ACE Inhibitors and Appearance of Renal Events in Hypertensive Nephrosclerosis

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Abstract—Nephrosclerosis constitutes a major cause of end-stage renal disease. Independently of blood pressure control, ACE inhibitors (ACEIs) are considered to be more nephroprotective than other antihypertensive agents. We have reviewed the long-term evolution of renal function in our series of essential hypertensive patients diagnosed as having nephrosclerosis when first seen in our unit. The analysis was performed depending on whether or not their antihypertensive therapy contained an ACEI alone or in combination for the whole follow-up. The end point was defined as the confirmation of a 50% reduction in creatinine clearance or entry in a dialysis program. A historical cohort of 295 patients was included in the analysis. Mean follow-up was 7.4 ± 3.9 years. Diabetes prevalence was higher in ACEI-treated patients (25.7% versus 7.1%, $P=0.000$), but the diagnosis of diabetic nephropathy could not be confirmed on clinical grounds, including renal biopsy. Twenty-three out of 183 (12.6%) patients in the ACEI group and 23 out of 112 (20.5%) patients in the non-ACEI group experienced a renal event ($P=0.0104$ by log rank test). Similar results were observed when only nondiabetic patients were considered for the analysis. Cox regression analysis showed that baseline serum creatinine, absence of ACEI administration, mean proteinuria during follow-up, and age were independent predictors for the development of a renal event. In hypertensive nephrosclerosis, therapy containing an ACEI alone or in combination significantly reduces the incidence of renal events. This effect is independent of blood pressure control. (*Hypertension*. 2001;38[part 2]:645-649.)

Key Words: hypertension, arterial ∎ nephrosclerosis ∎ renal insufficiency ∎ renin-angiotensin system ∎ angiotensin-converting enzyme inhibitors ∎ antihypertensive therapy

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The relation between elevated blood pressure (BP) and end-stage renal disease (ESRD) has been well established.[1] In fact, hypertensive nephrosclerosis constitutes a major cause of ESRD.[2,3] However, because of the very high prevalence of the disease, it has been considered that only a minority of patients with nephrosclerosis progresses to ESRD.[4,5] In agreement with this possibility, recent data from the Hypertension Optimal Treatment (HOT) study[6] have proved that a small percentage of essential hypertensive patients exhibits a progressive decay in renal function even in the presence of an adequate BP control. Nephrosclerosis is characterized by a slow rate of progression to end-stage renal failure.[7,8] For this reason, very long follow-ups, longer than the usual duration of trials looking at cardiovascular morbidity and mortality in arterial hypertension, are required to investigate the effect of different therapies on the evolution of renal function in essential hypertension.[8]

ACE inhibitors (ACEIs) alone or in combination have been shown to be particularly suited to arrest the velocity of progression to ESRD both in diabetic[9] and in nondiabetic renal disease.[10] Such a good effect seems to be related to different effects, among which is the decrease that they induce in urinary protein excretion; when this parameter is elevated, it seems to be of capital importance.[11] However, positive effects have been also shown in patients with proteinuria well below the nephrotic range.[12] In the particular case of nephrosclerosis, even though this diagnosis has been given in the list of nondiabetic nephropathies included in several studies,[10,12] no clear-cut therapeutic guidelines have been ever designed. In fact, BP control, independently of how it was obtained, has been usually considered the hallmark of therapeutic intervention.[4,5,8]

All these facts prompted us to review the evolution of our series of patients diagnosed at entry in our unit as being essential hypertensives with mild renal insufficiency secondary to nephrosclerosis. Our aim was to see if the presence of an ACEI in the therapy of these patients could alter the long-term prognosis in a significant manner.

