Kidney International, Vol. 63 (2003), pp. 1499–1507

The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL Study

William F. Keane,[1] Barry M. Brenner,[2] Dick de Zeeuw,[3] Jean-Pierre Grunfeld,[4] Janet McGill,[5] William E. Mitch,[6] Artur B. Ribeiro,[7] Shahnaz Shahinfar,[8] Roger L. Simpson,[8] Steven M. Snapinn,[8] and Robert Toto,[9] for the RENAAL Study Investigators

Department of Medicine, Hennepin County Medical Center, University of Minnesota Medical School, Minneapolis, Minnesota; Department of Medicine, Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; Department of Clinical Pharmacology, University of Groningen, Groningen, The Netherlands; Service de Nephrologie, Hopital Necker, Paris, France; Department of Medicine, Division of Endocrinology, Washington University, St. Louis, Missouri; Department of Medicine, Renal Division, Emory University, Atlanta,Georgia; Department of Medicine, Nephrology Division, Hospital Do Rim E Hipertensao, São Paulo, Brazil; Merck Research Laboratories, Merck & Co., Inc., Whitehouse Station, New Jersey; and Department of Medicine, Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas

The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL Study.

Background. Diabetic nephropathy has become the single most important cause of end-stage renal disease (ESRD) worldwide. Strategies to slow the rate of loss of renal function in these patients have been developed. We examined the risk factors that predict loss of kidney function (doubling of serum creatinine) or ESRD (dialysis or transplantation) in patients with type 2 diabetes in whom blood pressure was controlled.

Methods. We evaluated risk factors for doubling of serum creatinine or the development of ESRD in the Reduction of End Points in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study, which included 1513 patients with type 2 diabetes and nephropathy.

Results. Univariate analyses demonstrated a group of 23 risk factors that significantly predicted doubling of serum creatinine or ESRD. From these univariate analyses, a multivariate model was developed that demonstrated four independent risk factors: proteinuria, serum creatinine, serum albumin, and hemoglobin level. Proteinuria was the strongest and most consistent risk factor. The multivariate risk model was derived from only the placebo group and was similar to that derived for the total population, suggesting that the risk predictors for progression of kidney disease were independent of therapy.

Conclusion. After control of blood pressure in type 2 diabetic patients with nephropathy, proteinuria, degree of renal failure, serum albumin, and hemoglobin level are independent risk factors that predict renal outcomes. The level of proteinuria proved to be the most important risk for progressive kidney injury in these diabetic patients.

[1] Dr. Keane's current address is Merck & Co., Inc., P.O. Box 4, HM-219, West Point, PA 19486-0004, USA.
[2] Dr. Brenner's current address is Department of Medicine, Renal Division, Brigham and Women's HosMRB 404, Boston, MA 02115, USA.
[3] Dr. deZeeuw's current address is Department of Clinical Pharmacology, University of Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen, The Netherlands.
[4] Dr. Grunfeld's current address is Service de Nephrologie, Hopital Necker, 149 Rue de Sevres, 75743 PARIS cedex 15, France.
[5] Dr. McGill's current address is Department of Medicine, Division of Endocrinology, Washington University, Campus Box 8127, 660 S. Euclid, St. Louis, MO 63110, USA.
[6] Dr. Mitch's current address is Department of Medicine, Renal Division, Emory University, WMB Rm. 338, 1639 Pierce Drive, Atlanta, GA 30322, USA.
[7] Dr. Ribiero's current address is Department of Medicine, Nephrology Division, Hospital Do Rim E Hipertensao, RUA Borges Lagoa 960, 04038-001 Sao Paulo SP Brazil.
[8] Dr. Shahinfar, Dr. Snapinn, and Mr. Simpson's current addresses are Merck Research Laboratories, Merck & Co., Inc., P.O. Box 4, Mail Stop BLX-21, West Point, PA 19486-0004, USA.
[9] Dr. Toto's current address is Department of Medicine, Division of Nephrology, University of Texas Southwestern, 5325 Harry Hines Blvd., Dallas, TX 75390-8856, USA.

Key words: type 2 diabetes, nephropathy, risk factors, RENAAL.

Received for publication August 17, 2002
and in revised form October 28, 2003
Accepted for publication November 25, 2002

Type 2 diabetes is one of the fastest growing epidemics. Worldwide, an estimated 146 million people have this disease, and by the year 2010 the prevalence is expected to increase twofold [1]. Patients with type 2 diabetes are characterized as having a high cardiovascular morbidity and mortality, particularly in those with albuminuria [2–4]. Nephropathy, which occurs in approximately one third of type 2 diabetic patients, is the single most important cause of end-stage renal disease (ESRD) [5, 6]. Indeed, diabetic nephropathy in both Western and Asian countries constitutes approximately 40% of new patients receiving renal replacement therapies [7]. In the United States, type 2 diabetic nephropathy is also the principal cause

of the increase in incidence and prevalence of ESRD [5]. Until recently, no study had evaluated interventions designed to reduce the risk of developing ESRD in type 2 diabetics with nephropathy [8, 9]. Results from the Reduction of End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study have revealed a significant benefit of losartan beyond blood pressure lowering on the primary composite end point of doubling serum creatinine (DsCr), ESRD (defined as dialysis or transplantation), or death [8]. Benefits were also observed for each of the individual renal end points. The database from this clinical study provides a unique opportunity to evaluate risk factors for the progression of nephropathy in 1513 type 2 diabetics with nephropathy followed for an average of 3.4 years.

In patients with type 1 diabetes and nephropathy, as well as in renal diseases not caused by diabetes, factors associated with the progressive loss of renal function have been identified in several prospective and cross-sectional studies [10–17]. Apart from glycemic control, hypertension, proteinuria, dyslipidemia, and smoking are among the most important modifiable risk factors. In addition, age, gender, and serum creatinine level have been identified as nonmodifiable risk factors that predict progression of kidney disease.

There are no large-scale studies defining risk factors for progression of kidney disease in patients with nephropathy attributed to type 2 diabetes [17]. In this report, we systematically evaluated baseline demographic, clinical, and laboratory factors to assess their relative impact on the progression of renal disease as determined by DsCr or development of ESRD in the RENAAL study.

