Review Article

Hydralazine and Isosorbide Dinitrate in Heart Failure: From Evidence to Clinical Practice

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Abstract

The treatment of heart failure (HF) with reduced ejection fraction (HFrEF) has evolved significantly over time, with the emergence of various pharmacotherapies targeting different pathophysiological pathways. While neurohumoral antagonists like angiotensin converting enzyme (ACE) inhibitors and beta-blockers have become first-line therapies, the main paradigm shift occurred with medications with vasodilatory effects, including the combination of hydralazine and isosorbide dinitrate (H-ISDN). Although the role of H-ISDN has been overshadowed over time, it remains significant, particularly in certain populations.

With proven hemodynamic benefits in HF by reducing both preload and afterload, H-ISDN was initially tested in the 1980s in the Vasodilator Heart Failure Trial I (V-HeFT I), with promising results. Nevertheless, subsequent trials like V-HeFT II indicated that ACE inhibitors were superior to H-ISDN in reducing mortality.

Later, post-hoc analyses of V-HeFT trials suggested a potential benefit of H-ISDN among black patients. This prompted the African-American Heart Failure trial (A-HeFT), which demonstrated a significant reduction in mortality with H-ISDN in black patients with HFrEF, who were under standard HF treatment including ACE inhibitors.

Current guidelines recommend H-ISDN in black patients with HFrEF who remain symptomatic despite optimized therapy or in those who cannot tolerate ACE inhibitors or angiotensin receptor blockers. However, the use of H-ISDN in other racial groups and in certain clinical scenarios like decompensated HF or renal failure remains less clear due to limited evidence. In this article, we review the history, pharmacological mechanisms, and clinical evidence for the H-ISDN in the treatment of HFrEF.

Introduction

Throughout the years, the treatment of heart failure (HF) has changed with the discovery of new pathophysiology. From the 1950s until the 1960s, the cardiorenal concept prevailed in HF,[1] so diuretics and digitalis were used on the premise that they would increase water and salt excretion and improve myocardial contractility, leading to better heart function.[2] From the 1970s to the 1980s, however, it was discovered that ventricular ejection depended on the resistance to ejection of blood,[3] which motivated the use of drugs acting on the hemodynamics of the cardiovascular system, the vasodilating drugs.

The primary representation of these drugs was the combination of hydralazine (H) and nitrates. Despite their continued recommendation in HF treatment guidelines, they have often been overlooked and forgotten. In this article, we review the current evidence, mechanisms, and recommendations for the combination of H and isosorbide dinitrate (ISDN) (H-ISDN).

History

The neurohumoral paradigm of HF was highly accepted by the scientific community, promoting angiotensin-converting enzyme inhibitors (ACEi), beta receptor blockers (BB), mineralocorticoid receptor antagonists (MRA), angiotensin receptor blockers (ARBs), and angiotensin receptor/neprilysin inhibitors (ARNi) to the first line of treatment of HF with reduced ejection fraction (HFrEF).[4] This acceptance was due to large clinical trials consistently proving their efficacy in reducing mortality. The initial trials with ACEi were the CONSENSUS[5] (1987) and the SOLVD[6] (1991) trials - both confirming enalapril's effectiveness when compared to placebo. Later, the RALES[7] (1999) - with spironolactone, and the EMPHASIS-HF[8] (2011) - with eplerenone, consolidated the use of MRA in clinical practice. For BB, CIBIS-II[9] (1999), MERIT-HF[10] (1999), and COPERNICUS[11] (2001) confirmed the benefit of bisoprolol, metoprolol succinate, and carvedilol, respectively, in patients with HF.

Despite the currently accepted neurohumoral concept, the idea of using vasodilators in HF began in the 1970s with intravenous sodium nitroprusside, which was shown to reduce systemic vascular resistance, decreasing left ventricular diastolic filling pressures, and improving cardiac output in patients with HF.[12] These hemodynamic benefits led to the search for oral agents for patients with chronic HF. In 1974, Franciosa et al.[13] tested the use of ISDN oral in twelve 12 patients with HF, showing a reduction of the left ventricular end-diastolic pressure (LVEDP).[13] Three years later, Franciosa and Cohn studied the effect of H in 16 patients with HF, demonstrating a reduction in systemic vascular resistance similar to that obtained with nitroprusside, coupled with a more substantial increase in cardiac index.[14] In 1977, Massie et al.[15] then tested H-ISDN in 12 patients with severe chronic HF. The authors demonstrated that H-ISDN effectively reduced both ventricular filling pressures and systemic vascular resistance, yielding a hemodynamic benefit that was not attained when either H or ISDN was

Keywords

Heart Failure; Race;Hydralazine; Isosorbide Dinitrate.

