

Treatment of IgA Nephropathy with ACE Inhibitors: A Randomized and Controlled Trial

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Abstract. Some retrospective studies have suggested a beneficial influence of angiotensin-converting enzyme (ACE) inhibitors on the progression of IgA nephropathy (IgAN), but prospective and controlled studies demonstrating this effect are lacking. Forty-four patients with biopsy-proven IgAN, proteinuria ≥ 0.5 g/d, and serum creatinine (SCr) ≤ 1.5 mg/dl were randomly assigned either to receive enalapril ($n = 23$) or to a control group ($n = 21$) in whom BP was controlled with antihypertensives other than ACE inhibitors. Primary outcome was renal survival estimated by a 50% increase in baseline SCr. Secondary outcomes were the presence of a SCr > 1.5 mg/dl at the last visit and the evolution of proteinuria. Baseline clinical findings were similar at baseline between enalapril-treated and control group, and there were no differences in BP

control during follow-up. Mean follow-up was 78 ± 37 mo in the enalapril group and 74 ± 36 mo in the control group. Three patients (13%) in the enalapril group and 12 (57%) in the control group reached the primary end point ($P < 0.05$). Kaplan-Meier renal survival was significantly better in enalapril group than in control group: 100% versus 70% after 4 yr and 92% versus 55% after 7 yr ($P < 0.05$). Three patients in the enalapril group (13%) and 11 (52%) in the control group showed SCr > 1.5 mg/dl at the last visit ($P < 0.05$). Proteinuria significantly decreased in the enalapril group, whereas it tended to increase in the control group ($P < 0.001$ between groups). In conclusion, ACE inhibitors significantly improve renal survival in proteinuric IgAN with normal or moderately reduced renal function.

A considerable proportion (40 to 60% according to different series) of IgA nephropathy (IgAN) patients develop progressive renal insufficiency (1–4). Impairment in renal function, high BP, and proteinuria > 1 g/d are considered as the more important clinical predictors of an unfavorable evolution (1–6). With the exception of those patients who develop glomerular crescents or malignant hypertension, the rate of progression in IgAN patients with an unfavorable evolution is remarkably slow; end-stage renal failure develops in 20% of the cases after 10 yr and in 30% after 20 yr (1).

Notwithstanding to be the most common type of glomerular disease in the world, surprisingly few prospective and controlled studies focused on the therapy of IgAN have been performed. Corticosteroids have shown a beneficial effect on the progression of IgAN in some randomized clinical trials (7,8), but concerns about its possible side effects in a disease with such a lengthy clinical course have been raised. Fish oil induced a decline in the rate of progression in a controlled study (9), but other studies failed to confirm this beneficial influence (10).

Several multicenter and prospective studies have demon-

strated that ACE inhibitors induce a significant renoprotective effect on the progression rate of both diabetic and nondiabetic chronic proteinuric nephropathies (11,12,13). This beneficial influence is closely related to the known antiproteinuric effect of these drugs. ACE inhibitors also induce a drastic proteinuria reduction in IgAN (14–17), and retrospective studies have shown a slower rate of GFR decline in IgAN patients treated with ACE (18–20). However, prospective and controlled studies demonstrating a beneficial influence of ACE inhibitors on the progression of IgAN are lacking.

In 1990, we started a randomized, prospective clinical trial to assess the influence of enalapril on the evolution of IgAN patients with proteinuria > 0.5 g/d and a normal or moderately reduced (SCr < 1.5 mg/dl) renal function. Both hypertensive and normotensive patients were included in the trial. Our results show that ACE inhibitors significantly improve renal survival in comparison with nontreated patients.

Materials and Methods

The study was prospective and randomized, and it was performed in a single center. From September 1990 to September 1995, 44 adult patients attending our outpatient clinic were eligible for trial entry. The entry criteria were a biopsy-proven IgAN (defined by standard morphologic and immunohistochemical criteria), SCr ≤ 1.5 mg/dl, and urinary protein excretion ≥ 0.5 g/d in at least three consecutive determinations during the 6-mo period before randomization. Renal biopsies had been performed 42 ± 56 mo before the study (ranging from 8 to 75), and re-biopsies were not performed at trial entry. Patients were eligible independently of their BP values; only those cases with a severe hypertension, requiring more than two antihypertensive drugs for its control, or those with previous accelerated or

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malignant hypertension were excluded from the study. Other exclusion criteria were the diagnosis of secondary types of IgAN, including Schönlein-Henoch purpura, the presence of diabetes mellitus, liver, and systemic diseases and previous treatment with ACE inhibitors, corticosteroids, immunosuppressive drugs, or fish oil.