METHODS

Study design

RENAAL was an investigator-initiated, multinational, double-blind, randomized study comparing losartan versus placebo, in addition to conventional antihypertensive therapy, excluding angiotensin-enzyme converting (ACE) inhibitors or other angiotensin II receptor antagonists. The study was performed in 28 countries and in 250 centers and involved 1513 patients. The study design, inclusion and exclusion criteria, and the treatment protocols have been reported [8, 18]. Participants were considered to have type 2 diabetes if they were over 30 years old at time of diagnosis of diabetes, had no history of diabetic ketoacidosis, and did not require insulin within 6 months of diagnosis. Nephropathy was diagnosed if the urinary albumin:creatinine (Alb:Cr) ratio was >300 mg/g or a 24-hour urine protein was >500 mg. At randomization, patients were stratified according to degree of albuminuria (<2000 mg/g or ≥2000 mg/g). A serum creatinine of 1.3 to 3.0 mg/dL (1.5 to 3.0 mg/dL in males >60 kg); a glycosylated hemoglobin A_{1c} (HbA_{1c}) <12%; and age between 31 and 70 years were part of the inclusion criteria. All patients signed informed consent prior to enrollment, and the study was approved by the local Institutional Review Board of each participating center. After a 6-week run-in period, patients were randomized to treatment with losartan or placebo, and followed up for a mean of 3.4 years.

Before randomization, baseline blood biochemical studies were measured, and urine was obtained for determination of Alb:Cr ratio. All measurements were performed in a central laboratory. Trough blood pressure was measured three times in a sitting position after a resting period of at least 5 minutes and before ingestion of antihypertensive medications. The average of these measurements was recorded, and the mean arterial pressure was calculated as diastolic arterial pressure + 1/3(systolic arterial pressure − diastolic arterial pressure). Pulse pressure, an index of vascular compliance, was calculated as the difference between systolic and diastolic blood pressures. Glomerular filtration rates (GFR_{est}) were estimated for each patient using the Modification of Diet in Renal Disease (MDRD) formula [19], and expressed as GFR_{est} per 1.73 m^2 of body surface area.

The primary outcome measure of the RENAAL study was a composite end point of time-to-first event of DsCr or ESRD, or death from any cause. An independent, blinded end point committee adjudicated all clinical end points according to rigorous predefined guidelines. The combined end point used in the present analyses is DsCr or ESRD.

Statistical methods

Statistical Analysis System version 8 software was used for all analyses. Baseline differences between genders and among ethnic groups, and the interactions between gender and ethnic groups, were analyzed using ANOVA (analysis of variance models), and *P* values (unadjusted for multiplicity) were calculated. Potential risk factors (including baseline clinical, demographic, and laboratory data) were then assessed for association with the composite end point of ESRD or DsCr.

For each of the 29 baseline characteristics (all 16 routine laboratory parameters and 13 important demographic variables, chosen a priori), a univariate proportional hazards regression model was used to estimate the relative risk (i.e., the hazard ratio) and its 95% confidence interval. Variables that failed to have a significant effect were eliminated before developing multivariate models. For those laboratory variables that demonstrated substantial co-linearity (such as total serum cholesterol and low-density lipoprotein cholesterol) only one variable was included in the multivariate analyses. A multivariate analysis was then performed using a Cox regression model with a stepwise selection process, including all remaining variables, to identify those with independent

effects on the prespecified end points; a P value <0.01 was required for a variable to be added to the model and to remain in the model. Patients with missing data were excluded from the analysis. Urinary Alb:Cr was logarithmically transformed, and patients were censored at the time of death. Once the full regression model was determined, each independent risk factor was divided into quartiles, the hazard ratios relative to the lowest-risk quartile were computed, and the event rates in the quartiles were plotted using the Kaplan-Meier approach [20].

RESULTS

Baseline clinical, demographic, and laboratory data in the different ethnic groups by gender

Data presented here are for the pooled treatment groups. The multivariate risk model was derived from only the placebo group and was similar to that derived for the total population, suggesting that the risk predictors for progression of kidney disease were independent of therapy. In addition, the set of coefficients associated with the four selected variables did not differ significantly between the treatment groups ($P = 0.26$).

The RENAAL study provided a unique opportunity to compare baseline characteristics of various ethnic groups by gender. There were 956 men and 557 women, reflecting the male gender predominance of this disorder. The average age was 60.3 ± 7.3 years and 60.0 ± 7.5 years for men and women, respectively, proportioned as 735 Caucasians, 277 Hispanics, 252 Asians, 230 Blacks, and 19 subjects of other ethnic groups. Table 1 presents the baseline laboratory and clinical variables stratified by ethnic group and gender, along with P values for differences among ethnic groups and P values for differences between genders. There were no significant interactions between ethnic group and gender, except as noted in the table footnote. Several important demographic and clinical differences were evident among the various groups. The urinary Alb:Cr ratio tended to be highest in Hispanics and Asians, and lowest in Black patients; white blood cell counts also tended to be lower in Blacks. Within each ethnic group, clinical and laboratory parameters tended to be more abnormal in women. Except for Asian women, body mass index was higher in women, consistent with a greater prevalence of obesity. Systolic, diastolic, and pulse pressures; insulin use; degree of proteinuria; and levels of serum cholesterol and triglycerides were higher in women. Despite higher insulin usage, the degree of glycemic control tended to be worse in females. Smoking varied among gender and ethnic origin, and more Asian and Hispanic men smoked compared with women. Thus, at baseline, women appeared to have clinical and laboratory manifestations of type 2 diabetes and nephropathy that were more abnormal than those of men. Nonetheless, we determined that the impact of baseline risk factors on ESRD or DsCr was similar between genders and among ethnic groups (data not shown); therefore, we developed the risk model for the whole study population.

In a subset of patients ($N = 710$) in this study, 24-hour urine protein was also determined during the baseline period. The relationship between this 24-hour protein excretion rate and the measured urinary Alb:Cr ratio (on a morning specimen) was then calculated. Because proteinuria is not normally distributed, data were log-transformed prior to analyses, and then back-transformed to the original scale. The equation that best defined the relationship is 24-hour protein excretion = $8.9(\text{Alb:Cr})^{0.79}$. The Spearman correlation coefficient was 0.9 ($P < 0.0001$). Thus, urinary Alb:Cr ratio was highly correlated with 24-hour protein excretion rate, and was a clinically useful measure of proteinuria in these patients.

Univariate analysis of risk predictors for renal outcomes

By univariate analysis, we evaluated 29 categorical and continuous variables; 23 were found to have a significant impact on the development of the renal end points in the study population. There were no major gender-based differences or ethnic group differences when the combined or individual renal end points were evaluated by univariate analysis (data not shown). Therefore, we pooled all patients and focused our analysis on risk factors for the combined renal endpoints of DsCr or ESRD (Table 2).

