Clinical Use of an Orally Acting Converting Enzyme Inhibitor: Captopril

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SUMMARY An orally active inhibitor of the angiotensin converting enzyme, SQ 14,225 or captopril, was administered to 14 normal volunteers to evaluate its efficacy in inhibiting the pressor response to exogenous angiotensin I. The degree of blockade was dose-related up to 10 mg of captopril. Increasing the dose further merely prolonged the duration of the blockade. Subsequently, 39 patients with various types of hypertension including some on maintenance hemodialysis were treated chronically with captopril, i.e., 50 to 200 mg twice daily. The blood pressure (BP) reduction observed 1 hour following administration of the inhibitor was directly related to the baseline plasma renin activity (PRA) (r = 0.67, p < 0.001). Whenever blockade of the renin system alone did not lower BP to normal levels, additional sodium removal, e.g., by diuretics or ultrafiltration, brought it under control. In eight additional untreated patients with essential hypertension, captopril induced an increase in renal plasma flow, which correlated significantly with PRA. Six normotensive patients with refractory congestive heart failure were also studied hemodynamically following an acute dose of captopril. Cardiac function improved while peripheral resistance decreased. These data suggest that the renin angiotensin system participates actively in maintaining the BP of patients with hypertension and the afterload in patients with congestive heart failure, and that blockade of this system represents an effective advance in therapeutics. (Hypertension 2: 558-566, 1980)

KEY WORDS • converting enzyme inhibition • captopril • angiotensin I • renin • essential hypertension • azotemia • hemodialysis • kidney function • congestive heart failure

CURRENT study is providing increasing evidence that the renin-angiotensin system participates in the maintenance, if not generation, of several hypertensive states. Early results obtained with inhibitors of the renin system suggested that such agents might be clinically useful, but they have limitations due to the requirement of parenteral administration. Furthermore, saralasin, a competitive inhibitor of angiotensin II, has the disadvantage of an agonistic effect of its own; teprotide (SQ 20,881) is an effective inhibitor of angiotensin converting enzyme but interpretation of results has been somewhat complicated by the fact that the enzyme is identical with kininase II, a major route of bradykinin metabolism.

Nonetheless, combined data from these inhibitors of angiotensin have made it possible to assess the role of the renin-angiotensin system in a variety of conditions. In general, the bulk of the data obtained with saralasin seemed to suggest that angiotensin II plays an active role only when its levels are increased. However, the physiological significance of these results has been questioned because of the inherent agonistic properties of the drug. In contrast, teprotide has induced significant blood pressure (BP) reduction even in patients with "normal" renin essential hypertension, the degree of which was dependent on sodium balance. Indeed, in most patients, following salt restriction, BP normalized when angiotensin was blocked. Based on the findings of these studies, it was postulated that renin and sodium acting together are the main determinants of BP.

In patients with impaired renal function, hypertension is a common finding, and is nearly always associated with sodium and fluid retention. Most authors have found "low" or "normal" renin levels, but it has been suggested that these levels are inappropriately high relative to an expanded total body sodium. Sodium depletion is incompletely effective in treating hypertension in this setting, in part because of the associated stimulation of renin. Infusion of saralasin has produced variable results, but frequently leads to BP reduction after volume removal.

The renin angiotensin system has also been shown to participate in the control of afterload in normoten-
sive patients with congestive heart failure. Blockade of the renin system by intravenous administration of saralasin has been used to acutely decrease systemic resistance, which has resulted in improved cardiac function.20, 21

This report summarizes the short- and long-term effects of a recently developed orally active inhibitor of the angiotensin converting enzyme, captopril (SQ 14,225). In normal individuals it is a powerful inhibitor of the pressor effect of exogenous angiotensin I.22 We have studied the effects of captopril on BP and renal function in hypertensive patients and present preliminary evaluation of its efficacy in hemodialysis patients and of hemodynamic responses in patients with severe congestive heart failure.

Methods

Patients

Fourteen healthy male volunteers aged 21 to 32 years, weighing between 63 and 73 kg, were studied to evaluate the efficacy of captopril in inhibiting pressor responses to exogenous angiotensin I. The subjects were maintained on their regular salt intake and were admitted to hospital for 24 hours on the morning of the study.

