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Long-term comparison between captopril and nifedipine in the progression of renal insufficiency

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Long term comparison between captopril and nifedipine in the progression of renal insufficiency. To verify the hypothesis that angiotensin-converting enzyme (ACE) inhibitors possess a unique renoprotective effect in progressive chronic renal disease, we decided to compare the effects of an ACE inhibitor and a calcium antagonist on both hypertension and the progression of non-diabetic renal insufficiency in a long-term study. A four-year, multicenter, prospective, randomized trial was conducted on 142 hypertensive patients (pts) with established chronic renal failure from six Italian nephrology departments. They were on standard antihypertensive therapy with a low-protein diet and underwent twice-monthly surveillance for a one year pre-randomization period. After that year, 121 pts were randomly allocated to captopril or slow-release nifedipine therapies for a three-year study period. The progression of renal insufficiency was monitored every two months. Blood pressure control was significantly better after randomization than during the year of standard antihypertensive therapy. The progression rate before randomization (BR) was definitely higher before than after randomization (AR): Creatinine clearance (C_{Cr}) change BR = -0.46 ± 0.45 ml/min/month, creatinine clearance change AR = -0.23 ± 0.43 ml/min/month ($P < 0.01$). After randomization, the mean blood pressure values were virtually the same throughout the three year period of the study in the two groups treated by captopril (group I), or nifedipine (group II). The progression rate of renal insufficiency evaluated by 1/serum creatinine (group I = -0.00326 ± 0.0034 dl/mg/month vs. group II -0.00343 ± 0.0039 dl/mg/month, P = NS), C_{Cr} (group I = -0.22 ± 0.38 vs. group II -0.24 ± 0.4 ml/min, P = NS), and the clearance of ^{99m}Tc DTPA (group I = -0.20 ± 0.38 ml/min vs. group II = -0.22 ± 0.4 ml/min, P = NS) did not differ significantly between the two groups. Moreover, the analysis of variance performed on the patients who reached the end of the study did not show any differences between the two groups either. During the three-year follow-up 14 patients on nifedipine and seven patients on captopril therapy entered on chronic dialysis treatment and were considered as end-points. The log-rank test performed on the renal survival curves showed that the difference was not significant ($0.1 < P < 0.2$). Thus, the better control of hypertension achieved after randomization induced a slow-down in the progression rate of renal insufficiency. The reduction in the progression rate induced by the ACE inhibitor was no higher than that of the calcium antagonist (CA). Our data are consistent with the hypothesis that both CAs and ACE inhibitors possess a renoprotective effect.

A progressive deterioration in renal function inexorably occurs in most forms of chronic renal insufficiency following a critical reduction in functioning renal mass [1]. The mechanisms underlying the progression of renal disease are complex and probably multifactorial [2]. Systemic arterial hypertension (AH), which is a common complication of chronic renal failure, is considered one of the most important risk factors in accelerating the loss of function in the kidney with established parenchymal disease [3, 4]. On the basis of many experimental studies, it has been suggested that AH may favor glomerulosclerosis in association with compensatory glomerular hypertension [1, 5] and/or structural glomerular hypertrophy [6], both of which seem to mediate progressive glomerular injury. Since angiotensin-converting enzyme (ACE) inhibitors are capable of reducing both glomerular capillary hypertension and glomerular hypertrophy [7, 8], it has been postulated that they may have antihypertensive effects as well as a unique renoprotective action on progressive glomerular injury [9]. Preliminary observations and retrospective studies seem to confirm that ACE inhibitors are effective in delaying end-stage renal failure in all forms of chronic renal failure [10–12]. However, there are no prospective, randomized, long-term studies on humans analyzing the clinical value of a reduction in blood pressure or the beneficial effects of ACE inhibitors on the progression of chronic renal failure. We report the results of a controlled prospective, randomized multicenter trial on patients with mild-to-moderate non-diabetic chronic renal insufficiency in whom the long-term effects of an ACE inhibitor, captopril, were compared to those of a calcium antagonist (CA), nifedipine.