Methods

Patients

In a historical cohort of hypertensive patients followed in our hypertension unit from 1985 to 1995, we selected patients who were diagnosed of mild renal insufficiency due to hypertensive nephrosclerosis when they were first seen and who had been treated with a maintained therapy for ≥ 4 years. Arterial hypertension was defined as systolic BP ≥ 140 mm Hg and diastolic BP ≥ 90 mm Hg, and renal insufficiency was defined as a creatinine clearance <60 mL/min per 1.73 m². We excluded patients with malignant hypertension, sys-

temic diseases, primary renal diseases, primary aldosteronism, renovascular hypertension, pheochromocytoma, serum creatinine >354 μmol/L (4.0 mg/dL), or proteinuria >2.0 g/24 h.

Type 2 diabetes mellitus had been previously diagnosed in 55 patients. In this group, the presence of diabetic nephropathy was discarded on clinical grounds, including a renal biopsy when proteinuria was >1 g/d.

For the analyses, patients were classified as taking an antihypertensive therapy based on (1) ACEI alone or combined with other drugs (ACEI group) or (2) other drug(s) in the absence of an ACEI (non-ACEI group) during the whole follow-up. The analysis was performed both on the whole group and also on the group of nondiabetic patients.

Follow-Up

A complete medical history and physical examination were performed at entry. Data about presence of diabetes, smoking, and previous cardiovascular disease were collected. Attending our usual protocol, patients were followed at 3-month intervals for BP measurement and medication adjustment to achieve the usual BP goal. Blood sample and 24-hour urine collection were obtained at least twice a year to measure serum creatinine, glucose, total cholesterol, HDL- and LDL-cholesterol, triglycerides, serum uric acid, sodium, and potassium, as well as creatinine clearance and 24-hour proteinuria, natriuresis, and kaliuresis.

Outcome Variables

The primary end point was defined as a 50% reduction of creatinine clearance from baseline or need for dialysis on follow-up. Secondary variables included mean serum glucose, total cholesterol, proteinuria, and systolic and diastolic BP. These mean values were calculated as the average of successive determinations during follow-up for each patient.

Statistical Analysis

Results are expressed as mean$\pm$SD or 95% confidence intervals (95% CIs) as indicated. Statistical analyses were performed with the SPSS (version 8.0, SAS Institute). The significance of the differences in categorical and continuous variables among groups was examined by means of the Pearson χ^2 test and Student's t test, respectively. All tests were 2-tailed, and a P value <0.05 was considered statistically significant. A Kaplan-Meier survival analysis was performed, with log-rank as significance test for differences, to evaluate the impact of the antihypertensive therapy on renal function. Cox's regression analysis was performed, incorporating most important predictors of renal outcome: age, baseline serum creatinine, mean systolic BP, mean serum glucose, mean total cholesterol during follow-up, mean proteinuria, and antihypertensive therapy.

Results

Baseline Characteristics

Two hundred ninety-five patients with mean age 58.9$\pm$11.6 years (range, 26 to 82; 63.7% female) were included in the study. Mean follow-up was 7.4$\pm$3.9 years (7.1$\pm$3.7 years in ACEI group, n=183; and 7.7$\pm$4.4 years in non-ACEI group, n=112). Table 1 contains baseline characteristics of the whole group and of nondiabetic patients. Gender, age, baseline values of diastolic BP, pulse pressure, creatinine clearance, and proteinuria did not differ among groups. Mean baseline systolic BP was higher in the ACEI group than in the non-ACEI group (169$\pm$25 mm Hg versus 163$\pm$23 mm Hg, P=0.027). Table 1 shows the percentage of concomitant risk factors in both groups. Diabetes prevalence was higher in ACEI-treated patients (25.7% versus 7.1%, P=0.000). This fact explains the finding that fasting serum glucose values were significantly higher in ACEI-treated patients compared

with the whole group. When only nondiabetic patients were considered, BP findings were similar in the absence of different fasting serum glucose values.

