Original Article

Intensive Blood Pressure Reduction Is Beneficial in Patients with Impaired Cardiac Function Coexisting with Chronic Renal Insufficiency

Naofumi IKEDA, Hiromichi SUZUKI, Kenshi MORIWAKI, Souichi SUGAHARA, Yoshihiko KANNO, Hirokazu OKADA, and Hidetomo NAKAMOTO

Both in CHF (congestive heart failure) and CRI (chronic renal insufficiency), blood pressure reduction is beneficial for preservation of cardiac and renal function. However, it is uncertain how much blood pressure reduction is appropriate in patients with both CHF and coexisting CRI. In the present study, we examined whether intensive blood pressure reduction is more beneficial in these patients than the usually accepted level of reduction. Thirty-five men and 21 women of average age 63 ± 5 years suffering from both CHF and CRI were selected from 316 patients attending the Kidney Disease Center of Saitama Medical School Hospital. All participants had an ejection fraction (EF) of less than 55% as determined by echocardiography. Renal function was evaluated by 24-h creatinine clearance (GFR), and a GFR of less than 50 ml/min was regarded as indicating renal insufficiency. Patients were divided into 2 groups according to the target blood pressure: in group I, blood pressure (BP) was lowered to less than 120/75 mmHg and in group II, blood pressure was lowered to less than 130/80 but more than 121/76 mmHg. The daily doses of basic antihypertensive agents were amlodipine 5 to 20 mg, benazepril 2.5 to 5 mg, guanabenz 2 to 8 mg and furosemide 20 to 60 mg. At the end of a 2-year follow-up period, the BP in group I was controlled at the level of 118 ± 3/73 ± 4 mmHg with good maintenance of EF (46 ± 4 to 60 ± 4%) and GFR (44 ± 3 to 40 ± 3 ml/min). In group II, BP was maintained at 128 ± 4/81 ± 2 mmHg, accompanied by a reduction of EF (46 ± 4 to 42 ± 3%) and a significant reduction of GFR (44 ± 3 to 35 ± 3 ml/min). These results suggest that intensive blood pressure reduction might be beneficial in cases complicated by cardiorenal failure. (Hypertens Res 2002; 25: 41–48)

Key Words: chronic renal insufficiency, calcium channel blocker, ACE inhibitor, ejection fraction

Introduction

Loss of kidney function is accompanied by many cardiovascular alterations (1–5). Conversely, in heart failure, excessive sodium and water retention occur because of renal vasoconstriction, stimulation of the renin-angiotensin-aldosterone (RA) system, direct effects on the proximal convoluted tubules and increased renal sympathetic nerve activity (6, 7). This cardiorenal linkage is becoming an increasingly important and challenging problem in clinical practice, mainly because of the growing population of elderly people with impairments of both renal and cardiac function. Thus far, patients with renal dysfunction have usually been excluded from large-scale studies of congestive heart failure (8), and reciprocally, patients with heart failure have been excluded from chronic renal insufficiency trials (9–11). Moreover, there have been few studies examining strategies for treating patients suffering from congestive heart failure (CHF) with coexisting renal insufficiency, despite the fact that renal hemodynamics are markedly altered in CHF (12, 13).

Angiotensin-converting-enzyme (ACE) inhibitors are
known to be effective and well-tolerated in patients with heart failure and to be protective in patients with chronic renal failure. It is therefore likely that ACE inhibitors would be particularly beneficial in patients with heart failure complicated by renal insufficiency. However, several studies have indicated that the presence of significant renal impairment reduces hemodynamic benefits, such as increases in stroke volume, decreases in left ventricular filling pressure and systemic vascular resistance. Moreover, increases in the risk of adverse reactions during long-term ACE inhibition in patients with heart failure have been noted (13–16). In addition to pharmacological intervention for patients with chronic renal insufficiency and impaired cardiac function, the beneficial effects of achieving blood pressure reductions on progression of chronic renal insufficiency have been clearly demonstrated (9, 17). However, serious adverse reactions to ACE inhibitors are seen more frequently in hypertensive patients with renal insufficiency, especially when blood pressure is considerably reduced (18). To resolve this dilemma, we compared changes in renal function and left ventricular function and safety and effectiveness in patients with cardiac dysfunction coexisting with chronic renal failure over a 2-year period in two groups. One group was treated according to the usual goal of reducing blood pressure to less than 130/85 mmHg, but in the second, a low blood pressure goal of less than 125/75 mmHg was set.

