Original Article

Selection of the Dose of Angiotensin Converting Enzyme Inhibitor for Patients with Diabetic Nephropathy Depends on the Presence or Absence of Left Ventricular Hypertrophy

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

The coexistence of hypertension increases cardiovascular risks and the rate of deterioration of renal function for diabetic patients. For patients with left ventricular hypertrophy (LVH), the use of an angiotensin converting enzyme (ACE) inhibitor is known to be effective and well tolerated and to be protective against chronic renal insufficiency (CRI). However, serious adverse reactions to ACE inhibitors, such as the rapid deterioration of renal function, have been reported, making physicians hesitant to use these agents. To resolve this dilemma, we compared changes in renal function and left ventricular function and the safety and effectiveness of benazepril, an ACE inhibitor, in patients with diabetic nephropathy, with or without LVH. The age, sex, duration of diabetes, levels of blood pressure and blood glucose and rates of creatinine clearance (CrCl) were compared between 36 diabetic patients with LVH and 36 matched diabetic patients without LVH. The rates of CrCl in all patients were between 14 and 35 ml/min, and all patients received an ACE inhibitor before enrollment. The group comprised 43 men and 29 women, with a mean age of 56 ± 4 years. These patients were divided into three groups, each of which was subdivided into a group with and a group without LVH. Group I (without LVH) or I-L (with LVH) received a half dose of benazepril (2.5 mg daily), Group II (without LVH) or II-L (with LVH) received a normal daily dose of 5 mg benazepril, and Group III (without LVH) or III-L (with LVH) discontinued the administration of the ACE inhibitor. The follow-up period was 1 year and, during the study, blood pressure was maintained at less than 140/90 mmHg. If the blood pressure control was not satisfactory, benidipine, a calcium antagonist, and/or furosemide, a loop diuretic, and/or guanabenz, a central acting antihypertensive agent, were administered. In the diabetic patients with LVH, the administration of a normal dose of benazepril inhibited the decline of renal function and cardiac function (CrCl: 24.2 ± 1.5 to 22.0 ± 2.5 ml/min; EF (ejection fraction): 56 ± 3 to 54 ± 6%) compared to the other two groups. In patients without LVH, a half dose of benazepril preserved renal function (23.4 ± 2.6 to 22.0 ± 3.1 ml/min; EF: 54 ± 3 to 56 ± 3%). Discontinuation of the administration of ACE inhibitor led to the further progression of renal dysfunction and decreases in EF in patients with or without LVH. Our results provide some indications for the use of ACE inhibitors in diabetic patients when renal dysfunction and/or cardiac hypertrophy are present. (Hypertens Res 2002; 25: 865–873)

Key Words: left ventricular hypertrophy, ejection fraction, diabetic nephropathy

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Introduction

End-stage renal failure due to diabetes mellitus is the most common cause of prevalent and incident end-stage renal disease (ESRD) in Japan, as well as in some Western countries (1–5). Cross-sectional (6, 7) and longitudinal studies (8) have identified some factors associated with a high risk of nephropathy. These factors include elevated blood pressure, elevated glycosylated hemoglobin and cholesterol concentrations, smoking, advanced age, a high level of insulin resistance, male sex, and a high dietary protein intake. Among these factors, the control of systemic blood pressure is important in inhibiting the progression of chronic renal insufficiency in diabetic patients (9–11). Numerous studies have shown that, in patients with type 2 diabetes, hypertension, and microalbuminuria, angiotensin converting enzyme (ACE) inhibitors prevent a further increase in, and may reduce, increased albumin excretion (12, 13). Although some guidelines have proposed the cautious use of ACE inhibitors in diabetic patients with moderately progressed renal dysfunction (14, 15), a few decisive investigations have proposed that the use of ACE inhibitors is appropriate (16). ACE inhibitors have been shown to be disadvantageous when administered to hypertensive patients with moderately advanced renal dysfunction because they tend to accumulate in the patients, often leading to impairment of renal function (17, 18). In addition, various structural and functional alterations in the heart have been observed in these patients (6). In patients with cardiac impairment and renal dysfunction, these two conditions may influence each other. In particular, if cardiac function is impaired, renal dysfunction may be exaggerated (19). Although many investigators have proposed that ACE inhibitors are especially important for preventing cardiac disease mortality and morbidity in patients with diabetes (20), there are no results from prospective, placebo-controlled studies to clarify whether dose-adjustments of ACE inhibitors are needed to prevent the progression to ESRD in patients with type 2 diabetes and coexisting cardiac diseases. In this study, we tried to determine the adequate dose of an ACE inhibitor in diabetic patients with renal dysfunction with or without left ventricular hypertrophy (LVH).

