

Risk Scores for Predicting Outcomes in Patients with Type 2 Diabetes and Nephropathy: The RENAAL Study

William F. Keane,* Zhongxin Zhang,* Paulette A. Lyle,* Mark E. Cooper,[†] Dick de Zeeuw,[‡] Jean-Pierre Grunfeld,[§] James P. Lash,^{||} Janet B. McGill,[¶] William E. Mitch,** Giuseppe Remuzzi,^{††} Shahnaz Shahinfar,* Steven M. Snapinn,* Robert Toto,^{‡‡} and Barry M. Brenner,^{§§} for the RENAAL Study Investigators

*Merck & Co., Inc., Whitehouse Station, New Jersey; [†]Baker Heart Research Institute, Melbourne, Victoria, Australia; [‡]Department of Clinical Pharmacology, University Medical Center Groningen, Groningen, The Netherlands; [§]Service de Nephrologie, Hopital Necker, Paris, France; ^{||}University of Illinois at Chicago, Chicago, Illinois; [¶]Department of Medicine, Division of Endocrinology, Washington University, St. Louis, Missouri; **Department of Medicine, Renal Division, Emory University, Atlanta, Georgia; ^{††}Instituto Di Ricerche Farmacologiche Mario Negri, Laboratories Negri Bergamo, Bergamo, Italy; ^{‡‡}Division of Nephrology, Baylor College of Medicine, Houston, Texas; and ^{§§}Department of Medicine, Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Diabetic nephropathy is the most important cause of ESRD. The aim of this study was to develop a risk score from risk predictors for ESRD, with and without death, in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and to compare ability of the ESRD risk score and its components to predict ESRD. The risk score was developed from coefficients of independent risk factors from multivariate analysis of baseline variables and equals $(1.96 \times \log [\text{urinary albumin:creatinine ratio}]) - (0.78 \text{ serum albumin [g/dl]}) + (1.28 \times \text{serum creatinine [mg/dl]}) - (0.11 \times \text{hemoglobin [g/dl]})$. It was robust with respect to severity of nephropathy, gender, race, and treatment group. The risk score for ESRD or death was comparable. The four risk predictors for progression of kidney disease were independent of therapy. For combined treatment groups, the hazard ratio between the fourth and first quartiles of the ESRD risk score was 49.0, as compared with the corresponding hazard ratios for each component: 14.7 for urinary albumin:creatinine ratio, 9.2 for serum creatinine, 5.5 for hemoglobin, and 10.2 for serum albumin. The RENAAL risk scores for ESRD with or without death emphasize the importance of identification of level of albuminuria, serum albumin, serum creatinine, and hemoglobin to predict development of ESRD in patients with type 2 diabetes and nephropathy. Although albuminuria is a strong risk factor for ESRD, the contribution of serum albumin, serum creatinine, and hemoglobin level further enhances prediction of ESRD. Future trials with a similar patient population and outcomes measures should consider adjusting analyses for baseline risk factors.

Clin J Am Soc Nephrol 1: 761–767, 2006. doi: 10.2215/CJN.01381005

Diabetic nephropathy, especially related to type 2 diabetes, has become the single most important cause of ESRD worldwide. Although management of traditional risk factors such as hypertension, hyperlipidemia, and smoking to improve cardiovascular and renal outcomes continues to be important in patients with chronic kidney disease, there is growing recognition that nontraditional risk factors such as increased urinary albumin excretion, hypoalbuminemia, elevated serum creatinine levels, and/or decreased hemoglobin levels also may be important in the population with chronic kidney disease (1). The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

(RENAAL) study demonstrated significant benefits of treatment with losartan- versus placebo-based therapy in patients with type 2 diabetes and nephropathy (2). We aimed to explore further the risk predictors in the diabetic kidney disease population by developing ESRD and ESRD or death risk scores from risk predictors in the RENAAL study and to compare the ability of the ESRD risk score and its components to predict ESRD.

Materials and Methods

Study Design

RENAAL was a multinational, double-blind, randomized study that compared losartan versus placebo, in addition to conventional antihypertensive therapy (excluding angiotensin-converting enzyme inhibitors or other angiotensin II receptor antagonists), in 1513 patients with type 2 diabetes and nephropathy. Patients were followed for a mean of 3.4 yr. The study design (3) and results (2) have been reported. ESRD was defined as the need for long-term dialysis or renal transplantation. End points were classified by an expert end point classification committee that was blinded to study drug identification.