In a second study, 39 hypertensive patients, 28 men and 11 women, aged 10 to 65, were included. Nine patients had renovascular hypertension, 13, essential hypertension, and two, primary hyperaldosteronism. Seven patients had chronic azotemia, with plasma creatinine levels > 1.5 mg/dl (3.2 ± 0.5 mg/dl, mean ± SEM). Eight additional patients were on chronic hemodialysis treatment for 0.5 to 7 years. All of them had hypertension refractory to ultrafiltration and conventional antihypertensive therapy.

The effect of captopril on renal hemodynamics was assessed in an additional eight untreated patients with essential hypertension maintained on an unrestricted sodium intake.

In still another study, six nonhypertensive men with refractory congestive heart failure (four with idiopathic congestive cardiomyopathy, one with ischemic cardiomyopathy, and one with myotonic dystrophy) were included. Two patients were bedridden and unable to walk without shortness of breath for 3 and 6 months despite treatment with salt restriction, digitalis, and diuretics. The other four were symptomatic on minimal exertion. Serum creatinine was elevated in two patients at 2.7 and 1.7 mg/dl.

Procedures

In each normotensive volunteer, a dose-response relation for angiotensin I was first determined using ileu-5-angiotensin I (Schwartz-Mann). A single dose of captopril was then given by mouth; 15 minutes later, the intravenous dose of angiotensin I that had previously caused the maximum pressure rise was reinjected. If this was ineffective, due to the blocking action of the inhibitor, larger doses (3- to 8-fold) of angiotensin I were administered subsequently. Increasing doses of captopril (1, 2.5, 5, 10, and 20 mg) were tested similarly.

The protocol used to initiate captopril treatment in hypertensive patients has been described. In short, antihypertensive medication was discontinued, whenever possible 3 weeks prior to the study. The patients were hospitalized and maintained on a constant sodium and potassium intake of 100 mEq and 60 to 80 mEq per day respectively. Then captopril was started following a placebo period of 3 days. Blood samples for the measurements of plasma renin and angiotensin converting enzyme activity and plasma aldosterone and catecholamine levels were drawn on the last day of placebo and on Days 4 to 6 after starting captopril, 1 hour following the morning dose.

The protocol for the patients on maintenance hemodialysis differed in so far as all determinations were always done before and after hemodialysis. In some patients, treatment by captopril was complemented with "salt subtraction," i.e., following conventional dialysis, 1 to 2 liters of ultrafiltrate were replaced by equal volumes of 5% glucose.

After discharge from the hospital, all patients continued treatment with captopril, 50–200 mg twice daily. Diuretics were added in seven patients with essential hypertension and in five patients with nonterminal chronic renal failure. At 13 ± 2 weeks after starting captopril, an ambulatory BP profile was obtained in 17 patients using a portable recorder (Remler Corporation, San Francisco, California).

Renal plasma flow and glomerular filtration rate were estimated by a constant infusion technique employing as reference substance 131-I-OrthoIodohippurate and 125-I-sodium iothalamate (Amersham Radiochemical Pharmaceuticals). Following determination of two 20-minute control clearances, 50 mg of captopril were given by mouth. Renal clearances were determined during four periods of 20 minutes each between the 20th and the 100th minute after captopril administration. Sodium and potassium were determined in each urine collection. The two control renal clearances were averaged (control value) as well as the two determinations obtained between the 20th and the 60th minutes (E1) and between the 60th and 100th minute (E2) after captopril administration.

Patients with congestive heart failure underwent cardiac catheterization in the supine position. After a resting period of 30 minutes, baseline hemodynamic measurements were obtained at 15-minute intervals. Thereafter, 25 mg of captopril were administered orally. Hemodynamic measurements were repeated every 30 minutes for the following 2 hours and hourly thereafter until values had returned to baseline.

Analytical Methods

Plasma renin activity (PRA), plasma aldosterone levels, and 24-hour urinary excretion of aldosterone were measured by radioimmunoassay. The PRA was classified as "low," "normal," or "high" according to
the method previously described. Plasma angiotensin-converting enzyme activity was determined by the radioenzymatic method using a radiolabelled acylated tripeptide as substrate (Ventrex Corporation, Portland, Maine). Plasma catecholamines also were quantitated by a radioenzymatic method. Renal clearances were proportioned by conversion to 1.73 m² body surface area. Filtration fraction (FF) was expressed as GFR/ERPF. Renal resistance was calculated as the ratio of the mean arterial blood pressure (MAP) to renal blood flow (ERPF/1-Hematocrit).