Research Design and Methods

The primary objective of this study was to determine the effects of dose adjustment of an ACE inhibitor, under the tight control of blood pressure, on changes in the levels of serum creatinine in type 2 diabetic patients with or without LVH. All patients provided written informed consent to participate in the study, which was approved by the local Ethical Committee on Human Research at Saitama Medical School. Patients were instructed to follow a diet with a protein intake of less than 0.7 g per kg body weight and less than 9 g of salt daily.

Patients

Patients were diagnosed with type 2 diabetes according to criteria based on the World Health Organization Report of 1998 (21). Enrolled hypertensive patients had been treated with antihypertensive drugs, including one type of ACE inhibitor. The inclusion criteria included a rate of creatinine clearance (CrCl) in the range of 14 to 35 ml/min at the time of entry. Echocardiographic studies were performed on all patients, who were then divided into two groups according to the posterior wall thickness (PWT). Patients with a PWT of 12 mm or more were diagnosed as having LVH, and those with a PWT of below 12 mm were considered not to have LVH (22). The patients were excluded if they had had a myocardial infarction or cerebral vascular accident within the previous year, had had cardiovascular surgery, including a coronary bypass graft, within the previous year, or had Class III or IV congestive heart failure based on the New York Heart Association classification. Patients with nephrotic syndrome with proteinuria of more than 3 g daily were excluded. In addition, patients with an echocardiographically measured ejection fraction of less than 50% were excluded. The period of study was 1 year.

Seventy-two patients were selected from among 124 patients attending the Kidney Disease Center of Saitama Medical School and its five affiliated hospitals from 1995 to 1998, based on the criteria mentioned above. These patients were divided into three groups and subdivided into those with or without LVH. Group I (without LVH) or I-L (with LVH) received a half dose of benazepril (2.5 mg daily), Group II (without LVH) or II-L (with LVH) received a normal daily dose of 5 mg benazepril, and Group III (without LVH) or III-L (with LVH) discontinued the administration of the ACE inhibitor.

Study Protocol

Antihypertensive therapy was changed to treatments with the calcium channel blocker (CCB), benidipine, at a dose of 4 to 12 mg daily, and patients were randomized to one of three groups, irrespective of whether they had received previous treatment. In each clinic, antihypertensive therapy was adjusted according to the office blood pressure measured with a mercury sphygmomanometer and an appropriate cuff size after 15 min rest in a seated position. If a blood pressure of < 140 mmHg systolic or < 90 mmHg diastolic was not achieved in the clinical visits during the study period, either 1) a dose adjustment of benidipine up to 12 mg daily, and/or 2) the addition of furosemide up to 80 mg daily, and/or 3) the addition of guanabenz at a bedtime dose of 2 to 8 mg daily were made.

Blood Glucose Control

All patients had been treated with antiglycemic agents, in-
including insulin. Eighty-three percent (60 out of 72) received sulfonylureas derivatives (more than 90% received glibenclamide) and 75% (54 out of 72) received α-glucosidase inhibitors. If glycemic control (glycosilated hemoglobin (HbA1c) < 8.0%) was judged to be poor, the initiation of insulin therapy was encouraged. During the study period, 12% (8 out of 72) of patients were switched to insulin therapy from oral hypoglycemic agents.

Echocardiography

Left ventricular end-diastolic diameter and end-systolic diameter, ventricular septal wall thickness, and left posterior wall thickness were assessed by M-mode echocardiography after selecting the measurement section by B-mode echocardiography. Left ventricular mass index (LVMi) was calculated according to the Penn formula (22). Data were averaged over five cardiac cycles. Echocardiography was performed before each treatment and again at the end of the study. The interobserver agreement was 90% and the intraobserver agreement was 91%.