Patients and Methods

Patients

Fifty-six patients with heart failure and renal dysfunction were recruited from 316 patients attending the Kidney Disease Center of Saitama Medical College Hospital. The group comprised 35 men and 21 women, aged 44 to 84 years (mean, 63 ± 5). The cause of heart failure was ischemic heart disease in 28 patients, primary mitral or aortic valvular regurgitation in 12 patients, hypertensive heart in 10 patients and dilated cardiomyopathy in the remaining 6 patients. The cause of renal dysfunction was nondiabetic renal failure: glomerular diseases in 28 patients, hypertensive nephrosclerosis in 18, polycystic kidney disease in 6 and unidentified kidney disease in the remaining 4 patients (Table 1). All had a left ventricular ejection fraction of less than 55% as determined by echocardiography. Renal function was evaluated by 24-h creatinine clearance (19). A patient with a serum creatinine concentration of > 1.4 mg/dl or having a 24-h creatinine clearance of < 50 ml/min was regarded as suffering from renal insufficiency.

A patient was considered to have hypertension if 1) this was a clinical diagnosis indicated in the medical record; 2) arterial blood pressure was normal with ongoing antihypertensive therapy; or 3) at diagnosis there were 2 successive determinations of either a systolic arterial blood pressure of > 140 mmHg or a diastolic arterial blood pressure of > 90 mmHg.

All patients gave their written informed consent to participate in the study, which was approved by the local Ethical Committee on Human Research of the Saitama Medical College. Patients were instructed to follow a diet with a protein and salt intake of less than 0.7 g/kg and 9 g daily, respectively. A dietician checked the daily intake of protein based on the subject’s recall of his or her diet, and the daily intake of salt was estimated based on urinary sodium excretion.

Methods

Both pharmacological and non-pharmacological interventions were implemented. During the baseline period, antihypertensive treatments were switched to the combination of a long-acting calcium channel blocker (CCB), amlodipine, at a
dose of 5 mg and benazepril at a dose of 5 mg or 2.5 mg daily irrespective of whether patients had received previous treatment. Patients with serum creatinine values of less than 2 mg/dl were started on benazepril 5 mg daily. Patients with serum creatinine values greater than 2 mg/dl were started on benazepril 2.5 mg daily. If one of the ACE inhibitors other than benazepril was used for treatment of congestive heart failure and/or chronic renal insufficiency, approximately equivalent doses of benazepril were substituted. Blood pressure control was approached using the following step-wise therapeutic strategy: 1) dose adjustment of amlodipine up to 20 mg daily; 2) addition of furosemide up to 60 mg daily; and 3) addition of guanabenz at a bedtime dose of 2 to 8 mg daily. Combination therapies were used because they have previously been reported to be necessary for achieving target blood pressure goals in numerous large-scale clinical trials (20, 21). After a baseline evaluation, patients were randomly assigned either to a group (group II) with the usual blood pressure goal of 130/80 mmHg or to a second group (group I) with a low blood pressure goal of 120/75 mmHg or less.

Blood pressure was measured at least twice a month using a standardized sphygmomanometer. Two measurements were made with patients in a seated position for 5 and 10 min, respectively, and the average of the 2 values was taken as the blood pressure for the determination of the efficacy of treatment. During the study period, the patients’ other drug therapies for heart failure were kept constant, unless side effects occurred that were thought to be related either to these other medications or to the study drug itself. In addition, if the serum potassium concentration increased to greater than 5.5 mEq/l, a cation exchanger was prescribed. The patients were seen every 2 weeks until the study ended, until they required dialysis, or until they died. The serum creatinine, 24-h urinary excretion of creatinine and protein, and hematologic and serum tests including assays for urea, uric acid, blood urea nitrogen, electrolytes, etc. were obtained at the beginning and end of the baseline period and every month during follow-up.

