Continuum of Renoprotection with Losartan at All Stages of Type 2 Diabetic Nephropathy: A *Post Hoc* Analysis of the RENAAL Trial Results

GIUSEPPE REMUZZI,*† PIERO RUGGENENTI,*† ANNALISA PERNA,* BORISLAV D. DIMITROV,* DICK DE ZEEUW,‡ DARCY A. HILLE,§ SHAHNAZ SHAHINFAR,§ GEORGE W. CARIDES,§ and BARRY M. BRENNER,‖ FOR THE RENAAL STUDY GROUP

**Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Villa Camozzi, Ranica, and †Unit of Nephrology, Ospedali Riuniti, Azienda Ospedaliera, Bergamo, Italy; ‡University of Groningen, Groningen, The Netherlands; § Merck Research Laboratories, Blue Bell, Pennsylvania; and ‖Renal Division, Brigham and Women's Hospital, Boston, Massachusetts*

Abstract. Renin angiotensin system inhibitor therapy is seldom offered to individuals who have diabetes and advanced chronic kidney disease because of safety concerns. In this *post hoc*, secondary analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, angiotensin antagonism risk/benefit profile was assessed in 1513 individuals with type 2 diabetes and overt nephropathy. Incidence of ESRD, hospitalizations for heart failure, withdrawals for adverse events, and proteinuria during losartan or conventional treatment were compared within three tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). Losartan decreased the risk of ESRD by 24.6, 26.3, and 35.3% in highest, middle, and lowest tertiles, respectively. For every 100 patients with serum creatinine >2.0, 1.6 to 2.0, or <1.6 mg/dl, respectively, 4 yr of losartan therapy was estimated to save 18.9, 8.4, and 2.9 ESRD events and US$1,502,855, US$1,021,770, and US$528,591 costs for renal replacement therapy. Losartan also decreased the hospitalizations for heart failure by 50.2 and 45.1, in the highest and middle tertile, respectively. Withdrawals for adverse events other than heart failure were comparable between tertiles and treatment groups. Proteinuria decreased more on losartan than on placebo in all tertiles (highest, 24 *versus* −8%; middle, 16 *versus* −8%; lowest, 15 *versus* −10%). In proteinuric individuals with type 2 diabetes, losartan therapy reduced ESRD and hospitalizations for heart failure and was well tolerated at all levels of renal function. Angiotensin II antagonism is a suitable and well-tolerated treatment for individuals with type 2 diabetes even with GFR levels approaching renal replacement therapy.

Pharmacologic interruption of the renin angiotensin system (RAS) by angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) is increasingly advocated as a standard therapeutic intervention for patients with chronic nephropathies, regardless of whether systemic hypertension is an associated feature (1). Prospective, randomized, placebo-controlled trials found that, at comparable BP control, ACEi are more effective than non-ACEi therapy in limiting progression to ESRD in patients with type 1 diabetic nephropathy (2) or with nondiabetic, proteinuric chronic nephropathies (3–5). Two recent trials found that ARB losartan (6) and irbesartan (7) led to an improvement in renal outcomes in patients with type 2 diabetes and overt nephropathy. Despite this, many physicians are still reluctant to offer RAS inhibitor therapy to patients with advanced chronic kidney disease (CKD). Reasons for potential concern are hyperkalemia and acute renal function deterioration (8–10). In previous trials, however, these events were uncommon and fully ameliorated with treatment withdrawal (6–10). Although the experience in clinical trials may not be immediately translated to the clinical practice, these reassuring figures challenge the common belief that even a transient increase in serum potassium or creatinine levels should lead physicians to withdraw RAS inhibitor therapy (9). The rationale for such an attitude remains difficult to understand if one considers that in animal models RAS inhibition has been reported to be antiproteinuric and renoprotective even when treatment is initiated late in the course of renal disease (11). Similarly, *post hoc* analyses of the Ramipril Efficacy in Nephropathy trial found that RAS inhibitor therapy offers renoprotection and is well tolerated in patients with nondiabetic chronic nephropathies, even when the GFR is <30 ml/min per 1.73 m^2 (12).

Thus, to assess whether RAS inhibitor therapy is effective and tolerated in patients with type 2 diabetes and established

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Correspondence to Dr. Piero Ruggenenti, Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," "Mario Negri" Institute for Pharmacological Research, Via Gavazzeni 11, 24125 Bergamo, Italy. Phone: +39-035-319-888; Fax: +39-035-319-331; E-mail: manuelap@marionegri.it

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renal insufficiency, we studied the impact of renal function at baseline (serum creatinine 0.9 to 3.6 mg/dl) on disease progression and response to treatment in 1513 patients who were enrolled in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, a randomized, prospective trial aimed at exploring the specific renoprotective effect of ARB therapy in type 2 diabetic nephropathy (6,13). Results of these *post hoc* analyses form the basis of the present report.