Results

The time course of the changes in pressor responsiveness to exogenous angiotensin I after oral captopril in normal volunteers is shown in figure 1. The pressor response to angiotensin I is expressed as percentage of the control response determined before drug administration (time zero). Time-response curves of different doses of captopril were averaged. The magnitude and duration of inhibition were dose-related. One mg of captopril produced only slight (30%) inhibition and thus appeared to come close to a threshold dose. At this dose, near-complete recovery of responsiveness had occurred by \( \frac{1}{2} \) hours. Increasing doses of captopril produced progressively greater inhibition as well as duration of effect. Onset of inhibition was rapid and varied with the dosage. For example, the 20 mg dose produced nearly complete inhibition at 15 minutes, which lasted for over 2 hours; at 4 hours, the average systolic response was still inhibited by 40%.

Figure 2 illustrates the effect of captopril on plasma angiotensin-converting enzyme activity (ACE) in two groups of patients. Those with normal renal function (upper panel) decreased ACE from 73 ± 6 to 22 ± 6 nmoles/ml/min. During chronic treatment, levels 12 hours after the previous dose had returned to baseline (80 ± 8 nmoles/ml/min), then fell promptly after captopril (22 ± 4 nmoles/ml/min). In patients with impaired renal function (lower panel), ACE decreased similarly with captopril (86 ± 6 to 14 ± 3 nmoles/ml/min) but remained low (26 ± 7 nmoles/ml/min, \( p < 0.005 \)) up to 14 hours following the previous dose. The further fall after the morning dose was small (15 ± 7 nmoles/ml/min, \( p < 0.05 \)). Thus, the effect of captopril on ACE accumulates in patients with chronic renal failure, consistent with its known renal excretion.

Figure 3 summarizes the results of home BP recordings by a portable recorder in 17 patients on chronic
therapy. During the placebo period, BP averaged 178/114 ± 6/3 mm Hg. On chronic captopril therapy for a mean of 13 weeks, BP 14 hours after the previous evening dose of captopril and immediately preceding the morning dose, was at 140/89 ± 4/4 mm Hg. Following the morning dose, it fell further to a low of 129/85 ± 4/3 mm Hg (p < 0.05). During the day it rose to reach 138/91 ± 4/4 before the evening dose. Readministration of captopril induced a new slight BP drop. Despite these small BP changes related to the readministration of the drug, BP remained controlled throughout the day.

During the first 4–6 days of hospitalization, BP in 13 patients with essential hypertension was reduced from 169/111 ± 5/3 to 142/91 ± 5/2 mm Hg (p < 0.001); in nine with renovascular hypertension, from 183/111 ± 9/2 to 140/91 ± 7/4 mm Hg (p < 0.001), and in seven with chronic renal failure, from 181/116 ± 12/7 to 156/100 ± 9/5 mm Hg (p < 0.05).

Figure 4 depicts the diastolic blood pressure (DBP) changes obtained in 39 hypertensive patients 1 hour after the first dose of captopril. There was a significant correlation between pretreatment PRA and the induced fall in DBP (r = -0.67, p < 0.001). Patients with high PRA showed the greatest BP fall, but those with normal and even low PRAs also showed BP reductions. In the two patients with primary hyperaldosteronism and the lowest PRA, the BP did not decrease following inhibition of the angiotensin-converting enzyme. When the BP response observed after the first 4 to 6 days was compared to baseline PRA, a significant correlation was no longer apparent.

No weight gain was observed during BP reduction by captopril alone; in eight essential hypertensive patients in whom a metabolic study was done, weight remained constant during the first 3 days of treatment while BP fell from 172/110 ± 9/5 to 144/96 ± 6/4 mm Hg (fig. 5). These results are corroborated by measurements of 24-hour urinary sodium excretion, which rather than decreasing as one might expect with the BP fall, tended to increase. During the same period, 24-hour urinary excretion of aldosterone fell sharply from 13.6 ± 3 to 5.3 ± 2 mcg/24 hr (p < 0.01). The 24-hour excretion of potassium and creatinine remained practically unchanged.