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Methods

Patient selection

A formal prospective, multicenter, randomized controlled trial was planned in 1986. Eligible subjects were patients of both sexes between 18 and 70 years of age with established chronic renal failure, defined by a serum creatinine (S_{Cr}) concentration ranging between 1.8 to 5.0 mg/dl. Only women of non-child-bearing potential were included. In the trial design, patients were required to have: (a) a variation in plasma creatinine less than 50% during the three-month preliminary observation period; (b) a baseline diastolic blood pressure ≥ 95 mm Hg; (c) a good general as well as nutritional condition.

Patients were excluded if they had potentially reversible renal diseases, systemic diseases, severe cardiac or hepatic dysfunction, ankle edema or proteinuria greater than 5 g/24 hr and diabetes mellitus. Glomerulonephritis patients being treated

with steroids, non-steroid anti-inflammatory agents and cytotoxic drugs were also excluded.

Study design

At the end of the three-month preliminary observation, eligible patients in this outpatient study were encouraged to follow or continue with a realistic low protein diet containing 0.6 to 0.7 g protein/kg body weight per day and a low sodium diet with 60 to 100 μmol/sodium per day. A caloric supply of 32 to 35 kcal/kg/24 hr was advised. Concomitant treatment consisted of calcium carbonate during meals and allopurinol when needed. No particular phosphate restriction was prescribed and the use of vitamin D derivates was not allowed.

All the patients received traditional antihypertensive therapy either with a single antihypertensive drug or with various combinations of two or more agents. The most frequently used medications were atenolol 50 to 100 mg/daily, pembutolol 40 to 80 mg/daily, metoprolol 50 to 200 mg/daily, propanolol 60 to 160 mg/daily, furosemide 25 to 75 mg/daily, clonidine 0.150 to 0.450 mg/daily and hydralazine 50 to 75 mg/daily. Antihypertensive drugs were left unchanged or adapted throughout the one-year pre-randomization period in order to keep supine diastolic blood pressure less than 95 mm Hg for as long as possible. ACE inhibitors or calcium antagonists were not allowed during that year. The same observer examined the patients at bi-monthly intervals during the first year. Following the first-year control period, the patients were randomly allocated to ACE inhibitor (group I) or calcium antagonist (group II) treatment. After randomization a three-year study period was planned for each patient at bi-monthly intervals in their own nephrological outpatient clinics. The initial captopril dose was 12.5 mg. b.i.d. with a bia-weekly increase, either until blood pressure normalization or until a maximum dosage of 50 mg. b.i.d. was reached. The starting dose of nifedipine (slow release tablets) was 10 mg b.i.d., after which the dosage was titrated every two weeks, until blood pressure normalization was obtained or a maximum dose of 20 mg b.i.d. was administered. Furosemide (25 to 75 mg/daily) and subsequently clonidine (0.150 mg b.i.d.) were added if blood pressure had not been well controlled by captopril or nifedipine alone. Twice-daily out-patient blood pressure monitoring was advised for each patient in the two groups. An identical diet was continued as for the first year, and the clinical and laboratory check-ups were performed at the same twice-monthly intervals.

Bi-monthly surveillance included a complete morning clinical examination in which heart rate, systolic blood pressure and diastolic blood pressure were measured immediately before dose administration. Blood pressure was measured on the patient's same arm four times after five minutes resting in supine position (at consecutive 1-min intervals) and once in standing position. All blood pressure readings were performed with a calibrated automatic recorder (Dynamap, Critikon, Tampa, Florida, USA). The actual blood pressure value was considered as the average of the four measurements. Mean blood pressure (MBP) was calculated according to standard formula. At each examination, body weight, ECG and routine biochemical tests were performed, in particular, including serum creatinine and urea, sodium and potassium both in plasma and 24-hour urine, and 24-hour proteinuria. Creatinine clearance (C_{Cr}) was then measured simultaneously during water diuresis for three periods lasting 30 minutes each and averaged. Clearances were normalized to a body surface area of 1.73 m^2.

