

Original Research

Mini review: The clinical avenues of combined hydralazine-nitrate in subjects with heart failure with reduced ejection fraction

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Abstract

Background: Combined hydralazine-nitrate has an avenue in the management of subjects with heart failure with reduced ejection fraction. Exploring the pharmacotherapy in this context will facilitate the clinical utility of the combined therapy. **Objective:** The main objective of this mini-review was to evaluate the role of combined hydralazine-nitrate in subjects with heart failure with reduced ejection fraction. **Methods:** We conducted a literature search on Google scholar, MEDLINE, and PubMed to identify the randomized clinical trials on combined hydralazine-nitrate, in subjects with heart failure with reduced ejection fraction. 2760 articles were returned initially out of which 10 trials were conforming to the inclusion criteria. However, three trials were the focus for the current mini-review. **Key findings:** The current mini-review lends support to the use of combined hydralazine-nitrate in subjects with heart failure with reduced ejection fraction (HFrEF). The combination may offer subjects who have remained symptomatic with HFrEF despite optimum dosing of standard therapy. Black subjects with HFrEF have proved to benefit from combined hydralazine-nitrate. The combination (e.g. small dose of hydralazine 12.5-25 mg twice a day and isosorbide mononitrate 10 mg twice a day) may provide alternative clinical utility in subjects with contraindications (renal artery stenosis, creatinine clearance less than 30 mL/minute, sustained hyperkalemia) to the use of ACEinh, ARBs, and/or ARNI. Subjects with HFrEF on combined hydralazine-nitrate should be assessed and monitored for systolic BP (keep >120 mmHg) and subjects with chronic kidney disease (keep eGFR > 30 mL/min/1.73 m²). Hydralazine-nitrate was inferior to ACEinh (higher all-cause mortality and cardiovascular mortality). **Conclusion:** The current mini-review provides the key points to support the use of hydralazine-nitrate in subjects with heart failure with reduced ejection fraction..

Keywords: hydralazine-nitrate; heart failure with reduced ejection fraction (HFrEF); hydralazine; isosorbide dinitate; randomized clinical trials; Vasodilator Heart Failure Trial I (V-HeFT I); the Vasodilator Heart Failure Trial II (V-HeFT II); New York Heart Association (NYHA)

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INTRODUCTION

Hydralazine is a potent vasodilator that dilates the arterioles (reduces afterload) whereby it decreases peripheral vascular resistance and ultimately reduces blood pressure. The drug has a hemodynamic effect (increased cardiac output and stroke volume) in subjects with heart failure, without any significant change in pulmonary and systemic venous pressure. Hydralazine is an antioxidant that reduces nitric oxide (NO) consumption. Since the discovery of endothelium-derived relaxing factor in 1980, nitric oxide (NO) has been the focus of significant investigation. Although the effects of endothelium-derived NO in the vasculature well understood, in the last decade it has shown that NO released from cardiac endothelial cells and/or created inside cardiac myocytes itself has substantial autocrine/paracrine impacts on cardiac function. The heart might generate all three NO synthase (NOS) isoforms; Endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS).¹