Echocardiography

Left ventricular diameter, septal wall thickness, and left posterior wall thickness were assessed by M-mode echocardiography after selecting the measurement section by B-mode echocardiography. Data were averaged over 5 cardiac cycles. Left ventricular mass index was calculated from thickness and diameter values using the Penn conversion formula (22). Throughout the study, echocardiography was performed before treatment and at the 3rd, 6th, 12th and 24th month.

Exclusion Criteria

Exclusion criteria included pregnancy or lactation, diabetes mellitus, secondary glomerular diseases such as systemic lupus erythematosus, Wegener disease, myeloma etc., proteinuria in the nephrotic range of 3.0 g/day, and use of sedative or hypnotic drugs or any other drugs potentially affecting blood pressure during ambulatory monitoring, i.e., corticosteroids. Patients whose blood pressure values remained above 140/90 mmHg despite these treatments were excluded from the study.

Study Objectives

The primary goal was to assess the effect of blood pressure control on renal function as estimated by 24-h creatinine clearance and ejection fraction. Secondary analyses included the effect of randomization either to group I or II on urinary protein excretion, progression to end-stage renal failure, the frequency of major cardiovascular complications, and the total and cardiovascular mortality rate.

Statistical Analysis

The baseline characteristics of the two treatment groups were compared by Student’s $t$-test and $\chi^2$ test. Cumulative survival curves were constructed as time-to-first-event plots by Kaplan-Meier survivorship methods (23), and differences between the curves were tested for significance by the log-rank test using the Cox proportional-hazards regression model (24). Differences between treatment groups in post-randomization measures or events were evaluated by analysis of variance and by $\chi^2$ test. Association between mean blood pressure and ejection fraction or 24-h creatinine clearance were examined using simple linear regression analyses methods. All data are reported as the means $\pm$ SEM. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Baseline Characteristics and Their Changes during the Study (Table 2)

Baseline levels and changes of serum creatinine, blood urea nitrogen, hematocrit and serum potassium are shown in Table 2. There were no significant differences in these parameters between the two groups.

Changes in Systolic (Fig.1a) and Diastolic (Fig.1b) Blood Pressure

There were significant differences in both systolic and diastolic blood pressure between the two groups ($p < 0.05$). At the end of a 2-year follow-up period, BP in group I was controlled at the level of $118 \pm 4/73 \pm 3$ mmHg whereas BP in group II was maintained at the level of $128 \pm 4/81 \pm 2$ mmHg. The systolic and diastolic blood pressure of both groups were lowered significantly from the basal levels ($p < 0.05$).

Effect of Strict Blood Pressure Control on Cardiovascular Morbidity

There was one cardiovascular death and one death due to
Groups I and II experienced one cardiovascular death and two deaths due to acute myocardial infarction by log-rank testing, the combined risk of cardiovascular death was not significantly different between the two groups.