Received October 20, 2005. Accepted March 29, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

Address correspondence to: Dr. William F. Keane, Merck & Co., Inc., PO Box 4, UG4A-025, West Point, PA 19486-0004. Phone: 267-305-2018; Fax: 267-305-2845; E-mail: williamf_keane@merck.com

Statistical Analyses

Statistical Analysis System version 8 software was used for all analyses. We previously reported the significant independent baseline risk factors for the progression of renal disease to doubling of serum creatinine or the development of ESRD: albuminuria, hypoalbuminemia, increased serum creatinine, and decreased hemoglobin (2). Our purpose in this analysis was to identify the independent risk factors for the development of ESRD alone and to evaluate whether a risk score that is developed from the risk factors has a stronger predictive power than its components for ESRD in the RENAAL study. We also calculated the risk score for the composite end point of ESRD or death using a similar method.

Twenty-nine baseline categorical and continuous variables (including gender and race) were evaluated, and 23 of them had a significant impact on the development of ESRD. Multivariate analysis used a multivariate Cox regression model with backward selection process, with $P < 0.01$ required for inclusion in final model. The risk score was developed from the linear combination of covariates from the final relative hazard model.

Data presented here are for the pooled losartan and placebo treatment groups. The same risk factors were found in the placebo group, suggesting that the risk predictors for progression of kidney disease were independent of therapy.

To compare the predictive power between the risk score and each of the components, patients were stratified by quartiles for the risk score and each covariate. Quartile range, number of patients who had ESRD per 1000 patient-years of follow-up, and hazard ratios (HR) with respect to the first quartile were determined for combined treatment groups. In addition, Kaplan-Meier curves were generated by the risk score quartile and time-varying risk score quartile for the combined and individual treatment groups.

To validate the risk score, patients were classified further into deciles, and the crude ESRD rates within these categories were calculated. We refer to this as the naïve validation approach. Because of the potential optimistic bias of this approach, we also calculated ESRD rates using the jackknife approach, in which all 1513 patients were classified into deciles on the basis of a score that the patient had no part in developing (4). The distributions of events across quartiles and deciles of the risk score also were examined for gender and race.

The relationship among the four risk factors was explored. Mean and quartile range were calculated for each risk factor by subgroups of

proteinuria and serum creatinine. In addition, the correlations among the risk score, albuminuria, serum albumin, serum creatinine, hemoglobin level, and systolic and diastolic BP were tested using Pearson product-moment correlation coefficients. The robustness of the risk score was explored by deriving similar risk score equations using the four risk factors by treatment group and subgroups of dichotomized proteinuria and serum creatinine, gender, and race. The coefficients with 95% confidence intervals were provided.

Results

Of the 1513 patients who were randomly assigned in RENAAL, 341 patients developed ESRD. The relationship between the independent baseline risk factors and the development of ESRD was as follows: Risk score = $(1.96 \times \log [\text{urinary albumin:creatinine ratio (UACR; mg/g)}]) - (0.78 \times \text{serum albumin [g/dl]}) + (1.28 \times \text{serum creatinine [mg/dl]}) - (0.11 \times \text{hemoglobin [g/dl]})$, with a higher value representing a higher risk (Table 1).

In the RENAAL study, investigators aimed to treat BP to the goal of $<140/90$ mmHg. We tested for correlation between systolic and diastolic BP and the four elements of the risk score using Pearson product-moment correlation coefficient. Patients with higher BP had larger risk scores and, in particular, more albuminuria. BP did not correlate as well with other elements of the risk score. Although systolic BP is important in determining ESRD risk particularly in patients with type 2 diabetes, in RENAAL, it only explained 12 to 18% of the change in risk score from baseline (data not shown). This was due, in large part, to the fact that the vast majority of patients were on therapy with major reductions in BP from baseline (1).

