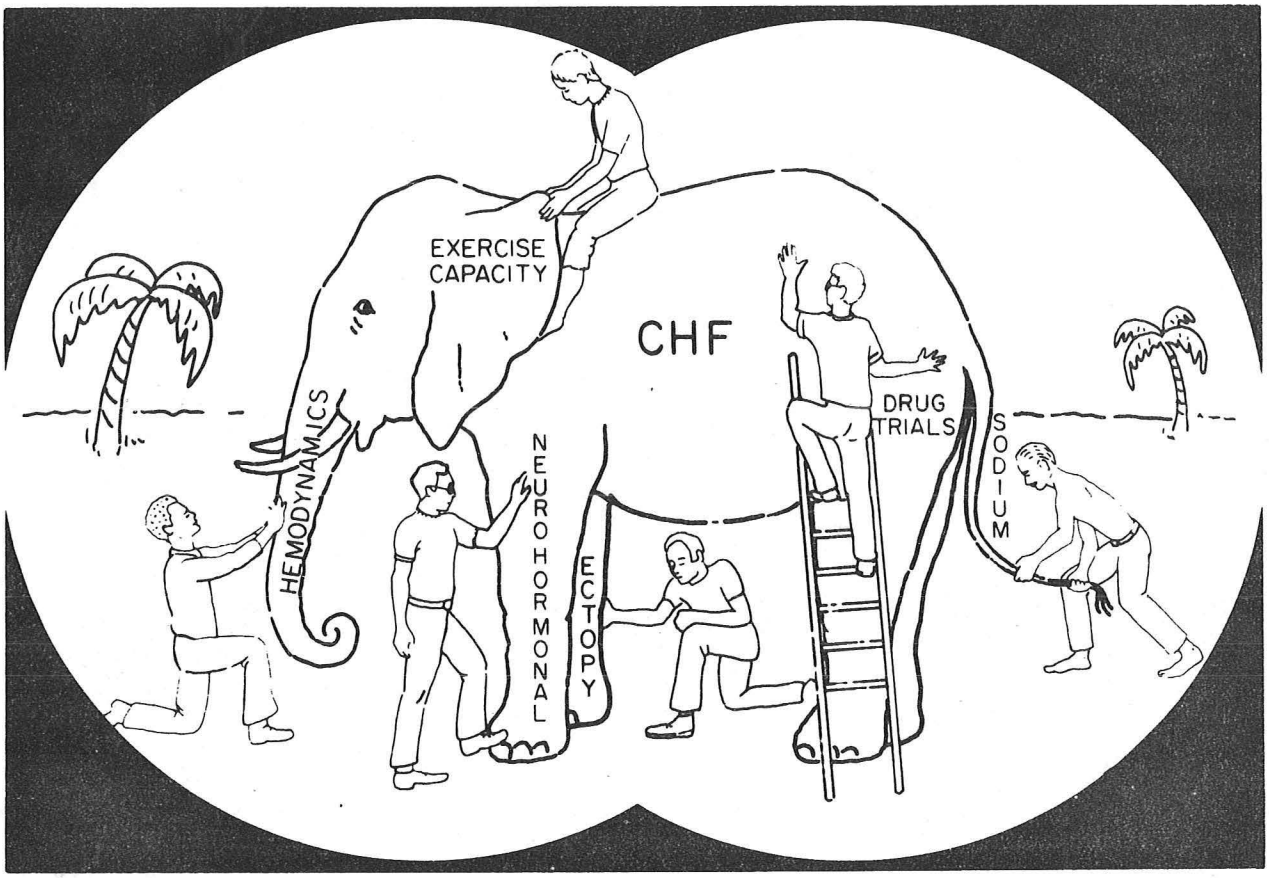
Heart

THE MULTIFACETTED ROLE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN CONGESTIVE HEART FAILURE



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INDEX

"A physician without physiology flounders along in an aimless fashion never able to gain any accurate conception of disease, practicing a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which."

Sir William Osler

I. Introduction

Heart failure is traditionally defined as that condition in which the heart is no longer able to pump an adequate supply of blood to meet the metabolic needs of the body. However, the current operational definition is that heart failure is a condition in which ventricular dysfunction is accompanied by reduced exercise capacity.

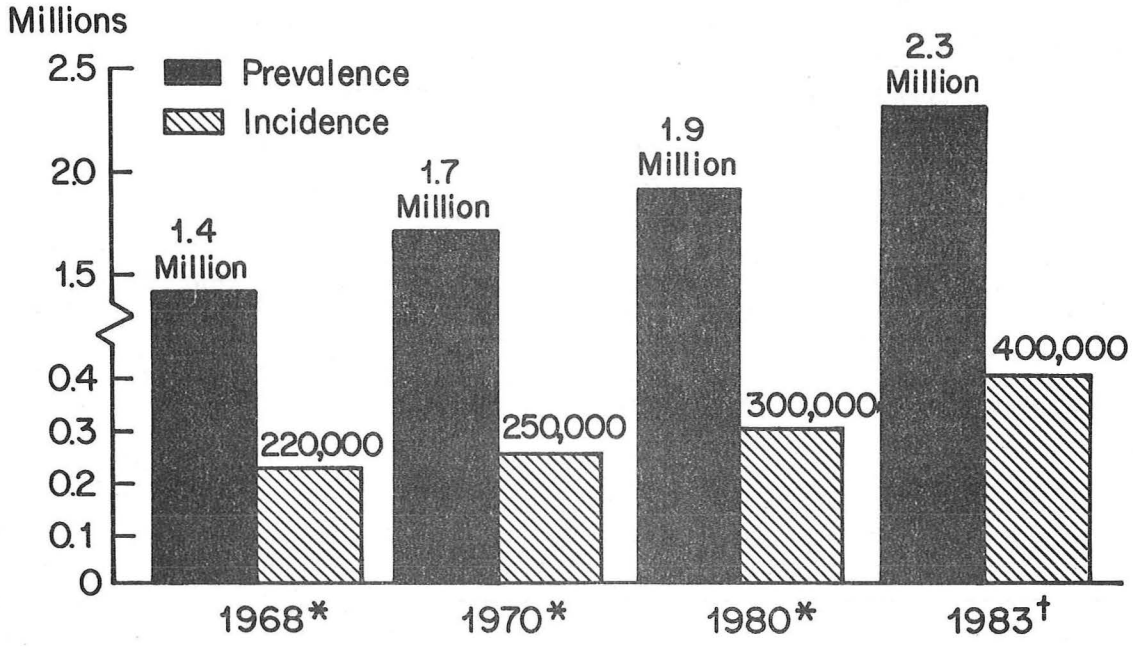
Congestive heart failure is not a disease but a symptom complex that ensues when the heart is damaged by a wide variety of pathological processes. The myocardium may be primarily dysfunctional (e.g. following myocardial infarction, cardiomyopathies), or be dysfunctional as a secondary result of some other process (e.g. valvular heart disease, intracardiac shunts). In addition, the ventricular dysfunction may be predominantly systolic, predominantly diastolic, or both systolic and diastolic.

The present discussion will focus on the most prevalent problem, namely, predominant systolic left ventricular dysfunction with cardiac dilatation, and the role of angiotensin converting-enzyme inhibitors in the management of this condition. The two most common causes of this condition are coronary artery disease and so-called idiopathic dilated cardiomyopathy.

Congestive heart failure is currently one of the most common diagnoses among hospitalized patients on general medical wards. Both the estimated prevalence and the incidence of congestive heart failure are increasing (Figure 1), despite a decrease in the incidence of acute myocardial infarction (1). For both men and women, the average annual incidence of heart failure doubles each decade from 45 to 75 years (2). For patients aged 65 to 74 years, the incidence of cardiac failure is 8.2 per 1000 for men and 6.8 per thousand for women, compared to 1.8 per thousand for men and 0.8 per thousand for women in the 45-54 year old age group. Thus, despite the dramatic benefits and excellent long-term survival in patients undergoing heart transplantation (3,4), a large number of patients are likely to be ineligible for heart transplantation because of their age. It is therefore appropriate to reevaluate the potential value of currently available modalities of medical therapy.

PREVALENCE AND INCIDENCE OF CHF IN THE U.S.

Population Aged 45 and Over



* Gibson TC et al: *J Chronic Dis* 1966:19:141-152
† Framingham rates applied to 1981 census
Adapted from McFate Smith W: *Am J Cardio* 1985:55:4A

Figure 1

The mainstays of medical therapy of heart failure are: (1) diuretics, (2) diet (low salt); (3) digitalis, and (4) vasodilators or ACE inhibitors.

A recent survey of physician practice in the management of congestive heart failure by Hlatky et al (5) suggests that more than 50% of physicians use diuretics alone as initial therapy for the patient with heart failure in normal sinus rhythm (Figure 2). Seven percent of these physicians surveyed used digitalis alone, 30% used digitalis and a diuretic and 9% used vasodilators alone as initial therapy. Although powerful loop diuretics, such as furosemide; ethacrynic acid and bumetanide, may be an extremely effective way of producing a natriuresis and diuresis initially, they may lose their salutary effects rapidly when administered in repeated large doses due to activation of the renin-angiotensin-aldosterone systems, with resultant sodium retention (6). At the same time, renal potassium and magnesium loss persists. This is potentially very detrimental to the patient. Both hypokalemia and hypomagnesemia are well recognized as potentiators or instigators of ventricular arrhythmias (7). In the light of this observation, it is appropriate to critically evaluate the potential role of vasodilators, with particular reference to the angiotensin-converting enzyme (ACE) inhibitors, as well as digitalis, in the management of heart failure.

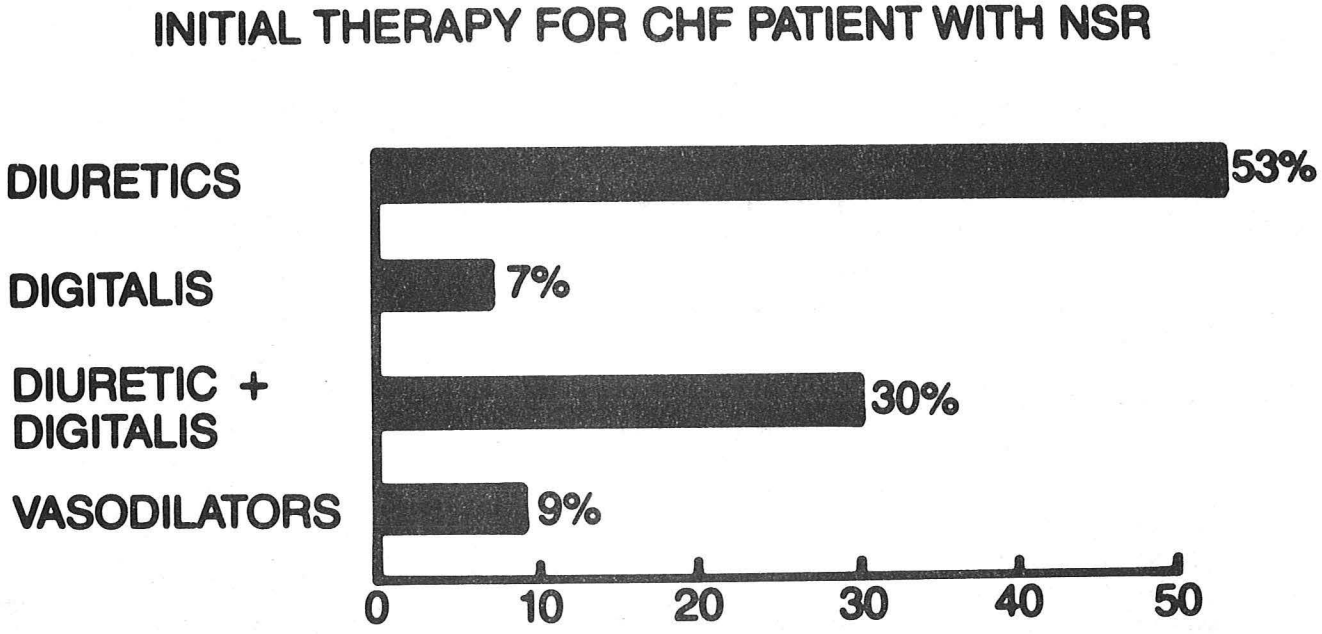


Figure 2
Physician practice in the management of congestive heart failure: Initial therapy for the patient with normal sinus rhythm. (From Hlatky MA, et al: J Am Coll Cardiol 8:966, 1986).