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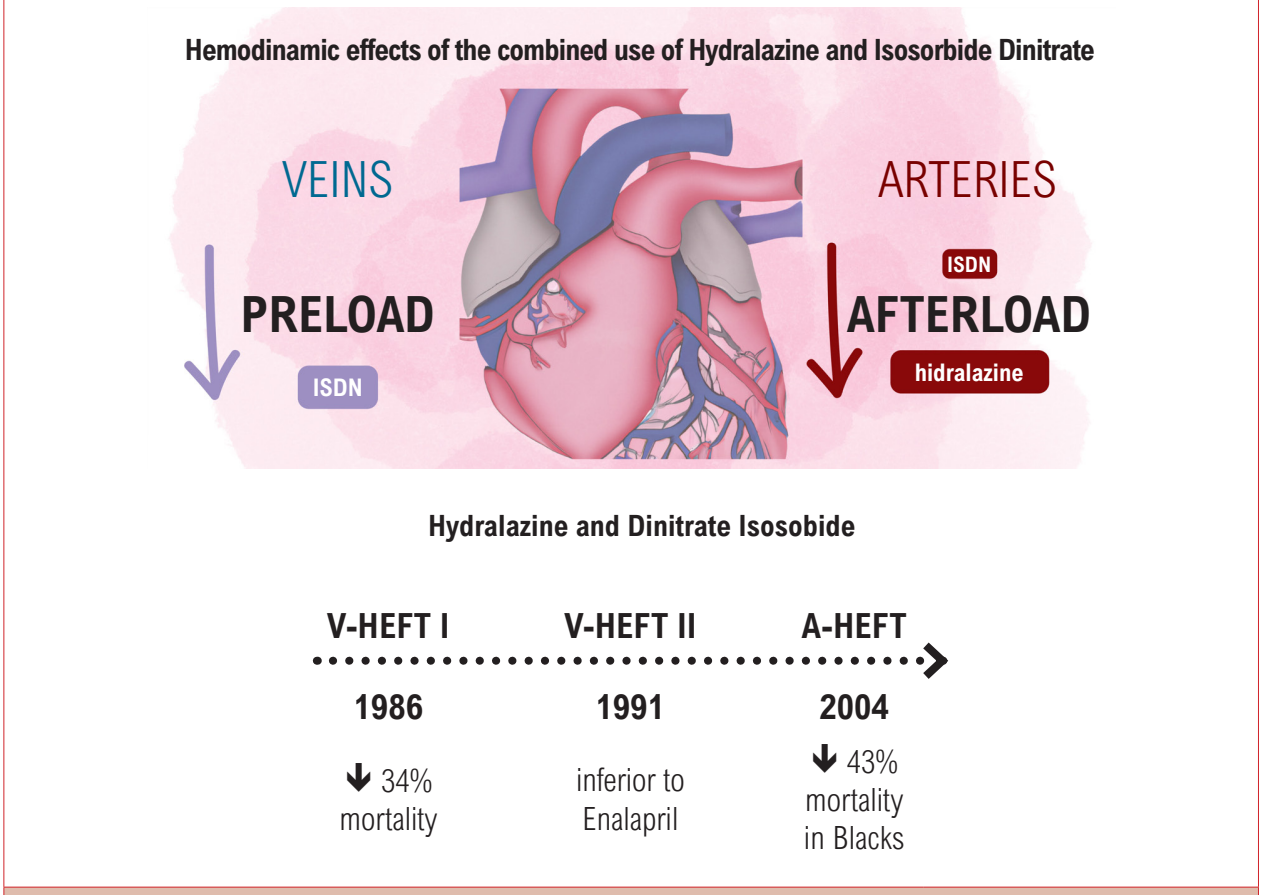
Central Illustration: Hydralazine and Isosorbide Dinitrate in Heart Failure: From Evidence to Clinical Practice



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Hydralazine and isosorbide dinitrate combined has favorable hemodynamic effects in heart failure. Its clinical efficacy was tested in three main clinical trials: the V-HeFT I in 1986 showed it reduces mortality against placebo; the V-HeFT II in 1991 showed to be inferior to enalapril; and the A-HeFT in 2004 showed it reduces mortality in blacks when added to standard HF therapy. Source: Created by the authors.

administered alone.[15] Such studies motivated the deeper search for the efficacy of the H-ISDN combination.[16] Originally, H was used in the treatment of hypertension,[14] meanwhile, ISDN was employed mainly in angina pectoris.[16] The idea behind associating them was to create a synergistic effect between an arterial vasodilator (H), which would reduce afterload, and a venous dilator (ISDN), reducing preload.[15]

In 1986, a large randomized trial known as the Vasodilator Heart Failure Trial I (V-HeFT I) was conducted to assess the effect of H-ISDN compared to placebo. The trial demonstrated a significant reduction in mortality rates among the group that received H-ISDN.[17]

Due to the growing use of highly effective neurohumoral antagonists in the nineties, the same group that conducted the V-HeFT I decided to make a comparison between ACEis and H-ISDN, creating the V-HeFT II.[17,18] In this trial, patients with chronic HF were randomly assigned to receive enalapril or H-ISDN. The results revealed a significant reduction in mortality in the enalapril group compared to H-ISDN.[18] Such evidence strengthened the use of ACEi over H-ISDN in clinical practice, relegating the latter to a secondary treatment option for HF.[4,19]

In 1987, Jay Cohn, author of the V-HeFT studies, submitted to the Food and Drug Administration (FDA) a patent for a H-ISDN pill, which led to the production of "BiDil", a single-pill containing H and ISDN.[20,21] Although the patent was approved, marketing of BiDil was denied by the FDA based on the results of V-HeFT II, which suggested that H-ISDN was inferior to ACEi.[22]

Later, after a post hoc analysis of V-HeFT trials suggesting that H-ISDN could be particularly beneficial among blacks,[23] the company NitroMed applied to the FDA for a "race-specific" patent on BiDil. The FDA asserted the approval of BiDil if there was a confirmatory trial of the drug in the treatment of HF in African Americans, which led NitroMed to promote the African-American Heart Failure Trial (A-HeFT).[20] The A-HeFT trial, published in 2004,[24,25] randomized African-American patients with HF to receive either H-ISDN or placebo in addition to optimized HF

treatment, including ACEi. The trial was ended prematurely, due to a clear benefit of H-ISDN on mortality.[25]

After analyzing A-HeFT results, the FDA approved, in 2005, the use of Bidil in the treatment of HF in black patients.[22] In parallel, guidelines for the management of HF made specific recommendations for H-ISDN, which consolidated its use in clinical practice.[4,19]

Timeline of the studies mentioned is described in Figure 1.