Materials and Methods

Study Design

The RENAAL trial was a multinational, double-blind, randomized study that compared losartan *versus* placebo, each in addition to conventional antihypertensive therapy, excluding ACEi and other angiotensin II receptor antagonists. The study was performed in 250 centers in 28 countries and involved 1513 patients. The protocol of the RENAAL trial was approved by the ethics committee and the institutional review board of each of the 250 centers involved. According to the Declaration of Helsinki, all patients provided signed, written informed consent before study entry. The study design, inclusion/exclusion criteria, and treatment protocols have been reported previously (6,13). Participants were considered to have type 2 diabetes when they were older than 30 yr at time of diagnosis of diabetes, had no history of diabetic ketoacidosis, and did not require insulin within 6 mo of diagnosis (6,14). As an index of nephropathy, increased urinary albumin:creatinine (Alb:Cr) ratio >300 mg/g or a 24-h urine protein >500 mg was required. At the time of randomization, patients were stratified according to degree of albuminuria (<2 g/g or ≥2 g/g). A serum creatinine >1.5 mg/dl in men (1.3 mg/dl in women or men <60 kg) to 3.0 mg/dl, a glycosylated hemoglobin (HbA_{1c}) <12%, and an age of 31 to 70 yr were part of the inclusion criteria. Patients with type 1 diabetes or a history of nondiabetic kidney disease were excluded. Non-losartan antihypertensive therapy (including diuretics, β-blockers, calcium channel blockers, α-blockers, or centrally acting agents) was maintained during the baseline phase. After a 6-wk lead-in period, patients were randomized to treatment with losartan or placebo and followed for a mean of 3.4 yr.

Before randomization, baseline sampling of blood for biochemical studies was performed, and a sample of urine was obtained for determination of Alb:Cr ratio. In a subset of patients, 24-h urine was collected in addition. Every 3 mo, blood was sampled and urine was collected. All measurements were performed in a central laboratory. Trough BP was measured three times in a sitting position after a resting period of at least 5 min and before ingestion of daily antihypertensive medications. The average of these measurements was recorded, and the mean arterial pressure was calculated as one third systolic pressure + two thirds diastolic pressure. Pulse pressure, an index of vascular compliance, was calculated as the difference between systolic and diastolic BP. GFR were estimated for each patient using the modified Modification of Diet in Renal Disease formula and expressed as the GFR per 1.73 m^2 of body surface area (15).

The primary efficacy parameter of present analyses was progression to ESRD, defined as the need for chronic dialysis or renal transplantation. Among the prespecified secondary end points of the trial (6,13), additional outcome variables considered in the present analyses were first hospitalizations as a result of heart failure. Adverse events leading to premature withdrawals–including hyperkalemia, worsening renal function, congestive heart failure, or left ventricular dysfunction (reported at the discretion of the investigators)—were also evaluated as safety parameters. All outcome variables were considered according to treatment randomization (losartan *versus* conventional therapy) and different levels of renal function (*e.g.*, tertiles of baseline serum creatinine concentration) at study entry.

Statistical Analyses

Data were analyzed on an intention-to-treat basis. Consistent with previous studies in nondiabetic CKD (12), to explore disease outcome and response to treatment according to different levels of baseline renal function, patients were considered separately within three subgroups (tertiles) with progressively decreasing basal serum creatinine concentration (highest tertile, >2.0 mg/dl; middle tertile, 1.6 to 2.0 mg/dl inclusive; lowest tertile, <1.6 mg/dl). This approach was aimed at identifying subgroups with identical number of patients to increase the power of the analyses and minimize the risk of bias. The tertiles were defined on the basis of serum creatinine levels because serum creatinine was the indicator of kidney function used at baseline evaluation to define the eligibility for inclusion into the RENAAL study (6,13). Details on the analyses of the composite end point, ESRD and adverse events, including congestive heart failure and left ventricular dysfunction, as far as changes in the mean arterial pressure and in the level of proteinuria during follow-up, are given elsewhere (6,13). Comparisons of baseline characteristics among tertiles and between the two treatment groups within each tertile were done using Wilcoxon rank-sum test, Fisher exact test, or χ^2 test as appropriate. Three group comparisons were performed within the three tertiles of baseline serum creatinine concentration (losartan *versus* placebo group in the lowest, middle, and highest tertiles, respectively). Specifically, comparisons within tertiles were carried out using a Cox model, accounting for the stratification factor (urinary albumin/creatinine ratio < or ≥2000 mg/g) and for the geographic region, as prespecified in the statistical analysis plan. Because of the *post hoc* nature of the analyses among tertiles, the multiple comparisons issue was addressed using the Bonferroni correction. The trend of the incidence of composite primary end point, heart failure and ESRD, across serum creatinine tertiles was evaluated through the Jonckheere-Terpstra test, a nonparametric test appropriate to evaluate a chi-square test for linear trend in the proportions. All P values were based on two-sided tests at a significance level of $P = 0.05$.

After the analyses per tertiles were performed, additional comparisons between the two treatment groups were done within predefined, NKF stages of CKD (16). The GFR of each individual patient was calculated by using the four-variables abbreviated Modification of Diet in Renal Disease Study Equation (15) GFR = $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if female) $\times$ 1.21 (if African-American). Then patients were allocated to the different National Kidney Foundation (NKF) stages according to their GFR as in Table 1.

Comparative analyses within stages II, III, and IV were done by using a Cox model as described previously for analyses within tertiles.

Table 1. Stratification of renal patients according to their NKF stage

Stage	GFR (ml/min per 1.73 m^2)	No. of Patients
I	≥90	0
II	60–89	95
III	30–59	1030
IV	15–29	387
V	<15	1

SAS version 8 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. Data were expressed as mean ± SD or median and interquartile (IQ) range, unless otherwise stated.

