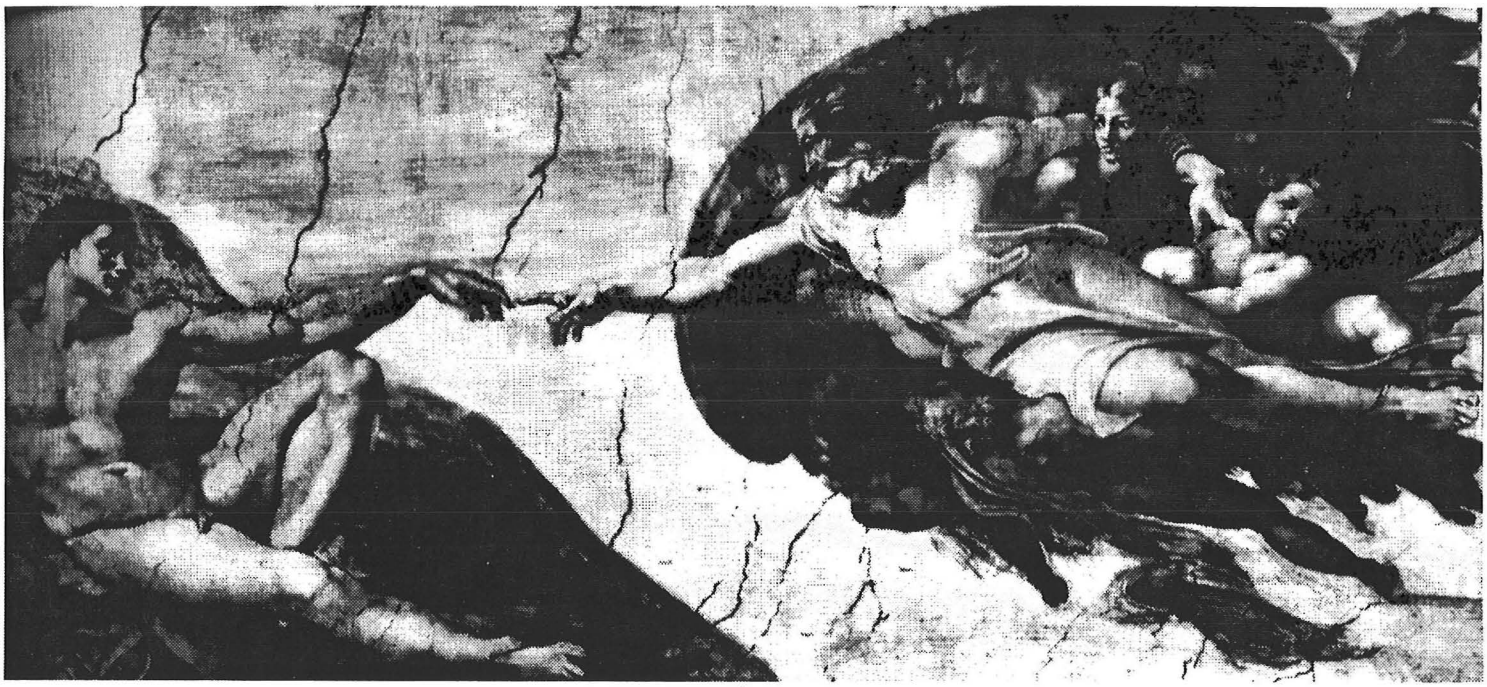
Medical Therapy for Congestive Heart Failure 1995



Genesis of New Approaches

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Grand Rounds May 11, 1995

Introduction

Despite medical advances for the treatment of congestive heart failure, including the use of angiotensin converting enzyme inhibitors, digitalis, and diuretics, the mortality for moderate to severe heart failure continues to be in excess of 40% per year for severely symptomatic patients and in excess of 25% per year for moderately symptomatic patients (1). While cardiac transplantation provides a means by which to prolong survival in heart failure, the high cost of transplant, limited donor supply of hearts, and specialized and expensive follow-up care make this alternative possible for a very small minority of patients with heart failure. Thus, better prevention of heart failure and improved medical care of patients with heart failure becomes critical. Digitalis, diuretics, and ACE inhibitors have an important role in the long-term treatment of congestive heart failure. Phosphodiesterase agents have a significant role in the *acute* treatment of heart failure, but may accelerate death if used chronically. ß-blockers clearly improve ventricular function and symptoms in patients with heart failure and data exists to suggest that these agents may prolong survival, although this has yet to be proven in a prospective fashion.

Pathophysiology of heart failure

Two pieces of information suggest that neurohormonal activation plays a major role in determining the survival of patients with congestive heart failure (2). First, both plasma catecholamines (3,4) and plasma renin activity (4,5) are activated in proportion to the severity of ventricular dysfunction and functional impairment present in patients with heart failure. Plasma norepinephrine has been shown to be an important prognostic marker for determining survival in these patients independent of ejection fraction indices (3). This latter piece of data suggests that norepinephrine may play a more active adverse role in determining survival rather than just being a marker of left ventricular dysfunction. Likewise, hyponatremia, which reflects the activation of the renin-angiotensin system, is a prognostic marker for survival in patients with severe heart failure (2,5).

The second piece of evidence that neurohormonal activation is prognostically important comes from the beneficial effect on survival seen when neurohormonal antagonists are administered. (2,6-9) ACE inhibitors have been shown to reduce mortality in heart failure, and indirect data suggest ß-blockers may do the same.

Thus, after the heart sustains an initial insult (myocardial infarction, myocarditis, valvular disease, idiopathic dilated cardiomyopathy, etc.), hypoperfusion and elevated filling pressures result in activation of the renin-angiotensin system and the sympathetic ner-

vous system (Figure 1)(10). These two systems tend to cross-activate each other. These events lead to: 1) salt and fluid retention 2) elevation of heart rate 3) short term increase in inotropy 4) ß-receptor downregulation and subsensitivity in the heart 5) cAMP mediated calcium overload in the myocyte 6) activation or release of other important neurohormones (Endothelin-1, TNFα and IL-1) and 7) long-term progressive left ventricular dysfunction and abnormal growth due to toxic and mitogenic effects on the myocyte. Angiotensin II and endothelin-1 are growth promoters for the cardiovascular system (11-13) and elevation of these neurohormones in heart failure may be responsible for production of hypertrophy and fibrosis. In addition, TNFα, which is elevated in congestive heart failure (14), is known in animal models to produce LV dilatation or creep (stretch induced compliance changes) as well as fibrosis and scar formation (15,16). In addition, TNFα has a negative inotropic effect on the mammalian heart (17,18). and TNFα and IL-1 can lead to uncoupling of the ß-adrenoreceptor from adenylate cyclase, thus reducing inotropic responsiveness to norepinephrine (19,20). Thus, activation of these neurohormonal systems may lead to long term left ventricular dysfunction, hypertrophy, and maladaptive remodeling (11,21).