### Changes in Proteinuria: Relationship with Low Blood Pressure Control (Table 2)

The low blood pressure goal did not significantly change the level of proteinuria from its baseline value, i.e., there were no significant differences in proteinuria between the groups.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
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<tr>
<td><strong>Serum creatinine (mg/dl)</strong></td>
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<tr>
<td>Group II</td>
<td>1.8 ± 0.6</td>
<td>1.9 ± 0.8</td>
<td>2.1 ± 0.9</td>
<td>2.4 ± 0.7*</td>
<td>2.5 ± 0.7*</td>
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<td>1.8 ± 0.9</td>
<td>1.9 ± 0.6</td>
<td>1.9 ± 0.7</td>
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<td><strong>Blood urea nitrogen (mg/dl)</strong></td>
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<tr>
<td>Group II</td>
<td>24 ± 6</td>
<td>26 ± 6</td>
<td>28 ± 9</td>
<td>29 ± 9</td>
<td>31 ± 8</td>
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<tr>
<td>Group I</td>
<td>24 ± 8</td>
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<td>26 ± 8</td>
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<td><strong>Hematocrit (%)</strong></td>
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<tr>
<td>Group II</td>
<td>36 ± 8</td>
<td>38 ± 8</td>
<td>35 ± 7</td>
<td>34 ± 7</td>
<td>32 ± 7*</td>
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<td>Group I</td>
<td>36 ± 5</td>
<td>37 ± 6</td>
<td>35 ± 7</td>
<td>37 ± 6</td>
<td>37 ± 7</td>
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<td><strong>Serum potassium (mEq/l)</strong></td>
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<tr>
<td>Group II</td>
<td>4.8 ± 0.5</td>
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<td>4.9 ± 0.8</td>
<td>5.1 ± 0.7</td>
<td>5.2 ± 0.6</td>
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<td>4.8 ± 0.6</td>
<td>4.9 ± 0.6</td>
<td>4.8 ± 0.6</td>
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<td><strong>Urinary protein (g/dl)</strong></td>
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<tr>
<td>Group II</td>
<td>1.0 ± 0.2 (28)</td>
<td>1.2 ± 0.3 (28)</td>
<td>1.1 ± 0.3 (17)</td>
<td>1.2 ± 0.3 (13)</td>
<td>1.1 ± 0.4 (13)</td>
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<td>1.2 ± 0.2 (21)</td>
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Group I: patients whose blood pressure were lowered to less than 120/75 mmHg. Group II: patients whose blood pressure were lowered to less than 130/80 mmHg. Figures in a parenthesis in the column of urinary protein are number of patients. There were no significant differences between the two groups. *p < 0.05, significant difference compared to the basal values.

### Changes in Creatinine Clearance: Relationship with Blood Pressure Control (Fig. 2)

Usual blood pressure control was associated with a more rapid decline in creatinine clearance (44 ± 3 ml/min). In group II, the level was significantly different from baseline at both 12 months (36 ± 3 ml/min) and 24 months (35 ± 3 ml/min). In contrast, patients in group I did not experience a significant reduction of creatinine clearance during the study (44 ± 4 to 40 ± 3 ml/min). There were difference in change in creatinine clearance between the two groups at 12 and 24 months (p < 0.05).

![Fig. 1. Changes in systolic and diastolic blood pressure throughout the study. Numbers below the figure represent the number of patients in each group who have not reached the end point and are still being followed up. *p < 0.05, significant difference between two groups.](image)

### Table 2. Basal Values and Changes in Serum Creatinine, Blood Urea Nitrogen, Hematocrit, and Serum Potassium and Urinary Excretion of Protein

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<td>26 ± 8</td>
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<tr>
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<td>36 ± 5</td>
<td>37 ± 6</td>
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Changes in Ejection Fraction: Relationship with Blood Pressure Control (Fig. 3)

The ejection fraction in group I tended to increase and, at its maximum, was 12% higher than the baseline value (46.4 to 60.4%; \( p < 0.05 \)). In contrast, there were no significant changes in ejection fraction in group II throughout the study (46.4 to 42.3%).

Effects of Treatment on Cardiac Structure (Table 3)

LVMI, intraventricular septal thickness and posterior wall thickness were not significantly altered in either group.

Effect of Low Blood Pressure Control on Kidney Survival (Fig. 4)

Kidney survival was significantly better in group I (\( p = 0.02 \)). In group II, 12 patients were introduced to maintenance dialysis therapy (6 to continuous ambulatory peritoneal dialysis and 6 to hemodialysis), whereas in group I, 6 patients were introduced to dialysis therapy (4 to continuous ambulatory dialysis therapy and 2 to hemodialysis). The Kaplan-Meier curves begin to diverge at 6 months and then continued to diverge over the next 18 months (\( p < 0.05 \)).