ESRD Cumulative Incidence and Direct ESRD-Related Costs Estimation

Within each baseline serum creatinine stratum, (*1*) <1.6 mg/dl, (*2*) 1.6 to 2.0 mg/dl inclusive, and (*3*) >2.0 mg/dl, the cumulative incidence of ESRD was estimated by using the cumulative incidence competing risks method (17). This approach accounts for the possibility that a patient may die before requiring dialysis or transplantation. There are two components to this estimate. The first component is the hazard (risk) function for ESRD conditional on ESRD-free survival. This component measures the risk that a patient experiences ESRD at time *t* given that the patient has survived up to time *t* without ESRD. This component was estimated by using the Nelson-Aalen estimator of the cumulative hazard (18). The second component to the cumulative incidence of ESRD is the ESRD-free survival function. This function measures the probability that a patient survives to time *t* without ESRD. We estimated this component using the Kaplan-Meier (KM) method (18). Then, these two components, (*1*) risk for ESRD conditional on ESRD-free survival and (*2*) ESRD-free survival, were multiplied and the products were summed over time to obtain the cumulative incidence of ESRD at the half-year increments, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 yr. Within each tertile, cumulative ESRD days per patient were estimated by subtracting the area under the KM ESRD-free survival curve from the area under the KM all-cause mortality survival curve at half-year increments (19). This allowed us to obtain the exact number of days per patient as related to the occurrence of the event (ESRD).

To estimate the economic burden of direct ESRD-related expenses, we calculated the cost associated with ESRD events for each patient by combining the number of days the patient experienced ESRD with the cost of ESRD over time. All costs were stated in $US and were discounted at the rate of 3% per year according to main principles of a formal economic analysis. Although there were a small number of kidney transplantations performed (three losartan, five placebo), for the purpose of the cost analysis, all individuals with ESRD were assumed to be treated with hemodialysis. Given that the cost of ESRD is greater at the onset of ESRD (20) and greater among individuals with diabetes (21), the longitudinal cost of ESRD for patients with diabetes was estimated by using 1997 and 1998 data from the U.S. Renal Data System (21). Thus, the average daily cost attributed to ESRD for individuals with diabetes was estimated to be $267 per day for the first 90 d after onset of ESRD and $147 per day thereafter (19). These estimates were used later to assess the cost reduction as related to the number of events saved (prevented) by treatment in each tertile of baseline serum creatinine. Extrapolations (simulations) of such reductions to obtain cost estimates on a European-wide level were also performed.

Results

Patients Characteristics

Overall, 1513 patients entered the study and were followed for a mean follow-up of 3.4 yr: 511 patients were in the highest (Scr 2.1 to 3.6 mg/dl), 508 were in the middle (Scr 1.6 to 2.0 mg/dl), and 494 were in the lowest (Scr 0.9 to 1.6 mg/dl) tertile. Within each tertile, the main baseline demographic, clinical, and laboratory characteristics were comparable between the two treatment groups (Table 2).

Outcomes

ESRD. As expected, the observed crude incidence of ESRD was significantly higher in the highest (40.5%) and middle (19.3%) tertiles as compared with the lowest (7.3%) tertile (trend test across tertiles, $P < 0.0001$). Losartan as compared with placebo treatment uniformly decreased the risk of ESRD by 24.6, 26.3, and 35.3% in the highest, middle, and lowest tertiles, respectively (Figures 1, left, and 2). The crude incidence of ESRD and the risk reduction (95% confidence interval) on losartan as compared with placebo in NKF stages II, III, and IV are shown in Table 3. ESRD risk reduction was associated with significantly ($P < 0.0001$) greater median percentage proteinuria reduction (*versus* baseline) on losartan than on placebo in the highest (24 *versus* −8%), middle (16 *versus* −8%), and lowest (15 *versus* −10%) tertiles, respectively (Figure 3). A similar trend to more proteinuria reduction on losartan than on placebo was observed also in NKF stages II, III, and IV (data not shown).

Hospitalizations for Heart Failure. The crude incidence of first hospitalizations for heart failure was higher in the highest (16.4%) and middle (15.0%) tertiles than in the lowest (11.1%) tertile (trend test across tertiles, $P = 0.02$). Losartan decreased the risk of first hospitalization for heart failure by 50.2 and 45.1% in the highest and middle tertiles, respectively, but was associated with a nonsignificant increased risk (42.5%) of hospitalizations in the lowest tertile (Figures 1 and 4). The crude incidence of hospitalizations for heart failure and the risk reduction (95% confidence interval) on losartan as compared with placebo in NKF stages II, III, and IV are shown in Table 3.

Tolerability. The incidence of adverse events leading to premature patient withdrawal was comparable among the three tertiles (Table 4) and within each tertile. Overall, 16 (1.1%) patients (10 [1.3%] on losartan) were withdrawn because of hyperkalemia. As expected, serum potassium levels tended to increase from the lowest to the highest tertile, and within each tertile, follow-up levels tended to be higher in patients who were taking losartan than in those who were taking placebo (Table 5). However, average follow-up differences between treatment groups within each tertile never exceeded 0.2 mEq/L. On the same line, serum potassium levels tended to increase from NKF stage II to NKF stage IV, and within each stage, follow-up levels tended to be higher in patients who were taking losartan than in those who were taking placebo. However, average differences between treatment groups within each tertile never exceeded 0.2 to 0.3 mEq/L (data not shown). The incidence of withdrawals as a result of increasing serum creatinine/acute renal failure was comparable between treatment groups within each tertile, with 26 (1.7%) patients (15 [2.9%] of patients in the highest tertile) prematurely withdrawn as a result of this adverse experience (Table 3). The same trend was observed in different NKF stages (data not shown).