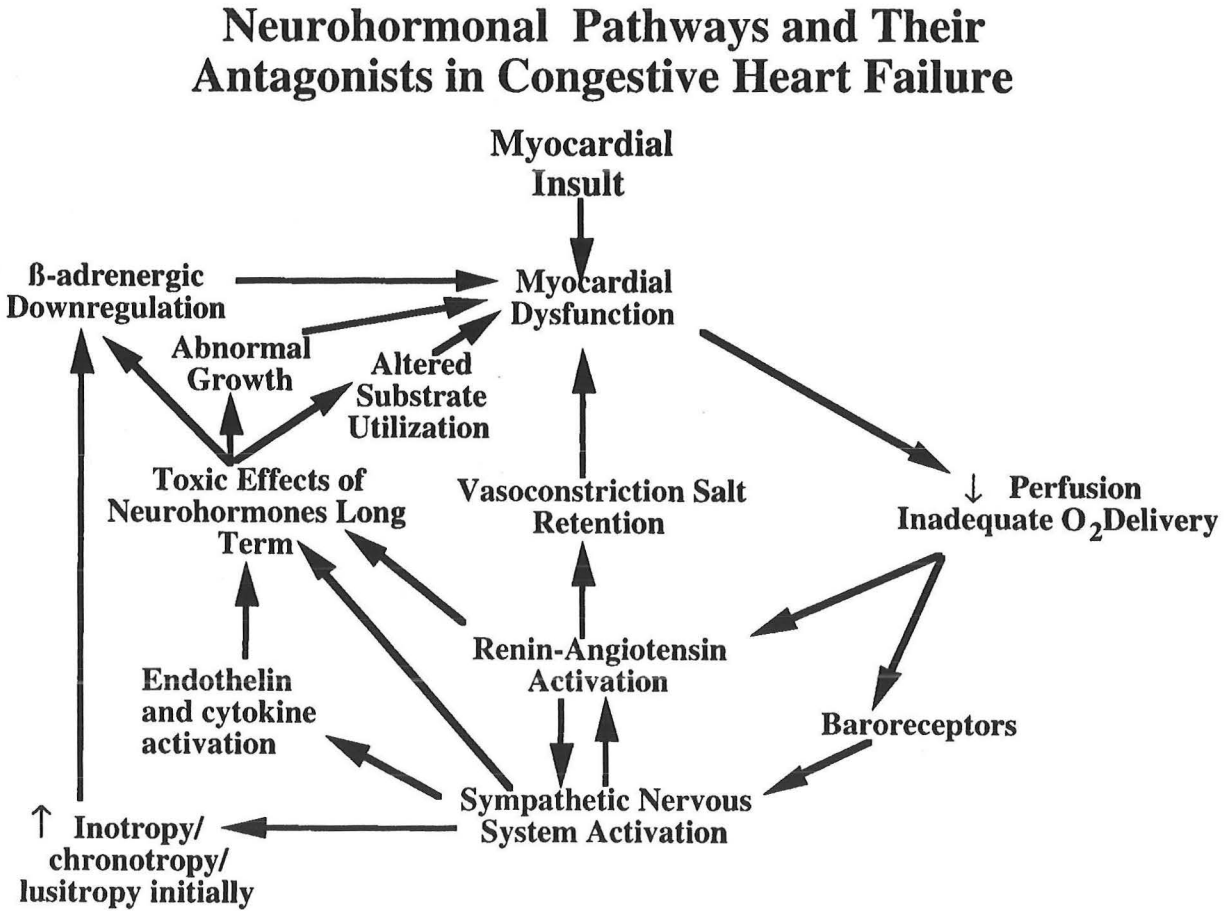


Figure 1

Diuretics

Mechanism of action- Diuretics are the most commonly used drugs for the treatment of heart failure. Diuretics act by preventing sodium reabsorption in the kidney and are defined by their site of action in the nephron. The most common diuretics for use in heart failure are the loop diuretics (furosemide, bumetanide, ethacrynic acid). Other diuretics such as thiazide diuretics and potassium sparing diuretics are also used alone or in combination with loop diuretics. Diuretics are excellent at reducing preload, fluid accumulation, and acutely improving dyspnea. There are several important adverse effects of diuretics. The most important effects include: 1) electrolyte disturbance (hypokalemia, hypomagnasemia) 2) hypovolemia 3) azotemia (especially in combination with NSAIDs) 4) activation of the renin-angiotensin system and 5) arrhythmias.

Electrolyte disturbance- Diuretics may result in total body and intracellular deficits of potassium and magnesium which may or may not be reflected by a measurable decrease in serum concentrations of these cations. Renal excretion of these cations are exacerbated by diuretic-induced hyperaldosteronism and metabolic alkalosis. The hypokalemia cannot be corrected until the hypomagnesemia is corrected. Once corrected, hypokalemia and hypomagnasemia are best prevented by the use of: 1) potassium supplements 2) potassium-sparing diuretics (which spare both potassium and magnesium) and 3) ACE inhibitors.

Hypovolemia- Overaggressive diuresis can result in hypovolemia, hypotension, fatigue, and pre-renal azotemia.

Azotemia- This may be particularly marked if the patient has pre-existing renal artery or renal disease or if the patient is taking nonsteroidal anti-inflammatory drugs (NSAID). The latter effect is caused by NSAID interference with the vasodilator action of prostaglandins within the kidney.

Activation of the renin-angiotensin system- Ikram (22) demonstrated that acute and chronic administration of furosemide results in activation of the renin-angiotensin system (Figure 2). Bayliss (23) later demonstrated that chronic administration of furosemide in patients with heart failure results in long term activation of the renin-angiotensin system (Figure 3). Significant inverse correlations were found between plasma renin activity and hemodynamic indices (cardiac output and pulmonary artery pressure) (22).

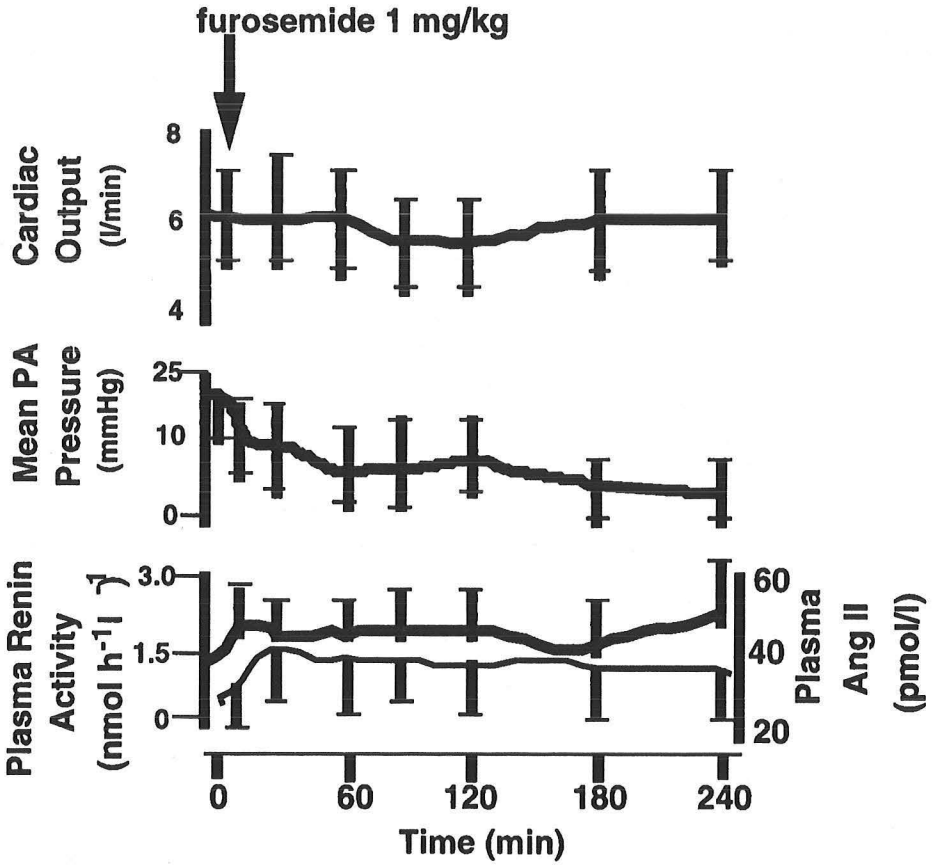


Figure 2

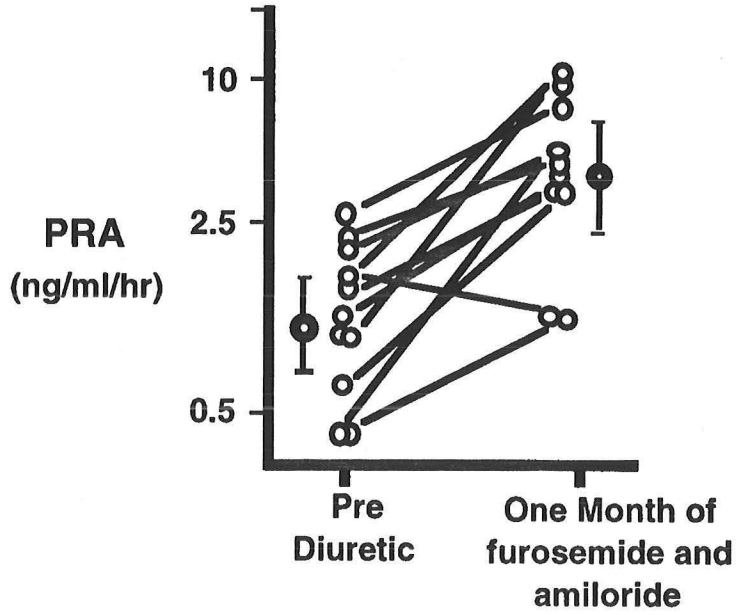


Figure 3

In addition, the SOLVD investigators found plasma renin activity was normal in patients with LV dysfunction from the SOLVD prevention (minimal or no symptoms) and treatment arms (symptomatic) who were not receiving diuretics and was significantly increased in patients on diuretic therapy (24).(Table I)

