Hydralazine and Isosorbide Dinitrate in Heart Failure
Historical Perspective, Mechanisms, and Future Directions

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Until the 1970s, treatment options for heart failure were limited to digitalis and diuretics. Although effective for symptoms, there was no evidence of mortality benefit with this combination, and it was an inadequate option for many patients with advanced symptoms. The search for more effective options led to strategies that modulated hemodynamics. Numerous physiological studies showed the dependence of ventricular function on vascular resistance, and drugs that reduced systemic vascular resistance improved cardiac performance. A pivotal study by Franciosa et al showed that sodium nitroprusside in patients with heart failure in the setting of acute myocardial infarction reduced left ventricular filling pressures from 22.7 ± 2.0 to 11.3 ± 1.6 mm Hg and led to a modest increase in cardiac output. A subsequent study revealed more striking improvements in patients with refractory heart failure, in whom nitroprusside reduced systemic vascular resistance by 50%, increased cardiac output by 56%, and reduced left ventricular filling pressure by 47%. These hemodynamic benefits with nitroprusside led to studies with oral agents, including hydralazine, isosorbide dinitrate (ISDN), prazosin, phentolamine, and minoxidil. Although these drugs did affect hemodynamics, none was as effective as nitroprusside individually. In 1977, Massie et al studied the combination of 2 oral agents, hydralazine and ISDN (H-ISDN) in class III to IV heart failure patients, proposing that simultaneously reducing preload with ISDN and afterload with hydralazine would result in a better response than with either drug individually. They found that H-ISDN reduced left ventricular filling pressure by 36%, increased cardiac index by 58%, and reduced systemic vascular resistance by 34%. Later, Pierpont et al compared H-ISDN with nitroprusside and showed that the 2 therapies had similar effects on wedge pressure reduction and cardiac index increase.

The Vasodilator–Heart Failure Trials I and II

Considering these hemodynamic benefits with H-ISDN, its effect on mortality was studied in the first Vasodilator–Heart Failure Trial (V-HeFT I), the first major randomized, placebo-controlled trial in cardiovascular medicine. The study compared H-ISDN or prazosin with placebo in 642 men with impaired systolic function and found that H-ISDN was associated with a trend toward mortality reduction (44.0% versus 38.7%; *P* = 0.09), which was significant at a prespecified 2-year end point (34% relative risk reduction; *P* = 0.028). In addition, H-ISDN improved ejection fraction at 8 weeks (2.9% versus 0.4%; *P* < 0.001) and 1 year (4.2% versus −0.1%; *P* < 0.001). Prazosin was not associated with either mortality or ejection fraction improvement. Subsequently, V-HeFT II compared H-ISDN and enalapril. The V-HeFT II study population was similar to that of V-HeFT I, and the results showed a trend toward improved all-cause mortality with enalapril compared with H-ISDN (38.2% versus 32.8%; *P* = 0.08). Interestingly, despite lesser mortality reduction, H-ISDN resulted in greater improvements in ejection fraction and exercise tolerance than enalapril (Figure 1). At 13 weeks, the change in ejection fraction was 3.3% for H-ISDN compared with 2.1% for enalapril (*P* = 0.03). Peak exercise oxygen consumption improved by 0.6 and 0.8 mL·kg⁻¹·min⁻¹ at 13 weeks and 6 months, respectively, with H-ISDN (*P* = 0.0001); no improvement was seen with enalapril. Although there was no placebo arm in V-HeFT II, the mortality rates with H-ISDN in V-HeFT II mirrored those in V-HeFT I, suggesting a benefit. These findings suggested that H-ISDN might play a role in heart failure, particularly among those intolerant of angiotensin-converting enzyme inhibitors.