Pharmacodynamics

Hydralazine

Hydralazine is a direct vasodilator of arterioles, commonly used to treat refractory arterial hypertension, hypertensive emergencies, pre-eclampsia, and, more recently, HFrEF, associated with ISDN.[26,27]

The mechanism of action of H requires further elucidation. Evidence suggests that it may involve intracellular calcium homeostasis, either by inhibiting the release of calcium by the endoplasmic reticulum of vascular smooth muscle cells or by inhibiting the phosphorylation of myosin in these cells.[26,28,29] This leads to muscle relaxation, resulting in arterial vasodilation, and therefore, lower peripheral vascular resistance, reducing afterload. On the other hand, it stimulates the release of epinephrine and norepinephrine through baroreceptors, increasing venous return and cardiac output.[17,30] This compensatory stimulation of the sympathetic nervous system causes one of its main side effects: reflex tachycardia, which can be mitigated by the association with BB.[26,31,32] Furthermore, it has been suggested that H has antioxidant effects, inhibiting the formation of reactive oxygen species such as superoxide, which interferes with nitric oxide (NO) metabolism.

Isosorbide dinitrate

ISDN is a direct vasodilator, affecting both arterial and venous vessels, but its primary action is on the venous component, which reduces preload and LVEDP. This organic nitrate acts by stimulating NO signaling, commonly used for treating angina pectoris, myocardial infarction, and congestive HF.[33-35]

NO exists in three isoforms (induced, neuronal, and endothelial) and is synthesized from L-arginine by the enzyme NO synthase (NOs), a process triggered by a variety of physical and chemical stimuli upon interaction with specific agonists.[36,37] Then, the endothelial NO diffuses to adjacent smooth muscle cells, where it binds to the soluble guanylate cyclase enzyme, leading to the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP), activating multiple kinases. This results in muscle relaxation and vasodilation through multiple mechanisms, reflecting an intimate relationship between NO and vascular homeostasis.[38-41] The pharmacodynamics of H-ISDN are summarized in Figure 2.

The mechanism of vasodilation induced by NO appears to be diminished in black patients due to lower bioavailability of NO, combined with a greater imbalance between NO and superoxides. Increasing bioavailability of NO could account for why these patients may have greater benefits from H-ISDN therapy, although this remains unproven.[25,42-44]

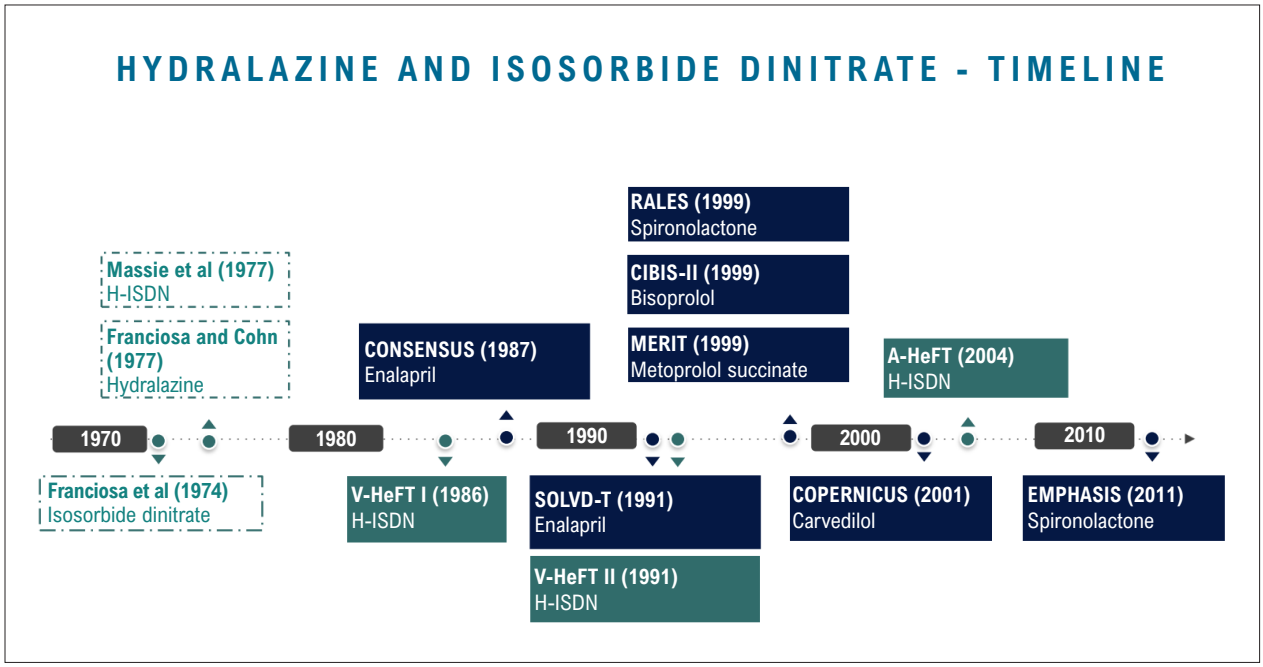

Figure 1 – *Timeline of evidence supporting the use of hydralazine and isosorbide dinitrate in heart failure. Source: Created by the authors; in blue: trials related to the neurohumoral paradigm of heart failure; in green: trials related to the hemodynamic theory of heart failure; in green dotted lines: early trials that tested the hypothesis of vasodilators in heart failure, but not with mortality as their primary outcome.*

The possible synergism between hydralazine and isosorbide dinitrate in heart failure

