided  $\alpha=0.05$ ). The final test for significance for mortality was set at  $\alpha=0.042$  after adjustment for four interim analyses using the O'Brien-Fleming group sequential boundary. Mortality risks within subgroup were assessed and compared using a Cox proportional hazard model. Exposure was censored at the time of heart transplantation in eight patients (six enalapril and two ISDN/HYD). For the comparison between treatment groups of survival rates at 2 years, 95% confidence intervals were used to generate the Greenwood standard errors using an asymptotically normal test statistic.

###### Non-Fatal Measures of Efficacy

Mean changes from baseline in exercise capacity, left ventricular ejection fraction, heart size and quality of life assessments were calculated for each variable for those patients with data available at each study visit. [Such an approach does not account for the differences in survival between treatment groups.] The observed treatment difference was evaluated for significance using two-sample t-tests. The chi-square statistic was used to test for significance of differences between groups in the number of hospitalizations and other major clinical events.

## 4.2.7 Results

### 4.2.7.1 Baseline Characteristics

A total of 804 patients were randomized to treatment with enalapril (n=403) or ISDN/HYD (n=401).

The patients enrolled in V-HeFT II were middle-aged men, of whom approximately 26-27% were black in each group (see Table 7). The most common cause of heart failure was coronary artery disease; slightly less than one-half of the patients had heart failure due to hypertension. The mean left ventricular ejection fraction was approximately 29%, and the mean oxygen consumption was approximately 13-14 mL/kg/min. The two treatment groups were well-matched for baseline characteristics, except that the mean duration of heart failure was longer in the ISDN/HYD group than in the enalapril group (p=0.0044), and the mean left ventricular internal dimensions were greater in the enalapril group than in the ISDN/HYD group (p=0.0192).

Table 7. Baseline Demographic and Clinical Characteristics; V-HeFT II

	<b>Enalapril n=403*</b>	<b>ISDN/HYD n=401*</b>
<b>Demographic features</b>		
Age (years; mean, SD)	60.6 (8.3)	60.6 (8.5)
Race (n, %)		
White	292 (72.5%)	282 (70.3%)
Black	106 (26.3%)	109 (27.2%)
Other	5 (1.2%)	10 (2.3%)
Duration of heart failure (mos; mean, SD)	31.2 (37.8)	40.2 (48.6)
<b>NYHA class (n, %)</b>		
Class I	24 (6.0%)	22 (5.5%)
Class II	200 (49.6%)	210 (52.4%)
Class III	178 (44.2%)	167 (41.7%)
Class IV	1 (0.3%)	2 (0.5%)
<b>Cardiovascular history (n, %)</b>		
Coronary artery disease	220 (54.6%)	213 (53.3%)
Alcohol excess	135 (33.5%)	147 (36.7%)
Hypertension	199 (49.6%)	182 (45.4%)
Diabetes	84 (20.8%)	80 (20.0%)
<b>Drug therapy (prior 6 mos; n, %)</b>		
Vasodilators	250 (62.0%)	247 (61.6%)
Antiarrhythmics	100 (24.8%)	106 (26.4%)
Sublingual nitroglycerin	64 (15.9%)	67 (16.7%)
Anticoagulants	84 (20.8%)	88 (22.0%)
<b>Clinical data (mean, SD)</b>		
Ejection fraction (%)	28.6 (10.9) (n=388)	29.4 (11.5) (n=384)
Maximal O <sub>2</sub> consumption (mL/kg/min)	13.8 (3.5) (n=398)	13.5 (3.5) (n=400)
Systolic/diastolic BP (mm/Hg)	125/78	127/78
Heart rate (beats/min)	78.4 (12.1)	77.3 (11.9)
Cardiothoracic ratio (%)	53.7 (6.0) (n=392)	53.0 (6.2) (n=392)
Left ventricular internal dimension (cm/m <sup>2</sup> )	3.6 (1.4) (n=170)	3.2 (1.2) (n=159)
Plasma norepinephrine (pg/mL)	593 (388) (n=372)	544 (297) (n=371)
Plasma renin activity (mg/mL/hr)	19.9 (52.6) (n=371)	15.7 (28.1) (n=366)

\* n= 403 or 401, unless otherwise specified

#### 4.2.7.2 Patient Disposition and Exposure to Study Medication

The first of 804 patients was enrolled in March 1986, the last patient was enrolled in September 1990, and the study was completed in February 1991. The mean follow-up period was 2.5 years (range: 6 months to 4.9 years).

In the ISDN/HYD treatment group, the majority (67.3%) of patients achieved the target dose of both HYD and ISDN tablets by 6 months; at that time, a higher proportion had achieved the target dose of HYD than of ISDN (81.3% HYD vs. 72.1% ISDN). Approximately three fourths (74.8%) of ISDN/HYD patients achieved the target dose of both study medications at any time during the study; a higher proportion of patients achieved the target dose of HYD than of ISDN (84.5% vs. 78.6%). In comparison, the percentage reaching target dose was consistently higher in the enalapril group. The proportion of enalapril-treated patients who achieved the target dose at 6 months and at any time during the study was 92.8% and 94.8%, respectively.

In the ISDN/HYD group, the average number of HYD tablets taken per day was 5.4 (target dose = 8 x 37.5 mg tablet), and the average number of ISDN tablets taken per day was 2.5 (target dose = 4 x 40 mg tablet). Therefore, the average daily dose of HYD was 199 mg/day (67% of target dose) and the average daily dose of ISDN was 100 mg/day (63% of target dose). In the enalapril group, the average number of tablets taken per day was 1.5 (target dose = 2 x 10 mg tablet); therefore, the average dose was 15 mg/day (75% of target dose).

In the ISDN/HYD group, most ( $\geq 74.3\%$ ) patients received treatment with HYD or ISDN for at least 6 months, and the majority ( $\geq 62.3\%$ ) received treatment for at least one year. The proportion of patients exposed to drug was consistently higher in the enalapril group than in the ISDN/HYD group; the proportion of patients exposed to HYD was similar to that exposed to ISDN.

By the time of the final clinic visit, 22% of the patients assigned to enalapril had discontinued the drug, and an additional 8% had reduced the dose. In the ISDN/HYD group, 29% of the patients had discontinued HYD and 10% had reduced the dose, whereas 31% had discontinued ISDN, and an additional 10% had reduced the dose. Compliance with the prescribed regimen averaged 86%.

Twenty-five patients in the ISDN/HYD arm received ACE inhibitors, whereas in the enalapril arm, 5 patients were treated with HYD and 15 with ISDN.

### 4.2.7.3 Efficacy Results

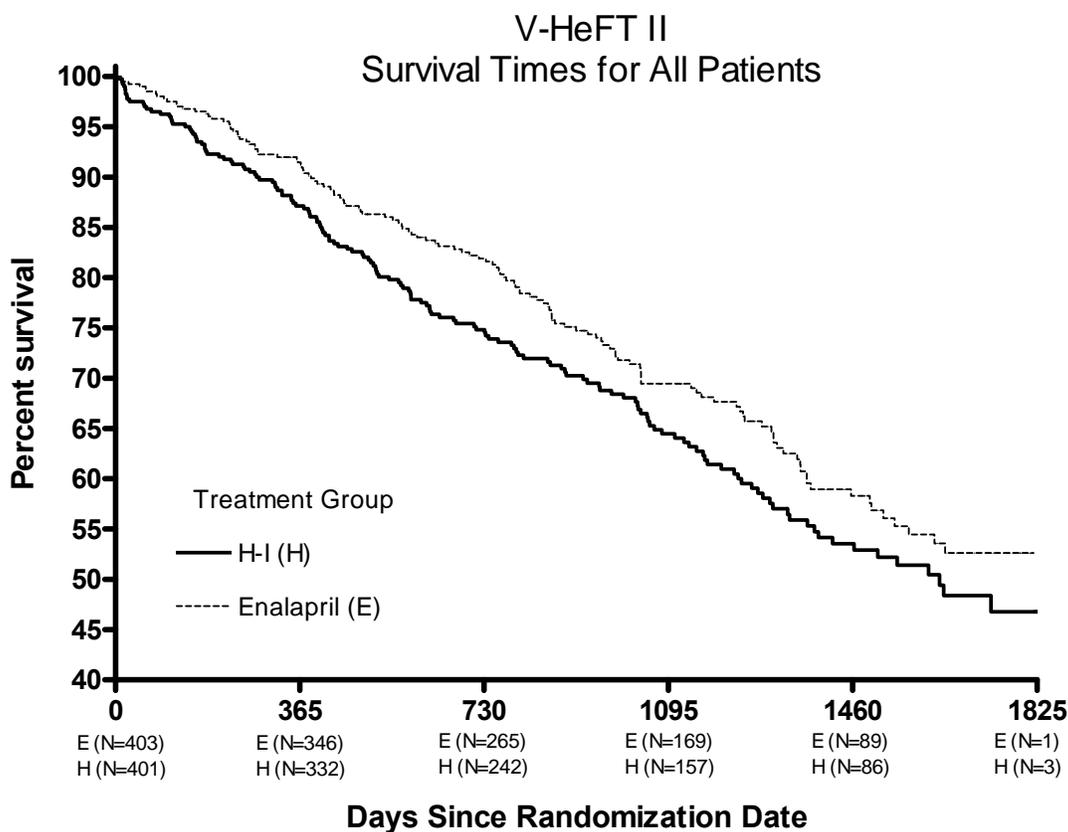
#### 4.2.7.3.1 Overall Mortality

By intention to treat, there were 132 deaths from all causes in the enalapril group (32.8%) as compared with 153 deaths in the ISDN/HYD group (38.2%; Table 8 and Figure 8). The log-rank p-value for the comparison of ISDN/HYD vs enalapril was 0.083. At the protocol-specified endpoint of 2 years, the cumulative mortality rate was 18% in the enalapril group and 25% in the ISDN/HYD group, a 28% difference in risk; p=0.016.

Table 8. Effects on All-Cause Mortality; V-HeFT II

<b># of Deaths (%) Enalapril (n = 403)</b>	<b># of Deaths (%) ISDN/HYD (n = 401)</b>	<b>ISDN/HYD: enalapril hazard ratio (95% CI)</b>	<b>Log-rank p-value</b>
132 (32.8%)	153 (38.2%)	1.23 (0.97, 1.55)	0.083

Figure 8. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality; V-HeFT II



#### 4.2.7.3.2 Retrospective Subgroup Analysis of Mortality

Retrospective analysis for death indicated that the treatment difference seen between ISDN/HYD and enalapril in the overall trial was seen across nearly all of the subgroups examined (Figure 9). However, one notable exception was black patients, who had been identified in V-HeFT I as being particularly responsive to the combination of ISDN/HYD. The hazard ratio for ISDN/HYD : enalapril was 1.32 in non-black patients but 1.01 for black patients, indicating that the superiority of enalapril over ISDN/HYD in the overall trial was driven primarily by a treatment difference in white patients (Figures 10, 11).

Further examination of other subgroup effects in V-HeFT II did not confirm most of the other subgroup hypotheses generated by the findings of V-HeFT I. Specifically, younger patients, diabetics and patients with lower systolic blood pressures responded better to ISDN/HYD than placebo in V-HeFT I but responded worse to ISDN/HYD than enalapril in V-HeFT II (ISDN/HYD : enalapril hazard ratios 1.36 in younger patients, 1.35 in diabetics and 1.37 in patients with lower systolic blood pressures). Except for race only one additional subgroup effect seen in V-HeFT I was confirmed in V-HeFT II. Specifically, patients with a left ventricular ejection fraction  $\leq 40\%$  responded best to ISDN/HYD (relative to enalapril hazard

ratio of 2.02 in patients with preserved ejection fractions as compared with 1.21 in patients with impaired ejection fractions).

It should be noted that the subgroup of patients who had previously participated in V-HeFT I and were enrolled and randomized into V-HeFT II responded to treatment with respect to mortality in a manner similar to those who had been newly recruited into V-HeFT II.

Figure 9. Hazard Ratios and 95% Confidence Intervals for Effect of ISDN/HYD on All-Cause Mortality in Subgroups; V-HeFT II

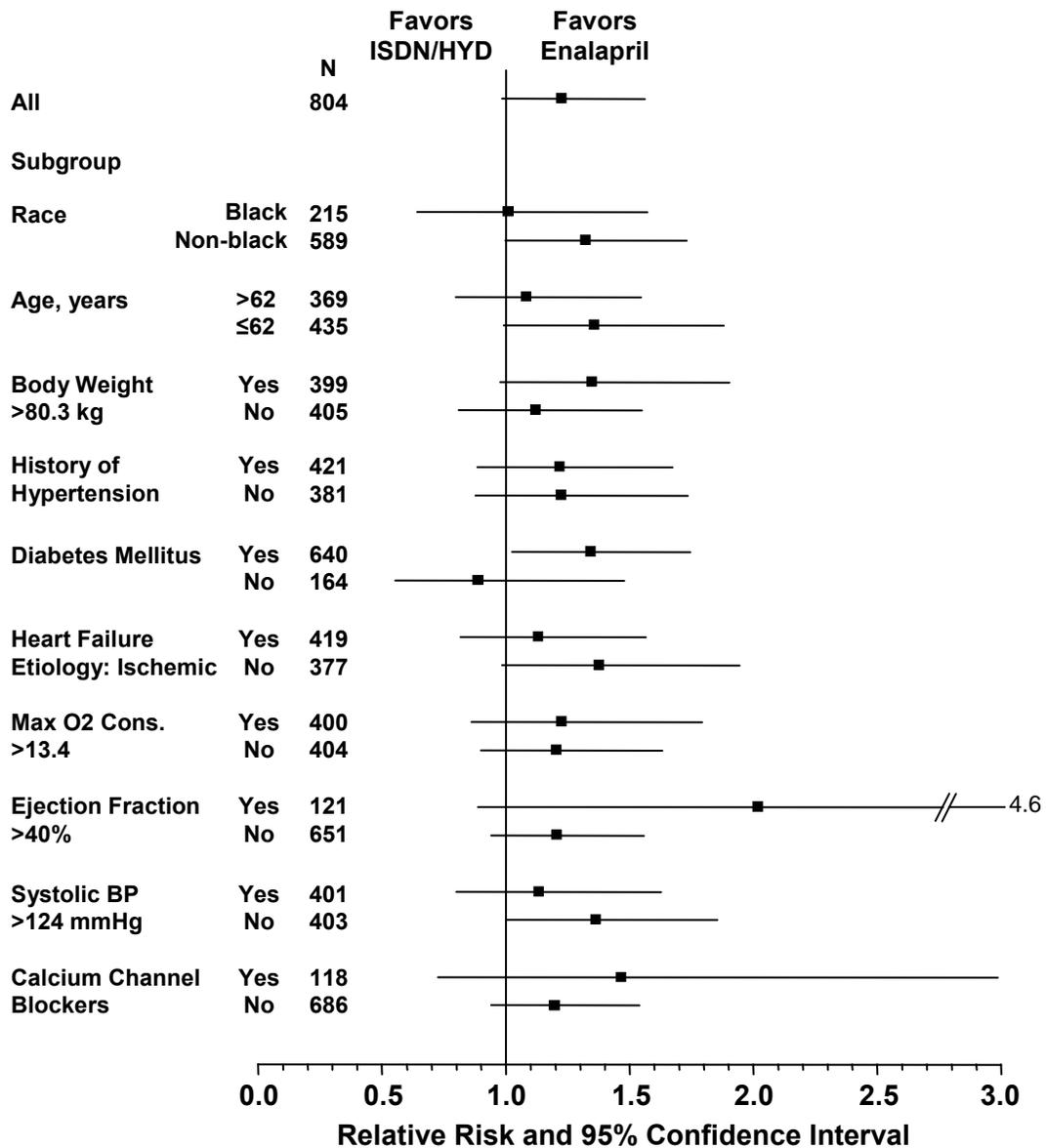


Figure 10. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in Black Patients; V-HeFT II

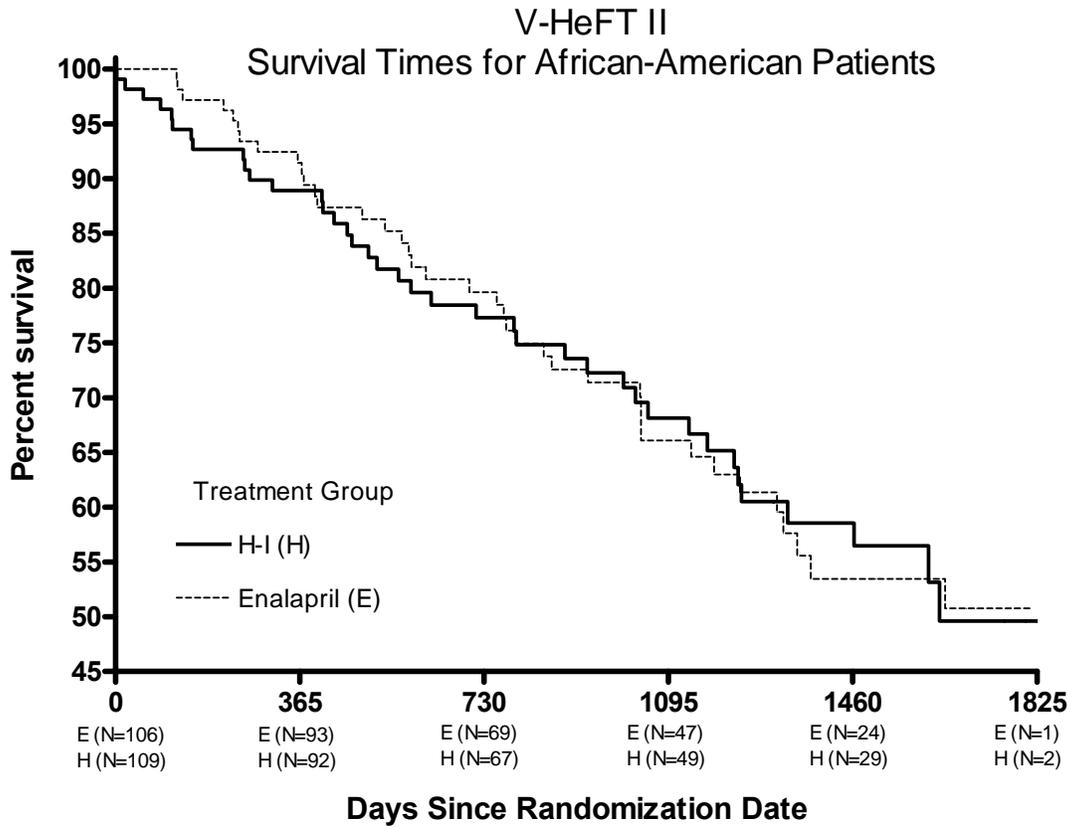
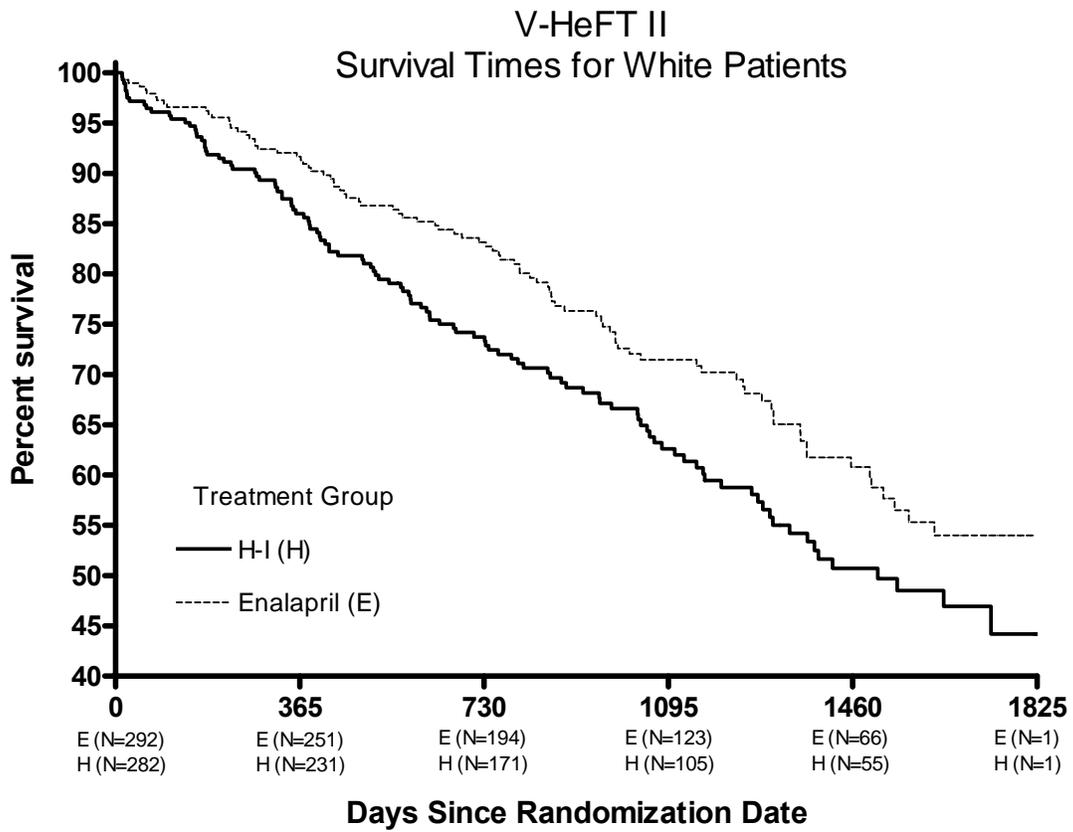


Figure 11. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in White Patients; V-HeFT II



#### 4.2.7.3.3 Hospitalizations

Although the occurrence of hospitalization was recorded in the trial at each visit, the dates of hospitalization were not recorded and the causes of hospitalization were not centrally adjudicated. Nevertheless, each investigative site provided an assessment of the cause of each hospitalization, and in general, the occurrence of hospitalization during the study was recorded at the patient's next regularly scheduled visit. If one assumed that a hospitalization occurred at the time it was recorded (rather than when it actually occurred), it is possible to construct a time-to-event analysis of the occurrence of hospitalization for heart failure — recognizing that a hospitalization may have actually occurred at any time between scheduled visits.