Clinical Measurements

Blood Pressure

Clinic blood pressure was measured between 9:00 and 11:00 AM in each clinic using a mercury sphygmomanometer with the patient in a seated position after 15 min rest. The first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively.

Laboratory Measurements

The serum creatinine, hematologic and serum tests, including measurements of uric acid, blood urea nitrogen and electrolytes and 24-h urinary excretion of protein and creatinine, were performed at the beginning and at the end of the baseline period and every month during the follow-up. HbA1c was determined by an ion-exchange high-performance liquid chromatography procedure using a Merck-Hitachi L-9100 glycated hemoglobin analyzer (Merck, Darmstadt, Germany).

Table 1. Characteristics of 72 Hypertensive Type 2 Diabetic Patients with Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>LVH (−)</th>
<th>LVH (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group III</td>
<td>Group I</td>
</tr>
<tr>
<td>Dose of ACE inhibitor (mg/day)</td>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>Number</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/4</td>
<td>6/6</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>12 8 3</td>
<td>11 8 4</td>
</tr>
<tr>
<td>Smokers</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Retinopathy (simplex/proliferative)</td>
<td>6/6</td>
<td>7/5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3 8 0.4</td>
<td>7.4 8 0.6</td>
</tr>
</tbody>
</table>

Values: mean 8 SEM. LVH, left ventricular hypertrophy. Group I comprises patients who were taking 2.5 mg benazepril daily. Group II comprises patients who were taking 5 mg benazepril daily. Group III comprises patients who were not taking benazepril. Group I-L comprises patients with LVH who were taking 2.5 mg benazepril daily. Group II-L comprises patients with LVH who were taking 5 mg benazepril daily. Group III-L comprises patients with LVH who were not taking benazepril.
Effects of Treatment on Blood Pressure

Patients without LVH (Fig. 1)
Systolic blood pressure was maintained below 140 mmHg, irrespective of the doses of ACE inhibitor throughout the study period. Diastolic blood pressure was maintained in the three groups at below 90 mmHg throughout the study period.

Patients with LVH (Fig. 1)
Both the systolic and diastolic blood pressure of all groups decreased significantly towards the end of the study period to the target levels of less than 140/90 mmHg. There were no significant differences among the three groups. The levels of systolic blood pressure at the start of the study were significantly higher (p < 0.05) in the patients with LVH than in those without LVH.

Effects of Treatment on 24-h CrCl

Patients without LVH (Fig. 2)
Patients treated with a dose of 5 mg benazepril and those who were not treated with benazepril showed a gradual decrease in CrCl throughout the study and a significant decrease at the end of the study (p < 0.05). The difference between the patients in Group I and the patients in Groups II and III achieved statistical significance at the end of the study period (p < 0.05). In the patients treated with a dose of 2.5 mg of benazepril, the rates of CrCl were maintained until 9 months; however, these rates were significantly lower at the end of the study than at the start of the study (p < 0.05).

Patients with LVH (Fig. 2)
The discontinuation of ACE inhibitor produced a gradual decrease in CrCl, and this decrease became statistically significant at 9 months. The dose of 2.5 mg of benazepril produced a significant decrease in CrCl at the end of the study, but the rates of CrCl of patients treated with 5 mg of benazepril did not show any significant changes throughout the study. There were significant differences between Groups I-L and II-L and between Groups II-L and III-L at the end of the study period (p < 0.05).

Effects of Treatment on Urinary Protein Excretion

Patients without LVH (Table 2)
Patients in Group I did not show any significant changes in urinary protein excretion. Patients in Group II showed a gradual but not significant increase in urinary protein excretion throughout the study; however, patients without ACE inhibitor showed a significant increase in the levels of protein excretion at both 6 months and the end of the study period (p < 0.05). There was a significant difference between...
the patients in both Groups I and II and the patients in Group III at these two points (p \textless 0.05).

Patients with LVH (Table 2)
The discontinuation of ACE inhibitor produced a significant increase in urinary protein excretion both at 6 months and the end of the study, although in the patients in both Groups I-L and II-L, urinary protein excretion did not change significantly throughout the study. There was a significant difference between the patients in Groups I-L and II-L and those in Group III-L.