II. Comparative Hemodynamic Effects of Vasodilators and ACE Inhibitors

A brief list of some of the major orally active vasodilators and ACE inhibitors that have been evaluated acutely and chronically in congestive heart failure is presented in Table I. The efficacy of these agents in heart failure may be assessed by their effects on hemodynamic variables (acute and/or chronic), symptomatic status (evaluated subjectively or objectively), and/or survival.

TABLE I
Major Orally Active Vasodilators and ACE Inhibitors

Arteriolar Vasodilators
Hydralazine
Minoxidil
Calcium entry blockers
Venodilators
Nitrates
Combined Arteriolar and Venodilators
Prazosin
ACE Inhibitors
Captopril
Enalapril

The fundamental concepts underlying the beneficial hemodynamic effects of vasodilator agents has been well understood for several years. In normal individuals, cardiac output is relatively insensitive to changes in left ventricular afterload. On the other hand, in patients with depressed ventricular function, increases in afterload result in a decrease in cardiac output; consequently, agents that produce a decrease in afterload may facilitate left ventricular ejection and result in an increase in stroke volume and cardiac output. Several agents, including hydralazine and minoxidil, have this as their major mode of action (8).

Vasodilators may also produce a decrease in left ventricular preload, with a resultant decrease in pulmonary congestion. This effect is beneficial unless the preload is reduced to such an extent that one is functioning on the steep portion of the Frank-Starling curve, at which time a further decrease in left ventricular filling pressure may result in decreases in stroke volume, cardiac output and ultimately systemic arterial blood pressure. This is a potential hazard with any agent that possesses preload-reducing properties. Certain agents, such as the nitrates, have major preload reducing effects (9). Other agents, including prazosin and the angiotensin-converting enzyme inhibitors, have mixed preload and afterload reducing effects i.e. they typically produce an increase in cardiac output and a concomitant decrease in left ventricular filling pressure (10,11).

The acute regional hemodynamic effects of the vasodilators listed in Table I are generally similar: they increase blood flow to the renal, cerebral and splanchnic vascular beds but do not acutely increase blood flow to exercising muscle (8,12,13,14). Their effects of the coronary circulation has also been studied. Rouleau et al (15) compared the effects of captopril, hydralazine and prazosin in patients with heart failure on the relationship between myocardial oxygen consumption and an index of myocardial oxygen demand (heart rate - systolic blood pressure double product). Captopril produced a consistent reduction in myocardial oxygen demand and a concomitant reduction in myocardial oxygen consumption; the response to prazosin was more variable, and hydralazine produced no significant change in either myocardial oxygen demand or oxygen consumption (15).

All of the agents mentioned in Table I produce acute hemodynamic effects. Most of these agents also possess chronic hemodynamic effects. The major exception to this rule is prazosin. Several investigators have documented the frequent occurrence of hemodynamic tolerance developing with the chronic administration of prazosin (16,17). In fact such tolerance may be detectable as early as the third day after commencing therapy. The contrast between the hemodynamic effects of repeated doses of prazosin versus captopril are shown in Figure 3 (18). This probably explains why prazosin has proven to be generally unsatisfactory as a chronic orally active vasodilator.

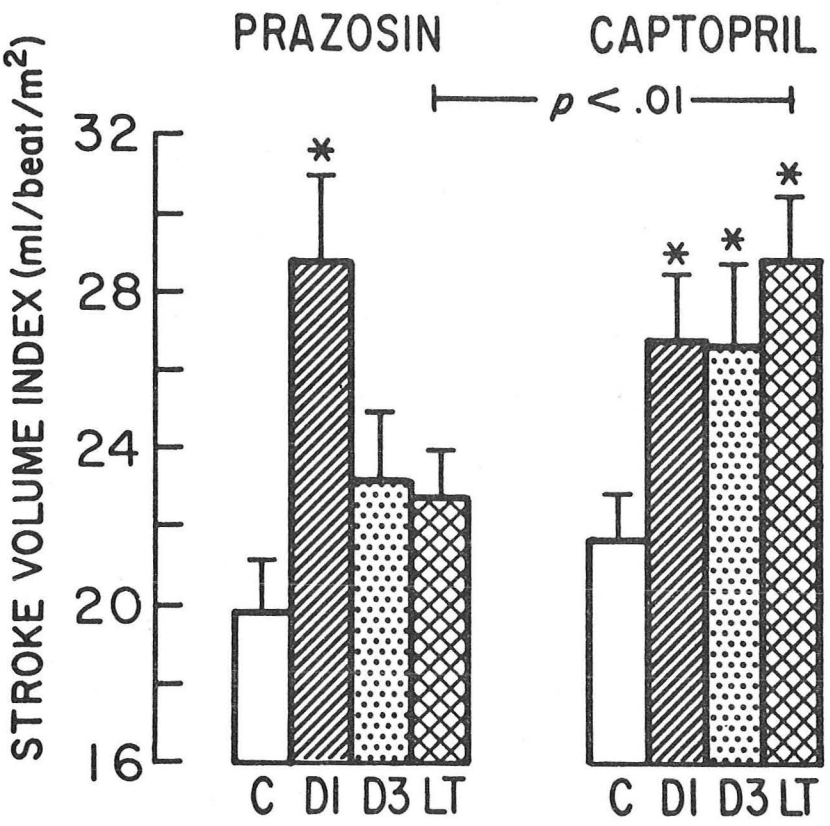


Figure 3
Serial values for stroke volume index during the course of sequential therapy with prazosin and captopril in 18 patients. C=baseline; D1 = first dose; D3 = day 3; LT = long-term. (From Packer M, et al: Am J Cardiol 57:1323, 1986).

III. Mechanism of Action of ACE Inhibitors

Despite extensive study over the past decade, our understanding of the mechanism of action of the ACE inhibitors continues to evolve and is still incomplete. The vast majority of the experimental data available relate to the use of captopril, a sulfhydryl containing ACE inhibitor. Consequently, I shall focus most of my attention on this agent. The second ACE inhibitor to be released for clinical use, enalapril maleate, requires metabolism by the liver to its active form, enalaprilate. It does not possess a sulfhydryl group, and has a longer duration of action than captopril (Figure 4) (19,20). There are currently more than 30 ACE inhibitors in various stages of evaluation: the major differences between these various agents seems to relate to (1) their duration of action and (2) the presence or absence of a sulfhydryl group, which has certain mechanistic implications.

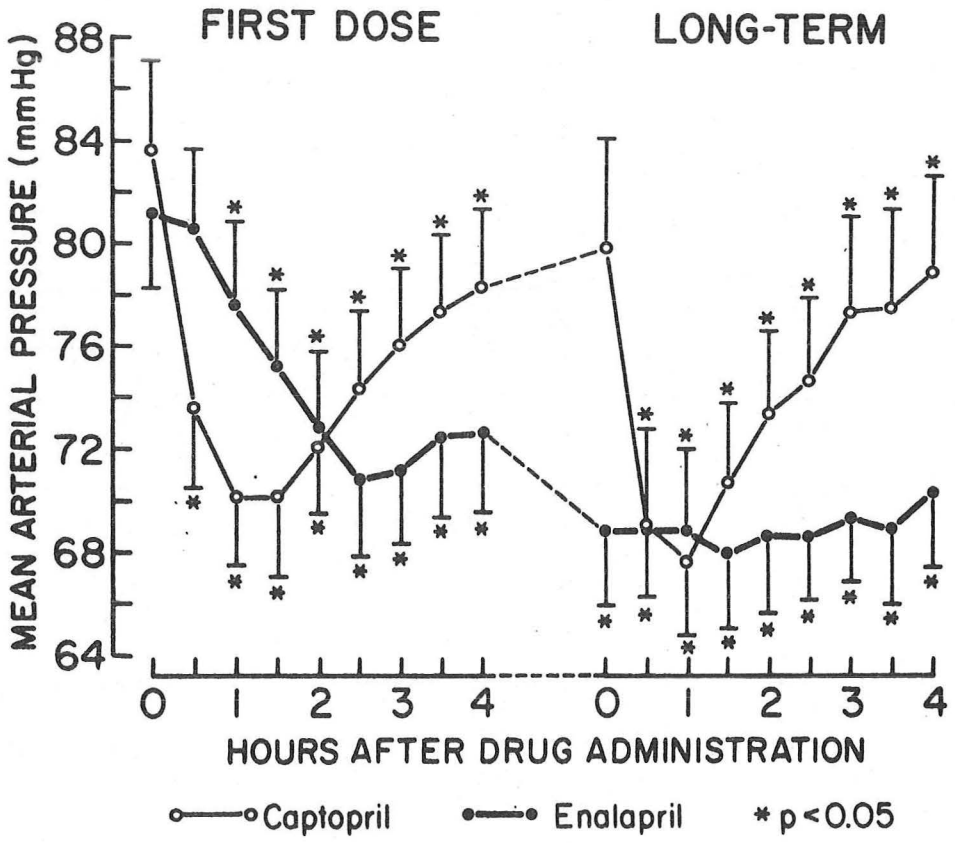


Figure 4
Sequential changes in mean arterial pressure after the administration of the first dose of captopril and enalapril and after doses of each drug during long-term therapy. (From Packer M, et al: N Engl J Med 315:847, 1986).

Our initial understanding of the mode of action of the ACE inhibitors was that they blocked the converting enzyme required for the conversion of angiotensin I (a relatively weak vasoconstrictor), to angiotensin II (a much more powerful vasoconstrictor). This would be expected to result in a decrease in circulating angiotensin II, as well as aldosterone, which is produced in response to increased concentrations of angiotensin II. There is a concomitant increase in angiotensin I, as well as plasma renin activity (PRA), by virtue of a negative feedback loop. However, since ACE inhibitors produce substantial hemodynamic effects even in the presence of low concentrations of PRA and angiotensin I, an alternative mechanism of action seems likely under these circumstances (21). Kininase II, the enzyme responsible for the breakdown of vasodilatory kinins, including bradykinin, appears to be essentially identical to the angiotensin-converting enzyme (22). Thus, it seems that a second mode of action of ACE inhibitors may be by blocking kininase II, and hence decreasing the rate of breakdown of vasodilator kinins (22). Although this effect can be demonstrated *in vitro*, it is much more difficult to prove *in vivo*, since the kinins are largely locally active tissue factors. It has consequently been difficult to demonstrate an increase in circulating vasodilatory

kinins, although there may be a detectable increase in urinary excretion of these substances (22).

A third mechanism of action appears to be confined to the sulfhydryl-containing ACE inhibitors, namely, stimulation of production of vasodilator prostaglandins (23). Zusman compared the effects of ACE inhibitors with differing chemical structures on prostaglandin E_2 biosynthesis by rabbit renomedullary interstitial cells and demonstrated convincingly that the ACE inhibitors that contained a sulfhydryl group, such as captopril, stimulated PGI_2 and PGE_2 biosynthesis, while those without the sulfhydryl moiety, such as enalapril, did not (23). Swartz et al (24) have also recently documented a captopril-induced increase in circulating PGE_2, without a significant change in 6-keto $PGF_{1\alpha}$ or thromboxane B_2, in normal volunteers. A more complicated schema for the mechanism of action of captopril is thus in order, and is illustrated in Figure 5 (23).