As shown in Figures 12, 13, and 14 time-to-event analyses for the occurrence of a heart failure hospitalization suggest the following:

- For the first 2 years of the study (the duration for which a meaningful proportion of the randomized patients were followed), there is little difference between the enalapril and ISDN/HYD groups in the overall trial.
- However, in black patients, for the first 2 years of the study, those in the ISDN/HYD group had a lower risk of hospitalization for heart failure than those in the enalapril group. For example, at the end of the first year, the cumulative heart failure hospitalization rate was 5.0% in ISDN/HYD patients vs 13.1% in enalapril patients. The groups converged after 2 years, but the number of patients who were followed beyond 2 years is small.
- In contrast, in white patients, for the first 2 years of the study, those in the ISDN/HYD group had a risk of hospitalization for heart failure similar to those in the enalapril group. For example, at the end of the first year, the cumulative heart failure hospitalization rate was 6.2% in ISDN/HYD patients and 6.3% in enalapril patients. The groups diverged after 2 years (with a lower risk in the enalapril group), but the number of patients who were followed beyond 2 years is small.

The patterns that emerge from these approximations are consistent with the patterns that emerged from the overall and subgroup analyses of survival.

Figure 12: Time to First Heart Failure Hospitalization – All Patients; V-HeFT II

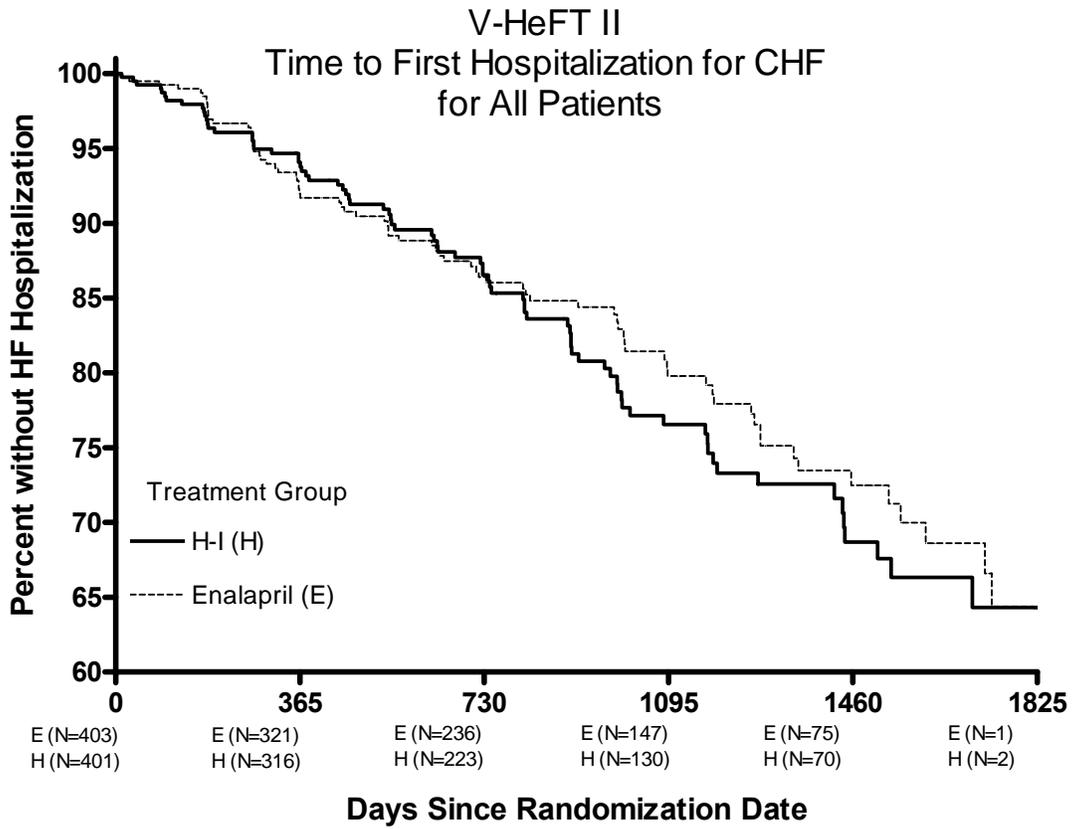


Figure 13: Time to First Heart Failure Hospitalization – Black Patients;  
V-HeFT II

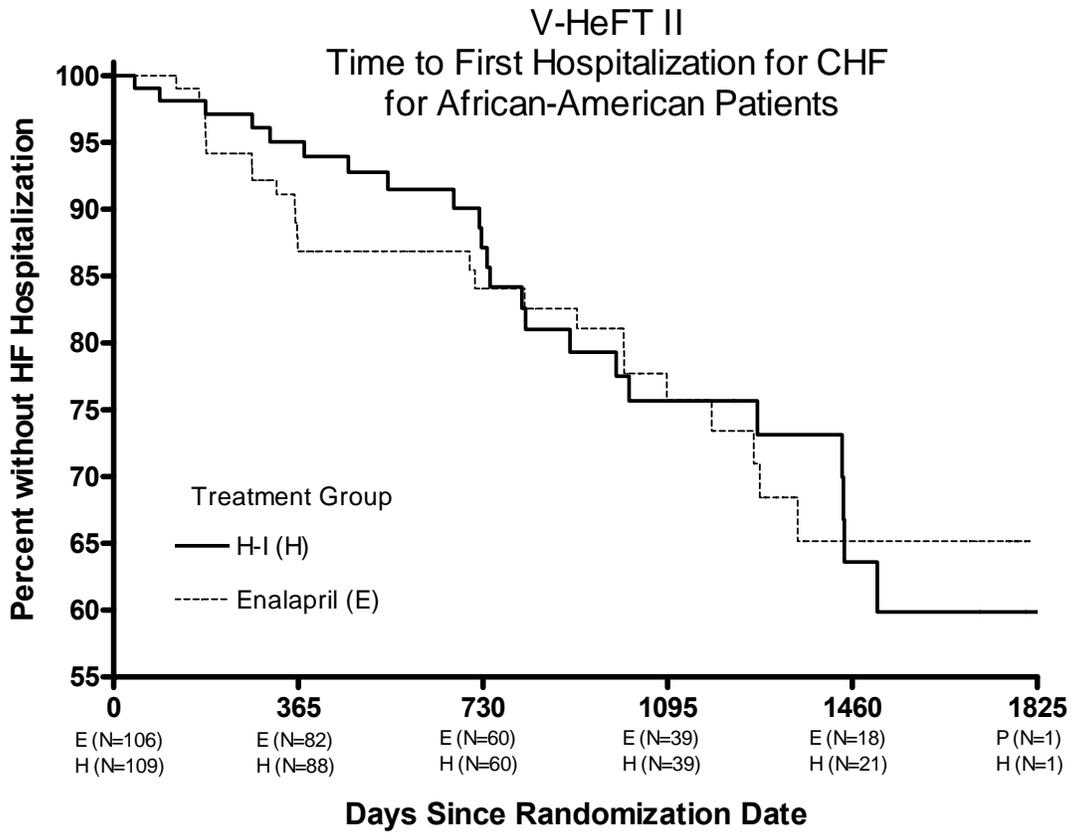
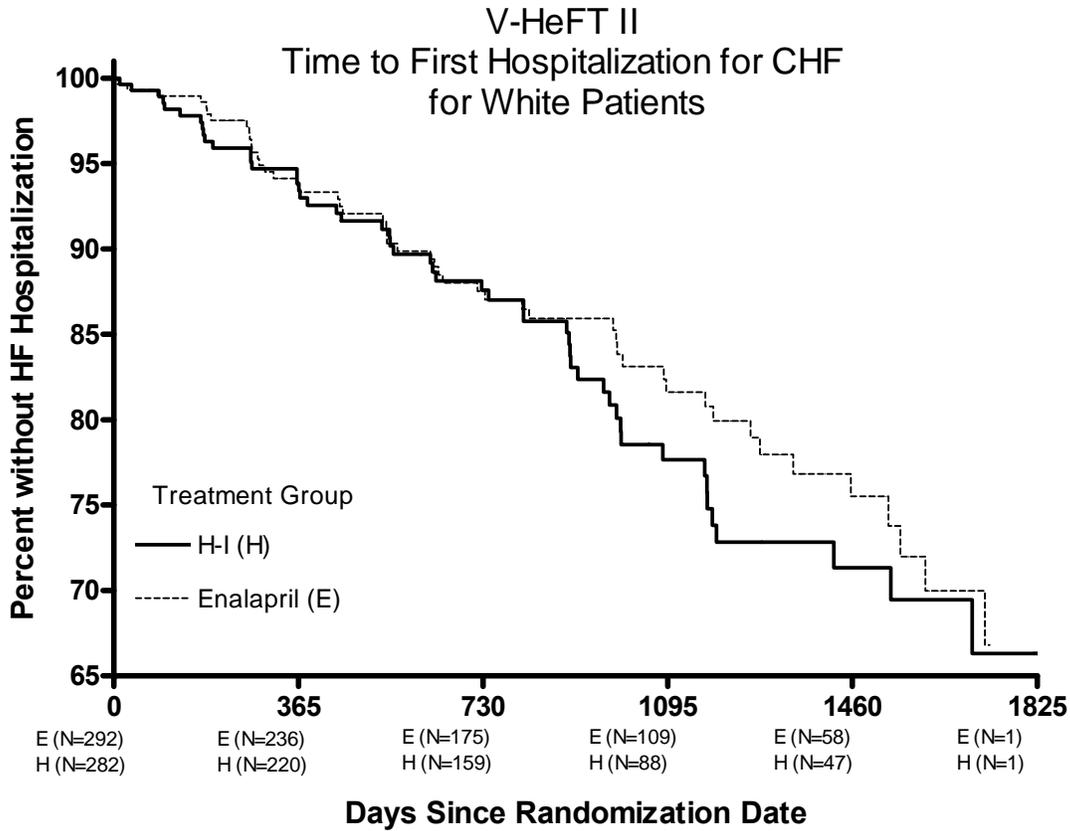


Figure 14. Time to First Heart Failure Hospitalization – White Patients; V-HeFT II



#### 4.2.7.3.4 Maximum Oxygen Consumption at Peak Exercise

Exercise capacity (as assessed by maximum oxygen consumption at peak exercise) was consistently greater in the ISDN/HYD group than in the enalapril group throughout the study (Table 9). The differences between the groups were significant or nearly so at most time points.

Table 9. Changes in Maximal Oxygen Consumption; V-HeFT II

	<b>Enalapril</b>	<b>ISDN/HYD</b>	<b>p-value*</b>
<b>Baseline</b>	(n=398)	(n=400)	
Mean (SD)	13.8 (3.5)	13.5 (3.5)	
<b>Month 3</b>	n=333	n=322	
Mean (SD)	13.9 (3.7)	14.1 (3.8)	
Mean change (SD)	-0.05 (2.4)	+0.41 (2.4)	p=0.0152
<b>Month 6</b>	n=302	n=289	
Mean (SD)	14.4 (3.6)	14.4 (4.2)	
Mean change (SD)	+0.25 (2.5)	+0.60 (2.7)	p=0.1099
<b>Month 12</b>	n=272	n=247	
Mean (SD)	13.8 (3.7)	14.2 (3.9)	
Mean change (SD)	-0.32 (2.7)	+0.24 (3.0)	p=0.0185
<b>Month 18</b>	n=222	n=187	
Mean (SD)	14.0 (3.4)	14.3 (4.0)	
Mean change (SD)	-0.24 (2.8)	+0.19 (3.2)	p=0.1462
<b>Month 24</b>	n=187	n=160	
Mean (SD)	13.9 (3.7)	14.4 (3.7)	
Mean change (SD)	-0.67 (2.7)	+0.16 (2.5)	p=0.0035

\* p-values refer to between-group comparisons

#### 4.2.7.3.5 Quality of Life

For all patients changes in quality of life were similar between the ISDN/HYD and the enalapril groups.

Of note, the improvement in quality of life with ISDN/HYD was primarily seen in black patients (Table 10). Specifically, in black patients, quality of life scores at twelve months in black patients improved by 0.67 units in the ISDN/HYD group but deteriorated by 1.04 units in the enalapril group (between group  $p=0.04$ ). In white patients, quality of life at twelve months improved by 0.24 units in the ISDN/HYD group and by 0.26 units in the enalapril group (between group  $p=0.97$ ). The race by treatment interaction  $p$ -value for changes in quality of life at twelve months was 0.09.

Table 10. Quality of Life\* in Black Patients; V-HeFT II

Time on Study	ISDN/HYD		Enalapril		p-Value
	# of Patients	QOL Change From Baseline	# of Patients	QOL Change From Baseline	
3 Months	87	-0.29	83	0.23	0.43
6 Months	86	-0.29	81	0.8	0.18
12 Months	71	-0.67	69	1.04	0.043

\* A Decrease in the “Quality of Life” score is favorable.

#### 4.2.7.3.6 Left Ventricular Ejection Fraction

At the time of the first post-randomization measurement (3 months), the mean change from baseline in left ventricular ejection fraction was significantly greater in the ISDN/HYD group than in the enalapril group ( $p=0.026$ ; Table 11). Although this difference in favor of ISDN/HYD persisted throughout the study, it was no longer significant after 3 months.

Table 11. Left Ventricular Ejection Fraction; V-HeFT II

	<b>Enalapril</b>	<b>ISDN/HYD</b>	<b>p-value*</b>
<b>Baseline</b>	n=388	n=384	
Mean (SD)	28.6 (10.9)	29.4 (11.5)	
<b>Month 3</b>	n=359	n=335	
Mean (SD)	31.0 (11.4)	32.3 (12.7)	
Mean change (SD)	+2.1 (6.7)	+3.3 (7.1)	p=0.026
<b>Month 12</b>	n=308	n=275	
Mean (SD)	31.3 (12.4)	32.6 (13.7)	
Mean change (SD)	+2.5 (8.4)	+3.6 (8.7)	p=0.12
<b>Month 24</b>	n=229	n=209	
Mean (SD)	31.6 (12.4)	33.1 (13.1)	
Mean change (SD)	+2.5 (8.5)	+3.1 (9.9)	p=0.53
<b>Month 36</b>	n=141	n=137	
Mean (SD)	33.5 (13.7)	32.9 (12.8)	
Mean change (SD)	+3.3 (10.3)	+3.7 (10.9)	p=0.68

\* p-values refer to between-group comparisons

#### 4.2.7.3.7 Other Endpoints

The duration of tolerable exercise was somewhat greater in the ISDN/HYD group than in the enalapril group, but the difference between the groups achieved significance only at the first post-randomization measurement (month 3) and was not significant thereafter.

The cardiothoracic ratio assessed on a chest x-ray was similar in the two groups throughout the duration of the study.

#### 4.2.7.4 Safety Results

##### 4.2.7.4.1 Adverse events regardless of relationship to study drug

Table 12 lists the number of patients who reported adverse events. At each visit, investigators questioned the patients using a preprinted list of adverse events known to be associated with use of ISDN or HYD or enalapril; adverse events not on the preprinted list were recorded under “other.” A listing of specific “other” events is not available.

Adverse events related to systemic vasodilation (e.g., headache) were more frequent in patients receiving ISDN/HYD than enalapril.

Table 12. Patients with Adverse Events; V-HeFT II

Preferred Term	Enalapril (n=403)		ISDN/HYD (n=401)	
	n	(%)	n	(%)
Lassitude/fatigue	330	81.9	326	81.3
Headache	242	60.0	307	76.6
Arthralgias	288	71.5	276	68.8
Nasal congestion	272	67.5	271	67.6
Dizziness	269	66.8	268	66.8
“Other”	262	65.0	246	61.4
Palpitation	217	53.8	227	56.6
Nausea and vomiting	237	58.8	213	53.1
Chest pain	187	46.4	178	44.4
Constipation	176	43.7	169	42.1

The proportion of patients who experienced one or more severe adverse events was higher in the ISDN/HYD group than in the enalapril group (53.4% vs 47.2%). The most frequent severe adverse events were headache (6.4% enalapril vs. 25.9% ISDN/HYD), lassitude/fatigue (23.1% enalapril vs 24.9% ISDN/HYD), arthralgias (15.1% enalapril and 17.0% ISDN/HYD), dizziness (9.2% enalapril vs. 10.5% ISDN/HYD), other (9.4% enalapril vs. 9.5% ISDN/HYD), nasal congestion (8.9% enalapril vs 7.7% ISDN/HYD), and nausea/vomiting (6.2% enalapril vs 7.5% ISDN/HYD).

#### 4.2.7.4.2 Adverse events leading to permanent withdrawal of study drug

A patient was considered to have discontinued ISDN/HYD prematurely if he permanently discontinued both study medications prior to study end.

A similar proportion of ISDN/HYD patients and enalapril patients discontinued the study drug(s) prematurely because of adverse events (2.0% enalapril vs. 2.5% ISDN/HYD). Adverse events leading to discontinuation of study medications were headache (0.7% enalapril vs. 1.2% ISDN/HYD), nausea (0.5% enalapril vs. 1.0% ISDN/HYD), dizziness/syncope (1.0% enalapril vs. 0.8% ISDN/HYD), and hypotension (0.2% enalapril vs. 0.2% ISDN/HYD). In addition, 1.5% and 1.8% of patients in the enalapril and ISDN/HYD groups, respectively, discontinued study medications due to “other” adverse events.

#### 4.2.7.4.3 Other safety topics

##### Vital signs

Following randomization, both systolic and diastolic blood pressures were consistently lower in the enalapril group than in the ISDN/HYD group; the difference between the two groups averaged about 5 mm Hg systolic and diastolic and was statistically significant at all time points.

Heart rate increased in the ISDN/HYD group and decreased in the enalapril group; the difference between the treatment groups in the mean change from baseline was statistically significant ( $p < 0.05$ ) at each analysis at time point through month twelve and marginally significant from month fifteen through month twenty-one.