**Effect of Treatment on Serum Potassium**

Patients without LVH (Fig. 3)
The discontinuation of ACE inhibitor produced a gradual increase in the levels of serum potassium and, at the end of the study, the levels rose significantly to 5.1 \pm 0.2 mEq/l relative to the levels at the start and relative to the levels in Group I. In Group II, treatment with a 5 mg dose of benazepril increased the levels of serum potassium beginning at 6 months after the start of the study. The levels were elevated to 5.5 \pm 0.3 mEq/l at the end of the study, significantly higher than the baseline values at the start of the study or than those of Group I (p \textless 0.05).

Patients with LVH (Fig. 3)
No significant differences were observed among the three groups of patients with LVH throughout the study, except at the end of the study when, in patients in Group III-L, a significant increase was found compared to the baseline values.

**Effects of ACE Inhibitor Treatment on the Levels of Hemoglobin**

Patients without LVH (Fig. 4)
In Group II, treatment with a 5 mg dose of benazepril induced a significant reduction in hemoglobin levels compared to the values at the start of the study. In the patients for whom ACE inhibitors were discontinued, the levels of hemoglobin decreased at 6 months and at the end of the study; however, this change did not achieve statistical significance.

Patients with LVH (Fig. 4)
After the start of the study, the levels of hemoglobin gradually decreased in all three groups. Although there were no sig-

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**Table 2. Changes in Urinary Protein Excretion in Type 2 Diabetic Patients with Nephropathy with or without LVH**

<table>
<thead>
<tr>
<th>Dose of ACE inhibitor (mg daily)</th>
<th>LVH (-)</th>
<th>LVH (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>Group I</td>
<td>1.2 \pm 0.6</td>
</tr>
<tr>
<td>5</td>
<td>Group II</td>
<td>1.2 \pm 0.3</td>
</tr>
<tr>
<td>0</td>
<td>Group III</td>
<td>1.4 \pm 0.5</td>
</tr>
</tbody>
</table>

Each group had 12 patients. Values: mean \pm SEM. L means co-existence of left ventricular hypertrophy. LVH, left ventricular hypertrophy. Groups I to III and I-L to III-L are described in the legend to Table 1. * p \textless 0.05, compared to the 0 month. # p \textless 0.05, 0 mg vs. 5 and 2.5 mg treated groups of with or without LVH.
Table 3. Echocardiographic Parameters in Hypertensive Type 2 Diabetic Patients with Diabetic Nephropathy with or without LVH

<table>
<thead>
<tr>
<th></th>
<th>2.5&lt;sup&gt;a&lt;/sup&gt; Group I</th>
<th>5&lt;sup&gt;a&lt;/sup&gt; Group II</th>
<th>0&lt;sup&gt;a&lt;/sup&gt; Group III</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
<td>Baseline</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>46.4 &lt;sup&gt;±&lt;/sup&gt; 5.8</td>
<td>47.6 &lt;sup&gt;±&lt;/sup&gt; 5.2</td>
<td>46.8 &lt;sup&gt;±&lt;/sup&gt; 5.1</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>29.5 &lt;sup&gt;±&lt;/sup&gt; 4.2</td>
<td>29.5 &lt;sup&gt;±&lt;/sup&gt; 3.3</td>
<td>29.1 &lt;sup&gt;±&lt;/sup&gt; 3.2</td>
</tr>
<tr>
<td>IVT (mm)</td>
<td>10.3 &lt;sup&gt;±&lt;/sup&gt; 0.4</td>
<td>10.3 &lt;sup&gt;±&lt;/sup&gt; 0.4</td>
<td>10.2 &lt;sup&gt;±&lt;/sup&gt; 0.9</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>11.2 &lt;sup&gt;±&lt;/sup&gt; 0.5</td>
<td>11.5 &lt;sup&gt;±&lt;/sup&gt; 0.9</td>
<td>11.7 &lt;sup&gt;±&lt;/sup&gt; 0.5</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>98 &lt;sup&gt;±&lt;/sup&gt; 11</td>
<td>100 &lt;sup&gt;±&lt;/sup&gt; 10</td>
<td>97 &lt;sup&gt;±&lt;/sup&gt; 9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>60 &lt;sup&gt;±&lt;/sup&gt; 3</td>
<td>60 &lt;sup&gt;±&lt;/sup&gt; 6</td>
<td>60 &lt;sup&gt;±&lt;/sup&gt; 5</td>
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</table>