Numerous major views concerning NO's actions have emerged. Endothelial cells continuously emit modest amounts of NO, which induces vascular smooth muscle relaxation and keeps the vasculature in a continuous vasodilation status. In response to local alterations, a low basal level of NO works as an endogenous auto-regulator of blood flow to tissues. During ischemia and reperfusion, NO promotes further vasodilation. Other locally produced variables, such as bradykinin, cause NO output in certain vessels. NO is involved in blood pressure control. Problems in NOS regulation can result in hypertension and vasospasm. Endothelial dysfunction and NO synthesis abnormalities linked to a number of illnesses.² The finding that the high output isoform of iNOS is expressed in the myocardium of patients with HF, combined with *in vitro* data indicating that iNOS expression can stimulate contractile dysfunction, has captivated the interest of many researchers in the possible role of NO in the pathophysiology of HF. NO has a negative feedback effect on beta-adrenergic signaling. Numerous years back, it found that intracoronary L-NMMA increased the contractile response to the adrenergic agonist dobutamine in DCM patients. Considering the lack of effect of acute NOS inhibition on baseline function, it was challenging to attribute these benefits to higher iNOS activity. Nevertheless, it currently seems that these findings are due to an improved relationship between eNOS and its activation by adrenergic receptor stimulation in the failing human heart. Changes in eNOS expression may potentially have an impact on diastolic function. The increased NO release generated a rightward shift in the diastolic pressure-volume relationship as well as an increase in left ventricular stroke work. These data support the idea that NO may enhance left ventricular diastolic performance in heart failure in order to sustain cardiac output. Other consequences of decreased eNOS expression include a decrease in myocardial O₂ utilization. NO action in the heart affects not just cardiac function but also cardiac anatomy, acting as an anti-hypertrophic factor. The separate contributions of NO synthase isoforms to cardiac architectural maintenance have substantial significance for the pathogenesis of heart failure.^{1,2}

The drug is highly acetylated (slow and rapid acetylator), highly protein bound, with pharmacogenomics as HLA-DRw4 variant that appears in 73.0% of subjects experiencing hydralazine-associated systemic lupus erythematosus (SLE). It has with short half-life (2-8 hour) in normal renal function and 7-16 hour in end-stage renal disease. Isosorbide dinitrate is a venodilator (reducing pre-load) that enhances the nitric oxide (NO) bioavailability (NO donor). Both hydralazine and isosorbide dinitrate reduces the intracardiac filling pressures therefore, reduces the adverse cardiac remodeling process and increases O₂ consumption at peak exercise.

In 1986, the Vasodilator Heart Failure Trial I (V-HeFT I) has proved that the combination of hydralazine (300 mg per day) and isosorbide dinitrate (160 mg per day) refer to as HISDN in 642 men has lower mortality (risk-reduction by 36.0% at 3 years) than placebo (follow-up averaged 2.3 years) with improved left ventricular function.³ Five years later in 1991, the Vasodilator Heart Failure Trial II (V-HeFT II) in 804 men has compared enalapril 20 mg/day with the combination of hydralazine 300 mg/day plus isosorbide dinitrate 160 mg/day (New York Heart Association [NYHA] I-II). The enalapril arm was found superior to the combination arm HISDN in terms of sudden cardiac death (18.0% versus 25.0%; $P=0.016$), 28.0% reduction in the risk of mortality at 2 years of follow-up but not at longer follow-up $P=0.08$.⁴ However, the Studies of Left Ventricular Dysfunction (SOLVD) has shown a similar 21.0% mortality rate in the enalapril arm (NYHA II-III) at 24 months but via pump failure.⁵ It noted that the subgroup analysis of SOLVD trial demonstrated a difference in survival between white and black subjects, in favor of the HISDN therapy.⁶ Furthermore, another evidence for less benefit from angiotensin converting enzyme inhibitor (ACEinh) demonstrated for the black subjects with heart failure with reduced ejection fraction (HFrEF).⁷ The African-American Heart Failure Trial (A-HeFT trial) of 1000 subjects has provided the evidence for the superiority benefit (higher mortality rate in the placebo group [10.2% vs. 6.2%, $P=0.02$]) of the HISDN (NYHA III or IV) in reducing the rate of death (43.0%) survival advantage, reducing hospitalization (33.0%) and improved the quality of life.⁸ More high certainty evidence for improved quality of life demonstrated by recent meta-analysis for HISDN (standardized mean difference [SMD] 0.24, 95% CI 0.04–0.44) versus placebo.⁹

A cohort study included hospitalized subjects from African-American race (5168) with LVEF <40%, followed for 18 months (mean age 65.2 years). Only 15.2% were receiving hydralazine and isosorbide dinitrate (H-ISDN) prior to index admission. The trial reported 1,275 deaths (24.7%), and the adjusted mortality rate was 22.1% for H-ISDN group versus 25.2% for untreated group ($p<0.009$); adjusted hazard ratio: 0.85 (95% confidence interval: 0.73 to 1.00; $p<0.057$). The trial concluded that H-ISDN exhibited lower mortality rates in African-American patients with HFrEF.