Chemical analyses of serum and urine were performed by standard clinical laboratory techniques. Twenty-four hour proteinuria was determined using a sensitive colorimetric method (modification of the Coomassie Blue method) [13]. The interassay coefficient of variation for urinary protein concentration was less than 5%. Serum and urine creatinine and urea nitrogen concentration were measured with a Technicon AutoAnalyzer. The reproducibility of the laboratory tests among the various centers (creatinine, in particular) was assessed at the beginning of the trial and after two years. The use of a common calibrant was planned to avoid discrepancies in proteinuria between the different centers. Compliance with diet was evaluated by twice-monthly measurements of blood urea nitrogen and 24-hour urinary nitrogen excretion. Protein intake was calculated from 24-hour urinary nitrogen according to Maroni, Steinman and Mitch [14], and was confirmed by an experienced dietician.

Clearances of ^{99m}Tc-DTPA were performed on the 48 patients followed up at two of the six nephrology centers that took part in the study (Bologna and S. Giovanni Rotondo). These measurements were taken at the beginning of the study and every six months thereafter. Five mCi of the radioisotopic marker were injected intravenously as single bolus during water loading; clearances were calculated from the slope of the plasma disappearance curve as previously reported [15].

The progression of renal insufficiency was evaluated for each patient on the basis of the following criteria: (a) the reciprocal of the serum creatinine concentration ($1/S_{Cr}$) over time [16] and (b) the regression line for C_{Cr} (mean of the 3 measurements). The rate of change in plasma clearance of ^{99m}Tc-DTPA as a measurement of GFR was also evaluated in the 48 patients enrolled at Bologna and S. Giovanni Rotondo.

Lastly, the need for dialysis (C_{Cr} below 4 ml/min) was considered as the end-point.

Statistical analysis

The results are expressed as means ± SD. The homogeneity check of patient distribution between the two pharmacological treatments was performed by means of the chi-square test for non-parametric data, while it was done by means of the F-test for parametric variables.

Regression lines for C_{Cr}, the $1/S_{Cr}$ and the ^{99m}Tc-DTPA clearance (when available) values over time were determined for each patient who completed the study at least one year after the randomization. The mean slopes were then calculated for each treatment group. The resulting values were then used to determine a mean value for the entire follow-up period. Student's two-tailed *t*-test was used to compare the results of the two groups.

The multivariate analysis of variance for repeated measurements (MANOVA) was performed on the patients who reached the end of the three-year study, to compare the effect of the two drugs on the time course of blood pressure, renal function and proteinuria. A multivariate test (Wilks test) and univariate tests (F-tests) were also performed.

Lastly, actuarial renal survival was calculated for both treatment groups and the log-rank test was used to assess the difference in the survival curves.

Table 1. Patient characteristics at randomization

	Group I captopril	Group II nifedipine	*P*
Number	60	61	
Sex (M/F)	34/26	36/25	NS
Age *years*	55 ± 10	55 ± 10	NS
Body weight *kg*	70 ± 11	69 ± 13	NS
SBP *mm Hg*	166 ± 19	164 ± 22	NS
DBP *mm Hg*	101 ± 14	99 ± 11	NS
S_{Cr} *mg/dl*	2.9 ± 0.9	3.0 ± 1.0	NS
C_{Cr} *ml/min*	30 ± 7	31 ± 8	NS
Proteinuria *g/24 hr*	1.66 ± 1.88	1.90 ± 1.85	NS
Underlying renal disease			
Glomerulonephritis	20	15	NS
Pyelonephritis or interstitial nephritis	10	13	NS
Polycystic kidney disease	5	7	NS
Nephroangiosclerosis	18	18	NS
Unknown	7	8	NS

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; S_{Cr}, serum creatinine.