b. Coexisting with LVH

<table>
<thead>
<tr>
<th></th>
<th>2.5&lt;sup&gt;b&lt;/sup&gt; Group I-L</th>
<th>5&lt;sup&gt;b&lt;/sup&gt; Group II-L</th>
<th>0&lt;sup&gt;b&lt;/sup&gt; Group III-L</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
<td>Baseline</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>46.2 &lt;sup&gt;±&lt;/sup&gt; 1.3</td>
<td>46.9 &lt;sup&gt;±&lt;/sup&gt; 1.5</td>
<td>46.3 &lt;sup&gt;±&lt;/sup&gt; 1.5</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>28.1 &lt;sup&gt;±&lt;/sup&gt; 0.7</td>
<td>29.4 &lt;sup&gt;±&lt;/sup&gt; 1.0</td>
<td>27.9 &lt;sup&gt;±&lt;/sup&gt; 0.9</td>
</tr>
<tr>
<td>IVT (mm)</td>
<td>11.8 &lt;sup&gt;±&lt;/sup&gt; 0.7</td>
<td>11.7 &lt;sup&gt;±&lt;/sup&gt; 1.0</td>
<td>11.2 &lt;sup&gt;±&lt;/sup&gt; 0.9</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>13.2 &lt;sup&gt;±&lt;/sup&gt; 0.5</td>
<td>13.5 &lt;sup&gt;±&lt;/sup&gt; 0.9</td>
<td>13.7 &lt;sup&gt;±&lt;/sup&gt; 0.5</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>118 &lt;sup&gt;±&lt;/sup&gt; 11</td>
<td>121 &lt;sup&gt;±&lt;/sup&gt; 10</td>
<td>117 &lt;sup&gt;±&lt;/sup&gt; 9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>50 &lt;sup&gt;±&lt;/sup&gt; 6</td>
<td>55 &lt;sup&gt;±&lt;/sup&gt; 6</td>
<td>52 &lt;sup&gt;±&lt;/sup&gt; 4</td>
</tr>
</tbody>
</table>

PWT, posterior wall thickness; IVST, intraventricular septal thickness; LVMi, left ventricular mass index; EF, ejection fraction.<sup>a</sup> Dose of ACE inhibitor (mg/day).<sup>b</sup> p < 0.05, compared to the 0 month. <sup>x</sup><sup>p</sup> < 0.05, compared to the Groups I-L and II-L. Values: mean <sup>±</sup> SEM. Number of patients: Groups I to III, and Groups I-L to III-L are described in the legend to Table 1.

Significant differences among the three groups, there were significant differences between the start and the end of the study for all three groups.

**Effect of Treatment on the Results of Echocardiography**

**Patients without LVH (Table 3)**

There were no significant differences in the echocardiographic changes in Groups I or II between the start and the end of the study. However, there was a significant difference between the baseline echocardiographic findings and those observed at the end of the study in patients without the ACE inhibitor. These differences were observed in PWT, LVMi and ejection fraction (EF). There were also significant differences between Groups I and II and III at the end of the study.

**Patients with LVH (Table 3)**

In patients not treated with ACE inhibitor, the EF decreased significantly at the end of the study. However, in patients treated with 5 mg or 2.5 mg of benazepril, the EF did not show any significant changes. Concomitantly with the changes in EF, PWT and LVMi were increased in patients who were not treated with the ACE inhibitor. However, no significant changes were observed in the patients of Groups I or II. There were significant differences between Group III and each of Groups I and II at the end of the study.

**Events**

All patients were followed for a year. No patient suffered from serious events such as acute myocardial infarction, cerebrovascular accidents or major cardiovascular diseases. Moreover, no patient needed to start dialysis therapy.

**Adverse Effects**

Cough was reported in 8% of patients, but all patients were asked to continue the study and agreed.