After informed consent had been obtained, patients were randomized to a control group (no ACE inhibitors) or to a group that received enalapril. Simple randomization was performed with a table of random numbers. Allocation concealment was performed by enclosing assignments in sequentially numbered, opaque closed envelopes. Target BP was $\leq 140/90$ mmHg in both groups. Treatment with enalapril started at a dose of 5 mg/d, and doses were later increased if necessary to achieve and maintain a BP $\leq 140/90$ mmHg until a maximal dose of 40 mg/d. If the target BP was not achieved with enalapril monotherapy, addition of other antihypertensive drugs was allowed. In the control group, antihypertensive drugs other than ACE inhibitors or angiotensin receptor blockers (ARB) were administered if necessary to maintain BP $< 140/90$ mmHg. Low-salt diets were prescribed only for hypertensive patients in the two groups; protein intake was not restricted.

A baseline examination (first visit) was performed after randomization, just before the onset of enalapril treatment in those patients assigned to the enalapril group or standard therapy in those assigned to the control group. SCr value obtained at this first visit was considered as the baseline SCr for every included patient. Patients were examined every 3 mo during the first year of follow-up and every 6 mo thereafter. Duration of follow-up was 76 ± 36 mo (29 to 120 mo). At each visit, a complete physical examination was performed and blood was sampled for standard hemogram, SCr, sodium, potassium, cholesterol, triglycerides, glucose, total proteins, and albumin. A 24-h urine collection was obtained at every visit, urine concentrations of sodium, potassium, creatinine, and proteinuria were measured, and 24-h urinary protein excretion and creatinine clearance were calculated at every visit. BP was measured at every visit with a standard mercury sphygmomanometer. Systolic and diastolic BP were measured after 5 min of rest in a sitting position; the average of two measurements was recorded. Mean arterial pressure (MAP) was calculated as the diastolic BP plus one third of the pulse pressure. Standard blood count, proteinuria, and blood chemistry were measured by routine techniques.

Outcome Measures

The primary end point was renal survival, estimated on the basis of a 50% increase in baseline SCr concentrations. Secondary end points were the presence of a SCr > 1.5 mg/dl at the last visit and the evolution of proteinuria over time.

Statistical Analyses

We estimated the sample size on the assumption (based on the results of previous retrospective studies) that a difference in renal survival (50% increase of baseline SCr) of 40% between enalapril-treated and control group will be observed during the follow up. For comparison of two groups at a one-sided level of significance of 5%, we calculated that at least 21 patients were needed in each group for the study to have 80 percent power.

Analysis of primary and secondary end points was by intention-to-treat. The values are expressed as mean \pm SD. For statistical analysis, we used paired and unpaired *t* test when appropriate. The χ^2 test was used for qualitative variables. Correlations were calculated with the Pearson correlation coefficient. The study of data evolution throughout the follow-up was performed with the ANOVA for repeated

measurements (ANOVA). Renal survival, estimated on the basis of a 50% increase in baseline SCr, was calculated by survival analysis according to the Kaplan-Meier method, and log-rank test was used for comparison of different groups. Stepwise multiple logistic regression analysis was performed to determine the inference of different parameters at baseline or during follow-up on renal survival. *P* < 0.05 was considered statistically significant.