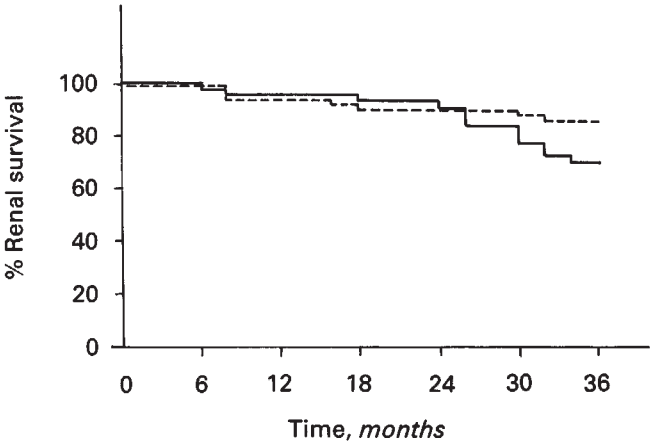

Fig. 1. *The renal non-survival curves of Group I (- - -, Captopril) and Group II (—, Nifedipine) patients studied for three years.*

Table 2. Patient outcome during the trial at baseline, and after 1, 2 and 3 years of antihypertensive therapy

	Control period	Group I captopril			Group II nifedipine		
		1st	2nd	3rd	1st	2nd	3rd
Patients who concluded, *N*	121	51	44	37	50	46	32
End-point need for dialysis	3	3	2	2	2	1	11
Non-renal death	—	—	1	—	—	—	—
Lack of cooperation	8	1	—	1	2	—	1
Drug intolerance	5	2	1	1	5	1	1
Concomitant disease	3	1	2	2	1	1	—
Other causes	2	2	1	1	1	1	1

Results

A total of 142 hypertensive patients (86 men) from six Italian Nephrology Departments were enrolled on the trial, after giving their informed consent. Their median age at entry was 56 years (range 22 to 69). During the first-year control period with standard antihypertensive treatment, 18 patients withdrew from the study either owing to adverse drug effects (such as asthma, severe bradycardia, orthostatic hypotension) or to an inability to comply with appointments, medical schedules or diet; three of the 18 patients who dropped out had concurrent illness or surgery. A further three patients reached the end-point, that is, a need for dialysis. Hence, 121 patients were randomly assigned to group I or group II. Before randomization the patients were not stratified according to the degree of renal impairment. However, S_{Cr} and C_{Cr} were not statistically different between the two groups at randomization (Table 1). Furthermore, the $1/S_{Cr}$ slope before randomization was not statistically different between groups I and II ($P = 0.710$). Twenty-one patients in group I and 24 patients in group II had a serum creatinine level of 3.0 mg/dl or over at the beginning of the study. The characteristics of the two study groups at randomization are shown in Table 1.

As can be seen in Table 2, 31 patients dropped out from the trial during the three-year study period (16 patients from group I and 15 from group II) due to concomitant diseases, non-renal death, lack of cooperation and drug intolerance. The main adverse effects were: Cough (2), taste disturbances (1) and rhinitis (1) in group I; headache (3), severe ankle edema (3) and severe flushing (1) in group II.

Twenty-one patients reached the end-point of the study (the need for dialysis): Seven patients in group I (11.6%) and 14 patients in group II (22.9%). The renal non-survival curves in the two groups of patients were reported in Figure 1. A statistically non-significant difference was found ($0.1 < P < 0.2$) in spite of the higher number of end-points in group II when the log-rank test between survival curves, in relation to the three year period of the study, was performed. However, the difference became more pronounced in the last year when 11 patients out of remaining 46 in the nifedipine group and only two patients out of the 44 left in the captopril group reached end-stage renal disease. The difference between the two groups for this last year was highly significant ($P < 0.005$). The end-point patients in both groups had a significantly higher S_{Cr} than non-end-point patients at the beginning of the study, while no difference was found in S_{Cr} at randomization between the group I and group II patients who reached the end-point. There was no difference between end-points and non-end-points as regards proteinuria and MBP (Table 3).

Blood pressure control

Mean blood pressure was significantly higher during the first year of standard antihypertensive therapy than during the three years after randomization. On the other hand, when a comparison was made between group I and group II no difference in the average blood pressure levels was observed at any time during the study (Fig. 2). In a very high percentage of patients, the ACE inhibitor and the captopril treatments led to a stable normalization of blood pressure. Furosemide was administered in 40% of group I patients and in 41% of group II patients, while 20% of group I and 16% of group II patients required the addition of clonidine. No patient required therapy to be discontinued as a result of either symptomatic hypotension, acute renal insufficiency or electrolyte abnormalities.

