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Acute and long-term effects of ACE inhibition on renal haemodynamics in glomerular and interstitial nephropathies

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Abstract Background

Angiotensin-converting enzyme (ACE) inhibitors are the drugs of choice for the treatment of hypertension in patients with non-diabetic nephropathies. However, not every trial has reported better results with ACE inhibitors (ACE-I) than with other drugs. This study investigates whether the acute and chronic effects of ACE inhibition on renal and glomerular haemodynamics are similar in glomerular and interstitial nephropathies.

Methods

We studied 20 hypertensive patients, on their usual diet, with mild-to-moderate chronic renal failure secondary to non-diabetic nephropathy. After a three-week wash out period, we determined plasma clearances of para-amino-hippurate and inulin before, and after acute oral administration of either enalapril or ramipril. This same test was carried out after one and two years of treatment with the same drug.

Results

Acute ACE inhibition causes a decrease of renal perfusion, glomerular filtration and pressure with an increase of afferent resistances. Long-term ACE inhibition is associated only with a decrease in renal perfusion, with a non-significant tendency to higher filtration fraction and lower afferent resistances. All the renal haemodynamic modifications mentioned above are present only in patients with glomerular diseases.

Conclusions

Renal and glomerular haemodynamic responses are not similar after acute and chronic ACE inhibition. Only patients with glomerular diseases show acute or long-term responses to ACE inhibition.

Introduction

The treatment of patients with diabetic and non-diabetic renal diseases with angiotensin-converting enzyme inhibitors (ACE-I) reduces urinary protein excretion and may slow the progression of renal failure more than any other antihypertensive treatment.¹⁻⁴ However, not every trial has shown a favourable effect of ACE-I. These contrasting results could depend on different pathophysiological mechanisms of renal failure progression in different nephropathies: for example, in autosomal polycystic kidney disease the protective effect of ACE-I seems to be absent.⁵

During a study planned to investigate the similarity of acute and long-term (two-year) responses to ACE inhibition in patients with chronic nephropathies, we noticed that glomerular and interstitial nephropathies did not display the same behaviour after both acute and long-term ACE inhibition. For this reason, we tried to gain more insight into these differences by indirectly calculating glomerular haemodynamics with Gomez formulae⁶ before and after acute and long-term ACE inhibition.

Patients and methods

From 1990 to 1993, we recruited patients with mild-to-moderate chronic renal failure (serum creatinine 1.5–3.0 mg/dl, i.e. 135–270 μ mol/l) secondary to non-diabetic glomerular or interstitial nephropathy. Glomerular nephropathy was diagnosed by means of renal biopsy, while interstitial nephropathy was determined by means of clinical history (analgesic abuse in three patients and lead exposure in one) and radiological criteria (three patients had an irregular renal profile). None of the patients considered to have interstitial nephropathy had proteinuria. Criteria for admission included untreated diastolic blood pressure (DBP) in the 90–114 mmHg range, and absence of nephrotic syndrome or 24-hour urinary protein > 4 g. We excluded patients with systemic diseases, chronic NSAID treatment, women of fertile age without reliable contraception, and patients with suspected secondary hypertension.

The patients who accepted to participate in this trial (approved by our Ethics Committee) were asked to stop any drug treatment with the exception of frusemide to control BP in some patients. No patients were on a low sodium and/or protein diet and no dietary indications were given during the entire study. After a three-week wash out period, all patients undertook a basal measurement of effective renal plasma flow (ERPF) with para-amino-hippurate (PAH) clearance and of glomerular filtration rate (GFR) with inulin clearance (CPAH and CInu respectively). CPAH and CInu were measured by means of the constant infusion method (plasma clearance) with a loading dose of 8 and 50 mg/kg, immediately followed by an infusion of 12 and 30 mg/minute of PAH and inulin, respectively, using an infusion pump (Perfusor® Secura, B. Braun Melsungen SA, Germany). The clearance measurements (corrected for body surface area) were done before (four

samples taken 30, 40, 50 and 60 minutes after the beginning of the infusion) and 30, 50, 70, 90, 110, 130, 150, 170 and 190 minutes after the randomised oral administration of either 5 mg enalapril (Merck Sharp & Dohme) or 2.5 mg ramipril (Hoechst).

Filtration fraction (FF) was calculated as GFR/ERPF and renal blood flow (RBF) as ERPF/1 - haematocrit (Ht).

