ESC HEART FAILURE
ESC Heart Failure 2019; **6**: 878–883
Published online 22 May 2019 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12459

PERSPECTIVE

Hydralazine and nitrates in the treatment of heart failure with reduced ejection fraction

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Abstract

Hydralazine and nitrate combination was the first treatment that showed improved survival of patients with heart failure with reduced left ventricular ejection fraction (HFREF) in the Vasodilator Heart Failure Trial (V-HeFT trial) in 1986. This showed a 34% reduction of mortality at 2 years of follow-up in patients with advanced heart failure (New York Heart Association Class IV). The angiotensin-converting enzyme inhibitor (ACEi), beta-blockers, mineralocorticoid receptor antagonists, and most recently sacubitril–valsartan have superseded the combination of hydralazine and nitrates. However, the latter combination does have a place bridging the survival gap of Black patients with HFREF when added to their standard therapy. This was demonstrated in the African-American Heart Failure Trial (A-HeFT trial) in 2004 when the risk reduction in the Black patients was 43% compared with that in the placebo. This combination may have a potential use in patients with contraindications to the use of ACEi, angiotensin receptor blockers, and sacubitril–valsartan. This is suggested by both the European Society of Cardiology (ESC) Guidelines and the guidelines of the National Institute for Health and Care Excellence (NICE). In this perspective, the role of the combination of hydralazine and nitrates in the treatment of HFREF is reviewed through a synopsis of the evidence base consisting of three randomized controlled studies, several further analyses of subgroups within those trials, a systemic review, and two large observational studies of registry cohorts. The place of the combination in the treatment cascades proposed by heart failure guidelines of the ESC and NICE is explored. This perspective is to remind us of their appropriate roles, particularly given the findings of underuse of this combination in people of African ancestry in Europe.

Keywords Hydralazine and nitrate combination; HFREF

Received: 13 September 2018; Revised: 21 April 2019; Accepted: 29 April 2019
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Having demonstrated in 1972 that vasodilators improve the impaired left ventricular ejection fraction (LVEF),[1] Cohn *et al*. published in 1986 the first randomized controlled trial that showed a survival benefit of therapy in patients with heart failure, Vasodilator Heart Failure Trial I (V-HeFT I).[2] Isosorbide dinitrate is a venous dilator, while hydralazine is an arterial dilator. Their use was aimed at reducing pre-load and after-load, respectively. V-HeFT I was a multi-centre, randomized, double-blind, placebo-controlled trial that enrolled 642 men. Those patients had a history of impaired cardiac function and reduced exercise tolerance. They were taking digoxin and diuretics. The patients were followed up for an average of 2.3 years. Data were collected on mortality, LVEF, exercise tolerance, and echocardiography. The trial had three arms using placebo, prazosin, and the combination of hydralazine (300 mg/day) and isosorbide dinitrate (160 mg/day). There was no difference in the survival rate between those in the placebo arm and those in the prazosin arm. However, the mortality rate was reduced in the group that received hydralazine and isosorbide dinitrate compared to the group on placebo.

The aim of therapy in V-HeFT I was to reduce the intracardiac filling pressures in the hope of reducing the adverse cardiac remodelling. There may have been the added benefit of enhancing nitric oxide (NO) bioavailability. Nitrates are NO donors, while hydralazine is an antioxidant through the reduction of NO consumption.

There was a 34% mortality-risk reduction at 2 years ($P < 0.028$); the cumulative mortality rates at 2 years were 25.6% in the hydralazine–nitrate group vs. 34.3% in the placebo group. At 3 years, the corresponding figures were 36.2% vs. 46.9%, respectively. The mortality-risk reduction

with hydralazine and isosorbide dinitrate combination became 36% by 3 years (*Figure 1*).