For comparison of the predictive power of the risk score and its components for ESRD, patients were categorized by the severity of the renal disease into quartiles. As shown in Table 2, the event rate per 1000 patient-years of follow-up increased with increasing albuminuria and serum creatinine and decreasing serum albumin and hemoglobin. Among the four components, baseline albuminuria was the strongest predictor of ESRD, with an event rate per 1000 patient-years of follow-up of

Table 1. Multivariate risk factors for ESRD and composite end point of ESRD or death^a

	Coefficient (95% CI)	HR (95% CI)	χ^2	P
ESRD				
serum creatinine (mg/dl)	1.28 (1.07 to 1.49)	3.59 (2.90 to 4.45)	137.7	<0.0001
log (UACR)	1.96 (1.55 to 2.38)	7.12 (4.70 to 10.80)	85.5	<0.0001
serum albumin (mg/dl)	-0.78 (-1.09 to -0.48)	0.46 (0.34 to 0.62)	25.1	<0.0001
hemoglobin (g/dl)	-0.11 (-0.18 to -0.04)	0.90 (0.84 to 0.96)	10.6	0.0011
ESRD or death				
serum creatinine (mg/dl)	0.97 (0.80 to 1.14)	2.63 (2.22 to 3.11)	123.6	<0.0001
log (UACR)	1.14 (0.86 to 1.43)	3.14 (2.35 to 4.19)	60.5	<0.0001
serum albumin (mg/dl)	-0.61 (-0.86 to -0.35)	0.54 (0.42 to 0.70)	22.0	<0.0001
HbA _{1c} (%)	0.08 (0.03 to 0.13)	1.08 (1.03 to 1.14)	8.5	0.0036
hemoglobin (g/dl)	-0.07 (-0.12 to -0.02)	0.93 (0.89 to 0.98)	6.8	0.0089

^aCI, confidence interval; HbA_{1c}, glycosylated hemoglobin; UACR, urinary albumin:creatinine ratio. To convert urinary UACR in mg/g to mg/mmol, multiply by 0.113; serum creatinine in mg/dl to $\mu\text{mol/L}$, multiply by 88.4; hemoglobin in g/dl to g/L, multiply by 10; and serum albumin in mg/dl to g/L, multiply by 10.

Table 2. Values of risk score components, ESRD rates, and hazard ratios by quartiles^a

	By Quartile			
	1	2	3	4
Baseline variable				
risk score	<3.0	3.0 to 4.0	4.0 to 5.1	>5.1
albuminuria (mg/g)	<558.0	558.0 to 1245.5	1245.5 to 2544.5	>2544.5
serum creatinine (mg/dl)	<1.5	1.5 to 1.8	1.8 to 2.2	>2.2
hemoglobin (g/dl) ^b	>13.8	12.5 to 13.8	11.3 to 12.5	<11.3
serum albumin (mg/dl) ^b	>4.1	3.8 to 4.1	3.5 to 3.8	<3.5
Rate per 1000				
risk score	6.7	22.4	84.5	257.2
albuminuria	18.7	32.5	75.6	227.8
serum creatinine	24.3	44.2	93.7	198.1
hemoglobin	27.9	74.7	82.2	136.8
serum albumin	24.6	42.6	66.3	204.8
HR (95% CI)				
risk score	1.00	3.31 (1.50 to 7.29)	13.58 (6.59 to 27.98)	49.03 (24.18 to 99.41)
albuminuria	1.00	1.77 (1.05 to 2.99)	4.29 (2.68 to 6.88)	14.69 (9.45 to 2.83)
serum creatinine	1.00	1.85 (1.19 to 2.87)	4.03 (2.69 to 6.03)	9.24 (6.32 to 13.50)
hemoglobin	1.00	2.80 (1.85 to 4.25)	3.11 (2.08 to 4.64)	5.50 (3.75 to 8.08)
serum albumin	1.00	1.81 (1.10 to 2.99)	2.85 (1.76 to 4.61)	10.21 (6.49 to 16.07)

^aHR, hazard ratio; Rate per 1000, number of ESRD end points per 1000 patient-years of follow-up. To convert urinary albumin in mg/g to mg/mmol, multiply by 0.113; serum creatinine in mg/dl to μmol/L, multiply by 88.4; hemoglobin in g/dl to g/L, multiply by 10; and serum albumin in mg/dl to g/L, multiply by 10.

^bQuartile based on reverse order.