Further analysis demonstrated a significant interaction between changes in blood pressure and race (Table 13). During the first 6 months, systolic blood pressure decreased markedly in white patients treated with enalapril, decreased to an intermediate degree in black patients regardless of treatment, and increased slightly in white patients treated with ISDN/HYD. Hence, black patients showed a greater blood pressure reduction with ISDN/HYD than white patients, whereas enalapril and ISDN/HYD produced similar hypotensive effects in white patients. Therefore, the pattern of blood pressure effect closely paralleled the pattern of survival effects with the two treatments in the two racial groups.

Table 13. Effect of Race on Change in Systolic Blood Pressure With Enalapril and ISDN/HYD; V-HeFT II

Time in Study	Non-black patients (mm/Hg)		Black patients (mm/Hg)		Race by treatment interaction p-value
	Enalapril	ISDN/HYD	Enalapril	ISDN/HYD	
4 weeks	-7.4	-0.3	-4.0	-3.3	0.0067
3 months	-6.2	+0.9	-2.6	-2.8	0.0033
6 months	-4.6	+0.8	-1.7	-1.3	0.0694

##### Lupus syndrome

No patient in either treatment group was permanently discontinued from the study because of arthralgia. The number of patients who had arthralgia that led to dose reduction was somewhat higher in the ISDN/HYD group (n=44, 11.0%) than in the enalapril group (n=26, 6.4%). The arthralgias were considered severe and possibly or probably related to the study medication in 31 patients, 15 (3.7%) in the enalapril group and 16 (4.0%) in the ISDN/HYD group. In 27 patients, 10 in the enalapril group and 17 in the ISDN/HYD group, arthralgias were associated with a significant increase ( $\geq 1:160$ ) in ANA titer that was not preexisting and represented a worsening from baseline; this increase was sustained ( $\geq 2$  consecutive assessments excluding baseline) in 8 patients in the enalapril group and 12 patients in the ISDN/HYD group. In addition, a total of 15 patients (8 in the enalapril group and 7 in the ISDN/HYD group) interrupted or discontinued at least one study drug due to suspected lupus-like syndrome.

### Clinical laboratory evaluations

No clinically relevant mean changes in values for clinical laboratory tests were seen during the study, except for small increases in blood urea nitrogen and serum creatinine in the enalapril patients as compared to the ISDN/HYD patients.

## 4.2.8 Summary and Conclusions for V-HeFT II

The findings of the second Vasodilator Heart Failure Trial (V-HeFT II) support the following conclusions:

- When compared with enalapril, the long-term administration of a combination of ISDN/HYD to middle-aged men with mild-to-severe heart failure treated with digitalis glycosides and diuretics was associated with a 23% greater risk of death. The p-value for this treatment difference 0.08 for the overall trial and 0.016 for the prespecified comparison of mortality rates at 2 years.
- The difference in survival between enalapril and ISDN/HYD seen in V-HeFT II was comparable in magnitude (23%) to the difference in survival seen in trials that have compared enalapril to placebo in mild-to-moderate heart failure (23% mortality reduction in a meta-analysis of all placebo-controlled trials of ACE inhibitors). Therefore, in the absence of V-HeFT I, the juxtaposition of the point estimates of V-HeFT II and the ACE inhibitors trials might suggest that the combination of ISDN/HYD had little effect on mortality in the majority of patients enrolled in V-HEFT II.
- It is therefore noteworthy that — although a superior survival effect of enalapril relative to ISDN/HYD was seen across nearly all of the subgroups examined — one notable exception was black patients. The hazard ratio for ISDN/HYD : enalapril was 1.32 in white patients but 1.01 for black patients, indicating that the superiority of enalapril over ISDN/HYD in the overall trial was driven primarily by the treatment difference seen in white patients. This could have occurred
  - if enalapril was particularly *ineffective* in black patients as stated in Section 2.2 (a re-analysis of the SOLVD trial database has supported an attenuated effect of enalapril in black patients), or
  - if the combination of ISDN/HYD was particularly *effective* in black patients (the subgroup analysis of V-HeFT I cited in Section 4.1.7.3.2 would support a particularly pronounced effect of the drug combination in black patients), or
  - if both possibilities were correct.
- Further examination of a retrospective analysis of other subgroup effects in V-HeFT II did not confirm most of the subgroup hypotheses generated by V-HeFT I. Specifically, younger patients, diabetics, and patients with lower systolic blood pressures, responded better than placebo to ISDN/HYD in V-HeFT I, but responded worse to ISDN/HYD than enalapril in V-HeFT II (ISND/HYD : enalapril hazard ratios of 1.36 in younger patients, 1.35 in diabetics and 1.37 in patients with lower systolic blood pressures). Except for race, only one other subgroup effect seen in V-HeFT I was confirmed in V-HeFT II. Specifically, as in V-HeFT I, patients with an ejection fraction < 40% responded better to ISDN/HYD than patients with a higher ejection fraction (hazard ratio of 2.02 in patients with preserved ejection fractions as compared with 1.21 in patients with impaired ejection fractions).

- Time-to-event analyses of hospitalization for heart failure showed that during the first two years of the study, black patients treated with ISDN/HYD had a lower risk of hospitalization for heart failure than black patients treated with enalapril, whereas in white patients, the risk of hospitalization for heart failure was similar in the two treatment groups.
- Both enalapril and the combination of ISDN/HYD were associated with comparable improvements in left ventricular ejection fraction (about 2-3 units). The magnitude of this increase is similar to that which has been historically reported with angiotensin-converting enzyme inhibitors, which increase left ventricular ejection fraction by 2-3 units when compared with placebo. These data are consistent with the finding in V-HeFT I that the combination of ISDN/HYD increases left ventricular ejection fraction in heart failure.
- The combination of ISDN/HYD produced improvements in maximal exercise capacity in V-HeFT II that were generally superior to those produced by enalapril. This finding is noteworthy since several trials have reported that ACE inhibitors improve maximal exercise capacity.
- For all patients changes in quality of life were similar between the ISDN/HYD and the enalapril groups. At twelve months, a treatment difference in favor of ISDN/HYD was primarily seen in black patients with little difference seen in white patients (interaction  $p=0.09$ ). This finding reinforces the impressions gained from V-HeFT I that future trials might appropriately seek to confirm the efficacy of ISDN/HYD, using an endpoint that measured both symptomatic and prognostic effects of drugs.
- Enalapril lowered both systolic and diastolic blood pressure more than the combination of ISDN/HYD. However, the greater hypotensive effects of enalapril were seen primarily in white patients. ISDN/HYD lowered systolic blood pressure more in black patients than white patients.
- The differences observed between ISDN/HYD and enalapril on survival, maximal exercise capacity and left ventricular ejection fraction reinforce the finding of V-HeFT I that the mechanisms by which drugs exert their vasodilator effects are relevant in determining their efficacy in the treatment of heart failure.
- The long-term administration of a combination of ISDN/HYD was associated with headache, dizziness and other vasodilator-type adverse reactions.
- A meaningful proportion of patients failed to attain target doses of ISDN/HYD. Clinical benefits were seen despite the use of lower-than-target doses, suggesting that future trials might appropriately target lower doses of ISDN/HYD.

The findings of V-HeFT II reinforced many of the key findings of and hypotheses derived from V-HeFT I. When taken together, the two trials suggest that the combination of ISDN/HYD may produce symptomatic and prognostic benefits that are particularly apparent in black patients; that such an effect might be most readily detected by an endpoint that simultaneously measures both effects; and that this benefit might be achieved at doses lower than the target doses used in V-HeFT I and V-HeFT II.

## 5.0 TRIALS WITH ISOSORBIDE DINITRATE AND HYDRALAZINE ADMINISTERED AS A COMBINATION PRODUCT

### 5.1 African American Heart Failure Trial (A-Heft)

#### 5.1.1 Study Overview

The African American Heart Failure Trial (A-HeFT) was a multicenter, randomized, double-blind, parallel group, placebo-controlled study conducted at 180 sites in the United States under the sponsorship of NitroMed. A-HeFT can be distinguished from V-HeFT I and V-HeFT II in the following ways:

- A-HeFT enrolled only African American patients.
- A-HeFT enrolled men and women.
- A-HeFT enrolled patients with New York Heart Association (NYHA) class III-IV symptoms.
- A-HeFT enrolled patients with heart failure due to left ventricular systolic dysfunction.
- A-HeFT enrolled patients generally taking ACE inhibitors/ARBs, beta blockers and/or aldosterone antagonists, in addition to diuretics and digitalis glycosides.
- ISDN/HYD were formulated and administered as a fixed-dose combination tablet.
- Target doses in A-HeFT were ISDN 40 mg TID and HYD 75 mg TID.

In contrast, V-HeFT I and V-HeFT II enrolled all races but only men who had class II-VI symptoms, had heart failure associated with both impaired and preserved ejection fraction, were generally taking only digitalis glycosides and diuretics and were titrated to target doses of ISDN 40 mg QID and HYD 75 mg QID; the drugs were administered as individual agents.

Hence, A-HeFT focused on the subgroups that were concordantly identified in both V-HeFT I and V-HeFT II as showing the most favorable survival effects of ISDN/HYD: African Americans and patients with systolic dysfunction.

#### 5.1.2 Study Organization

The Steering Committee provided leadership for the overall trial. Its primary responsibilities were to periodically meet to review study status, make recommendations and approve all protocol amendments, and to oversee the conduct of the study.

The members of the Committee were:

- Anne L. Taylor, M.D., University of Minnesota (chair)
- Kirkwood F. Adams, Jr., M.D., University of North Carolina at Chapel Hill
- Peter Carson, M.D., Veterans Affairs Medical Center
- Jay N. Cohn, M.D., University of Minnesota
- Keith Ferdinand, M.D., Xavier University College of Pharmacy
- Elizabeth Ofili, M.D., Morehouse School of Medicine
- Adeoye Olukotun, M.D., Clinical and Regulatory Strategies
- Malcolm Taylor, M.D., University of Mississippi School of Medicine
- Clyde W. Yancy, Jr., M.D., University of Texas Southwestern Medical Center
- Susan Ziesche, R.N., Minneapolis VA Hospital

The Independent Central Adjudication Committee was responsible for the review of subject information in order to determine if clinical events that occurred during the course of the trial met pre-defined criteria for efficacy endpoints. The Committee adjudicated the following clinical events: deaths, all hospitalizations, unscheduled emergency room visits and unscheduled office/clinic visits for the treatment of HF, and new heart transplant listings. The decisions of the Committee were used for the final efficacy analyses.

The members of the Committee were:

Peter Carson, M.D., Veterans Affairs Medical Center, Washington, DC (chair)  
Inderjit S. Anand, M.D., Veterans Affairs Medical Center, Minneapolis, MN  
Jalal Ghali, M.D., Louisiana State University, Health Sciences Center, Shreveport, LA  
Joann Lindenfeld, M.D., University of Colorado, Health Sciences Center, Denver, CO  
Allan B. Miller, M.D., University of Florida Health Science Center, Jacksonville, FL  
Christopher M. O'Connor, M.D., Duke University Medical Center, Durham, NC  
Felix E. Tristani, M.D., Cold Springs, MN

A Data and Safety Monitoring Board composed of clinicians and a statistician who did not participate in the trial, periodically reviewed study results, evaluated the treatments for excess events, determined whether the basic trial assumptions remained valid, and made recommendations to the A-HeFT Steering Committee and NitroMed. In addition to periodic reviews of the safety data from the trial, the DSMB reviewed the results of two interim analyses for the reassessment of sample size, which were performed to ensure that the assumptions regarding the composite score primary efficacy endpoint remained valid during the study.

The members of the Committee were:

David DeMets, Ph.D., University of Wisconsin (chair)  
Richard Grimm, M.D., Hennepin County Medical Center  
Pamela Ouyang, M.D., Johns Hopkins University  
Jackson Wright, Jr., M.D., Case Western Research University

An independent Statistical Data Analysis Center (Ralph D'Agostino, Jr., Ph.D., Wake Forest University) received interim data from the data management center at Medifacts International (the Contract Research Organization for the trial) and performed the statistical analyses for the DSMB.

### 5.1.3 Study Population

A-HeFT enrolled African American or black patients. A person was defined as "African American" or black if he/she designated himself or herself as such. In addition, patients were required to fulfill all of the following inclusion criteria and none of the following exclusion criteria.

### 5.1.3.1 Inclusion Criteria

- Men or women, at least 18 years old.
- Chronic heart failure of at least 3 months' duration.
- NYHA class III-IV symptoms.
- Receiving appropriate therapy for heart failure, which was expected (but not required) to include a diuretic, an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist and a beta blocker and could have also included digitalis, spironolactone or other medications. Patients receiving beta blockers were to have been taking them for at least three months.
- Symptomatically stable while receiving a stable treatment regimen for heart failure. Stability was defined as no change in signs or symptoms of heart failure, no weight change of > 2.5%, and no permanent changes in heart failure medication in the two weeks prior to randomization.
- Resting left ventricular ejection fraction  $\leq 35\%$ , or a resting left ventricular internal dimension > 2.9 cm/m<sup>2</sup> BSA (or > 6.5 cm) combined with a left ventricular ejection fraction < 45%, within the prior 6 months.
- Outpatient or inpatient (if patient was ready for hospital discharge).
- Ability to comprehend and complete the Minnesota Living with Heart Failure questionnaire.

### 5.1.3.2 Exclusion Criteria

- Female who was pregnant, nursing, or of childbearing potential while not practicing effective contraceptive methods.
- Significant valvular heart disease, obstructive hypertrophic cardiomyopathy, active myocarditis, or uncontrolled hypertension.
- Unstable angina, myocardial infarction or cardiac surgery including percutaneous transluminal coronary angioplasty within three months or likely to require coronary artery bypass grafting or percutaneous transluminal coronary angioplasty during the ensuing year.
- Cardiac arrest or a sustained ventricular tachycardia considered life threatening and requiring intervention within three months, unless treated with an implantable cardiac defibrillator.
- Stroke within three months.
- Parenteral inotropic therapy within one month.
- Rapidly deteriorating or uncompensated heart failure such that cardiac transplantation would be likely over the ensuing one year.
- Symptomatic hypotension.
- Significant hepatic, renal, or other disease that might limit survival over the ensuing one year.
- Any condition which, in the opinion of the investigator or medical monitor, would jeopardize the evaluation of efficacy or safety.
- Any contraindications to the use of isosorbide dinitrate or hydralazine.
- Receipt of another investigational drug or device within 3 months.
- Requirement for hydralazine, long-acting nitrates or phosphodiesterase type 5 inhibitors like sildenafil (Viagra®), vardenafil (Levitra®) or tadalafil (Cialis®) at study entry.

## 5.1.4 Study Plan

Patients fulfilling all inclusion criteria and none of the exclusion criteria were randomized to receive either BiDil® or matching placebo (in a 1:1 ratio) for the remainder of the study. Randomization was stratified according to the use of beta blockers at baseline.

BiDil® was supplied in the form of tablets containing a fixed-dose combination of isosorbide dinitrate 20 mg plus hydralazine 37.5 mg. Patients were initially instructed to take 1 tablet three times daily, which was to be increased to 2 tablets three times daily 3-5 days later if the medication was well tolerated. The goal was to achieve the target dose of 120 mg/day of isosorbide dinitrate and 225 mg/day of hydralazine (2 tablets TID). These doses were approximately 25% lower than the target doses used in V-HeFT I and V-HeFT II. The study medication was added to pre-existing medications used for the treatment of heart failure.

If the medication was not tolerated at the target dose, the patient was prescribed the highest tolerated dose of the study medication and the doses of other medications could be adjusted as clinically indicated. Patients continued to receive the study medication even if they sustained a clinical endpoint unless they experienced intolerable adverse events, life threatening laboratory abnormalities, cardiac transplantation or pregnancy, or whenever the investigator considered it in the patient's best interest. Patients who stopped taking the study medication for adverse events remained in the trial and complied with all scheduled visits and assessments.

Following randomization, each patient was to be seen as an outpatient every three months until either reaching a maximum of 18 months of treatment or until the last patient randomized had completed 6 months. [Because of the early termination of the study, patients recruited in the latter months of the trial were not followed for a minimum of 6 months.] At each visit, patients were assessed for the occurrence of major clinical events and adverse events. Quality of life was assessed by the Minnesota Living with Heart Failure Questionnaire at baseline and every 3 months. In addition, 2-dimensional echocardiograms and measurements of brain natriuretic peptide were performed at baseline and at 6 months.

## 5.1.5 Study Assessments

### 5.1.5.1 Primary Efficacy Endpoint

The primary efficacy parameter was a composite score of clinical outcomes, calculated as the sum of the patient's vital status during the first 18 months of the study; heart failure hospitalization status during the first 18 months; and change in quality of life at 6 months. Specifically,

#### *Vital status during study*

- If patient died, the score for this component would be -3
- If patient was alive at the end of the trial, the score for this component would be 0

*Heart failure hospitalization status during the study*

- If patient was hospitalized for heart failure, the score for this component would be -1
- If patient was never hospitalized for heart failure, the score for this component would be 0

A hospitalization for heart failure was defined as a hospital admission, whose primary reason was worsening symptoms or signs of heart failure, and during which the patient required intravenous medications specifically for the treatment of heart failure, and which lasted more than one calendar day.

*Change in quality of life (Minnesota Living with Heart Failure) at 6 months relative to baseline*

- If quality of life improved  $\geq 10$  units, then the score for this component would be +2
- If quality of life improved  $\geq 5$  and  $< 10$  units, then the score for this component would be +1
- If quality of life changed  $< 5$  units, then the score for this component would be 0
- If quality of life worsened  $\geq 5$  and  $< 10$  units, then the score for this component would be -1
- If quality of life worsened  $\geq 10$  units, then the score for this component would be -2

Each patient's composite score was obtained by summing the three components. As a result, the worst possible score was -6, i.e., the patient showed marked worsening of quality of life (-2) at 6 months, was hospitalized for heart failure (-1), and died (-3). The best possible score was +2, i.e., the patient was alive (0), was never hospitalized for heart failure (0), and showed marked improvement in quality of life at 6 months (+2). By design, each patient had a score of 0 upon entry into the trial, since the composite reflects a change from an individual's baseline status.

The composite score used in A-HeFT was developed specifically for this study and had not been used in other heart failure trials; it was developed in an attempt to incorporate changes in quality of life while also including the occurrence of major clinical events (death or hospitalization for heart failure).

### 5.1.5.2 Secondary Efficacy Variables

- Individual components of the composite score primary endpoint
  - Death
    - Time to death using time-to-event methods
    - Adjudicated causes of death
  - Hospitalizations
    - Time to first hospitalization
    - Total number of hospitalizations for heart failure
    - Total number of hospitalizations for any reason
    - Total days in hospital
    - Number of adjudicated unscheduled emergency room and office/clinic visits

An unscheduled emergency room visit or unscheduled office/clinic visit was classified as due to heart failure, other cardiac causes or non-cardiac causes. Emergency room visits and office/clinic visits were attributed to worsening heart failure if the patient had worsening signs and symptoms of heart failure and received intravenous medication specifically for the treatment of heart failure.

- Quality of life
  - Change in overall score, and physical and emotional component scores relative to baseline during the trial
- Newly recognized need for cardiac transplantation

Listing of a patient for cardiac transplantation following persistent decline in functional capacity, repeated hospitalization for heart failure and need for intravenous treatment with positive inotropic or vasodilator drugs.

- Echocardiographic measures
  - Change from baseline at six months in left ventricular ejection fraction, left ventricular internal diastolic dimension and left ventricular wall thickness
- Serum levels of brain natriuretic peptide

All deaths, hospitalizations, unscheduled emergency room visits and unscheduled office visits were adjudicated by the Independent Central Adjudication Committee.

### 5.1.5.3 Safety Assessments

Safety assessments consisted of monitoring and recording all treatment-emergent adverse events and serious adverse events and the performance of physical examinations (which included the measurement of vital signs at every visit). Given the well-characterized safety profile of the components of BiDil® (ISDN/HYD), there was no routine monitoring of hematology, blood chemistry and urine values.