Results

A total of 44 patients with biopsy-proven IgAN and fulfilling the trial criteria entry were randomly assigned to receive enalapril treatment (treatment group, *n* = 23) or to a control group without ACE inhibitors (control group, *n* = 21) (Figure 1). The baseline demographic, clinical, and laboratory characteristics of the two groups were similar (Table 1). Most of the patients were aged < 40 yr, and male patients predominated in the two groups. Renal function, estimated by SCr concentrations and creatinine clearances, was similar in the two groups. Mean proteinuria values at baseline were 2 ± 1.3 g/d in the treatment group (range, 0.5 to 5.3 g/d) and 1.7 ± 0.8 g/d in the control group (range, 0.5 to 3.5 g/d) (*P* = NS). Proteinuria in the nephrotic range (>3.5 g/d) was observed at baseline in 4 (17%) of 23 patients of the treatment group and 1 (4%) or 21 of the control group, but none of them showed a complete

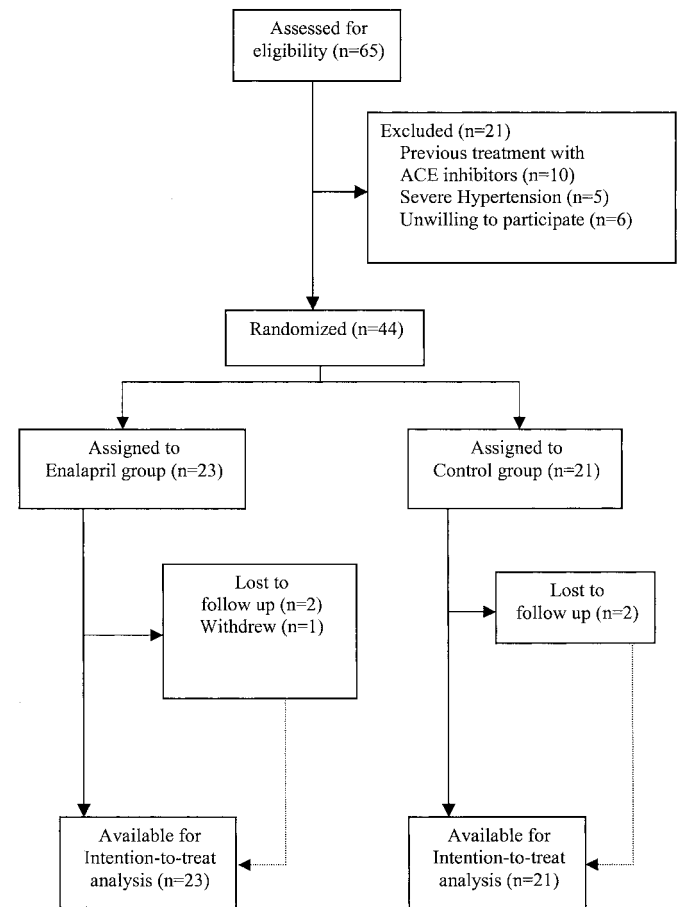


Figure 1. Trial profile. One patient of the enalapril group withdrew during the follow-up because of her intention to become pregnant.

Table 1. Clinical characteristics of patients at baseline

	Enalapril-Treated Group (n = 23)	Control Group (n = 21)	P
Age (yr)	27.8 ± 12	29.9 ± 12.3	NS
Gender (M/F)	15/8 (65/34%)	12/9 (57/42%)	NS
SCr (mg/dl)	1 ± 0.2	0.9 ± 0.2	NS
CrCl (ml/min)	102 ± 25	99 ± 22	NS
Proteinuria (g/d)	2 ± 1.3	1.7 ± 0.8	NS
MBP (mmHg)	102 ± 11	98 ± 12	NS
Patients with BP >140/90	47%	43%	
Follow up (mo)	78 ± 37	74 ± 36	NS

nephrotic syndrome (serum total proteins and albumin were within normal limits, and no edema was detected on physical examination). Urine sediment showed a persistent microhematuria in all the included patients in the two groups. There were no significant differences in systolic, diastolic, and mean BP. The number of patients with BP higher than 140/90 mmHg at baseline was similar in the two groups: 11 (47%) of 23 in the treatment group and 9 (43%) of 21 in the control group (Table 1). Follow-up was 78 ± 37 mo in the treatment group (ranging from 36 to 120 mo) and 74 ± 36 in the control group (29 to 108 mo).