Different mechanisms have been proposed to explain a potential synergistic effect between H and ISDN. The combination of ISDN with H has favorable hemodynamic effects that are central to the management of HFrEF, as it contributes to reducing both preload and afterload (Figure 3, Central Illustration).[45]

Moreover, NO influences the signaling of several molecules, particularly in cysteine residues, through a process called S-nitrosylation, which affects cardiac contractility. While superoxides facilitate this process, high concentrations of superoxides have the opposite effect, inhibiting this signaling mechanism and impairing the NO pathway. In HF, there is an increase in superoxide production, which affects the NO synthesis, suggesting the role of nitroso-redox signaling in this disease.[43–44] Hydralazine possesses antioxidant properties that inhibit the production of superoxides. This enhances and prolongs the action of ISDN by attenuating tolerance to this medication and improving the bioavailability of NO in the blood vessels (Figure 4).[46,47]

Evidence from preclinical science

In the early 1990s, studies in animals were developed to understand the role of H and nitrates in HF. After clinical studies had shown that this combination was beneficial,[45,48,49] Bauer and Fung investigated the interaction between H and organic nitrates.[50] They conducted an *in vitro* and *in vivo* study using HF rat models to determine whether H could preserve the favorable preload effects of nitroglycerin, an organic nitrate just like isosorbide.[17,48]

In the *in vivo* experiment, two groups of rats were allocated to receive either nitroglycerin alone or a combination of nitroglycerine plus H. The first group showed initial reductions in LVEDP, but no significant changes in left ventricular end-systolic pressure (LVESP). The LVEDP later returned to near-baseline levels, indicating the development of drug tolerance. The second group exhibited a sustained decrease in both LVESP and LVEDP following the administration of H bolus, persisting for an extended duration. This suggests that the combination mitigates nitroglycerin tolerance.

In the *in vitro* experiment, isolated rat aortic rings were incubated with one of three solutions: a control solution (Krebs-bicarbonate), nitroglycerin alone, or a combination of nitroglycerin plus H. In this *in vitro* experiment, pre-incubation with nitroglycerin induced vascular tolerance to this drug, which was not affected by the presence of H. Because of that, a synergistic effect between hydralazine and nitrates does not appear to result from local interaction.

Nitrate tolerance may result from systemic compensatory changes, and the *in vivo* experiment suggests that H preserves the preload effects of nitroglycerin. Moreover, the interaction between H and nitrates cannot be explained by their pharmacokinetics, since there were no changes in the metabolite's plasma concentration. Another hypothesis the preservation of renal