During the entire procedure, blood pressure (BP) was recorded every 5 minutes using an indirect recording sphygmomanometer by an oscillometric method (Colin ABPM 630, Nippon Colin Co, Komaki City, Japan), with the cuff over the brachial artery of the contralateral arm to the infusion.

Plasma PAH and inulin concentrations were determined colorimetrically by means of the N-1 naphthylethylenediamine and the anthrone method, respectively, using a Corning 258 spectrophotometer (Ciba Corning Ltd, Halstead, Essex, UK). This method has been validated by our group,⁷ and particular care was taken to avoid any interference between the two tracers during storage and the readings from standard curves.⁸

Acute responses were determined as the differences between the means of the four measurements before ACE-I administration and the means of the nine measurements after ACE inhibition, since some preliminary experiments on four patients showed that, 190 minutes following oral administration of both enalapril and ramipril, there was average residual ACE activity of 14% (³HHip-Gly-Gly assay, Ventrex Lab. Inc., Portland MA, USA) and the plasma levels of both enalaprilat and ramiprilat were within the therapeutic range (unpublished results).

The same ACE-I was then prescribed on a daily basis chronically in order to achieve a sitting DBP of < 90 mmHg (with or without frusemide, up to 40 mg for enalapril and up to 10 mg for ramipril). The patients were then followed up monthly, by means of sitting and standing BP measurements and determinations of plasma and urinary creatinine, urea, urate, electrolytes, ACE activity (to check patients' compliance), urinary total protein and albumin excretion, 24 hours after the last dose of drug.

After one and two years, PAH and INU clearances were repeated, with an identical protocol, 24 hours after the last dose of drug, as indicated below:

CPAH & C _{inu} before and after 5 mg enalapril or 2.5 mg ramipril po	CPAH & C _{inu} before and after 5 mg enalapril or 2.5 mg ramipril po	CPAH & C _{inu} before and after 5 mg enalapril or 2.5 mg ramipril po
Baseline	One year	Two years
	ACE-I chronic therapy	

Gomez's formulae were calculated as follows:

$$\text{Filtration pressure} = \Delta P_F = \text{GFR} / K_{FG}$$

$$P_{glo} = \Delta P_F + P_{Bow} + \pi_G = \text{glomerular pressure}$$

$$\pi_G = 5 * (C_M - 2)$$

Plasma protein concentration within the

glomerular capillaries = $C_M = TP/FF * \ln(1/1 - FF)$
where:

K_{FG} (the gross filtration coefficient) is estimated as 0.0812 ml/sec/mmHg.

P_{Bow} (the hydrostatic pressure in Bowman's space) is estimated as 10 mmHg.

π_G (the oncotic pressure within the glomerular capillaries) can be obtained from C_M and calculated from TP (total protein concentration) and FF.

Filtration dysequilibrium is postulated along the glomerular capillaries.

From Ohm's law:

$$R_a = ([MBP - P_{glo}] / RBF) * 1328 = \text{afferent resistances}$$

$$R_e = (\text{GFR} / K_{FG} * [RBF - \text{GFR}]) * 1328 = \text{efferent resistances}$$

RBF can be calculated from ERPF and haematocrit (Ht) using the standard formula:

$$RBF = ERPF / (1 - Ht)$$

1328 is the conversion factor to dyne-sec-cm⁵. GFR, ERPF and RBF are expressed in ml/second.

MBP = mean BP calculated as (2*diastolic BP + systolic BP)/3.

For more details on Gomez formulae the reader is referred to a previous paper from our group, where the use and limitations of these formulae are discussed and the references about their use by other groups and in other settings are reported.⁹

ANOVA and Fisher exact test were employed to compare the baseline clinical characteristics of the patients. Repeated measure ANOVA was used to compare the variables, both acutely and chronically. Data are presented as mean \pm SEM.

StatView 5.0.1 by SAS Institute Inc. was the statistical software employed.

Results

Table 1 shows the baseline anthropological and clinical data of our patients.

Fifteen patients (75%) had a glomerular nephropathy (10 IgA nephropathy, three focal glomerulosclerosis, one Schoenlein-Henoch glomerulopathy and one Alport syndrome), while five (25%) had an interstitial nephropathy (analgesic- or lead-related, except one case in which no obvious cause could be found). The percentage of patients taking frusemide and its mean daily dose over a two-year period were not different between the two groups, as well as the mean of the monthly measurements of sodium and urea excretion over the same period of time.