In our univariate model, proteinuria, the degree of kidney dysfunction and anemia, and serum phosphorus and albumin levels were strong predictors of DsCr or ESRD. Dyslipidemia also was associated with a greater hazard for development of a renal end point. Systolic blood pressure, but not diastolic blood pressure, had modest but significant effect on development of the renal end points. Similarly, mean arterial pressure and, to a greater degree, pulse pressure had a significant effect on the renal end points. However, it should be recognized that in the RENAAL study blood pressures were aggressively treated (target <140/90 mm Hg), and the design compared losartan-based conventional antihypertensive therapy to placebo plus conventional antihypertensive treatment. When each of the risk factors was divided into quartiles, the effects of the risks were graded and continuous.

Multivariate analysis of risk predictors for renal outcomes

From univariate analysis, we built a multivariate model using only the significant covariates and eliminating variables that demonstrated co-linearity (Table 3). In addition, we excluded GFR_{est} when constructing this model because calculation of GFR_{est} included many of the variables that were of interest in our risk predictions. As in the univariate analyses, we observed no important gender or ethnic differences in covariates that significantly impacted on the development of the DsCr or ESRD end point. The influ-

Table 1. Baseline clinical demographic and laboratory parameters in various ethnic groups by gender

Variable	Asian ($N = 252$)		Black ($N = 230$)		Hispanic ($N = 277$)		Caucasian ($N = 735$)		P value for ethnic differences	P value for gender differences
	Male ($N = 171$)	Female ($N = 81$)	Male ($N = 136$)	Female ($N = 94$)	Male ($N = 149$)	Female ($N = 128$)	Male ($N = 492$)	Female ($N = 243$)		
Age *years*	59 (7.4)	60 (7.1)	59 (7.9)	59 (7.4)	58 (7.7)	60 (7.3)	61 (7.3)	61 (7.2)	< 0.001	$= 0.23$
Body mass index[a] kg/m^2	25 (4.0)	25 (5.3)	30 (5.4)	35 (6.3)	27 (5.7)	30 (7.3)	30 (5.2)	33 (6.4)	< 0.001	< 0.001
Insulin use %	49	57	55	76	53	63	61	75	< 0.001	< 0.001
Smoking[a] *<1 year*	28	5	21	19	21	9	19	15	$= 0.39$	< 0.001
Sitting systolic blood pressure *mm Hg*	149 (17.1)	158 (22.0)	149 (18.8)	152 (18.3)	148 (19.7)	153 (19.2)	153 (18.5)	158 (20.4)	< 0.001	< 0.001
Sitting diastolic blood pressure *mm Hg*	82 (10.9)	80 (10.4)	84 (11.7)	81 (9.9)	83 (9.9)	82 (8.9)	83 (10.5)	82 (10.5)	$= 0.54$	$= 0.009$
Mean arterial pressure *mm Hg*	104 (10.9)	106 (12.2)	105 (11.7)	105 (10.9)	105 (11.2)	106 (10.5)	106 (11.1)	107 (11.9)	$= 0.1$	$= 0.16$
Pulse pressure *mm Hg*	66 (16.1)	78 (19.5)	65 (17.9)	71 (16.3)	65 (17.6)	71 (17.2)	70 (17.0)	76 (17.7)	< 0.001	< 0.001
Urine Alb:Cr (mean) *mg/g*	1819 (1524)	2580 (2395)	937 (843)	1623 (1432)	2307 (1665)	2659 (2218)	1591 (1511)	1986 (1778)	< 0.001	< 0.001
Alb:Cr (median) *mg/g*	1356	2129	686	1278	1473	2075	1068	1403	< 0.001	< 0.001
Serum albumin *g/dL*	3.8 (0.5)	3.8 (0.4)	3.8 (0.4)	3.6 (0.4)	3.7 (0.5)	3.6 (0.5)	3.9 (0.4)	3.8 (0.4)	< 0.001	< 0.001
Serum creatinine *mg/dL*	1.9 (0.4)	1.9 (0.5)	1.9 (0.4)	1.8 (0.5)	1.9 (0.5)	1.8 (0.5)	1.9 (0.5)	1.8 (0.5)	$= 0.25$	< 0.001
Glomerular filtration rate *mL/min/1.73* m^2	40 (10.3)	34 (10.5)	44 (9.9)	39 (11.5)	42 (11.6)	37 (11.6)	44 (11.8)	38 (11.3)	< 0.001	< 0.001
Serum cholesterol										
Total *mg/dL*	220 (49.7)	246 (50.3)	213 (49.7)	237 (56.6)	223 (49.5)	254 (58.8)	216 (53.9)	244 (57.3)	$= 0.005$	< 0.001
LDL *mg/dL*	140 (47.7)	153 (47.5)	133 (46.4)	148 (50.2)	144 (42.6)	158 (51.3)	135 (41.8)	148 (44.2)	$= 0.004$	< 0.001
HDL *mg/dL*	44 (15.3)	52 (18.8)	48 (13.6)	53 (15.1)	41 (12.1)	48 (17.2)	40 (12.1)	49 (15.8)	< 0.001	< 0.001
Serum triglycerides *mg/dL*	197 (159.2)	230 (217.3)	163 (114.1)	176 (102.1)	21.6 (194.4)	242 (140.7)	221 (188.6)	255 (245.2)	< 0.001	$= 0.005$
Serum calcium *mg/dL*	3.8 (0.6)	9.4 (0.6)	9.4 (0.5)	9.4 (0.5)	9.3 (0.5)	9.3 (0.6)	9.4 (0.5)	9.5 (0.5)	$= 0.002$	$= 0.006$
Serum phosphorus *mg/dL*	3.8 (0.6)	4.3 (0.6)	3.7 (0.6)	4.1 (0.7)	4.0 (0.7)	4.3 (0.6)	3.7 (0.6)	4.1 (0.6)	< 0.001	< 0.001
White blood count[a] mm^3	7.4 (1.8)	7.2 (1.5)	6.2 (2.4)	7.0 (2.1)	7.5 (2.9)	7.3 (1.8)	7.6 (1.9)	7.6 (2.0)	< 0.001	$= 0.46$
PMN %	65 (8)	66 (8)	59 (11)	60 (9)	65 (8.2)	64 (9)	65 (8)	63 (11)	< 0.001	$= 0.027$
Hemoglobin *g/dL*	12.8 (1.9)	11.1 (1.6)	12.6 (1.6)	11.0 (1.3)	12.9 (1.9)	11.7 (1.7)	13.3 (1.6)	12.0 (1.6)	< 0.001	< 0.001
Serum uric acid *mg/dL*	6.8 (1.6)	6.8 (1.7)	7.0 (1.6)	7.0 (1.7)	7.0 (1.9)	6.5 (1.7)	6.7 (1.6)	6.3 (1.7)	$= 0.006$	$= 0.002$
Glycosylated hemoglobin %	8.1 (1.4)	8.2 (1.5)	8.9 (1.8)	8.9 (1.6)	8.7 (1.8)	9.0 (1.9)	8.2 (1.5)	8.5 (1.5)	< 0.001	$= 0.036$

Abbreviations are: Alb:Cr, albumin creatinine ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PMN, polymorphonuclear leukocytes.