Table 3. Mean values at randomization in the end-point and non-end-point patients

	Non-end points (100 pts)		End points (21 pts) Group I captopril (7 pts)		Group II nifedipine (14 pts)
			NS		
Sex (M/F)	59/41	– NS –	3/4	– NS –	8/6
			$P < 0.0001$		
S_{Cr} *mg/dl*	2.7 ± 0.7	$P < 0.0001$ –	3.8 ± 1.03	– NS –	3.9 ± 0.78
			NS		
Mean blood pressure *(mm Hg)*	117 ± 11.6	– NS –	125 ± 10.4	– NS –	123 ± 11.2
			NS		
Proteinuria *g/24 hr*	1.73 ± 1.8	– NS –	1.58 ± 1.8	– NS –	1.66 ± 1.3

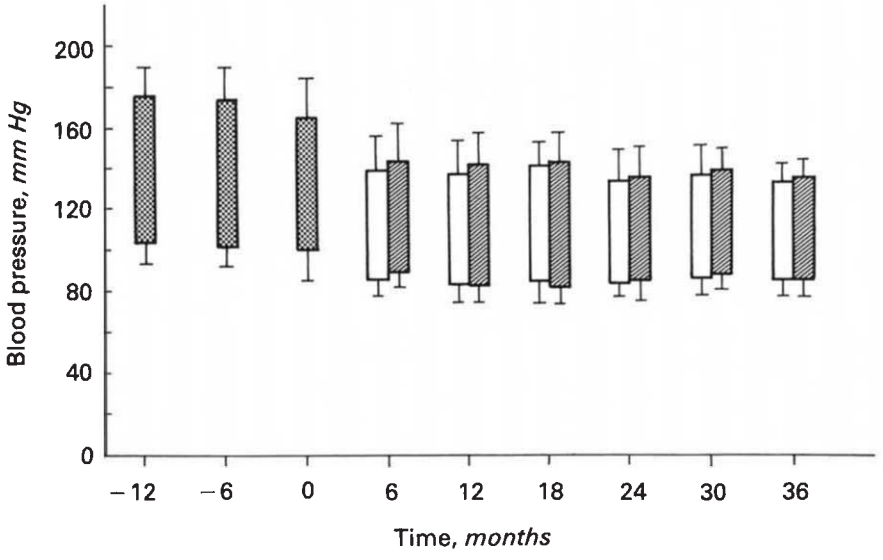

Fig. 2. *Average blood pressure levels in chronic renal failure patients during the first year of standard antihypertensive therapy and during the 3 year period after randomization.* Symbols are: (▨) standard antihypertensive therapy; (□) Group I (Captopril); (▨) Group II (Nifedipine).

Table 4. Mean slope of reciprocal serum creatinine ($1/S_{Cr}$) versus time and mean rate of decline of creatinine clearance (C_{Cr}) during standard antihypertensive therapy and during captopril and nifedipine therapies

		Standard antihypertensive therapy	Captopril therapy	Nifedipine therapy
$1/S_{Cr}$ *dl/mg/month*	Mean	− 0.0062	− 0.00326[a]	− 0.00343[a]
	SD	± 0.0038	± 0.00340	± 0.00390
C_{Cr} *ml/min/month*	Mean	− 0.46	− 0.22[a]	− 0.24[a]
	SD	± 0.45	± 0.38	± 0.40

[a] $P < 0.01$ vs. standard therapy.

Progression of renal insufficiency

The progression of renal insufficiency was examined in the 101 patients (51 on captopril and 50 on nifedipine) who completed at least one year after randomization. In the year of standard antihypertensive therapy, the average slope in reciprocal serum creatinine plots was −0.0062 ± 0.0038 dl/mg/month and in the three years after randomization it was −0.0033 ± 0.0039 dl/mg/month ($P < 0.01$). When we compared the captopril group with the nifedipine group, the rate of change in renal function did not differ significantly (Table 4). The mean decline in C_{Cr} was 0.46 ± 0.45 ml/min/month during the standard antihypertensive therapy and 0.23 ± 0.43 ml/min/month after randomization ($P < 0.001$).