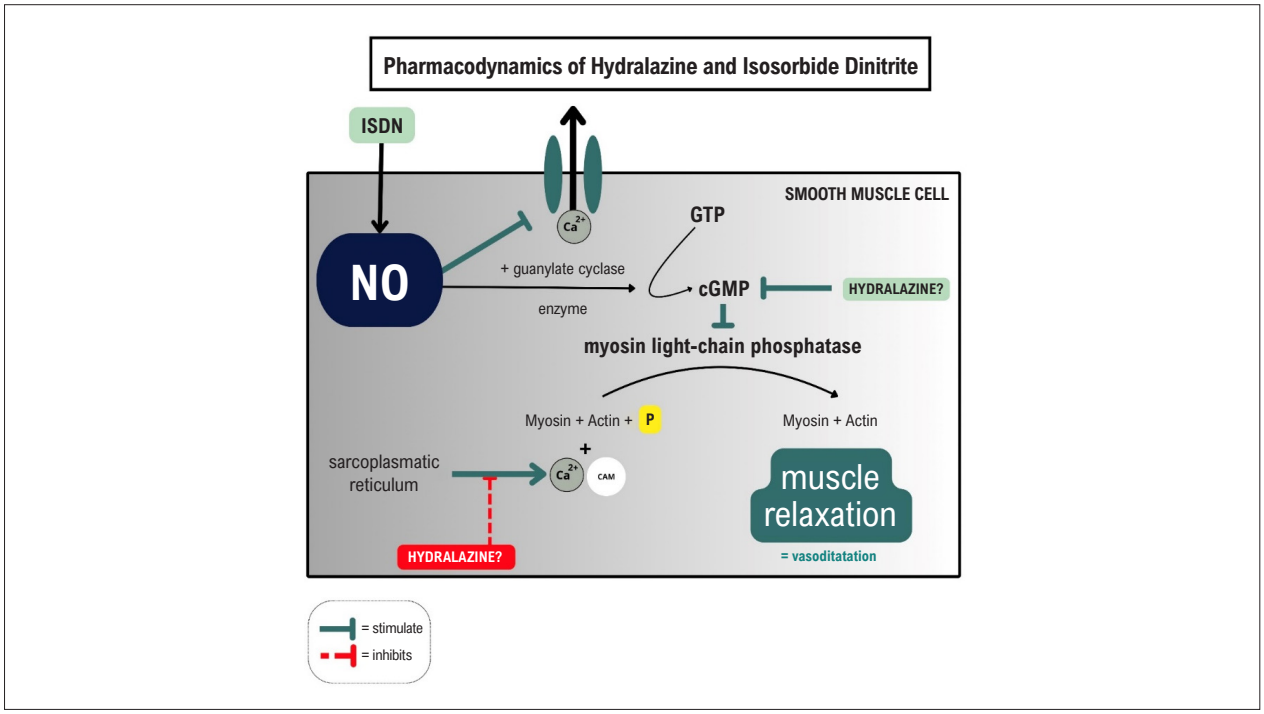

Figure 2 – *Pharmacodynamics of hydralazine and isosorbide dinitrate leading to vasodilation. Source: Created by the authors. ISDN: isosorbide dinitrate; NO: nitric oxide; GTP: guanosine triphosphate; cGMP: cyclic guanosine monophosphate; P:phosphate; Ca2+: calcium; CAM: calmodulin; ISDN is an organic nitrate converted to NO in the smooth muscle cell. NO enhances calcium removal from cytosol via calcium pumps. Beyond that, along with soluble guanylate cyclase, NO catalyzes the conversion of GTP into cGMP, which acts on intracellular signaling of several kinases, resulting in calcium decrease and stimulation of myosin light-chain phosphatase enzyme, that dephosphorylates mysosin-actin filaments. Without calcium and phosphate, muscle contraction is inhibited, leading to vasodilation of the vessels. The way through which hydralazine contributes to this is not well established, but evidence suggests it's related to stimulation of cGMP and myosin phosphatase and inhibition of calcium release from the sarcoplasmic reticulum.*

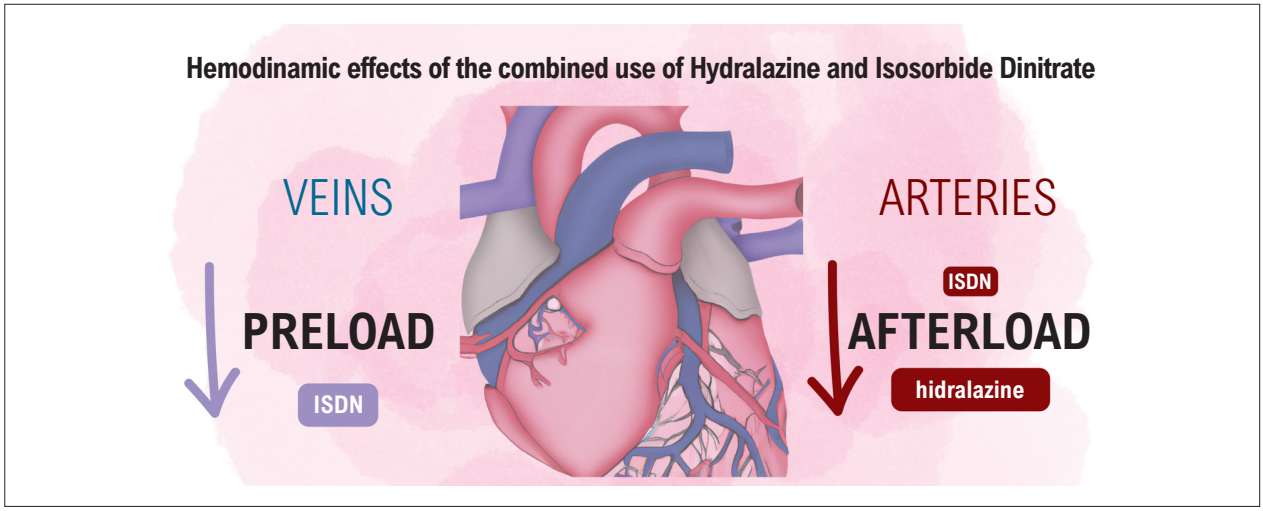

Figure 3 – *Pharmacodynamics of hydralazine and isosorbide dinitrate leading to vasodilation. Source: Created by the authors. ISDN: isosorbide dinitrate; NO: nitric oxide; GTP: guanosine triphosphate; cGMP: cyclic guanosine monophosphate; P:phosphate; Ca2+: calcium; CAM: calmodulin; ISDN is an organic nitrate converted to NO in the smooth muscle cell. NO enhances calcium removal from cytosol via calcium pumps. Beyond that, along with soluble guanylate cyclase, NO catalyzes the conversion of GTP into cGMP, which acts on intracellular signaling of several kinases, resulting in calcium decrease and stimulation of myosin light-chain phosphatase enzyme, that dephosphorylates mysosin-actin filaments. Without calcium and phosphate, muscle contraction is inhibited, leading to vasodilation of the vessels. The way through which hydralazine contributes to this is not well established, but evidence suggests it's related to stimulation of cGMP and myosin phosphatase and inhibition of calcium release from the sarcoplasmic reticulum.*

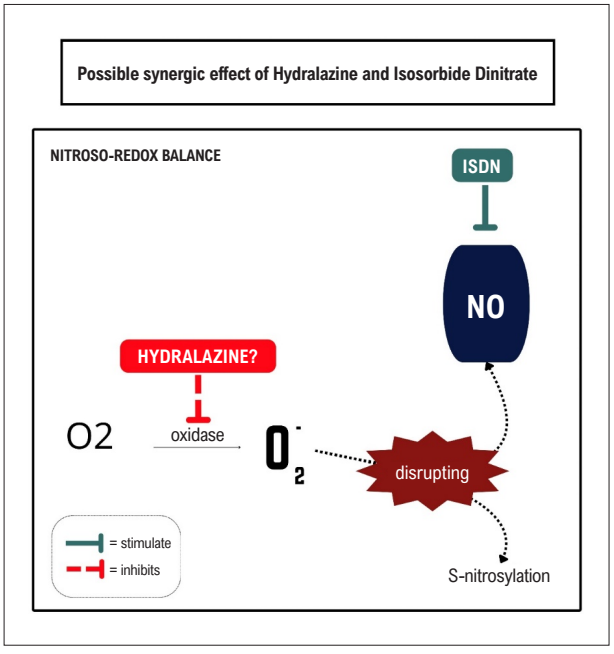

Figure 4 – Possible synergic effect of hydralazine and isosorbide dinitrate. Source: Created by the authors. ISDN: isosorbide dinitrate; NO: nitric oxide; O-2: superoxide. Enzymes called oxidases convert O2 to O-2, which disrupts the NO pathway and S-nitrosylation. A possible synergic effect is proposed for the combined use of ISDN and Hydralazine. ISDN stimulates NO pathway while Hydralazine may inhibit oxidases, thus preventing the impairment of NO pathway and enhancing its action.