Rationale

Few trials have evaluated the effectiveness of combined hydralazine-nitrate (HISDN) in clinical practice. Landmark trials has demonstrated that HISDN use in African-American subjects



with HFrEF, improve the quality of life and minimizes HF-related hospitalization, and mortality rates. The subpopulation of African subjects with HFrEF deserve special attention due to less effect of other common therapy.

OBJECTIVE

Combined hydralazine-nitrate (HISDN) has an avenue in the management of subjects with heart failure with reduced ejection fraction. Exploring the pharmacotherapy in this context will facilitate the clinical utility of the combined therapy. The objective of the current mini-review was to evaluate the role of combined hydralazine and nitrates in subjects with HF with reduced ejection fraction.

METHODS

We conducted a literature search on Google scholar, MEDLINE, and PubMed to identify the randomized clinical trials on combined hydralazine-nitrate in subjects with heart failure, with reduced ejection fraction. The Medical Subheadings used: heart failure; hydralazine-isosorbide dinitrate (HISDN); hydralazine-nitrate; randomized clinical trials; heart failure with reduced ejection fraction (HFrEF). The period for the literature search was 1980 to 2022. 2760 articles returned initially out of which 10 trials were conforming to the inclusion criteria. However, three trails were the main focus for the current mini-review.^{3,4,8}

RESULTS AND DISCUSSIONS

The clinical utility of hydralazine-nitrate in HFrEF

The V-HeFT I trial of 642 men has compared HISDN to placebo with a primary outcome of mortality. The trial has proved that in all-cause mortality HISDN group 12.1% compared to placebo group (19.5%). This effect of HISDN has maintained lower mortality than placebo (risk-reduction by 36.0%) at 3 years after which it diminished with improved left ventricular function ($P < 0.028$).³ Reduction in mortality in the Hydralazine-nitrate group was 38% after 1 year, 25% after 2 years, 28% over the entire follow-up period (follow-up averaged 2.3 years). The improvement in ejection fraction at year 1 for placebo group was (30.3%) versus HISDN (34.5%), $P < 0.001$ versus baseline [Table 1].

The V-HeFT II trial of 804 men has compared enalapril 20 mg/day with the combination of hydralazine (H) 300 mg/day plus isosorbide dinitrate (ISDN) 160 mg/day (New York Heart Association [NYHA] I-II) with mortality as primary outcome. The enalapril arm superior to the combination arm HISDN in terms of sudden cardiac death (18.0% versus 25.0%; $P = 0.016$), and 28.0% reduction in risk of mortality at 2 years of follow-up but not at longer follow-up $P = 0.08$. The reduction in mortality in the enalapril group was 33.6% after one year, 28.2% after 2 years, 14% after 3 years. The LVEF increased in both groups, however; the increase was more in the first 13 weeks in the HISDN group⁴ [Table 1].

The A-HeFT trial of 1000 subjects provided the evidence for the superiority benefit. Higher mortality rate seen in the placebo group versus the HISDN (NYHA III or IV) [10.2% versus 6.2%, $P = 0.02$], while combination HUSDN shows reducing the rate of death (43.0%, hazard ratio-HR= 0.57; $P = 0.01$) survival advantage, reducing hospitalization (33.0%), and improving the quality of life (-5.6 ± 20.6 versus -2.7 ± 21.2 , $P = 0.02$) [8 Table 1]. The SOLVD trail subgroup analysis demonstrated a difference in survival between white and black subjects, in favor of the HISDN therapy.⁵ Furthermore, another evidence for less benefit from angiotensin converting enzyme inhibitor (ACEinh) demonstrated for the black subjects with heart failure with reduced ejection fraction (HFrEF).⁷ A recent systematic review and meta-analyses of randomized placebo-controlled trials evaluating contemporary HFrEF pharmacotherapy and reporting health-related quality of life (HRQoL) as an outcome demonstrated improved HRQoL over placebo with HISDN (SMD 0.24, 95% CI 0.04–0.44) versus placebo. The meta-analysis concluded that ARBs, ARNIs, SGLT2 inhibitors, ivabradine, HISDN, and intravenous iron improved HRQoL in patients with HFrEF.⁹