### 5.1.6 Statistical Plan and Analyses

#### 5.1.6.1 Sample Size Determination and Interim Monitoring Plan

The primary endpoint of the trial was the clinical composite score, which combined information regarding the occurrence of death and hospitalization for heart failure during the treatment period together with change in quality of life at 6 months relative to baseline to generate a single score, whose value could range from +2 to –6. The original sample size for the study was 600 patients, i.e., 300 patients per treatment group, which was expected to provide 80% power to detect a 0.5 unit difference in the primary endpoint ( $\alpha=0.05$ ), assuming that enrollment would be completed in 6 months and the mean duration of treatment would be 8-9 months. These estimates were based on the data collected in V-HeFT II.

Because the primary efficacy variable had not been used previously in a heart failure trial, NitroMed was uncertain about the validity of the study assumptions regarding the magnitude and variability of the treatment effect and wished to utilize interim results to re-estimate the sample size of the study. Normally, increasing sample size based on an interim estimate of a treatment difference would be expected to substantially inflate the probability of a type I error. However, in 1999, statisticians at the FDA had developed a new group sequential test procedure that — by modifying the weights used in the traditional repeated significance two-sample mean test — was able to preserve the probability of a type I error at originally targeted level while providing a substantial gain in power if the sample size were increased<sup>95</sup>.

Working with the FDA and using the method of Cui et al., NitroMed designed A-HeFT as a group sequential design with two interim analyses of the primary endpoint at 25% and 50% information time followed by a final analysis at the end of the study (total of 3 planned looks). For each of the two planned interim analyses, a statistician (independent of both NitroMed and the Data and Safety Monitoring Board) would provide a sample size estimate to the Data and Safety Monitoring Board. However, only the results of the second interim analysis would be communicated to NitroMed and used to modify the sample size if necessary. This second interim analysis was planned to occur at 50% information time — when approximately 300 patients had completed six months in the study. O'Brien-Fleming type boundaries were used; the two-sided p-values required for statistical significance were 0.00001 at the first interim look, 0.0052 for the second interim look and 0.0480 at the final look, reflecting a penalty of 0.002 as a result of the group sequential procedure.

In addition to these considerations, NitroMed and the FDA agreed — before the start of the study — to increase the sample size based on the data available at the interim analysis to theoretically attain  $\alpha=0.02$ , in order to increase the strength of evidence provided by the study. To implement this agreement, NitroMed agreed to utilize a target  $\alpha=0.02$  (rather than 0.05) in the sample size calculations when the trial was resized at the time of the second interim analysis. As a result, based on the treatment difference observed during the second interim analysis, the sample size for the study was increased from 600 to 1100. Note however that the p-value considered to demonstrate statistical significance remained at  $p = 0.048$ .

No plan for early termination of the trial for a mortality benefit was devised.

#### 5.1.6.2 Actions of the Data and Safety Monitoring Board

The Data and Safety Monitoring Board carried out the interim monitoring plan as follows:

##### March 19, 2002

The Data and Safety Monitoring Board met for the first time to reach agreement on the operations of the Board. There was no review of blinded or unblinded data. At the time of the meeting, 221 patients had been randomized, and 3 patients had died. The Board adopted procedures to evaluate data and for the re-estimation of sample size.

##### August 23, 2002

The Data and Safety Monitoring Board carried out its first interim analysis to look at data after approximately 150 patients had completed the 6-month visit. [Specifically, 137 patients had completed the 6-month visit.] At the time of the meeting, 310 patients had

been randomized, and 8 had died. Data were presented to the Board as Group A and Group B. Treatment differences were observed (favoring Group B in all parameters) for deaths (3 vs 5), hospitalizations (7 vs 17) and quality of life (-8.6 vs -2.5). NitroMed was informed that data variability for the primary endpoint was similar to that anticipated by protocol; no recommendation for protocol modification was made at this time.

#### March 3, 2003

The Data and Safety Monitoring Board carried out its second interim analysis to look at the data after approximately 300 patients had completed the 6-month visit. [Specifically, 313 patients had completed the 6-month visit.] At the time of the meeting, 528 patients had been randomized, and 23 had died. Data were presented to the Board as Group A and Group B. Treatment differences were observed (favoring Group A) for deaths (10 vs 13) and favoring Group B for quality of life (-7.4 vs -1.1). The composite score also favored Group B (-0.38 on control and 0.01 on treatment). Although the magnitude of the difference in the composite score was somewhat less than that specified in the protocol, the variability was similar. The DSMB provided several sample size options to NitroMed which selected an increase in sample size to 1100 (based on the FDA recommendation to size the study so that an  $\alpha$  of 0.02 could theoretically be attained) and agreed to meet again one year later.

#### March 13, 2004

The Data and Safety Monitoring Board carried out its third data review one year after the second interim analysis. At the time of the meeting, 798 patients had been randomized and 59 had died. Data were presented initially to the Board as Group A and Group B. Treatment differences were observed (favoring Group B) for deaths (21 vs 38). The difference in deaths was associated with a log-rank Z value of 2.37 ( $p=0.018$ ). The DSMB decided to unblind itself and Group B was identified as the group receiving BiDil®. Recognizing that no boundaries to terminate the trial for mortality had been formulated at the start of the study, the DSMB established an O'Brien-Fleming type group sequential alpha spending function as described by Lan and DeMets to guide further decision making. Of note, the treatment difference in mortality seen at this meeting fell just below the boundary value specified by the newly formulated boundaries. The DSMB recommended one additional safety review to take place in approximately 3-5 months.

#### July 7, 2004

The Data and Safety Monitoring Board carried out its final data review. At the time of the meeting, 1014 patients had been enrolled in the trial, and 75 had died. Data were presented as BiDil® and placebo. Treatment differences were observed for deaths (27 vs 48); this difference was associated with long rank  $Z=2.47$  with a  $p=0.0132$ . [The nominal p-value for the monitoring boundary at this time was 0.031.] The DSMB adjourned so that additional analyses could be carried out. On July 9<sup>th</sup> these analyses were discussed by the DSMB and showed treatment differences (BiDil® vs placebo) for deaths (27 vs 48,  $p=0.012$ ), first hospitalizations for heart failure (64 vs 103,  $p=0.001$ ), quality of life (-7.5 vs -2.5,  $p=0.002$ ), worsening heart failure as an adverse event (66 vs 94,  $p=0.023$ ) and the composite score primary endpoint (+0.13 vs -0.39,  $p=0.0001$ ). In view of crossing of the monitoring boundary for the mortality difference and considering the consistency of the treatment benefit across all major endpoints, the Data and Safety

Monitoring Board unanimously agreed to recommend early termination of the trial and to notify the Steering Committee and NitroMed of their recommendation.

Following consultation with the FDA, NitroMed stopped A-HeFT on July 19, 2004. At this point, 1050 patients had been enrolled in A-HeFT, and of these, 951 patients had reached a minimum of 3 months on study and thus, would have had the opportunity to participate in the first scheduled post-baseline quality of life measurement.

### 5.1.6.3 Statistical Analyses

#### 5.1.6.3.1 Primary Endpoint

The primary endpoint of the trial was the clinical composite score, which combined information regarding the occurrence of death and first hospitalization for heart failure during the entire treatment period together with changes in quality of life at 6 months relative to baseline into a single score, whose values could range from +2 to -6. Differences between the two treatment groups were tested for significance by the two-sample t-test, as modified based on the method of Cui et al<sup>95</sup>. The primary analysis specified no adjustment for covariates. The primary analysis population was based on the intention-to-treat principle and consisted of all randomized patients, whether or not they received at least one dose of study medication. This was the primary efficacy population for the primary endpoint and for all-cause mortality.

It was anticipated that various components of the composite score primary endpoint would be missing at the end of the trial. To accommodate this possibility, the protocol specified that the worst possible score would be assigned to each component with missing data (-3 for patients without data on vital status; -1 for patients with missing heart failure hospitalization data; and -2 for patients without quality of life data). Given the early termination of the trial, a large number of patients recruited during the 6 months before study termination could not undergo a 6-month quality of life assessment. As a result, if a 6-month quality of life assessment was not available as defined by the protocol, the last available on-study assessment before 6 months was used. Even so, 99 patients had been recruited so close to the early termination date of the study that some did not have the opportunity to undergo even a 3-month quality-of-life assessment. Some returned for a final study close out visit, but most did not. Therefore, if a post-baseline quality of life assessment was not available, the patient was assigned a worst score of -2.

Of note, at the conclusion of the trial, no patients were lost to follow-up for the assessment of vital status; 24 patients (2.3%) were lost to follow-up for the assessment of heart failure hospitalization and were assigned the worst score for this component (-1); and 81 patients (7.7%) had no quality of life measurement performed after starting study medication and were assigned the worst score (-2) for this component.

The following subgroups were analyzed for the composite score primary endpoint and for mortality: age (less than 65 years or at least 65 years); gender (male or female); etiology of heart failure (ischemic or non-ischemic); baseline systolic blood pressure (more or less than 125 mm Hg); patients with or without history of hypertension, diabetes mellitus or chronic renal insufficiency at baseline; and patients taking or not taking the following medications at baseline:

angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, aldosterone antagonists, non-aldosterone antagonist diuretics, and digoxin.

#### 5.1.6.3.2 Secondary Endpoints

Kaplan-Meier survival curves were used to display time-to-event analyses for death; for first hospitalization for heart failure; and for death or first hospitalization for heart failure. Patients who had cardiac transplantation were censored at the time of transplantation. Survival curves were compared using the log-rank test. Hazard ratios and 95% confidence intervals were generated using the Cox proportional hazards model.

For all variables other than the primary efficacy variable (the composite score) and the time-to-event survival analyses, comparisons were carried out on patients with paired data, with no imputation for patients with missing data. The change from baseline in Minnesota Living with Heart Failure quality of life overall score and its physical and emotional components was analyzed by two-sample t-tests. The number of hospitalizations for heart failure and for any cause and the total number of days in the hospital for heart failure and for any reason were analyzed by the Wilcoxon rank sum test.

The safety population consisted of all patients who were randomized, received at least one dose of study medication, and had at least one post-baseline measurement of safety.

### 5.1.7 Results

#### 5.1.7.1 Baseline Characteristics

A total of 1050 patients were randomized into A-HeFT, 532 to placebo and 518 to BiDil®.

The patients enrolled in A-HeFT were middle-aged men and women (Table 14). The most common cause of heart failure was hypertensive heart disease; less than one-fourth of the patients had heart failure due to ischemic heart disease. More than 90% of the patients had NYHA class III symptoms. In general, the two treatment groups were well-matched for baseline characteristics; more men were randomized to the placebo group ( $p=0.01$ ) and baseline diastolic blood pressure was higher in the BiDil® group ( $p=0.002$ ).

Table 14. Baseline Demographic and Clinical Characteristics; A-HeFT

	<b>BiDil® (N = 518)</b>	<b>Placebo (N = 532)</b>
<b>Age (years)</b>	56.8 (12.7)	56.9 (13.3)
<b>Sex, men/women (n)</b>	290/228†	340/192
<b>Etiology of heart failure, n (%)</b>		
Ischemic	121 (23.4)	121 (22.7)
Idiopathic	127 (24.5)	147 (27.6)
Hypertensive	207 (40.0)	199 (37.4)
Valvular	13 (2.5)	17 (3.2)
Other	50 (9.7)	48 (9.0)
<b>Ejection fraction, %, mean (SD)</b>	23.9 (7.3) n = 517	24.2 (7.5) n = 532
<b>Left ventricular internal diastolic dimension (cm), Mean SD</b>	6.5 (0.9) n = 330	6.5 (1.0) n = 332
<b>Baseline NYHA class, n (%)</b>		
I	1 (0.2)	1 (0.2)
II	9 (1.7)	2 (0.4)
III	493 (95.2)	503 (94.7)
IV	15 (2.9)	25 (4.7)
Missing	0 (0.0)	1 (0.2)
<b>Systolic blood pressure, mm Hg mean (SD)</b>	127.2 (17.5)	125.3 (18.1)
<b>Diastolic blood pressure, mm Hg mean (SD)</b>	77.6 (10.3)†	75.6 (10.6)
<b>Heart rate, beats/min Mean (SD)</b>	74.2 (12.3)	73.1 (11.0)

† p &lt; 0.05 relative to placebo

Approximately 90% of the patients enrolled in A-HeFT had a history of hypertension, 53% had hyperlipidemia, and 41% had diabetes mellitus (Table 15). With respect to cardiovascular history, the groups were well-matched except for hyperlipidemia and diabetes mellitus, which were more frequent in BiDil®-treated patients (p = 0.04 and 0.012, respectively).

The majority of the patients in A-HeFT were taking diuretics (92%), beta blockers (83%), angiotensin-converting enzyme inhibitors (75%), anti-thrombotic agents (72%) and digitalis glycosides (60%). The two groups were similar with respect to baseline medications, except for the more frequent use of anti-diabetic medications in the BiDil® group.

Table 15. Baseline Cardiovascular History and Treatment; A-HeFT

	<b>BiDil® (N = 518)</b>	<b>Placebo (N = 532)</b>
<b>Cardiovascular history (n, %)</b>		
History of hypertension	472 (91.1)	468 (88.0)
Arrhythmias	169 (32.6)	184 (34.6)
Diabetes mellitus	232 (44.8)	197 (37.0)
Hyperlipidemia	289 (55.8)	263 (49.4)
Cerebrovascular disease	79 (15.3)	74 (13.9)
Peripheral vascular disease	58 (11.2)	71 (13.3)
Chronic obstructive lung disease	91 (17.6)	110 (20.7)
Chronic renal insufficiency	84 (16.2)	97 (18.2)
Valvular disease	186 (35.9)	194 (36.5)
Previous revascularization	111 (21.4)	96 (18.0)
Pacemaker or implantable defibrillator	86 (16.6)	92 (17.3)
Previous myocardial infarction	152 (29.3)	152 (28.6)
Current angina	75 (14.5)	78 (14.7)
Current smoking	143 (27.6)	140 (26.3)
Previous smoking	306 (59.1)	336 (63.2)
<b>Background medications (n, %)</b>		
Diuretics	473 (91.3)	494 (92.9)
Angiotensin-converting enzyme inhibitors	386 (74.5)	400 (75.2)
Angiotensin receptor blockers	124 (23.9)	112 (21.1)
Beta blockers	434 (83.8)	437 (82.1)
Calcium channel blockers	109 (21.0)	104 (19.5)
Digitalis glycosides	304 (58.7)	324 (60.9)
Aldosterone antagonists	208 (40.2)	201 (37.8)
Anti-arrhythmics class I and III	52 (10.0)	62 (11.7)
Anti-thrombotic agents	380 (73.4)	381 (71.6)
Lipid lowering agents	219 (42.3)	206 (38.7)
Insulin	97 (18.7)	67 (12.6)
Oral hypoglycemic drugs	156 (30.1)	119 (22.4)
Potassium supplement	256 (49.4)	271 (50.9)

### 5.1.7.2 Patient Disposition and Exposure to Study Medication

The duration of a patient's participation in the trial was longer for those treated with BiDil® (379 days) than for those treated with placebo (355 days),  $p=0.04$ . This difference was due to the higher withdrawal rate from the study for placebo patients than for BiDil® patients (14.1% vs 9.5%), largely due to a higher withdrawal rate for death in placebo patients (10.2% vs 6.2%).

In contrast, the duration of exposure to the study drug was shorter in BiDil®-treated patients than in placebo-treated patients (298 days vs 314 days). This difference was related to the higher frequency of withdrawals for adverse events in BiDil®-treated patients than placebo-treated patients (21.1% vs 12.0%).

As shown in Table 16, patients were more likely to remain on treatment with placebo than on treatment with BiDil® at each time point in the trial.

Table 16. Patients on Study Drug at Various Time Points [n (%)]; A-HeFT

Time on Study	BiDil® (n = 517)	Placebo (n = 527)
3 months	368 (71.2)	417 (79.1)
6 months	317 (61.3)	333 (63.2)
9 months	260 (50.3)	269 (51.0)
12 months	220 (42.6)	228 (43.3)
15 months	169 (32.7)	186 (35.3)
18 months	139 (26.9)	146 (27.7)

The target dose of BiDil® in A-HeFT was 6 tablets daily (2 tablets TID; 120 mg daily of ISDN and 225 mg daily of HYD). This target dose was achieved at least once in 473 (89.8%) of placebo-treated patients, but in only 352 (68.1%) of BiDil®-treated patients. BiDil®-treated patients were less likely to be titrated to target doses due to the greater frequency of adverse events in this group relative to placebo. The mean number of tablets prescribed per day was consistently less in BiDil®-treated patients than in placebo-treated patients over the course of the trial, Table 17. For example, at 6 months, on average patients in the BiDil® group were prescribed 29.3 mg TID of ISDN and 56.3 mg TID of HYD whereas patients in the placebo group were prescribed 34 mg TID of ISDN (placebo equivalent) and 63.8 mg TID of HYD (placebo equivalent).

Table 17. Mean Number of Study Drug Tablets Prescribed Per Day at Various Times

Time on Study	Mean (SD) # of Tablets Prescribed Per Day	
	BiDil® (N = 517)	Placebo (N = 527)
3 months	4.4 (2.1) (n=368)	5.0 (1.9) (n=417)
6 months	4.5 (2.0) (n=317)	5.1 (1.8) (n=333)
9 months	4.8 (1.9) (n=260)	5.2 (1.7) (n=269)
12 months	4.8 (1.9) (n=220)	5.3 (1.6) (n=228)
15 months	4.9 (1.7) (n=169)	5.3 (1.7) (n=186)

During the course of the study, 78 (14.8%) of placebo patients and 65 (12.6%) of BiDil® patients received open-label treatment with long-acting nitrates, and 15 (2.8%) of placebo patients and 14 (2.7%) of BiDil® patients received open-label hydralazine.

### 5.1.7.3 Efficacy Results

#### 5.1.7.3.1 Primary Efficacy Analysis

By intention-to-treat, patients in the BiDil® group had a significantly better clinical composite score during the course of the trial than patients in the placebo group (-0.16 vs -0.47,  $p = 0.016$  by 2-sample t-test<sup>95</sup>, Table 18).

Table 18. Primary Efficacy Endpoint; A-HeFT

Composite score	BiDil® (N = 518)	Placebo (N = 532)	p-value
Mean (SD)	-0.16 (1.93)	-0.47 (2.04)	0.016

Detailed analysis showed that each component of the composite endpoint contributed to the observed treatment difference (Table 19).