[a] A significant interaction occurred between gender and ethnic grouping with regard to body mass index, smoking, and white blood cell counts. Females consistently demonstrated greater body mass index across all races except Asians. Asian and Hispanic men are more likely to smoke than women, while Black and Caucasian men and women smoke at similar rates. Men in all ethnic groups, except Caucasians, had lower white blood cell counts, while both African American men and women had the lowest white blood cell counts.

Table 2. Univariate analysis for renal end points of doubling serum creatinine (DsCr) or end-stage renal disease (ESRD) ($N = 1513$)

Variable (unit of measure for hazard ratio calculation)	Hazard ratio[a]	95% CI	*P* value
Age (per 10 years)	0.74	0.66–8.3	<0.0001
Male gender (male or female)	0.67	0.56–0.80	<0.0001
Ethnicity (relative to Caucasian)			
Asian	1.6	1.3–2.1	<0.0001
Black	1.04	0.8–1.4	~0.8
Hispanic	1.8	1.5–2.3	<0.0001
Other	2.7	1.5–4.8	<0.0009
Body mass index *kg/m²*	0.98	0.96–0.99	0.008
Sitting systolic blood pressure (per 10 mm Hg)	1.14	1.09–1.19	<0.0001
Sitting diastolic blood pressure (per 10 mm Hg)	1.07	0.99–1.17	~0.1
Pulse pressure *mm Hg*	1.01	1.01–1.02	<0.0001
Mean arterial pressure *mm Hg*	1.02	1.01–1.03	<0.0001
Smoking (<1 year)	1.04	0.82–1.31	<0.75
Insulin use (yes or no)	1.4	1.13–1.64	~0.001
Serum creatinine *mg/dL*	2.9	2.5–3.4	<0.0001
GFR_{est} *mL/min/1.73 m²*	0.94	0.93–0.95	<0.0001
Urine Alb:Cr *log*	13.4	10.2–17.6	<0.0001
Serum albumin (per 0.5 g/dL)	0.40	0.37–0.44	<0.0001
Total cholesterol (per 100 mg/dL)	1.9	1.3–1.6	<0.0001
LDL cholesterol (per 50 mg/dL)	1.4	1.21–1.40	<0.0001
HDL cholesterol *mg/dL*	1.0	0.99–1.01	0.67
Triglycerides (per log mg/dL)	1.7	1.2–2.4	0.002
Lp(a) (per log mg/dL)	1.004	1.002–1.007	0.0008
Calcium *mg/dL*	0.34	0.28–0.40	<0.0001
PO_4 *mg/dL*	2.1	1.8–2.4	<0.0001
Hemoglobin *mg/dL*	0.75	0.71–0.80	<0.0001
WBC *mm³*	1.06	1.03–1.09	0.0005
WBC, PMN %	1.02	1.01–1.03	0.001
HgA_{1C} %	1.01	0.95–1.06	0.85
Uric acid *mg/dL*	1.01	0.96–1.06	0.79

Abbreviations are: CI, confidence interval; Alb:Cr, albumin creatinine ratio; GFR_{est} estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein(a) WBC, white blood count; PMN, polymorphonuclear leukocytes; PO_4, phosphate; HgA_{1C}, glycosylated hemoglobin.

[a] Hazard ratio, change in risk per unit of measure. Hazard ratios >1 indicate increasing risk with increasing parameter value (i.e., increasing proteinuria and/or increasing serum creatinine); hazard ratios <1 indicate decreasing risk with increasing parameter value (i.e., decreasing serum albumin and/or hemoglobin).

(Log) data were logarithmically transformed prior to analysis.

Table 3. Multivariate analysis for doubling serum creatinine (DsCr) or end-stage renal disease (ESRD) ($N = 1300$ patients with available data)

	Hazard ratio[a]	95% Confidence interval	*P* value
Urine albumin:creatinine *log*, *mg/g*	6.2	4.4–8.7	<0.0001
Serum creatinine *mg/dL*	2.1	1.7–2.5	<0.0001
Serum albumin (per 0.5 g/dL)	0.70	0.61–0.80	<0.0001
Hemoglobin *g/dL*	0.89	0.84–0.95	=0.0001

[a] Hazard ratios >1 indicate increasing risk with increasing parameter value (i.e., increasing proteinuria and/or increasing serum creatinine); hazard ratios <1 indicate decreasing risk with increasing parameter value (i.e., decreasing serum albumin and/or hemoglobin).

ence of these risk factors specifically on the DsCr or ESRD are presented as Kaplan-Meier curves (Fig. 1) for the entire study population.

From the 23 significant variables noted on univariate analyses, only four had a significant, independent impact on the development of the renal end points (Table 3). Of note, proteinuria was the most important for achieving the renal end points, as measured both by the chi-square value associated with each variable and by the hazard ratios associated with the highest risk relative to the lowest risk quartiles for each variable. The influence of proteinuria was striking. Individuals in the highest quartile developed DsCr or ESRD within 6 to 12 months after initiation of the study. By 48 months, the Kaplan-Meier event rate approached 80% (Fig. 1). The degree of renal dysfunction, as measured by the serum creatinine level, also predicted those who were at greater risk for the combined renal endpoint. In individuals with entry serum creatinine of >2.1 mg/dL, over 60% reached a renal end point during follow-up (Fig. 1). The relationship between the development of a renal end point and severity of functional impairment at baseline reflects, in part, that the disease in these individuals is progressing at a rapid rate. Lower hemoglobin and lower serum albumin were significant and independent risk factors for DsCr or ESRD. As shown in Figure 1, even a modest degree of anemia was associated with increased risk for renal outcomes. Individuals who had normal hemoglobin (>13.8 g/dL) demonstrated a Kaplan-Meier event rate for DsCr or ESRD that was approximately 20%, whereas those with a hemoglobin of <11.2 g/dL demonstrated a Kaplan-Meier event rate for DsCr or ESRD that approximated 60% (Fig. 1).

In the RENAAL study, blood pressure was aggressively treated both at baseline and throughout the study (requiring on average 3.6 agents in addition to study drug) to levels of approximately 140/75 mm Hg in the losartan or placebo treatment arms. Thus, it is not surprising that blood pressure per se did not show a major and independent effect on renal outcomes.