The main finding of the nonrandomized, single-center, case-control cohort of patients with advanced HF is that, despite similar systemic blood pressure targets, careful, protocol-driven administration of oral Isosorbide /Hydralazine can produce favorable hemodynamic improvements incremental to standard neurohormonal therapy. 266 consecutive patients met all inclusion and exclusion criteria. Subjects monitored for a mean of 26.3 months. Study revealed that when I/H is added to regular neurohormonal blockade, there may be a substantial reduction in all-cause mortality and a reduction in clinical adverse outcomes when compared to standard neurohormonal inhibition alone. Researchers also discovered that race had no bearing on this impact. The addition of oral vasodilators in those who have evidence of hemodynamic abnormalities and adequate systemic blood pressures enables restoration of optimal hemodynamic balance, which may translate into accumulative intermediate- and long-term benefits, even though neurohormonal blockade can effectively delay disease progression in advanced HF. A statistically significant reduction in filling pressures and an increase in cardiac output were attained in the 2 groups as compared to baseline hemodynamic testing. However, only the I/H group showed a statistically significant decline in estimated SVR and systolic blood pressure; this decline was less pronounced in the control group. Additionally, individuals receiving I/H saw larger increases in cardiac output and cardiac index. Throughout the course of the research, there was no difference between the two therapy groups' rates of total cardiac transplantation or HF re-hospitalization. Regardless of race, the I/H group's better results were achieved, albeit there was a general tendency toward greater relevance for the African-American population.¹⁰

Through an observational study conducted in veterans' affairs hospitals in USA. A group of African Americans with HFrEF from 105 VHA medical institutions made up the overall observational sample for 18 months. The objective of this



