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ACE Inhibitors to Prevent End-Stage Renal Disease: When to Start and Why Possibly Never to Stop: A *Post Hoc* Analysis of the REIN Trial Results

PIERO RUGGENENTI,*† ANNALISA PERNA,* and GIUSEPPE REMUZZI*†
on behalf of Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN)
**Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases, "Aldo e Cele Daccò" Villa Camozzi, Ranica, Italy; and †Unit of Nephrology, Ospedali Riuniti, Azienda Ospedaliera, Bergamo, Italy.*

Abstract. In this *post hoc*, secondary analysis of the Ramipril Efficacy In Nephropathy (REIN) trial, an angiotensin-converting enzyme (ACE) inhibition risk/benefit profile was assessed in 322 patients with nondiabetic, proteinuric chronic nephropathies and different degrees of renal insufficiency. The rate of GFR decline (ΔGFR) and the incidence of end-stage renal disease (ESRD) during ramipril or non–ACE inhibitor treatment were compared within three tertiles of basal GFR. ΔGFR was comparable in the three tertiles, whereas the incidence of ESRD was higher in the lowest tertile than in the middle and highest tertiles. Ramipril decreased ΔGFR by 22%, 22%, and 35% and the incidence of ESRD by 33% ($P < 0.05$), 37%, and 100% ($P < 0.01$) in the lowest, middle, and highest tertiles, respectively. ΔGFR reduction was predicted by basal systolic ($P < 0.0001$), diastolic ($P = 0.02$), and mean ($P < 0.001$) BP and proteinuria ($P < 0.0001$) but not by basal GFR ($P = 0.12$). ESRD risk reduction was predicted by basal proteinuria ($P < 0.01$) and GFR ($P < 0.0001$) and was strongly dependent on treatment duration ($P < 0.0001$). Adverse events were comparable among the three tertiles and within each tertile in the two treatment groups. Thus, disease progression and response to ACE inhibition do not depend on severity of renal insufficiency. The risk of ESRD and the absolute number of events saved by ACE inhibition is highest in patients with the lowest GFR. However, renoprotection is maximized when ACE inhibition is started earlier and when long-lasting treatment may result in GFR stabilization and definitive prevention of ESRD.

Since the first angiotensin-converting enzyme (ACE) inhibitor, captopril, was approved for the treatment of arterial hypertension, most doctors have been reluctant to offer such therapy to patients with renal failure. Reasons for potential concern have been acute renal function deterioration and hyperkalemia (1). This bias prevented patients with advanced renal failure from taking part in the prospective, large-scale clinical trials that eventually found ACE inhibitors to be a class of drugs that offer significant renal protection (2,3). As a consequence and somehow paradoxically, the risk/benefit profile of ACE inhibitor therapy in patients with advanced renal insufficiency is poorly defined so far. Even more disturbing, a large proportion of renal patients who might theoretically benefit from this treatment is not currently offered the only therapy that may delay progression of the disease to end-stage renal failure and need for dialysis. Actually, a recent review emphasized that even a transient increase in serum creatinine levels leads to physician reticence to stay the course with ACE inhibitor therapy (4). This behavior is further encouraged by advice from some investigators to withhold these medications when creatinine levels exceed 3 mg/dl (5). The rationale for such an attitude remains elusive if one considers that ACE inhibition in animal models is remarkably antiproteinuric and provides renoprotection even when treatment is initiated late in the course of the disease (6). This is why the Ramipril Efficacy In Nephropathy (REIN) study–a randomized, prospective trial aimed at exploring the specific renoprotective effect of ACE inhibition therapy in proteinuric, chronic nephropathies (7,8)—did not use severe renal insufficiency as an exclusion criterion. This offered the investigators the unique opportunity for *post hoc* analyses on the impact of renal function (GFR, 10 to 100 ml/min per 1.73 m^2) on disease progression and response to treatment. Results of these analyses form the basis of the present report.

