

VASODILATOR OF CHOICE IN MANAGEMENT OF HEART FAILURE

Pages with reference to book, From 55 To 57

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INTRODUCTION

Annual mortality rate of congestive heart failure due to systolic dysfunction with conventional treatment ranges from 15-50% depending upon functional class. Since the use of vasodilators in the management of heart failure due to systolic dysfunction resulted in symptomatic improvement and increase in exercise tolerance, many vasodilators have been tried. Angiotensin converting enzyme inhibitors have shown promising results in decreasing mortality rate and sudden death. All ACE inhibitors are not showing similar results. This article will discuss the different trials done so far, their outcome and the choice of vasodilator in the management of congestive heart failure. Our basic concept about congestive heart failure has been of heart failure due to myocardial dysfunction with dilated left ventricle and depressed ejection fraction. Recently attention has been focused into the following classification: a) systolic dysfunction with depressed ejection fraction such as due to dilated cardiomyopathy where treatment is digoxin, diuretics and vasodilators. This is the largest group and has mortality rate ranging from 15-50% per year depending upon functional class; b) 30-40% of cases with heart failure present with diastolic dysfunction with normal ejection fraction such as due to hypertrophic cardiomyopathy, restrictive cardiomyopathy, where caution is advised on the use of diuretics and vasodilators. Role of digoxin is controversial unless coexisting atrial fibrillation exists. Prognosis has not been studied in such groups but they do better than with systolic dysfunction¹. In this article, attention is focused on heart failure with systolic dysfunction. In heart failure peripheral vasoconstriction causing increased preload and after-load results in peripheral congestion, progressive deterioration of LV function and premature death. Guha et al in 1974 showed hemodynamic improvement by using nitroprusside which caused arterial and venous relaxation². Prazosin, alpha adrenoreceptor antagonist a balanced vasodilator, produced similar hemodynamic effects according to some studies but some studies showed no benefit. It did not improve survival which was thought to be either due to tachyphylaxis or failure of the drug to have favourable effect on the course of heart failure^{3,4}. Hydralazine an arteriolar vasodilator has not shown any improvement in symptoms or exercise tolerance⁵. Isosorbide dinitrate predominant venous dilator did show reduction in symptoms and increase in exercise tolerance⁶. Massie et al in 1977 and Pierpont et al in 1978 showed beneficial results of combined administration of hydralazine and isosorbide dinitrate^{7,8}. So far attention was paid to see improvement in symptoms and exercise tolerance in these studies but effect on mortality by these vasodilators was not discussed. In 1985, Veterans Administration Cooperative Trial (V-HeFT I) was completed by using prazosin - balanced vasodilator, combination of isosorbide dinitrate (ISDN) and hydralazine as balanced vasodilator and placebo to see the effect on mortality. Prazosin did not differ from placebo. Mortality rate decreased by 38% after 1 year in hydralazine ISDN group as compared to placebo, 25% after 2 years and 23% after 3 years. In placebo there was 4 year mortality rate of 54% due to sudden death and progressive deterioration of heart failure (Table I).

TABLE I. Percent mortality rate in hydralazine isosorbide dinitrate group in V-HeFT I.

Year	HYD. ISDN group	Placebo	Reduction
1	12.1	19.5	38
2	25.6	34.3	25
3	36.2	46.9	23
4	49.7	53.6	7

Failure of prazosin to show improvement in survival may be due to tachyphylaxis or lack of favourable effect on cause of heart failure⁹. It was known that ACE inhibitors decrease peripheral resistance by decreasing vasoconstriction caused by angiotensin II whereas other conventional vasodilators stimulate renin angiotensin system. Captopril, a balanced vasodilator showed improvement in symptoms and exercise tolerance¹⁰ but effect of ACE inhibitors on mortality was studied in consensus trial in NYFIAFC W failure patients. In this trial enalapril was tried which showed 6 months mortality rate of 29% as compared to 48% in placebo (40% reduction in mortality rate) and after 1 year 47% as compared to 63% in placebo (25% reduction in mortality). No effect on sudden cardiac death was observed¹¹ (Table II).

TABLE II. Percent mortality rate in enalapril and placebo group in consensus trial.