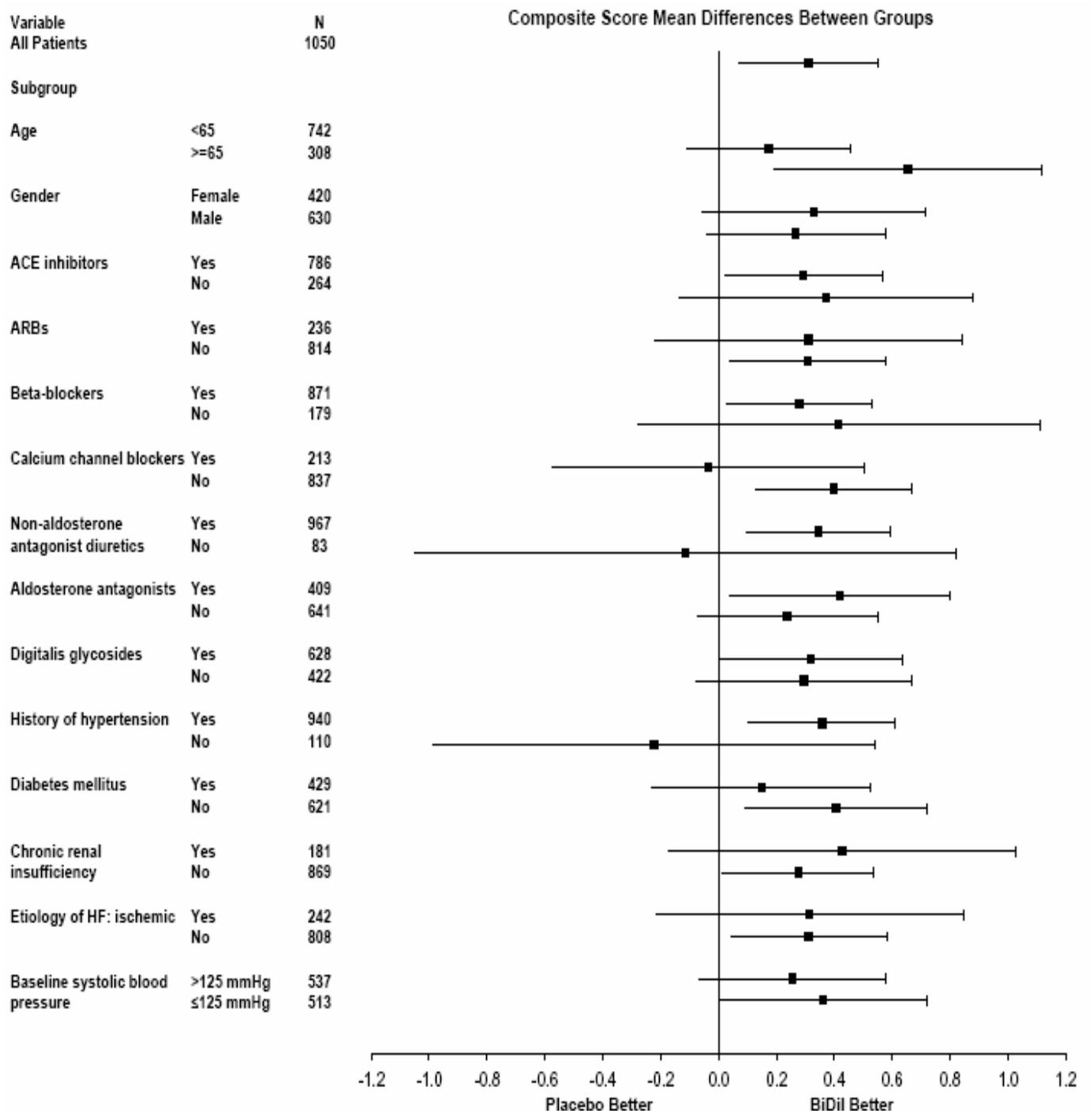
Table 19. Component Scores for Primary Efficacy Endpoint; A-HeFT

Component	Score	BiDil® (N = 518) n (%)	Placebo (N = 532) n (%)
<b>Death</b>			
Yes	-3	32 (6.2)	54 (10.2)
No	0	486 (93.8)	478 (89.8)
Missing	-3	0 (0.0)	0 (0.0)
<b>First hospitalization for heart failure</b>			
Yes	-1	85 (16.4)	130 (24.4)
No	0	420 (81.1)	391 (73.5)
Missing	-1	13 (2.5)	11 (2.1)
<b>Change in quality of life score at 6 months (or earlier) relative to baseline</b>			
Improvement $\geq 10$ units	2	180 (38.1)	166 (33.4)
Improvement $\geq 5$ and $< 10$ units	1	49 (10.4)	56 (11.3)
Change $< 5$ units	0	117 (22.6)	126 (23.7)
Worsening $\geq 5$ and $< 10$ units	-1	46 (8.9)	32 (6.4)
Worsening $\geq 10$ units	-2	80 (16.9)	117 (23.5)
Missing	-2	46 (8.9)	35 (6.6)

Contributing to the treatment difference on the composite score was the finding that the BiDil®-treated group had fewer deaths (32 vs 54 for the placebo group), fewer patients with a first hospitalization for heart failure (85 vs 130), more patients with marked ( $\geq 10$  unit) improvement in quality of life (180 vs 166) and fewer patients with marked ( $\geq 10$  unit) worsening in quality of life (80 vs 117).

The treatment difference on the clinical composite score was seen consistently across nearly all of the subgroups examined (Figure 15). The subgroups in whom the treatment estimate did not favor BiDil® were generally those with the fewest patients.

Figure 15. Effect of BiDil® on Composite Score in Subgroups (Mean ± 95%CI)



### 5.1.7.3.2 Secondary Endpoints – Components of Composite Score

BiDil® not only exerted a favorable effect on the clinical composite, but also exerted a favorable effect on each of its individual components, when considered individually.

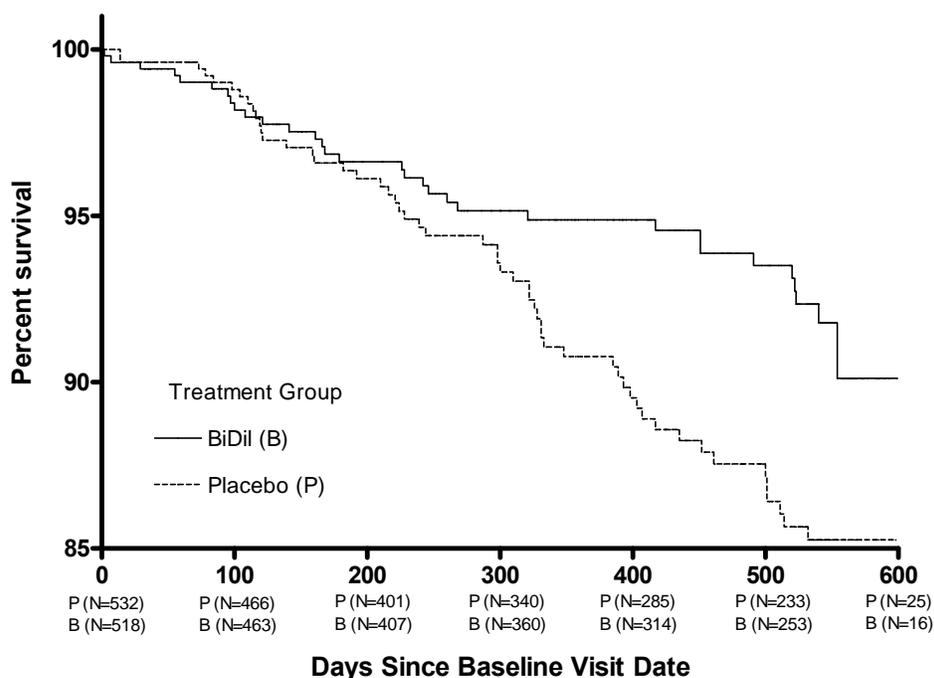
### 5.1.7.3.3 Mortality

By intention to treat, 54 patients (10.2%) in the placebo group, but only 32 patients (6.2%) of the BiDil® group died during the study. This difference reflected a 43% reduction in relative risk (p=0.012; Table 20 and Figure 16).

Table 20. Effect of BiDil® on All-Cause Mortality; A-HeFT

n (%)	BiDil® (n = 518)	Placebo (n = 532)	Hazard ratio (95% CI)	Log-rank p-value
All-cause mortality	32 (6.2%)	54 (10.2%)	0.57 (0.37, 0.89)	0.012

Figure 16. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality; A-HeFT



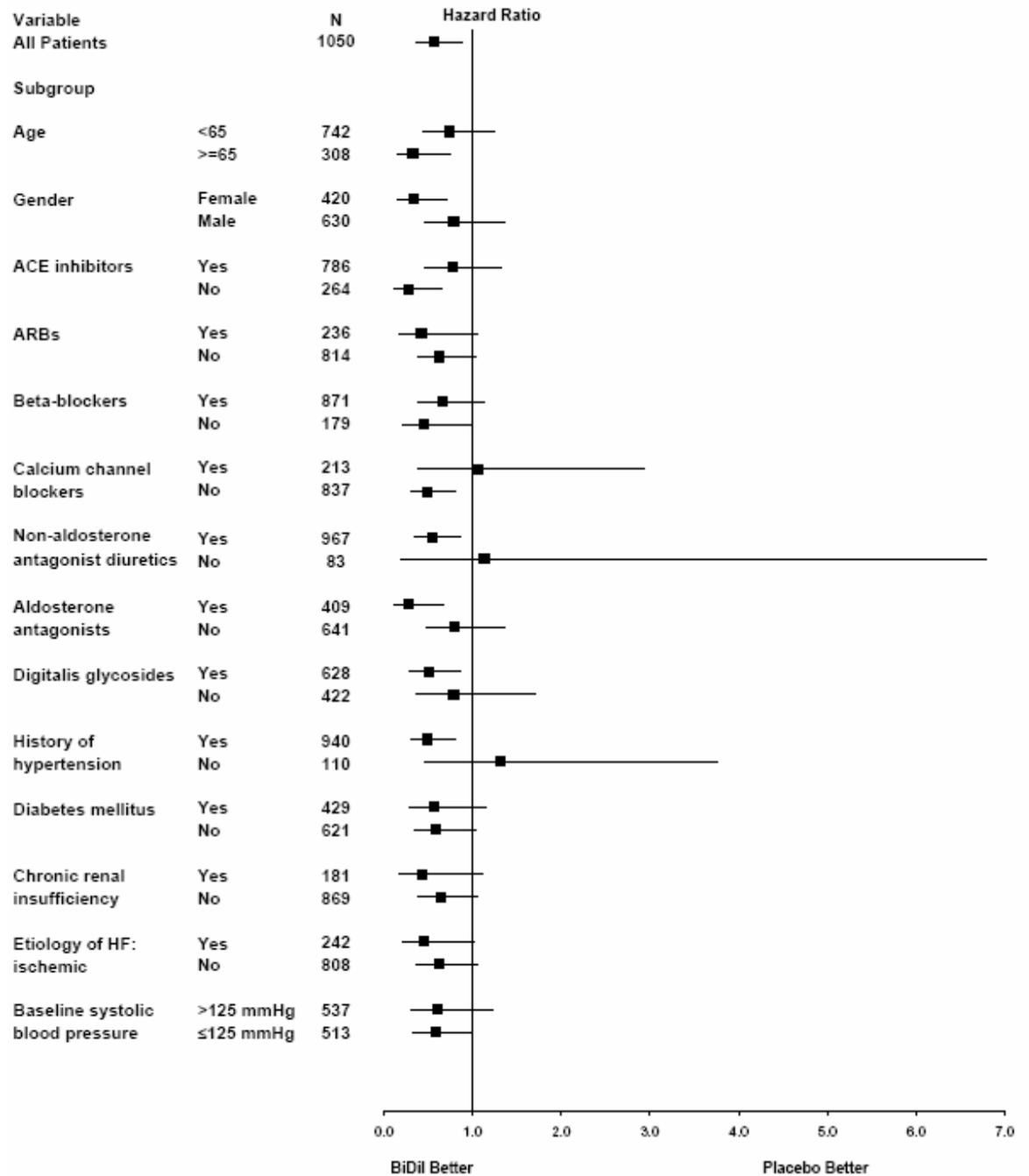
The reduction in the overall risk of death seen in BiDil®-treated patients was related to a reduction in heart failure deaths (i.e., sudden cardiac deaths and pump failure deaths). Other modes of death were distributed similarly across the two treatment groups (Table 21).

Table 21. Mode of Death; A-HeFT

<b>Category of Death (n %)</b>	<b>BiDil® (N = 518)</b>	<b>Placebo (N = 532)</b>
Total number of deaths	32 (6.2)	54 (10.2)
Heart failure deaths	21 (4.1)	42 (7.9)
Sudden cardiac death	17 (3.3)	24 (4.5)
Pump failure death	4 (0.8)	16 (3.0)
Death due to myocardial infarction	0 (0.0)	2 (0.4)
Non-heart failure cardiovascular death	5 (1.0)	3 (0.6)
Death due to cerebrovascular accident	4 (0.8)	3 (0.6)
Death due to other vascular event	1 (0.2)	0 (0.0)
Non-cardiovascular death	6 (1.2)	9 (1.7)

A reduction in the risk of death was seen consistently across nearly all of the subgroups examined (Figure 17). As in the case of the primary endpoint, the subgroups in which the treatment estimate did not favor BiDil® were generally those with the fewest patients (representing 20% or less of the patients).

Figure 17. Hazard Ratios and 95% Confidence Intervals for Effect of BiDil® on All-Cause Mortality in Subgroups; A-HeFT



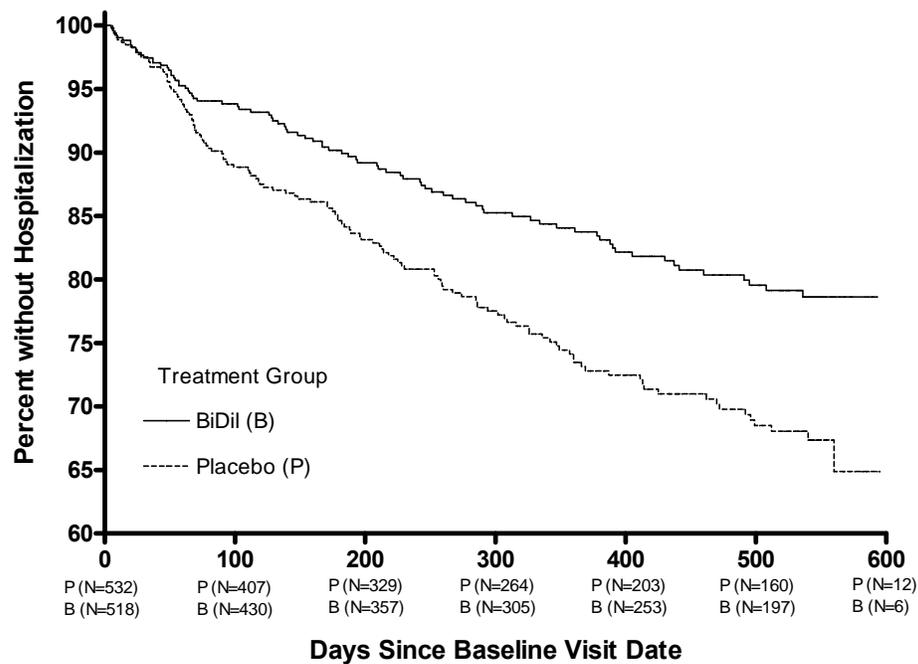
### 5.1.7.3.4 Hospitalizations for Heart Failure

By intention to treat, 130 patients (24.4%) in the placebo group, but only 85 patients (16.4%) of the BiDil® group were hospitalized at least once for worsening heart failure during the study. This difference reflected a 39% reduction in relative risk ( $p < 0.001$ ; Table 22 and Figure 18).

Table 22. Effect of BiDil® on Risk of Hospitalization for Heart Failure; A-HeFT

	<b>BiDil® (n = 518)</b>	<b>Placebo (n = 532)</b>	<b>Hazard ratio (95% CI)</b>	<b>Log- rank p- value</b>
Hospitalization for heart failure	85 (16.4%)	130 (24.4%)	0.61 (0.46, 0.80)	< 0.001

Figure 18. Kaplan-Meier Time-to-Event Curves for Heart Failure Hospitalization; A-HeFT

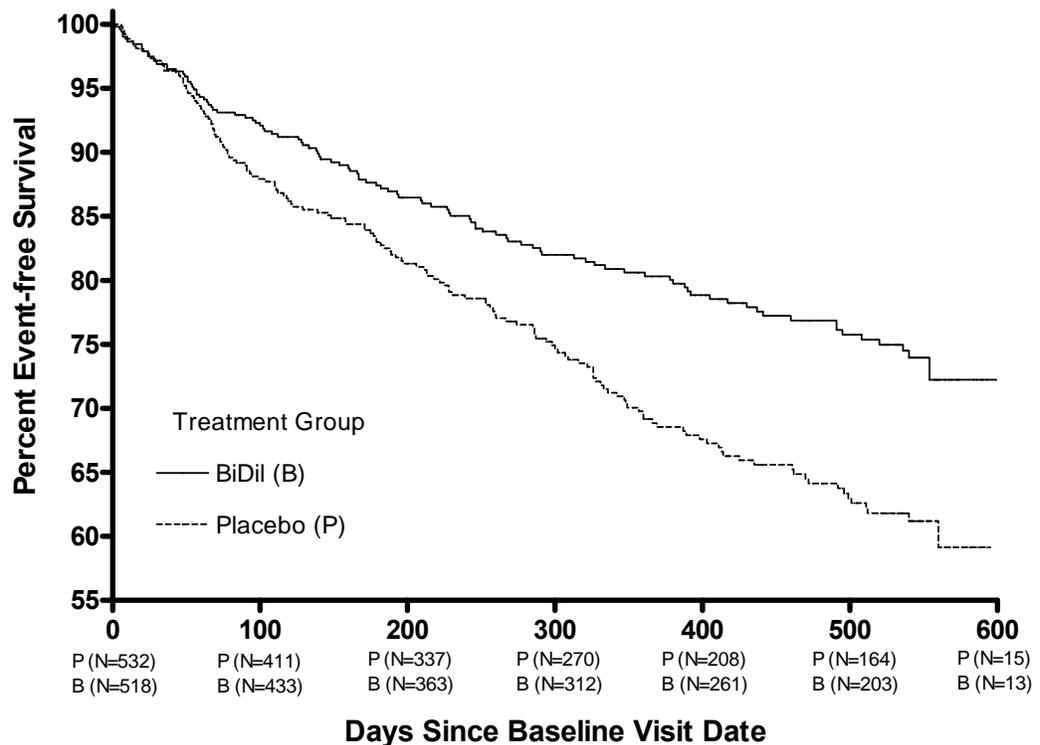


Because death and hospitalization represent competing risks, the effect of BiDil® on the combined risk of all-cause mortality or hospitalization for heart failure was assessed even though this was not a prespecified analysis. By intention to treat, 158 patients (29.7%) in the placebo group, but only 108 patients (20.8%) in the BiDil® group died or were hospitalized for worsening heart failure during the study. This difference reflected a 37% reduction in risk ( $p < 0.001$ ; Table 23 and Figure 19).

Table 23. All-Cause Mortality or Hospitalization for Heart Failure; A-HeFT

	<b>BiDil® (n = 518)</b>	<b>Placebo (n = 532)</b>	<b>Hazard ratio (95% CI)</b>	<b>Log-rank p-value</b>
All-cause mortality or hospitalization for heart failure	108 (20.8%)	158 (29.7%)	0.63 (0.49, 0.81)	<0.001

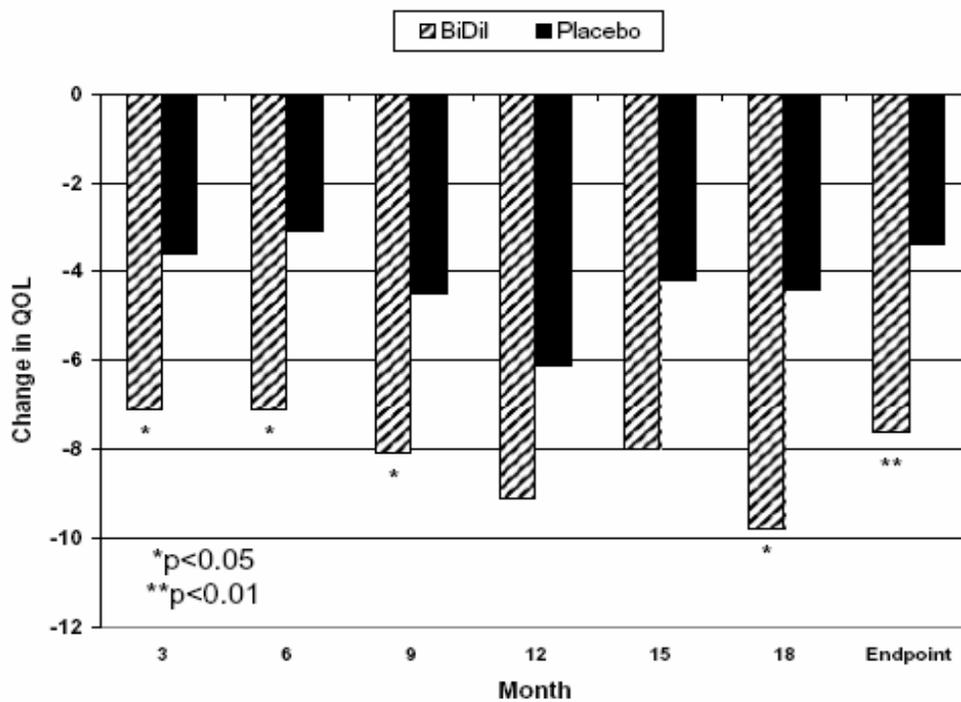
Figure 19. Kaplan-Meier Time-to-First Event Analysis of All-Cause Mortality or Hospitalization for Heart Failure; A-HeFT



### 5.1.7.3.5 Quality of Life

When compared with placebo, BiDil®-treated patients experienced greater improvements in quality of life, as assessed by the Minnesota Living with Heart Failure questionnaire, at most visits during the course of the study relative to baseline (Figure 20, Tables 24, 25). [A decrease in score denotes improvement in quality of life; endpoint refers to last available measurement.] The improvement was seen primarily in the physical domain of the questionnaire.