Table I

Chronic Effects of Diuretics on Renin-Angiotensin Activation in the SOLVD Study

	Controls	Prevention Patients		Treatment Patients	
		No diuretics	Diuretics	No diuretics	Diuretics
PRA (ng/ml/hr)	0.6	0.7	1.0*	0.7	1.7*†
	n=56	n=121	n=30	n=9	n=71

*p<0.05 vs patients not on diuretics; †p=0.3 vs prevention patients on diuretics

Arrhythmias- The combination of electrolyte disorders with activation of the neuroendocrine system (sympathetic nervous system and renin-angiotensin system) can create a dangerous melieu which can predispose the heart failure patient to malignant arrhythmias and sudden death (25).

Effect on Survival- No prospective survival study of diuretics has been performed in patients with heart failure. However, analysis of patients with coronary artery disease being treated in the MRFIT (26) trial and retrospective case-controlled study of hypertensive patients suffering cardiac arrest (27) suggest that diuretics in some high risk populations may produce a dose related increase in mortality (Figure 4).

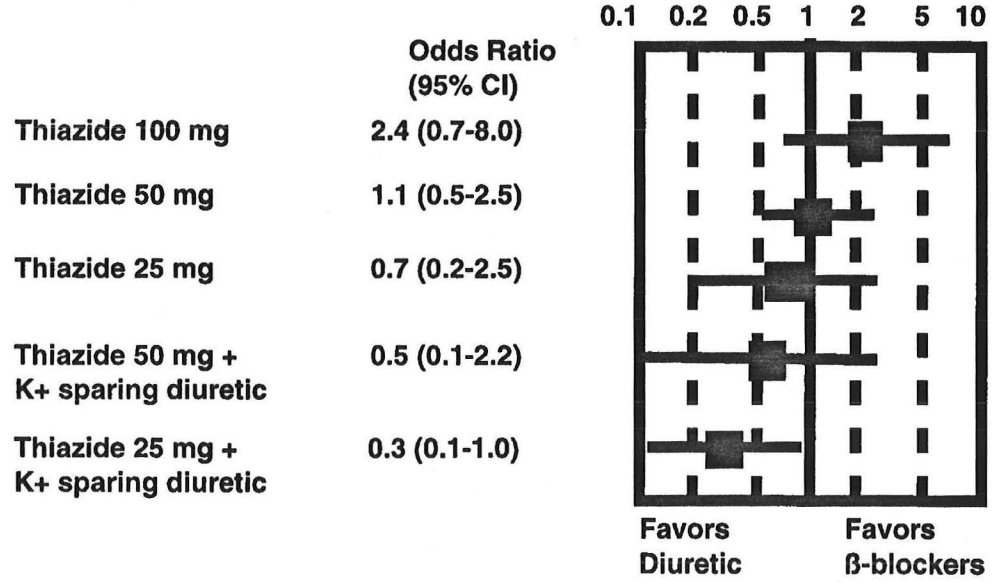


Figure 4

Digitalis

Mechanism of action- Digitalis preparations have been used for edema since it was described in 1785 by Sir William Withering. Digitalis preparations work primarily by inhibiting NaK-ATPase. This leads to activation of the sodium-calcium exchanger in the sarcolemma and increased intracellular calcium concentration. This produces improvement in contractile state. However, digitalis also has two other important effects: 1) improvement in myocardial relaxation and 2) neurohormonal antagonism. Eichhorn et al demonstrated that acute infusion of deslanoside (a fast acting digitalis) in patients with heart failure resulted in improvement in relaxation (28). In addition, the more impaired the relaxation (i.e. the more LV dysfunction present), the more improvement was seen after deslanoside. Ferguson and associates demonstrated with microneurography that administration of digitalis resulted in a reduction in sympathetic nerve traffic peripherally (29). This suggests digitalis may alter baroreflex desensitization in heart failure and reduce neurohormonal activation.

Clinical Trials showing Efficacy- In 1980, Arnold examined the effect of open label digoxin withdrawal and readministration in 9 patients with heart failure (30). He found that withdrawal resulted in elevation of pulmonary capillary wedge pressure and a reduction in cardiac output and stroke work. Readministration of digoxin resulted in a reduction in wedge pressure and an increase in stroke work.

Lee and associates examined the effect of digoxin in a double-blind, placebo-controlled crossover study of 25 patients without atrial fibrillation (31). The severity of heart failure (by sign and symptom score) was reduced by digoxin in 14 patients. Patients who best responded had more severe heart failure, more left ventricular dilatation, and an S_3 gallop. The presence of the gallop was the strongest correlate of the response to digoxin.

The Captopril and Digoxin trial was a multicenter, double-blind, placebo-controlled study comparing the effects of captopril treatment with those of digoxin during maintenance diuretic therapy in patients with mild to moderate heart failure (32). Compared to placebo, captopril resulted in improved exercise time and New York Heart Association class but digoxin did not (Table II). However, digoxin treatment increased left ventricular ejection fraction (4.4% increase) compared with captopril therapy (1.8% increase) and placebo (0.9% increase). Need for increased diuretics and hospitalizations were more frequent in the placebo group than either active arm. This study was biased against digoxin because most study patients had been receiving digoxin before the study and were withdrawn from digoxin therapy before randomization. Those who deteriorated on digoxin withdrawal were

not entered into the trial. Thus, those who most likely would have benefited from digoxin, were not entered.

Table II

Results of the Captopril-Digoxin Multicenter Study

	Treatment	N	Baseline Mean	Endpoint Mean (6M)	Mean Change
Exercise Time	Captopril	101	572	653	82*
	Digoxin	95	564	618	54
	Placebo	97	552	587	35
NYHA	Captopril	100	2.31	2.10	-0.20*
	Digoxin	95	2.32	2.22	-0.09
	Placebo	98	2.27	2.29	0.02
LVEF	Captopril	87	26.0	27.8	1.8
	Digoxin	82	26.0	30.4	4.4‡
	Placebo	78	26.3	27.2	0.9

*p<0.05 vs placebo; ‡p<0.05 vs placebo and captopril

In 1989, DiBianco and colleagues reported the results of a 12-week, double-blind, placebo-controlled trial comparing the effects of digoxin, milrinone, or the combination of the two versus placebo (33). Digoxin alone or milrinone alone significantly improved exercise time versus placebo, but the combination of the two did not (Figure 5). In addition, digoxin alone, milrinone alone, and the combination of the two significantly reduced the need for cointervention (need for additional heart failure therapy) during the 12 week study period.