The acute effects of captopril on the renal hemodynamics of eight patients with essential hypertension are summarized in table 1. At the end of period E2, arterial pressure was reduced by 8.8% ± 1.8% (range, 1–17.3%). A significant increase in renal plasma flow of 11.8% ± 4% (range, 6–33%; p < 0.01) occurred after captopril, while calculated renal resistance decreased by 16.4% ± 4.1% (p < 0.01). Glomerular filtration rate and urinary sodium excretion were not altered by captopril. Note that the early decrease in potassium excretion shown here was not sustained in the 24-hour balances shown in figure 5.

In seven patients with essential hypertension and in five patients with chronic azotemia, captopril alone did not normalize BP; diuretics had to be added before or after discharge from the hospital to control the BP. In all patients on previous therapy consisting of beta-blockers and diuretics, and in some of an additional vasodilating drug, the BP remained high at 178/115 ± 6/2 mm Hg. In the hospital, off all antihypertensive therapy, the patients showed slightly higher BP, at 182/118 ± 6/4 mm Hg. Captopril alone during the initial 4 to 6 days reduced BP to 150/96 ± 6/4 mm Hg (p < 0.001). With the addition of diuretics, the BP decreased further to 132/88 ± 5/3 mm Hg (p < 0.05). Administration of captopril increased PRA from 5.1 ± 1.4 to 17.5 ± 6.5 ng/ml/hr (p < 0.05) while plasma aldosterone fell from 22.6 ± 5.8 to 10.6 ± 1.8 ng/100 ml, and ACE activity decreased from 79 ± 6 to 17 ± 4 nmoles/ml/hr (p < 0.001). The addition of diuretics increased PRA further whereas plasma aldosterone levels and ACE hardly changed.

Sixteen hypertensive patients were treated by captopril for at least 1 year (fig. 6). In the hospital, cap-
Captopril alone markedly reduced their BP from 176/113 ± 6/4 to 144/90 ± 6/2 mm Hg (p < 0.001). In eight of them, a diuretic was added after discharge from the hospital to control BP. Following 6 and 12 months of continued treatment, BP remained low at 133/90 ± 5/2 and 129/88 ± 4/3 mm Hg respectively.

In eight patients on chronic hemodialysis with "uncontrollable" hypertension, BP on previous therapy averaged 179/105 ± 6/3 mm Hg. Treatment with captopril alone normalized BP in four of these (fig. 7), whose pretreatment PRA values were the highest (8.9-97 ng/ml/hr). Four other patients underwent a process of "salt-subtraction," in which plasma ultrafiltration was performed after routine dialysis and the volume replaced with 5% dextrose to prevent acute volume depletion. These patients initially demonstrated the lowest renin values (0.71 to 6.9 ng/ml/hr). When captopril was added thereafter, the entire group reached acceptable BP levels (134/76 ± 7/5 mm Hg) during chronic therapy.

Six normotensive patients with congestive heart failure were studied before and after converting enzyme blockade. Hemodynamic studies are summarized in figure 8. Pump function was improved, as reflected by an increase in cardiac index associated with a decrease in left ventricular filling pressure.

**Figure 4.** Correlation between control plasma renin activity and diastolic blood pressure reduction 1 hour following the first dose of captopril in 32 patients with different types of hypertension.

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**Table 1.** Effect of Captopril on Mean Arterial Pressure (MAP) and Renal Function in Eight Patients with Essential Hypertension on Unrestricted Sodium Intake

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>GFR (ml/min-1)</th>
<th>ERPF (ml/min-1)</th>
<th>FF</th>
<th>Urine V (µmole/min-1)</th>
<th>UK V (µmole/min-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>119 ± 9</td>
<td>130 ± 4</td>
<td>518 ± 34</td>
<td>0.26 ± 0.02</td>
<td>183 ± 39</td>
<td>70 ± 11</td>
</tr>
<tr>
<td>Period E1</td>
<td>111 ± 8†</td>
<td>122 ± 5*</td>
<td>556 ± 43†</td>
<td>0.23 ± 0.02†</td>
<td>181 ± 42*</td>
<td>49 ± 11†</td>
</tr>
<tr>
<td>(% change)</td>
<td>-6.8 ± 1.2</td>
<td>-6 ± 3.7</td>
<td>+9.8 ± 1</td>
<td>-13.4 ± 3.3</td>
<td>-1.2 ± 10</td>
<td>-32 ± 9</td>
</tr>
<tr>
<td>Period E2</td>
<td>109 ± 8†</td>
<td>129 ± 7*</td>
<td>582 ± 47†</td>
<td>0.23 ± 0.02†</td>
<td>160 ± 30*</td>
<td>40 ± 6†</td>
</tr>
<tr>
<td>(% change)</td>
<td>-8.8 ± 1.8</td>
<td>-1.4 ± 2.9</td>
<td>+11.8 ± 4</td>
<td>-11.3 ± 2.6</td>
<td>-3 ± 13</td>
<td>-38 ± 8</td>
</tr>
</tbody>
</table>