Figure 20. Mean Change in Minnesota Living with Heart Failure Questionnaire Overall Score at Each Visit and at Endpoint; A-HeFT



N	BiDil	423	369	307	269	226	198	512
	Placebo	441	371	305	250	218	184	528

Table 24. Change in Overall, Emotional, and Physical Scores in Minnesota Living with Heart Failure Questionnaire at Six Months; A-HeFT

	<b>BiDil® (N = 518)</b>	<b>Placebo (N = 532)</b>	<b>p-value</b>
<b>Overall score</b>			
n	369	371	
Baseline Mean (SD)	52.5 (24.5)	51.1 (26.0)	
Difference Mean (SD)	-7.1 (20.6)	-3.1 (21.3)	0.011
<b>Physical score</b>			
n	369	371	
Baseline Mean (SD)	22.7 (10.9)	21.9 (11.3)	
Difference Mean (SD)	-3.0 (9.7)	-1.3 (9.7)	0.017
<b>Emotional score</b>			
n	369	370	
Baseline Mean (SD)	10.8 (7.7)	10.5 (7.9)	
Difference Mean (SD)	-1.5 (6.2)	-0.5 (6.4)	0.036

Table 25. Change in Overall, Emotional and Physical Scores in Minnesota Living with Heart Failure Questionnaire at Endpoint\*; A-HeFT

	<b>BiDil® (N = 518)</b>	<b>Placebo (N = 532)</b>	<b>p-value</b>
<b>Overall score</b>			
n	512	528	
Baseline Mean (SD)	50.9 (24.9)	50.8 (25.5)	
Difference Mean (SD)	-7.6 (22.6)	-3.4 (22.7)	0.003
<b>Physical score</b>			
n	512	528	
Baseline Mean (SD)	22.1 (11.0)	22.0 (11.2)	
Difference Mean (SD)	-3.5 (10.5)	-1.4 (10.6)	0.002
<b>Emotional score</b>			
n	512	528	
Baseline Mean (SD)	10.4 (7.8)	10.4 (7.8)	
Difference Mean (SD)	-1.3 (6.8)	-0.7 (6.5)	0.129

\* Endpoint defined as last measurement on study.

### 5.1.7.3.6 Other Secondary Endpoints

#### 5.1.7.3.6.1 Total Number of Hospitalizations and Hospital Days

When compared with placebo, patients in the BiDil® group had fewer hospitalizations for heart failure and spent fewer days in the hospital for heart failure,  $p < 0.01$  (Tables 26, 27). Patients in the BiDil® group also had fewer hospitalizations and spent fewer days in the hospital for any reason, but the differences were not significant. Hospitalizations in the BiDil® group were shorter than in the placebo group, whether they were for heart failure or for any reason.

Table 26. Hospitalizations for Heart Failure; A-HeFT

	<b>BiDil® N=518</b>	<b>Placebo N=532</b>	<b>p-value</b>
Total number of hospitalizations for heart failure	173	251	
Mean number of hospitalizations for heart failure per patient	0.3	0.5	0.002
Hospitalizations by frequency			0.008
0	433	402	
1	44	69	
2	20	38	
3	10	7	
≥ 4	11	16	
Total number of hospital days for heart failure	1167	1995	
Mean number of days in the hospital for heart failure per patient	2.3	3.8	0.001
Mean number of days per hospitalization for heart failure	6.7	7.9	

Table 27. Hospitalizations for Any Reason; A-HeFT

	<b>BiDil® N=518</b>	<b>Placebo N=532</b>	<b>p-value</b>
Total number of hospitalizations for any reason	435	559	
Mean number of hospitalizations for any reason per patient	0.8	1.1	0.14
Hospitalizations by frequency			0.17
0	316	311	
1	99	85	
2	50	59	
3	24	30	
≥ 4	29	47	
Total number of hospital days for any reason	2626	3902	
Mean number of days in the hospital for any reason per patient	5.1	7.3	0.11
Mean number of days per hospitalization for any reason	6.0	7.0	

#### 5.1.7.3.6.2 Newly Recognized Need for Cardiac Transplantation

The number of patients with an adjudicated need for heart transplantation was similar in the two treatment groups (3 in the BiDil® group and 5 in the placebo group), p=0.726.

#### 5.1.7.3.6.3 Total Number of Emergency Room and Office Visits

There was no difference between placebo and BiDil® in the number of emergency room visits or unscheduled office/clinic visits for heart failure.

#### 5.1.7.3.6.4 Echocardiographic Evaluation of Left Ventricular Function

Analysis of changes from baseline in the echocardiographic measurements of left ventricular ejection fraction, left ventricular internal dimension and left ventricular wall thickness has not yet been completed or submitted to the FDA.

#### 5.1.7.3.6.5 Brain Natriuretic Peptide

Analysis of changes from baseline in serum levels of brain natriuretic peptide has not yet been completed or submitted to the FDA.

### 5.1.7.4 Safety Results

Table 28 displays the proportion of patients with at least one adverse event, the number with at least one serious adverse event (other than an endpoint event) and the number who permanently discontinued treatment with the study drug due to an adverse event.

Table 28. Overview of Patients with Adverse Events; A-HeFT

<b>Adverse Event Category (#, %)</b>	<b>BiDil® n = 517</b>	<b>Placebo n = 527</b>
Patients with at least one adverse event	475 (91.9%)	432 (82.0%)
Patients with at least one serious adverse event (excluding endpoint events)	181 (35.0%)	183 (34.7%)
Patients who permanently discontinued study drug due to adverse events	109 (21.1%)	63 (12.0%)

#### 5.1.7.4.1 Adverse events regardless of relationship to study drug

Table 29 lists the number of patients with an adverse event that occurred in at least 2% of patients in either treatment group, whether or not patients were taking the study medication. In general, adverse events related to systemic vasodilation (headache, dizziness, hypotension, tachycardia and sinusitis [sinus congestion]), or reflecting gastrointestinal distress (nausea and vomiting) were more frequent in BiDil®-treated than placebo-treated patients. In contrast, adverse events related to worsening heart failure (heart failure, dyspnea, increased cough and peripheral edema) were more common in placebo-treated patients than in BiDil®-treated patients.

Four events (nausea, heart failure, hypotension and sinusitis) were significant at the 0.05 level; headache and dizziness were significant at the 0.0001 level.

Table 29. Adverse Events Occurring in  $\geq 2\%$  of Patients in Either Group; A-HeFT

<b>Adverse Event*</b>	<b>BiDil® (n = 517) n (%)</b>	<b>Placebo (n = 527) n (%)</b>
Headache	256 (49.5)	111 (21.1)
Dizziness	165 (31.9)	72 (13.7)
Pain	84 (16.2)	85 (16.1)
Chest pain	81 (15.7)	80 (15.2)
Infection	70 (13.5)	67 (12.7)
Asthenia	70 (13.5)	59 (11.2)
Dyspnea	65 (12.6)	92 (17.5)
Nausea	50 (9.7)	32 (6.1)
Heart failure	49 (9.5)	80 (15.2)
Bronchitis	43 (8.3)	34 (6.5)
Hypotension	41 (7.9)	23 (4.4)
Hypertension	33 (6.4)	33 (6.3)
Accidental injury	29 (5.6)	36 (6.8)
Increased cough	27 (5.2)	41 (7.8)
Gout	27 (5.2)	32 (6.1)
Diarrhea	27 (5.2)	30 (5.7)
Peripheral edema	25 (4.8)	37 (7.0)
Abdominal pain	25 (4.8)	35 (6.6)
Back pain	24 (4.6)	28 (5.3)
Insomnia	23 (4.4)	24 (4.6)
Syncope	23 (4.4)	20 (3.8)
Sinusitis	22 (4.3)	9 (1.7)
Anemia	21 (4.1)	26 (4.9)
Ventricular tachycardia	21 (4.1)	14 (2.7)
Hyperglycemia	20 (3.9)	18 (3.4)
Palpitations	20 (3.9)	14 (2.7)
GI disorder	20 (3.9)	14 (2.7)
Urinary tract infection	19 (3.7)	26 (4.9)
Pneumonia	19 (3.7)	21 (4.0)
Rhinitis	19 (3.7)	14 (2.7)
Constipation	18 (3.5)	28 (5.3)
Depression	18 (3.5)	25 (4.7)
Paresthesia	18 (3.5)	12 (2.3)
Vomiting	18 (3.5)	10 (1.9)
Pharyngitis	17 (3.3)	24 (4.6)
Dyspepsia	16 (3.1)	24 (4.6)
Blurred vision	16 (3.1)	7 (1.3)
Hypokalemia	15 (2.9)	18 (3.4)

<b>Adverse Event*</b>	<b>BiDil® (n = 517) n (%)</b>	<b>Placebo (n = 527) n (%)</b>
Hyperlipemia	15 (2.9)	10 (1.9)
Arrhythmia	14 (2.7)	20 (3.8)
Abnormal kidney function	14 (2.7)	7 (1.3)
Pruritus	13 (2.5)	13 (2.5)
Hyperkalemia	12 (2.3)	20 (3.8)
Flu syndrome	12 (2.3)	18 (3.4)
Asthma	12 (2.3)	15 (2.8)
Edema	12 (2.3)	14 (2.7)
Rash	12 (2.3)	14 (2.7)
Nausea vomiting	11 (2.1)	11 (2.1)
Dehydration	11 (2.1)	11 (2.1)
Cellulitis	11 (2.1)	9 (1.7)
Tachycardia	11 (2.1)	6 (1.1)
Diabetes mellitus	10 (1.9)	15 (2.8)
Lung disorder	10 (1.9)	15 (2.8)
Cramps leg	10 (1.9)	12 (2.3)
Hypoglycemia	10 (1.9)	11 (2.1)
Acute kidney failure	8 (1.5)	15 (2.8)
Increased weight	8 (1.5)	13 (2.5)
Cerebrovascular accident	7 (1.4)	13 (2.5)
Increased sputum	6 (1.2)	11 (2.1)

\* A patient can have more than one event or type of event; each patient is counted once in each category.

#### 5.1.7.4.1 Serious adverse events regardless of relationship to study drug

Table 30 lists the numbers of patients with a serious adverse event that occurred in at least 1% of the patients in either treatment group, whether or not patients were taking the study medication. In general, adverse events related to systemic vasodilation or tachycardia (chest pain, ventricular tachycardia, syncope, arrhythmia, hypotension and dizziness) were somewhat more common in BiDil®-treated patients, whereas adverse events related to worsening heart failure or other major clinical events (heart failure, dyspnea, cerebrovascular accident and myocardial infarction) were more common in placebo-treated patients. Only the incidence of reports of heart failure was significant ( $p < 0.001$ ).

Table 30. Serious Adverse Events Occurring in  $\geq 1\%$  of Patients in Either Group; A-HeFT

<b>Serious Adverse Event*</b>	<b>BiDil® N = 517 n (%)</b>	<b>Placebo N = 527 n (%)</b>
Chest pain	33 (6.4)	29 (5.5)
Heart failure	16 (3.1)	41 (7.8)
Ventricular tachycardia	14 (2.7)	8 (1.5)
Pneumonia	12 (2.3)	8 (1.5)
Syncope	11 (2.1)	8 (1.5)
Dyspnea	10 (1.9)	12 (2.3)
Arrhythmia	9 (1.7)	7 (1.3)
Hypotension	8 (1.5)	3 (0.6)
Cerebrovascular accident	7 (1.4)	13 (2.5)
Heart arrest	7 (1.4)	9 (1.7)
Dizziness	7 (1.4)	0 (0.0)
Diabetes mellitus	6 (1.2)	5 (0.9)
Cellulitis	6 (1.2)	2 (0.4)
Acute kidney failure	5 (1.0)	8 (1.5)
Lung disorder	5 (1.0)	6 (1.1)
Infection	5 (1.0)	5 (0.9)
Angina pectoris	5 (1.0)	5 (0.9)
Hyperglycemia	5 (1.0)	5 (0.9)
Hypoglycemia	5 (1.0)	5 (0.9)
Dehydration	5 (1.0)	4 (0.8)
Anemia	5 (1.0)	3 (0.6)
Bronchitis	5 (1.0)	3 (0.6)
Coronary artery disease	5 (1.0)	2 (0.4)
Cerebral ischemia	5 (1.0)	1 (0.2)
Myocardial infarction	4 (0.8)	9 (1.7)
Abdominal pain	4 (0.8)	8 (1.5)
Hypertension	4 (0.8)	7 (1.3)
Accidental injury	3 (0.6)	8 (1.5)

\* Excludes endpoint events such as death or hospitalization for heart failure. A patient can have more than one event or type of event; each patient is counted only once in each category.

### 5.1.7.4.3 Adverse events leading to permanent withdrawal of study drug

Table 31 lists the number of patients with an adverse event that led to the permanent withdrawal of the study drug. The adverse events that were seen most frequently in the BiDil®-treated group were also the most common cause of withdrawal of the study drug, e.g., headache, dizziness, asthenia, chest pain, nausea and hypotension.

Table 31. Adverse Events Occurring in  $\geq 0.4\%$  of Patients in Either Group and Leading to Permanent Discontinuation of Study Drug

Adverse Event*	BiDil® N = 517 n (%)	Placebo N = 527 n (%)
Headache	38 (7.4)	4 (0.8)
Dizziness	19 (3.7)	4 (0.8)
Asthenia	12 (2.3)	1 (0.2)
Chest pain	8 (1.5)	2 (0.4)
Nausea	8 (1.5)	2 (0.4)
Hypotension	7 (1.4)	3 (0.6)
Pain	4 (0.8)	1 (0.2)
Heart failure	3 (0.6)	4 (0.8)
Heart arrest	3 (0.6)	3 (0.6)
Paresthesia	3 (0.6)	0 (0.0)
Diarrhea	2 (0.4)	2 (0.4)
Confusion	2 (0.4)	2 (0.4)
Chills	2 (0.4)	1 (0.2)
Malaise	2 (0.4)	1 (0.2)
Abdominal pain	2 (0.4)	1 (0.2)
Kidney failure	2 (0.4)	1 (0.2)
Ventricular fibrillation	2 (0.4)	0 (0.0)
Palpitations	2 (0.4)	0 (0.0)
Syncope	2 (0.4)	0 (0.0)
Nausea vomiting	2 (0.4)	0 (0.0)
Abnormal kidney function	2 (0.4)	0 (0.0)
Dyspnea	1 (0.2)	4 (0.8)
Cerebrovascular accident	1 (0.2)	3 (0.6)
Constipation	1 (0.2)	3 (0.6)
Dyspepsia	1 (0.2)	2 (0.4)
Myocardial infarction	0 (0.0)	4 (0.8)
Rash	0 (0.0)	3 (0.6)
Rectal hemorrhage	0 (0.0)	2 (0.4)
Hypoglycemia	0 (0.0)	2 (0.4)

\* Excludes endpoint events such as death or hospitalization for heart failure. A patient can have more than one event or type of event; each patient is counted only once in each category.

#### 5.1.7.4.4 Other safety topics

##### Vital signs

There was little change in heart rate during the trial, and heart rate responses did not differ between the two treatment groups. In contrast, both systolic and diastolic blood pressure in BiDil®-treated patients were significantly lower than in placebo-treated patients (Table 32).

Table 32. Mean Change in Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure (BP); A-HeFT

Time on Study	Change in Heart Rate (bpm)		Change in Systolic BP (mm Hg)		Change in Diastolic BP (mm Hg)	
	BiDil®	Placebo	BiDil®	Placebo	BiDil®	Placebo
3 Months	1.3 n = 434	1.3 n = 468	-3.2* n = 436	1.1 n = 469	-3.4* n = 436	0.3 n = 467
6 Months	1.3 n = 387	0.0 n = 375	-1.9* n = 389	1.2 n = 375	-2.4* n = 389	0.8 n = 375
9 Months	2.3 n = 312	1.4 n = 305	-4.7* n = 313	0.4 n = 304	-3.3* n = 313	0.2 n = 304
12 Months	1.5 n = 271	0.7 n = 257	-3.1* n = 276	2.0 n = 258	-2.8* n = 276	0.9 n = 258
15 Months	1.6 n = 221	1.7 n = 217	-3.1* n = 225	0.9 n = 217	-2.9* n = 225	0.7 n = 217
18 Months	3.0 n = 196	0.4 n = 175	-3.4* n = 197	1.2 n = 175	-3.0* n = 197	0.3 n = 175

\*p<0.05 comparison of BiDil® to placebo, two-sample t-test

##### Angioedema

Six BiDil®-treated patients and one placebo-treated patient experienced an adverse event classified as angioedema. The events were identified as serious in two BiDil®-treated patients and no placebo-treated patients; these two serious events are described below.

- The first patient experienced facial and lip swelling five days after the initiation of BiDil®. He was treated in an emergency room with diphenhydramine, dexamethasone, and methylprednisolone and discharged after improvement was noted. Study drug was discontinued.

- The second patient was randomized to A-HeFT and approximately seven months later experienced shortness of breath and swelling of the lips and tongue following ingestion of his morning medications; he then became unresponsive. Emergency medical services administered fluids and diphenhydramine, resulting in return of his mental status. In the Emergency Room he was treated with diphenhydramine and methylprednisolone; the lip and tongue swelling improved, and he was discharged and advised to discontinue his angiotensin-converting enzyme inhibitor and refrain from alcohol. No action was taken with respect to study drug administration.

#### Lupus syndrome

Although reports of arthralgias (but not other arthritic symptoms) were somewhat more frequent in BiDil®-treated patients (8 vs 2), only one patient was reported to have developed “lupus-like symptoms” after one year of treatment. Her symptoms resolved following treatment with hydroxychloroquine for 7 weeks without a change in the study drug.

### 5.1.8 Summary and Conclusions for A-HeFT

The findings of the African American Heart Failure Trial (A-HeFT) support the following conclusions:

- The long-term administration of a combination of ISDN/HYD (as BiDil®) to black men and women with moderate-to-severe heart failure generally treated with ACE inhibitors/ARBs, beta blockers and/or aldosterone antagonists along with diuretics and digitalis glycosides was associated with a 43% reduction in the relative risk of death ( $p=0.012$ ).
- The survival benefit of BiDil® in A-HeFT was accompanied by a significant improvement in the primary endpoint of the trial ( $p=0.016$ ), which combined information about the occurrence of death, first hospitalization for heart failure and change in quality of life into a single variable.
- The long-term administration of ISDN/HYD (as BiDil®) to black men and women reduced the relative risk of hospitalization for heart failure by 39% ( $p < 0.001$ ). BiDil® also reduced the combined relative risk of death or hospitalization for heart failure by 37% ( $p < 0.001$ ).
- When compared with placebo, patients in the BiDil® group had fewer hospitalizations for heart failure and spent fewer days in the hospital for heart failure, (both  $p < 0.01$ ). Patients in the BiDil® group also had fewer hospitalizations and spent fewer days in the hospital for any reason, but the differences were not significant. Hospitalizations in the BiDil® group were shorter than in the placebo group, whether they were for heart failure or for any reason.
- BiDil®-treated patients experienced greater improvements in quality of life, as assessed by the Minnesota Living with Heart Failure questionnaire, at most visits during the course of the study.
- Worsening heart failure as an adverse event was reported less frequently in patients in the BiDil® group than those in the placebo group (9.5% vs 15.2%). Worsening heart failure as a

serious adverse event was reported less frequently in patients in the BiDil® group than those in the placebo group (3.1% vs 7.8%).

- The clinical benefits of BiDil® were associated with a persistent decrease in systolic and diastolic blood pressure, which did not become attenuated over time. This observation reinforces the findings of V-HeFT I, that hemodynamic tolerance did not develop during long-term treatment with the drug combination.
- The long-term administration of BiDil® was associated with headache, dizziness and other vasodilator-type reactions similar to those reported earlier in V-HeFT I and V-HeFT II.

