International Journal of Cardiology 196 (2015) 61–69

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Hydralazine and nitrates alone or combined for the management of chronic heart failure: A systematic review

Mohamed Farag [a,*], Thato Mabote [a], Ahmad Shoaib [a], Jufen Zhang [a], Ashraf F. Nabhan [c], Andrew L. Clark [a], John G. Cleland [b]

[a] Department of Cardiology, Castle Hill Hospital, Hull York Medical School (at University of Hull), Kingston upon Hull HU16 5JQ, UK
[b] National Heart & Lung Institute, Imperial College, London, UK
[c] Postgraduate Medical School, Ain Shams University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 3 April 2015
Accepted 27 May 2015
Available online 3 June 2015

Keywords:
Chronic heart failure
Systematic review
Hydralazine
Nitrate
Morbidity
Mortality

ABSTRACT

Background: Hydralazine (H) and nitrates (Ns), when combined, reduced morbidity and mortality in some trials of chronic heart failure (CHF). It is unclear whether either agent used alone provides similar benefits. We aimed to evaluate the effects of H and/or N in patients with CHF.
Methods: A systematic review of randomised trials assessing the effects of H and N in CHF. For meta-analysis, only the endpoints of all-cause mortality and cardiovascular mortality were considered.
Results: In seven trials evaluating H&N in 2626 patients, combination therapy 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, when compared to angiotensin converting enzyme inhibitors (ACEIs), combination therapy was associated with higher all-cause mortality (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). For N alone, ten trials including 375 patients reported all-cause mortality and showed a trend to harm (13 deaths in those assigned to nitrates and 7 to placebo; OR 2.13; 95% CI 0.88–5.13; p = 0.09). For H alone, three trials showed no difference in all-cause mortality compared to placebo (OR 0.96; 95% CI 0.37–2.47; p = 0.93), and two trials suggested inferiority to ACEI (OR 2.28; 95% CI 1.03–5.04; p = 0.04).
Conclusions: Compared to placebo, H&N reduces mortality in patients with CHF. Whether race or background therapy influences benefit is uncertain, but on direct comparison H&N appears inferior to ACEI. There is little evidence to support the use of either drug alone in CHF.

1. Background

The therapy of chronic heart failure (CHF) has advanced dramatically over the last 20–30 years [1]. Good medical treatment with angiotensin converting enzyme inhibitors (ACEIs), beta adrenoceptor antagonists (BB) and mineralocorticoid receptor antagonists (MRAs), now approximately doubles life expectancy [2]. However, mortality rates remain high, particularly in the first year after a hospitalisation for heart failure [3]. ACEIs were initially thought to mediate their benefit, at least in part, through their action as vasodilators, and other vasodilators have also been tried. In particular, the combination of hydralazine (H) and nitrates (Ns) was shown to be beneficial in the V-HeFT-I trial [4].

Nitrates are prescribed to patients with CHF although often for the relief of angina rather than for their effects on the symptoms of heart failure, venous capacity, or vascular resistance. Hydralazine is used in some countries, but is either not available, or rarely used in many others. A series of trials has suggested that the H&N combination may reduce morbidity and mortality, and that this combination may be almost as effective as ACEIs [4–6]. Evidence is most compelling amongst patients of African-American origin or similar (AAOS), but it is unclear whether racial origin is an important determinant of benefit [6]. There are many other uncertainties related to the use of these agents. For instance, it is not known whether they need to be used in combination, or whether one component of the combination delivers all or most of the benefit. Indeed, it is possible that the combination could be less effective than either agent used alone. Moreover, the effects of H and/or N may or may not have been altered by the changes in background heart failure therapy. It is unclear whether H and/or N improve symptoms, although it is widely believed that they do. It is also uncertain whether H and/or N

Abbreviations: AAOS, African-American origin or similar; ACEIs, angiotensin converting enzyme inhibitors; ARNIs, angiotensin receptor neprilysin inhibitors; ARBs, angiotensin receptor blockers; BB, beta adrenoceptor antagonists; CHF, chronic heart failure; H, hydralazine; IHD, ischaemic heart disease; ISDN, isosorbide dinitrate; ISMN, isosorbide mononitrate; LVSD, left ventricular systolic dysfunction; MRAs, mineralocorticoid receptor antagonists; Ns, nitrates; NYHA, New York Heart Association.

* Corresponding author.
E-mail address: mohamedfarag@nhs.net (M. Farag).

http://dx.doi.org/10.1016/j.ijcard.2015.05.160
0167-5273/

Table 1
Trials evaluating the use of H and N combination in chronic heart failure.