Year	Placebo group	Enalapril group	% reduction
1/2 year	48	29	40
1 year	63	47	25
Sudden cardiac death	14	14	-

Captopril digoxin MRG study showed no difference in survival over 6 months period in the three groups (captopril diuretic group, digoxin diuretic group, diuretic group). Majority of patients were in NYHAFC II. Captopril diuretics group showed increased exercise tolerance, decrease in ventricular arrhythmia but ejection fraction was not affected. Digoxin diuretics group showed increase in ejection fraction and ventricular arrhythmia was increased by 4%¹². Preffer et al demonstrated attenuation of progressive ventricular enlargement with eaptopril with decrease in left ventricular filling pressure and improvement in exercise tolerance after anterior wall myocardial infarction¹³. Though this study was done with captopril, it may hold true with any other ACE inhibitor. Giles et al compared captopril with lisinopril and found both to be equal in safety profile. Lisinopril increased ejection fraction, functional capacity and quality of life as compared to captopril¹⁴. Packer et al have demonstrated captopril to be less effective in heart failure patient with renal insufficiency as compared to lisinopril¹⁵. Cohn et al conducted V-HcFT II comparing enalapril with hydralazine isosorbide dinitrate (ISDN) and found incidence of sudden death 17% in enalapril group and 46% in hydralazine ISDN group. Decrease in sudden death was thought to be due to non-vasodilator mechanism (Table III).

TABLE III. Percent mortality rate in V-HeFT III.

Year	Enalapril group	HYD. ISDN group	% reduction
1	9	13	31
2	18	25	28
3	31	36	14
4	42	47	11
Sudden death	37%	46%	20

Previously conducted consensus trial did not show decrease in sudden death. Mortality rate was lower in enalapril group than hydralazine ISDN group in 3 years of follow-up but mortality rate after 4 years was similar in both groups which suggested that vasodilators delay death but do not prevent progression of the disease¹⁶. Recently published hydralazine captopril trial in Nfl-IA FC III, IV heart failure patients by Fonarow et al in JACC showed significant decrease in mortality (19%) in captopril group as compared to hydralazine ISDN group (49%). This reduced mortality in captopril group was due to decrease in sudden death. One year incidence of sudden death in captopril treated group was 5% as compared to 37% in hydralazine ISDN group (Table IV).

TABLE IV. Mortality rate in Ily-c trial.

Year	Captopril ISDN group	HYD. ISDN group	% reduction
1/2 year	19	33	42
1 year	19	49	61
Sudden death	5	37	86

These results are in marked contrast to V-HeFT II where incidence of sudden death was 37% and consensus showed no reduction in sudden death in enalapril group. ACE inhibitors influence sudden death by direct antagonism of neuroendocrine activation, antagonism of angiotensin II mediated progressive ventricular hypertrophy, prevention of aldosterone and diuretic induced hypokakmia, direct decrease of myocardial venous oxygen consumption by cardiac renin angiotensin system and restoration of baroreceptor activity. Significant reduction in incidence of sudden death in captopril seen in this study and not in V-HeFT II or consensus - may be due to prevention of nitrate tolerance by captopril nitrate interaction which is not present with other ACE inhibitors and this nitrate tolerance prevention may add benefit of nitrate to that of ACE inhibitors¹⁷. SAVE investigators found improved survival and reduction in morbidity and mortality due to major cardiovascular events from long term administration of captopril as compared to placebo in patients with asymptomatic LV dysfunction after myocardial infarction. No difference in incidence of sudden death was observed between the two groups. Risk reduction was 19 percent from mortality from all causes¹⁸. SOLVED investigators found 8% risk reduction in mortality from all causes as compared to placebo. No significant reduction in mortality was found from cardiovascular causes as compared to placebo¹⁹. From these trials it has become obvious that combination of hydralazine ISDN have lower mortality than placebo⁹. ACE inhibitors have lower mortality than combination of hydralazine ISDN¹⁶. This lower mortality in ACE inhibitors and not with conventional vasodilators, may be due to sympathetic stimulation of nervous system without alteration of angiotensin II mediated progressive ventricular enlargement, central autonomic changes and baroreflex abnormalities¹⁷. Among ACE inhibitors lower mortality has been

observed in captopril vs placebo group than enalapril vs placebo group showing superiority of captopril over enalapril^{18,19}. Reduction in sudden death was first documented in V-HeFT II in enalapril group - predominantly in NYHA FC I, and II heart failure patients. Present study of Fonarow et al has shown significant reduction in mortality in captopril ISDN group and this reduction in mortality was due to significant decrease in sudden death in NYHA FC III and IV patients. Till more trials are done to compare the mortality rate between other ACE inhibitors in combination with nitrates, it is not unwise to say that captopril is so far the vasodilator of choice. One should look for adverse reactions of hypotension, rising creatinine level, hyperkalemia if patient already on spironolactone. Increased incidence of renal failure has been seen and this may be due to factors which stimulate renin angiotensin system and cause renal function to be dependent upon angiotensin II. These factors are dehydration secondary to diuresis, heart failure by itself, hyponatremia and preexisting renal insufficiency.

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