18.7 in the first quartile (albuminuria < 558.0 mg/g [63.1 mg/mmol]) and 227.8 at the last quartile (≥2544.5 [287.5]). Even so, the risk score had a better predictive power than albuminuria alone. For the same patients, the event rate per 1000 patient-years of follow-up was only 6.7 in the first quartile (score < 3.0) and 257.2 at the last quartile (score ≥ 5.1). Therefore, using the risk score improved predictive power for ESRD versus using albuminuria alone, especially for low-risk patients. The relative predictive power can be assessed using the HR for each covariate: The HR between the fourth and first quartiles of the risk score was 49.0, as compared with the corresponding HR for each component: 14.7 for albuminuria, 9.2 for serum creatinine, 5.5 for hemoglobin, and 10.2 for serum albumin. Therefore, the predictive power of the risk score on ESRD increases at least three-fold as compared with albuminuria alone (Table 2).

The applicability of the risk score was evaluated further by examination of the crude ESRD rates by mean risk score deciles (Figure 1). The ESRD rates rose with increased mean risk decile from the fifth to 10th deciles. The risk score was tested for optimistic bias by application of a jackknife procedure, which resulted in similar distribution of the events by mean risk score decile (data not shown). Likewise, the distribution of events by mean risk score decile showed that the risk score was predictive for ESRD in both genders and both white and nonwhite races (data not shown).

Figure 2 shows the Kaplan-Meier curves for ESRD stratified by quartile of risk score. Consistent treatment effects were seen

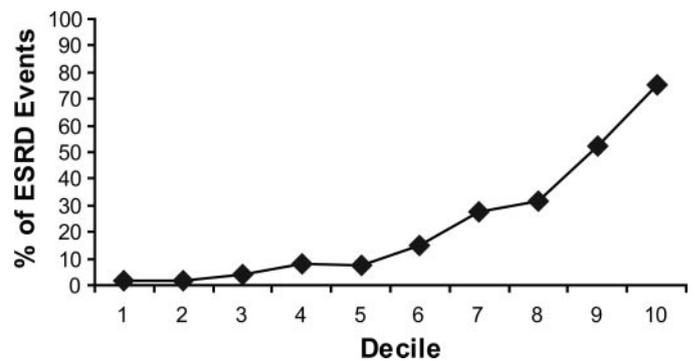


Figure 1. Crude ESRD rates stratified by decile of mean risk score.

in patients across all quartiles (Figure 3). The test for treatment-by-quartile interaction was NS ($P = 0.59$).

Time-varying covariate analyses showed that at 36 mo, approximately 54% of patients in fourth quartile had developed ESRD (i.e., for a hypothetical cohort of patients who remain in the fourth quartile throughout the trial, 54% would be expected to develop ESRD within 36 mo). For patients in the first through third quartiles, 1 to 10% developed ESRD at 36 mo. At month 36, approximately 58% of the patients in the placebo group versus approximately 50% of the patients in the losartan group who were in the fourth quartile of the risk score had developed ESRD, reflecting the influence of losartan treatment on slowing the progression of albuminuria and development of ESRD.

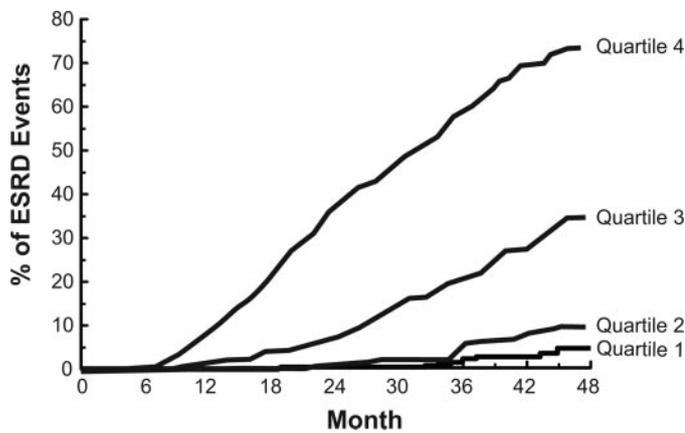


Figure 2. Kaplan-Meier curve for ESRD end point stratified by quartile of risk score.

Quartile 1: Hazard ratio (HR) 0.02 (95% confidence interval [CI] 0.01 to 0.04), $P < 0.0001$.

Quartile 2: HR 0.07 (95% CI 0.05 to 0.10), $P < 0.0001$.

Quartile 3: HR 0.27 (95% CI 0.21 to 0.35), $P < 0.0001$.

Quartile 4: Reference.