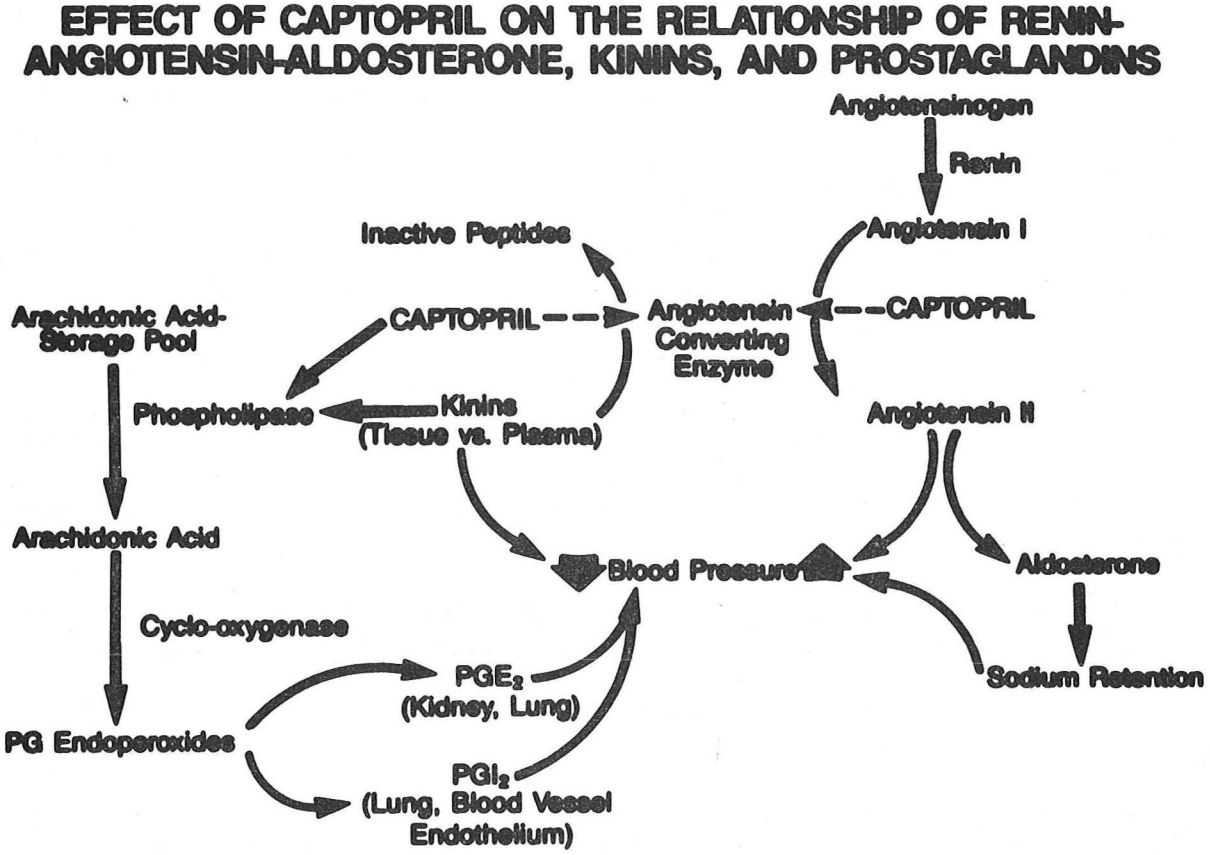


Figure 5
(From Zusman RM: Kidney Int 25:969, 1984).

The presence of a sulfhydryl moiety on an ACE inhibitor may have certain other important and distinctive effects. First, stimulation of prostacyclin (PGI_2) biosynthesis may be beneficial in the reduction of reperfusion arrhythmias (25). Second, the ability to act as a sulfhydryl donor may have important implications with regard to attenuating tolerance to long-acting nitrate preparations. It is well known that N-acetylcysteine may result in a restoration of the hemodynamic effects of long-acting nitrates by acting as a sulfhydryl donor (26). A recent study in isolated rat hearts, compared the effects of ramipril (a non-sulfhydryl containing ACE inhibitor) to captopril, and N-acetylcysteine (27). Captopril and N-acetylcysteine had potentiated the effects of isosorbide dinitrate on coronary flow to a similar degree; this effect was not observed for the combination of ramipril and isosorbide dinitrate. These sulfhydryl-related effects are enjoying considerable attention, and may confer potential advantages to this class of ACE inhibitors in certain situations. However, it is worth recognizing that these effects can generally be blocked by the concomitant adminstration of indomethacin or other non-steroidal anti-inflammatory agents.

Captopril has also recently been shown to inhibit platelet aggregation *in vivo*, but not *in vitro*, and to inhibit the generation of oxygen free radicals (28,29). It is uncertain whether other ACE inhibitors also possess these properties.

There is a further level of complexity to the understanding of the mechanism of action of ACE inhibitors. Dzau has demonstrated that the tissue effects of the ACE inhibitors may far outlast and outweigh their effects on circulating hormones and that they are involved in an autocrine or paracrine system (30,31). Thus, much of the effect of the ACE inhibitors at a tissue level may not be explicable on the basis of changes in circulating hormones. Indeed, the major changes in circulating hormones may only occur as a "spill-over" phenomenon. It is consequently very difficult to assess to what extent the beneficial effects produced by an ACE inhibitor in a particular system is the result of *inhibition* of the renin-angiotensin-aldosterone system (with secondary effects on norepinephrine) versus an *augmentation* of the effects of vasodilator substances, such as kinins and vasodilator prostaglandins.

IV. Effects of ACE Inhibitors on Symptomatic Status and Exercise Tolerance

Among the vasodilators, the ACE inhibitors as a group have proven singularly successful with regard to improving symptomatic status and exercise tolerance. Because a placebo effect may be observed in as many as 30% of patients with congestive heart failure, it is imperative to give particular credence to placebo-controlled, randomized studies. Several placebo-controlled studies have documented a substantial improvement in symptomatic status and exercise tolerance in response to prolonged administration of captopril (32-36). The largest of these studies was a multicenter, placebo-controlled study of captopril in which 49 patients received captopril and 42 received placebo, for at least a 3 month period (33). In this study, 81% of patients were slightly, moderately or greatly improved by captopril compared to 28% on placebo, and exercise duration increased by 24.3% on captopril compared to 0.4% on placebo (Figure 6).

The available controlled studies suggest that captopril does not produce an acute effect on exercise tolerance, that the beneficial effect is progressive with time, and that by 18 months to 2 years there is no evidence of tolerance to the medication. The fact that exercise tolerance does not improve acutely suggests that the vasoconstriction with resultant limitation of limb blood flow is not due to the acute effects of angiotensin II, but may be related to other factors, including sodium content in the vessel wall (36-40).

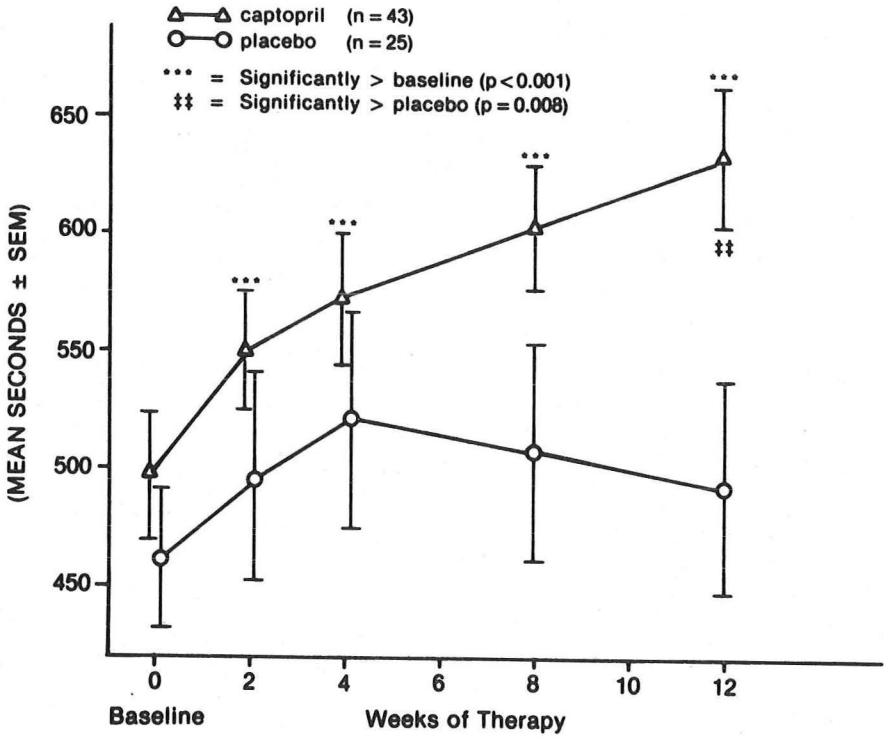


Figure 6
The effect of captopril versus placebo on exercise tolerance. (From The Captopril Multicenter Research Group: J Am Coll Cardiol 2:755, 1983).

Several other ACE inhibitors have also been shown to increase exercise tolerance in placebo-controlled studies, including enalapril and lisinopril (41-45). The available studies on enalapril have generally shown a less impressive effect on exercise tolerance than captopril while the multicenter study of lisinopril showed a somewhat greater effect on exercise tolerance than captopril, in the dosages chosen. Whether these differences are real and drug related, or are due to some other extraneous factor, remains to be determined.

The generally salutary effects of ACE inhibitors on symptomatic status and exercise tolerance should be compared with the effects of other orally-active vasodilators. A placebo-controlled trial of prazosin from this institution was the first to demonstrate the general lack of efficacy of this vasodilator over a 6-month treatment period (46) (Figure 7). Likewise, hydralazine has not generally proven superior to placebo in terms of its effects on symptomatic status or exercise tolerance (47). In

addition, it frequently causes an increase in fluid retention (8,47). This problem is even more marked with minoxidil (8). In contradistinction, oral nitrate preparations, such as isosorbide dinitrate have been shown to increase exercise tolerance modestly, but significantly (48,49). The combination of hydralazine and isosorbide dinitrate may also improve exercise tolerance (50).

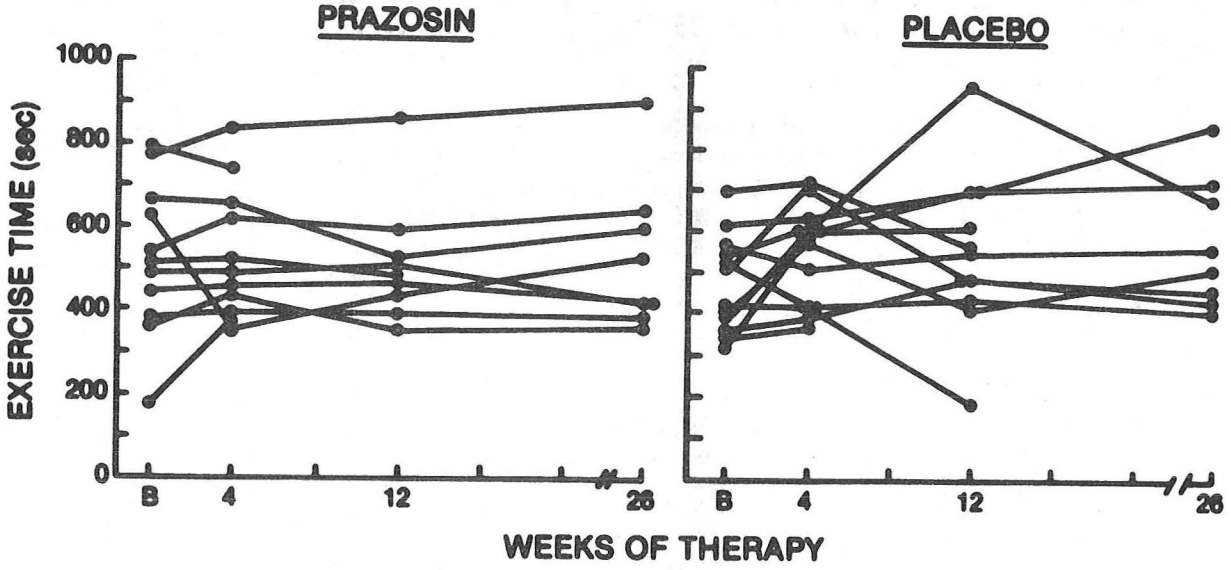


Figure 7

The effect of prazosin versus placebo on exercise tolerance. (From Markham RV, et al: Am J Cardiol 51:1346, 1983).