Shortly thereafter in 1987, the first randomized controlled clinical trial in the treatment of heart failure using an angiotensin-converting enzyme inhibitor (ACEi) was published.[3] This was followed by several trials in different populations. Most of the trials of ACEi in heart failure with reduced LVEF (HFREF) were successful at improving symptoms, reducing hospitalization, and reducing mortality. The publicity of ACEi eclipsed the achievement of V-HeFT I trial.

The competition was formally settled through the V-HeFT II study led by Cohn comparing enalapril with the combination of hydralazine and nitrates in 1991.[4] In this trial, 804 men on digoxin and diuretics for heart failure were randomized to either 20 mg/day of enalapril or 300 mg/day of hydralazine combined with 160 mg/day of isosorbide dinitrate. The mortality rate was significantly lower in the enalapril arm (18%) than in the hydralazine and isosorbide dinitrate arm (25%) (0.016), signifying a 28% reduction in the risk of mortality at 2 years of follow-up. However, overall, this was not demonstrated during longer follow-up, as there was no significant difference in mortality (0.08) (*Figure 2*).

The lower mortality in the enalapril arm was attributable to a reduction in sudden cardiac death. This effect was more prominent in patients with less severe heart failure [New York Heart Association (NYHA) I–II]. However, it was interesting that the O_2 consumption at peak exercise increased more by the combination of hydralazine and isosorbide dinitrate ($P < 0.05$), while the LVEF increased with both regimens during the 2 years.

The V-HeFT II study showed 18% mortality rate in the enalapril arm at 24 months. The Studies of Left Ventricular Dysfunction SOLVD-Treatment study published on the same day and in the same journal showed a similar 21% mortality rate in the enalapril arm (NYHA II–III) at 24 months.[5] Despite the similar mortality rates at 24 months, for the patients in the enalapril arms of both studies, it is difficult to explain that enalapril was superior to hydralazine and nitrate combination (in V-HeFT II) through the reduction of sudden cardiac death, whereby the impact of enalapril compared with placebo in the SOLVD-Treatment trial was through reduction of mortality through pump failure. The patients in the SOLVD-Treatment trial tended to have a lower ejection fraction and higher chance of underlying ischaemic heart disease than

Figure 1 Survival in all patients recruited into V-HeFT I (from Cohn *et al.*[2]). ISDN/HYD, isosorbide dinitrate/hydralazine.

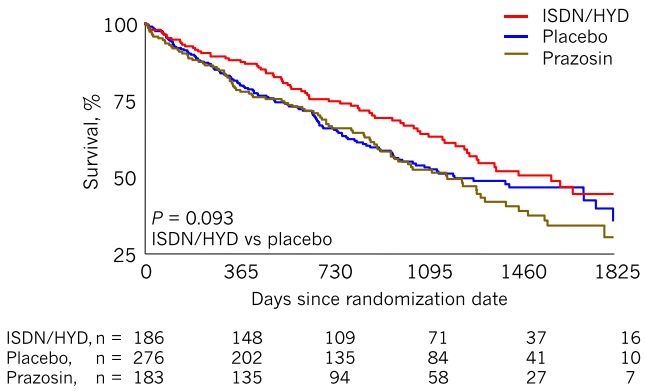
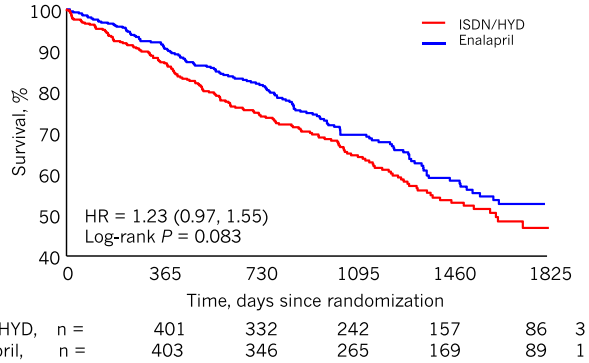


Figure 2 Survival in all patients in the V-HeFT II trial (from Cohn *et al.*[4]). HR, hazard ratio; ISDN/HYD, isosorbide dinitrate/hydralazine.