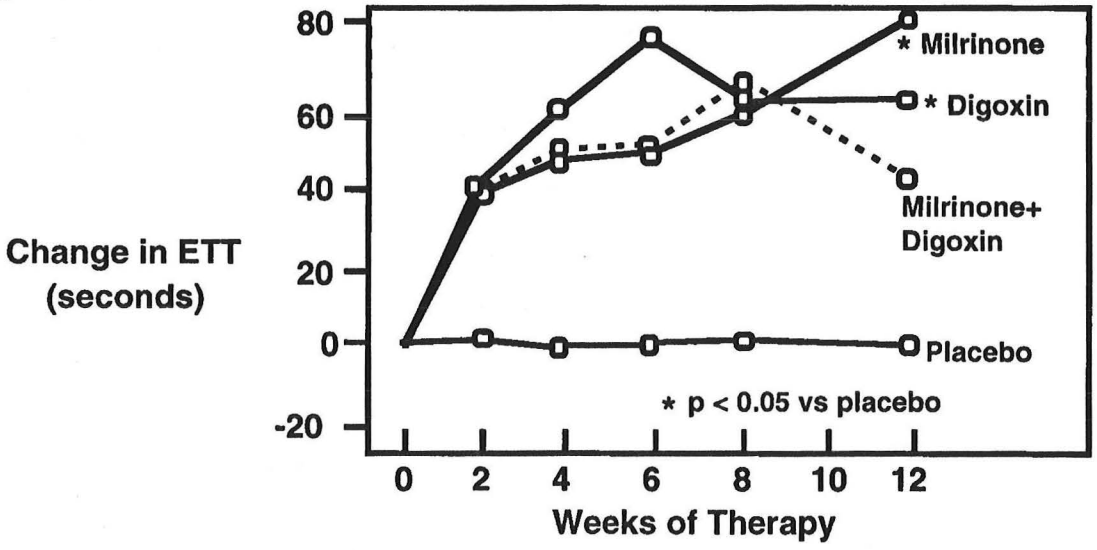


Figure 5

Two more recent trials, the RADIANCE study (34) and the PROVED (35) trial have shown the clinical benefit of digoxin therapy (Figure 6). In the RADIANCE study, 178 patients with moderate heart failure, EF < 0.35, and sinus rhythm were studied over 12 weeks in a double-blind, placebo-controlled fashion. Patients on ACE inhibitors and digoxin were randomized to continuing digoxin or switched from digoxin to placebo. Worsening heart failure developed in 23 placebo patients as compared to 4 patients in the digoxin group ($p<0.001$). All measures of functional capacity deteriorated in the patients receiving placebo as compared with those continuing digoxin ($p=0.033$ for maximal exercise tolerance, $p=0.01$ for submaximal exercise endurance, and $p=0.019$ for NYHA functional class). Patients switched to placebo also had decreased ejection fractions ($p=0.001$) and increases in heart rate ($p=0.001$). The PROVED trial was of similar design in 88 patients who were not taking ACE inhibitors. This trial demonstrated worsened maximal exercise capacity ($p=0.003$) and lower ejection fractions ($p=0.016$) in those switched to placebo compared to those continuing digoxin.

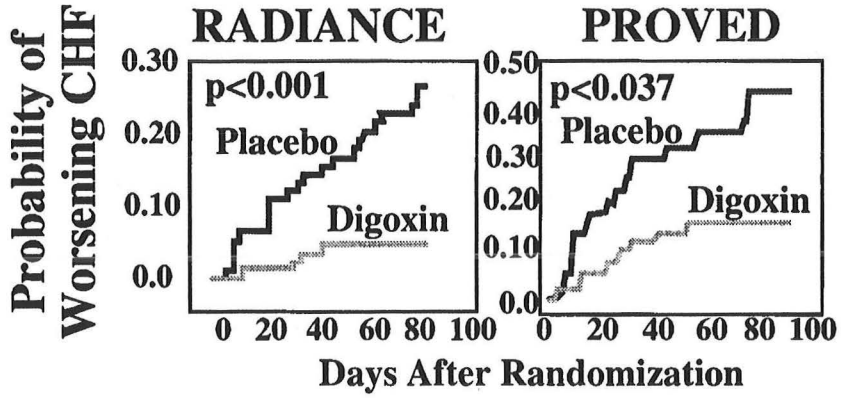


Figure 6

Effect on survival- The NIH sponsored DIG trial has completed randomization of 8000 patients and is completing follow-up. This trial will likely not show a big survival effect of digitalis either positive or negative as the trial has yet to be stopped. The results will be out in 1-2 years.

Adverse effects- Digitalis toxicity is the most significant adverse effect of these agents. It should be remembered that quinidine, verapamil, and amiodarone have all been shown to decrease total body clearance of digoxin. In patients with renal insufficiency or pre-renal azotemia due to heart failure, digitalis levels and evidence of toxicity must be closely monitored. Digitalis toxicity may result in nausea and vomiting, anorexia, and arrhythmias. For severe, life threatening arrhythmias, purified digoxin-specific Fab fragments are available.

ACE Inhibitors

Mechanism of action- ACE inhibitors work by antagonizing the conversion of angiotensin I to the vasoconstrictive and mitogenic angiotensin II, indirectly causing vasodilatation and decreasing aldosterone secretion.

Hemodynamic effects- The short and long-term effects of ACE inhibitors on hemodynamics were studied by the Captopril Multicenter Research Group (36). In an open label trial, 104 patients had a right heart catheterization. Favorable acute hemodynamic effects included improved cardiac index, stroke work, and reductions in systemic and pulmonary vascular resistance and left and right heart filling pressures. After 8 weeks of therapy, repeat catheterization demonstrated sustained hemodynamic benefit.

Sharpe made hemodynamic and echocardiographic assessments of 36 patients with moderate heart failure before and 3 months after randomization to either placebo (n=18) or enalapril (n=18) (37). He found improved exercise tolerance and functional class, reduced ventricular dimensions, reduced filling pressures with increased stroke volume in the enalapril group.

Exercise effects- Both the Captopril-Digoxin Multicenter study (32) and the Captopril Multicenter Research Group (38) have shown improvement in exercise tolerance with ACE inhibitors. In the trial by the Captopril Multicenter Research Group, 92 patients with refractory heart failure were randomized to captopril (n=50) or placebo (n=42). There was a 24% mean increase in exercise tolerance with captopril (495 ± 22 to 614 ± 27 seconds) as compared with 0.4% with placebo ($p<0.01$). There was also an increase in ejection fraction from 0.19 ± 0.02 to 0.22 ± 0.02.

Effect on Survival- In 1987, the CONSENSUS trial study group published their landmark trial of the effects of enalapril on mortality in 253 patients with severe heart failure (NYHA class IV) (8). The addition of enalapril reduced mortality by 40% (from 44% to 26%) at 6 months.(Figure 7)

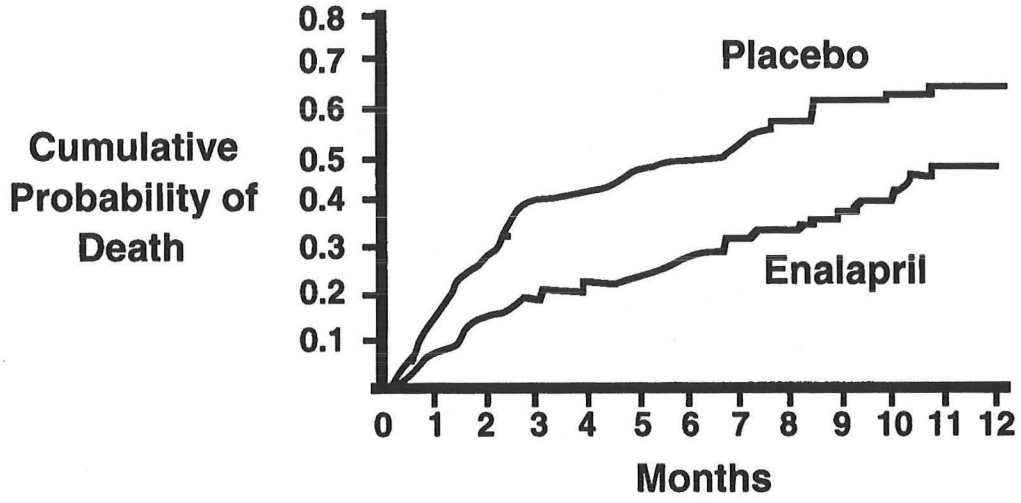


Figure 7

In V-HeFT II, 804 men with mild to moderate heart failure (NYHA class II-III) were placed on enalapril (n=403) or hydralazine plus isosorbide dinitrate (n=401)(6). Despite greater improvement in left ventricular ejection fraction and exercise time in the group receiving hydralazine plus isosorbide dinitrate, the group receiving enalapril had a better survival. The most likely reason for this is preferential reduction in plasma norepinephrine in the enalapril group in the first few months of therapy and antagonism of the renin-angiotensin system. However, despite this initial reduction in norepinephrine, plasma norepinephrine continued to rise over the subsequent 2 years of follow-up.