Development of a Combination Product

On the basis of V-HeFT I and II results, an application was filed with the Food and Drug Administration for a methods patent on the H-ISDN combination in 1987, which would give marketing rights for the combination specifically for heart failure. The patent was approved, leading to the production of BiDil, a single-pill equivalent to the generic H-ISDN. After bioequivalence was proved, a New Drug Application was filed to market BiDil, which the Food and Drug Administration did not accept, arguing that the mortality benefit in V-HeFT I was of marginal statistical significance, whereas V-HeFT II suggested that H-ISDN was inferior to angiotensin-converting enzyme inhibitors.
Racial Differences in Heart Failure Outcomes
Emerging data in the 1990s suggested that heart failure in blacks was associated with worse outcomes. An analysis of the Studies of Left Ventricular Dysfunction data revealed that after adjustment for multiple confounders, blacks had higher all-cause mortality, pump failure mortality, and combined death or heart failure hospitalizations. On the basis of these differences, it was conceivable that the response to therapy might differ among races also. Indeed, retrospective analysis of V-HeFT I and II suggested an association between race and drug response. In V-HeFT I, blacks had a survival benefit from H-ISDN (hazard ratio, 0.53; 95% confidence interval, 0.29 to 0.98), whereas whites did not (hazard ratio, 0.88; 95% confidence interval, 0.63 to 1.24). Results from V-HeFT II revealed that although whites had a better survival with enalapril compared with H-ISDN (31% versus 39%; P=0.02), there was no difference with either therapy in blacks (37% versus 36%; P=0.96). With no placebo arm in V-HeFT II, it cannot be determined whether the equivalence of the 2 drugs in blacks was due to a better response to H-ISDN or a worse response to enalapril. It should be noted, however, that these data are limited by the wide confidence intervals around the effect estimates, and that the study was not powered to assess noninferiority among blacks. In addition, these were secondary analyses of observations within clinical trials not designed to address this issue specifically. Hence, these results may merely represent a chance finding.

The results of these retrospective analyses led to the granting of a new methods patent for the use of H-ISDN to treat blacks with heart failure. However, the Food and Drug Administration decided, consistent with levels of evidence typically needed for approval, that these results were inadequate for approving BiDil as a new drug in this population and suggested the need for a prospective trial, leading to the landmark African-American Heart Failure Trial (A-HeFT).

African-American Heart Failure Trial
The A-HeFT enrolled self-identified blacks with class III to IV symptoms and evidence of left ventricular dysfunction within 6 months preceding randomization, including left ventricular ejection fraction of $\leq 35\%$ or $> 45\%$ with a left ventricular internal end-diastolic diameter of $> 2.9 \text{ cm/m}^2$ body surface area (or $> 6.5 \text{ cm}$). Patients were on optimal therapy as tolerated, including angiotensin-converting enzyme inhibitors ($\approx 69\%$) or angiotensin receptor blockers ($\approx 17\%$), $\beta$-blockers ($\approx 74\%$), aldosterone blockade ($\approx 39\%$), digoxin ($\approx 60\%$), and diuretics ($\approx 90\%$). The initial dose of H-ISDN was a single pill containing 37.5 mg hydralazine and 20 mg ISDN taken 3 times a day, uptitrated to the goal of 2 pills 3 times a day, for a total daily dose of 120 mg ISDN and 225 mg hydralazine. The primary outcome was a weighted composite score of death, heart failure hospitalization, and change in quality of life. After enrolling 1050 patients, the trial was terminated early because there was a 43% relative mortality benefit with H-ISDN (10.2% versus 6.2%; P=0.01); there were also significant improvements in each component of the composite score. After reviewing the results and discussing the appropriateness of labeling a drug for blacks only, the Cardiovascular and Renal Drugs Advisory Committee voted unanimously in favor of approving BiDil, making it the first drug ever approved for treatment in a single race.

Race-Based Indication
Not surprisingly, approval of H-ISDN specifically for blacks resulted in dialogs in both the scientific and bioethical arenas. Critics argued that approving a drug only for blacks would prevent its use in other patients who might benefit, and that race is at best a crude marker for underlying genetic and physiological variations. Schwartz pointed out in an editorial on racial profiling in medicine that “[r]ace is a social construct, not a scientific classification …. After 400 years of social disruption, geographic dispersion, and genetic intermingling, there are no alleles that define the black people of North America as a unique population or race.” Interestingly, in the 2000 Census, 7 million people identified themselves as members of >1 race. Other concerns were that this approval was setting a new precedent that would incentivize trials in less diverse populations and result in diversion of resources away from searching for better therapeutics and toward the quest for niche markets. Although several participants in the Food and Drug Administration hearing expressed concern about race-based labeling, only 2 of the 9 members voted against such labeling. Proponents argued that although race is admittedly a poor marker of variation, the benefits of the drug in blacks were too great to ignore.
Race as a Surrogate of Alternate Mechanisms of Benefit