Among the four risk factors, proteinuria and serum creatinine were positively correlated with each other but negatively correlated with serum albumin and hemoglobin. As shown in Table 3, patients who had baseline proteinuria <2000 mg/g (226 mg/mmol) had overlapping quartile ranges of serum creatinine, serum albumin, and hemoglobin with patients who had baseline proteinuria ≥ 2000 mg/g (226 mg/mmol). Similar results were seen when patients were stratified by baseline serum creatinine <2 or ≥ 2 mg/dl (176.8 $\mu\text{mol/L}$). None of the risk factors could be reproduced by the other ones. For different subpopulations, similar risk score equations were derived using the four risk factors. As shown in Table 4, when patients were stratified by renal disease severity, either baseline proteinuria <2000 or ≥ 2000 mg/g (226 mg/mmol) or baseline serum creatinine <2 or ≥ 2 mg/dl (176.8 $\mu\text{mol/L}$), by gender, white or nonwhite race, and treatment group, the four parameters were almost independent risk factors for each subgroup even though the number of outcomes was reduced dramati-

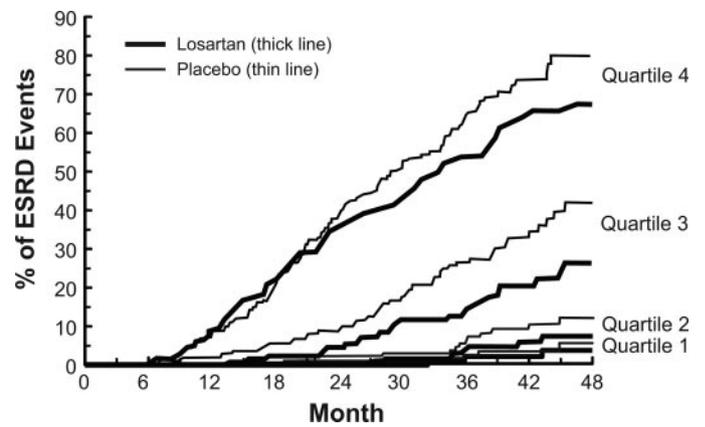


Figure 3. Kaplan-Meier curve for ESRD end point stratified by quartile of risk score and displaying treatment effects.

Quartile 1: HR 0.95 (95% CI 0.24 to 3.79), $P =$ not significant (NS).

Quartile 2: HR 0.43 (95% CI 0.19 to 0.98), $P = 0.044$.

Quartile 3: HR 0.51 (95% CI 0.33 to 0.79), $P = 0.003$.

Quartile 4: HR 0.81 (95% CI 0.62 to 1.06), $P =$ NS.

cally. The coefficients for each risk factor vary somewhat with subgroups, but the 95% confidence intervals overlap each other. In particular, the risk scores are very similar between losartan and placebo treatment groups.

Of the 1513 patients who were randomly assigned in RENAAL, 555 patients developed ESRD or died. The risk score for the composite end point of ESRD or death was as follows: Risk score (ESRD or death) = $(1.14 \times \log [\text{UACR}]) - (0.61 \times \text{serum albumin [g/dl]}) + (0.97 \times \text{serum creatinine [mg/dl]}) - (0.07 \times \text{hemoglobin [g/dl]}) + (0.08 \times \text{glycosylated hemoglobin [HbA}_{1c} \text{ %}])$ (Table 1). In this case, HbA_{1c} entered the model. The frequency table shows that the two risk scores are highly comparable in their abilities to predict outcomes (Table 5).

Discussion

In the RENAAL study of 1513 patients who had type 2 diabetes and nephropathy and in whom BP was treated aggressively, 341 patients developed ESRD. Independent risk factors

Table 3. Summary of risk factors by subgroups^a

Subgroup	n	Mean (Quartile Range: 25th to 75th Percentiles)			
		UACR (g/g) ^b	Serum Creatinine (mg/dl)	Serum Albumin (mg/dl)	Hemoglobin (g/dl)
UACR (g/g)					
<2	1012	0.7 (0.4 to 1.2)	1.8 (1.5 to 2.1)	3.9 (3.7 to 4.1)	12.8 (11.5 to 14.1)
≥ 2	501	3.5 (2.6 to 4.5)	2.0 (1.6 to 2.4)	3.5 (3.2 to 3.8)	12.0 (10.7 to 13.1)
Serum creatinine (mg/dl)					
<2	965	1.0 (0.5 to 2.1)	1.6 (1.4 to 1.8)	3.8 (3.6 to 4.1)	12.9 (11.7 to 14.1)
≥ 2	548	1.6 (0.8 to 3.1)	2.4 (2.2 to 2.6)	3.7 (3.5 to 4.0)	11.9 (10.6 to 13.1)