Females were present only in the former group, and proteinuria, not unexpectedly, was the only clinical variable that was significantly different between the two groups (F=5.8, p=0.03).

It is noteworthy that the afferent arteriolar resistance tended to be higher in glomerular disease patients, even if this increase did not reach statistical significance.

Table 2 shows the acute effects on renal and glomerular haemodynamic variables, 30 to 190 minutes after the first oral dose, of either enalapril (5 mg) or of ramipril (2.5 mg) (mean of nine deter-

Table 1 Basal clinical and renal and glomerular haemodynamic variables (mean±SEM). Urinary protein excretion is the only variable significantly different between the two groups. ANOVA or FET where appropriate.

	Glomerular	Interstitial	p
n	15	5	
Female	3	0	ns
Age (years)	46±3	54±3	0.17
Body weight (kgs)	72±3	76±3	0.44
Taking frusemide	6 (40%)	3 (60%)	ns
Mean frusemide daily dose (mg)	10±3	22±10	0.14
Drug (enalapril/ramipril)	7/8	2/3	ns
UNaV (meq/24-hour)	167±15	183±9	0.54
UureaV (g/24-hour)	23±1	26±2	0.25
MBP (mmHg)	114±3	109±3	0.65
ERPF (ml/minute/1.73 m ²)	303±19	342±22	0.29
Haematocrit	0.40±0.01	0.43±0.01	0.32
RBF (ml/minute/1.73 m ²)	516±38	602±45	0.24
GFR (ml/minute/1.73 m ²)	79±3	76±6	0.73
FF	0.270±0.016	0.225±0.020	0.15
Uprotein (g/24 hours)	1.0±0.2	0.0±0.0	0.03
Pglo (mmHg)	60±1	60±2	0.78
Ra (dyne.sec.cm ⁻⁵)	8806±696	6564±679	0.08
Re (dyne.sec.cm ⁻⁵)	3148±303	2425±228	0.18

See list of abbreviations.

minations), not divided according to the type of nephropathy and thus considered as a sample of non-diabetic kidney disease patients. Acute ACE inhibition (up to three hours after oral administration), did not appreciably modify BP, but caused a 5% decrease in RBF and ERPF (F=5.8, p=0.03 and F=5.9, p=0.03 respectively), an 8% decrease in GFR (F=8.8, p=0.01), a 3% decrease of Pglo (F=4.6, p=0.05) and a 12% increase in Ra (F=4.6, p=0.05), without appreciable modifications of FF and Re. Figures 1 and 2 depict these same data separately for the two types of kidney disease. It is evident that the decreases in ERPF and GFR, as well as the decrease in Pglo and the increase in Ra, occurred only in patients with glomerular disease (F=9.5, p=0.008 and F=8.8, p=0.01 respectively).

Table 3 shows the long-term effects of one and two years of chronic treatment with the same ACE inhibitor (enalapril or ramipril) on renal and glomerular haemodynamic variables. MBP

Table 2 Basal renal and glomerular haemodynamic variables before and after acute ACE inhibition (mean±SEM). (Repeated measure ANOVA)

	Before	After	F	p
MBP (mmHg)	113±3	111±2	1.5	0.24
RBF (ml/minute/1.73 m ²)	537±31	510±35	5.8	0.03
ERPF (ml/minute/1.73 m ²)	312±15	295±19	5.9	0.03
GFR (ml/minute/1.73 m ²)	78±3	72±4	8.8	0.01
FF	0.258±0.013	0.251±0.013	1.4	0.26
Pglo (mmHg)	60±1	58±1	4.6	0.05
Ra (dyne.sec.cm ⁻⁵)	8183±580	9178±976	4.6	0.05
Re (dyne.sec.cm ⁻⁵)	2947±237	2836±206	1.6	0.23

See list of abbreviations.