No significant differences in BP measurements were observed between the two groups during the follow-up, as shown in Figure 2. According to the study design, enalapril doses were increased if necessary to achieve a BP < 140/90 mmHg. Mean enalapril dose throughout the follow-up was 21 ± 9 mg/d, ranging from 5 to 40 mg/d. In six patients (26%) of the treatment group, addition of other antihypertensives was required to achieve the targeted BP (nifedipine in two, amlodipine in two, atenolol in one, diuretics in one). In the control group, fourteen patients (66%) received antihypertensives different from ACE inhibitors during the follow-up, to maintain BP within targeted values (nifedipine in four, amlodipine in two, atenolol in three, amlodipine plus diuretics in three, and doxazosin in 2).

Primary Outcome

Three patients in the treatment group (13%) and 12 in the control group (57%) reached the primary end point of a 50% SCr increase during the study ($P < 0.05$).

As is shown in Figure 3, the probability of renal survival, estimated on the basis of an increase in SCr to more than 50% above baseline values, was significantly better in the treatment group than in the control group. Four years after the onset of the study renal survival was 100% among enalapril-treated patients in comparison with 70% in the control group ($P < 0.05$). After 7 yr of follow-up, these probabilities were 92% and 55%, respectively ($P < 0.05$). SCr at baseline in the three enalapril-treated patients who reached the primary end point were 0.9, 1.4, and 1.4 mg/dl, corresponding to creatinine clearances of 120, 75, and 60 ml/min, respectively.

By univariate analysis, treatment with enalapril and the

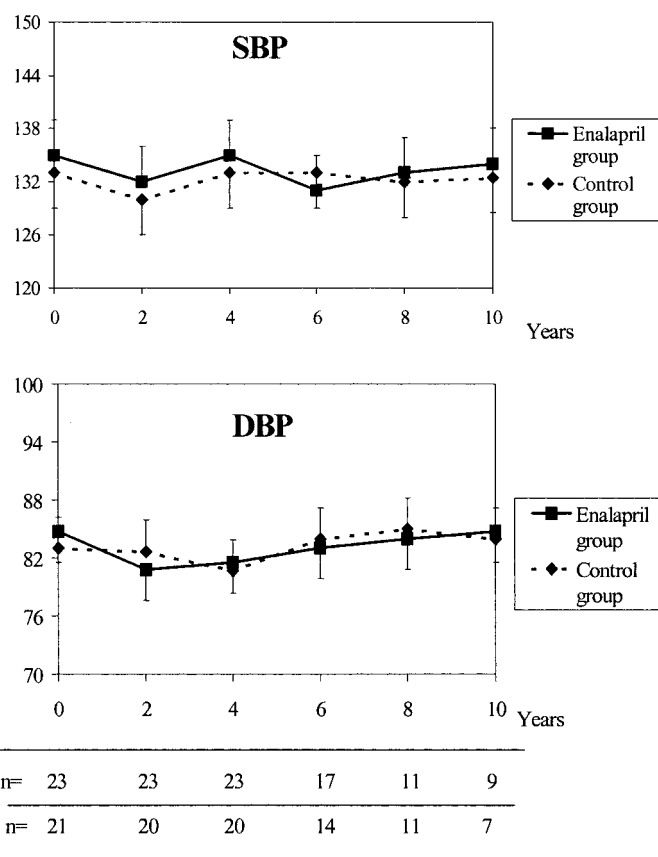


Figure 2. Evolution of systolic (SBP) and diastolic (DBP) blood pressure during the study.

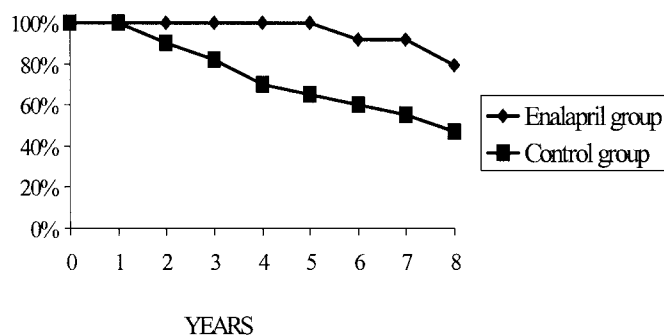


Figure 3. Probability of renal survival (>50% increase of baseline serum creatinine) in enalapril-treated group and control group.

reduction in proteinuria between baseline and 1 yr were the only factors statistically associated with renal survival (Table 2). No effect on the risk of reaching the primary end point was found for gender, age, baseline SCr, and creatinine clearance, baseline proteinuria, baseline BP, or mean values of BP during follow-up. By multivariate analysis, only treatment with enalapril remained as an independent predictor of renal survival (OR, 0.18; 95% CI, 0.03 to 0.87; $P = 0.04$).