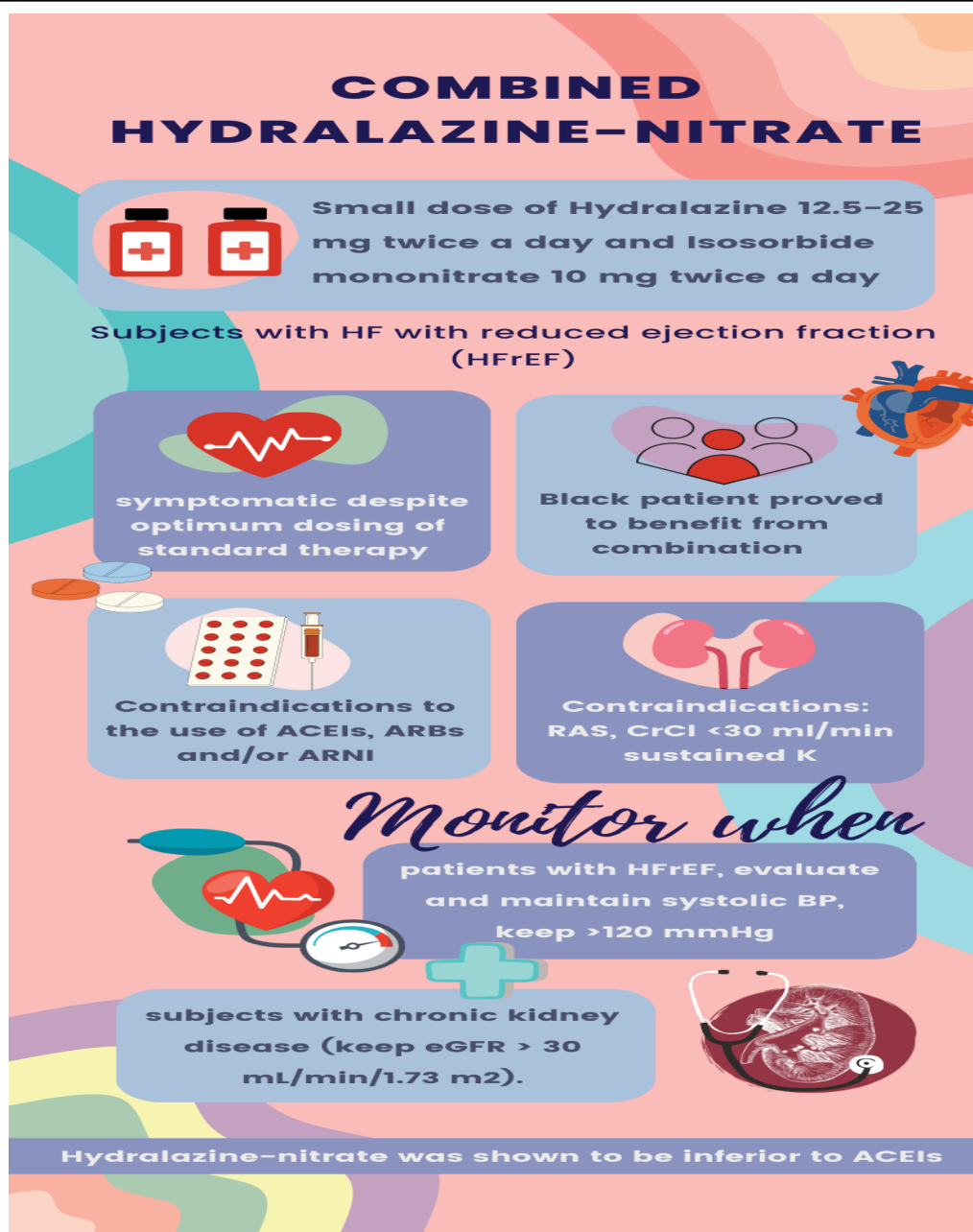


Figure 1. Graphical abstract combined Hydralazine-nitrate

investigation was to assess the therapeutic efficacy of H-ISDN on death rates in patients who were African-American and had HFrEF. 5,168 African-American patients with HF (mean age: 65.2 years) made up the final group, and 15.2% of them had had H-ISDN treatment prior to index admission. There were 1,275-recorded fatalities (24.7%) after 18 months. At 18 months, the adjusted death rate for patients getting H-ISDN therapy was 22.1%, compared to 25.2% for patients who were not receiving treatment ($p = 0.009$); the adjusted hazard ratio was 0.85 (95% confidence interval: 0.73 to 1.00; $p = 0.057$). This observational research of actual clinical practice reveals that African Americans with HFrEF may benefit from using H-ISDN. Using H-ISDN linked to a 15% decreased mortality risk

throughout the 18 months of follow-up after hospitalization. Improvements in H-ISDN treatment drug adherence might lead to even better results. All African-American patients with HFrEF who do not have contraindications to this medication given consideration for H-ISDN therapy, according to previous studies and the most recent data.¹¹

In a systematic review of seven randomized clinical conducted in 2015, the H-ISDN combination reduced all-cause mortality (OR 0.72; 95% CI 0.55-0.95; $P = 0.02$), and cardiovascular mortality (OR 0.75; 95% CI 0.57-0.99; $P = 0.04$) compared to placebo. However, H-ISDN was inferior (higher all-cause mortality) to ACEInh (OR 1.35; 95% CI 1.03-1.76; $p = 0.03$), and cardiovascular

mortality (OR 1.37; 95% CI 1.04-1.81; $p=0.03$).¹²

The HISDN can be used in subjects with HFrEF provided their systolic blood pressure (BP) >120 mmHg, and in subjects with chronic kidney disease where estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m². The dosing for the combined therapy of hydralazine-nitrate should be initiated at the lowest possible dose of hydralazine 12.5–25 mg twice a day and isosorbide mononitrate 10 mg twice a day. Hydralazine contraindicated in subjects with coronary artery disease or mitral valve rheumatic heart disease.