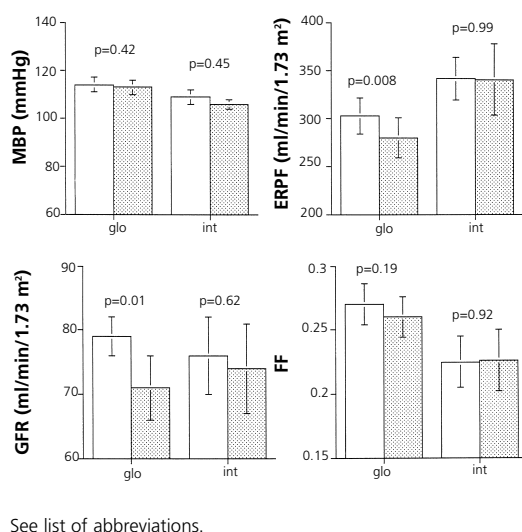
decreased by 10% and 9% after one and two years, respectively. (F=14.8, p<0.0001); for RBF, the corresponding decreases were 8% and 16% (F=13.1, p<0.0001) while for ERPF, they were 5% and 14% (F=12.0, p=0.0001). GFR did not change and FF remained constant after one year, but showed a 9% increase in the second year, which did not reach statistical significance (F=2.7, p=0.08). Rather surprisingly, the calculated glomerular haemodynamic variables did not change appreciably over two years, apart from a non-significant tendency for Ra to increase (F=2.6, p=0.09). However, when we divided the patients according to their type of nephropathy (see Figure 3), we found that only patients with glomerular disease showed a decrease in MBP and ERPF (F=16.9, p<0.0001 and F=10.7, p=0.005, respectively) as well as in Ra, (see Figure 4) which was much more evident in the first year (F=3.8, p=0.04).

Table 4 shows the main differences between acute and chronic responses to ACE inhibition. While ERPF decreased in both circumstances, GFR and Pglo decreased acutely but were unchanged chronically. Not surprisingly, FF tended to increase chronically. Ra showed the opposite behaviour, increasing acutely but decreasing chronically, while Re was not modified by either acute or long-term ACE inhibition. It should be remembered that these differences were significant only in patients with glomerular diseases.

Discussion

In this study, we have applied Gomez formulae to investigate the variations in glomerular haemodynamic variables during acute and long-term ACE inhibition in patients with glomerular and interstitial nephropathies. The use of Gomez formulae to indirectly calculate glomerular haemodynamic

Figure 1 Renal haemodynamics before (white) and after (shaded) acute ACE inhibition in patients with glomerular (glo) or interstitial (int) kidney disease. (Repeated measure ANOVA)

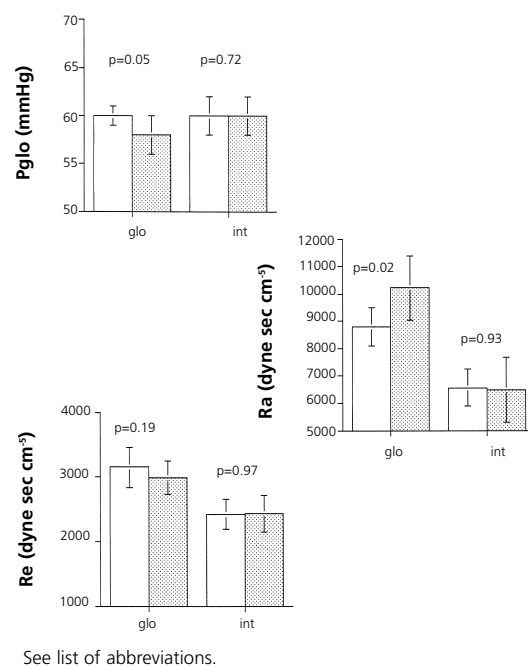


variables presents some problems. Their major drawbacks are the lack of discrimination between juxtamedullary and cortical nephron populations, the necessity to postulate fixed values for pressures in the Bowman's space and for K_{FG} , and the (reasonable) assumption of filtration dysequilibrium in the human kidney. However, since we were interested only in the relative changes and not in the absolute values of the calculated variables, we think it reasonable to consider our results valid, provided that they are regarded as approximations. For a more detailed discussion of this topic, the reader is referred elsewhere.⁹

The main findings of this study can be summarised as follows:

- 1) Acute ACE inhibition in patients with non-diabetic glomerular nephropathies and mild chronic renal failure decreases renal perfusion

Figure 2 Glomerular haemodynamics before (white) and after (shaded) acute ACE inhibition in patients with glomerular (glo) or interstitial (int) kidney disease. (Repeated measure ANOVA)