Follow-Up

Mean BP values, proteinuria, and serum glucose during follow-up can also be seen in Table 1. BP values remained significantly more elevated in the ACEI group than in the non-ACEI group, even though patients were taking more drugs. This finding was independent of whether or not the group of diabetics was considered for the analysis. In ACEI group, 43 (23%) patients received monotherapy; a calcium channel blocker was added in 84 (46%); a diuretic, in 75 (41%) patients; and a β-blocker, in 16 (9%). In non-ACEI group, a calcium channel blocker was administered in 75 (67%) patients, 37 (33%) received a β-blocker, and 35 (31%) were treated with a diuretic.

Evolution of Renal Function

Twenty-three out of 183 (12.6%) patients in ACEI group and 23 out of 112 (20.5%) patients in the non-ACEI group experienced a renal event. As shown in the Figure, there were significant differences between groups in the time-to-event analysis (P=0.0104) (Table 1). Thirteen patients reached the need of dialysis: 7 (3.8%) were receiving an ACEI; and 6 (5.4%), non-ACEI treatment. Thirty-three patients reached the 50% reduction of creatinine clearance: 16 (8.8%) were on an ACEI and 17 (15.1%) were on non-ACEI treatment. Results were similar when the analysis was performed in nondiabetic patients (Figure). Thirteen out of 136 (9.6%) patients in the ACEI group and 21 out of 104 (20.2%) patients in the non-ACEI group experienced a renal event. Time-to-event analysis revealed a significant difference among groups (log rank test P=0.0092) (Table 1). Eight patients reached the need for dialysis: 3 (2.2%) in ACEI group and 5 (4.9%) in non-ACEI group. Twenty-six patients reached the 50% reduction of creatinine clearance: 10 (7.4%) treated with ACEI and 16 (15.3%) receiving non-ACEI therapy. Cox regression analysis adjustment for confounding variables (age, baseline serum creatinine, mean BP values, mean proteinuria, serum glucose and total cholesterol values during follow-up, and smoking status) showed that baseline serum creatinine, mean proteinuria during follow-up, non-ACEI administration, and age are independent predictors for developing of renal events (Table 2).

Discussion

This is a retrospective study in which we have evaluated the effect of ACEI-based therapy on the progression of chronic renal insufficiency in patients with hypertensive nephrosclerosis. Most studies about progression of renal function consider that the doubling of serum creatinine or entry in dialysis constitutes the primary end point.[9,10] Our design differs on this point, because the primary event was defined as a 50% reduction of creatinine clearance from baseline or the need for dialysis. We took advantage of the fact that we measured creatinine clearance using 24-hour urine collection in each patient on each visit. Urine collection is also used for the determination of proteinuria. An estimation of glomerular

TABLE 1. Baseline Characteristics, Concomitants Risk Factors, Mean Values During Follow-Up, and Renal Events