When the captopril and the nifedipine groups were separately analyzed, the rate of change showed no statistical difference (P = NS). Lastly, in the 48 patients whose GFR was evaluated by ^{99m}Tc-DTPA, the rate of decline in GFR was 0.20 ± 0.38 ml/min/month in the captopril group and 0.22 ± 0.40 ml/min/month in the nifedipine group (P = NS). When the creatinine clearances and the GFR values obtained by the radioisotopic marker were correlated, we found a highly significant correlation ($r = 0.89$, $P < 0.001$) between the two methods.

To examine the role of blood pressure control on the progression of renal insufficiency in more detail, we plotted the average MBP obtained during the three-year treatment period with $1/S_{Cr}$. No statistical correlation was found between the two variables (data not shown). Therefore, we subdivided the patients according to the average of all the recordings of the MBP levels during the three-year post-randomization follow-up period. One group consisted of patients whose MBP levels were constantly below or equal to 100 mm Hg, while the other group consisted of patients with levels equal to or higher than 110 mm Hg, irrespective of the antihypertensive drug used. Patients with unstable blood pressure values during the follow-up were excluded. We observed that patients in the group

Table 5. Average values of mean blood pressure (MBP), creatinine clearance (C_{Cr}) and proteinuria in the 69 patients who underwent all the scheduled controls during therapy with captopril (Group I) or nifedipine (Group II)

		Time *months*			
	Group	0	12	24	36
MBP	I	121 ± 11	103 ± 8	100 ± 10	100 ± 11
mm Hg	II	121 ± 11	103 ± 10	102 ± 9	103 ± 12
C_{Cr}	I	31 ± 8	32 ± 11	29 ± 12	25 ± 8
ml/min	II	30 ± 11	31 ± 14	29 ± 17	25 ± 16
Proteinuria	I	1.5 ± 2	1.0 ± 1.0	1.5 ± 2.3	1.3 ± 1.9
g/24 hours	II	1.7 ± 2	1.5 ± 1.6	1.3 ± 1.0	1.7 ± 2.0

Data are means ± SD.

with MBP constantly below 100 mm Hg had a significantly reduced level of proteinuria over time (on average 40% at the end compared to the beginning of the study) and a slower deterioration in renal function measured by $1/S_{Cr}$ in comparison to the other group of patients (−0.0027 ± 0.0021 mg/dl/month vs. −0.0053 ± 0.0038 mg/dl/month, respectively; $P < 0.05$).

Sixty-nine patients managed to conclude the three year period. In these patients (32 in group I and 37 in group II) the multivariate analysis of variance for repeated measures (MANOVA) was performed to compare the effect of the two drugs on the time course of MBP, $1/S_{Cr}$, C_{Cr}, and proteinuria. The multivariate test showed no significant differences between the nifedipine and captopril groups in the four variables taken as a whole. Univariate tests were also performed to investigate the effect of the two drugs on each variable. The tests showed no significant differences for MBP (F-value 0.902, $P = 0.346$) $1/S_{Cr}$ (F-value = 0.917, $P = 0.342$), proteinuria (F-value 0.11, $P = 0.741$) or for the C_{Cr} (F-value 0.031, $P = 0.861$). The behavior of MBP, C_{Cr} and proteinuria in this group of patients is shown in Table 5.

Moreover, in both groups we found no statistically significant correlation between the slope in reciprocal serum creatinine and the proteinuria trend during the three-year study period.

Dietary compliance was estimated by 24-hour urinary urea excretion and dietary interview in each patient; the results were then averaged for each group. In the control period (standard therapy) the patients consumed a mean of 0.78 ± 0.18 g of protein per kilogram per day. The patients in group I (captopril) had a mean of 0.76 ± 0.15 g of protein per kilogram per day, as compared with 0.77 ± 0.19 g of protein per kilogram per day in patients in group II (nifedipine), with no difference between the groups. Moreover, body weight remained substantially unchanged in all the patients.