Materials and Methods

Study Design

A detailed description of the REIN study design and results has been published elsewhere (7,8). Study participants were patients of either gender, aged between 18 and 70 yr, with urinary protein excretion ≥1 g/24 h over at least 3 mo and creatinine clearance in the range of 20 to 70 ml/min per 1.73 m^2, who had not received ACE inhibition therapy for at least 3 mo. Exclusion criteria were treatment with corticosteroids, nonsteroidal anti-inflammatory

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Correspondence to Dr. Piero Ruggenenti, Clinical Research Center "Aldo e Cele Daccò" Villa Camozzi, "Mario Negri" Institute for Pharmacological Research, Via Gavazzeni 11, 24125 Bergamo, Italy. Phone: 39-035-319.888; Fax: 39-035-319.331; E-mail: ruggenenti@marionegri.it
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drugs, or immunosuppressive drugs, heart failure (New York Heart Association class III or higher), acute myocardial infarction or cerebrovascular accident in the previous 6 mo, severe uncontrolled hypertension (diastolic BP ≥115 mmHg and/or systolic BP ≥220 mmHg), evidence or suspicion of renovascular disease, urinary tract infection, obstructive uropathy, diabetes type 1, collagen disease, cancer, higher serum aminotransferase concentrations, chronic cough, drug or alcohol abuse, pregnancy, breast-feeding, and ineffective contraception.

According to baseline urinary protein excretion rate, patients were separated before randomization into two strata (stratum 1, 1.0 to 2.9 g/24 h; stratum 2, ≥3 g/24 h) and were then randomly assigned 1.25-mg capsules of ramipril or placebo on a 1:1 basis within each stratum. The study drug dose was increased every 2 wk up to 2.5 mg/d or 5 mg/d until trough diastolic BP (measured in the morning before study drug administration) was reduced to <90 mmHg. Antihypertensive agents (but not ACE inhibitors) were introduced, and their doses were adjusted appropriately to achieve and maintain diastolic BP <90 mmHg. In patients already receiving antihypertensive agents, the study drug dose was increased and the dose of other antihypertensive agents progressively reduced to avoid symptomatic hypotension. In each patient, the broad aim was to adjust the dose of the study drugs to achieve and maintain the target BP with the minimum dose of concomitant antihypertensive agents. ACE inhibitors or antagonists to angiotensin II receptor could not be added to the study drugs during the study period.

At baseline at 1, 3, 6 mo after randomization and every 6 mo thereafter, patients had their GFR centrally evaluated at Mario Negri Institute for Pharmacological Research by the plasma clearance of nonradioactive iohexol (9). The main objective of the study was to compare the effect of the two study treatments (ramipril *versus* conventional) on ΔGFR and progression to end-stage renal disease (ESRD) in patients with comparable levels of BP control and different underlying renal diseases.

The protocol of the REIN trial was approved by the ethics committee and the institutional review board of each of the 14 hospitals involved. According to the Declaration of Helsinki, all patients provided signed, written informed consent before study entry.

Statistical Analyses

Data were analyzed on an intention-to-treat basis. Details on the analyses of GFR decline and renal endpoints are given elsewhere (7,8). Patients were considered separately within three subgroups (tertiles) with progressively increasing basal GFR (lowest, middle, highest tertiles). Comparisons among tertiles and between the two treatment groups within each tertile were done by using Wilcoxon rank sum test, Fisher exact test, or log-rank test as appropriate. SAS version 8 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. All P values were based on two-sided tests at <0.05. Data were expressed as mean ± SD or median and interquartile (IQ) range, unless otherwise stated. The IQ range obtained using the first and third quartile of values distribution served as a measure of data dispersion that is less influenced than absolute range by extreme values.