^aTo convert UACR in mg/g to mg/mmol, multiply by 0.113; serum creatinine in mg/dl to $\mu\text{mol/L}$, multiply by 88.4; hemoglobin in g/dl to g/L, multiply by 10; and serum albumin in mg/dl to g/L, multiply by 10.

^bGeometric mean for UACR.

Table 4. Risk score coefficients by subgroups

Subgroup	Risk Score Coefficients (95% CI)			
	Log (UACR)	Serum Creatinine (mg/dl)	Serum Albumin (mg/dl)	Hemoglobin (g/dl)
All patients	1.96 (1.55 to 2.38)	1.28 (1.07 to 1.49)	−0.78 (−1.09 to −0.48)	−0.11 (−0.18 to −0.04)
UACR (g/g)				
<2	1.29 (0.51 to 2.06)	1.47 (1.09 to 1.85)	−1.26 (−1.95 to −0.56)	−0.20 (−0.32 to −0.08)
≥2	1.90 (0.99 to 2.82)	1.18 (0.92 to 1.44)	−0.65 (−1.01 to −0.29)	−0.05 (−0.13 to 0.03)
Serum creatinine (mg/dl)				
<2	2.21 (1.55 to 2.86)	1.85 (0.97 to 2.74)	−0.54 (−1.05 to −0.03)	−0.13 (−0.24 to −0.01)
≥2	1.73 (1.19 to 2.27)	1.00 (0.61 to 1.38)	−0.93 (−1.32 to −0.54)	−0.10 (−0.18 to −0.02)
Gender				
male	2.09 (1.50 to 2.68)	1.12 (0.84 to 1.41)	−0.68 (−1.10 to −0.26)	−0.10 (−0.20 to −0.01)
female	1.74 (1.14 to 2.33)	1.65 (1.28 to 2.02)	−0.98 (−1.45 to −0.51)	−0.06 (−0.17 to 0.05)
Race				
white	1.94 (1.29 to 2.59)	1.40 (1.10 to 1.70)	−0.83 (−1.33 to −0.33)	−0.13 (−0.24 to −0.02)
nonwhite	1.96 (1.41 to 2.51)	1.17 (0.86 to 1.48)	−0.76 (−1.16 to −0.37)	−0.10 (−0.19 to −0.02)
Treatment				
losartan	2.07 (1.40 to 2.75)	1.27 (0.95 to 1.58)	−0.93 (−1.39 to −0.46)	−0.13 (−0.24 to −0.03)
placebo	1.93 (1.40 to 2.47)	1.33 (1.02 to 1.63)	−0.72 (−1.13 to −0.30)	−0.09 (−0.17 to −0.01)

for the development of ESRD were albuminuria, increased serum creatinine, hypoalbuminemia, and decreased hemoglobin level, which demonstrated that these nontraditional risk factors are important in patients with diabetic kidney disease. We present the relationship between the independent risk factors and developed a risk score to predict ESRD in patients with type 2 diabetes and kidney disease. This relationship was shown to be applicable to both genders, and it also was independent of ethnicity, initial level of BP, and treatment intervention. Patients with renal disease progression often die before reaching ESRD (5); therefore, we also examined the risk score for the composite end point of ESRD or death. It was compa-

rably effective in predicting outcome. HbA_{1c} entered the model when the risk score for the composite end point of ESRD or death was calculated.

Albuminuria is a critical baseline risk predictor for ESRD in this and other studies of patients with diabetic nephropathy (6,7). Level of albuminuria is the most important clinical marker for future renal events, and UACR should be monitored in all patients with diabetic nephropathy. In RENAAL, there was a nearly linear relationship between progression to ESRD and albuminuria at baseline and on treatment (6). However, the effect of treatment with losartan on albuminuria was responsible for only 50% of the effect of losartan on ESRD (6).