blood flow due to the addition of H, which modulates the activation of renal neurohormonal factors like sympathetic and renin-angiotensin-aldosterone systems.[49]

Wilson et al.,[51] in 2009, investigated the influence of a fixed dose of H-ISDN in Left Ventricular hypertrophy (LVH) and myocardial remodeling in hypertension-induced diastolic HF. Two groups of mice were divided to receive either saline or an aldosterone infusion. Adding H-ISDN was able to prevent hypertension, but it did not revert the LVH induced by aldosterone, since the left ventricular (LV) weight/body weight ratio remained increased. Likewise, H-ISDN did not induce any changes in the perivascular and interstitial fibrosis caused by aldosterone. On the other hand, H-ISDN improved the diastolic function, as shown by a decrease in the mitral A/E ratio, indicating a more compliant LV.

Animal studies also showed potential beneficial effects of H-ISDN in vascular inflammation and exercise capacity. It was shown that H-ISDN reduces the levels of cell adhesion molecules, indicating a reduction in vascular inflammation. Exercise capacity, as measured by running distance, also increased, possibly due to improvement of diastolic function and ventricular-arterial coupling, as a result of lower vascular inflammation and stiffness. These data suggest that H-ISDN improves diastolic function and exercise capacity, possibly through vascular-ventricular interconnections that impact LV filling and ejection rates, but not because it affects myocardial remodeling or fibrosis.

Evidence from clinical trials in heart failure

The effect of the combination of H-ISDN on HF outcomes was tested in the three main clinical trials: V-HeFT I, V-HeFT II, and A-HeFT (Central Figure).

The V-HeFT I trial tested the concept that adding a vasodilator therapy could improve hemodynamics in HF.[17] The authors recruited 642 men with HF in 11 Veterans

Administration (VA) hospitals in the United States and randomized them to receive H-ISDN, prazosin, or placebo. Inclusion criteria required cardiac dilatation and/or low ejection fraction (below 45%) by radionuclide angiography, associated with low functional capacity confirmed by peak VO2 below 25 mL/kg/min. H-ISDN resulted in a 34% lower mortality compared to placebo ($p<0.028$) in the first two years of follow-up, although for the entire follow-up period (average, 2.3 years), the reduction in mortality with H-ISDN had borderline statistical significance ($p\sim0.05$). In addition, H-ISDN improved the LV ejection fraction (LVEF) by 4.3% ($p<0.001$) in one year compared to placebo.

Later, the V-HeFT II trial randomized 804 patients with HF and the same inclusion criteria as the V-HeFT I to receive H-ISDN or enalapril.[18] In the V-HeFT II trial, mortality at two years of follow-up was significantly lower with enalapril (18%), compared with H-ISDN (25%, $p=0.016$), although this was not statistically significant ($p=0.08$) for the entire follow-up period (average, 2.5 years). The lower mortality in the enalapril group was driven by lower sudden cardiac death. Despite the higher mortality, H-ISDN resulted in significantly greater enhancements in LVEF and functional capacity than enalapril.

A smaller trial, the Hy-C, showed lower mortality with an ACEi compared with H in patients with advanced HF.[52] A hemodynamic protocol initially used nitroprusside to obtain specific pulmonary artery catheter measurements. Patients were then transitioned to either captopril or hydralazine, but both groups could receive isosorbide dinitrate.

A post-hoc analysis revealed varying responses based on race in the V-HeFT trials.[23] In V-HeFT I, where blacks constituted approximately one-fourth of the sample, H-ISDN demonstrated significantly lower mortality compared with placebo/prazosin for blacks (hazard ratio [HR] 0.53; 95% confidence interval [CI] 0.29 to 0.98), while no significant difference was observed among whites (HR 0.88; 95% CI 0.63 to 1.24). Conversely, in V-HeFT II, enalapril showed a significant reduction in mortality compared to H-ISDN in whites (31 vs. 39%, $p=0.02$), but there was no difference between the groups among black patients (37 vs. 37%, $p=0.96$).

Because of this race-related response, suggesting that blacks with HF may have a more favorable response to H-ISDN, a trial was designed to test the effect of adding H-ISDN in blacks. The A-HeFT trial randomized 1050 blacks with HFrEF, and NYHA class III or IV, to receive H-ISDN vs placebo added to standard therapy, which included ACEi/ARB, betablockers, and spironolactone.[25] The study was terminated early due to significantly lower mortality in the H-ISDN group compared to placebo (HR 0.57, $p=0.01$) over a mean follow-up of 10 months. H-ISDN also reduced the risk of hospitalization for HF and improved quality of life, resulting in significantly better results in the primary endpoint compared to placebo.

Recently, an open-label, single-center trial tested the addition of H to standard therapy in 408 patients with decompensated HF, left ventricular ejection fraction (LVEF) <35% and mitral regurgitation.[53] After a mean follow-up of 3.5 years, H significantly reduced the combined endpoint of cardiovascular death and HF hospitalization (HR 0.613, 95% CI 0.427–0.877, $p<0.001$), compared with controls. In this study, only 94 (46 in the hydralazine and 48 in the control group) of patients used ISDN. The trial's population, its single-center and open-label design impose limitations on the ability to draw conclusive insights on the role of isolated H in HF.