**Discussion**

Hypertension occurs in more than 60% of patients with type 2 diabetes (23). In addition, in patients with diabetes mellitus, hypertension magnifies the risk of cardiovascular diseases and renal failure significantly (24). As reported in several studies, LVH is associated with a higher cardiovascular risk (25). Furthermore, patients with hypertension and diabetes mellitus develop LVH and diastolic dysfunction initially, but ultimately develop systolic dysfunction and left ventricular dilation (26). Conversely, aggressive treatment of increased blood pressure levels improves the prognosis for these patients, particularly if appropriate antihypertensive agents, such as ACE inhibitors, are used (27, 28). Thus, ACE inhibitors are most likely suitable for the treatment of diabetic patients with renal failure and LVH. However, there have been few prospective studies examining the effects of antihypertensive therapy on these patients.

In this study, the discontinuation of ACE inhibitors produced a gradual decrease in CrCl and, at 1 year, the decreases in CrCl reached significance. In patients with non-diabetic chronic renal diseases, dihydropyridine CCB without ACE...
inhibitors or without tight blood pressure control produced more proteinuria (29). Moreover, if ACE inhibitors were added to the antihypertensive treatment with dihydropyridine CCB, the degree of proteinuria was minimized (30). These findings are in accordance with a previous study which suggested that dihydropyridine CCB should not be used to preserve renal function in the absence of an ACE inhibitor (31). In this study, antihypertensive therapy using a combination of ACE inhibitor and the CCB, benidipine, was employed. Benidipine, a dihydropyridine derivative CCB, was developed in Japan and has a unique attribute in renal regulation (32, 33). Data from two trials have demonstrated that, if an ACE inhibitor is used in concert with a dihydropyridine CCB, a reduction is seen in proteinuria, as well as in cardiovascular events (34, 35). These previous data strongly support our current finding that combination therapy with an ACE inhibitor and dihydropyridine CCB reduces blood pressure levels satisfactorily with beneficial protective effects for LVH and nephropathy in hypertensive patients with diabetic nephropathy. In diabetic nephropathy, previous data have shown that the degree of reduction in proteinuria depends on the level of blood pressure control and that the various antihypertensive drugs have a comparable antiproteinuric effect when the mean blood pressure is reduced below 100 mmHg (i.e., 130/85 mmHg) (36). In this study, the target blood pressure control level was less than 140/90 mmHg and the mean blood pressures were 101 and 102 mmHg in patients without and with LVH, respectively. The difference between these results and the previous findings might be explained by the fact that the patients enrolled in this study were treated with ACE inhibitors before the start of the study. Similar findings were reported in a short-term clinical study in which urinary excretion of protein increased after the cessation of the ACE inhibitor (37). In a recent clinical trial using losartan, an angiotensin receptor antagonist, continuous administration of losartan resulted in protection of diabetic patients with nephropathy against progression of renal disease (38). Because proteinuria is considered to be a surrogate marker for the progression of chronic renal diseases (12), it is likely that discontinuation of the ACE inhibitor produced an accelerated progression of renal dysfunction in diabetic patients with nephropathy. Taken together, these results suggest that in clinical practice, the discontinuation of ACE inhibitors for patients with chronic renal diseases, irrespective of diabetic or non-diabetic origin, might produce a faster decline of renal function.

Of interest, the results of this study show that, in diabetic patients with nephropathy and LVH, a normal dose of the ACE inhibitor, benazepril, is effective in slowing the progression of chronic renal insufficiency and in the regression of LVH. In comparison to the findings in diabetic patients with LVH and nephropathy, a normal dose of the ACE inhibitor produced a greater decline of renal dysfunction, evaluated by CrCl, than that observed using a half dose of the drug. To explain the different effects of a normal and a half dose of the ACE inhibitor on the decline of renal function, accompanied by the various changes in the levels of serum potassium and hemoglobin observed in the present study, at least two major factors might be taken into consideration.

First, ACE inhibitors are known to have a beneficial effect on the progression of human diabetic nephropathy, beyond that achieved by lowering the blood pressure per se (39). The mechanisms of the renoprotective effect of ACE inhibitors still remain unclear, but reduction in proteinuria via beneficial effects on glomerular hemodynamics, and/or on the permeability and size-selective function of the glomerulus, may play an important role (39). In the groups with or without LVH, a normal and a half dose of ACE inhibitor maintained similar levels of urinary protein excretion. It is unlikely, therefore, that the antiproteinuric effects of the two doses of the ACE inhibitor are different. Previous data have shown that proteinuria remained during down-titration of an ACE inhibitor (40). Moreover, this finding does not seem to be artifactual because it was seen in nearly all the patients in the present study (data not shown). It is suggested, therefore, that there may be sustained beneficial renal effects after shifting from a normal to a low dose of the ACE inhibitor.