In the NIH sponsored SOLVD study, 6797 patients with an EF ≤ 0.35 were studied. Of these patients, 2569 patients had mild to moderate symptoms of heart failure and were randomized to placebo (n=1284) or enalapril (n=1285) in the "Treatment" trial (7) and followed for 41 months. Enalapril treatment resulted in a 16% reduction in death (95% CI = 5-26%, p=0.0036), primarily due to a reduction in pump failure death.(Figure 8)

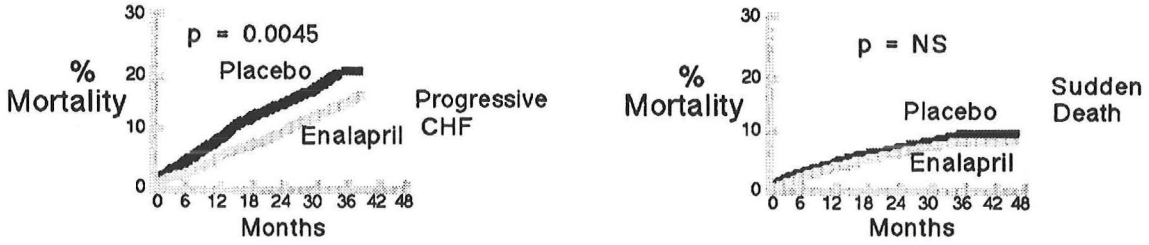


Figure 8

In addition, 4228 patients with no symptoms of heart failure but an EF ≤ 0.35 were randomized to placebo (n=2117) or enalapril (n=2111) in the "Prevention" trial and

followed for 37 months (39). Despite a large number of crossover patients from placebo to open label ACE inhibitor (about 40%) enalapril resulted in a cardiovascular risk reduction of 12% (CI = -3 to 26%, p=0.12) and a 20% reduction in hospitalization (95% CI = 9-30%, p<0.001).

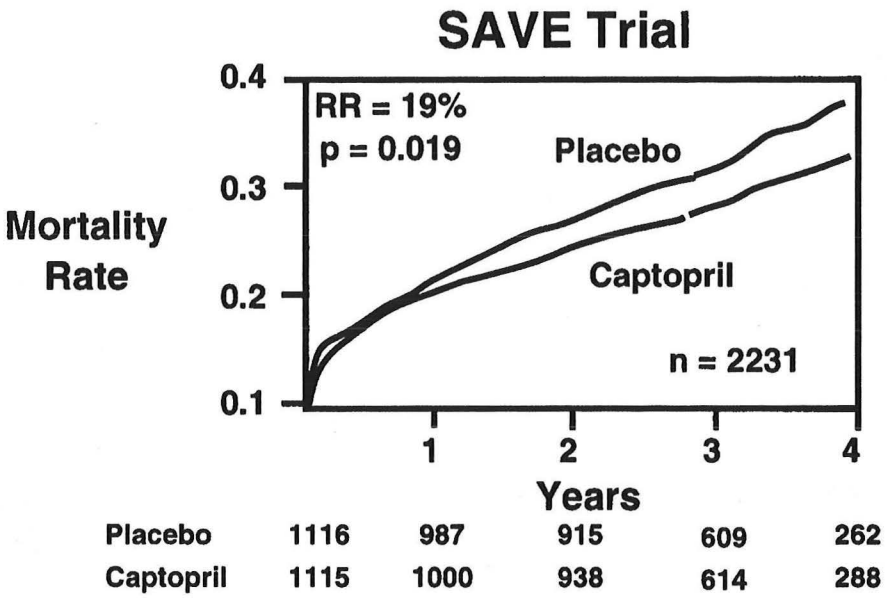


Figure 9

In 1992 the SAVE investigators reported their findings of the effect of ACE inhibitors on mortality in 2231 post myocardial infarction patients with an EF ≤ 0.40 (40). (Figure 9) Patients were randomized 3-16 days after infarction to placebo (n=1116) or captopril (n=1115) and followed for 42 months. All cause mortality was reduced in the captopril group by 19% (95% CI 3-32%, p=0.019). In addition, captopril resulted in a 37% reduction in cardiovascular death (p<0.001), and like the SOLVD trial, a 25% reduction in myocardial infarction was seen (p=0.015).

Adverse Effects- The most important side effects include: 1) hypotension on therapy initiation 2) cough 3) hyperkalemia and 4) increased creatinine.

Inotropic Agents

Milrinone-

Milrinone is a Phosphodiesterase III inhibitor which works by preventing cAMP degradation. This results in augmented protein kinase activation and improved calcium flux within the myocyte. Milrinone is both an inotropic agent and vasodilator.

Acute hemodynamic evaluation of oral milrinone has demonstrated that this agent increases contractility (as reflected by peak +dP/dt), cardiac output, and myocardial work while reducing pulmonary capillary wedge pressure, systemic and coronary vascular resistance (41-44).

Clinical efficacy- The Digoxin-Milrinone study by DiBianco (33) demonstrated that milrinone improved exercise duration over placebo during 12 weeks of follow-up (Figure 5).

Effect on Survival- The PROMISE trial examined the effect of milrinone on survival in patients (n=1088) with moderate to severe heart failure who were receiving ACE inhibitors (1). In this study, with a median follow-up of 6.1 months, there was a 28% increase in cardiovascular mortality in the milrinone treated group. The increase in mortality was greatest in the most sick patients (i.e. NYHA class IV). The cause of increased mortality was an increase in sudden death (arrhythmias) (45).

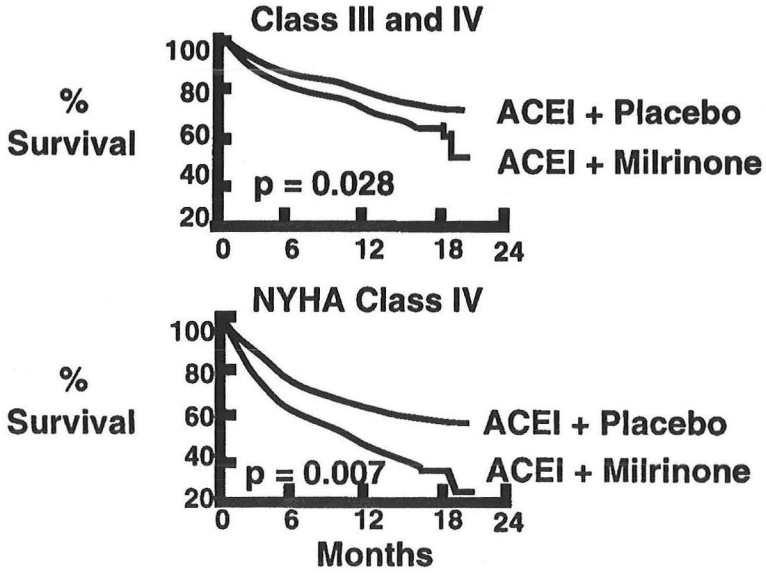


Figure 10

Xamoterol-

This agent is a highly selective β_1 antagonist with partial beta-agonist properties. Thus, it acts much like a sympathomimetic agent. Xamoterol improves contractility, ejection fraction, relaxation rate and reduces left ventricular filling pressures (46,47).

Clinical efficacy- The German-Austrian Xamoterol trial randomized 433 patients with mild to moderate heart failure to xamoterol (n=220), digoxin (n=104), or placebo (n=109) (48). Compared to placebo, xamoterol improved exercise duration and work done on a bicycle ergometer while digoxin showed no benefit over placebo.

Effect on Survival- The Xamoterol in Severe Heart Failure trial randomized 516 patients with moderate to severe heart failure (NYHA class III-IV) despite ACE inhibitors to xamoterol (n=352) or placebo (n=164) and followed the patients for 13 weeks (49). Despite the short follow-up, there was a significant increase in mortality with xamoterol ($p=0.02$).

Flosequinan-

Flosequinan is a balanced arterial and venous vasodilator with inotropic actions independent of ß-receptors (50-52). This agent produces a dose related increase in myocardial work, cardiac index, stroke volume index, and oxygen consumption and reduces myocardial efficiency (50).