Of interest, the overall incidence of cardiovascular events, including acute myocardial infarction, stroke, and angina, was comparable between tertiles and between treatment groups within each tertile (Table 3). On the contrary, there were more withdrawals because of heart failure or left ventricular dys-

Table 2. Baseline characteristics of 1513 patients with type 2 diabetes and overt nephropathy according to tertile of baseline serum creatinine concentration and randomization to losartan or placebo treatment

	Lowest Tertile (Range, 0.9–1.6 mg/dl; Mean ± SD, 1.4 ± 0.1 mg/dl)		Middle Tertile (Range, 1.6–2.0 mg/dl; Mean ± SD, 1.8 ± 0.1 mg/dl)		Highest Tertile (Range, 2.1–3.6 mg/dl; Mean ± SD, 2.4 ± 0.3 mg/dl)	
	Losartan	Placebo	Losartan	Placebo	Losartan	Placebo
Patients (*n*)	239	255	264	244	248	263
Asian/black/white/hispanic/other (%)	12/19/52/16/1	12/17/48/22/1	17/15/46/20/2	21/13/51/14/1	18/16/45/20/1	20/11/49/17/2
Clinical parameters						
Age (yr)	59.6 ± 7.4	60.2 ± 7.5	60.7 ± 7.2	60.3 ± 7.6	59.6 ± 7.4	60.5 ± 7.4
male gender (%)	53	58	65	73	67	64
body mass index (kg/m^2)	30.9 ± 6.6	29.8 ± 6.2	30.0 ± 5.9	29.3 ± 5.9	29.0 ± 6.4	29.2 ± 6.4
systolic BP (mmHg)	149 ± 18	149 ± 19	152 ± 19	153 ± 20	154 ± 19	157 ± 20
diastolic BP (mmHg)	82 ± 10	83 ± 10	83 ± 10	82 ± 11	82 ± 11	83 ± 10
mean BP (mmHg)	104 ± 11	105 ± 11	106 ± 11	106 ± 13	106 ± 11	108 ± 11
oral antidiabetic drugs/insulin (%/%)	55/62	55/58	48/59	53/55	42/64	42/64
smoking (%)	20	20	20	15	18	15
Laboratory parameters						
HbA_{1C} (%)	8.7 ± 1.7	8.7 ± 1.7	8.6 ± 1.6	8.4 ± 1.6	8.3 ± 1.6	8.2 ± 1.4
total cholesterol (mg/dl)	228 ± 54	227 ± 54	227 ± 57	229 ± 52	227 ± 55	230 ± 60
HDL cholesterol (mg/dl)	47 ± 17	47 ± 14	45 ± 15	44 ± 15	43 ± 14	44 ± 14
triglycerides (mg/dl)	239 ± 195	222 ± 208	207 ± 174	241 ± 235	194 ± 168	213 ± 150
potassium (mEq/L)	4.5 ± 0.5	4.6 ± 0.5	4.6 ± 0.4	4.6 ± 0.5	4.7 ± 0.5	4.7 ± 0.5
uric acid (mg/dl)	6.2 ± 1.6	6.1 ± 1.5	6.8 ± 1.7	6.9 ± 1.6	7.0 ± 1.7	7.1 ± 1.7
creatinine clearance (ml/min per 1.73 m^2)						
mean ± SD	50.7 ± 6.0	50.8 ± 5.7	39.1 ± 2.7	39.1 ± 2.8	28.9 ± 3.4	28.8 ± 3.3
range	43.1–76.7	44.5–76.7	34.5–43.1	34.5–43.1	19.2–33.7	21.6–33.7
median albumin/creatinine ratio (g/mg)	947	882	1045	1178	1737	1800

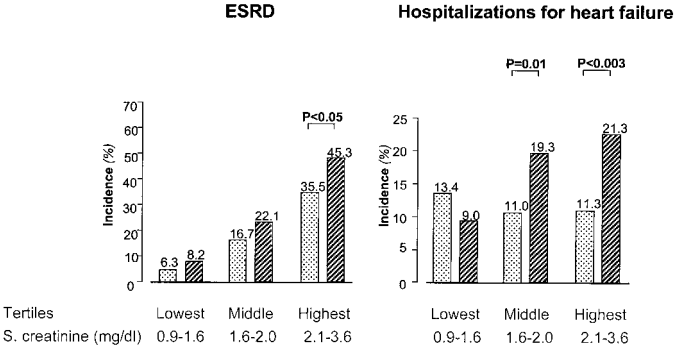

Figure 1. Incidence of ESRD (left) and first hospitalizations for heart failure (right) in 1513 patients with type 2 diabetes and overt nephropathy according to treatment and tertiles of basal serum creatinine concentration. ▨, placebo; ▩, losartan.

function in patients with higher serum creatinine levels at baseline, being 29 (6%) and 30 (6%) cases reported in the highest and middle tertiles, respectively, as compared with 20 (4%) cases reported in the lowest tertile. Of note, this trend was entirely explained by withdrawals among placebo-treated patients in the highest (9%) and middle (8%) tertiles. In addition, losartan was associated with a reduction in withdrawals as a result of heart failure or left ventricular dysfunction in the highest and middles tertiles (Table 3). A similar trend in cardiovascular events was observed in NKF stages II, III, and IV (data not shown).