Several small studies have compared captopril to other agents in head-to-head comparisons. Bayliss et al compared the effects of captopril to prazosin in a randomized, double blind, cross-over study in 19 patients with congestive heart failure (51). After 1 month of captopril treatment, 15 patients were symptomatically improved and their exercise tolerance increased by 35%; after 1 month of prazosin treatment, 5 patients improved subjectively, 8 were worse and there was a mean increase in exercise tolerance of only 4%. Lilly et al compared the effects of captopril to hydralazine in a small study of 16 patients with heart failure (52). Exercise duration increased by 21% in those treated with captopril compared to 0.4% for those treated with hydralazine. In addition, they noted a marked increase in circulating norepinephrine in the hydralazine treated group but no change in those treated with captopril. The calcium channel antagonists also have major vasodilator effects; however, in addition, they also have negative inotropic effects, which may limit their potentially beneficial effects in patients with heart failure. The effects of captopril and nifedipine were compared in 26 patients with congestive heart failure in a randomized, cross-over study by Agostoni et al (53). Patients were studied for 2 months on each drug. Captopril significantly improved NYHA Class and exercise tolerance, while increasing cardiac output and decreasing pulmonary capillary wedge pressure. Conversely, nifedipine was not associated with any significant improvement in symptoms or exercise tolerance, 12 patients had an increase in weight and 11 an increase in peripheral edema. The results of studies directly comparing the effects of

an ACE inhibitor to isosorbide dinitrate, or a hydralazine/isosorbide combination are currently awaited.

V. Effects of ACE Inhibitors on the Kidney

The effects of ACE inhibitors on the kidney have been reviewed extensively by Dr. Bob Toto in a recent Grand Rounds (August 6, 1987). I shall therefore only touch on this subject as it relates to congestive heart failure.

In patients with congestive heart failure, the resultant decrease in cardiac output is accompanied by a decrease in renal blood flow. The end-result of this process is activation of the renin-angiotensin-aldosterone system. In turn, the renin-angiotensin-aldosterone system then plays an important role in regulating renal function (54-58). Angiotensin II has several important effects on the kidney: (1) it increases systemic resistance in most vascular beds, thereby channeling the available blood flow to the vital organs, including the kidneys; (2) it causes vasoconstriction of both the renal afferent and efferent arterioles; (3) it decreases glomerular filtration rate and renal blood flow resulting in an increased filtration fraction; and (4) it directly stimulates proximal tubular sodium reabsorption.

The use of an ACE inhibitor may consequently counteract all of these effects (58-60). In general, the resultant effect is beneficial with an increase in renal blood flow, glomerular filtration rate, natriuresis and diuresis. However, under certain circumstances the kidney may be critically dependent on angiotensin II to maintain the perfusion pressure to the kidney, and in particular the efferent arteriolar constriction (61,62). Packer et al (62) have identified three conditions under which ACE inhibitors may result in a deterioration in renal function in the setting of congestive heart failure: (1) relative hyponatremia, with resultant marked activation of the renin-angiotensin-aldosterone system and constriction of the efferent arteriole; (2) diabetes mellitus, which is associated per se with impaired constriction of the efferent arteriole (63); and (3) the use of long-acting ACE inhibitors, e.g. enalapril or lisinopril. Packer et al have suggested that these 3 variables are independent determinants of the risk of developing renal insufficiency, and that the risk is cumulative (Table II) (62).

TABLE II

No. of Risk Factors	% Pts Developing Renal Insufficiency
0	13%
1	38%
2	76%
3	100%

Independent risk factors: (1) hyponatremia, (2) treatment with long-acting ACE-inhibitor, (3) diabetes mellitus

After Packer M: Am J Cardiol 60:179, 1987

The duration of action of the ACE inhibitor does seem to be an important variable affecting the incidence of renal insufficiency. Captopril has its maximal hemodynamic effect within 60-90 minutes and mean arterial pressure returns to baseline by 5-6 hours (20). Conversely, lisinopril has a sustained hemodynamic effect for up to 36 hours (64), while enalapril falls somewhere between these two extremes (20). The duration of effect on the efferent arteriole per se is unknown but presumably bears some relationship to the duration of systemic hemodynamic effects. In head-to-head comparisons of captopril (mean dose 100mg/day) and lisinopril (mean dose 12mg/day), the BUN increased in 5% of those treated with captopril as compared to 18% of those treated with lisinopril ($p<0.05$) (65). In the study of enalapril versus captopril by Packer et al, in which comparatively large doses of captopril (150mg daily) and enalapril (40 mg daily) were administered, 23% of those treated with captopril and 43% of those treated with enalapril developed worsening azotemia (20). There was also a high incidence of hypotension and renal insufficiency in the initial patients entered into the CONSENSUS study until the first dose of enalapril was reduced from 5 mg b.i.d. to 2.5 mg daily in those with hyponatremia (66). It thus seems wise to start with low doses of ACE inhibitors (e.g. captopril 6.25 mg or enalapril 2.5 mg), particularly in patients who are hyponatremic, diabetic or marginally hypotensive at the outset. A case can also be made for preferring shorter acting ACE inhibitors in these patients.

VI. Digitalis Versus ACE Inhibitors

The use of digitalis in the management of patients with congestive heart failure who are in sinus rhythm remains controversial. Arnold et al (67) demonstrated that chronic digoxin therapy had a sustained, beneficial hemodynamic effect and Lee et al (68) showed that digoxin therapy may result in symptomatic improvement in patients with a dilated left ventricle and a third heart sound. On the other hand, Gheorghiade and Beller (69) and Fleg et al (70) showed that digoxin therapy could be discontinued in

the vast majority of patients with stable heart failure in sinus rhythm without any adverse long-term effects. Although there has been no major placebo-controlled study to document its efficacy, digoxin has remained one of the cornerstones of the medical therapy of congestive heart failure. Indeed, virtually every study of vasodilator or ACE inhibitor therapy to date has required that these agents be added to standard therapy, i.e. digitalis and diuretics. For this reason, the findings from a recently reported double-blind study that compared the effects of digoxin, captopril and placebo in 300 patients with mild-moderate heart failure, who were only on diuretics, is of particular importance (71). In this study, the diuretic dosage could be adjusted as required in all three groups. The captopril dosage was 50mg t.i.d., and the digoxin dosage 0.125 to 0.375 mg daily. The serum digoxin concentration was maintained at greater than 0.7 ng/ml by dosage adjustments regulated by a central co-ordinating committee. Patients were followed at regular intervals for at least 6 months. The primary objective of this prospective, randomized, double-blind, multicenter trial was to determine whether or not treatment with captopril or digoxin, in addition to diuretic maintenance therapy, would lead to improvement in exercise tolerance over a period of six months.

The cardinal information from this study is shown in Table III. Captopril produced a significant increase in exercise tolerance time (+17%) and a significant improvement in NYHA Class (+41%) as compared to placebo ($p<0.05$), but did not result in a significant increase in left ventricular ejection fraction. Conversely, digoxin produced a significant increase in left ventricular ejection fraction ($p<0.01$) without a concomitant significant improvement in NYHA Class or exercise tolerance, when compared to placebo. In addition, captopril produced a significant decrease in ventricular arrhythmias compared to digoxin in those patients with more than 10 ventricular premature beats per hour ($p<0.05$).

TABLE III

CAPTOPRIL/DIGOXIN/PLACEBO STUDY

300 Patients: Digoxin 96; Captopril (50 mg tid) 104; Placebo 100

		Change From Pre-Treatment	
Pre-Treatment	**Captopril**	**Digoxin**	**Placebo**
ETT 563sec	**+17%***	**+11%**	**+9%**
LVEF 26%	**+1.8%**	**+4.4%****	**+0.9%**
VPB 67/h	**-15/h**	**+61/h**	**+33/h**
FC 2.3	**+41%*****	**+31%**	**+22%**

Difference * from placebo ($p<0.05$), ** from placebo ($p<0.005$), and captopril ($p<0.05$), * from placebo ($p<0.01$).**

Captopril-Digitalis Research Group,

J Am Coll Cardiol 1987; 9:203A

Two other observations relating to this study are potentially important. There was a significant reduction in hospitalizations and emergency room visits ($p<0.05$) in both the captopril and the digoxin-treated patients, compared to the placebo group. This occurred despite the fact that diuretic dosage was increased in 30% of the placebo group as compared to only 10% in the captopril or digoxin groups.

These data clearly document that in patients with mild to moderate congestive heart failure, treated with diuretics alone, the addition of digoxin may have some beneficial effects. However, on balance, these results seem to favor the use of captopril, particularly if one is concerned about ventricular arrhythmias. Since approximately 40% of patients with congestive heart failure die suddenly, concern about ventricular arrhythmias in these patients seems appropriate (72). Other independent investigators have previously reported a decrease in ventricular arrhythmias in the setting of congestive heart failure in patients treated with captopril (42) and enalapril (73), respectively. Although the mechanism of this antiarrhythmic effect is uncertain, it seems possible that it may be a class effect of ACE inhibitors.

The question of the efficacy of adding an ACE inhibitor rather than increasing diuretics in patients with congestive heart failure with increasing fluid retention, has also been addressed. Bocanelli et al (74) studied 15 patients with moderate congestive heart failure not completely controlled on digoxin 0.25 mg daily and furosemide 25 mg daily. They compared the effects of adding captopril 12.5-50mg b.i.d. with increasing furosemide doses (25-100mg daily), in a randomized, double-blind study for 3 months. Exercise tolerance and symptomatic improvement occurred in parallel in both treatment groups. However, echocardiographic parameters improved significantly more in those treated with captopril. In contradistinction, Richardson et al (75) found that captopril alone as monotherapy could not replace diuretic therapy in 14 patients with moderate heart failure being treated with furosemide 40mg and amiloride 5mg daily.

VII. ACE Inhibitors, Sodium and Potassium

There are four major determinants of sodium, potassium and water balance in patients with congestive heart failure, namely neurohumoral factors (renin, angiotensin, aldosterone, vasopressin), renal factors, pharmacologic interventions, and dietary sodium and water intake (Table IV) (76,77).