Results

Overall, 322 patients who had at least three GFR evaluations (including baseline) entered into the study (median follow-up, 31 mo; IQ range, 21 to 49 mo); 107 were in the lowest tertile, 108 were in the middle tertile, and 107 were in the highest tertile. Thirty-four patients (11%) (19 on ramipril and 15 on placebo plus conventional treatment) had a concomitant, chronic cardiovascular disease. Within each tertile, main baseline demographic, clinical, and laboratory characteristics were comparable between the two treatment groups, with the only exception of a significantly higher prevalence of male patients on ramipril treatment in the middle tertile (Table 1). At study entry, only 54 (17%) of patients were already on ACE inhibitor therapy (11, 12, and 27% in the lowest, middle, and highest tertiles, respectively; $P \leq 0.005$ lowest or middle tertile *versus* highest tertile). All of them had withdrawn from previous ACE inhibitor therapy for at least 3 mo before study entry. Median (IQ range) ramipril or conventional treatment duration was significantly shorter in the lowest tertile (24 [14 to 38] mo) than in the middle tertile (32 [24 to 51] mo; $P = 0.0004$) and in the highest tertile (31 [26 to 52] mo; $P = 0.0002$). Mean ± SEM ΔGFR was comparable in the lowest, middle, and highest tertiles (0.44 ± 0.05 *versus* 0.52 ± 0.08 *versus* 0.38 ± 0.07 ml/min per 1.73 m^2 per mo, respectively), whereas—as expected—the incidence of events was significantly higher in the lowest (50.5%; $P < 0.0001$ *versus* middle and highest tertiles) and middle tertiles (17.6%; $P < 0.01$ *versus* highest tertile) as compared with the highest (4.7%) tertile. Within each tertile (Figures 1 through 3), ramipril as compared with conventional treatment uniformly decreased ΔGFR (by 22%, 22%, and 35%) and the incidence of ESRD (by 33%, 37%, and 100%) in the lowest, middle, and highest tertiles, respectively. In the highest tertile, the overall incidence of ESRD was relatively low regardless of treatment allocation, with only 5 patients (11%) in the control group progressing to ESRD. Risk reduction achieved statistical significance in the lowest ($P < 0.05$) and highest ($P < 0.01$) tertiles. In slope-based analysis of ΔGFR, there was a significant interaction of treatment effect with the level of basal systolic ($P < 0.0001$), diastolic ($P = 0.02$), and mean ($P < 0.001$) BP and proteinuria ($P < 0.0001$) but not with basal GFR ($P = 0.12$) (Table 2). In time-to-event analysis of ESRD, there was a significant interaction of treatment effect with basal proteinuria ($P < 0.01$) and GFR ($P < 0.0001$). Risk reduction was strongly dependent on treatment duration ($P < 0.0001$).

Overall, in patients with adult polycystic kidney disease (APKD), the incidence of renal events (ESRD) was higher (32%) than in those with chronic glomerular disease (25%) and was not significantly affected by ACE inhibitor therapy.

The incidence of major adverse events was comparable in the three tertiles (Table 3) and was comparable within each tertile in ramipril and conventionally treated patients. In no tertile did GFR significantly decrease after 1 or 3 mo of ramipril or conventional treatment (data not shown). Only four patients (three on ramipril) were withdrawn because of persistent hyperkalemia (serum potassium ≥6 mEq/L), despite concomitant diuretic therapy, optimized acid-base balance, and—in diabetic patients—intensified metabolic control. Follow-up serum potassium levels were higher in ramipril than in conventionally treated patients, but differences between treatment groups were statistically significant only in the lowest tertile and never exceeded 0.5

Table 1. Per tertile GFR baseline characteristics of 322 patients with nondiabetic, proteinuric chronic nephropathies

Parameter	Lowest		Middle		Highest	
	Conventional	Ramipril	Conventional	Ramipril	Conventional	Ramipril
Patients *n*	55	52	56	52	46	61
GFR (ml/min per 1.73 sqm)						
range	10.5 to 32.7	13.6 to 32.6	32.7 to 50.6	33.0 to 50.8	50.9 to 101.0	51.7 to 100.9
mean ± SD	23.4 ± 5.3	25.0 ± 5.2	41.1 ± 5.2	41.0 ± 5.2	63.0 ± 10.0	67.0 ± 13.3
Clinical parameters						
age (yr)	50.3 ± 13.6	49.5 ± 12.3	52.3 ± 14.3	48.8 ± 14.0	46.3 ± 12.8	48.8 ± 14.0
male gender (%)	71%	73%	68%	87%	78%	77%
systolic BP (mmHg)	147.4 ± 17.0	149.4 ± 17.8	146.1 ± 18.9	142.9 ± 16.8	143.5 ± 16.0	144.1 ± 20.0
diastolic BP (mmHg)	89.3 ± 11.1	92.0 ± 12.7	90.5 ± 11.0	89.2 ± 9.6	90.8 ± 10.9	89.6 ± 12.5
mean BP (mmHg)	108.7 ± 11.1	111.2 ± 13.2	109.0 ± 12.6	107.1 ± 10.7	90.8 ± 10.7	107.7 ± 14.0
Diagnosis						
glomerular disease (%)	35%	50%	52%	60%	57%	64%
APKD or interstitial nephritis (%)	11%	10%	9%	2%	2%	6%
other or unknown (%)	54%	40%	39%	38%	41%	30%
Laboratory parameters						
serum creatinine (mg/dl)	3.2 ± 0.7	3.1 ± 0.9	2.0 ± 0.4	2.0 ± 0.4	1.5 ± 0.3	1.4 ± 0.3
creatinine clearance (ml/min per 1.73 sqm)	29.4 ± 9.2	31.0 ± 12.5	46.8 ± 11.8	48.3 ± 12.1	67.5 ± 15.7	71.1 ± 19.1
proteinuria (g/24 h)	3.7 ± 2.2	4.1 ± 3.3	3.2 ± 2.3	3.6 ± 2.9	3.1 ± 2.3	2.8 ± 2.0
total cholesterol (mg/dl)	238.8 ± 59.5	237.9 ± 54.0	250.7 ± 51.1	243.8 ± 68.0	245.4 ± 53.2	247.0 ± 83.0
triglycerides (mg/dl)	192.8 ± 126.0	195.7 ± 133.9	174.4 ± 94.4	172.2 ± 94.6	168.9 ± 96.6	214.9 ± 216.9
potassium (mEq/l)	4.7 ± 0.6	4.5 ± 0.6	4.4 ± 0.6	4.3 ± 0.5	4.3 ± 0.5	4.4 ± 0.4