Although the V-HeFT I and II trials primarily assessed the balanced vasodilatory effects of the H-ISDN combination, there was later a shift in the thinking, although not prospectively studied, regarding the likely mechanism of this therapy toward a pathophysiological construct that may (or may not) be more operative in blacks than in whites.22,27 Subsequent data suggested that blacks have differences in nitric oxide (NO) homeostasis and impairments in NO-mediated cardiovascular effects compared with whites.28–32 Nitric oxide is an important mediator of a wide range of processes, including maintenance of vascular tone, myocardial hypertrophy and remodeling, and maintenance of the cellular redox balance.32–37 Because ISDN is an NO donor and hydralazine has antioxidant properties that help prevent NO degradation, it is possible that the NO-mediated effects of H-ISDN could be responsible for the preferential treatment benefit in blacks.

Nitroso-Redox Balance and Heart Failure

Nitric oxide plays a complex role in the maintenance of cardiovascular health and exerts its broad-ranging influence through several mechanisms that rely on a balance between NO and reactive oxygen species, such as superoxide (Figure 2).33 Because heart failure is associated with elevations in reactive oxygen species,38–40 maintenance of the NO–reactive oxygen species balance, called the nitroso-redox balance, may play a central role in the pathophysiology of heart failure. An understanding of the mechanisms of action of NO and the deleterious effects of oxidative stress can help explain some of the fundamental biochemical changes in heart failure.35

One mechanism of NO signaling is accomplished through S-nitrosylation of an assortment of effector proteins. S-nitrosylation occurs when NO is directly transferred to cysteine thiol residues of effector proteins, resulting in activation of a wide range of signaling mechanisms.33,41 Downstream effects of this process include activation of the cardiac ryanodine receptor, which is pivotal in regulating intracellular calcium concentrations and contractility.52 Reactive oxygen species facilitate S-nitrosylation when present at physiological levels but disrupt the process when present at high levels.42,43 When exposed to excessive superoxide, the ryanodine receptor is hyponitrosylated, resulting in altered calcium homeostasis and impaired contractility.43 Inhibiting production of xanthine oxidase–derived superoxide results in
improvement in calcium handling and contractility. Thus, maintenance of the nitroso-redox balance is important in the maintenance of cardiac contractility. In addition, S-nitrosylation plays a role in a number of mechanisms that regulate endothelial function, blood flow, and blood pressure through its effects on smooth muscle Ca\(^{2+}\)-ATPase and other targets.\(^{41,45}\)

A second mechanism of NO action is the activation of guanylyl cyclase and production of intracellular cGMP, an important regulator of many physiological processes, including endothelial function and vasomotor tone. Heart failure is associated with endothelial dysfunction that is at least partially a result of nitroso-redox imbalance.\(^{47-51}\) Increasing heart failure severity is associated with worse endothelial dysfunction.\(^{52,53}\) This impairment is likely both a marker of disease severity and a contributor to heart failure progression through increased afterload and myocardial ischemia.\(^{53-55}\)

Another NO effect is through formation of peroxynitrite (OONO\(^{-}\)), a toxic free radical that forms from the union of superoxide and NO in the setting of high levels of both, eg, heart failure.\(^{46}\) Peroxynitrite has many deleterious effects ranging from induction of myocyte apoptosis to lipid peroxidation, DNA damage, and cell necrosis.\(^{56-58}\) It also irreversibly inhibits the mitochondrial respiratory chain when present in high concentrations.\(^{58,59}\)

Considering the biological actions of NO and the consequences of oxidative stress and nitroso-redox imbalance, it is conceivable that an intervention that increases NO availability or decreases the production of ROS might improve heart failure outcomes.