The main results of outcome-driven trials with H-ISDN in HF are summarized in Table 1.

Clinical practice

National and international guidelines provide similar recommendations, with slight differences, for using H-ISDN in patients with HFrEF (Table 2). The AHA/ACC/HFSA guidelines (2022) adopts IA recommendation for patients self-identified as African American, in NYHA functional class III-IV and HFrEF who are receiving optimized therapy to improve symptoms and reduce morbidity and mortality.[19] The ESC guidelines (2021) adopts IIA recommendation for NYHA class II-IV patients self-declared as black with LVEF ≤35% (or <45% combined with LV dilation), despite the use of ACEIs (or ARNI), a BB, and an ARM, to reduce the risk of hospitalization due to HF or death.[4] And the Brazilian guidelines for chronic and acute HF (2018) adopts IB recommendation for self-declared black patients with symptomatic systolic dysfunction in functional class III-IV (NYHA), despite optimized therapy.[54]

However, the benefit of using H-ISDN in HF patients from other ethnic origins is less clear. While there was no definitive proof of reduced mortality in white patients with the use of H-ISDN in previous trials, there was an improvement in ejection fraction and exercise tolerance. Currently, AHA/ACC/HFSA and ESC guidelines recommend that H-ISDN can be considered (with limited data) in patients with HFrEF with current or previous symptoms, who cannot receive first-line agents such as ACEI/ ARB/ARNI due to drug intolerance or renal failure (Table 2).

An important point for clinical practice is the formulation used and its titration to the effective dose. In the V-HeFT studies, the drugs were administered in separate pills (start dose of 37.5 mg of H and 20 mg of ISDN, in four daily doses) with a target dose of 300 mg of H and 160 mg of ISDN. In the A-HeFT study, the combination was administered in a single pill (BiDil®, containing 37.5 mg of H + 20 mg of ISDN, in three daily doses), with a target dose of 225 mg of H and 120 mg of ISDN. In Brazil, the presentations of H are 25 or 50 mg tablets, while those of ISDN vary from 5 or 10 mg tablets (taken every 6-8 hours). For these reasons, the doses taken to reach the target would be 3 to 4 daily doses, i.e., a greater number of tablets.

Although the H-ISDN combination has been recommended by current guidelines, insufficient prescription has been observed in daily practice. In the United States, a study showed that only 7.8% of black patients with indications for using H-ISDN were receiving this treatment on an outpatient basis.[55] After a hospitalization for HF, only 4.5% of black patients and 2.6% of white patients were prescribed H-ISDN.[56] In another study, using a database with 26,439 patients aged 18-64 years with recently diagnosed HF, the adherence to long-term treatment with H-ISDN was the lowest of five classes of drugs recommended by guidelines for treatment of HFrEF (ACEi/ ARB; BB; MRA and H-ISDN).[57] Some reasons for this lack of adherence to guidelines may be linked to hypotension and dizziness associated with target doses of H-ISDN, in addition to the amount of pills and a regimen of three to four daily intakes.

Table 1 – Hard-endpoint-driven clinical trials testing the Hydralazine and Isosorbide Dinitrate in heart failure

Study	Year of publication	Population	N	Baseline HF treatment	Intervention	Comparator	Main result	Comments
V-HEFT I[17]	1986	Men, VO2p < 25 mL/kg/min + cardiac dilatation* or LVEF < 45%†	642	Vasodilators: 37%‡ SL nitroglycerin: 20%	H-ISDN Target dose: H 75mg qid + ISDN 40 mg qid Average daily dose: H 270 mg, ISDN 136 mg	Prazosin Target dose: 5 mg qid Average daily dose: 19 mg or Placebo	Lower 2-year mortality with H-ISDN (26%) vs placebo (34%, p<0.028)	
V-HEFT II[18]	1991	Men, VO2p < 25 mL/kg/min + cardiac dilatation* or LVEF < 45%†	804	Vasodilators, including ACEi, were withdrawn during the study, while digoxin and diuretics were "optimized"	H-ISDN Target dose: H 75mg qid + ISDN 40 mg qid Average daily dose: H 199 mg, ISDN 100 mg	Enalapril Target dose: 10 mg bid Average daily dose: 15 mg	Lower 2-year mortality with enalapril (18%) vs H-ISDN (25%, p 0.016).	H-ISDN resulted in higher improvement in LVEF and VO2p than enalapril
Hy-C[52]	1992	Advanced HF referred to cardiac Tx, NYHA III/IV, PCWP ≥20 mmHg and/or CI ≤ 2.2 L/min/m^2	104	Digoxin: 63% ISDN¶: 85%	H Target dose#: 150 mg qid	Captopril Target dose#: 100 mg qid	Lower 1-year mortality with captopril (18%) vs H (49%), p=0.05	Crossover was high, difference in mortality was driven by higher rates of sudden death with H
A-HEFT[25]	2004	Black (60% men), NYHA III/IV, LVEF < 35% or LVEF <45% + LV diastolic diameter > 65 mm	1050	ACEi: 69% ARB: 17% BB:74% MRA: 38% Digoxin: 60%	H-ISDN Target dose: 75 mg tid + ISDN 40 mg tid Average daily dose: H 143 mg, ISDN 76 mg	Placebo	Lower mortality with H-ISDN vs placebo (HR: 0.57, p=0.01), mean follow-up 10 months§	H-ISDN also reduced hospitalization for HF and improved quality of life scores
Hsiao et al[53]	2023	Decompensated HF, NYHA III/IV, LVEF < 35% + MR (EROA > 30 mm^2)	408	ACEi/ARB: 81% BB:76% MRA: 62% Digoxin: 60%	H Target dose: 50 mg qid Average daily dose: 264 mg	No H	Lower rate of the combined endpoint CV death + HF hospitalization with H (HR 0.61, p=0.002)	Open label design, single center. Only 23% used ISDN (both groups)