DISCUSSION

Data presented here are for the pooled treatment groups. The multivariate risk model was derived from only the placebo group and was similar to that derived for the total population, suggesting that the risk predictors for progression of kidney disease were independent of therapy. In addition, the set of coefficients associated with the four selected variables did not differ significantly between the treatment groups ($P = 0.26$). Thus, to increase the robustness of our analyses, the entire population was used in this analysis.

It is noted that we have excluded death as an end point in this analysis, which requires us to assume that death is noninformative with respect to renal end points. That is, we have to assume that, had they lived, patients who died would have had renal end points at the rate predicted by

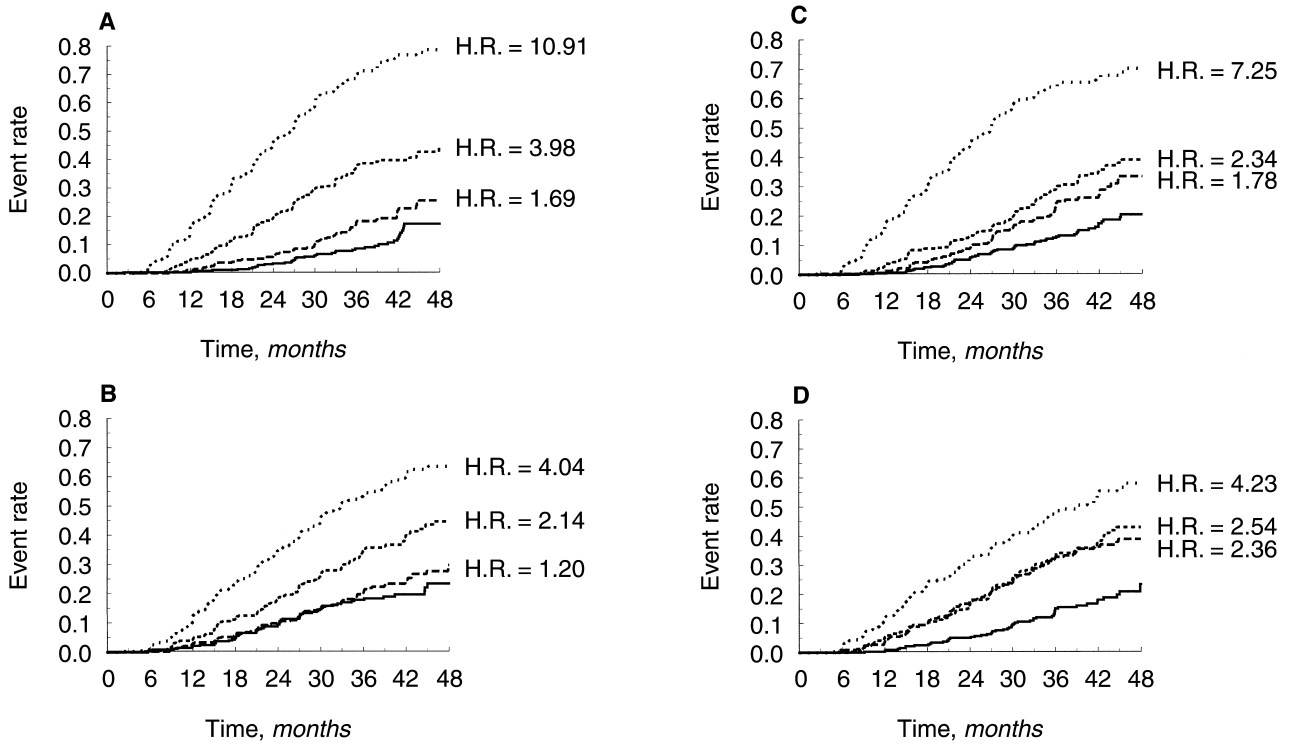

Fig. 1. Kaplan-Meier estimates of event rate for doubling serum creatinine (DsCr) or end-stage renal disease (ESRD) stratified by quartiles. (*A*) Baseline urine albumin creatinine (Alb:Cr) ratio. The hazard ratio (HR) for each quartile was calculated and compared with that of the patients with the lowest values, who are in the reference quartile with a HR of 1.0. (—), Reference value Alb:Cr ratio >2.6 or >4.4 g protein/24 hours; (—), Alb:Cr ratio of 1.2 to 2.6 or 2.4 to 4.4 g protein/24 hours; (—), Alb:Cr ratio of 0.56 to 1.1 or 1.3 to 2.3 g protein/24 hours; (···), Alb:Cr ratio of <0.56 or <1.3 g protein/24 hours. (*B*) Baseline serum creatinine. The HR for each quartile was calculated and compared with that of the patients with the lowest values, who are in the reference quartile with a HR of 1.0. (—), Reference value of serum creatinine >2.1 mg/dL; (—), serum creatinine 1.8 to 2.1 mg/dL; (—), serum creatinine 1.5 to 1.7 mg/dL; (···), serum creatinine <1.5 mg/dL). (*C*) Baseline serum albumin. The HR for each quartile was calculated and compared with that of the patients with the highest values, who are in the reference quartile with a HR of 1.0. (···), Reference value of serum albumin <3.6 g/dL; (—), serum albumin 3.6 to 3.8 g/dL; (—), serum albumin 3.9 to 4.0 g/dL; (—) serum albumin >4.0 g/dL. (*D*) Baseline hemoglobin. The HR for each quartile was calculated and compared with that of the patients with the highest values, who are in the reference quartile with a HR of 1.0. (···), Reference value of hemoglobin <11.2 g/dL; (—), hemoglobin 12.4 to 11.2 g/dL; (—), hemoglobin 13.8 to 12.5 g/dL; (—), hemoglobin >13.8 g/dL.

their baseline data. There is no way of knowing whether or not this assumption is true, a limitation of this analysis. The risk factors for death are quite different than the risk factors for renal end points. For example, the most powerful risk factor for death is age, which is not a risk factor for renal end points.

The principal new finding of this study is that baseline urine Alb:Cr ratio is the most powerful independent predictor of DsCr or ESRD in type 2 diabetic patients with nephropathy. This relationship was applicable to both genders and all ethnic groups. In addition, this effect persisted independent of the level of blood pressure. Our findings regarding the predictive power of proteinuria confirm and expand on observational studies in the Pima Indians and other populations [2–4, 7, 14, 21–23]. In these studies, proteinuria was also a powerful predictor of ESRD. Our findings extend this observation to a larger, ethnically diverse population followed carefully in a clinical trial over an average of 3.4 years. Because of the size and long-term follow-up of our study cohort, we were able to show that proteinuria is the most powerful predictor of a renal event. This finding is of great importance because proteinuria is easily quantifiable by measuring the urinary Alb:Cr ratio, and is a modifiable risk factor in type 2 diabetics with nephropathy. Unfortunately, many type 2 diabetic patients who undergo clinical examination with blood pressure and serum creatinine measurement do not have urine protein or albumin measured [24]. We found that in clinical practice the level of urine Alb:Cr ratio is the most important clinical marker for future renal events. Therefore, urine Alb:Cr ratio should be measured in all type 2 diabetic patients, whether normotensive or hypertensive.