Association between Blood Pressure Reduction and Changes in Ejection Fraction or 24-h Creatinine Clearance (Fig. 5)

Mean blood pressure (\( mBP \)) (systolic blood pressure + 2 diastolic blood pressure / 3) was used to analyze the univariate correlation with 24-h creatinine clearance and ejection fraction. Delta \( mBP \) (\( mBP \) at 12 or 24 months - \( mBP \) at baseline) of both groups was inversely associated with 24-h creatinine clearance (\( r = -0.33; p < 0.003 \)), but was not as...
associated with ejection fraction.

Doses of Amlodipine, Furosemide and Guanabenz

Seventy-five percent of patients required furosemide administration in either group, and the average dose was 48.5 ± 8.6 mg daily. Guanabenz was administered in more than 50% of cases in each group, at an average dose of 3.2 ± 0.8 mg daily. The average dose of amlodipine was 12.6 ± 0.4 mg daily in group I and 8.2 ± 0.2 mg daily in group II (p < 0.01). Sodium polystyrene sulfonate was administered at an average dose of 8.6 ± 1.2 g daily to prevent elevation of the levels of serum potassium in 25% of patients in either group.

Discussion

The present study demonstrates that strict blood pressure control with antihypertensive drugs, including ACE inhibitors and long-acting calcium antagonists, prevents progression of renal dysfunction and results in improved cardiac function in patients with cardiac dysfunction and coexistent renal dysfunction.

In patients with chronic renal insufficiency, several large-scale clinical trials have demonstrated that the more blood pressure is reduced, the better renal function is preserved (9, 11, 17). In addition to the effects of lowering blood pressure, ACE inhibitors are known to provide protection against mild- to moderate-progressive deterioration of renal function in patients with cardiac dysfunction and coexistent renal dysfunction. In patients with chronic renal insufficiency, several large-scale clinical trials have demonstrated that the more blood pressure is reduced, the better renal function is preserved (9, 11, 17). In addition to the effects of lowering blood pressure, ACE inhibitors are known to provide protection against mild- to moderate-progressive deterioration of renal function in patients with various renal diseases (7, 11). However, there have been no large, long-term randomized trials of ACE inhibitors in patients with CHF and coexistent renal insufficiency. One possible reason for this is that the effective dose of ACE inhibitors for patients with renal dysfunction remains to be clarified. Moreover, physicians are reluctant to use ACE inhibitors because of the reduced excretion and prolonged half-life that is associated with renal impairment. Thus, it has been documented that benazepril does not accumulate in the plasma of patients with mild to moderate renal function over a 1-year treatment period. In addition, the pharmacokinetics of the metabolite benazeprilat are affected by renal impairment, which results in slower elimination (25). Furthermore, some studies suggest that the renoprotective properties of ACE inhibitors may depend, at least in part, on limitation of the traffic of proteins and their consequent toxicity (10). In the present study, we started treatment with a relatively low dose of benazepril in patients with cardiac dysfunction and coexisting renal insufficiency. We could find no significant differences in urinary excretion of protein between the two blood pressure groups. In some patients of either group, greatly reduced urinary protein excretion was observed; however, these effects were not consistent. This is in accordance with a previous study on patients with nondiabetic proteinuria nephropathies, in which the glomerular filtration rate was shown to be less likely to decline with time, irrespective of the blood pressure level achieved (17).

In CHF, impaired cardiac function produces unphysiological retention of sodium and water through the changes in neurohormonal effectors such as the sympathetic nervous system, the renin-angiotensin system, etc., and through alterations in renal blood flow and tubular reabsorption at both proximal and distal tubules. Among the hormonal factors, the renin-angiotensin-aldosterone system is activated, resulting in decreased renal perfusion, increased tubular reabsorption of sodium and water and increased sympathetic nervous system activity (6, 26). This led to the hypothesis that ACE inhibitors would benefit patients with heart failure, and the role of ACE inhibitors in the treatment of CHF is now well-defined (16). In addition, ACE inhibition is clearly associated with improved survival or fewer cardiovascular events among patients with CHF and near-normal renal function (16). In spite of this advantage of ACE inhibitors in heart failure, functional renal insufficiency occurs due to the loss of angiotensin-mediated systemic and intrarenal vasoconstrictor effects, which are needed to maintain renal perfusion pressure and glomerular filtration rate in low-output states (27).