*V-HeFT: Veterans Administration Cooperative Vasodilator-Heart Failure trial, A-HeFT: African-American Heart Failure trial, SL: Sublingual, H: hydralazine, ISDN: isosorbide dinitrate, H-ISDN: hydralazine–isosorbide dinitrate; MR: Mitral regurgitation; EROA: effective regurgitant orifice area; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers; MRA: mineralocorticoid receptor antagonists; BB: beta receptor blockers; LVEF: left ventricle ejection fraction; VO2p: peak oxygen consumption; Tx: transplantation; qid: four times a day; tid: three times a day; bid: two times a day; PCWP: Pulmonary capillary wedge pressure; CI: cardiac index; CV: cardiovascular. *Defined as cardiothoracic ratio > 0.55 on X-ray or left ventricular diameter >27 mm/m^2. † Measured by radionuclide ventriculography. ‡ The study reported that 35-40% used vasodilators at baseline, without specifying which type of drug. § Trial stopped early due to higher mortality in the placebo group. ¶ ISDN was given to all patients in the Hydralazine group and to those in the Captopril group if patient had history of coronary artery disease or PCWP persisted ≥ 20 mmHg. # Drug doses were adjusted with pulmonary artery catheter to maintain optimal hemodynamic status while nitroprusside therapy was gradually withdrawn.*

Gaps of evidence

The racial definition may not be a sufficiently accurate marker to determine physiological and genetic variations. Genotype-phenotype studies have demonstrated that endothelial NO synthase polymorphism may be associated with worse event-free survival, regardless of race, suggesting that non-black HF patients could also benefit from H-ISDN treatment.[58,59] We have to point out the difficulty in translating the results obtained in the previous trials to our Brazilian population, markedly characterized by miscegenation of different ethnicities. Furthermore, there are controversies regarding the concept of a "race-specific" drug, as it raises questions about the ethical implications of targeting drugs based on racial or ethnic backgrounds.

Early studies on HFrEF with predominantly non-black populations compared the effect of H-ISDN with the vasodilator prazosin or placebo (V-HeFT) or enalapril (V-HeFT II), which is not representative of the current HF treatment standard.[17,18] There are insufficient data to guide the use of H-ISDN in association with ARNi. There are no randomized studies using other nitrate formulations such as isosorbide mononitrate or propatylnitrate in HF patients, and there are no specific recommendations for these formulations in this scenario.

The data are insufficient to assess the sex-related differential effect since the V-HeFT trials included only men and, in the A-HeFT trial, women represented 40%. In a post hoc analysis of A-HeFT, women had a greater mortality reduction than men

Table 2 – Class of recommendation and level of evidence for the combination hydralazine/isosorbide dinitrate in heart failure across different guidelines

Clinical setting	AHA/ACC/HFSA (2022)	ESC (2021)	Brazilian (2018)
Self-identified black patients with HFrEF in NYHA III-IV on optimized therapy to improve symptoms; decreased risk of hospitalization and mortality	COR: I LOE: A	COR: IIa LOE: B	COR: I LOE: B
Previously or currently symptomatic HFrEF patients (independently of race) who cannot receive or have contraindications to ACEi/ARB/ARNi	COR: IIb LOE: C-LD*	COR: IIb LOE: B	COR: I LOE: B

*COR: class of recommendation; LOE: level of evidence; HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; AHA: American Heart Association; ACC American College of Cardiology; HFSA: Heart Failure Society of America; ESC: European Society of Cardiology. *LD: limited data.*

with the use of H-ISDN, but due to differences in baseline characteristics, this analysis should be considered exploratory only and not conclusive.[60]

Data supporting the use of H-ISDN in decompensated HF are also limited. There are multiple theoretical benefits for using H-ISDN in this scenario since HF decompensation is associated with a disruption of NO signaling and increased oxidative stress. In a retrospective study, patients admitted for decompensated HF who were discharged with H-ISDN in addition to an ACEI or ARB showed a more significant improvement in cardiac index and systemic vascular resistance, and to lower all-cause mortality rate compared to those receiving only ACEi or ARB.[61] So far, no trial has evaluated H-ISDN on HF-related endpoints in patients with HF and preserved ejection fraction.

Regarding potential use of H-ISDN in patients with renal failure, data are also scarce. The A-HeFT study showed no significant interaction between "history of renal failure" and the effect of H-ISDN. A small randomized, proof-of-concept study on 44 HFrEF patients with cardiorenal syndrome demonstrated only a trend toward improvement in the 6-minute walk test in patients using H-ISDN compared with standard care at six months.[62] In a retrospective study from the United States Renal Data System database, 6,306 patients on dialysis using H-ISDN were compared to 75,509 who did not use H-ISDN. H-ISDN was independently associated with reduced mortality (HR 0.48; 95% CI 0.43-0.54); however, the incidence of myocardial infarction and admission for HF were higher in those using H-ISDN.[63]

Author Contributions

Conception and design of the research: Fernandes-Silva MM; Analysis and interpretation of the data: Gama ACKA; Writing of the manuscript: Fernandes-Silva MM, Gama ACKA, Saito GYK, Goulart BC, Lofrano-Alves MS; Critical revision of the manuscript for content: Fernandes-Silva MM, Mol EE, Lofrano-Alves MS.

Potential conflict of interest

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This article does not contain any studies with human participants or animals performed by any of the authors.

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