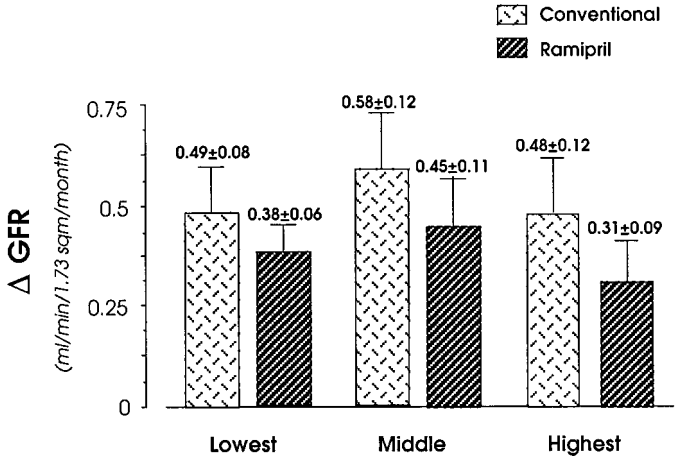

Figure 1. GFR decline in 322 patients with proteinuric, chronic nephropathies according to treatment and tertiles of basal GFR. There were no significant differences among the groups. Values are mean ± SEM.

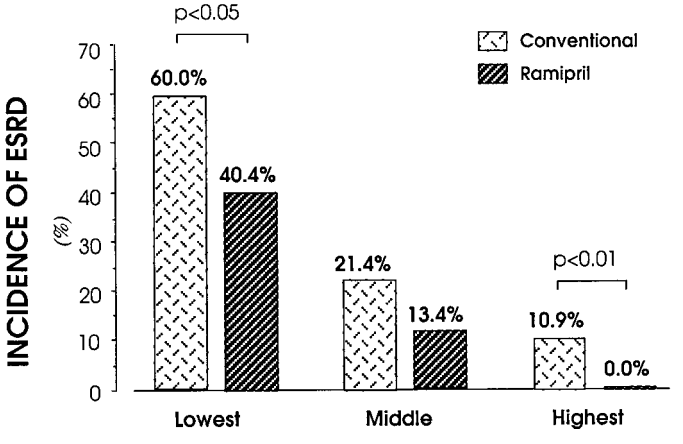

Figure 2. Incidence of end-stage renal disease (ESRD) in 322 patients with proteinuric, chronic nephropathies according to treatment and tertiles of basal GFR.

mEq/L. Within each tertile, follow-up hematocrit and hemoglobin concentrations were comparable in the two treatment groups (data not shown). Altogether, only 12 patients (3.7%) withdrew from the study due to serious (fatal in 4 cases) cardiovascular events (6 on ramipril and 6 on conventional treatment) during the follow-up period.