In addition to proteinuria and level of renal dysfunction, our results demonstrated that two other independent risk factors contributed to the development of DsCr or ESRD: anemia and hypoalbuminemia. Although the reduction in serum albumin can be explained, in part, by the magnitude of proteinuria, other factors (e.g., inflammation and nutrition) may also contribute to this reduction in serum albumin. In this regard, the relation-

ship of slightly higher total white blood cell count (and specifically polymorphonuclear neutrophil counts) to the combined renal end point is of interest, suggesting a potential role for inflammation [25, 26]. Recent studies have shown that a low serum albumin and hemoglobin at the time of initiation of renal replacement therapy is also associated with increased morbidity and mortality [27, 28]. Our multivariate analyses reveal that these four risk factors were of paramount importance in explaining achievement of renal outcomes.

Several potentially important risk factors identified on univariate analysis (such as age, gender, ethnicity, blood pressure, and lipids) failed to be significantly associated with the progression of renal disease in the multivariate analyses. In this model, male gender had a lower risk and younger age had a higher risk of progression of kidney disease. However, considering the more severe disease present in women, this gender difference was not present on multivariate analyses (Table 3). Similarly, although Asians and Hispanics, relative to Caucasians, had a greater risk for a renal end point, proteinuria was more severe in these populations.

Although our data indicated that blood pressure failed to achieve significance in the multivariate analyses, the reasons for this are complex. It is known that elevated blood pressure, particularly systolic blood pressure, increases the risk for development of ESRD [7, 29–33]. As indicated in the univariate analyses, there was a significant effect of blood pressure on renal outcomes. It is possible that our inability to identify blood pressure as an independent risk factor on multivariate analyses was because blood pressure was aggressively treated in most patients at the time of entry into the study and following randomization. Thus, although baseline blood pressure was not an independent predictor of renal outcomes, controlling blood pressure is critically important because it is well established that the cardiovascular risk from hypertension is much greater in patients with diabetes compared with those without the disease across a wide range of blood pressures [7, 30–33]. For these reasons, we believe it is absolutely essential to lower blood pressure to a level of $<$130 mm Hg systolic and $<$80 mm Hg diastolic, as promulgated by the National Kidney Foundation [34].

Similarly, elevated total serum cholesterol and low-density lipoprotein cholesterol were evident in patients in this study and adversely impacted renal outcomes on univariate analyses. Considering the strong relationship between proteinuria and elevated cholesterol levels, it is not surprising that this risk is overwhelmed by the impact of proteinuria alone.

A potentially important risk that failed to demonstrate statistical significance was the HbA_{1c} level at entry. Most of the patients in this study did not have optimal glycemic control at entry, but that this did not predict achievement of an adverse renal end point is consistent with some, but not all, recent reports in type 2 diabetes [17, 35–38]. On the other hand, our finding that a modest degree of anemia in type 2 diabetic patients with nephropathy affects the progression of kidney disease is novel. Although the mechanism whereby anemia might influence progression of kidney disease is currently unknown, altered oxygen delivery to the interstitial structures of the kidney, and changes in cardiac function could potentially be of importance [39, 40]. The availability of agents to treat anemia in these patients may benefit renal outcomes [41–43]; however, it is not known whether anemia may be a nonmodifiable consequence of more severe renal disease.

CONCLUSION

Proteinuria is the single most powerful predictor of adverse renal outcomes in association with progression of nephropathy in patients with type 2 diabetes and nephropathy. Because proteinuria is not reflected in routine laboratory testing unless urinalysis is performed, it is imperative that it be assessed in all type 2 diabetic patients to identify those at risk for progressive renal disease. The availability of the urinary Alb:Cr ratio as a diagnostic test provides an important opportunity to further improve the prognosis of individuals with type 2 diabetes and nephropathy.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Paulette A. Lyle for assistance with the manuscript and to Deanna Gunderson and Lisa Lee for manuscript preparation.

Conflict of interest statement: Grant support was provided by Merck & Co., Inc. This investigator-initiated study was supported by Merck Research Laboratories, Merck & Co., Inc. Dr. Keane, Dr. Brenner, Dr. de Zeeuw, Dr. Grunfeld, Dr. McGill, Dr. Mitch, Dr. Ribeiro, and Dr. Toto were paid by Merck for their services as clinical investigators in this study and have served as consultants to the company. During the conduct of this study, Dr. Toto was the recipient of an NIH Mid-Career Investigator Award, DK 02818-01A1. Mr. Simpson and Dr. Keane, Dr. Snapinn, and Dr. Shahinfar have been employees of Merck and may own stock or hold stock options in Merck. Dr. Keane recently joined Merck as an employee.

Reprint requests to William F. Keane, M.D., Merck & Co., Inc., P.O. Box 4, HM-219, West Point, PA 19486-0004.
E-mail: williamf_keane@merck.com.

APPENDIX

Independent Steering Committee: B.M. Brenner (Chairman and Principal Investigator), M.E. Cooper, D. de Zeeuw, J.P. Grunfeld, W.F. Keane, K. Kurokawa, J. McGill, W. E. Mitch, H-H. Parving, G. Remuzzi, A. B. Ribeiro, M. Schluchter.

Independent Data Safety Monitoring Committee: C.E. Mogensen (Chairman), M. Fifer, L. Fisher, P. Kowey, D. Schlondorff, G. Viberti, P. Whelton.

Independent End Point Committee: S. Haffner (Chairman), J. Carrozza, D. Kolansky, L. Raij, D. Sica, R. Toto.