Economic Evaluations

Figure 5 shows the cumulative ESRD days per randomized patient by treatment group and according to duration of follow-up and different tertiles of baseline serum creatinine concentration. Table 6 shows the days on ESRD saved by losartan therapy according to duration of follow-up and different tertiles of baseline serum creatinine concentration. The reduction in ESRD days resulted in a decrease in direct costs associated with ESRD of $9862, $7417, and $4013 per patient in the highest, middle, and lowest tertiles, respectively, over 4 yr. After accounting for the cost of losartan, the reduction in ESRD days resulted in a net savings of $8083, $5548, and $2105 per patient for each tertile, respectively.

Discussion

The present *post hoc* analysis offers a new paradigm in the treatment of progressive nephropathy of type 2 diabetes: (*1*) Losartan is well tolerated in patients with type 2 diabetes and advanced renal insufficiency, and (*2*) severe renal insufficiency *per se* may not be a specific contraindication to losartan therapy. In type 2 diabetic nephropathy, the renoprotective effect

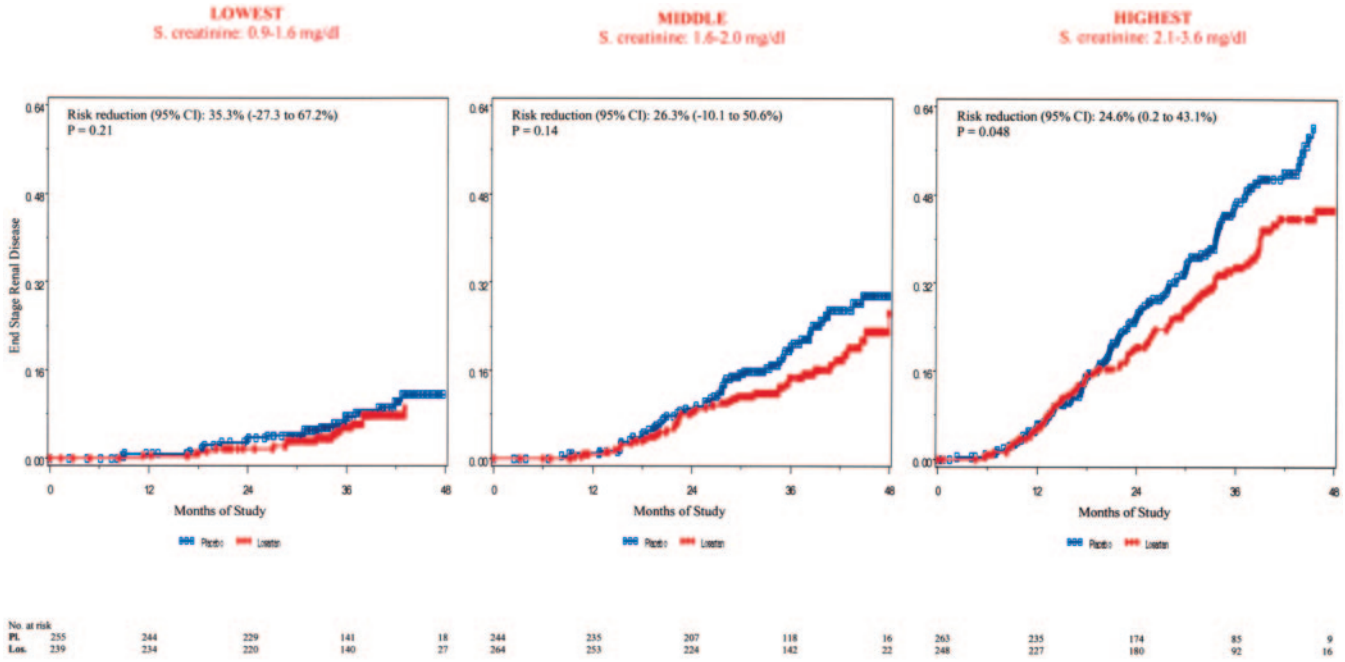

Figure 2. Kaplan-Meier curves of the percentage of patients with type 2 diabetes and overt nephropathy with ESRD according to treatment and tertiles of basal serum creatinine concentration.

exerted by losartan was independent of the severity of renal insufficiency. Angiotensin II blockade by losartan therapy was dialysis saving in all three subgroups of patients, including those with very severe renal dysfunction, and was well tolerated. In particular, losartan-treated patients with advanced renal insufficiency (baseline GFR 19.7 to 33.7 ml/min per 1.73 m^2) as compared with placebo-treated patients had their risk of doubling of serum creatinine, ESRD and death, or ESRD alone reduced by 27.4 and 24.6%, respectively. This is the first large, randomized, controlled study that demonstrates that losartan may be suitable to use in very advanced stages of type 2 diabetic nephropathy. These findings are in harmony with previous evidence from *post hoc* analyses of the Ramipril Efficacy in Nephropathy study (12), which showed that ACEi therapy uniformly decreased the risk of ESRD in patients with nondiabetic proteinuric chronic nephropathies, including those with more renal insufficiency whose baseline GFR (10.5 to 32.7 ml/min per 1.73 m^2) was comparable to those estimated for our patients with type 2 diabetes in the highest tertile.