DOI: 10.1002/ehf2.12459

did those recruited into the V-HeFT II trial, although there were more patients in NYHA Class III in the latter. It is difficult to explain the differences in the impact of enalapril on patients recruited in the same era. The characteristics of the patients randomized to enalapril in the two trials are shown in *Table 1*.

Although a subgroup analysis is frequently frowned upon as an unreliable post hoc analysis, one needs to take note of the lack of difference in the survival between enalapril and the combined vasodilators hydralazine and isosorbide dinitrate amongst the 215 Black patients recruited into V-HeFT II trial.[6] In contrast, the 574 White patients recruited into the V-HeFT II trial demonstrated a significantly better survival rate amongst the patients in the enalapril arm (P = 0.02)[6] (*Figure 3*).

Interestingly, in the V-HeFT I trial, there was a 22% lower risk of death overall with the combination therapy of hydralazine and nitrates, though this was not statistically significant.

Table 1 The characteristics of the patients receiving enalapril in the V-HeFT II and SOLVD-Treatment trials

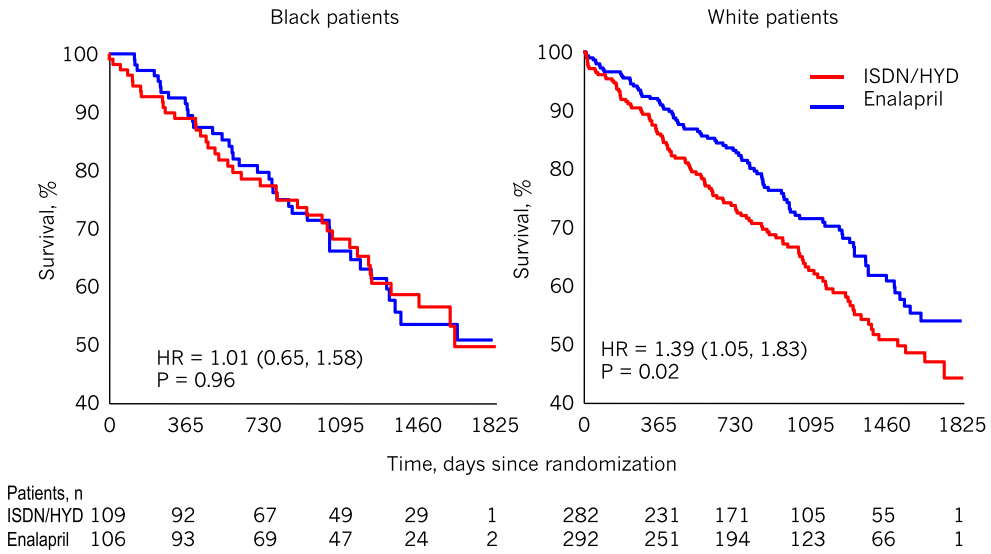
Characteristic	V-HeFT II	SOLVD-Treatment
Number of patients	403	1285
Age (year)	60.6	60.7
White race (%)	72.5	79.2
Ejection fraction (%)	28.6	24.8
NYHA Class I (%)	6	11.4
NYHA Class II (%)	49.6	56.8
NYHA Class III (%)	44.2	30.1
NYHA Class IV	0.2	1.5
Ischaemic heart disease (%)	54.3	70.2

The benefit appears to be derived from the impact of the combined vasodilator therapy with hydralazine and isosorbide dinitrate in the 128 Black patients (47% reduction, with P = 0.04), whereas there was no significant survival difference between the placebo and treatment arms amongst the 324 White patients (12% reduction with P = 0.47)[7] (*Figure 4*).