**Nitric Oxide and Black Race**

Blacks appear to have worse impairment in NO-mediated mechanisms, which may explain the potential, but unproven, race-related differences in heart failure outcomes and responses to therapy.\(^{28,31,32}\) Studies have shown alterations in endothelial function and abnormal vascular responses to a number of pharmacological and physiological stressors that are surrogates of NO activity. Stein et al\(^{31}\) showed that healthy blacks had an attenuated NO-mediated vasodilator response to both methacholine (stimulant of endothelium-dependent NO release) and nitroprusside (endothelium-independent vasodilator/exogenous NO donor) compared with whites. Cardillo et al\(^{28}\) showed that normotensive blacks had blunted vasodilatory responses to both acetylcholine (endothelium-dependent release of NO) and nitroprusside. Androne et al\(^{60}\) assessed vascular function in heart failure patients and showed a significant reduction in endothelium-dependent, flow-mediated vasodilation in blacks compared with whites. Kalinowski et al\(^{60}\) showed important differences in the steady-state balance of NO, superoxide, and peroxynitrite in endothelial cells of blacks. Using nanosensor electrode technology to measure levels of NO, O2\(^{-}\), and OONO\(^{-}\), they found that increased production of superoxide by NAD(P)H-oxidase in blacks results in excess peroxynitrite formation and reduced levels of NO.\(^{30}\) From these data, it is conceivable that therapies aimed at augmenting NO availability might improve outcomes in blacks and could explain the potential, but unproven, racial differences in response to H-ISDN therapy.

**Genetic Heterogeneity and Race**

The Genetic Risk Assessment and Heart Failure (GRAHF) substudy of the A-HeFT assessed how genetic heterogeneity in the endothelial NO synthase might account for the response to H-ISDN.\(^{61}\) In this study, in which 352 patients participated, there were 61 heart failure hospitalizations (17.3%) and 12 deaths (3.4%); H-ISDN was associated with a trend toward improved composite score and quality of life score. When analyzed by genotype, H-ISDN improved the composite score among Glu298 homozygotes but not those with the Asp298 codon, is seen. FDC I/H indicates fixed-dose combination isosorbide dinitrate/hydralazine. Reprinted from McNamara et al\(^{61}\) with permission of the publisher. Copyright © 2009, Elsevier.

![Figure 3. Treatment effects of hydralazine–isosorbide dinitrate (H-ISDN) by nitric oxide synthase-3 polymorphisms. (A) Change in composite score and (B) Change in Quality of Life score.](image-url)

**Figure 3.** Treatment effects of hydralazine–isosorbide dinitrate (H-ISDN) by nitric oxide synthase-3 polymorphisms. (A) Change in composite score and (B) Change in Quality of Life score. Significantly improved composite score and quality of life (QoL) with H-ISDN in patients with the Glu298 codon, but not in those with the Asp298 codon, is seen. FDC I/H indicates fixed-dose combination isosorbide dinitrate/hydralazine. Reprinted from McNamara et al\(^{61}\) with permission of the publisher. Copyright © 2009, Elsevier.
that some white patients might also benefit from H-ISDN. Because of the small number of participants and the low event rate in the GRAHF study, many of these analyses should be considered exploratory and hypothesis generating. Given the multiplicity of post hoc analyses performed in this study, the statistical analyses did not meet the standard criteria for adjudicating the finality of these findings. These need to be systematically replicated in other populations.

Hydralazine–Isosorbide Dinitrate in White Heart Failure Patients

Although A-HeFT proved the effectiveness of H-ISDN in self-identified blacks, it did not show H-ISDN to be ineffective in other populations. Although white patients did not appear to derive a mortality benefit in the retrospective analysis of V-HeFT I,20 these data are from an era in which optimal medical therapy was radically different. Rather than reviewing individual subgroup findings, we should assess treatment-by-subgroup interaction analyses, which were not provided in these investigations. These secondary analyses may represent a chance finding. In addition, despite the lack of a mortality benefit, there was an improvement in ejection fraction and exercise tolerance in whites treated with H-ISDN in V-HeFT II20; in fact, these improvements were greater with H-ISDN than with enalapril.20 Finally, there was no difference in the number of hospitalizations for heart failure or all-cause hospitalization between whites and blacks in either trial.20 Thus, the role of H-ISDN in nonblack patients with heart failure remains uncertain.