Discussion

A one-year standard antihypertensive therapy and a low-protein diet were planned before randomization so that only patients who had already been controlled regularly at bimonthly intervals would be admitted to the study. Indeed, it has been clearly documented [17] that frequent clinical examinations have beneficial effects on the progression of renal failure. Furthermore, the study of a population already being submitted to a low-protein diet for some time prior to randomization eliminates possible misinterpretations caused by sharp variations in protein intake. Indeed, many experimental and clinical observations show that a protein restriction may slow down the progression of chronic renal failure [18, 19].

Strong criticisms have been leveled against the use of the reciprocal of serum creatinine and creatinine clearance to follow the progression of chronic renal failure [20]. In fact, the correlation of $1/S_{Cr}$ with true GFR must depend upon the consistency of the urinary creatinine excretion rate, whereas it is now recognized that urinary creatinine can be modified by changes in dietary protein [20]. The use of C_{Cr} should avoid this problem, and indeed, several authors have recently supported its clinical value in measuring GFR during water diuresis [21]. However, tubular secretion of creatinine may to some extent also be affected by dietary intake [21]. Hence, both $1/S_{Cr}$ and C_{Cr} may be inaccurate in measuring the progression rate of renal insufficiency when significant changes in protein intake occur. In our patients such problems were overcome by the constant protein intake maintained throughout the study. Moreover, renal function was also monitored in approximately 40% of our patients by means of ^{99m}Tc-DTPA clearance, whose utility in measuring GFR accurately has been confirmed in subjects with renal insufficiency [22].

At first our study underlined the importance of the control of systemic hypertension *per se* in patients with chronic renal failure. Better blood pressure control was associated to a lower rate of decline in renal function during the three-year study period with ACE inhibitor and calcium antagonist treatment. Although systemic hypertension has been considered to be a major risk factor for progressive renal disease, careful documentation of its deleterious effects has only been derived from experimental models [3, 4]. Moreover, evidence that antihypertensive therapy retards the progression of chronic renal failure in humans is limited to retrospective studies [23] or to a small number of patients followed up for a limited period of time [10, 12]. In our large population of prospectively studied patients, antihypertensive treatment with an ACE inhibitor and a calcium antagonist (CA) produced a significantly better control of blood pressure than with standard antihypertensive therapy. This was not altogether unexpected since ACE inhibitors and CAs have both been shown to be effective antihypertensive drugs which can improve hypertensive patients' quality of life, mitigating the side-effects common to other antihypertensive agents [24, 25]. Indeed, our patients achieved better compliance to the therapy after randomization. Better blood pressure control was associated to a lower rate of decline in renal function during the three-year study period with ACE inhibitor and calcium antagonist treatment. Indeed, after randomization, the subgroup of patients whose mean blood pressure level was equal to or below 100 mm Hg showed a net decrease in proteinuria and in the progression rate compared to the subgroup of patients whose MBP levels were higher than 110 mm Hg. These data further confirm the role of aggressive blood pressure control *per se* in renal damage and stress the need for a target blood pressure level which is significantly below what is routinely considered to be acceptable.

It has been postulated on the basis of animal experiments that ACE inhibitors have a unique renoprotective action on progressive glomerular injury [7, 8]. In fact, the prevention of adaptive glomerular capillary hypertension and/or the mitigation of adaptive morphological changes with ACE inhibitors in various

experimental models does actually protect against the subsequent development of structural injury within the remaining glomeruli. Although it is not thoroughly understood how relevant such animal studies are in humans with renal disease, some retrospective studies [8] or prospective short-term trials on small patient samples [11, 12] appear to confirm that the control of systemic hypertension by ACE inhibitors may be effective in slowing down the progression rate of renal failure.