Clinical efficacy- The FACET trial randomized 322 patients with moderate heart failure (NYHA class II-III) and LVEF ≤ 0.35 on ACE inhibitors and digoxin to flosequinan 100 mg once daily (n=110), flosequinan 75 mg twice daily (n=102), or placebo (n=110) (53). After 16 weeks, 100 mg flosequinan produced an increase in median exercise time compared with placebo ($p<0.05$) while the higher dosage of 75 mg twice daily did not exhibit a significant increase in exercise time.

The REFLECT study randomized 193 patients with class II-III heart failure and an EF < 0.40 to flosequinan 100 mg daily (n=93) or placebo (n=100) (54). After 12 weeks, exercise time increased preferentially in the flosequinan group ($p=0.022$ vs placebo).

Effect on Survival- The PROFILE trial randomized 2304 patients with class III-IV heart failure and LVEF ≤ 0.35 despite ACE inhibitors and digoxin to flosequinan or placebo (55). After 22 months, a 43% excess mortality was seen in the flosequinan group as compared to placebo ($p<0.05$).

Vesnarinone-

Vesnarinone is a quinolinone derivative which augments contractility not by increasing cAMP, but by increasing intracellular sodium due to prolonged opening of sodium channels (56, 57).

Effect on Survival- The Vesnarinone study group randomized 253 patients with EF < 0.30 and moderate to severe heart failure (class II-IV) to high dose vesnarinone 120 mg daily, moderate dose vesnarinone 60 mg daily, or placebo (58). The high dose arm was

terminated for increased mortality, and the 60 mg (n=239) vs placebo (n=238) arms were continued with 6 months follow-up. Vesnarinone 60 mg daily reduced mortality by 50% (95% CI = 20-69%, p=0.003)(Figure 11) and quality of life improved to a greater extent in the vesnarinone group over 12 weeks (p=0.008). The high dose arm probably increased mortality due to a predominant inotropic effect while the low dose arm prolonged life as low dose has little inotropic effect and significant anti-cytokine activity.

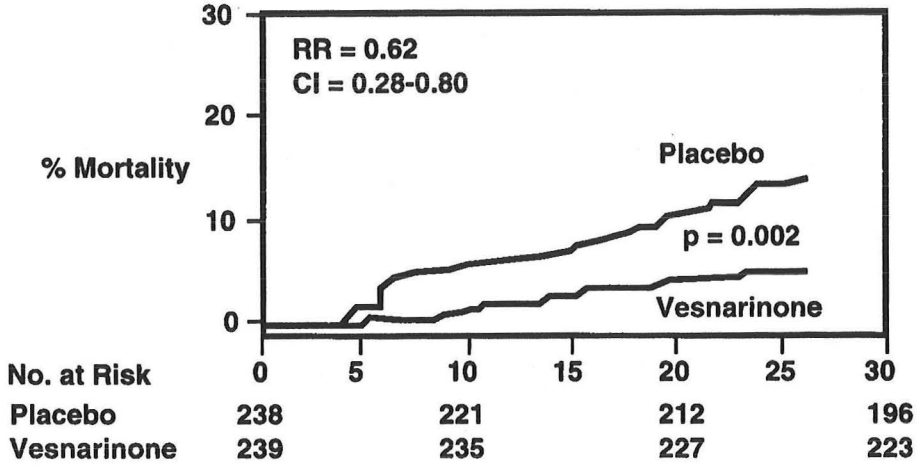


Figure 11

The VEST trial will examine the effect of Vesnarinone in a second mortality trial.

Adverse effects- Reversible neutropenia occurs in 2.5%. (58)

Intermittent Dobutamine-

Dobutamine is a ß-adrenergic agonist with positive inotropic and lusitropic (relaxation) properties (44). The use of dobutamine in patients with congestive heart failure acutely results in an increase in heart rate, cardiac output, stroke work, and a concomitant increase in myocardial oxygen consumption (43,44,59,60). Raising oxygen consumption in a heart which is already energy starved may have adverse consequences long-term (61,62). Pulmonary capillary wedge pressure does not change significantly with dobutamine (43,60). As with oral ß-agonists (63), tolerance develops after approximately 72 hours of infusion and this is most likely due to ß-receptor downregulation (63,64). As previous investigators had found (using right heart catheterization and serial endomyocardial biopsies) that patients improved their cardiac output and ATP/creatine ratio in heart tissue after a 3 day infusion of dobutamine (65), a trial of intermittent dobutamine was attempted (66). In this trial, a double-blind placebo controlled trial design was employed and the dobutamine patients received a mean dose of 8 µg/kg/min. The dobutamine patients increased exercise time as compared to placebo ($p<0.05$). However, the trial was stopped due to excess deaths in the dobutamine group. Thus, intermittent

dobutamine must be considered as a last ditch effort to improve patient symptomotology with the patient's understanding that it may shorten survival.

Ibopamine

Mechanism of action- Ibopamine is a dopamine congener which is converted after absorption to N-methyldopamine (diisobutyric ester of epinine) (67,68). This is hydrolyzed by plasma esterases to epinine. Epinine activates DA_1 and DA_2 receptors. The drug exerts its effect through peripheral (arterial) vasodilation and mild inotropy (67,69).

Hemodynamic effects- After oral administration, cardiac output and stroke volume increase by 20-25% and systemic and pulmonary vascular resistance drop by 5-20% over 3-6 hours (68-72). However, immediately after administration, ventricular filling pressures and pulmonic arterial pressure may transiently increase at higher dosages (69,72). The mechanism of this biphasic response is unclear.

Neurohormonal effects- Long-term therapy may result in a reduction in plasma renin activity and norepinephrine levels (73,74). The latter effect is presumably due to presynaptic DA2 agonism which may inhibit the release of norepinephrine from presynaptic nerve endings (75). Ibopamine reduces angiotensin II levels and studies have shown that ibopamine reduces cardiac (tissue) ACE levels after MI in rats (76).

Clinical efficacy- In a large 6 month study of 150 elderly patients with heart failure, ibopamine was as effective as captopril in improving exercise tolerance and symptoms (77). The recent Dutch Ibopamine Multicenter Trial (DIMT) randomized 64 patients with moderate heart failure and an EF $\leq$ 0.45 to ibopamine (n=22), digoxin (n=22), or placebo (n=20) (74). No background therapy (such as ACE inhibitors was allowed). After 6 months of therapy, ibopamine and digoxin resulted in improvement in exercise time (+48 seconds for ibopamine and +17 seconds for digoxin, both $p<0.05$ vs placebo). Plasma norepinephrine decreased in the group receiving ibopamine (-24 pg/ml) and digoxin (-98 pg/ml). A smaller double-blind ibopamine trial (n=25) failed to show an effect of ibopamine on exercise capacity, oxygen consumption, or ventilatory threshold (71).

Effect on survival- The effect of ibopamine on survival in patients with heart failure is being prospectively tested in the second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME II) trial. Despite these promising effects, ibopamine may not yet be a viable option for heart failure treatment due to the biphasic hemodynamic response and an unknown effect on mortality.

Pimobendan

Mechanism of action-Pimobendan is a benzimidazole-pyridazinone derivative that is thought to augment contractility by 1) increasing the affinity of the regulatory site on troponin C for calcium and 2) having a modest inhibitory effect on phosphodiesterase III (78).

Hemodynamic effects- Acute administration of pimobendan results in a dose dependent increase in resting cardiac index and lowered pulmonary capillary wedge pressure without a significant change in heart rate and systemic arterial pressure (79). One chronic study of pimobendan demonstrated no significant change in ejection fraction with pimobendan (78).

Clinical efficacy- Two randomized, placebo controlled studies have shown an improvement in exercise duration with pimobendan as compared to placebo (78,79). The larger of these two trials, involving 198 patients, found a significantly better effect on exercise duration and maximal oxygen consumption with 5.0 mg of pimobendan as compared to 10 mg daily (78). In addition, the 5.0 mg group had the best improvement in quality of life as measured by a standardized questionnaire (78,80).

Effect on survival- No prospective study of survival has been performed. Thus, the effects of pimobendan on survival are unknown.