Here we found that, despite comparable risk reduction within the three tertiles, the dialysis-saving potential of losartan therapy was greatest in the highest compared with the middle or lowest tertile of serum creatinine. Indeed, for every 100 patients who were to be treated over a theoretical follow-up of 4 yr, 18.9 ESRD events (4.7 per 100 patient-years) would be saved in the highest tertile as compared with 8.4 events (2.1 per 100 patient-years) and 2.9 (0.7 per 100 patient-years) events that were to be saved in the middle and lowest tertiles, respectively. It is estimated that this treatment effect would correspond to US$1,502,855, $1,021,770, and $528,591 reduction in the cost of ESRD for every 100 patients with type 2 diabetes and nephropathy and serum creatinine >2.0 mg dl, between 1.6 and 2 mg/dl, and <1.6 mg/dl, respectively. If one assumes that losartan treatment should be extended to the ~700,000 individuals who in the European Community meet the entry criteria of the RENAAL study, (22) half of whom, conceivably, are not on RAS inhibitor therapy (6,7), then it is estimated that 26,000 cases of ESRD could be prevented and that ESRD-related costs could be decreased by $2.5 billion over 4 yr. On the basis of the ESRD events saved by losartan therapy in different tertiles of serum creatinine, it can be estimated that over the same treatment period ~15,000, 7,000, and 2,500 cases of ESRD and ~$1.2, $0.9, and $0.5 billion could be saved in ESRD-related costs among patients with baseline serum creatinine >2.1 mg/dl, 1.6 to 2.0 mg/dl, or <1.6 mg/dl, respectively. Similar figures are predicted if one assumes that losartan treatment is extended to U.S. patients who have diabetes and similar renal characteristics.

In addition to more renal events, patients with advanced CKD had a higher incidence of first hospitalizations for heart failure, a trend that was reduced by losartan therapy. Indeed, in contrast to what was seen in the placebo group, on losartan treatment, the incidence of heart failure did not seem to be dependent on serum creatinine levels at study entry and was comparable among tertiles. Actually, the positive effect of angiotensin II antagonism seemed to be driven by the reduction of events observed in patients with baseline creatinine ≥ 1.6 mg/dl, who, on average, had their risk of hospitalization decreased by at least 45%. Consistently, a similar trend was seen in premature withdrawals because of congestive heart failure or left ventricular dysfunction. Again, the positive effect of losartan increased for increasing levels of baseline serum creatinine, so the risk of symptomatic left ventricular dysfunction decreased by up to 75% in patients with a basal serum creatinine

Table 3. Incidence of ESRD and hospitalization for CHF in 1513 patients with type 2 diabetes and overt nephropathy according to NKF stages and randomization to losartan or placebo treatment[a]

NKF Stage	GFR (ml/min per 1.73 m^2)	No. of Patients	ESRD on Losartan (%)	ESRD on Placebo (%)	Risk Reduction (%; 95% CI)	*P* (Losartan *versus* Placebo)	CHF on Losartan (%)	CHF on Placebo (%)	Risk Reduction (%; 95% CI)	*P* (Losartan *versus* Placebo)
II	60–89	95	1 (2.7)	6 (10.3)	82 (−64 to 98)	0.13	5 (13.5)	5 (8.6)	−42 (−400 to 60)	0.58
III	30–59	1030	64 (12.1)	87 (17.3)	33 (8 to 52)	0.02	55 (10.4)	71 (14.1)	29 (−1 to 50)	0.06
IV	15–29	387	81 (43.6)	101 (50.3)	23 (−4 to 43)	0.08	29 (15.6)	50 (24.9)	41 (6 to 63)	0.03

Stage I (GFR ≥90 ml/min per 1.73 m^2) and stage V (GFR <15 ml/min per 1.73 m^2) were not considered because they included only 0 and 1 patient, respectively. CHF, congestive heart failure; CI, confidence interval.

of 2.1 mg/dl or more (corresponding to a calculated GFR of 33.7 ml/min per 1.73 m^2 or less). Conversely, there was an opposite, nonsignificant trend to more hospitalizations for heart failure among losartan-treated patients with better renal function. These findings, however, must be taken with caution because the relatively small number of events in this subgroup and the wide confidence intervals suggest that the observed differences merely reflect a random chance effect. Actually, the trial was not powered to evaluate the cardiovascular events. Moreover, although congestive heart failure was diagnosed on the basis of predefined criteria given in the study protocol, some bias in data reporting and interpretation cannot be definitely ruled out. Despite these limitations, however, there is compelling evidence that losartan therapy is beneficial to most patients who have diabetes and combined kidney and cardiac failure.

Losartan therapy was well tolerated. Overall, the incidence of major adverse events was comparable in both the losartan and the placebo treatment groups. As well, within the tertiles, no significant 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 the highest serum creatinine levels at study entry. However, even in the highest tertile, these events were relatively uncommon (less than one case observed for every 100 patients) and were similarly reported in the losartan- and placebo-treated patients. Only a small, clinically irrelevant and statistically nonsignificant number of patients on losartan therapy prematurely withdrew from the study because of worsening renal function or acute renal failure in the highest tertile. Thus, the benefit of delaying or preventing progression to ESRD and therefore the need for chronic renal replacement therapy largely exceeded the possible drawback of marginal and transient changes in serum creatinine levels—a phenomenon not even clearly demonstrated—during losartan therapy within each tertile over the same observation period. Thus, even in individuals with type 2 diabetes and CKD, the risk of acute renal function deterioration is relatively small (actually, this event was reported in <0.3% of the RENAAL patients), provided ischemic kidney disease (that may affect up to 40% of patients who have diabetes and hypertension and renal insufficiency (23)) is reasonably excluded before RAS inhibitor therapy is started. To this purpose, pretreatment Doppler ultrasound screening for bilateral renal artery stenosis or unilateral renal artery stenosis to a single functioning kidney may help to identify patients who are at risk of ACEi- or ARB-induced acute renal failure.