Few randomized heart failure trials have published follow-up renal function data. In one of these, the Cooperative North Scandinavian Enalapril Survival Study (CONSEN...
SUS) trial (15), the effect of high-dose enalapril (average dose, 17 mg daily) in patients with severe New York Heart Association (NYHA) class IV CHF was examined. Serum creatinine more than doubled in 11% of patients, increased by 30% to 100% in 24%, by less than 30% in 41%, and decreased in 24%. In SOLVD (Studies of Left Ventricular Dysfunction) (28), into which less severely ill patients (NYHA class II to III) were enrolled and studied to determine the effect of a lower dose of enalapril (average dose, 11.2 mg/dl), the proportion of patients in whom serum creatinine increased by more than 2 mg/dl was only slightly greater in the enalapril-treated group (10.7%) than in the placebo group (7.7%). From these results, it is likely that ACE inhibitors should be used at a relatively low dose in patients with congestive heart failure and coexistent renal impairment.

The restriction of arbitrary usage of ACE inhibitors required a larger dose of amlodipine in the lower blood pressure group than in the usual blood pressure group. Using a pig model of rapid-pacing induced heart failure, Kribbs et al. (29) showed that combination therapy with amlodipine and fosinopril improved the cardiac index by decreasing wall stress, in addition to reducing total systemic resistance in the ACE inhibition group. This provided evidence that, when application of a maximum or sufficient dose of ACE inhibitors is limited in patients with CHF and chronic renal insufficiency, combination therapy with ACE inhibitors and CCB could be effective for improving left ventricular dysfunction via reduction of blood pressure.

The dihydropyridine CCB adversely affects glomerular barrier function in nondiabetic chronic nephropathies, which may contribute to accelerated progression of the disease. This seems to be a specific effect that is exacerbated by uncontrolled hypertension and minimized by strict blood pressure control and/or concomitant ACE inhibitor therapy. In the PRAISE study (Prospective Randomized Amlodipine Survival Evaluation), when hypertension had to be controlled, treatment with amlodipine in combination with ACE inhibitors resulted in favorable effects in patients with nonischemic CHF. In a previous clinical study of patients with CHF undergoing ACE inhibition treatment, the institution of concomitant amlodipine therapy was found not to be associated with increased hemodynamic compromise or mortality but rather may have yielded favorable effects, at least in a subset of patients (30). Recently, Philbin et al. reported that in hospitalized patients with congestive heart failure and coexisting renal insufficiency (31), any clinical benefit from ACE inhibitor use was limited to older patients with CHF and moderate or severe renal insufficiency. The major differences between these studies and our study are likely to be related to differences in the study population, especially with regard to age and serum creatinine levels. In their study, the mean age was 74 years, compared to 66 years in the present study. In addition, their serum creatinine levels were higher (3.9 vs. 1.1 vs. 2.5 vs. 0.9 mg/dl). Lastly, but much more importantly, the levels of cardiac function are different between their follow-up studies and our current study. In their studies, the mean left ventricular ejection fraction of patients with CHF and coexisting renal dysfunction was 37%, whereas in our patients the average ejection fraction was 46%. These three factors exert a significant influence on cardiorenal function in patients with impaired cardiac function and coexisting renal insufficiency.

**Study Limitations**

The patients studied in this clinical trial had a wide range of cardiac and renal diseases. It is unclear which combination (e.g., valvular disease and nephrosclerosis, etc.) presents the greatest risk for progression of renal dysfunction and severity of cardiac impairment. However, it is difficult to examine all possible combinations of cardiac and renal diseases. Secondly, the arbitrary dose reduction of an ACE inhibitor might restrict the beneficial pharmacological actions of ACE inhibitors on cardiac function in assumed blood pressure levels (32).

In conclusion, strict blood pressure control with a relatively small dose of ACE inhibitor and a long-acting calcium antagonist resulted in cardio- and renal protection in hypertensive patients with impaired cardiac function and chronic renal insufficiency.

**References**