Sex and Outcomes in the African-American Heart Failure Trial

Women with heart failure are underrepresented in many clinical trials.63–66 Importantly, V-HeFT I and II included only men.54,55 In A-HeFT, women made up nearly 40% of the study.22 In a post hoc analysis of A-HeFT,66 women treated with H-ISDN appeared to have a survival benefit (hazard ratio, 0.33; 95% confidence interval, 0.16 to 0.71), whereas men did not (hazard ratio, 0.79; 95% confidence interval, 0.46 to 1.35). However, there was no significant treatment interaction by sex ($P=0.470$), and no differences were seen in quality of life or heart failure hospitalizations. Moreover, there were several differences in the A-HeFT trial between the sexes, with women at baseline having lower hemoglobin and creatinine levels, less renal insufficiency, higher body mass index and systolic blood pressure, and more diabetes mellitus. Thus, these analyses are at best exploratory and do not prove a differential sex response to H-ISDN.

Role in Acute Decompensated Heart Failure

Acute decompensated heart failure is associated with oxidative stress67–69 and disrupted NO signaling,70 affecting ventricular and vascular function related to hemodynamic status.71,72 (Figure 4). There are multiple theoretical benefits of H-ISDN in acute decompensated heart failure. It can help restore NO balance,73,74 can modulate systemic hemodynamics in acute decompensated heart failure patients presenting with elevated blood pressure,75–77 and provides seamless therapy spanning inpatient to outpatient care.78 In-hospital initiation of H-ISDN has been associated with lower all-cause mortality78 and improved hemodynamics,79 suggesting a need for prospectively assessing this therapy in acute decompensated heart failure.

Pulmonary Hypertension and Right Ventricular Function

Pulmonary hypertension is common in heart failure80–83 and affects right ventricular function,84,85 both of which, in turn, affect heart failure prognosis.81,86–91 Elevated pulmonary vascular resistance in heart failure is a result of dysregulation of smooth muscle tone and remodeling of the pulmonary vasculature.92 These abnormalities are partially attributed to pulmonary vascular endothelial dysfunction resulting from impaired NO availability and increased endothelin expression.93 In the pulmonary vasculature, NO plays an important role in determining both basal vascular tone and dilation to endothelium-dependent stimuli.93–95 Studies have shown that NO-dependent pulmonary vasodilation is impaired in heart failure,96–98 suggesting a potential role for agents that improve NO bioavailability. In systolic heart failure, H-ISDN
had marked short-term effects on pulmonary vascular resistance and result in more reduction than either agent alone over 3 months. In short-term studies, a decrease in pulmonary artery pressures in response to vasodilators is associated with improved right ventricular function. Although H-ISDN improves left ventricular ejection fraction, the large mortality benefit observed in A-HeFT relative to the modest 2.8-unit improvement in left ventricular ejection fraction raises the possibility of alternative explanations, including potential effects on right ventricular function. The responses of pulmonary artery pressures and right ventricular function to H-ISDN, however, have never been assessed.

Synergistic Effects Between Hydralazine and Isosorbide Dinitrate

It should be noted that, although the data suggest benefit with the H-ISDN combination in heart failure, the synergistic effects of hydralazine and ISDN on outcome benefit, as opposed to hemodynamic modulation, have never been tested or established. The rationale that hydralazine potentiates ISDN through an antioxidant effect has been hypothesized on the basis of observations, without examination of outcomes with each drug individually compared with the combination. Thus, the more rigorous criterion for defining the superiority of combination therapy, ie, demonstrating that the combination is superior to either constituent agent alone, has never been studied with respect to H-ISDN therapy in heart failure.