As expected, serum potassium levels tended to be higher and withdrawals because of severe hyperkalemia tended to be more frequent in patients who had more severe renal insufficiency and were on losartan therapy. However, the average increase in serum potassium associated with losartan therapy never exceeded the 0.2 mEq/L, and, altogether, <1% of patients with baseline serum creatinine >1.6 or 2.1 mg/dl were prematurely withdrawn because of severe hyperkalemia. Even more impor-

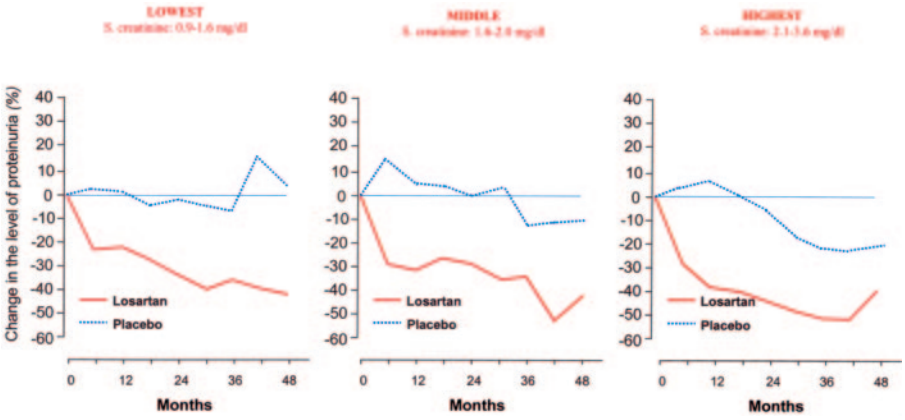

Figure 3. Median changes from baseline in the level of proteinuria throughout the whole study period in 1513 patients with type 2 diabetes and overt nephropathy according to treatment and tertiles of basal serum creatinine concentration.

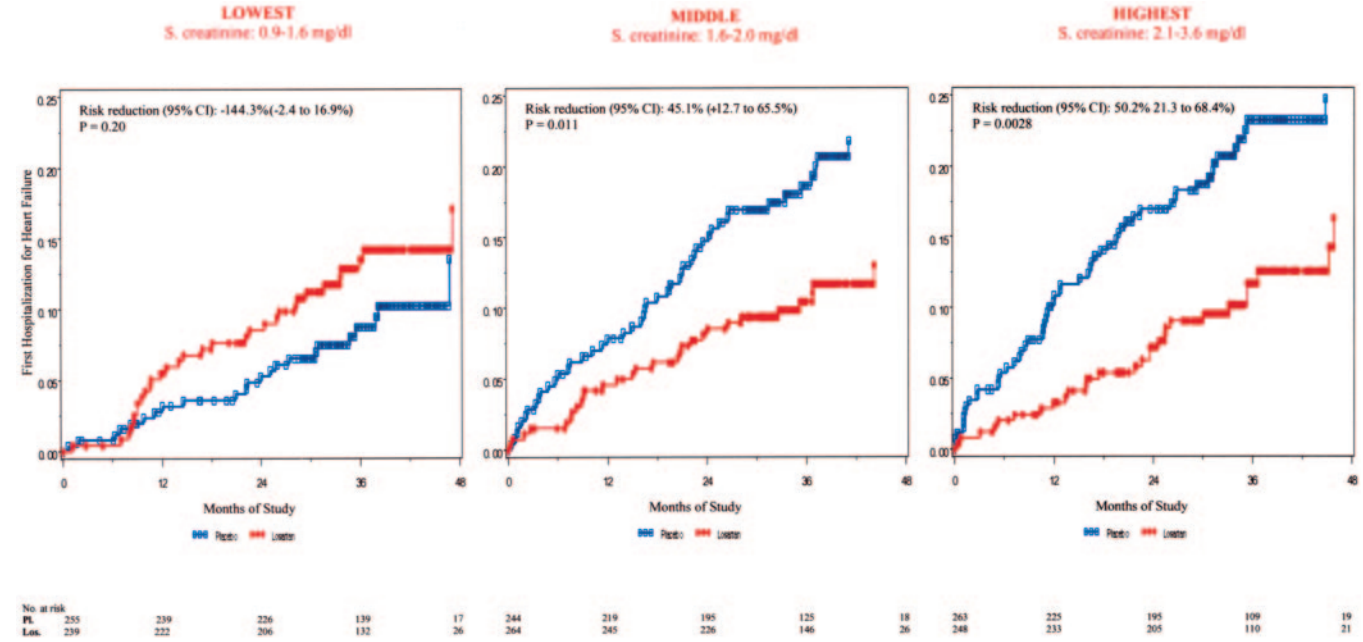

Figure 4. Kaplan-Meier curves of the percentage of patients with type 2 diabetes and overt nephropathy with a first hospitalization for heart failure according to treatment and tertiles of basal serum creatinine concentration.

tant, no excess of sudden deaths or cardiovascular deaths attributable to hyperkalemia was observed in losartan-treated patients as compared with control subjects in the study group as a whole and within each tertile, including the highest one. These findings extend the evidence from previous trials that hyperkalemia is normally manageable and seldom (in <1.5 to 1.9% of cases) requires withdrawal of RAS inhibitor therapy (6,7). In addition, no deaths in these studies were attributed to hyperkalemia (6,7). Altogether, these findings challenge the common belief that ACEi or ARB should be avoided in individuals who have type 2 diabetes and CKD.