ß-adrenergic Blocking Agents

Despite the hemodynamic and survival benefit provided by ACE inhibitors, plasma norepinephrine continues to rise over time (81) and the mortality of patients treated with an ACE inhibitor remains high (1). Multiple small trials of ß-adrenergic blockade have been performed to date and all have consistently shown two things: 1) ß-adrenergic blockade when given carefully in a controlled fashion is safe and 2) consistent improvement in left ventricular function and functional class is demonstrated. In fact, no ß-blocker trial of greater than 1 month duration has failed to show an improvement in left ventricular function (10,82,83). (Table III)

Table III

Controlled Trials of ß-blockers

Trial	Nos.	Pre LVEF	Post LVEF	↑Exercise	↓Symptoms
Engelmeier et al (84)	8	.13±.06	.18±.05	Yes	Yes
Ikram et al*(85)	15	.47±.13	.44±.15	No	-----
Currie et al*(86)	10	-----	-----	No	-----
Gilbert et al (87)	23	.26±.07	.35±.11	No	Yes
Pollock et al (88)	12	.19±.07	.23±.08	Yes	Yes
Woodley et al (89)					
all patients	29	.23±.08	.29±.11	No	Yes
IDC	13	.26±.06	.35±.10	No	Yes
ISCDC	16	.21±.08	.23±.09	No	Yes
Metra et al (90)	40	.20±.07	.30±.12	Yes	Yes
Olsen et al (91)	54	.20±.06	.31±.12	Yes	Yes
MDC (92)	380	.14±.03	.31±.16	Yes	Yes
Bristow et al (93)	139	.24±.07	.30±.12	No	No
Wisenbaugh (94)	24	.23±.08	.33±.12	No	-----
Paolisso et al (95)	10	-----	-----	Yes	Yes
Krum et al (96)	49	.17±.07	.24±.11	Yes	Yes
Eichhorn et al (97)	24	.22±.10	.33±.13	-----	Yes
Fisher et al (98)	50	.22±.08	.29±.11	Yes	Yes

IDC = Idiopathic dilated cardiomyopathy; ISCDC = Ischemic dilated cardiomyopathy.
*Denotes trial of only 1 month duration.

Effects on hemodynamics and energetics-

Eichhorn has shown with bucindolol (open label) (99) and metoprolol (double-blind, placebo-controlled) (97) that left ventricular ejection fraction and performance improves with 3 months of ß-blockade in patients with dilated cardiomyopathy.(Figure 12)

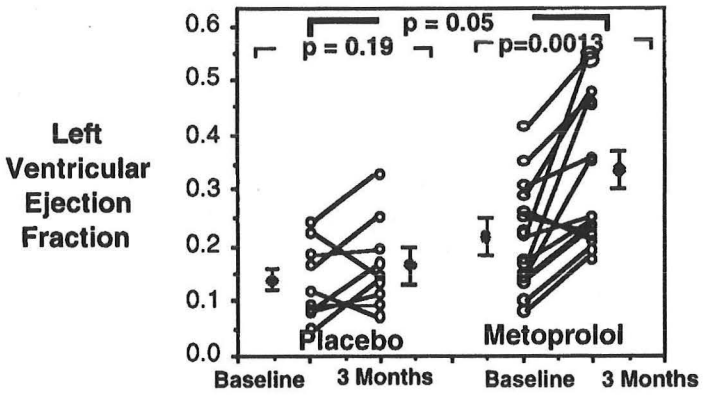


Figure 12

The improvement in performance seen in the study by Eichhorn is probably due to improved contractility.(Figure 13)

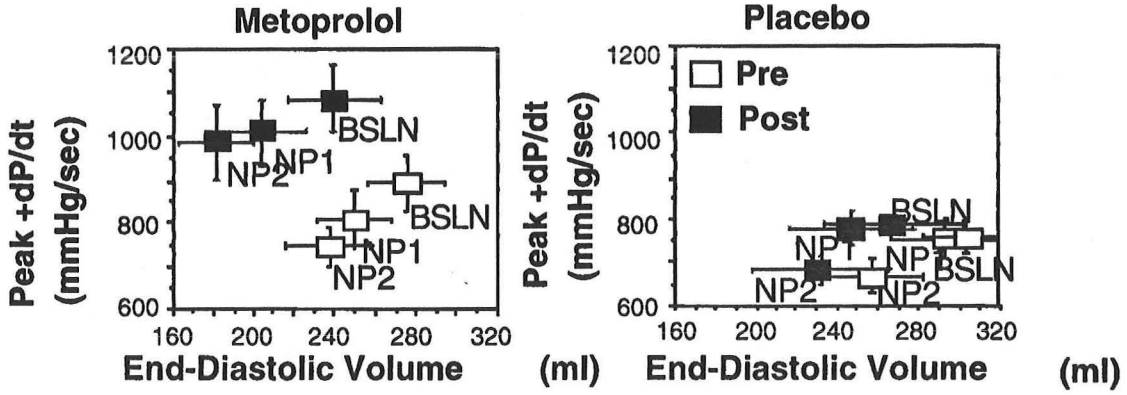


Figure 13

In addition, left ventricular mechanical work increased while myocardial oxygen consumption decreased suggesting improved myocardial efficiency. Eichhorn also found a strong inverse relation between change in coronary sinus norepinephrine (a measure of adrenergic activation of the heart) and myocardial respiratory quotient (a surrogate measure of substrate utilization) (97). These data suggests that ß-blockade may work by shifting substrate utilization from fatty acids to carbohydrate use, a more efficient fuel.

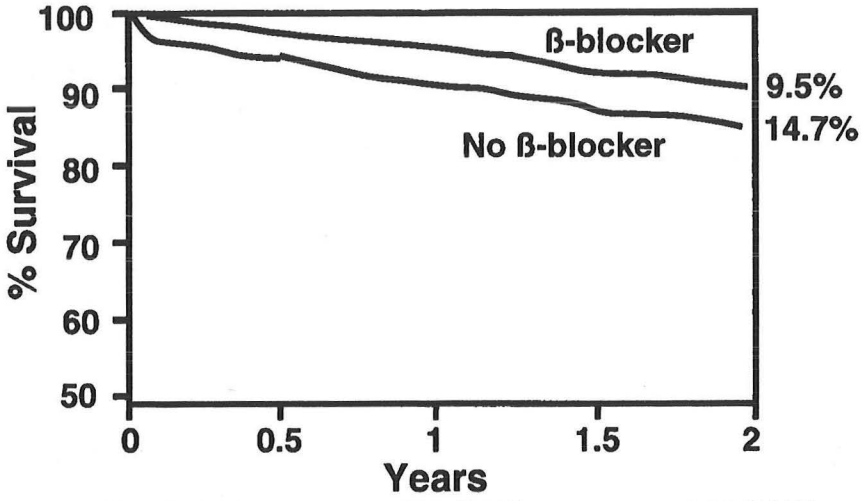
Bristow and colleagues demonstrated in a double-blind, placebo-controlled trial of bucindolol that improvement in left ventricular ejection fraction is a dose related phenomenon with larger dosages producing preferential effects (93). In addition, this study and that of Woodley (89) demonstrated differences in the response to ß-blockers for patients with non-ischemic dilated cardiomyopathy versus ischemic cardiomyopathy.

Hall and Eichhorn demonstrated in an echocardiographic study that left ventricular ejection fraction does not improve with ß-blockade until at least 1 month of therapy, and may worsen slightly on initial administration (100). In addition, after 18±5 months of follow-up, they found that left ventricular mass regressed, volumes diminished, and the ventricle assumed a more elliptical (rather than spherical) configuration. These data are the first to suggest that reverse remodeling may occur in patients with congestive heart failure.

Effects on survival-

Chadda retrospectively examined the effects of ß-blockers on survival in patients who received propranolol or placebo in a double-blind fashion after a myocardial infarction in the NIH sponsored ß-blocker Heart Attack Trial (BHAT) (101). He found that propranolol reduced mortality, cardiovascular mortality, and sudden death versus placebo. However, the greatest benefit was in patients with evidence of heart failure at presentation.