Secondary Outcomes

Three patients (13%) in the enalapril treatment group (the same patients who reached the primary end point) and 11

Table 2. Variables influencing renal survival^a

Variable	Univariate Analysis		
	Odds Ratio	95% CI	P
Age at baseline	0.97	0.92 to 1.02	0.35
Gender	1.09	0.30 to 3.91	0.89
SCr at baseline	1.03	0.98 to 1.06	0.56
Creatinine clearance at baseline	1.02	0.99 to 1.05	0.18
SBP at baseline	1.01	0.97 to 1.04	0.54
DBP at baseline	0.98	0.93 to 1.05	0.78
Proteinuria at baseline	0.90	0.52 to 1.57	0.73
Proteinuria decrease	0.98	0.96 to 0.99	0.025
Treatment with enalapril	0.11	0.02 to 4.99	0.0063

^a SBP, systolic BP; DBP, diastolic BP. Proteinuria decrease means the percentage of reduction in urinary protein excretion between baseline and 1 yr.

patients in the control group (52%) showed SCr ≥ 1.5 mg/dl at the last visit ($P < 0.05$). Mean SCr and creatinine clearance did not show significant changes during follow-up in the enalapril-treated group: 1 ± 0.2 mg/dl (0.5 to 1.4) at baseline and 1.2 ± 0.5 mg/dl (0.5 to 3.3) at the last visit and 102 ± 25 ml/min (60 to 150) at baseline and 95 ± 30 ml/min (31 to 150) at the last visit, respectively. Excluding the three patients of this group who reached the primary and secondary outcomes, renal function showed a remarkable stability within normal values in the remaining 20 patients treated with enalapril. In the control group, mean SCr significantly increased from 0.9 ± 0.2 mg/dl (0.6 to 1.4) to 1.9 ± 1.9 mg/dl (0.7 to 10) ($P < 0.001$) and creatinine clearance decreased from 99 ± 22 ml/min (62 to 145) to 64 ± 31 ml/min (6 to 140) ($P < 0.001$) (between-group comparison, $P < 0.001$).

Proteinuria showed a significant decrease in the treatment group: from 2 ± 1.3 g/d (0.5 to 5.3) at baseline to 0.9 ± 1 g/d at the last visit ($P < 0.001$). No significant changes in proteinuria were observed in the control group: 1.7 ± 0.8 g/d at baseline, and 2 ± 1.8 g/d at the last visit (between-group comparison, $P < 0.001$). Proteinuria had decreased significantly by the first year of treatment in the enalapril group, from 2 ± 1.3 g/d to 1.2 ± 1.1 g/d (0 to 4.5) ($-36 \pm 40.1\%$, ranging from -100% to 50% of the baseline values) ($P < 0.001$), whereas no significant changes were observed in the control group: 1.8 ± 1.5 g/d (0.2 to 6) ($+23 \pm 79\%$; -60 to $+216\%$) by the first year of follow-up (between-group comparison, $P < 0.001$). Proteinuria reduction in the enalapril group was seen irrespective of patient's baseline proteinuria and level of serum creatinine.

Enalapril was well tolerated in all the patients assigned to the treatment group, and no patient withdrew from the study due to enalapril side effects. Serum potassium levels showed a mild increase at the onset of enalapril treatment, but they were < 5.5 mEq/L during the follow-up in all the cases, and no treatments to reduce serum potassium levels were needed. Five patients

withdrew from the study; in one woman of the treatment group, enalapril was interrupted after 36 mo of treatment because of her intention to become pregnant. Four patients (two in the treatment group, two in the control group) were lost to follow up between 29 mo and 76 mo after randomization.