The survival benefits of BiDil® in black men and women with moderate-to-severe heart failure generally treated with ACE inhibitors/ARBs, beta blockers and/or aldosterone antagonists along with diuretics and digitalis glycosides (43% reduction in relative risk in A-HeFT) were similar in magnitude to the survival benefits seen with a combination of ISDN/HYD in black men with mild-to-severe heart failure generally receiving only digitalis glycosides and diuretics (47% reduction in relative risk in V-HeFT I).

The reduction in heart failure related hospitalizations reduced by BiDil® in black patients with moderate-to-severe heart failure treated with ACE inhibitors/ARBs, beta blockers and/or aldosterone antagonists along with diuretics and digitalis glycosides was concordant with the reduction in heart failure hospitalizations observed with a combination of ISDN/HYD in black men with mild-to-severe heart failure generally receiving digitalis and diuretics (V-HeFT I and V-HeFT II).

The improvement in quality of life produced by BiDil® in black patients with moderate-to-severe heart failure generally treated with ACE inhibitors/ARBs, beta blockers and or aldosterone antagonists as well as digitalis glycosides, and diuretics (A-HeFT) was concordant with the improvement in quality of life seen with a combination of ISDN/HYD in black men with mild-to-severe heart failure generally receiving only digitalis glycosides and diuretics (V-HeFT II).

The concordance of these findings in black patients at distinct ends of the heart failure spectrum supports the conclusion that BiDil® reduces the risk of death as well as the risk of heart failure hospitalizations and improved the quality of life across a wide range of symptoms and background medications.

## 6. 0 Summary of Isosorbide Dinitrate and Hydralazine for Heart Failure

### 6.1 Rationale for Combining Isosorbide Dinitrate and Hydralazine

The combination of ISND/HYD was first proposed as an orally active means of replicating the hemodynamic effects of nitroprusside,<sup>76,77</sup> which was known to produce striking improvements in cardiac performance when given intravenously. Isosorbide dinitrate acted primarily to dilate venous capacitance vessels and hydralazine acted primarily to dilate arterial resistance vessels.<sup>61,68</sup> Together the combination produced hemodynamic benefits superior to that which could be achieved when either drug was administered alone.

Did the hemodynamic improvement produced by the combination of ISDN/HYD result in clinical benefits? Small- to intermediate-sized controlled trials of HYD alone<sup>65,66</sup> and ISDN alone<sup>71, 74-75</sup> failed to demonstrate improvement in symptoms or exercise tolerance in patients with heart failure. The lack of improvement in these trials may have been related to their small size and the selection of a low dose, but may also have been related to the limitations of monotherapy. Each drug has characteristics that may address a deficiency of the other. For example, HYD alone has been implicated in provoking ischemic events in some patients with heart failure who had underlying coronary artery disease;<sup>99</sup> this effect could be ameliorated by concomitant administration of ISDN. ISDN alone was frequently associated with the development of hemodynamic tolerance during prolonged therapy,<sup>81-83</sup> such tolerance could be minimized by the concomitant administration of HYD.<sup>90-93</sup>

Three large-scale multicenter controlled clinical trials have been carried out to evaluate the efficacy of a combination of ISDN/HYD in patients with chronic heart failure (Table 33). Two of the trials were placebo-controlled, and one was an active controlled trial versus the angiotensin-converting enzyme inhibitor, enalapril. Two of the trials were carried out with ISDN and HYD administered as individual drugs,<sup>96,97</sup> one trial was performed using a combination product of ISDN/HYD (BiDil®).<sup>98</sup>

Table 33. Characteristics of Major Trials with ISDN/HYD in Heart Failure

	<b>V-HeFT I</b>	<b>V-HeFT II</b>	<b>A-HeFT</b>
<b>Sponsor</b>	Veterans Affairs	Veterans Affairs	NitroMed
<b>Number of Patients</b>	642	804	1050
<b>Gender</b>	Men	Men	Men & women
<b>Race</b>	All races	All races	African Americans
<b>Drugs Studied</b>	Placebo ISDN/HYD Prazosin	Enalapril ISDN/HYD	Placebo ISDN/HYD
<b>Target Doses of ISDN/HYD</b>	ISDN 40 mg QID HYD 75 mg QID	ISDN 40 mg QID HYD 75 mg QID	ISDN 40 mg TID HYD 75 mg TID
<b>ISDN/HYD</b>	As individual products	As individual products	As fixed-dose combination tablet (BiDil®)
<b>Severity of Heart Failure</b>	Mild-to-severe	Mild-to-severe	Moderate-to-severe
<b>Background Therapy for Heart Failure</b>	Digoxin Diuretics	Digoxin Diuretics	Digoxin Diuretics ACE inhibitors/ARBs Beta blockers Aldosterone antagonists

## 6.2 V-HeFT I

The first major trial to evaluate the clinical efficacy of the combination of ISDN/HYD was the first Vasodilator in Heart Failure Trial (V-HeFT I). [This trial was also the first to evaluate the effect of any orally effective regimen on the survival of patients with heart failure.] The trial evaluated two different vasodilator regimens (and placebo) in 642 men: (1) a combination of and ISDN (40 mg QID) and HYD (75 mg QID) and (2) monotherapy with prazosin (5 mg QID). Both treatments had been shown to exert balanced vasodilator effects on systemic arteries and veins in a manner similar to that seen with an intravenous infusion of nitroprusside.

The key findings of this trial are summarized below:

- The long-term administration of a combination of ISDN/HYD to middle-aged men with mild-to-severe heart failure generally treated only with digitalis glycosides and diuretics was associated with a 22% reduction in the relative risk of death ( $p=0.093$ ) — a magnitude of effect similar to that reported when angiotensin-converting enzyme inhibitors were evaluated in the treatment of patients with heart failure.<sup>100</sup>
- A reduction in the risk of death similar to that seen in the overall trial was seen across nearly all of the subgroups examined retrospectively. However, the most striking effect was seen in black patients who experienced a 47% reduction in relative risk, as compared with white patients who experienced only a 12% reduction in relative risk, interaction  $p=0.15$  (Figures 21, 22). The survival effect in black patients with ISDN/HYD was statistically significant in its own right ( $p=0.04$ ), even though black patients were the smallest group examined and comprised only 30% of the patients in the trial.
- Further retrospective examination of subgroup effects suggested that other subgroups might also respond well (with respect to survival) to the combination of ISDN/HYD. These subgroups included: younger patients (age < 59) [33% reduction in risk when compared with 9% reduction in risk in older patients]; patients with diabetes mellitus [25% reduction in risk when compared with 5% reduction in risk in nondiabetics]; patients with lower systolic blood pressure (< median) [26% reduction in risk when compared with 14% reduction in risk in patients with higher systolic blood pressure]; and patients with an ejection fraction < 40% [25% reduction in risk when compared with 17% reduction in risk in patients with preserved ejection fractions].
- For the first two years of the study (the duration for which a meaningful proportion of the randomized patients were followed), the risk of hospitalization for heart failure was lower in the ISDN/HYD group than in the placebo group. A treatment effect in black patients contributed importantly to the overall differences.
- Although maximal exercise capacity was not significantly increased by the combination of ISDN/HYD in the overall trial, the magnitude of the functional improvement in black patients at twelve months (who had an increase by 1.64 mL/kg/min) was twice that seen in non-black patients (who had an increase by 0.84 mL/kg/min). This observation suggested that future trials might appropriately seek to confirm the efficacy of ISDN/HYD using an endpoint that measured the effects of the drug on both clinical status and survival.
- The long-term administration of a combination of ISDN/HYD was associated with a consistent improvement in left ventricular ejection fraction (about 3-4 units). The magnitude of this increase was somewhat larger than has been historically reported with angiotensin-converting enzyme inhibitors (which increase left ventricular ejection fraction by 2-3 units).<sup>101,102</sup> Demonstration of the persistence of this effect for 2 years suggested that hemodynamic tolerance did not develop to the combination of ISDN/HYD during the course of the long-term treatment of patients with heart failure.

- The long-term administration of prazosin, another drug with arterial and venous vasodilating effects, did not have favorable effects on survival, left ventricular ejection fraction or maximal exercise capacity. The lack of prazosin’s efficacy may have been related to the development of tolerance to its hemodynamic effects<sup>103</sup> — a phenomenon that may have been avoided by the concomitant administration of ISDN/HYD. This finding suggests that the mechanisms by which drugs exert their vasodilator effects are relevant in determining their efficacy in the treatment of heart failure.
- The long-term administration of the combination of ISDN/HYD was associated with headache, dizziness and other vasodilator-type reactions.
- A meaningful proportion of patients failed to achieve target doses of both ISDN and HYD. Clinical benefits were seen despite the use of lower-than-target doses, suggesting that future trials might appropriately target lower doses of ISDN/HYD.

Figure 21. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in Black Patients; V-HeFT I

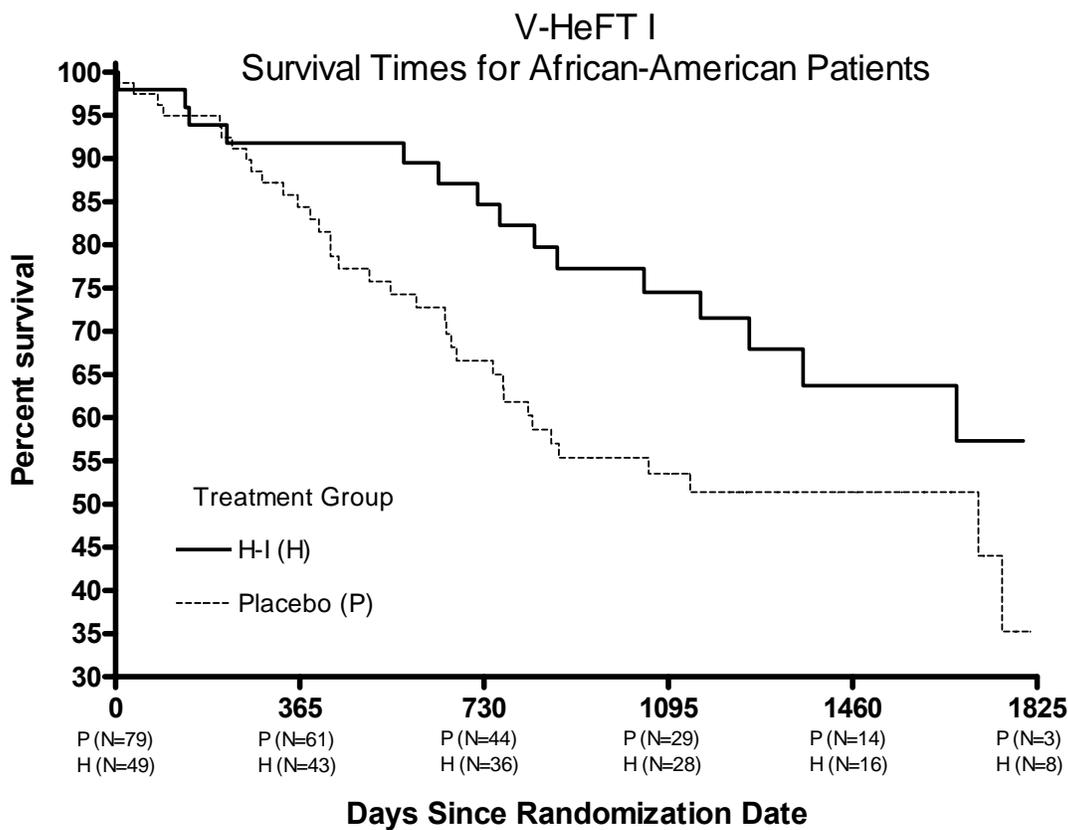
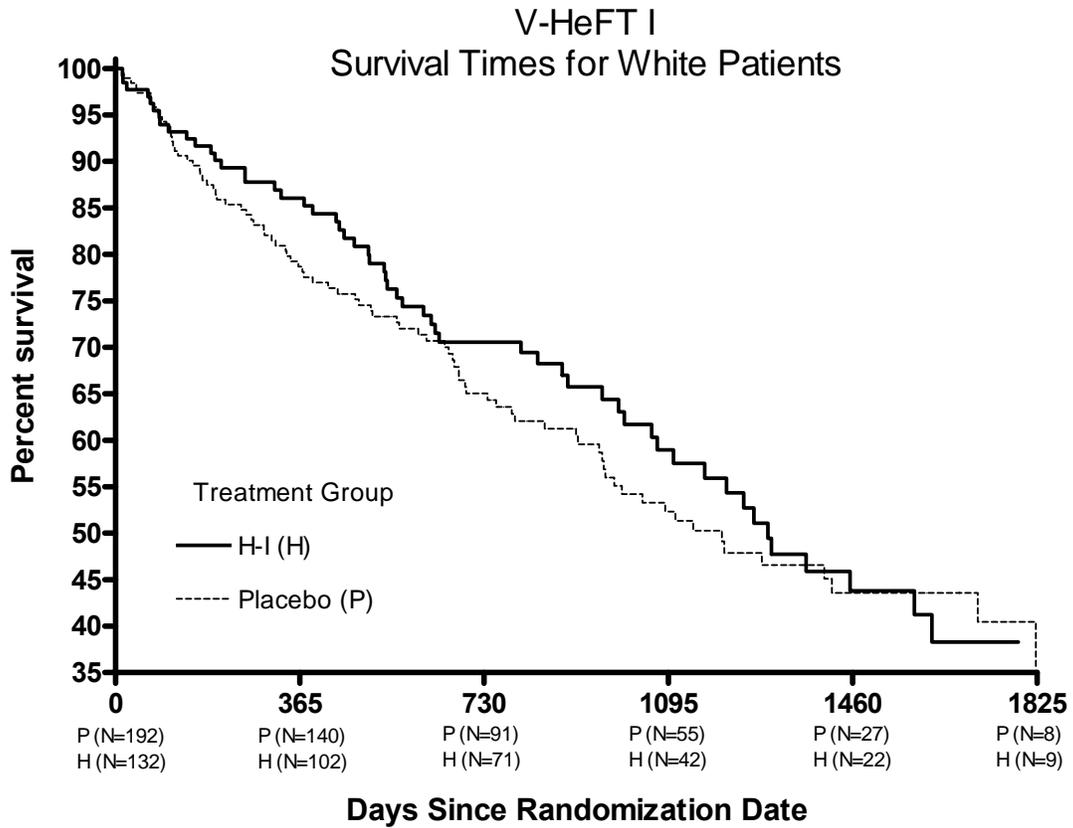


Figure 22. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in White Patients; V-HeFT I



The findings of V-HeFT I suggested that the combination of ISDN/HYD was likely to have symptomatic and survival benefits when used in the treatment of heart failure and retrospectively, that certain subgroups of patients, notably black patients might be particularly sensitive to the ability of the drug combination to improve exercise capacity, reduce the risk of heart failure hospitalization and reduce the risk of death.

### 6.3 V-HeFT II

Could the pattern of benefit seen with the combination of ISDN/HYD in V-HeFT I be replicated in a second trial? In the second Vasodilator in Heart Failure Trial (V-HeFT II), the combination of ISDN (40 mg QID) and HYD (75 mg QID) was compared with the angiotensin-converting enzyme inhibitor enalapril (10 mg BID) in 804 men. The design of V-HeFT II was nearly identical to V-HeFT I (nearly identical inclusion and exclusion criteria, methods and endpoints), except that patients in the control group received enalapril, which had been shown to reduce mortality in an earlier trial (CONSENSUS).<sup>104</sup> The key findings of this trial are summarized below:

- When compared with enalapril, the long-term administration of a combination of ISDN/HYD to middle-aged men with mild-to-severe heart failure generally treated only with digitalis glycosides and diuretics was associated with a 23% greater relative risk of death. The p-value for this treatment difference was 0.08.
- The difference in survival between enalapril and ISDN/HYD seen in V-HeFT II (23%) was comparable in magnitude to the difference in survival seen in trials that have compared enalapril to placebo in mild-to-moderate heart failure (23% mortality reduction in a meta-analysis of all placebo-controlled trials of ACE inhibitors<sup>100</sup>). Therefore, in the absence of V-HeFT I, the juxtaposition of the point estimates of V-HeFT II and the ACE inhibitors trials might suggest that the combination of ISDN/HYD had little effect on mortality in the majority of patients enrolled in V-HEFT II.
- It is therefore noteworthy that — although a superior survival effect of enalapril (when compared with ISDN/HYD) was seen across nearly all of the subgroups examined retrospectively — one notable exception was black patients (Figures 23, 24). The hazard ratio for ISDN/HYD : enalapril was 1.32 in white patients but 1.01 for black patients, indicating that the superiority of enalapril over ISDN/HYD in the overall trial was driven primarily by the treatment difference seen in white patients. This could have occurred
  - if enalapril was particularly *ineffective* in black patients (a re-analysis of the SOLVD trial database has supported an attenuated effect of enalapril in black patients<sup>16</sup>) or
  - if the combination of ISDN/HYD was particularly *effective* in black patients (the subgroup analysis of V-HeFT I cited in Section 4.1.7.3.2 of this document would support a particularly pronounced effect of the drug combination in black patients), or
  - if both possibilities were correct.
- Further examination of other subgroup effects in V-HeFT II did not confirm most of the other subgroup hypotheses generated by the findings of V-HeFT I. Specifically, younger patients, diabetics and patients with lower systolic blood pressure responded better to ISDN/HYD than placebo in V-HeFT I but responded worse to ISDN/HYD than enalapril in V-HeFT II (ISDN/HYD : enalapril hazard ratios of 1.36 in younger patients, 1.35 in diabetics

and 1.37 in patients with lower systolic blood pressure). Except for race, only one additional subgroup effect seen in V-HeFT I was confirmed in V-HeFT II. Specifically, patients with a left ventricular ejection fraction < 40% responded best to ISDN/HYD (hazard ratio of 2.02 in patients with preserved left ventricular ejection fractions as compared with 1.21 in patients with impaired left ventricular ejection fractions).

- Time-to-event analyses of hospitalization for heart failure showed that during the first two years of the study, black patients treated with ISDN/HYD had a lower risk of hospitalization for heart failure than black patients treated with enalapril, whereas in white patients, the risk of hospitalization for heart failure was similar in the two treatment groups. These findings are noteworthy given the established effects of enalapril in reducing the risk of hospitalization for heart failure.<sup>100,105</sup>
- Both enalapril and the combination of ISDN/HYD were associated with comparable improvements in left ventricular ejection fraction (about 2-3 units). The magnitude of this increase is similar to that which has been historically reported with angiotensin-converting enzyme inhibitors which increase ejection by 2-3 units when compared with placebo.<sup>101,102</sup> These data are consistent with the finding in V-HeFT I that the combination of ISDN/HYD increases left ventricular ejection fraction in heart failure.
- The combination of ISDN/HYD produced improvements in maximal exercise capacity in V-HeFT II that were generally superior to those produced by enalapril. This finding is noteworthy since several trials have reported that ACE inhibitors improve maximal exercise capacity.<sup>101,106,107</sup>
- The combination of ISDN/HYD produced changes in quality of life in all patients that were similar to those produced by enalapril. At 12 months, a treatment difference in favor of ISDN/HYD was primarily seen in black patients with little difference in white patients (interaction p=0.09). This finding reinforces the impressions gained from V-HeFT I that future trials might appropriately seek to confirm the efficacy of ISDN/HYD, using an endpoint that measured both the symptomatic and prognostic effects of the drugs.
- Enalapril lowered both systolic and diastolic blood pressure more than the combination of ISDN/HYD. However, the greater hypotensive effects of enalapril were seen primarily in white patients. ISDN/HYD lowered systolic blood pressure more in black patients than white patients.
- The differences observed between ISDN/HYD and enalapril on survival, maximal exercise capacity and left ventricular ejection fraction reinforce the finding of V-HeFT I that the mechanisms by which drugs exert their vasodilator effects are relevant in determining their efficacy in the treatment of heart failure.