The use of HISDN in subjects with HFrEF with contraindication to the use of ACEinh, ARBs, and angiotensin-receptor neprilysin inhibitor (ARNI) supported by the European Society of cardiology (ESC-2016,¹³ and National Institute of Clinical Excellence (NICE-2018¹⁴) guidelines.

Recently, in 2020 the Denmark investigators have initiated the DANISH randomized, double blind, placebo-controlled trial in patients with chronic HEART failure (DANHEART). This long-term trial (4 years) was a 2 × 2 factorial trial of HISDN in patients with chronic heart failure (H-HeFT) and metformin in patients with chronic heart failure and diabetes or pre-diabetes (Met-HeFT). The primary endpoint in H-HeFT is a combined endpoint of death or hospitalization with worsening heart failure compared to placebo. The trial will provide whether HISDN will confer benefit in subjects with HFrEF.¹⁵

Combined hydralazine-nitrate has an avenue in the management of subjects with HFrEF. Exploring the pharmacotherapy in this context will facilitate the clinical utility of the combined therapy. The current pharmacotherapy for subjects with HFrEF challenged with the substantial health care burden of re-hospitalization, poor prognosis and death. Therefore, searching and researching for new molecules are highly warranted.

Current and future prospects for pharmacotherapy option in subjects with HFrEF

The major breakthrough in pharmacotherapy of HFrEF established by the **sacubitril-valsartan** (entresto) which has reduced the mortality and hospitalizations (20.0%) due to HF compared to enalapril in the landmark trial PARADIGM.¹⁶ In 2018, the French pharmacovigilance retrospective analysis (8845 patients on entresto) of 142 reports adverse drug reactions due to sacubitril-valsartan (entresto) 91 were serious (64.1%), of which 13.2% were due to angioedema, acute renal failures ($n = 36$, 39.6% of the 91 patients), and arterial hypotension ($n = 16$, 17.6%).¹⁷ However, the therapy of entresto may still increase the incidence of reported serious angioedema^{18,19} as more population was on this ground-breaking therapy. Recently in 2020, the dapagliflozin (Farxiga®) in patients with heart failure (DAPA-HF) trial has shown that the addition of dapagliflozin (sodium-glucose cotransporter-2 [SGLT-2] inhibitor) to standard HF guideline-directed medical therapy in New York Heart association [NYHA] class II-IV HFrEF patients conferred protection from worsening HF or cardiovascular mortality, regardless of the presence or absence of diabetes.²⁰ Grounded on this study, the United States Food and Drug Administration (FDA) recently

approved dapagliflozin for treatment of HFrEF.²¹

Within this context of progression in treatment options for HFrEF, the VICTORIA trial (multinational, randomized, double blind, placebo-controlled trial) presents another pharmacologic option for chronic HFrEF with vericiguat.²² The trial (published in 2021) has enrolled 5050 at 616 sites that have been followed-up for 10.8 months. The trial revealed significantly lower incidence of death from cardiovascular causes with vericiguat than with placebo. Vericiguat is an oral soluble guanylate cyclase (sGC) stimulator that enhances the cyclic guanosine monophosphate (GMP) pathway. sGC is an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO).

Omecamtiv Mecarbil is a novel selective myocardial myosin activator compared to placebo in 8256 patients with symptomatic HFrEF (GALACTIC-HF) followed for 21.8 months. The drug has shown lower incidence of the primary endpoint (first heart-failure event or cardiovascular death) than the placebo (37.0% versus 39.1%, $P = 0.03$). However, the drug did not show effect on cardiovascular death or on symptoms (as measured by the Kansas City Cardiomyopathy Questionnaire-KCCQ).²³

Summary of the mini-review

The current mini-review provides the following key points to support the use of HISDN in subjects with HFrEF: Cardiologists may offer nitrates and hydralazine to subjects who have remained symptomatic with heart failure despite optimum dosing of standard therapy of selective beta-blocker, angiotensin converting enzyme inhibitor (ACEinh)/angiotensin receptor blocker (ARB)/ ARNI (sacubitril-valsartan), aldosterone antagonist (aldosterone/epirenone), and loop diuretics (furosemide/torsemide).