Study/design	Treatment	Control	Treatment (n)	Control (n)	Age (yrs)	Women (%)	Race (%)	Follow-up	Background therapy	SR (%)	IHD (%)	NYHA III/IV (%)	LVSD (%)	HR (mean)	SBP (mean)	DBP (mean)
Franciosa [8], parallel	Combination (H 100 mg + ISDN 40 mg) PO	Placebo	11	11	54	NR	NR	90 min	D, L	NR	54%	91%	100%	84	113	NR
Unverferth [9], parallel	Combination (H 225 mg + ISDN 160 mg) PO	Placebo	7	11	57	24%	NR	12 weeks	D, L	NR	0%	94%	100%	NR	NR	NR
V-HeFT I [4], parallel	Combination (H 300 mg + ISDN 160 mg) PO	Placebo	186	273	58	0%	60% white 40% black	2.3 years	D, L	NR	44%	NYHA II/IV 100%	100%	83	119	76
Lin [10], parallel	Combination (H 200 mg + Sorbitrate 80 mg) PO	Enalapril 20 mg PO	60	60	68	0%	NR	1 year	D, L	NR	30%	NYHA II/IV 100%	100%	NR	130	80
V-HeFT II [5], parallel	Combination (H 300 mg + ISDN 160 mg) PO	Enalapril 20 mg PO	401	403	61	0%	63% white 37% black	2.5 years	D, L	86	53%	43%	100%	78	126	78
Ghose [11], parallel	Combination (H 100 mg + ISDN 60 mg) PO	Placebo, captopril 100 mg PO	50	51, 52	41	43%	NR	1 year	D, L	NR		52%	100%	NR	NR	NR
A-HeFT [6], parallel	Combination (H 225 mg + ISDN 120 mg) PO	Placebo	518	532	57	40%	100% black	3 years	D, L, ACEI/ARB, BB, MRA	83%	23%	99.9%	100%	NR	126	77

ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BB: beta adrenoceptor antagonists, DBP: diastolic blood pressure, D: digitalis, H: hydralazine, HR: heart rate, IHD: ischaemic heart disease, ISDN: isosorbide dinitrate, L: loop diuretic, LVSD: left ventricular systolic dysfunction, MRA: mineralocorticoid receptor antagonist, NR: not reported, NYHA: New York Heart Association, SR: sinus rhythm, SBP: systolic blood pressure.

confer a different effect on different heart failure phenotypes (for example, heart failure with normal ejection fraction, heart failure with reduced ejection fraction, ischaemic heart disease, and valve disease).

We therefore sought to analyse all clinical trials that had used H or N, either alone or in combination, in patients with CHF in order to describe the characteristics of patients recruited to these trials, to describe

Table 2
Adverse effects reported with the use of H and N combination in chronic heart failure.

Study	Treatment	Control	Combination adverse effects (% of patients)	Control adverse effects (% of patients)
Franciosa [8]	Combination (H 100 mg + ISDN 40 mg) PO	Placebo	None	None
Unverferth [9]	Combination (H 225 mg + ISDN 160 mg) PO	Placebo	Headache (several patients)	Headache (several patients)
V-HeFT I [4]	Combination (H 300 mg + ISDN 160 mg) PO	Placebo	Headache 12.4%*	Headache 0.4%
			Dizziness 6.5%*	Dizziness 1.8%
			Gastrointestinal 3.8%	Gastrointestinal 1.8%
			Nervous system 3.8%	Nervous system 0.4%
			Rash 1.6%	Rash 0%
			Arthralgia 1.6%	Arthralgia 0%
			Possible lupus 1.6%	Possible lupus 0.7%
Lin [10]	Combination (H 200 mg + Sorbitrate 80 mg) PO	Enalapril 20 mg PO	Headache 8.6%*	Headache 0%
			Dizziness 5.2%	Dizziness 6.7%
			Gastrointestinal 1.7%	Gastrointestinal 1.7%
			Presyncope 1.7%	Presyncope 1.7%
			Facial flushing 1.7%	Facial flushing 0%
			Palpitation 5.2%	Palpitation 0%
			Cough 0%	Cough 10%*
V-HeFT II [5]	Combination (H 300 mg + ISDN 160 mg) PO	Enalapril 20 mg PO	Headache 73%*	Headache 54%
			Rash 31%	Rash 33%
			Arthralgia 63%	Arthralgia 65%
			Palpitation 51%	Palpitation 46%
			Nausea 44%	Nausea 52%
			Fatigue 76%	Fatigue 79%
			Symptomatic hypotension 20%	Symptomatic hypotension 28%*
			Taste disturbance 28%	Taste disturbance 28%
			Nasal congestion 63%	Nasal congestion 63%
			Cough 29%	Cough 37%*
Ghose [11]	Combination (H 100 mg + ISDN 60 mg) PO	Placebo, captopril 100 mg PO	Hypotension	Hypotension
			Mild renal dysfunction	Mild renal dysfunction
A-HeFT [6]	Combination (H 225 mg + ISDN 120 mg) PO	Placebo	Headache 47.5%*	Headache 19.2%
			Dizziness 29.3%*	Dizziness 12.3%

H: hydralazine, ISDN: isosorbide dinitrate.
* This value was significantly higher than the corresponding value for the other treatment ($p < 0.05$).