Notably, patient compliance and close monitoring accounted for the remarkably good risk/benefit profile of RAS inhibitor therapy in clinical trials. However, a higher incidence of adverse events is expected in routine clinical practice, in particular when the standard of care achieved in controlled studies cannot be ensured. In these circumstances, the risk of life-threatening hyperkalemia cannot be definitely excluded, and RAS inhibitor therapy should always be considered with great caution.

In conclusion, within the limits of *post hoc* analyses and of low number of events in the lowest tertile, our present findings strongly suggest that, regardless of the level of renal function, losartan is an appropriate therapy for individuals who have type 2 diabetes with overt nephropathy, provided that acceptable metabolic control is achieved and ischemic kidney disease is reasonably excluded. Treatment is also more renoprotective and cost-effective for levels of renal function between 10 and 30 ml/min and may even reduce the excess of symptomatic heart failure associated with decreased renal function. Losartan therapy was renoprotective in patients with type 2 diabetes and renal insufficiency and should be considered even when the GFR approximates levels approaching renal replacement therapy. This is important given that it is estimated that only 50%

Table 4. Adverse events leading to patient withdrawal in 1513 patients with type 2 diabetes and overt nephropathy according to tertile of baseline serum creatinine and randomization to losartan or placebo treatment[a]

Event	Lowest Tertile		Middle Tertile		Highest Tertile	
	Losartan	Placebo	Losartan	Placebo	Losartan	Placebo
Death	0	0	2[b]	0	1[c]	0
Cardiovascular events	10	13	12	12	10	12
myocardial infarction	5	4	1	5	6	7
stroke	3	5	7	5	1	1
angina/coronary disease	2	4	4	2	3	4
Heart failure/left ventricular dysfunction	9	11	10	20	6	23[d]
Increasing serum creatinine/ARF	1	2	3	5	9	6
Chronic renal insufficiency/failure	4	1	3	8	11	10
ESRD	1	0	2	4	8	13
Hyperkalemia	2	1	5	3	3	2
Angioedema	0	0	0	1	1	0
Hypertension/uncontrolled BP	3	0	3	3	1	1
Uncontrolled diabetes	0	2	0	1	0	0
Cancer	1	3	2	0	1	0
Other	6	13	14	14	19	20

[a] ARF, acute renal failure.
[b] Cardiac arrest.
[c] Brain death.
[d] $P < 0.01$ *versus* Losartan.

Table 5. Basal and mean follow-up serum potassium levels in 1513 patients with type 2 diabetes and overt nephropathy according to tertile of baseline serum creatinine and randomization to losartan or placebo treatment

Serum Potassium (mEq/L)	Lowest Tertile		Middle Tertile		Highest Tertile	
	Losartan	Placebo	Losartan	Placebo	Losartan	Placebo
Basal	4.5 ± 0.5	4.6 ± 0.5	4.6 ± 0.5	4.6 ± 0.5	4.7 ± 0.5	4.7 ± 0.5
Follow-up	4.8 ± 0.2[a]	4.6 ± 0.1[b]	4.9 ± 0.1[a]	4.7 ± 0.1[b]	4.9 ± 0.1[a]	4.7 ± 0.1[b]

[a] $P < 0.001$ *versus* basal.
[b] $P < 0.001$ *versus* Losartan.

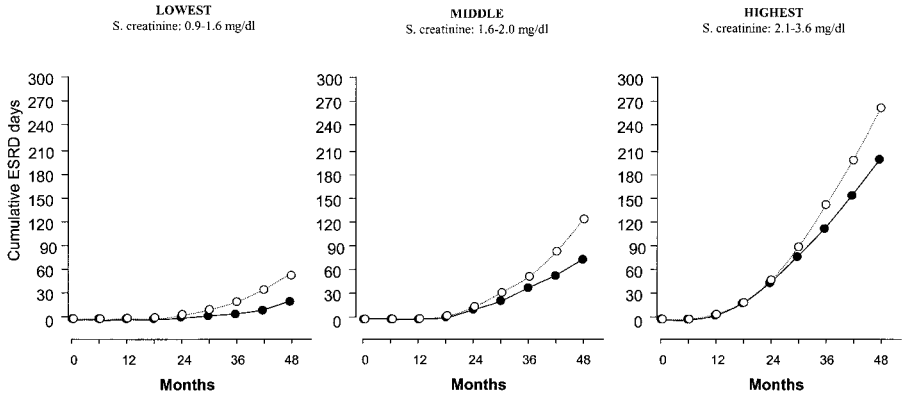

Figure 5. Cumulative ESRD days throughout the whole study period in 1513 patients with type 2 diabetes and overt nephropathy according to treatment and tertiles of basal serum creatinine concentration.

of patients in need are currently offered this renoprotective treatment, (6,7) a figure that decreases to 11 to 12% when the GFR is severely impaired (13).

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Table 6. Days of ESRD saved by losartan therapy according to duration of follow-up and different tertiles of baseline serum creatinine concentration

Follow-up (Days)	Tertiles		
	Lowest	Middle	Highest
180	0.0	0.0	0.4
360	0.6	0.1	0.7
540	2.1	0.3	0.6
720	5.2	3.6	7.0
900	10.1	7.5	17.3
1080	15.8	15.7	29.3
1260	22.0	30.2	44.9
1440	29.0	47.9	59.2

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