Primary Investigators: ***Argentina*** *(17 patients):* F. Inserra, L. Juncos; ***Austria*** *(15 patients):* C. Gurdet, J.R. Patsch, H. Toplak; ***Brazil*** *(58*

patients): S. Silveiro, V. Woronik, T. Zanella; ***Canada*** *(1 patient):* E. Burgess, T.C. Monchesky; ***Chile*** *(26 patients):* F. González; ***Costa Rica*** *(33 patients):* M. Vinoccour; ***Czech Republic*** *(33 patients):* P. Boucek, R. Chlup, J. Olsovsky, P. Sifalda; ***Denmark*** *(16 patients):* P. Christensen; ***France*** *(12 patients):* T. Hannedouche, P. Passa, M. Rodier; ***Germany*** *(12 patients):* B. Boehm, H.-D. Bundschu, U. Leonhardt; ***Hong Kong*** *(92 patients):* J. Chan, K. Lam; ***Hungary*** *(10 patients):* S. Sonkodi; ***Israel*** *(37 patients):* D.J. van Dijk; ***Italy*** *(26 patients):* G. Piras, G. Remuzzi, F. Santeusanio; ***Japan*** *(96 patients):* R. Abe, Y. Ando, T. Fujita, T. Hanafusa, M. Haneda, T. Haneda, Y. Hashimoto, T. Ida, Y. Iino, S. Ishibashi, S. Ito, H. Kakuta, M. Kanazawa, T. Kanda, M. Kasuga, M. Kato, T. Koike, H. Kurahachi, H. Kuzuya, K. Matoba, D. Nagasaku, K. Ohshiro, K. Okada, S. Owada, H. Sakai, J. Seino, C. Shigemasa, T. Shoji, Y. Tsubakihara, N. Ujihara, N. Ura, T. Watanabe, I. Yamaji, Y. Yamasaki, M. Yoshinari, N. Yoshioka; ***Malaysia*** *(21 patients):* C.T. Chua, Z. Morad; ***Mexico*** *(67 patients):* R. Correa, J. Herrera; ***New Zealand*** *(3 patients):* R. Scott; ***Peru*** *(42 patients):* R. Zavala; ***Portugal*** *(10 patients):* B. Carvalho; ***Russia*** *(26 patients):* M. Shestakova, G. Zalevskaya; ***Singapore*** *(11 patients):* K. S. Wong; ***Slovak Republic*** *(2 patients):* M. Pavlovic; ***Spain*** *(67 patients):* J.M. Bronsons, M.M. Campos Pastor, D. del Castillo-Caba, F. Diz-Lois, F. Escobar-Jiménez, M.T. Gonzalez-Alvarez, D. Lorenzo, A. Martínez-Castelao, J.M. Martínez García, A. Tejedor-Jorge, M. Valles-Prats; ***The Netherlands*** *(7 patients):* J-E. Heeg, R. Gansevoort, P.L. Rensma; ***United Kingdom*** *(56 patients):* C. Fox, E. Hillhouse, M. MacLeod, M. MacMahon, J. Mclay, P. O'Hare, V. Patel, H. Tindall, J.P. Vora, J.U. Weaver; ***United States*** *(686 patients):* S. Abramson, J.R. Allison III, J. Anderson, G. Appel, M. Avram, G. Bakris, Y. Barri, J. Beard, D. Bell, J. Benabe, R. Benedetti, W. Bennett, W.K. Bolton, J.P. Brennan, M. Broder, M. Cabezas-Mijuste, D. Calhoun, A. Carr, L. Chan, B. Chandler, Jr., G. Chao, D. Chapman, J. Chinn, J. Christensen, J. Chung, C. Clinkingbeard, G. Collins, C. Corder, D. Crittenden, P. Dandona, M. Davis, R. DeFronzo, V. DeQuattro, G. Dolson, J. Douglas, M. Doyle, M. Eckert-Norton, A. Edin, M. El Shahawy, D. Elson, J.G. Evans, G. Fain III, T. Ferguson, J. Fica, C. Fisher, D. Fitz-Patrick, D. Frid, R. Galagan, L. Gaudiani, J. Geohas, M. Goldberg, R. Goldberg, J. Gorkin, R. Goulah, R. Graf, M. Greenspan, A. Guasch, C. Guerin, N. Gupta, C.E. Guthrow, S. Haffner, J. Hamilton, L.L. Hamm, L. Hancock, J. Hawkins, K. Hershon, W. Herzog, J. Holtzman, J. Insel, G. Jilly, L. Jovanovic, L. Katz, G. Kaysen, G. Keightley III, D. Kereiakes, G. Kershaw, B. Kerzner, R. Khairi, C. Kilo, M. Kipnes, R. Kipperman, L. D. Knoll, W. Kraus, J. Lash, J. LeLevier, S. Lerman, F.M. Lester, B. Levine, R. Louard, K. Ma, R. Maddox, D. Mapel, S. Martin, R. Mayfield, J. McGill, J.F. McNeer, J. Miller, S. Miller, B. Miskin, M. Mohan, T. Mooney, B. Musa, P. Nachman, A. Nafziger, J. Nardandrea, Jr., M. Nunēz, L. Olansky, P. Pagnozzi, J. Pappas, T. Parker, T. Patel, B. Phillipson, J. Pino, D. Pitts, P. Raskin, P. Reber, E. Reisin, J. Ringold, V. Roberts, D. Roh, J. Rosenstock, N. Rossi, E. Rubin, L. Rubin, D. Ruff, M. Salem, R. Santangelo, Y. Segal, K.S. Self, S. Sharma, J. Sloand, L. K. Smith, R. Solomon, C. Spellman, B. Spinowitz, D. Steward, W. Suki, S. Swan, A. Swislocki, M. Tonkon, R. Toto, N.D. Vaziri, S. Vicks, J. Villamizar, R. Vranian, T. Walden, F. Wei, M. Weinberg, M. Weir, C. Williamson, L. Wruble, W. Yeung, F. Ziel,; ***Venezuela*** *(31 patients):* A. Perez, J. Weisinger.

Coordinating Center, Merck Research Laboratories: S. Shahinfar (Study Director); R. Simpson, D. Ramjit, S. Thompson-Bell, B. McVan, D. Fong, R. Poston, G. Drucker, M. McFadden-Neyer, M. Hinz, C. Assang, D. Brown, S. Mereminsky, C. Curry, G. McPeters, B. Bertino (Program Coordinators); J. Lorfing, B. Koslowski, C. Wagner, C. Arena (International Liaisons); S. Snapinn, Z. Zhang, H. Zhang, C. White, A. Carides, D. Snavely (Statisticians); D. Wolf, J. Sickel, C. Shanahan, K. Morgan, S. Plourde (Data Coordinators); B. Vanslembrouck, (Clinical Supply Coordinator).

Request for Single Reprints: William F. Keane, M.D., Merck & Co., Inc., P.O. Box 4, HM-219, West Point, PA 19486-0004, USA. E-mail, williamf_keane@merck.com.