Discussion

This analysis establishes that the renoprotective effect exerted by ACE inhibition in chronic nephropathies is independent of the severity of renal failure. ACE inhibition was dialysis-saving in all three subgroups of patients, including those with very severe renal dysfunction, and was remarkably safe. Consistent with previous findings (10,11), the data also shows that renoprotection conferred by ACE inhibitors is time-depen-

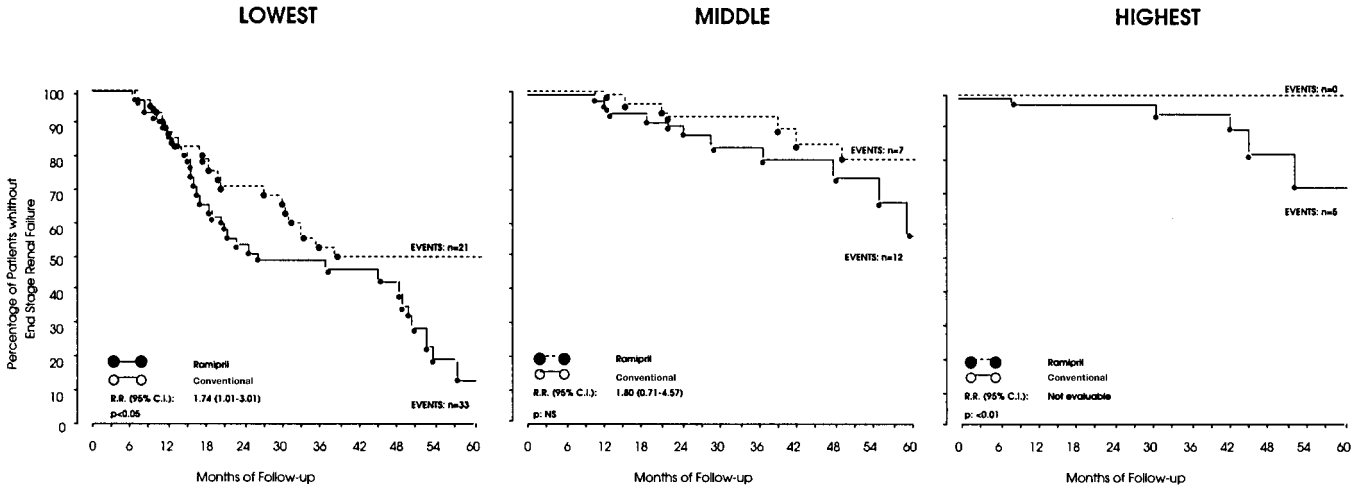

Figure 3. Kidney survival in 322 patients with proteinuric, chronic nephropathies according to treatment and tertiles of basal GFR.

Table 2. Univariate analysis of the interaction between treatment effect on ΔGFR or end-stage renal disease (ESRD) and baseline patients characteristics

Parameter	ΔGFR	ESRD
Age	0.31	0.48
Gender	0.17	0.08
Systolic BP	<0.0001	0.56
Diastolic BP	0.02	0.13
Mean BP	<0.001	0.71
Diagnosis	0.37	0.32
Proteinuria	<0.0001	<0.01
GFR	0.12	<0.0001
Total cholesterol	0.08	0.92
Triglycerides	0.23	0.23

dent and that treatment started at earlier stages of the disease considerably stabilizes renal function and prevents the need of dialysis.

Findings that the rate of GFR decline in patients recruited into the REIN study was comparable within each tertile indicate that in proteinuric, nondiabetic chronic nephropathies the disease progresses independently of the severity of renal dysfunction and rather suggest that the higher risk of terminal renal failure seen in patients with more depressed GFR is just the consequence of more advanced renal disease. This observation is remarkably consistent with previous analyses that show that faster GFR decline in chronic renal disease is significantly predicted by higher arterial BP and proteinuria but not by basal GFR (12). Consistent with previous studies (12), systolic more than diastolic BP predicted progression to ESRD and response to ACE inhibitor therapy, a finding that further reinforces the current concept that systolic hypertension should be considered as an important target for antihypertensive treatment that is targeted at improving the outcome of chronic nephropathies.

Of note, even response to ramipril treatment was not dependent on the severity of renal excretory dysfunction. Indeed, ACE inhibition uniformly slowed GFR decline and progression to ESRD within each tertile of basal GFR. In particular, ramipril therapy had a consistent renoprotective effect, even in patients quite closed to terminal renal failure (basal GFR, 10 to 30 ml/min per 1.73 m^2), who, as compared with conventionally treated patients, had their GFR decline decreased by 22% and risk of ESRD reduced by 33%. To the best of our knowledge, this is the first large study that definitely demonstrates that ACE inhibitors are worth using even in very advanced forms of renal failure. Actually, two previous studies (13,14), which indeed found a trend to slower GFR decline in ACE inhibitor *versus* conventionally treated patients, did not have the power for finding differences in event rates. Another one found an effect on events but not on GFR (15).