TABLE IV

DETERMINANTS OF NA^+, K^+ AND H_2O BALANCE IN HEART FAILURE

1. NEUROHUMORAL
   - Increased renin – angiotensin – aldosterone activity
   - Increased sympathetic nervous system activity
   - Increased vasopressin (ADH)
   - Altered response to prostaglandins
   - Decreased response to ANF
2. RENAL
   - Decreased glomerular filtration rate
   - Increased proximal tubular sodium reabsorption
   - Decreased distal tubular Na delivery
3. PHARMACOLOGIC
   - Diuretics
   - Vasodilators (especially minoxidil, hydralazine)
4. DIETARY NA AND H_2O INTAKE

Renin release is under the control of several factors: (1) decreased stretch of the juxtaglomerular apparatus leads to increased renin production; (2) an increase in filtered Na^+ is sensed by the macula densa of the kidney and results in a decreased glomerular filtration rate and decreased filtered Na^+; (3) the sympathetic nervous system regulates renin release in response to the upright posture; and (4) circulating factors: increased dietary K^+ leads to decreased renin release, decreased dietary K^+ leads to increased renin release, increased angiotensin II leads to a decrease in renin release, increased circulating ANF may inhibit renin release. The effect of an increase in plasma renin activity is to act on angiotensinogen, a circulating $alpha_2$ globulin to produce angiotensin I. This in turn is converted to angiotensin II by the converting enzyme (Figure 5). *Angiotensin II* has 4 major effects: (1) increased vasoconstriction; (2) increased aldosterone production; (3) direct stimulation of the thirst center; and (4) increased vasopressin release. *Aldosterone* in the setting of heart failure is released largely in response to increased renin-angiotensin system activity. In turn, it has 2 major functions: (1) regulation of extracellular fluid volume; and (2) regulation of potassium excretion, via its effects on the distal convoluted tubule. *Vasopressin (ADH)* is released in response to certain osmotic, and non-osmotic factors (atrial stretch receptors, baroreceptors, angiotensin II, endorphins). The major consequences of an increase in circulating vasopressin are vasoconstriction and water retention. The net result of these hormonal and other various factors acting in concert is that hyponatremia and hypokalemia are common occurrences in patients with congestive heart failure.

A. Hyponatremia

In the setting of congestive heart failure, hyponatremia is an important finding because it implies: (1) activation of the neurohumoral system, and hence a late stage of decompensation, and (2) an adverse prognosis for survival.

The relationship between hyponatremia and activation of the neurohumoral system has been characterized by several different investigators. There is a striking inverse correlation between serum sodium concentration and both PRA and aldosterone (78,79). Of equal interest is the observation that there is also a strong inverse correlation between serum sodium concentration and the vasodilator prostaglandin, PGE_2 (Figure 8) (79). Thus, hyponatremia is a marker for activation of both the intrinsic vasoconstrictor and vasodilator systems. These observations have led to the realization that in patients with severe heart failure and hyponatremia, there is activation of the intrinsic vasoconstrictor systems (renin-angiotensin-aldosterone, catecholamines, vasopressin) and the vasodilator systems (vasodilator prostaglandins, kinins, ANF), and that a delicate balance exists between these two systems. This balance may be disturbed by the administration of agents that reduce the effect of the intrinsic vasodilators, e.g. non-steroidal anti-inflammatory agents, with a resultant hemodynamic deterioraton (79). The presence of hyponatremia has also been shown to be predictive of a marked hemodynamic response to ACE inhibitors, and a greater likelihood of hypotension and renal insufficiency when these agents are administered (62,80). Therefore, it is particularly advisable to commence with small doses of ACE inhibitors in these patients, and to ensure that they are volume repleted before treatment commences.

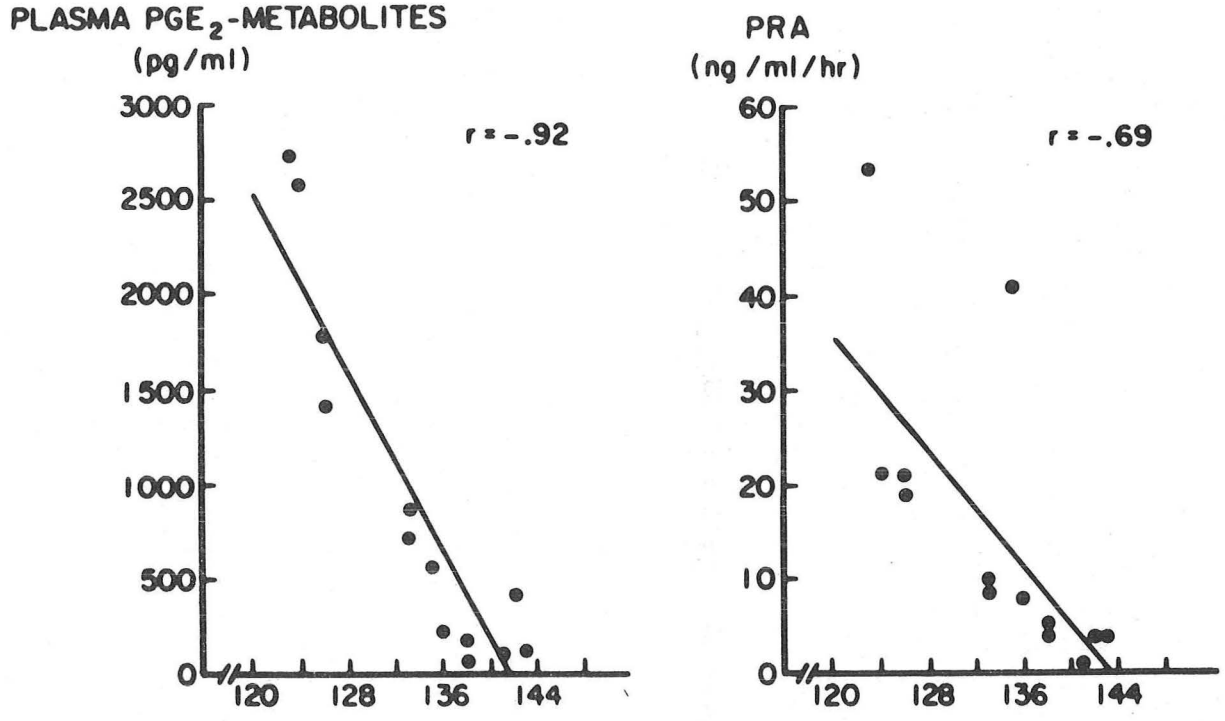


Figure 8

Relationship between serum sodium concentration and plasma PGE_2 metabolites or plasma renin activity. (From Dzau, et al: N Engl J Med 310:347, 1984).

The ACE inhibitor captopril has been shown to be effective in reversing hyponatremia. Packer et al (77) documented a steady increase in serum sodium concentration in response to captopril therapy in 12 patients over a 2 week period (Figure 9). On the other hand, Dzau et al found that in order for this effect to occur, captopril had to be used in conjunction with a loop diuretic (81). It is not certain whether this effect is a class effect for all ACE inhibitors. In contradistinction to the marked increase in serum sodium concentration that may occur in response to captopril, no such effect has been documented when other classes of vasodilators (i.,e. prazosin, hydralazine) or inotropic/vasodilators (amrinone) are used (77).

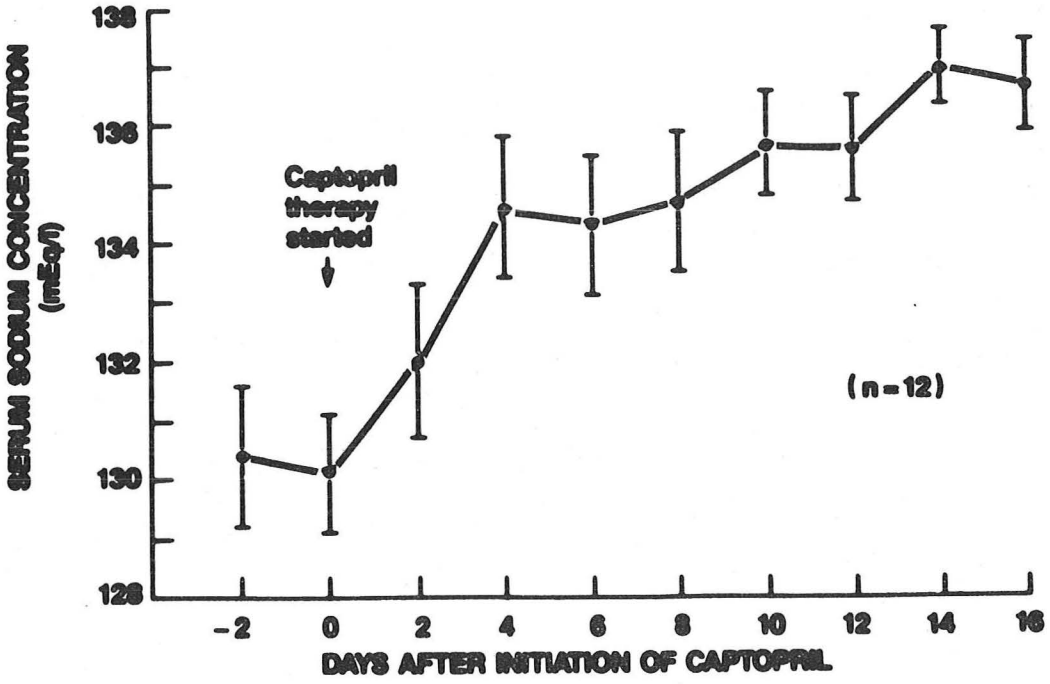


Figure 9
The effect of repeated captopril administration on hyponatremia. (From Packer M, et al: Ann Int Med 100:782, 1984).

It is important to emphasize that hyponatremia does not represent total body sodium depletion. On the contrary, total body sodium appears to be generally increased in patients with congestive heart failure (82) (Table V). It is likely that renin is released in response to a perceived or "relative" sodium depletion. For this reason, it is totally inappropriate to administer normal saline to correct this dilutional hyponatremia. The use of diuretics is also generally ineffective since they do not promote a net free water clearance in this setting and only serve to further activate the renin-angiotensin-aldosterone system (6).

TABLE V

ELECTROLYTE AND HORMONAL PROFILES IN CHF PATIENTS ON PLACEBO

	Normal Renin (n=6)	p	High Renin (n=7)
Total body sodium E/P %	105±6	NS	103±8
Total body potassium E/P %	100±8	p<0.05	85±13
total body K^+ on captopril (mmol)	+24±129	p<0.05	+223±157*
Serum sodium (mmol/L)	144±3	p<0.05	136±7
Serum potassium (mmol/L)	3.7±0.1	p<0.05	3.3±0.4
serum K^+ on captopril (mmol/L)	+0.2±0.3	NS	0.5±0.6*
Angiotensin II (pmol/L)	18±9	p<0.05	132±98
Aldosterone (ng/L)	6±6	P<0.05	28±18

E = Expected; P = Predicted normal

Cleland et al, Eur Heart J 6:681, 1985

Hyponatremia may also be an important predictor of survival in patients with severe heart failure (83). Lee and Packer have suggested that the use of ACE inhibitors, not only causes a reversal of hyponatremia in such patients, but that this correction of hyponatremia may be associated with an improvement in survival (83).

B. Hypokalemia

Hypokalemia is an even more common occurrence than hyponatremia in the setting of congestive heart failure. In contradistinction to hyponatremia, hypokalemia is indicative of total body potassium depletion (82) (Table V). The potential reasons for hypokalemia have been outlined previously (Table IV). It is readily evident from Table V that potassium depletion is most severe in those with an activated renin-angiotensin-aldosterone-system. It is also clear that administration of the ACE inhibitor captopril resulted in a marked increase in both serum potassium concentration and total body potassium stores. Hypokalemia is of considerable concern in patients with congestive heart failure, because it may produce or aggravate ventricular arrhythmias (7). Since patients with severe congestive heart failure have a high degree of ambient ventricular arrhythmias, it is generally believed that hypokalemia should be avoided if at all possible in these patients (72). This can be achieved by: (1) addition of potassium supplements, although this is frequently insufficient; (2) use of potassium sparing diuretics, although these agents are often not sufficiently potent to be used except in combination with loop diuretics; and (3) use of an ACE inhibitor in addition to a diuretic.