Discussion

Some retrospective studies (18–20) have shown a beneficial influence of ACE inhibition on the progression rate of IgAN. Our study is the first to show in a prospective and randomized design, a clearly beneficial effect of enalapril, an ACE inhibitor, on the long-term outcome of IgAN patients with proteinuria ≥ 0.5 g/d and normal or moderately reduced renal function (baseline SCr < 1.5 mg/dl). Only 3 (13%) of 23 patients treated with enalapril reached the primary outcome of the study (50% increase of baseline SCr), in comparison with 12 (57%) of 21 patients in the control group. Renal survival (Figure 3) showed a significant difference between enalapril-treated and control group: 100% versus 70%, respectively, 4 yr after the onset of the study, and 92% versus 55%, respectively, after 7 yr of follow-up.

Proteinuria showed a significant decrease in the enalapril-treated group, whereas it did not show significant changes in the control group. Our results confirm previous studies reporting an antiproteinuric effect of ACE inhibitors in IgAN even in normotensive patients (14–18). By univariate analysis, proteinuria reduction between baseline and 1 yr correlated to renal survival (Table 2). These results agree with previous studies that reported a strong correlation between the proteinuria reduction induced by ACE inhibitors and their long-term renoprotective effect (11–14,21,22). Proteinuria has been shown to have a causal role in the progression of renal dysfunction in diabetic and nondiabetic renal diseases, and the mechanisms implicated in this harmful influence are being progressively clarified (23).

By contrast, the beneficial influence of enalapril appeared to be largely independent of its antihypertensive effect. Thus, BP values in control group patients, in whom antihypertensive agents different from ACE inhibitors or AT1 receptor antagonists were used, were similar to enalapril-treated group during the study (Figure 2). Furthermore, univariate and multivariate analysis did not find any association between BP values and renal survival. We would like to emphasize that our patients were included in the study independently of their BP; in fact, more than one half of the patients (53% in the enalapril group and 57% in the control group) had BP values $< 140/90$ mmHg at the onset of the study.

In subanalysis of the large studies that have clearly established a renoprotective role of ACE inhibitors on the progression rate of nondiabetic renal diseases (11,12), a specific beneficial influence on the evolution of included patients with IgAN could not be demonstrated. Seventy-five IgAN patients were included in the REIN study; 39 were allocated in the ramipril-treatment group, and 36 in the control group. Although a trend to a slower progression rate was observed among the ramipril-treated patients, it failed to achieve statistical significance (24). In the AIPRI study, a significant ben-

eficial influence of benazepril on the subgroup of patients with glomerular diseases could be demonstrated, but specific data about patients with IgAN were not described (11). Mean follow-up of patients included in the REIN and AIPRI studies was shorter than 3 yr.

We think that the longer follow-up of our study (76 ± 36 mo) was crucial for our success in demonstrating a significant beneficial influence of enalapril on IgAN patients; as classical descriptions of the disease have remarked, the progression rate of IgAN in the majority of those patients that develop chronic renal insufficiency is very slow (1–6).

Most of the prospective studies designed to analyze the influence of ACE inhibition on the progression rate of proteinuric nephropathies have included patients with chronic renal insufficiency (11,12,24). IgAN patients included in the REIN study had baseline SCr values of 1.9 ± 0.7 and 2.1 ± 0.9 mg/dl for patients in the ramipril and in the control groups, respectively. In keeping with other retrospective studies (18–20), we had observed in a retrospective analysis of our patients with IgAN and chronic renal insufficiency, a significant slowing in the progression of the disease among those treated with ACE inhibitors (25). These data prompted us to treat all IgAN patients showing chronic renal insufficiency with ACE inhibitors as a general policy, whereas only IgAN patients with normal or only moderately reduced renal function ($\text{SCr} < 1.5$ mg/dl) were included in this prospective study. Our results showing that ACE inhibition significantly decreases the risk of progression toward renal failure in IgAN patients with proteinuria but with preserved renal function are particularly interesting; they indicate that a more ambitious objective (not merely to slow the progression rate of chronic renal failure, but to avoid the onset of renal deterioration) of ACE inhibition could be obtained when these drugs are administered in proteinuric IgAN patients before the appearance of renal insufficiency. It should be stressed that baseline renal function in two of the three patients in the enalapril-treated group who reached both the primary (50% increase of baseline SCr during the study) and secondary ($\text{SCr} > 1.5$ mg/dl at the last visit) outcomes was in the lower limits of normality (SCr of 1.4 mg/dl, with creatinine clearances of 75 and 60 ml/min). In the remaining 20 patients of the enalapril-treated group, renal function showed a remarkable stability during the long-term follow-up of the study.