REFERENCES

1. Amos AF, McCarty DJ, Zimmet P: The rising global burden of diabetes and its complications: Estimates and projections to the year 2010. *Diabet Med* 14(Suppl 5):S1–S85, 1997
2. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–360, 1984
3. Jarrett RJ, Viberti GC, Argyropoulos A, *et al*: Microalbuminuria predicts mortality in non-insulin-dependent diabetics. *Diabet Med* 1:17–19, 1984
4. Schmitz A, Vaeth M: Microalbuminuria: a major risk factor in non-insulin-dependent diabetes. A 10-year follow-up study of 503 patients. *Diabet Med* 5:126–134, 1988
5. USRDS: Annual Data Report, Chapter 2. Incidence and Prevalence of ESRD. *Am J Kidney Dis* 34:540–550, 1999
6. Ritz E, Rychlik I, Locatelli F, Halimi S: End-stage renal failure in type 2 diabetes, a medical catastrophe of worldwide dimensions. *Am J Kidney Dis* 34:795–808, 1999
7. Ismail N, Becker B, Strzelczyk P, *et al*: Renal disease and hypertension in non-insulin-dependent diabetes mellitus. *Kidney Int* 55:1–28, 1999
8. Brenner BM, Cooper ME, de Zeeuw D, *et al*: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
9. Lewis EJ, Hunsicker LG, Clarke WR, *et al*: 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
10. Peterson JC, Adler S, Burkart JM, *et al*: Blood pressure control, proteinuria and the progression of renal disease. *Ann Intern Med* 123:754–762, 1995
11. Hunsicker LG, Adler S, Caggiula A, *et al*: Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 51:1908–1919, 1997
12. Breyer JA, Bain RP, Evans JK, *et al*: Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. The Collaborative Study Group. *Kidney Int* 50:1651–1658, 1996
13. Hovind P, Rossing P, Tarnow L, *et al*: Progression of diabetic nephropathy. *Kidney Int* 59:702–709, 2001
14. Ruggenenti P, Perna A, Gherardi G, *et al*: Chronic proteinuric nephropathies: Outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am J Kidney Dis* 35:1155–1165, 2000
15. Goldschmid MG, Domin WS, Ziemer DC, *et al*: Diabetes in urban African-Americans. II. High prevalence of microalbuminuria and nephropathy in African-Americans with diabetes. *Diabetes Care* 18:955–961, 1995
16. Prospective Diabetes Study UK: (UKPDS). IX: Relationships of urinary albumin and N-acetylglucosaminidase to glycaemia and hypertension at diagnosis of type 2 (non-insulin-dependent) diabetes mellitus and after 3 months diet therapy. *Diabetologia* 36:835–842, 1993
17. Ravid M, Savin H, Lang R, *et al*: Proteinuria, renal impairment, metabolic control, and blood pressure in type 2 diabetes mellitus. A 14-year follow-up report on 195 patients. *Arch Intern Med* 152:1225–1229, 1992
18. Brenner BM, Cooper ME: 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
19. Levey AS, Bosch JP, Lewis JB, *et al*: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130:461–470, 1999
20. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481, 1958
21. Ballard DJ, Humphrey LL, Melton LJ, *et al*: Epidemiology of persistent proteinuria in type II diabetes mellitus. Population-based study in Rochester, Minnesota. *Diabetes* 37:405–412, 1988
22. Nelson RG, Newman JM, Knowler WC, *et al*: Incidence of end-stage renal disease in Type 2(non-insulin-dependent) diabetes mellitus in Pima Indians. *Diabetologia* 31:730–736, 1988
23. Nelson RG, Pettitt DJ, Carraher MJ, *et al*: Effect of proteinuria on mortality in NIDDM. *Diabetes* 37:1499–1504, 1988
24. McClellan WM, Knight DF, Karp H, *et al*: Early detection and treatment of renal disease in hospitalized diabetic and hypertensive

patients: Important differences between practice and published guidelines. *Am J Kidney Dis* 29:368–375, 1997
25. Phillips AN, Neaton JD, Cook DG, *et al*: Leukocyte count and risk of major coronary heart disease events. *Am J Epidemiol* 136:59–70, 1992
26. Stenvinkel P, Heimburger O, Paultre F, *et al*: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55:1899–1911, 1999
27. 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 (1 Suppl 2):S119–S122, 2001
28. Keane WF, Collins AJ: Influence of comorbidity on mortality and morbidity in patients treated with hemodialysis. *Am J Kidney Dis* 24:1010–1018, 1994
29. Adler AI, Stratton IM, Neil HA, *et al*: Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. *BrMed J* 321:412–419, 2000
30. Klag MJ, Whelton PK, Randall BL, *et al*: Blood pressure and end-stage renal disease in men. *N Engl J Med* 334:13–18, 1996
31. Hansson L, Zanchetti A, Carruthers SG, *et al*: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998351:1755–1762, 1998
32. Yusuf S, Sleight P, Pogue J, *et al*: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342:145–153, 2000
33. Heart OPE: (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355:253–259, 2000
34. Bakris GL, Williams M, Dworkin L, *et al*: Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 36:646–661, 2000
35. Christensen PK, Rossing P, Nielsen FS, *et al*: Natural course of kidney function in type 2 diabetic patients with diabetic nephropathy. *Diabet Med* 16:388–394, 1999
36. Ruggenenti P, Gambara V, Perna A, *et al*: The nephropathy of non-insulin-dependent diabetes: Predictors of outcome relative to diverse patterns of renal injury. *J Am Soc Nephrol* 9:2336–2343, 1998
37. Nosadini R, Velussi M, Brocco E, *et al*: Course of renal function in type 2 diabetic patients with abnormalities of albumin excretion rate. *Diabetes* 49:476–484, 2000
38. Nelson RG, Bennett PH, Beck GJ, *et al*: Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. Diabetic Renal Disease Study Group. *N Engl J Med* 335:1636–1642, 1996
39. Silverberg DS, Wexler D, Blum M, *et al*: The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 35:1737–1744, 2000
40. Fine LG, Bandyopadhay D, Norman JT: Is there a common mechanism for the progression of different types of renal diseases other than proteinuria? Towards the unifying theme of chronic hypoxia. *Kidney Int* 57 (Suppl 75):S22–S26, 2000
41. Collins AJ, Ma JZ, Xia A, *et al*: Trends in anemia treatment with erythropoietin usage and patient outcomes. *Am J Kidney Dis* 32(6 Suppl 4):S133–S141, 1998
42. Kuriyama S, Tomonari H, Yoshida H, *et al*: Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 77:176–185, 1997
43. Jungers P, Choukroun G, Oualim Z, *et al*: Beneficial influence of recombinant human erythropoietin therapy on the rate of progression of chronic renal failure in predialysis patients. *Nephrol Dial Transplant* 16:307–312, 2001