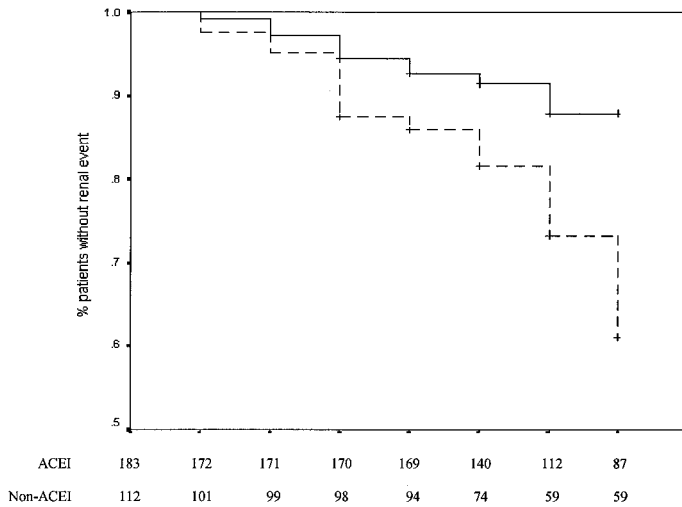|	General Population (n=295)		Nondiabetic Population (n=240)	
	ACEI (n=183)	Non-ACEI (n=112)	ACEI (n=136)	Non-ACEI (n=104)
Baseline characteristics				
Age, y	59.1±11.3	58.6±12.1	57.9±11.8	58.6±12.4
Gender, % (male/female)	36/64	37/63	36/64	36/64
Follow-up, y	7.1±3.7	7.7±4.4	7.2±3.6	7.7±4.3
Systolic BP, mm Hg	169±25	163±23*	169±25	162±23*
Diastolic BP, mm Hg	98±16	96±14	99±16	95±14
Pulse pressure, mm Hg	71±22	67±16	70±24	67±17
Serum creatinine, μmol/L	115±40	111±39	115±42	113±39
Creatinine clearance, mL/min	48±9	49±7	48±9	49±7
Serum glucose, mmol/L	6.33±2.00	5.88±1.55*	5.55±0.78	5.61±0.61
Total cholesterol, mmol/L	5.95±1.19	5.87±1.11	5.95±1.19	5.87±1.14
Proteinuria, mg/24 h	113±476	121±525	104±519	119±534
Concomitant risk factors, %				
Previous CV disease	18.6	11.6	19.9	11.5
Diabetes	25.7	7.1†	...	...
Smoking	19.1	23.2	24.3	24.0
Mean values during follow-up				
Systolic BP, mm Hg	152±14	147±15†	151±14	147±15*
Diastolic BP, mm Hg	88±7	86±7*	89±7	86±7†
Pulse pressure, mm Hg	63±13	61±13	62±12	61±13
Proteinuria, mg/24 h	116±385	165±455	73±289	147±422
Serum glucose, mmol/L	6.38±1.61	5.88±1.33†	5.71±0.67	5.60±0.56
Total cholesterol, mmol/L	5.95±0.85	5.81±0.93	5.95±0.88	5.82±0.93
Drugs, n	2.1±0.8	1.4±0.5†	2.0±0.8	1.4±0.5†
Renal events	23 (12.6%)	23 (20.5%)*	13 (9.6%)	21 (20.2%)†

Values are mean±SD. CV indicates cardiovascular.
*P<0.05 with respect to ACEI patients; †P<0.01 with respect to ACEI patients.

filtration rate is a much more accurate method to estimate the evolution of renal function.[11,12]

As already mentioned, studies related to the velocity of progression of renal insufficiency in nephrosclerosis need long-term follow-up periods because of the slow decline of renal function in these patients. A recent meta-analysis performed to determine the efficacy of ACEI in slowing the progression of renal disease showed that the mean time follow-up in most studies is 3 years.[13,14] This study describes one of the longest follow-ups (7.4±3.9 years) published in literature and includes the biggest series of patients with nephrosclerosis published. Our results show that in patients with hypertensive nephrosclerosis and mild renal insufficiency, therapy based on ACEI alone or in combination reduces the risk of renal events compared with that in patients not receiving this class of drugs. The risk of a renal event is 2 times higher in patients who did not receive an ACEI as a part of their antihypertensive therapy. The increase in risk was observed in spite of a better BP control. These findings are in agreement with previous, recently reviewed clinical trials about the beneficial renal-protective effects of ACEI.[13,14]

On the other hand, lowering elevated systemic BP has been shown to be beneficial for the kidney not only by impeding the development of renal ischemia but also by reducing intraglomerular pressure.[15] This effect could have been particularly positive for the group not receiving an ACEI because they exhibited lower BP values during the follow-up. The degree of BP observed in our patients is clearly above that recommended by recent guidelines.[16,17] A more strict BP control to values <130/85 mm Hg could have resulted in a better outcome of our patients and could have jeopardized the good results attributed to ACEI. Nevertheless, a recent study[18] shows that in patients with nephrosclerosis, strict BP control obtained with different antihypertensive agents did not seem to further protect renal function. In contrast, strict control of BP slows the decay in renal function in patients presenting with chronic renal failure when proteinuria is >3 g/24 h.[19] The presence of mild renal insufficiency does not impede the attainment of the usual goal BP (<140/90 mm Hg) as shown in the HOT study, even though more medication was required.[20]