Several limitations of our study should be considered. Current therapeutic guidelines recommend BP values $< 130/80$ mmHg in patients with proteinuria > 1 g/d (26). Our trial was designed before the publication of those studies supporting these recommendations; BP was therefore targeted to $\leq 140/90$ mmHg in both groups. We do not know whether or not a more strict control of BP in both groups might have changed the results of our study; however, as it is shown in Figure 2, mean systolic and diastolic BP values throughout the follow up were very near 130 mmHg for systolic and 80 mmHg for diastolic BP. On the other hand, patients requiring more than two antihypertensive drugs were not included in the study; therefore, our results could not be applicable to IgAN patients with severe hypertension. Other currently well-identified factors

influencing the progression of renal diseases, such as smoking or hyperlipidemia, were not considered at the design of the study. Nevertheless, when retrospectively analyzed, there were no differences between both groups in the proportion of patients taking statins or other lipid-lowering drugs nor in the proportion of smokers. Our study did not include analysis of ACE gene polymorphisms. A previous study showed that DD genotype in IgAN patients was associated with a higher risk for progression to chronic renal failure and with a higher antiproteinuric response to ACE inhibition (27).

Dihydropyridine calcium channel blockers (DCCB) (amlodipine and nifedipine) were used for BP control in nine patients (47%) of the control group and in four patients (17%) of the enalapril group. This difference, although statistically nonsignificant, might have influenced the results of the study. However, although DCCB lack the antiproteinuric effect of nondihydropyridine ones (28), no detrimental effects of DCCB on proteinuria or on the progression of renal failure have been observed in the majority of studies. Moreover, DCCB were not introduced at the onset of our study, but after several years of follow-up in the majority of the patients that received these drugs.

Some prospective studies have reported an antiproteinuric and renoprotective effect of steroids on IgAN (7,8,29). Pozzi *et al.* (8) included 86 patients with $\text{SCr} < 1.5$ mg/dl and proteinuria between 1 and 3.5 g/d in a prospective study to compare steroid treatment (0.5 mg/kg on alternate days for 6 mo, plus three intravenous pulses of methylprednisilone at the beginning of months 1, 3, and 5) with supportive therapy. Renal survival, estimated by a 50% increase of baseline serum creatinine, was significantly better in the steroid group than in the control group: 81% versus 64% after 5 yr. Fish-oil treatment has also shown a beneficial influence in some studies. Donadio *et al.* (9) included 106 patients with $\text{SCr} < 3$ mg/dl and proteinuria > 1 g/d in a prospective study to compare fish-oil treatment with placebo. Renal survival (estimated by a 50% increase of baseline SCr) after 2 yr of treatment was significantly better in the fish-oil group than in the placebo group: 94% versus 67%. However, other randomized and controlled studies have failed to confirm this beneficial effect of fish-oil in IgAN (10,30).

On the basis of the results of these few randomized and controlled trials, evidence-based clinical guidelines recommend steroids for IgAN patients with significant proteinuria and fish-oil treatment when a slow progressive decline of renal function appears; BP should be controlled with ACE inhibitors (31). We think that, according to our results, ACE inhibitors could be the first therapeutic option in IgAN patients with persistent proteinuria (≥ 0.5 g/d) irrespective of BP values. Moreover, this treatment should be preferably initiated when renal function is still normal to more effectively prevent the appearance and progression of renal failure. More aggressive therapies, such as steroids or steroids combined with cytotoxic drugs (32), could be reserved for those patients in whom renal function deteriorates or proteinuria increases despite ACE inhibition. However, further prospective studies designed to compare ACE inhibitors (or the more recently introduced ARB) with steroids or fish-oil in the treatment of IgAN would certainly provide very valuable data.

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