Black subjects with heart failure with reduced ejection fraction (HFrEF) have proved to benefit from nitrates and hydralazine.

The combination of nitrate and hydralazine may have a prospective clinical utility in subjects with contraindications (renal artery stenosis, creatinine clearance less than 30 mL/minute, sustained hyperkalemia) to the use of ACEinh, ARBs, and ARNI.

The European Society of cardiology (ESC-2016) and National Institute of Clinical Excellence (NICE-2018) guidelines supported the use of combined hydralazine-nitrate in subjects with HFrEF with contraindication to the use of ACEinh, ARBs, and ARNI.

In the subjects with HFrEF (with contraindication to the use of ACEinh, ARBs, and ARNI) it is reasonable to use a small dose of hydralazine 12.5-25 mg twice a day and isosorbide mononitrate 10 mg twice a day.

Subjects with HFrEF on combined hydralazine-nitrate should be assessed and monitored for systolic BP (keep >120 mmHg) and subjects with chronic kidney disease (keep eGFR > 30 mL/min/1.73 m²). However, clearly stated that HISDN was inferior to ACEinh (higher all-cause mortality and cardiovascular mortality).¹²



CONCLUSIONS

The current mini- review provides the key points to support the use of hydralazine-nitrate in subjects with heart failure with reduced ejection fraction (HFrEF).

The clinical implication of the current mini-review findings on current clinical practice are:

Cardiologists may offer combined hydralazine-nitrate to subjects who have remained symptomatic with heart failure despite optimum dosing of standard therapy.

Black subjects with heart failure with reduced ejection fraction (HFrEF) have proved to benefit from hydralazine-nitrate.

The combination of hydralazine-nitrate may have a prospective clinical utility in subjects with contraindications (renal artery stenosis, creatinine clearance less than 30 mL/minute, sustained hyperkalemia) to the use of ACEinh, ARBs, and ARNI.

AUTHOR CONTRIBUTION

All of the authors were responsible for the study concept, design, acquisition and analysis of observed data, have contributed equally to the preparation whole manuscript, literature review, developing and proof reading. All authors have approved the manuscript and its submission to the journal. The authors have not published or submitted any related papers from the same study. This article is not under consideration or submission for any other journals.

ABBREVIATIONS

ACEinh	angiotensin converting enzyme inhibitor
A-HeFT	African-American Heart Failure Trial
ARB	angiotensin receptor blocker
ARNI	angiotensin-receptor neprilysin inhibitor
BP	blood pressure
DAPA-HFDapagliflozin	in patients with heart failure
DANHEART	DANish randomized, double-blind, placebo controlled trial in patients with chronic HEART failure
eNOS	endothelialoxide synthase
ESC	European Society of cardiology

eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
HISDN	hydralazine-isosorbide dinitrate
H-HeFT	hydralazine-isosorbide dinitrate in patients with chronic heart failure factorial trial
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
HRQoL	health-related quality of life
iNOS	inducible nitric oxide synthase
KCCQ	Kansas City Cardiomyopathy Questionnaire
Met-HeFT	metformin in patients with chronic heart failure factorial trial
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
HLA-DR ^{w4}	gene variant in subjects experiencing hydralazine-associated systemic lupus erythematosus (SLE)
NYHA	New York Heart Association
NICE	National Institute of Clinical Excellence
SGLT-2	sodium-glucose cotransporter-2
sGC	soluble guanylate cyclase
SLE	systemic lupus erythematosus
SMD	standardized mean difference
SOLVD	Studies of Left Ventricular Dysfunction
V-HeFT I	Vasodilator Heart Failure Trial I
V-HeFT II	Vasodilator Heart Failure Trial II

CONSENT FOR PUBLICATION

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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