The injudicious use of an ACE inhibitor may result in either hypo or hyperkalemia. If an ACE inhibitor is administered to a patient who is already on potassium supplements or a potassium sparing diuretic, *hyperkalemia* may occur. Conversely, if a patient who is normokalemic on treatment with an ACE inhibitor and a diuretic suddenly discontinues the ACE inhibitor, *hypokalemia* may ensue.

Hypomagnesemia may be at least as important as hypokalemia in patients with congestive heart failure (84). The potassium-sparing diuretics triamterene and amiloride appear to result in a conservation not only of potassium but also of magnesium (84). Whether the ACE inhibitors possess a similar beneficial effect on magnesium balance remains to be determined.

VIII. Survival in Congestive Heart Failure

A. Determinants of Survival

Unless there is an underlying remediable cause, for example, a surgically correctable valvular lesion, the diagnosis of congestive heart failure implies a poor prognosis for survival. Patients with new onset heart failure have less than a 50% chance of surviving 5 years (Figure 10), (85) while those with severe heart failure despite good medical therapy may have less than a 50% chance of surviving 6-12 months (1).

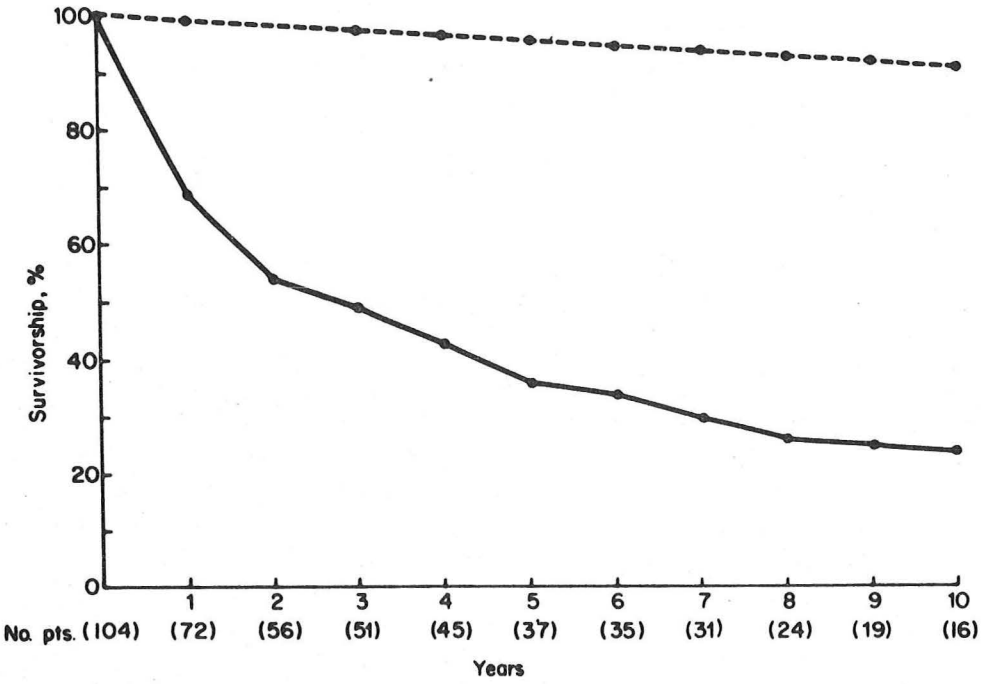


Figure 10
Survival in 104 patients with idiopathic dilated cardiomyopathy. (From Fuster V, et al: Am J Cardiol 47:525, 1981).

No single variable is totally predictive of survival in patients with congestive heart failure. However, a number of different variables have been identified that all contain prognostic information (Table VI). In general, the greater the number of adverse prognosticators present, the worse the likelihood of survival.

TABLE VI

FACTORS THAT DETERMINE SURVIVAL IN PATIENTS WITH CONGESTIVE HEART FAILURE

1. **Etiology of heart failure**

2. **Degree of LV dysfunction**
   - **Cardiac index; PCW pressure; SWI**
   - **LV ejection fraction, & improvement in LVEF**

3. **Symptomatic status**
   - **NYHA Class**
   - **Exercise tolerance**

4. **Degree of neurohumoral activation**
   - **Plasma renin activity (serum sodium)**
   - **Plasma norepinephrine level**

5. **Ventricular arrhythmias**

The etiology of heart failure has been found to be important in some studies (86,87). In these studies, those with coronary artery disease had a worse prognosis than those with an idiopathic dilated cardiomyopathy. However, this has not been a consistent finding. The degree of left ventricular dysfunction clearly is an important prognosticator for survival. The left ventricular ejection fraction is a strong predictor of survival if a wide range of patients with heart failure are considered (88). However, it provides very little independent prognostic information in patients with NYHA Class IV symptoms (83). The same observations generally hold true for other hemodynamic variables such as pulmonary capillary wedge pressure, cardiac index and stroke work index.

Symptomatic status and exercise tolerance provide independent and additive prognostic information to that provided by assessments of left ventricular function (88,89). Thus, a patient with a left ventricular ejection fraction of 20% who has poor exercise tolerance is likely to have a worse prognosis than a patient with a comparable left ventricular ejection fraction and better exercise tolerance (88).

Neurohumoral variables also provide important prognostic information. Cohn et al (90) were the first to demonstrate the prognostic importance of circulating norepinephrine concentrations, in a wide range of patients with heart failure (Figure 11). Subsequently, Lee and Packer (83) demonstrated that hyponatremia (a marker of activation of the neurohumoral system and hence a late stage in congestive heart failure) was a powerful adverse prognosticator in patients with severe heart failure (Figure 12).

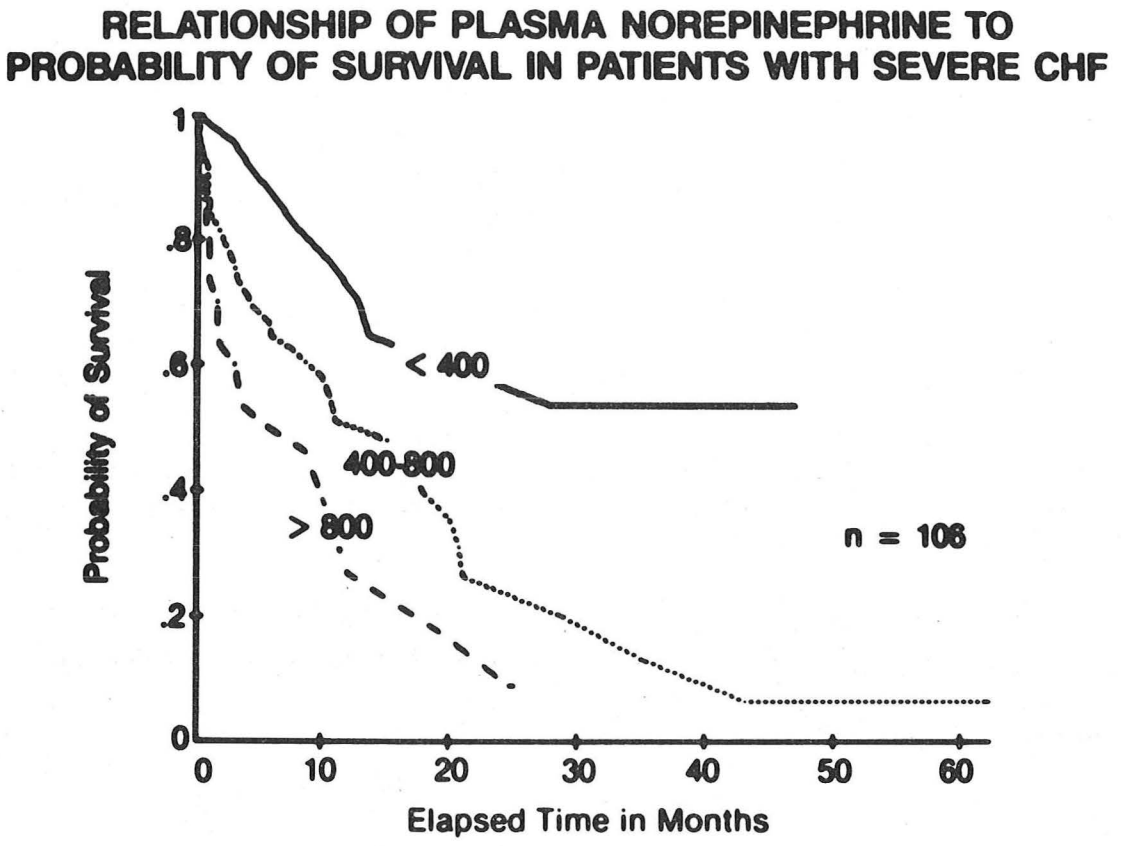


Figure 11
Life table analyses of survival, according to tercile based on level of plasma norepinephrine (PNE). (From Cohn JN, et al: N Engl J Med 311:819, 1984).

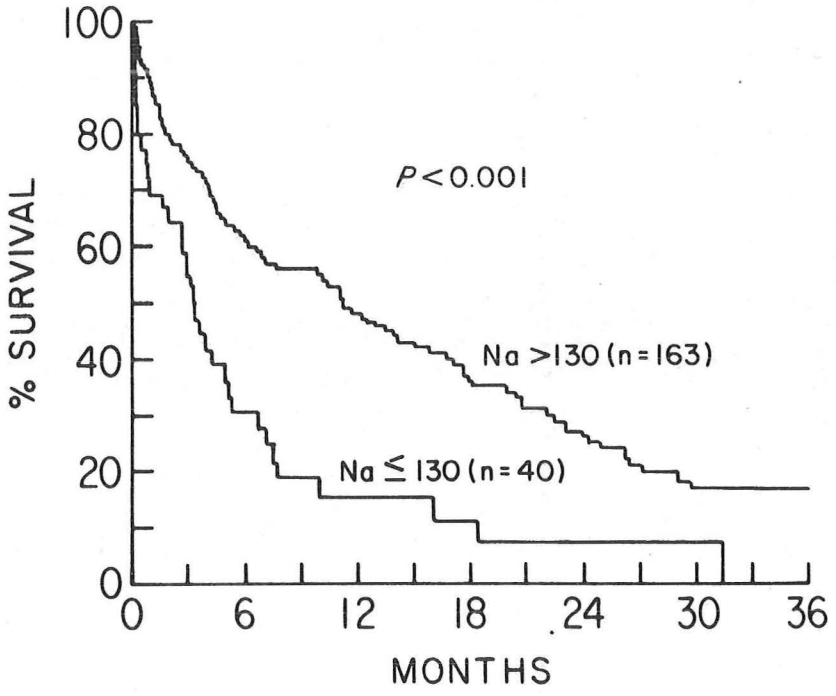


Figure 12
Cumulative rates of survival in patients with severe chronic heart failure based on pretreatment serum sodium concentration. (From Lee WH, Packer M: Circulation 73:257, 1986).

The relationship of ventricular arrhythmias to mortality in patients with severe congestive heart failure is interesting. More than 50% of patients with severe heart failure have complex ventricular arrhythmias, including short runs of non-sustained ventricular tachycardia, on 24-hour ambulatory monitoring, and approximately 40% of patients with congestive heart failure die suddenly (72). However, it appears that ventricular arrhythmias are more predictive of total mortality than sudden death in this group of patients (Table VII) (72). Thus, arrhythmias too may be largely a manifestation of the severity of the cardiac dysfunction.