While ACEi reduces all-cause mortality of patients with HFREF by 16–20% at 5 years, ACEi is less effective in lowering blood pressure (BP) in Black patients, a fact confirmed in an analysis of the SOLVD trials. In the latter trials, a total of 1196 White patients and 800 Black patients were recruited. An average of 15 mg/day of enalapril reduced BP in a matched White cohort of patients by 5/3 mmHg but not in the Black patients with heart failure. The Black patients had a worse prognosis (death rate 12.2 vs. 9.7/100 patient-years) without treatment and did not have the expected benefit on treatment despite similar compliance rates. Enalapril therapy is associated with a significant reduction in the risk of hospitalization for heart failure amongst White patients with HFREF, but not amongst similar Black patients. Therefore, Black patients with HFREF may not gain the full benefits of ACEi treatment.[8]

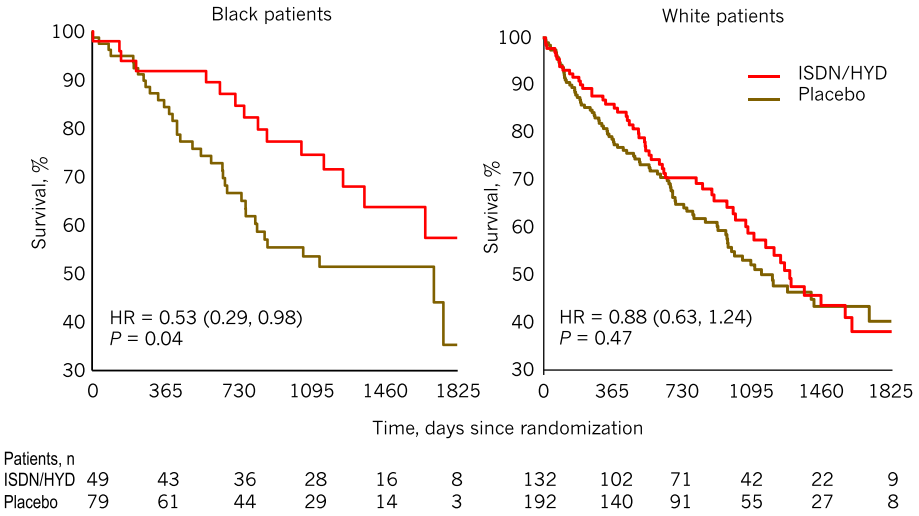
The observations in the post hoc analyses of V-HeFT I and V-HeFT II and the evidence from the pooled analysis of the SOLVD-Treatment and prevention arms formed a perfect scientific basis for the design of the African-American Heart Failure trial (A-HeFT trial) published in 2004.[9] In this trial, a fixed dose of isosorbide dinitrate and hydralazine was added to optimal medical therapy as deemed appropriate at that era, compared with optimal medical therapy alone, to look if the combined vasodilator therapy would provide additional

Figure 3 Survival in Black patients and White patients in the V-HeFT II trial (from Carson *et al.*[6]). HR, hazard ratio; ISDN/HYD, isosorbide dinitrate/hydralazine.



DOI: 10.1002/ehf2.12459

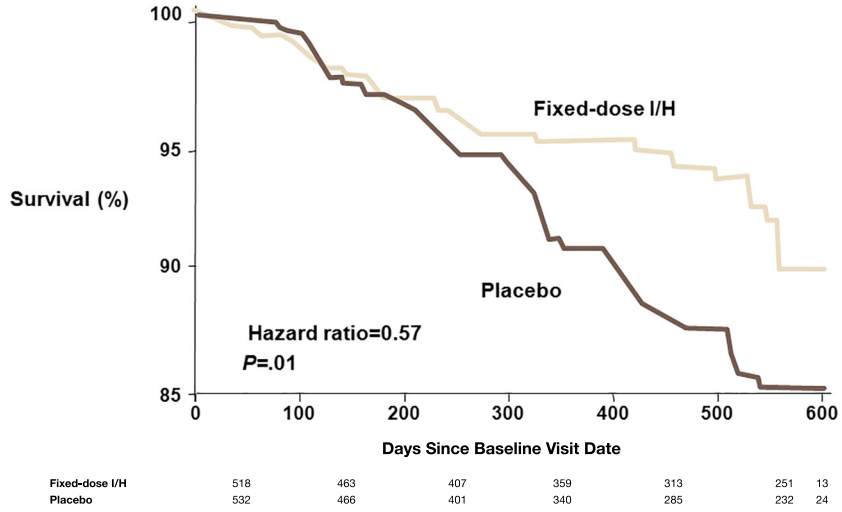
Figure 4 Survival in Black patients and White patients in the V-HeFT I trial (from Cohn *et al.*[7]). HR, hazard ratio; ISDN/HYD, isosorbide dinitrate/hydralazine.