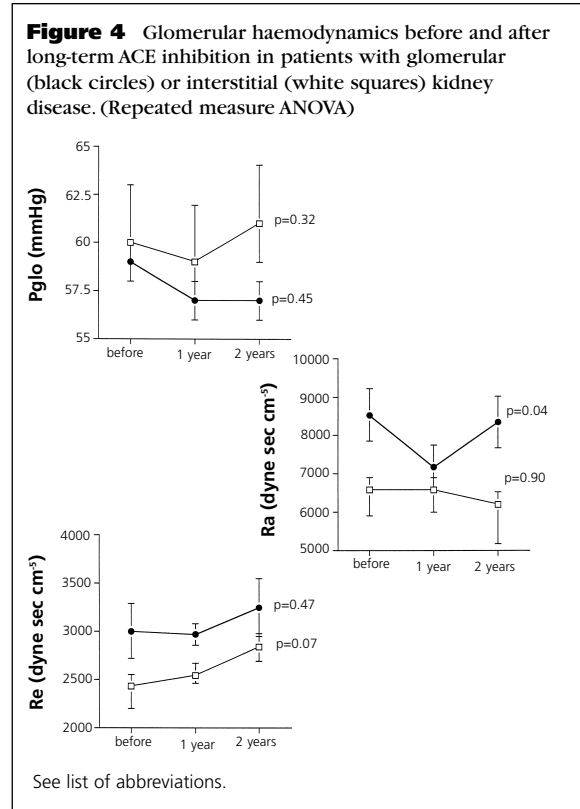
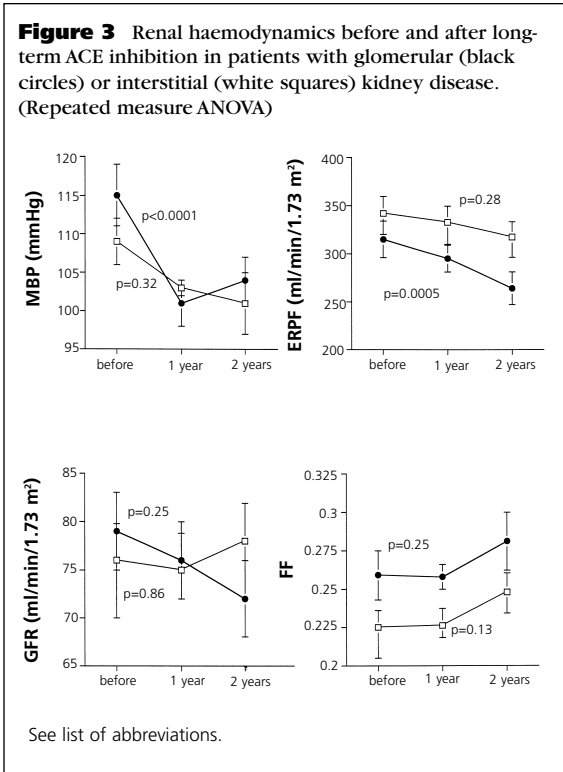
and glomerular filtration, leaving BP and filtration fraction unchanged. These findings are at variance with those obtained in normal subjects and those with essential hypertension. At the glomerular level, glomerular pressure decreases and afferent resistance increases.

- 2) After long-term ACE inhibition, the patients with glomerular nephropathies showed a decrease in renal perfusion, with a maintained filtration, despite a drop in BP. Filtration fraction increased (close to statistical significance). At the glomerular level, only Ra decreased (again close to statistical significance), while Pglo and Re remained unchanged.

Table 3 Basal renal and glomerular haemodynamic variables before and after one and two years of chronic ACE inhibition (mean±SEM). (Repeated measure ANOVA)

	Before	One year	Two years	F	p
MBP (mmHg)	113±3	102±2	103±2	14.8	<0.0001
RBF (ml/minute/1.73 m ²)	558±31	516±22	469±25	13.1	<0.0001
ERPF (ml/minute/1.73 m ²)	323±15	306±12	279±14	12.0	0.0001
GFR (ml/minute/1.73 m ²)	78±3	75±3	74±3	0.9	0.40
FF	0.249±0.013	0.249±0.007	0.272±0.014	2.7	0.08
Pglo (mmHg)	60±1	58±1	58±1	1.5	0.24
Ra (dyne.sec.cm ⁻⁵)	7947±562	6956±441	7709±599	2.6	0.09
Re (dyne.sec.cm ⁻⁵)	2830±219	2841±95	3124±215	1.8	0.18

See list of abbreviations.