TABLE VII

RELATIONSHIP OF VEA TO MORTALITY IN HEART FAILURE

	No. of patients	Mortality (%)/ average follow-up (mo)	% patients with VT	Relation of VT to total mortality	Relation of VT to SUD
Huang et al.	35	11/34	60	No	No
Costanzo-Nordin et al.	55	16/?	40	No	No
Meinertz et al.	74	26/11	49	Yes	Yes
Unverferth et al.	69	35/12	41	Yes	---
Holmes et al.	31	45/14	39	Yes	No
Wilson et al.	77	65/12	51	Yes	No

Packer, Circulation 1985; 72:681

B. Vasodilators and ACE Inhibitors

The question whether vasodilators and/or ACE inhibitors can improve survival in patients with heart failure has been unanswered until recently. Cohn et al reported the results of the Veterans Administration Co-operative Study (VHeFTI) (87). This study comprised 642 men with impaired cardiac function and reduced exercise tolerance who were randomized to prazosin 20mg per day, a combination of hydralazine 300mg per day and isosorbide dinitrate 160mg per day, or placebo, in addition to digitalis and diuretics. For the first 2-year period there was a cumulative reduction in mortality in the hydralazine/isordil group of 34 percent compared to the placebo group ($p<0.028$) (Figure 13). The survival in the prazosin-treated group did not differ significantly from that of the placebo-treated group. In addition, the mortality in the patients with coronary artery disease was significantly higher ($p<0.02$) than in those without this disorder. Thus, this study demonstrated for the first time that some vasodilators (hydralazine/isordil combination) might improve survival in patients with heart failure.

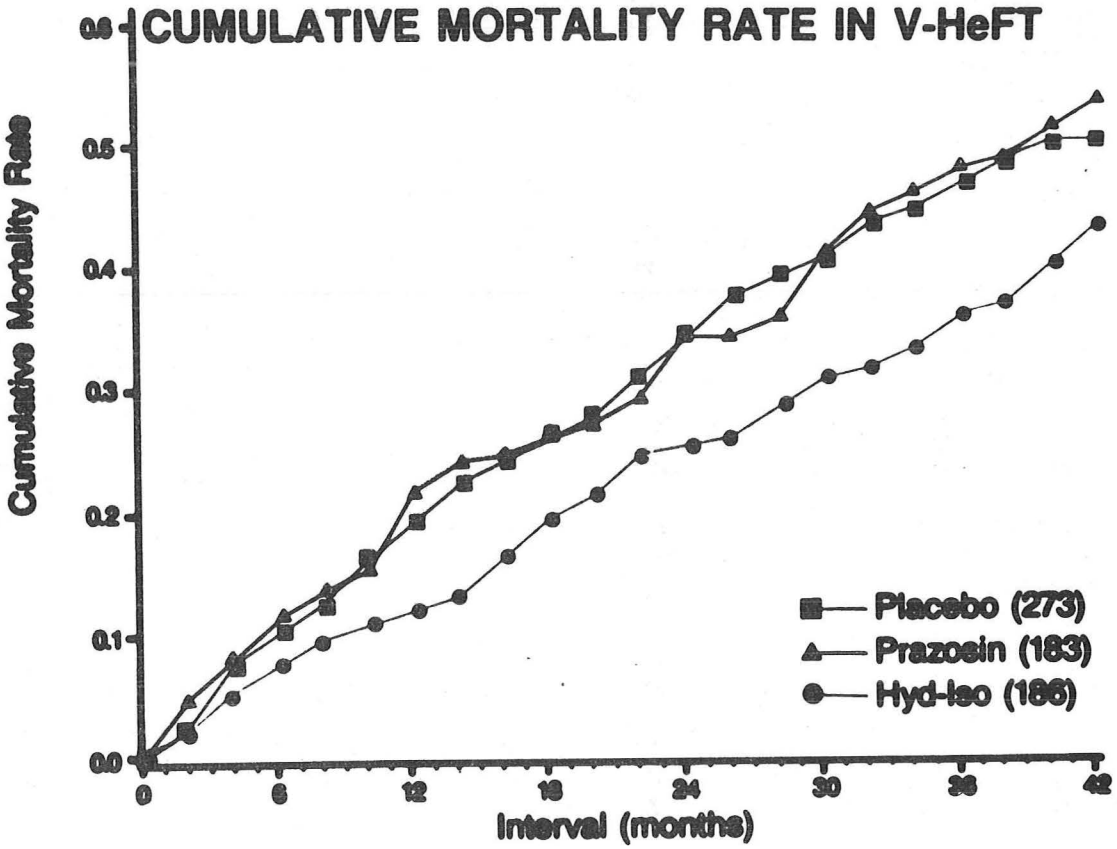


Figure 13
(From Cohn JN, et al: N Engl J Med 314(24):1547, 1986).

There seemed to be good reason to suspect that ACE inhibitors might improve survival at least as much as a hydralazine/isordil combination. Not only do ACE inhibitors improve ventricular function and improve exercise tolerance, but they decrease myocardial oxygen consumption, counteract neurohumoral activation, and decrease ventricular arrhythmias. In 1985, Furberg and Yusuf (91) from the National Heart, Lung, and Blood Institute reported the findings from a meta-analysis of all the available placebo-controlled studies of patients with heart failure treated with nitrates, hydralazine, beta-blockers or ACE inhibitors. In this report, 10 out of 264 (4%) of patients treated with ACE inhibitors as compared to 22 out of 265 (8%) of patients treated with placebo died during the study period, an odds ratio of 0.46 ($p<0.05$). In the same year, Pfeffer et al (92) demonstrated that in rats with an experimental myocardial infarction, treatment with captopril from days 21 to 365 resulted in a significantly improved survival versus treatment with placebo.

The CONSENSUS Trial from northern Scandinavia (Figure 14) (66) was the first large multicenter study to unequivocally demonstrate an improvement in survival in patients with heart failure treated with an ACE inhibitor. In this study of 253 patients with severe NYHA Class IV heart failure, patients were treated with enalapril versus placebo, in addition to digitalis and diuretics. The crude mortality rate at the end of six months (primary end-point) was 26 percent in the enalapril group and 44

percent in the placebo group - a reduction of 40% (p=0.002); at the end of 1 year, mortality was reduced by 31% in the enalapril group versus the placebo group (p=0.001). This study was discontinued prematurely because it was deemed unethical to continue the study in the light of these findings.

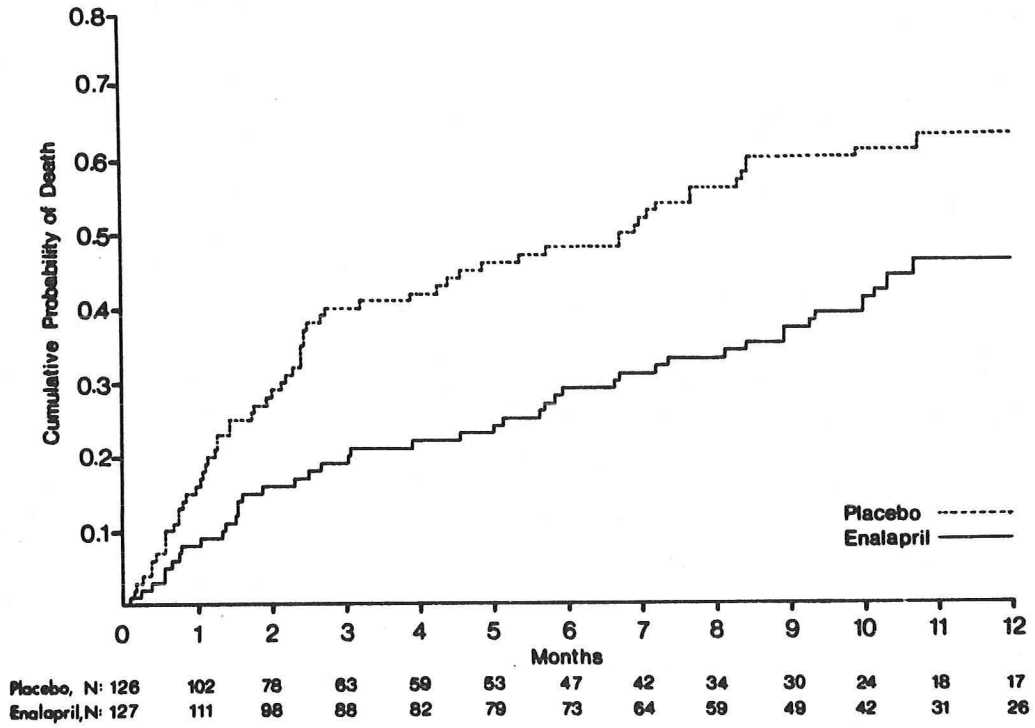


Figure 14
Cumulative probability of death in the enalapril and placebo groups. (From CONSENSUS Trial Study Group: N Engl J Med 316:1429, 1987).

Scientifically rigorous comparable data concerning effects on survival are not available for other ACE inhibitors. However, Kleber et al reported a significant (p=0.041) improvement in event-free survival in 59 patients with mild-moderate heart failure treated with captopril versus placebo after 270 days of treatment (93). From the available evidence it seems very likely that both enalapril and captopril improve survival in patients with congestive heart failure. This may be a class effect of ACE inhibitors, but further data are needed before such a conclusion can be drawn. The mechanism of improvement in survival is likely to be multifactorial.

IX. ACE Inhibitors in the Prevention of Overt Congestive Heart Failure

Patients with end-stage congestive heart failure have an extremely poor prognosis. It is therefore imperative to try to prevent the occurrence of heart failure, if at all possible. From an epidemiological standpoint, the two major antecedents of heart failure are hypertension and coronary artery disease (2). More effective treatment of hypertension and prevention of coronary artery disease (cessation of cigarette smoking, lipid lower agents) are consequently important considerations. The limitation of the size of a myocardial infarction when it occurs, as was discussed by Dr. David Hillis in his recent Grand Rounds (March 17, 1988), is a later but equally important stage of intervention in the prevention of heart failure. The amount of myocardium destroyed as the result of one or more infarctions is ultimately a major determinant of the occurrence of subsequent heart failure. However, the patient's fate is not sealed at the time of the infarction, unless there has been massive damage. In most patients there is a clinically silent interval between the time of the myocardial insult and the occurrence of overt heart failure. This interval may last from months to years, depending on the magnitude of the insult. During this time, which starts soon after the infarction, progressive left ventricular dilatation, remodelling and hypertrophy occur, and ultimately heart failure may ensue (94,95). *Limitation of left ventricular dilatation now seems to be an important objective in the secondary prevention of congestive heart failure.* The inverse relationship between the left ventricular ejection fraction at rest and survival rate following myocardial infarction has been recognized for some time. However, in a recent elegant study of 605 patients followed for 6½ years after acute myocardial infarction, White et al demonstrated convincingly that left ventricular end systolic volume is the primary determinant of survival in these patients (96). For the same left ventricular ejection fraction, patients with dilated ventricles had a much poorer survival than those with less ventricular dilatation (Figure 15).