benefit in Black patients with advanced heart failure. Thus, 1050 Black patients with heart failure and dilated ventricles with NYHA III or IV functional class were randomized to the combined vasodilator therapy or placebo, in addition to standard therapy. The trial was terminated early owing to significantly higher mortality rate in the placebo group (10.2% vs. 6.2%, 0.02). The mean primary composite score was significantly better in the treatment group (0.01). The combination therapy resulted in 43% reduction in the rate of death from any cause (0.01) and 33% relative reduction in the rate of first heart failure hospitalization (0.001) and in an improvement in the quality of life (0.02). Therefore, the addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure including neurohormonal blockers is efficacious and increases survival amongst Black patients with advanced heart failure (*Figure 5*).[9]

In their systemic review of the trials of hydralazine and nitrate combination in the treatment of HFREF, Farag *et al.*,[10] concluded that the combination reduces the all-cause mortality and the cardiovascular mortality, but the evidence base suggests that the combination remained inferior to treatment with ACEi.

Figure 5 A-HeFT: 43% relative risk reduction for mortality derived from the addition of hydralazine and nitrates in Black patients with heart failure with reduced left ventricular ejection fraction (from Taylor *et al.*[9]). I/H, isosorbide dinitrate/hydralazine.



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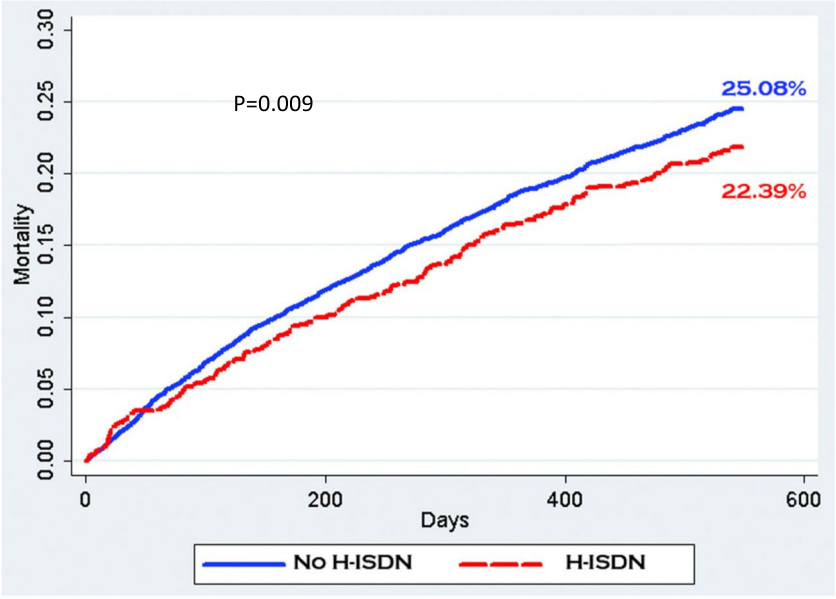
The European Society of Cardiology (ESC) Guidelines in 2016 explored the role of the hydralazine and nitrate combination in the treatment of HFREF.[11] The guidelines correctly pointed out that in the non-Black patients, the evidence for the use of the combination came from relatively small randomized controlled trials of men only, whose basic treatment was limited to diuretics and digoxin, making their applicability difficult to ethnicities other than Black patients of African descent. This said, the guidelines suggested another role for this combination in the patients unable to tolerate either ACEi or angiotensin receptor blocker (ARB), based on the V-HeFT 1 trial.[11] The use of this combination in those patients with HFREF intolerant of ACEi and ARB was also proposed in the National Institute for Health and Care Excellence (NICE) guidelines for heart failure in 2018.[12] Interestingly, while the ESC guidelines' treatment algorithm limits the use of the combination to those with resistant symptoms in whom all other options had been explored (very low in the cascade),[11] the NICE guidelines' treatment algorithm leaves the choice of timing to the specialist while specifying the use of the combination in the Black patients as per the A-HeFT study population who remained symptomatic despite triple therapy with ACEi, beta-blockers, and mineralocorticoid receptor antagonists.[12]