Table 5. Patient counts by deciles between ESRD risk score and ESRD or death risk score

Decile of ESRD Score ^a	Decile of Risk Score for ESRD or Death ^b									
	1	2	3	4	5	6	7	8	9	10
1	131	21	0	0	0	0	0	0	0	0
2	21	100	30	0	0	0	0	0	0	0
3	0	30	96	25	0	0	0	0	0	0
4	0	0	24	91	33	4	0	0	0	0
5	0	0	1	35	82	33	0	0	0	0
6	0	0	0	1	36	80	34	0	0	0
7	0	0	0	0	0	33	97	22	0	0
8	0	0	0	0	0	1	21	106	23	0
9	0	0	0	0	0	0	0	23	113	15
10	0	0	0	0	0	0	0	0	15	136

^aRENAAL ESRD risk score ($n = 341$) = $(1.96 \times \log [\text{UACR}]) - (0.78 \times \text{serum albumin [g/dl]}) + (1.28 \times \text{serum creatinine [mg/dl]}) - (0.11 \times \text{hemoglobin [g/dl]})$.

^bRENAAL ESRD/death risk score ($n = 555$) = $(1.14 \times \log [\text{UACR}]) - (0.61 \times \text{serum albumin [g/dl]}) + (0.97 \times \text{serum creatinine [mg/dl]}) - (0.07 \times \text{hemoglobin [g/dl]}) + (0.08 \times \text{HbA}_{1c} [\%])$.

The value of the RENAAL ESRD risk score is that it demonstrates that factors in addition to albuminuria predict ESRD: hypoalbuminemia, increased serum creatinine level, and decreased hemoglobin level. Although the four factors were correlated with each other, one still worked beyond the correlation and could not be fully predicted by the others. The inclusion of these factors improved the risk prediction for progression of nephropathy to ESRD from 50% with consideration of albuminuria alone to >80% when the risk score was used. Hypoalbuminemia worsens as renal function deteriorates (8) and may be related to albuminuria, inflammation, and nutrition. Low serum albumin at initiation of dialysis has been associated with increased morbidity and mortality in dialysis patients (9,10). As expected, the incidence of ESRD increased with increasing serum creatinine (e.g., 40.5% in the serum creatinine 2.1 to 3.6 mg/dl [185.6 to 318.2 $\mu\text{mol/L}$] tertile versus 7.3% in the 0.9 to 1.6 mg/dl [79.6 to 141.4 $\mu\text{mol/L}$] tertile) (11). Anemia is common in diabetic kidney disease and contributes to cardiovascular morbidity and mortality in patients with nephropathy (12,13). Anemia also was identified as an independent predictor for progression to ESRD in this study (14). Even mild anemia (<13.8 g/dl [138 g/L]) was associated with increased risk. After adjustment for known risk factors for ESRD, the average increase in relative risk was 11% for each 1 g/dl (10 g/L) decrease in hemoglobin concentration. The contribution of each factor on ESRD was robust regardless of whether patients were at low or high risk, as defined by either baseline proteinuria < or \geq 2000 mg/g (226 mg/mmol) or baseline serum creatinine < or \geq 2 mg/dl (176.8 $\mu\text{mol/L}$), also regardless of gender, white/non-white race, and treatment group. The four risk predictors for progression of kidney disease in the risk score were independent of therapy.

Control of hypertension is of primary importance in patients with diabetic nephropathy. Current guidelines state that the BP goal in patients with diabetes is \leq 130/80 mmHg. Because BP was treated aggressively and equivalent levels were achieved in both treatment groups in the RENAAL study, this may have resulted in our inability to identify BP as an independent risk factor in multivariate analyses. However, it is possible—but unlikely—that the lack of correlation may have been because hypertension was not associated with risk for ESRD.

Glycemic control is important in this population, and HbA_{1c} entered the model only when the risk score for the composite end point of ESRD or death was calculated. This is consistent with observations of other large observational studies that demonstrated a role for glycemic control in cardiovascular disease but not kidney disease (15).

Identifying covariates that are highly associated with outcome plays an important role in clinical trial design. In the International Conference on Harmonization guidelines, investigators are advised to identify the covariates that may influence the primary outcome and to prespecify the method to be used to account for them to compensate for any imbalance between groups (16). The risk score that combines the identified important covariates helps to avoid the use of multiple covariates to adjust for the treatment effect in statistical analyses. The

homogeneity of the treatment effect across severity of disease can be explored by using subgroup analysis of the risk score.