- The long-term administration of a combination of ISDN/HYD was associated with headache, dizziness and other vasodilator-type reactions.
- A meaningful proportion of patients failed to achieve target doses of ISDN/HYD. Clinical benefits were seen despite the use of lower-than-target doses, suggesting that future trials might appropriately target lower doses of ISDN/HYD.

Figure 23. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in Black Patients; V-HeFT II

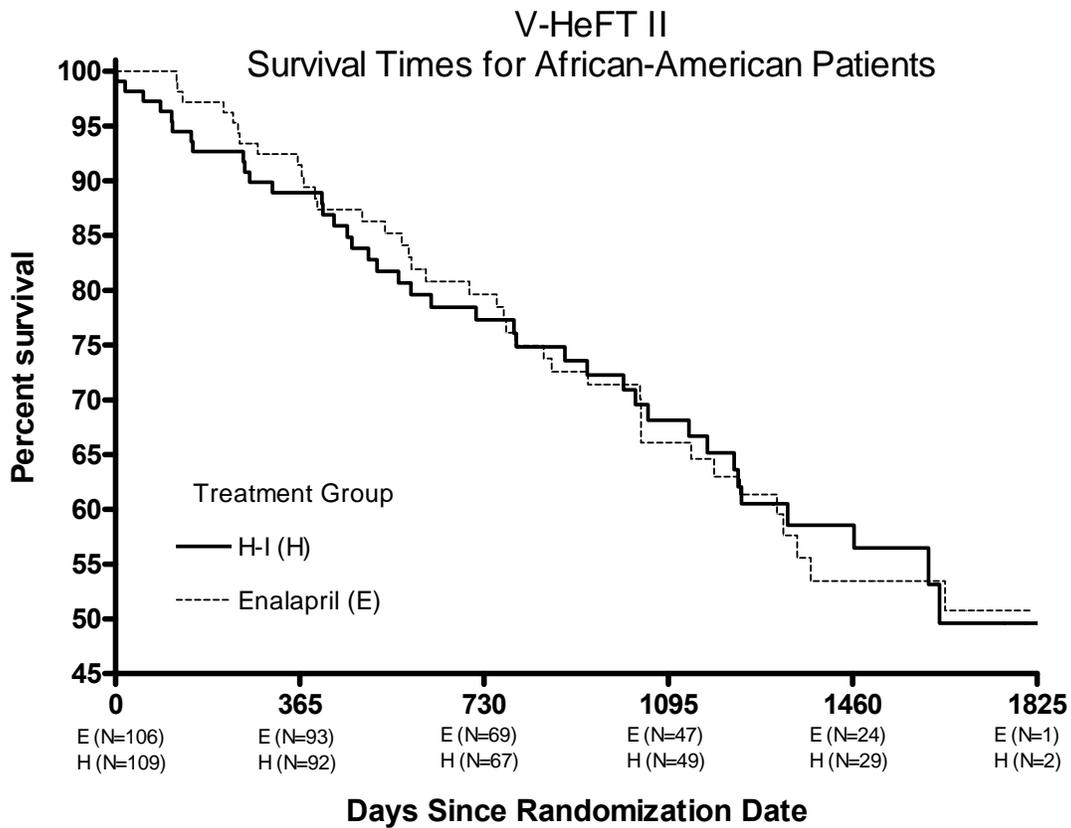
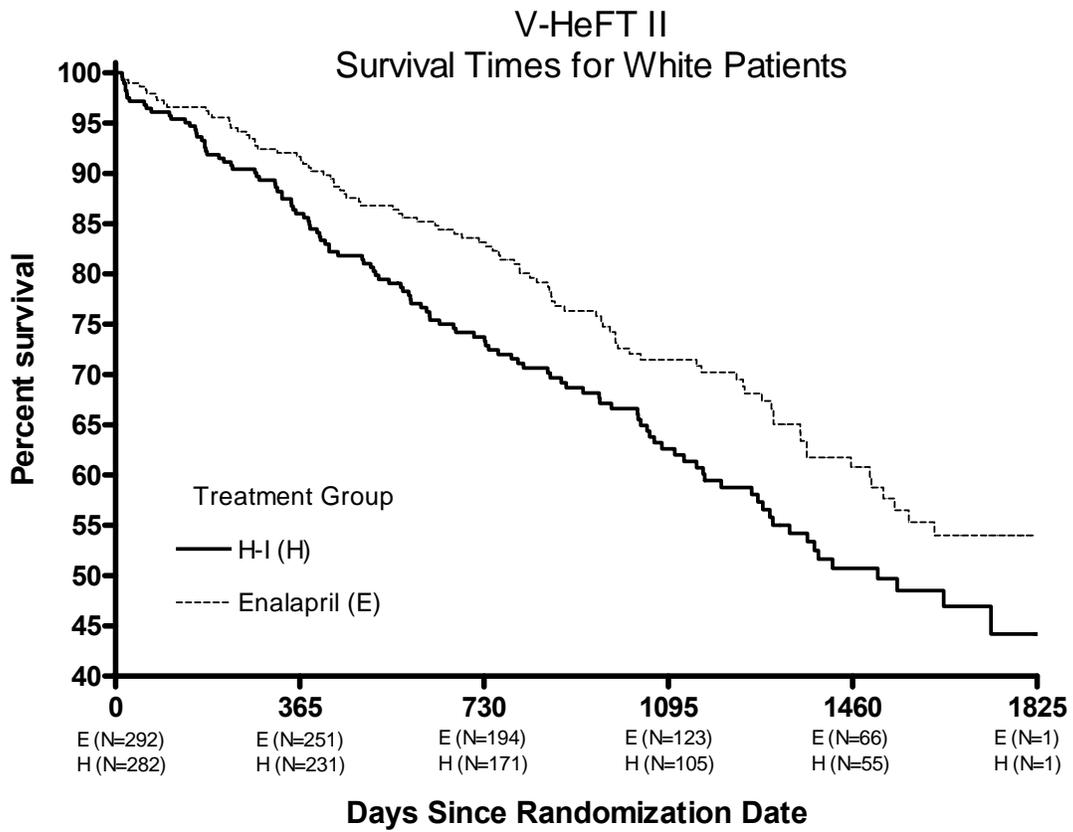


Figure 24. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality in White Patients; V-HeFT II



Hence, the initial and retrospective findings of V-HeFT II reinforced many (but not all) of the key findings of and hypotheses derived from V-HeFT I. When taken together and analyzed by subgroups, the two trials suggest that the combination of ISDN/HYD may produce symptomatic and prognostic benefits that are particularly apparent in black patients; that such an effect might be most readily detected by an endpoint that simultaneously measured both effects; and that this benefit might be achieved at doses lower than the target doses used in V-HeFT I and V-HeFT II.

Is a preferential effect of ISDN/HYD in black patients with heart failure biologically plausible?

- Whereas coronary artery disease is the major cause of heart failure in white patients, the major predisposing factor to heart failure in black patients is hypertension (90% of the patients in A-HeFT had a history of hypertension).<sup>43-45</sup>
- Hypertension in black patients is not generally due to the activation of neurohormonal mechanisms (black patients with hypertension are generally hyporesponsive to ACE inhibitors and beta blockers) but appears to be related to a vascular deficiency of nitric oxide — which has been attributed to both a decrease in vascular synthesis of nitric oxide and an increase in the destruction of nitric oxide as a result of enhanced vascular oxidative stress.<sup>30-33,37,38,40-44</sup>
- This deficiency of nitric oxide may explain why heart failure develops disproportionately in black patients and why (once developed) heart failure progresses more rapidly to death in black than in white patients.<sup>4-14</sup>
- Isosorbide dinitrate causes its vasodilator effects by acting as a nitric oxide donor in vascular smooth muscle.<sup>80</sup> However, such an action might have little utility if the nitric oxide generated were rapidly destroyed in an environment of enhanced oxidative stress.<sup>34-36</sup> Such enhanced destruction has been postulated to lead to the development of nitrate tolerance.<sup>84-87</sup> Hydralazine has anti-oxidant properties,<sup>88,89</sup> which may act to preserve endogenously generated nitric oxide as well as nitric oxide generated by the administration of isosorbide dinitrate. The combination of both drugs may therefore act to increase vascular nitric oxide.
- The ability of ISDN/HYD to increase vascular nitric oxide may be most helpful in patients most likely to have a vascular deficiency of nitric oxide. Black patients are one such group.<sup>37</sup>

These biochemical and physiological observations are consistent with the retrospective subgroup analyses of V-HeFT I and V-HeFT II and suggested that a confirmatory study of the use of a combination of ISDN/HYD in heart failure would be most successful if it focused on patients most likely to exhibit a vascular nitric-oxide deficiency. As a result, a third large-scale clinical trial of ISDN/HYD was carried out in African Americans.

## 6.4 A-HeFT

The African-American Heart Failure Trial (A-HeFT) was a multicenter, randomized, double-blind, parallel group, placebo-controlled study conducted at 180 sites in the United States that enrolled 1050 patients with heart failure. A-HeFT differed from V-HeFT I and II in the following ways:

- A-HeFT enrolled only African-American patients.
- A-HeFT enrolled men and women.
- A-HeFT enrolled patients with NYHA class III-IV symptoms.
- A-HeFT enrolled patients with heart failure due to left ventricular systolic dysfunction.
- A-HeFT enrolled patients generally taking ACE inhibitors, beta blockers and/or aldosterone antagonists in addition to diuretics and digitalis glycosides.
- ISDN/HYD were formulated and administered as a fixed-dose combination (BiDil®).
- Target doses in A-HeFT were ISDN 40 mg TID and HYD 75 mg TID.

In contrast, V-HeFT I and V-HeFT II enrolled all races but only men, who had class II-IV symptoms, had heart failure associated with both impaired and preserved ejection fraction, were generally taking only digitalis glycosides and diuretics and were titrated to target doses of ISDN 40 mg QID and HYD 75 mg QID; the drugs were administered as individual agents.

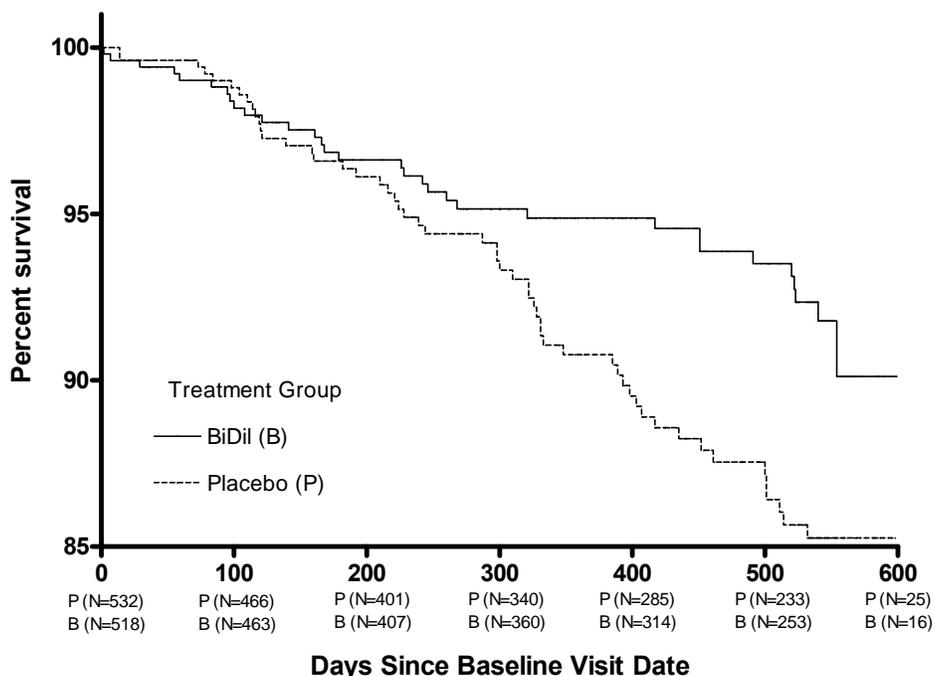
Hence, A-HeFT focused on the two subgroups that were concordantly identified in both V-HeFT I and V-HeFT II as showing the most favorable survival effects with ISDN/HYD: black patients and patients with systolic dysfunction.

The key findings of A-HeFT are summarized below:

- The long-term administration of a combination of ISDN/HYD (as BiDil®) to black men and women with moderate-to-severe heart failure generally treated with ACE inhibitors, beta blockers and/or aldosterone antagonists along with digitalis glycosides and diuretics was associated with a 43% reduction in the relative risk of death to placebo ( $p=0.012$ ; Figure 25).
- The survival benefit of BiDil® in A-HeFT was accompanied by a significant improvement in the primary endpoint of the trial ( $p=0.016$ ), which combined information about the occurrence of death, hospitalization for heart failure and quality of life into a single variable.
- The long-term administration of a combination of ISDN/HYD (as BiDil®) to black men and women with heart failure reduced the relative risk of hospitalization for heart failure by 39% ( $p<0.001$ ). BiDil® also reduced the combined relative risk of death or hospitalization for heart failure by 37% ( $p < 0.001$ ).
- When compared with placebo, patients in the BiDil® group had fewer hospitalizations for heart failure and spent fewer days in the hospital for heart failure, both  $p < 0.01$ . Patients in the BiDil® group also had fewer hospitalizations and spent fewer days in the hospital for any reason, but the differences were not significant. Hospitalizations in the BiDil® group were shorter than in the placebo group, whether they were for heart failure or for any reason.

- BiDil®-treated patients experienced statistically significant improvements in quality of life relative to placebo, as assessed by the Minnesota Living with Heart Failure questionnaire, at most visits during the course of the study. This finding is concordant with a similar benefit of ISDN/HYD in black patients on quality of life in V-HeFT II, which compared the drug combination to enalapril.
- Worsening heart failure as an adverse event was reported less frequently in patients in the BiDil® group than those in the placebo group (9.5% vs 15.2%). Worsening heart failure as a serious adverse event was reported less frequently in patients in the BiDil® group than those in the placebo group (3.1% vs 7.8%).
- The clinical benefits of BiDil® were associated with a persistent decrease in systolic and diastolic blood pressure, which did not become attenuated over time. This observation reinforces the findings of V-HeFT I, that hemodynamic tolerance did not develop during long-term treatment with the drug combination.
- The long-term administration of a combination of ISDN/HYD was associated with headache, dizziness and other vasodilator-type reactions similar to those reported earlier in V-HeFT I and V-HeFT II.

Figure 25. Kaplan-Meier Time-to-Event Curves for All-Cause Mortality; A-HeFT



## 6.5 Consistency of Findings in the V-HeFT and A-HeFT Trials

### 6.5.1 Consistency of Effect on Survival

The survival benefit of BiDil® in black patients with moderate-to-severe heart failure generally treated with ACE inhibitors, beta blockers and/or aldosterone antagonists as well as digitalis glycosides and diuretics (43% reduction in relative risk in A-HeFT,  $p=0.012$ ) was similar in magnitude to the survival benefit seen with a combination of ISDN/HYD in black patients with mild-to-severe heart failure generally receiving only digitalis glycosides and diuretics and (47% reduction in relative risk in V-HeFT I,  $p=0.044$ ; Table 34).

The concordance of these findings in patients over the heart failure spectrum supports the conclusion that BiDil® reduces the risk of death in black patients across a wide range of symptoms and background medications.

Table 34. Effect of ISDN/HYD on All-Cause Mortality in Black Patients with Heart Failure

Patient Population	Placebo	ISDN/HYD	Hazard ratio (95% CI)	Log-rank p-value
Class II-IV heart failure generally receiving only digitalis glycosides and diuretics (V-HeFT I)	35 / 79*	15 / 49	0.53 (0.29, 0.98)	0.044
Class III-IV heart failure generally receiving ACE inhibitors/ARBs, beta blockers, and/or aldosterone antagonists, digitalis glycosides, diuretics, etc. (A-HeFT)	54 / 532	32 / 518	0.57 (0.37, 0.89)	0.012

\* number of deaths / number at risk

### 6.5.2 Consistency of Effect on Hospitalizations for Heart Failure

The administration of ISDN/HYD was associated with a reduction in the risk of hospitalization for heart failure in black patients with mild-to-severe heart failure generally receiving only digitalis glycosides and diuretics (seen in V-HeFT I and V-HeFT II) as well as in black patients with moderate-to-severe heart failure generally treated with digitalis, diuretics, ACE inhibitors/ARBs, beta blockers and/or aldosterone antagonists (seen in A-HeFT). Specifically,

- In V-HeFT I, in black patients, at the end of the first year, the cumulative rate of heart failure hospitalization was 17.2% in placebo patients but only 6.3% in ISDN/HYD patients.
- In V-HeFT II, in black patients, at the end of the first year, the cumulative rate of heart failure was 5.0% in ISDN/HYD patients vs 13.1% in enalapril patients.
- In A-HeFT, in black patients, BiDil® reduced the relative risk of hospitalization for heart failure by 39% ( $p < 0.001$ ).

The concordance of these findings in patients over the heart failure spectrum supports the conclusion that BiDil® reduces the risk of hospitalization for heart failure in black patients across a wide range of symptoms and background medications.

### 6.5.3 Consistency of Effect on Quality of Life

The improvement in quality of life produced by BiDil® in black patients with moderate-to-severe heart failure generally treated with ACE inhibitors/ARBs, beta blockers and/or aldosterone antagonists as well as digitalis glycosides, diuretics and other therapies (seen in A-HeFT) was concordant with the improvement in quality life seen with a combination of ISDN/HYD in black men with mild-to-moderate heart failure generally receiving only digitalis glycosides and diuretics (seen in V-HeFT II; Table 35). It is noteworthy that the magnitude of the benefit differs in part because different quality of life scales were used on the two trials and because the comparator drug was placebo in A-HeFT but was enalapril in V-HeFT II.<sup>108,109</sup>

The concordance of these findings in patients at over the heart failure spectrum supports the conclusion that BiDil® improves the symptoms of heart failure that impair quality of life in black patients across a wide range of symptoms and background medications.

Table 35. Change in Quality of Life Produced by ISDN/HYD in Black Patients with Heart Failure at 6 and 12 Months; V-HEFT II and A-HeFT\*

	<b>Control</b>	<b>ISDN/HYD</b>	<b>p-value</b>
<b>V-HeFT II; comparison with enalapril</b>			
Mean difference at 6 months	+0.8	-0.29	0.18
Mean difference at 12 months	+1.04	-0.67	0.04
<b>A-HeFT; comparison with placebo</b>			
Mean difference at 6 months	-3.1	-7.1	0.011
Mean difference at 12 months	-6.0	-9.1	0.129

\* Different scales for measuring quality of life were used in V-HeFT II and A-HeFT

## 7.0 Conclusions

The combined findings from three large-scale controlled clinical trials support the approval of a combination of isosorbide dinitrate and hydralazine for the treatment of heart failure in black patients. The benefits of treatment include:

- A meaningful reduction in the risk of death in patients with mild-to-severe symptoms generally treated only with digitalis glycosides and diuretics and in patients with moderate-to-severe symptoms generally treated with ACE inhibitors/ARBs, beta blockers, digitalis glycosides, diuretics and/or aldosterone antagonists.
- A meaningful reduction generally in the risk of hospitalization for heart failure in patients with mild-to-severe symptoms treated only with digitalis glycosides and diuretics and in patients with moderate-to-severe symptoms generally treated with ACE inhibitors/ARBs, beta blockers, digitalis glycosides, diuretics and/or aldosterone antagonists.
- A meaningful improvement in quality of life in patients with mild-to-severe symptoms generally treated only with digitalis glycosides and diuretics and in patients with moderate-to-severe symptoms generally treated with ACE inhibitors/ARBs, beta blockers, digitalis glycosides, diuretics and/or aldosterone antagonists.
- The results of these three studies demonstrate that the combination of isosorbide dinitrate and hydralazine is safe and generally well tolerated as treatment for heart failure. The most common adverse events observed among patients receiving the ISDN/HYD combination in all three studies were headache, dizziness and other vasodilator-type reactions.
- The data support the following indication: “BiDil is indicated for the treatment of heart failure in black patients. BiDil® has been shown to reduce the risk of mortality from any cause, to reduce the risk of heart failure hospitalization and to improve quality of life.”

## 8.0 References

Copies of References are provided on the attached CD.

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