In the real world, two observational studies looked at the use of the combined hydralazine and nitrates in the treatment of patients with HFREF. On the basis of the patients in the Get With The Guidelines - Heart Failure (GWTG-HF) registry, Khazanie *et al.*[13] noted that amongst those older than 65 years with HFREF, 22.7% were Black and 18.2% had estimated Glomerular Filtration Rate (eGFR) $<$ 30 mL/min/1.73 m^2, the latter being a contraindication for the use of ACEi or ARB. In these two groups of patients, the use of the combined hydralazine and nitrates was low, and the adherence to therapy was also low (46%). These are the explanations proposed for the failure of the latter combination to significantly reduce the cumulative incidence at 3 years of mortality or readmissions. On the other hand, Ziaeian *et al.*[14] found that from amongst the Veterans Affairs African American patients hospitalized for heart failure in the 6 years between 2007 and 2013 who did not have a contraindication to the hydralazine and nitrates combination, were not intolerant of ACEi or ARB, and did not have advanced chronic kidney disease, 5168 patients fulfilled the criteria for the treatment combination as per the A-HeFT trial (their mean age was 65.2 years). Only 15.2% of these patients received the combination therapy and had an adjusted mortality rate at 18 months of 22.1% compared with an adjusted mortality rate of 25.2% for the untreated patients (P = 0.009) (*Figure 6*). These observational studies showed low use of the combination even in the population from whom the evidence for its effectiveness was obtained, and with much lower effectiveness than that demonstrated in the randomized controlled trials, probably due to low adherence rate.

In my own practice, I use hydralazine and nitrate combination for the Black patients with HFREF who remain symptomatic despite triple therapy with ACEi, beta-blockers, and

Figure 6 Cumulative mortality rates over days since discharge for patients treated and not treated with hydralazine–isosorbide dinitrate (H-ISDN) (from Ziaeian *et al.*[14]).



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mineralocorticoid inhibitors, provided that their systolic BP was >120 mmHg. In addition, I use the combination of hydralazine and nitrates in patients with HFREF of any racial group who have advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), provided that their systolic BP is >120 mmHg. I advocate in these patients the use of a small dose of hydralazine 12.5–25 mg twice a day and isosorbide mononitrate 10 mg twice a day asymmetrically.

The epidemiology of heart failure is not constant. In addition to the ageing of the population, which is associated with increased incidence of heart failure and increased incidence of compromised kidney function, there are effects of migration and the establishment of new communities of patients from certain ethnic groups such as Black patients of African ancestry, a reality that would increase the relevance of the combined hydralazine and nitrates for these populations based on the aforementioned evidence base. Indeed, Brewster[15] just published the survey of the use of this combination therapy in African ancestry patients in Europe and found that it is underused.

I would like to remind physicians and cardiologists to consider the important implications of the A-HeFT study when treating Black patients with HFREF. It would be interesting if the cardiology community was prepared to obtain trial evidence on the use of hydralazine and nitrate combination in patients with advanced kidney disease and HFREF who are not on renal replacement therapy and who are of any ethnic origin.

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