An important limitation of the risk score validation *via* examination of ESRD events by quartiles and deciles was that few events occurred in the lower quartiles and deciles. An additional important limitation was that this analysis used clinical trial data, and the same data from which score was derived to validate score; however, the outcome of the application of the jackknife procedure causes us to be optimistic about the broad applicability of this score. Because the risk score was derived from the Cox model using RENAAL baseline data, the absolute risk score may not be interpretable. The difference in risk score between patients suggests relative risks on the development of ESRD.

The RENAAL risk score for ESRD emphasizes the importance of identification of level of albuminuria, hypoalbuminemia, increased serum creatinine, and decreased hemoglobin level to predict the development of ESRD in patients with type 2 diabetes and nephropathy. Although albuminuria is a very strong predictor for ESRD, the contribution of serum albumin, serum creatinine, and hemoglobin level further enhances the prediction of ESRD. Future trials with a similar patient population and outcome measures as those of the RENAAL study should consider adjusting analyses for baseline risk factors.

Acknowledgments

This study was supported by Merck Research Laboratories, Merck & Co., Inc.

Preliminary results of these analyses were presented as a poster at the annual meeting of the American Society of Nephrology, November 1, 2002, Philadelphia, PA.

W.F.K., D.d.Z., J.-P.G., J.M., W.E.M., G.R., R.T., and B.M.B. were paid by Merck for their services as clinical investigators in this study and have served as consultants to the company. W.F.K., Z.Z., P.A.L., S.S., and S.M.S. are or have been employees of Merck and may own stock or hold stock options in the company.

References

1. Keane WF, Brenner BM, de Zeeuw D, Grunfeld JP, McGill J, Mitch WE, Ribeiro AB, Shahinfar S, Simpson RL, Snapinn SM, Toto R: The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL study. *Kidney Int* 63: 1499–1507, 2003
2. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
3. Brenner BM, Cooper ME, de Zeeuw D, Grunfeld JP, Keane WF, Kurokawa K, McGill JB, Mitch WE, Parving HH, Remuzzi G, Ribeiro AB, Schlachter MD, Snavely D, Zhang Z, Simpson R, Ramjit D, Shahinfar S: The losartan renal protection study: Rationale, study design and baseline characteristics of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan). *J Renin Angiotensin Aldosterone Syst* 1: 328–335, 2000
4. Tukey J: Bias and confidence in not quite large samples. *Ann Math Stat* 29: 614, 1958

5. Thomas MC, Cooper ME, Shahinfar S, Brenner BM: Dialysis delayed is death prevented: A clinical perspective on the RENAAL study. *Kidney Int* 63: 1577–1579, 2003
6. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65: 2309–2320, 2004
7. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
8. Wheeler DC, Townend JN, Landray MJ: Cardiovascular risk factors in predialysis patients: Baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study. *Kidney Int Suppl* 84: S201–S203, 2003
9. Shearer GC, Kaysen GA: Proteinuria and plasma compositional changes contribute to defective lipoprotein catabolism in the nephrotic syndrome by separate mechanisms. *Am J Kidney Dis* 37[Suppl 2]: S119–S122, 2001
10. Kalantar-Zadeh K, Kopple JD, Humphreys MH, Block G: Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. *Nephrol Dial Transplant* 19: 1507–1519, 2004
11. Remuzzi G, Ruggenti P, Perna A, Dimitrov BD, de Zeeuw D, Hille DA, Shahinfar S, Carides GW, Brenner BM: Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy. A post hoc analysis of the RENAAL trial results. *J Am Soc Nephrol* 15: 3117–3125, 2004
12. Hsu CY, McCullough CE, Curhan GC: Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: Results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* 13: 504–510, 2002
13. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ: Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 38: 955–962, 2001
14. Mohanram A, Zhang Z, Shahinfar S, Keane WF, Brenner BM, Toto RD: Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. *Kidney Int* 66: 1131–1138, 2004
15. Stratton IM, Adler AE, Neil AW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* 321: 405–412, 2000
16. International conference on harmonisation; guidance on statistical principles for clinical trials; availability—FDA Notice. *Fed Reg* 63: 49583–49598, 1998

See related editorial, “More Work to Do on Renin-Angiotensin System Blockade,” on pages 611–613.