We found that, despite comparable ΔGFR reduction in the three tertiles, dialysis risk reduction was actually lower in the lowest tertile as compared with the middle or highest GFR tertiles. This can be reconciled by considering that ramipril-associated risk reduction was a function of treatment duration and that patients in the lowest tertile had been treated for a shorter period compared with patients with more preserved GFR. On the other hand, patients with more advanced renal insufficiency experienced a remarkably higher incidence of events, which, despite less risk reduction, translated into a higher absolute number of dialyses saved in the 10 to 30 ml/min GFR category than in higher GFR categories. Thus, according to our present analyses, patients who might benefit most from ACE inhibitors are actually the ones not offered treatment. Risk reduction failed to achieve the statistical significance in the middle tertile, probably because of the high prevalence of male patients on ramipril treatment. Indeed, previous analyses of the REIN study found that ramipril decreased renal events less effectively in male than in female patients (16). That men are at increased risk of progression is consistent with the results of the RENAAL study in patients with type 2 diabetes with overt nephropathy (17).

Table 3. Serious adverse events leading to patient withdrawal

	Lowest Tertile		Middle Tertile		Highest Tertile	
	Conventional	Ramipril	Conventional	Ramipril	Conventional	Ramipril
Death	0	1	1	1	0	1
Cardiovascular events	2	0	1	1	2	2
Worsening of renal function	2	1	1	0	0	0
Hyperkalemia	1	2	0	1	0	0
Cough	1	1	0	0	1	1
Uncontrolled BP	0	1	2	0	0	1
Cancer	0	0	2	2	0	0
Other	1	1	1	1	2	2
Total	7	7	8	6	5	7

Finding more events and less benefit from ramipril therapy in patients with APKD than in those with chronic glomerulonephritis was consistent with previous evidence that APKD carries a worse prognosis and is less responsive to renoprotective treatments—including low protein diet and intensified BP control (18)—than other chronic nephropathies, including chronic glomerular diseases.

Ramipril therapy was tolerated well. Overall incidence of major adverse events was comparable in ramipril and conventional treatment groups. Furthermore, among and within tertiles no differences were recorded in the incidence of major side effects between treatment groups. As predicted, a nonsignificant trend to more withdrawals because of worsening renal function or hyperkalemia was observed in patients with lowest GFR at study entry. However, even in the lowest tertile, these events were extremely uncommon (<3 cases observed in every 100 patients) and equally reported in ramipril and conventionally treated patients. Equally reassuring was the evidence that, at variance with previous reports in diabetic nephropathy, no short-term GFR decrease was observed in ramipril-treated patients, including those in the lowest GFR tertile. Indeed, the risk of acute renal function deterioration was most likely prevented by temporary diuretic withdrawal before randomization and exclusion of patients with clinical suspicion of volume-depletion or renovascular disease (3). These findings, combined with the evidence that ramipril therapy resulted in an average increase in serum potassium that never exceeded 0.5 mEq/L and had no appreciable effects on patients' hematocrit or hemoglobin concentrations, clearly document an excellent tolerability profile, even in patients with very severe, near end-stage renal failure.

The incidence of serious (fatal and nonfatal) cardiovascular events was remarkably lower in the REIN study than in previous trials on ACE inhibitor therapy in patients with or without chronic renal disease. This was probably because patients at highest risk (*i.e.*, those with a serious cardiovascular event in the 3 mo before basal evaluation) were not selected for study participation and because those in the trial had their risk minimized by optimal BP control (according to the guidelines of the early 1980s) and by uniform adherence to a Mediterranean diet. The comparable incidence of events in the two treatment groups was consistent with previous evidence that, in virtually all trials in nondiabetic chronic nephropathies, ACE inibitors failed to exert any appreciable cardioprotective effect (19). These findings, however, must be taken with caution, because none of the above trials were designed and powered to detect a significant effect of ACE inhibitor therapy on major cardiovascular events.

Thus, ACE inhibition therapy should be offered to all patients with proteinuric chronic nephropathies, regardless of renal function. Maximal renoprotection is achieved when the treatment is started early in the course of the disease (GFR >50 ml/min). Treatment is also renoprotective for levels of renal function between 10 and 30 ml/min, indicating the need not to withhold ACE inhibitors, even when GFR approximates levels requiring replacement therapy. This message will never be emphasized enough, given the fact that it can be estimated that $<20\%$ of patients in need are currently offered this renoprotective treatment, a figure that decreases to 11 to 12% if the GFR is severely impaired.

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