In addition, these drugs may have an antiproteinuric action [26]. Hence, we decided to study the long-term effects of ACE inhibitor administration on hypertensive patients with non-diabetic chronic renal failure. We chose not to compare captopril with a placebo because we thought this comparison would have been unethical, considering the length of our study and the likely consequent systemic cardiovascular risk for the untreated patients. We decided to compare captopril with the CA, namely nifedipine, because CAs, being both effective and safe antihypertensive agents, are widely used in patients with chronic renal failure [25]. Another reason why CAs were selected for comparison with ACE inhibitors was that many of their effects on renal hemodynamics seem to be quite unlike those of the latter drugs. In fact, CAs decrease the ability of the kidney to autoregulate the renal blood flow and the glomerular filtration rate, and they decrease afferent renovascular resistance [27]. In contrast, ACE inhibitor administration results in efferent vasodilation while the afferent vasculature is practically unaffected [8, 27]. Hence, from a theoretical point of view, CAs do not seem particularly apt to preventing the glomerular hemodynamic changes that are judged to be involved in the progression of renal disease. Some experimental studies [28, 29], though not all [30, 31], confirm the above theoretical consideration because CAs seem to adequately control blood pressure without affecting progressive renal disease.

In our multicenter prospective study, the administration of an ACE inhibitor over a three-year period did not confer superior protection against progressive renal damage in comparison to a CA. In fact, when captopril was compared to nifedipine, the former did not seem to significantly better stabilize renal function, while the rate of progression was practically the same in the two treatment groups.

How can we reconcile our results with the experimental data and the preliminary observations in humans?

First of all, in many of the previous studies [11, 12] ACE inhibitors were compared with drugs other than CAs. Hence, it is quite plausible that both ACE inhibitors and CAs have an intrinsic renoprotective action. Recent experimental studies have suggested the CAs are as effective as ACE inhibitors in preventing progressive renal damage [31] and in mitigating renal diseases characterized by mesangial cell proliferation [32]. Moreover, the relatively low rate of progression found in our patients, in comparison to the period of standard antihypertensive therapy and compared to the mean progression rate that had previously been reported by various authors [23, 33], may further uphold this hypothesis.

Secondly, an interaction between dietary protein intake and the renin-angiotensin system has been reported. In fact, plasma renin activity varied according to the level of dietary protein, being higher on a high protein diet [34]. Indeed, it has been demonstrated that the effect of ACE inhibitors on glomerular permselectivity depends on the previous dietary protein intake [35]. Thus it can be argued that the lack of any difference found in our patients between captopril and nifedipine may be partly due to their moderately low protein intake.

Thirdly, ACE inhibitors might prevent the progression of renal damage only when renal function is slightly reduced, without having any effects on more advanced renal failure [36]. In a rat remnant kidney model, in fact, ACE inhibition effectively preserved the structure of glomeruli with early or no sclerotic lesion, whereas it exerted little effect on glomeruli with advanced sclerotic lesions.

Finally, the higher number of end-points in the nifedipine group, compared to the number in the captopril group, although not statistically significant, warrants further consideration. The slightly higher number of patients having S_{Cr} of 3.0 mg/dl or over at the beginning of the study in the group II (24 vs. 21) could partly account for the difference in the number of end-points between the two groups. Furthermore, it cannot be excluded that a larger or longer trial would have demonstrated a more favorable effect of ACE inhibitors (type II error).

We can therefore conclude that both CAs and ACE inhibitors have been able to slow down the progression rate of our hypertensive patients. It is at present unknown whether this protection is solely due to better blood pressure control or to other non-hemodynamic factors, such as the absence of deleterious metabolic effects [37], or to the attenuation of mesangial cell proliferation and mesangial expansion [9], or to some sort of protection against progressive atherosclerosis [38, 39].

In conclusion, our multicenter trial stresses the importance of good pressure control in the protection of human kidney damage. Our data do not definitively support the belief that ACE inhibitors have a unique renoprotective effect, independent of blood pressure control, because CAs that induce an equal blood pressure reduction slow down the progression of renal insufficiency to the same extent as the ACE inhibitors. However, it is worthwhile noting that our data were obtained from protein-restricted subjects and may not be applicable to subjects on a free protein intake. Moreover, our patients were at a relatively advanced stage of renal failure, thus the superiority of ACE inhibitors over CAs at an early stage of renal damage cannot be excluded. Lastly, our data are consistent with the hypothesis that in renal insufficiency ACE inhibitors and CAs both possess an intrinsic renoprotective effect, not necessarily exerted in the same way.

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