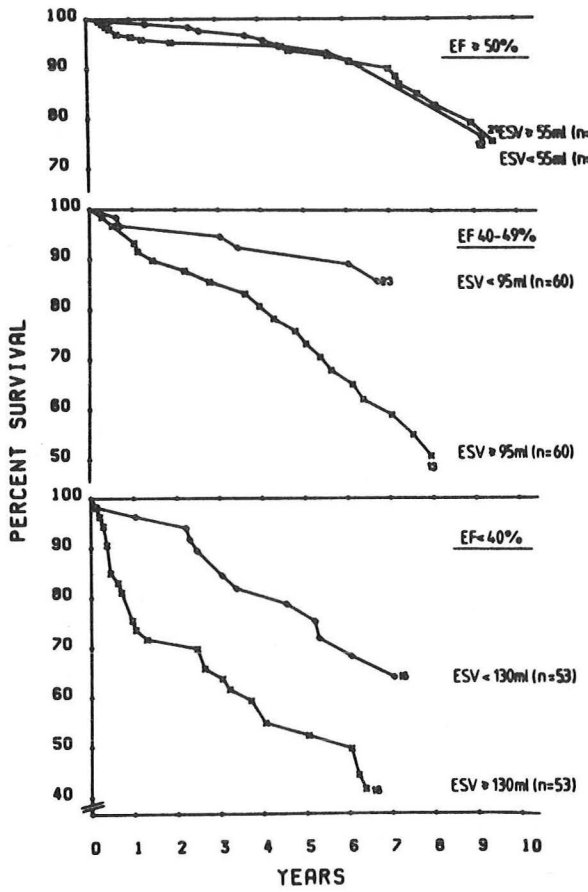


Figure 15

Actuarial survival curves for three groups of left ventricular ejection fraction (≥50%, 40% to 49%, and <40%). Each group was subdivided according to whether the end-systolic volume was above or below the median for that group. (From White HD, et al: Circulation 76:47, 1987).

Angiotensin converting enzyme inhibitors have been shown to reduce myocardial infarct size in experimental animals (97). In addition, the observations of Pfeffer et al concerning the beneficial effects of later administration of ACE inhibitors in their rat model of myocardial infarction, are pertinent (92). These investigators produced acute myocardial infarctions of varying sizes in 3 month old Wistar rats by ligation of the left anterior descending coronary artery and allowing the animals to recover. At three weeks after the infarction, these animals were randomized to plain drinking water or captopril (2g/liter) added to the drinking water. These animals were then followed for 365 days. As noted previously, the captopril treated animals had significantly better survival than the placebo treated rats; this effect was most marked in rats with moderate sized infarcts (20-40% of the left ventricular wall) (92). The captopril-treated rats also showed less dilatation of the left ventricle than those treated with placebo, with lower left ventricular filling pressures (98). Thus, the reduction in ventricular volumes of captopril-treated compared to untreated rats with infarcts was the result of both a downward displacement of the pressure-volume relation (less ventricular distension) and an attenuation of the rightward shift of that relation (less ventricular dilatation), which occurs with time in untreated

rats with myocardial infarcts (Figure 16) (98). These authors have suggested that captopril may have similar beneficial effects in man (99).

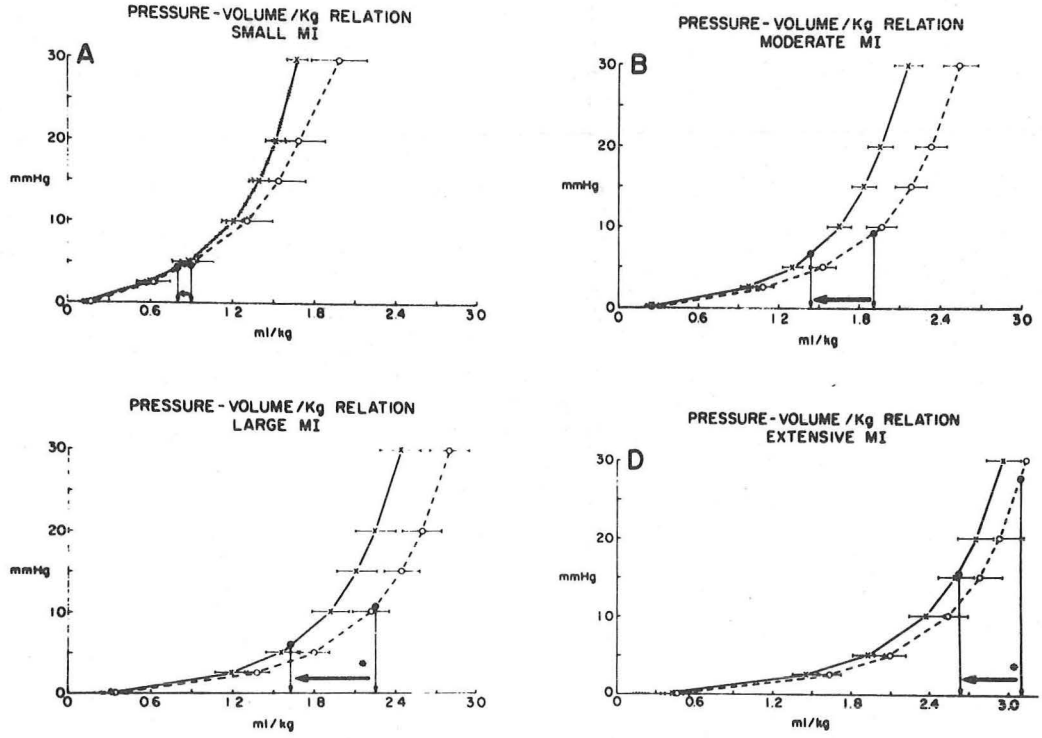


Figure 16
Pressure-volume relationships in rats with (A) small, (B) moderate, (C) large, and (D) extensive infarcts treated with captopril (X) or placebo (O). (From Pfeffer JM, et al: Circ Res 57:84, 1985).

A recent study by Sharpe et al (100) demonstrates rather convincingly that the observations of Pfeffer and his associates may indeed be applicable to man. In a randomized, double-blind study, 60 patients with left ventricular dysfunction (left ventricular ejection fraction <45%) but without clinical evidence of heart failure 1 week after Q wave myocardial infarction, received captopril 25 mg three times a day, furosemide 40 mg daily, or placebo. Left ventricular volumes were measured at 1,3,6,9 and 12 months with two-dimensional echocardiography. The captopril-treated group showed no significant change in left ventricular end-diastolic volume index, but left ventricular end-systolic volume index was significantly reduced, and stroke volume index and left ventricular ejection fraction were significanty increased, from 1 month onwards (Figure 17 and 18). Conversely, the furosemide and placebo treated groups showed significant increases in left ventricular volumes, with stroke volume unchanged and ejection fraction slightly reduced. These differences between the captopril-treated and the furosemide or placebo-treated groups, were statistically significant at the $p<0.05$ level, and held true for both anterior and inferior infarcts. There are two large, multicenter studies, namely the Survival and Ventricular Enlargement (SAVE) study, using captopril, and the Studies of Left Ventricular Dysfunction (SOLVD) study,

using enalapril, that are currently ongoing. These studies will further address the effects of ACE inhibitors on survival in patients with overt heart failure, and their ability to prevent the occurrence of overt heart failure in patients with asymptomatic left ventricular dysfunction. They will hopefully provide the definitive answer to both these questions, but their results are unlikely to be known for several years. In the interim, the data from the study by Sharpe et al are sufficiently striking to merit serious attention (100).

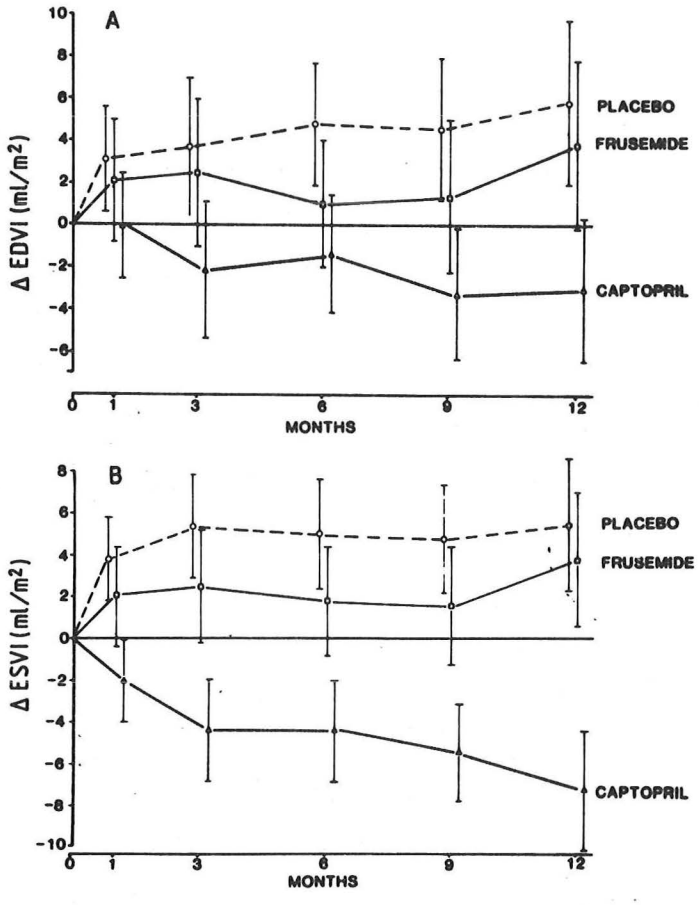


Figure 17
Adjusted mean differences from baseline at 1,3,6,9 and 12 months for the three treatment groups for (A) LVEDVI and (B) LVESVI. (From Sharpe DN, et al: Lancet #8580(1):255, 1988).

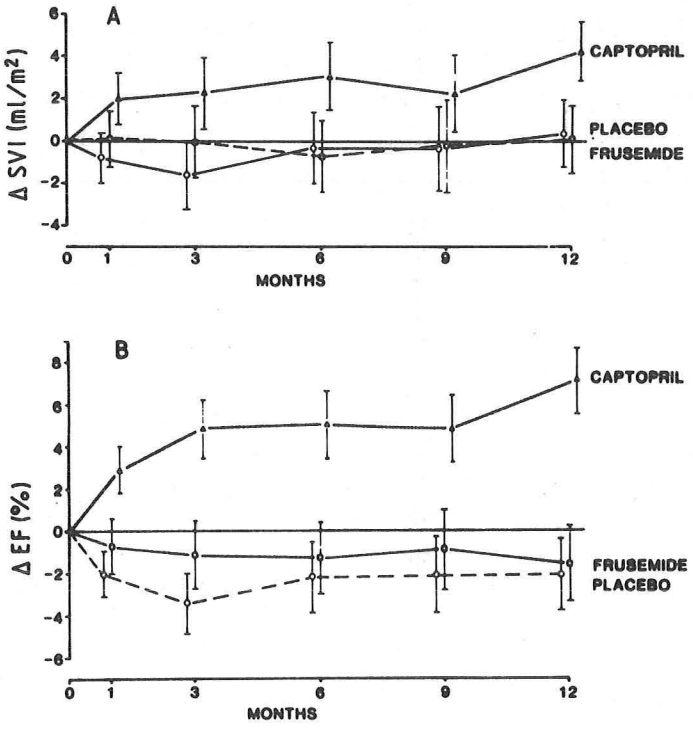


Figure 18
Adjusted mean differences from baseline at 1,3,6,9 and 12 months for the three treatment groups for (A) LV stroke volume index and (B) LV ejection fraction. (From Sharpe DN, et al: Lancet #8580(1):255, 1988.

X. Conclusions

This review has attempted to elucidate the multifacetted role of ACE inhibitors in patients with congestive heart failure. The incidence of side-effects of these agents is surprisingly low when used in the appropriate dosage (generally no more than 150mg for captopril or 20mg per day for enalapril). They produce sustained beneficial hemodynamic and symptomatic improvements in most patients with congestive heart failure. Their neurohumoral effects are advantageous and generally result in a normalization of sodium and potassium balance and a reduction in ventricular arrhythmias. They may produce greater symptomatic benefit than digoxin as second-line therapy for patients with heart failure on diuretics, and improve survival in these patients. Finally, recent data suggest that they may prevent or delay the development of left ventricular dilatation and overt heart failure in patients with asymptomatic left ventricular dysfunction.

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