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) are proportioned by conversion to 1.73 m² body surface area. NS = not significant, *p < 0.05, †p < 0.01 compared to control (paired t test).
Stroke index increased with no change in heart rate, and total peripheral resistance decreased. The PRA was high in five of the patients. It increased in all six from $21 \pm 9.4$ to $46 \pm 17.4$ ng/ml/hr ($p < 0.05$) at the time of maximal hemodynamic response to captopril. Plasma norepinephrine levels were high in all patients, the two with the most severe functional limitations exhibiting the highest values of 1.52 and 2.92 ng/ml respectively. Captopril slightly reduced norepinephrine levels from $1.29 \pm 0.37$ to $1.04 \pm 0.26$ ng/ml while plasma aldosterone decreased from $60 \pm 10.3$ to $30 \pm 7$ ng/100 ml ($p < 0.005$). Plasma epinephrine did not change significantly, remaining at $0.26 \pm 0.08$ before and $0.27 \pm 0.07$ ng/ml after captopril administration.

In general, captopril was very well tolerated. Notwithstanding, five patients (three with renal failure) developed a skin rash of short duration. The dose of captopril was usually reduced, and the drug was actually discontinued in only one patient. Five patients (four with renal failure) experienced diminished taste, which also disappeared spontaneously. None of our patients has developed any sign of nephrotoxicity or leukopenia.

Discussion

Blockade of angiotensin converting enzyme by oral administration of captopril has proven to be an effective antihypertensive therapy. Both suppressed responses to exogenous angiotensin I and reduced values of plasma ACE confirm its efficacy in humans. Its antihypertensive effect has been relatively rapid, and near maximal within 2 hours after administration, only gradually diminishing during a 12-hour interval (fig. 3). Chronic ambulatory monitoring has confirmed the effect first demonstrated during hospital trials. At the doses used to treat hypertension, the amplitude of the BP fall was not dose-dependent. Indeed, 25 mg of captopril was sufficient to induce an antihypertensive effect comparable to the one obtained subsequently with higher doses. Increasing the dose prolonged the blocking effect, which was still complete for more than 6 hours after administration of 200 mg of captopril. This is in total agreement with the findings in normal volunteers who exhibited a complete blockade of angiotensin conversion for more than 2 hours after ingestion of 20 mg of captopril (fig. 1).

Blockade of angiotensin-converting enzyme by oral administration of captopril has lowered BP in patients with most types of hypertension, but it failed to induce a BP drop in the two patients with primary hyperaldosteronism. On captopril therapy alone, BP was actually 140/90 mm Hg in 30% of all our patients while they were hospitalized. However, in seven patients with essential hypertension, in one with renovascular hypertension due to bilateral renal artery stenosis, and in five with chronic azotemia, additional diuretic therapy was necessary to achieve BP normalization after discharge from the hospital. Similarly, in four dialyzed patients with dialysis-
resistant hypertension, BP was controlled only after decreasing total body sodium by additional salt removal. In all patients, twice daily administration of the drug appeared sufficient to control BP throughout the day.

There was a significant correlation between baseline PRA and BP reduction 1 hour after the first dose of captopril. The BP fall was most marked in patients with high PRA, but even patients with low PRA showed some BP drop. If captopril acts only through blockade of ACE, this observation would suggest that even low PRA may contribute to the maintenance of elevated BP, for example, through increased arteriolar receptor responsiveness to circulating angiotensin II. However, because converting enzyme has been shown to be identical with kininase II, blockade may also lead to accumulation of bradykinin. Thus, we cannot rule out the possibility that the BP reduction observed in our patients with low renin levels may be partly due to a bradykinin effect.