3) Surprisingly, both the acute and the long-term renal and glomerular haemodynamic effects were absent in patients with interstitial diseases.

Concerning the first result, it is known that, in normal subjects and essential hypertensives, ACE inhibition causes an increase in ERPF, with no substantial changes in GFR and FF. In chronic renal failure patients, there have been surprisingly few studies on the effects of acute ACE inhibition; however, from the review of the effects of ACE-I on renal function in non-diabetic chronic renal diseases by ter Wee & Epstein,³ it can be argued that both GFR and ERPF tend to decrease more in short-term studies (range <1-26 weeks) than in long-term ones (52-156 weeks) with a calculated FET of 0.006 and 0.03 for GFR and ERPF, respectively. Although the comparison of effects seen after hours with those seen after days to weeks of treatment is debatable, our results support the view that the acute and short-term modifications of renal haemodynamics produced by ACE-I are different from the long-term ones, presumably because of the increased intrarenal levels of angiotensin II (Ang II) in circumstances of decreased renal perfusion. This view is supported by the lack of decrease in GFR that we observed after long-term ACE inhibition. The Pglo decrease could be secondary to the slight non-significant drop in Re, since a K_{FG} increase is hardly compatible with ACE inhibition. The Ra increase could be interpreted as an acute compensatory response, possibly triggered by the angiotensin-independent GFR autoregulation.¹⁰ No Ra increase could be detected in the long-term part of this study. The disappearance of both the Ra increase and the GFR decrease with long-term ACE inhibition sug-

Table 4 Differences between acute and long-term responses to ACE inhibition in patients with glomerular, but not interstitial, nephropathies.

	Acute	Long-term
ERPF	↓	↓
GFR	↓	→
FF	→	→↑
Pglo	↓	→
Ra	↑	↓→
Re	→	→

See list of abbreviations.

gests that these two changes occurring after acute ACE inhibition are linked, and suggests a GFR autoregulation mechanism operating close to the breaking point.

Long-term ACE inhibition clearly allows renal haemodynamics to reach a more stable regulation. Despite a decrease in MBP, only RBF and, of course, ERPF decrease consistently over time (-5-8% at the first and -14-16% at the second year). The decrease in renal perfusion is probably the most sensitive index of renal function deterioration over time, while the increase of filtration fraction, of borderline significance in this study, sustains glomerular filtration. The absence of modifications of efferent resistances and the presence of a borderline significant decrease in afferent resistances are probably due to chronic intrarenal ACE inhibition.

Abbreviations used

MBP	Mean blood pressure
ERPF	Effective renal plasma flow
GFR	Glomerular filtration rate
FF	Filtration fraction
Pglo	Glomerular pressure
Ra	Afferent resistances
Re	Efferent resistances

In conclusion, the most striking differences between acute and chronic ACE inhibition (see Table 4) concern the inverse behaviour of afferent resistances (i.e. increasing acutely and decreasing chronically) and the presence of GFR and Pglo decreases after acute, but not chronic ACE inhibition. In our opinion, the acute modifications should originate mainly from haemodynamic adjustments to the sudden decrease of Ang II levels, while the long-term ones result mainly from chronic ACE inhibition.

The most surprising finding, however, is the absence of any modification of systemic, renal and glomerular haemodynamic variables after both acute and long-term ACE inhibition in patients with interstitial nephropathies. The most obvious explanation is that the intrarenal renin-angiotensin system in this kind of kidney disease is so strongly inhibited or inactive that an additional inhibition does not modify any haemodynamic variable. This might be expected to blunt the decrease in BP elicited by the drugs, however the patients with an interstitial nephropathy tended to have a lower BP before starting therapy, so that it is difficult to compare their response with that of glomerular disease patients. Since the findings of this study were unanticipated, unfortunately the number of interstitial nephropathy patients is small. For this reason these results must be considered preliminary and, of course, should be confirmed by studies specifically designed.

In conclusion, the striking difference we observed between the response to ACE-I of patients with glomerular and interstitial non-dia-

betic nephropathies makes it worthwhile to extend our studies to a larger number of patients, especially those with interstitial kidney disease. Our results, may provide novel and essential information about mechanisms of renal failure progression and about better management of kidney diseases.

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