In the Cardiac Arrhythmia Suppression Trial (CAST), the effect of antiarrhythmic agents on mortality after myocardial infarction was tested (102,103). An excess mortality was seen with encainide or flecainide treatment compared to placebo. However, when the patients with an ejection fraction ≤ 0.40 were retrospectively examined, survival to death/cardiac arrest was significantly better in patients receiving beta-blockers by 43% at 30 days ($p=0.03$), 46% at 1 year ($p=0.0001$) and 33% at 2 years ($p<0.0001$) than in patients not taking beta-blockers (82).(Figure 14) Survival from arrhythmic death/cardiac arrest was significantly better in beta-blocker patients by 66% at 30 days ($p=0.0019$), 53% at 1 year ($p=0.0001$) and 36% at 2 years ($p=0.0003$). Kaplan-Meier survival analysis over 2.5 years, adjusted for antiarrhythmic and placebo therapy showed that beta-blocker patients had a significantly better prognosis for survival from death, arrhythmic death, and cardiac arrest.



ß-blocker	718 (100%)	637 (95%)	386 (91%)
No ß-blocker	1893 (100%)	1539 (90%)	938 (85%)

Figure 14

The Metoprolol in Dilated Cardiomyopathy (MDC) Trial demonstrated a morbidity and mortality (combined endpoint) benefit in patients with dilated cardiomyopathy (92). In this study, 388 patients were randomized to metoprolol or placebo. All patients were taking angiotensin converting enzyme inhibitors. Morbidity was defined as need for transplantation and follow-up was for 18 months. The results of this small trial demonstrated no overall difference in death, but a marked reduction in need for transplantation in the group receiving metoprolol. This represents a 36% risk reduction (p=0.058) in morbidity and mortality beyond angiotensin converting enzyme inhibitors alone. While there was no difference in death between the groups, there was a disproportionate number of transplants in the placebo group. In addition, during the follow-up period, 41% of the placebo group required hospitalization for heart failure as compared to 24% of the metoprolol group (p=0.005).

The Cardiac Insufficiency Bisoprolol Study (CIBIS) trial randomized 641 patients with moderate heart failure to the $ß_1$ selective agent bisoprolol or placebo (9). While this trial was underpowered and while only half of the patients were titrated to target dosage, there was a trend in favor of bisoprolol (p=0.22, RR=0.80, CI=0.56-1.15). In the subgroup of patients who had no prior history of myocardial infarction, there was a clear survival benefit (p=0.034). In addition, the use of a $ß_1$-selective agent in the CIBIS and MDC trials (bisoprolol in the CIBIS trial and metoprolol in the MDC trial) left the $ß_2$ receptor unblocked, thus begging the question as to whether selective ß-antagonists are as effective as non-selective agents for reducing sudden death (105). (Figure 15)

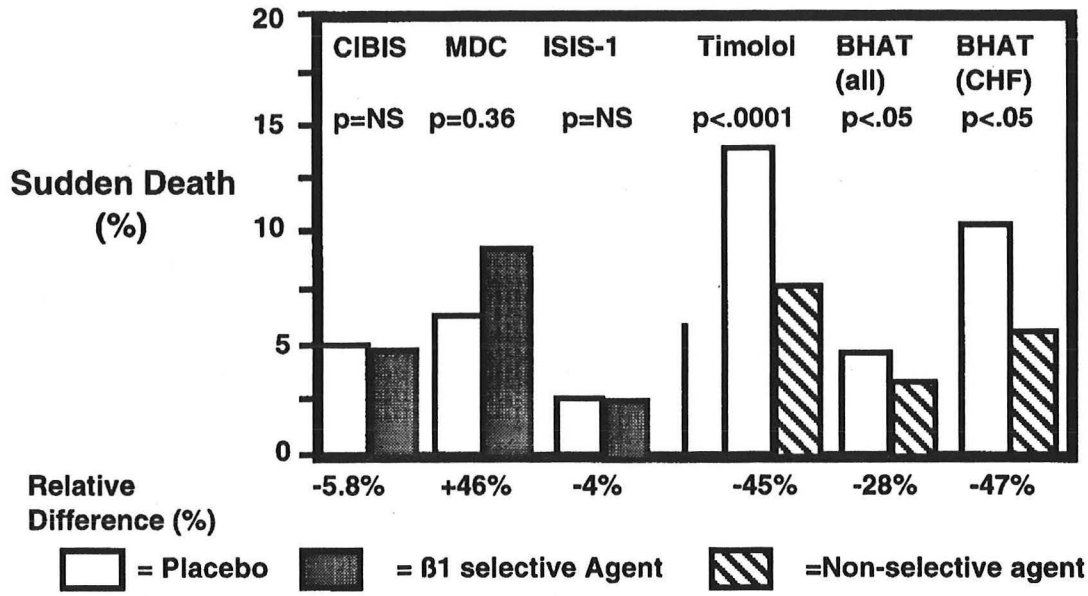


Figure 15

The Carvedilol Trials were recently stopped by the Data and Safety Monitoring Committee for a survival benefit of carvedilol. While the details of these trials have not been revealed, it should be noted that these trials were designed as exercise trials in patients with mild to moderate heart failure and patients were pre-selected based on exercise response.

The NIH-VA sponsored ß-Blocker Evaluation of Survival Trial (BEST) just began randomization May 1995 (106). This study will evaluate in a prospective fashion whether ß-adrenergic blockade will reduce mortality in patients on optimal medical therapy (ACE inhibitors and digitalis). The study will recruit 2800 patients with EF≤0.35 and NYHA class III-IV heart failure.

Calcium Channel Blockers

Mechanism of action- These agents produce powerful vasodilator effects and variable negative inotropic effects by interfering with transmembrane calcium transients. As congestive heart failure may be a state of myocyte calcium overload (107) with elevated afterload and vascular resistance, one might speculate that calcium antagonists might be beneficial in patients with heart failure. Two generations of calcium antagonists currently exist. The first generation agents (verapamil, diltiazem, nifedipine) have direct negative inotropic effects on myocytes while the second generation agents (amlodipine, felodipine) are much more vascular selective.

Effects of calcium antagonists on ventricular function- Not unexpectedly, the addition of a first generation calcium antagonist to the regimen of a heart failure patient results in depression of myocardial contractility (108,109). However, this is often offset by peripheral vasodilation which reduces afterload and allows maintenance of cardiac output and often acute improvement in ejection fraction (109,110). While the short term effects on hemodynamics may appear to be beneficial, long term therapy results in ventricular enlargement (108).

Long-term effects on exercise tolerance and symptomatology- Although both ß-blockers and calcium antagonists exert negative inotropic effects acutely, long-term therapy with ß-blockers are beneficial while therapy with first generation calcium antagonists appears to be deleterious (108, 111,112). The latter agents produce no improvement in exercise time (108,112) and a significantly higher incidence of hospitalization for worsening heart failure (112, 113). The reason for this appears to be the activation of neurohormonal systems, especially the renin-angiotensin system with calcium antagonists when given to patients with heart failure (108,114-117). Such activation of the renin-angiotensin system results in fluid retention, ventricular enlargement, worsening vasoconstriction and perhaps maladaptive remodeling.

By contrast, more recent studies with second generation calcium antagonists are more promising. A recent study with amlodipine demonstrated sustained improvement in exercise tolerance over 8 weeks (118) and the PRAISE trial was recently concluded, demonstrating no adverse effect of amlodipine on mortality in patients with heart failure. In fact, in the subset of patients with no coronary disease, there was a mortality benefit (unpublished data). These data suggest that the more vascularly selective calcium antagonists may not activate the renin-angiotensin system like the first generation agents.

Summary

Agent	Effect on on LVEF	Effect on Symtoms	Effect on Ex.Tolerance	Effect on Survival
Diuretics	→	↓	→↑	→↓
Digitalis	↑	↓	↑	?→
ACE Inhibitors	→↑	↓	↑	↑↑
Inotropes				
Milrinone	→	↓	↑	↓↓
Xamoterol	→	↓	↑	↓↓
Flosequinan	→↑	↓	↑	↓↓
Dobutamine	→	→↓	↑	↓↓
Ibopamine	?	→↓	→↑	?
Pimobendan	→	→↓	→↑	?
Vesnarinone	→	→↓	→	↓↓ (High dose) ↑↑ (Low Dose)
ß-blockers	↑↑	↓	→↑	↑↑
Calcium antagonists				
1st generation	→	↑	→	?↓
2nd generation	→	↓	↑	→↑

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