Second, blood pressure changes might be important. In the patients with LVH, the levels of both systolic and diastolic blood pressure were maintained throughout the study. In the case of preexisting renal insufficiency, fewer functional nephrons—i.e., “remnant nephrons”—are present, and thus those that are present function at a relatively higher baseline pressure to maintain stable renal function. Under these circumstances, if the renin-angiotensin system activity is reduced, the resultant reduction in intraglomerular pressure is proportionally greater in the remnant nephrons. Thus, the fewer functional nephrons, the greater the likelihood that glomerular filtration rate (GFR) will decrease when the renin-angiotensin system activity is reduced (41). In the present study, although the concentrations of benazepril were not measured, the available data indicate that, in advanced chronic renal insufficiency, the doses of benazepril are generally increased due to reduction of excretion of the drug (42).

In turn, it remains to be resolved why, in the patients with LVH, a half but not a normal dose of the ACE inhibitor failed to prevent the progression of chronic renal dysfunction. Compared to the initial decline of CrCl in the patients without LVH, in the patients with LVH treated with a half dose of the ACE inhibitor the CrCl slowly decreased towards the end of the study. If the concentrations of benazepril were excessive for preserving remnant renal function in the patients with LVH, a similar initial decline in CrCl would be expected in the patients without LVH. However, the pattern of the decline in CrCl was different in these patients. Increases in LVH and LV mass, with a concomitant reduction of EF, may produce a decrease in renal blood flow (RBF), which in turn would reduce the GFR. Although we did not measure RBF in the present study, a reduction of EF is known to be associated with a reduction of RBF. In the patients with
LVH treated with a half dose, because EF was decreased (although without achieving statistical significance), the possibility cannot be denied that a subtle reduction of EF might reduce RBF, in association with a gradual reduction of CrCl.

In the group of patients without LVH, the levels of hemoglobin in those treated with a normal dose of the ACE inhibitor might have been influenced by the reduction of GFR and the ACE inhibitor itself, because both factors are known to reduce erythropoiesis (43). In the group of patients with LVH, the hemoglobin data seems to be unexplained. The changes in the levels of serum potassium seem much more confusing, probably due to the effects of daily intake, which were not fully evaluated in this study.

There are several limitations to the present study. First, although varying pathogenic mechanisms, such as hyperlipidemia, and other metabolic abnormalities, such as parathyroid hormone associated with progressive disease in diabetic patients, might have affected the outcome, we investigated only whether the dose of ACE inhibitor was a significant factor associated with the progression of diabetic nephropathy. The second, and perhaps most important, criticism of this study is that the patients were studied while under a relatively moderate dietary restriction for diabetic nephropathy. This is reflected by the fact that, although the patients were instructed to reduce their salt intake to a level of 9 g daily, the average urinary sodium excretion was approximately 10 g daily (data not shown). Therefore, our data might have underestimated the effects of diet on the progression of diabetic nephropathy. Finally, the observation period of this study was only 1 year. Because previous large clinical studies that tried to elucidate the effects of antihypertensive drugs on the course of the progression of chronic renal disease have been carried out for at least 2 years (38; 44), a longer-term study will provide more clear-cut evidence on the treatment of patients with diabetic nephropathy.

In conclusion, we demonstrate that, in diabetic and hypertensive patients, antihypertensive treatment without an ACE inhibitor is deleterious to the prevention of the development of progressive renal disease, in spite of its moderate control of hypertension. In addition, this study suggests that, in these patients, the optimal dose of ACE inhibitor for specific renal effects in association with or without LVH may not be the same, notwithstanding the antiproteinuric effect. Further long-term studies will be needed to conclusively determine the mechanism by which dose adjustment provides beneficial effects on cardiac disease in patients with diabetic nephropathy.

References