Use of Hydralazine–Isosorbide Dinitrate in Clinical Practice

The heart failure management guidelines give a Class I recommendation for the use of H-ISDN in self-identified black patients with symptomatic systolic heart failure on optimal therapy. Use of H-ISDN in addition to optimal therapy is a Class IIA recommendation for nonblack patients and a Class IIB recommendation for those intolerant of angiotensin-converting enzyme inhibition or angiotensin receptor blocker therapy. However, a recent study showed that only 7.3% of eligible black outpatients are actually receiving H-ISDN. In a registry of hospitalized heart failure patients, only 4.5% of blacks and 2.6% of whites were discharged home on H-ISDN. The reasons for this trend are multiple. Despite the mean systolic blood pressure of 127.2 ± 17.4 mm Hg in the treatment arm of A-HeFT, almost 30% of the patients complained of dizziness with H-ISDN use. Is it possible that dizziness and other side effects are more common in real-life heart failure patients who, in general, tend to be older, to have more comorbidities, and to take more medications. A large pill burden related to thrice-a-day dosing could further deter some patients and result in suboptimal compliance. In addition, in the practice setting, titration of the combination therapy to maximum doses, perhaps more slowly than in the trial setting, may impose practical logistic barriers for both patients and physicians. Many heart failure patients have erectile dysfunction and wish to use medications like sildenafil that limit the concomitant use of nitrate therapy. In the case of BiDil specifically, cost may be an important consideration. Regardless of all these issues, there remains a huge gap between guideline recommendations and clinical use of H-ISDN.

Generic Versus Combination Hydralazine–Isosorbide Dinitrate Preparation

There has been no head-to-head comparison of the generic and combination H-ISDN (BiDil) preparations. Interestingly, all 3 trials, VHeFT I, VHeFT II, and A-HeFT, used different H-ISDN preparations. Both V-HeFT I and V-HeFT II used Isordil, an ISDN tablet; V-HeFT I used 37.5-mg hydralazine capsules; V-HeFT II used 37.5-mg hydralazine tablets; and A-HeFT used the combination pill. To investigate the pharmacokinetic differences between these formulations, Tam et al performed a bioequivalence study in healthy volunteers 18 to 40 years of age. All subjects received reference H-ISDN solution (37.5 mg/10 mg) orally, and slow acetylators (59% of the study population, n = 55) were identified and randomized to receive a single oral dose of H-ISDN (37.5 mg/10 mg) from a hydralazine capsule plus an ISDN tablet, a hydralazine tablet plus an ISDN tablet, or fixed-dose combination. The maximum concentrations (Cmax) and areas under the curve were similar for ISDN preparations. The Cmax values were 65.9 ± 53.9, 28.2 ± 15.8, and 51.5 ± 54.3 ng/mL, and the area under the curve values were 32.6 ± 13.4, 23.3 ± 15.1, and 32.6 ± 18.5 ng · h/mL for hydralazine and the V-HeFT I, V-HeFT II, and A-HeFT formulations, respectively. In addition, Cmax and area under the curve normalized to body weight and Cmax and area under the curve ratios were compared. The 3 formulations were not bioequivalent, with the hydralazine concentrations of the tablet form being lower than in the capsule or the combination pill. Whether these differences affected clinical outcomes is not known. Considering the study population for the bioequivalence study consisted of normal volunteers, and that there are no head-to-head outcome trials, it is difficult to draw any specific conclusions regarding generic versus the combination preparation. Because BiDil is also a thrice-a-day regimen, there is a general feeling that generic therapy may be a cheaper alternative without any compliance downside. Indeed, the American College of Cardiology and the American Heart Association heart failure guidelines recommend using “a combination of hydralazine and nitrates.” If a once- or twice-a-day combination preparation becomes available, it may have a potential benefit in terms of both pharmacokinetics and compliance compared with the thrice-a-day preparations.

Conclusions

There remain many promises and unanswered questions regarding H-ISDN therapy in heart failure, ranging from efficacy and mechanism of action to defining optimal patient population and timing of therapy. Considering the persistent suboptimal outcomes and a significant opportunity for improvement in therapy for these patients, further research related to the use of H-ISDN in heart failure seems warranted.

Disclosures

None.
References


Key Words: heart failure | hydralazine | isosorbide dintrate | nitric oxide
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_Circulation_. 2011;123:2414-2422
doi: 10.1161/CIRCULATIONAHA.110.012781
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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