The BP-lowering effect of ACE inhibition may be larger than expected because reduction of angiotensin II levels not only reverses arteriolar constriction but also decreases secretion of aldosterone. Unlike most antihypertensive drugs that almost invariably induce sodium retention, captopril had no such effect. The lack of sodium retention can be partly explained by this reduced aldosterone secretion. Moreover, antagonizing intrarenal effects of the renin system may also counteract sodium retention. Thus, in patients with essential hypertension maintained on unrestricted sodium intake, acute administration of captopril was associated with an increase in renal plasma flow, the magnitude of which was positively correlated with PRA (not shown in table 1). In addition, since glomerular filtration rate was not altered, filtration fraction fell in all patients. These results strongly suggest that angiotensin II participates in the regulation of renal vascular tone and more precisely at the level of the efferent arterioles of the glomeruli. Because sodium depletion has a potentiating effect on BP reduction induced by converting enzyme blockade, the lack of sodium retention can be expected to enhance the therapeutic efficacy of captopril.

Certainly there was no tendency for "escape" from antihypertensive efficacy during long-term treatment up to 1 year (fig. 6), although an occasional patient required additional diuretics.

Sodium depletion and diuretics have long been used to treat essential hypertension and hypertension associated with chronic renal failure. These measures alone often fail to normalize BP. This may be due to the well-known reactive rise in renin induced by sodium depletion, since specific blockade of angiotensin II generation leads to normalization of BP in practically all patients. Thus, blockade of the pressor effect of the compensatory rise in renin induced by diuretics makes it possible to "titrate" the amount of sodium that has to be removed to normalize BP. The decrease in total body sodium induced by furosemide shifts the BP from a renin-independent state to a situation of renin dependency. Accordingly, with blockade

**Figure 7.** Long-term response to captopril alone is shown in four dialysis patients with hypertension resistant to conventional therapy. Pre-dialysis plasma renin ranged from 8.9 to 97 ng/ml/hr.

**Figure 8.** Hemodynamic studies in six patients with congestive heart failure demonstrate significant improvement in cardiac index and stroke index simultaneous with a drop in left ventricular filling pressure at the time of reduced blood pressure and peripheral resistance (from Turini et al., see ref. 26).
of the renin-angiotensin system, BP may be adjusted by choosing the appropriate dose of diuretics. Moreover, if hypotension occurs, the dose of captopril should not be reduced, since even very small doses inhibit angiotensin conversion. Blood pressure recovers after a short withdrawal of the diuretic.

It is of considerable interest that ACE does not return to normal levels in patients with chronic azotemia (fig. 2) at periods up to 14 hours, and that skin rash, the most common limiting side effect of the drug, occurred most often in these patients. These findings would suggest accumulation of the agent or its metabolites, which are known to be renally excreted, and provide a guiding principle in reducing the dosage in azotemic patients.

Captopril was also effective in lowering BP of chronic hemodialysis patients with previously "uncontrollable" hypertension. In these patients, captopril was effective alone whenever plasma renin activity was "high." However, when renin values were not clearly elevated, additional measures to systematically remove sodium were necessary to control BP. All patients reached acceptable levels when the two approaches were combined.

The data obtained with captopril in patients with chronic congestive heart failure suggest that blockade of the renin system improves their cardiac function. The marked decrease in systemic vascular resistance resulted in these patients in an increase in stroke index simultaneously with a drop in left ventricular filling pressure. Right atrial pressure was also reduced, and this decreased the left ventricular filling pressure further, and possibly myocardial oxygen consumption. Whether these beneficial effects on cardiac function from inhibition of the renin angiotensin system persist when captopril is administered chronically remains to be established. If so, captopril might be a useful vasodilator agent for treating congestive heart failure. Notwithstanding, these data are in complete agreement with earlier observations suggesting that the renin system plays an important role in determining afterload of normotensive patients with congestive heart failure.

In sum, converting enzyme blockade with captopril is a potent and well-tolerated approach to lowering BP of hypertensive patients and to enhancing cardiac function of patients with congestive heart failure. When it is used with diuretics or other means of sodium removal, the vast majority of hypertensive patients can be effectively treated.

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