Our findings support the hypothesis that the reduction in risk seen when ACEI therapy is used, is partly independent of

A:
p=0.0104
log−rank
test

B:
p=0.0092
log−rank
test

Kaplan-Meier analysis for ACEI (solid line) and non-ACEI (dashed line) groups. The number of patients in each group at each time point during follow-up is shown at the bottom of the Figure. A, General population; B, nondiabetic population.
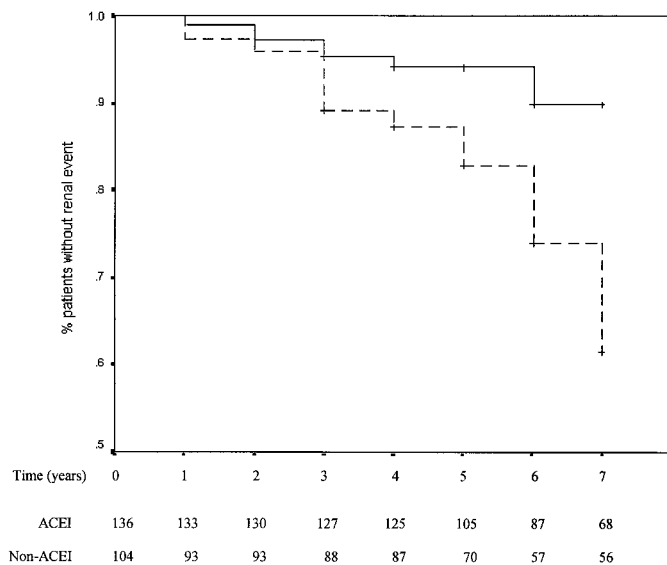
BP control. ACEI, through a diminution in angiotensin II formation, reduces not only intraglomerular pressure but also the release of extracellular matrix and collagen from mesangial and tubular cells, thereby impeding glomerular and interstitial fibrosis.[21,22] These effects are partly mediated by a decrease in glomerular cytokine release.[23] These effects could continue to explain the favorable effect of ACEIs, in the absence of the hallmark effect of these drugs in renal protection, that is based on their antiproteinuric capacity.[11]

Interestingly, the presence of mild renal insufficiency in a relevant percentage of the general population has been recently described.[24] These patients present elevations in serum creatinine values and a marked increase in cardiovascular risk, similar to that described for essential hypertensive patients with similar increases in serum creatinine.[6,25] The description of the characteristics of the people presenting mild renal insufficiency in the general population shows, according to the authors,[24] that there is no difference in the prevalence of arterial hypertension among those with and those without renal damage. However, they describe that the prevalence of left ventricular hypertrophy (LVH) is 3 to 4 times higher in those with renal insufficiency.[24] This finding is interesting because, as in patients with diabetes, a proportion of the population could develop renal insufficiency, which like LVH could represent the existence of target organ damage accompanying small elevations in BP.[16]

Our study has several limitations related to its retrospective character and to the absence of a randomized distribution of therapies. Even so, we believe the findings point clearly in the

TABLE 2. Cox's Regression Analysis of Confounding Factors

	General Population		
	Hazard Ratio	CI 95%	*P*
Age	1.08	1.04–1.11	0.0000
Creatinine	2.75	1.48–5.12	0.0027
mProteinuria	3.35	2.31–4.86	0.0000
non-ACEI	1.99	1.09–3.64	0.0263

mProteinuria indicates mean proteinuria during follow-up.

Hazard ratios for age, serum creatinine, and mean proteinuria are 1 year, 88.4 μmol/L (1 mg/dL), and 1 g/24 h increases, respectively. Variables excluded from the initial model are as follows: mean BP values, mean serum glucose, and mean total cholesterol values during follow-up, as well as smoking status.

direction of ACEI for the therapy in this particular group of patients. Further studies are needed to confirm our results because the topic is of great relevance for the cost-effectiveness of mild renal insufficiency in essential hypertension.

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