Kidney International, Vol. 67, Supplement 93 (2005), pp. S48–S51

Baseline predictors of end-stage renal disease risk in patients with type 2 diabetes and nephropathy: New lessons from the RENAAL Study

SHAHNAZ SHAHINFAR, TANYA DICKSON, ZHONGXIN ZHANG, WILLIAM F. KEANE, BARRY M. BRENNER, FOR THE RENAAL INVESTIGATORS

Merck Research Laboratories, West Point, Pennsylvania; Clinical Product Development, Merck and Co. Inc., West Point, Pennsylvania; and Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

Treatment of diabetic nephropathy represents a significant economic burden, one that currently cannot be met in many regions in the world. The incidence of diabetes in the United States and Europe continues to rise, while regions such as Asia, the Pacific, and Latin America are facing a pandemic [1]. These regions do not have the medical or financial resources necessary to face this burden. In addition, present knowledge of the risk factor(s) that contribute to progressive diabetic nephropathy is limited. Therefore, the ability to identify those patients at high risk of end-stage renal disease (ESRD), and the power to focus therapeutic modalities to delay the progression to ESRD, are severely lacking.

The RENAAL study represents a large repository of clinical information that allows a greater understanding of nephropathy in patients with type 2 diabetes. The RENAAL study was initiated to investigate the long-term renal protective role of losartan in patients ($N = 1513$) with type 2 diabetes and nephropathy [defined as urinary albumin to creatinine ratio of 300 mg/g and serum creatinine values greater than 1.3 mg/dL (female) and 1.5 mg/dL (male)]. Patients were randomized to either losartan or placebo, with additional antihypertensive medications added until the goal blood pressure of <140/90 mm Hg was reached. Patients were followed for a mean of 3.4 years. The population of RENAAL was ethnically diverse, with Asians accounting for 17%, blacks 15%, Hispanics 18%, and whites 48% of the patients. The study demonstrated that losartan, compared with placebo, significantly reduced the incidence, and delayed the time to the composite outcome of a doubling of serum creatinine concentration (DSCr), ESRD (defined as the need for dialysis or transplantation), or death (risk reduction 16%, $P = 0.02$) [2]. RENAAL also demonstrated for the first time that blockade of angiotensin II by losartan delayed ESRD and the composite end point of ESRD or death in these patients [2]. It is estimated that the reduction in ESRD risk observed in the RENAAL study corresponds to a 2-year delay in the need for dialysis or transplantation [2], and represents a net reduction in treatment costs of US $3522 per patient over 3.5 years [3].

In an effort to identify those risk factors associated with the progression of renal disease in patients with type 2 diabetes, analysis of 29 prespecified baseline characteristics was performed [4, 5]. Analyses revealed that baseline proteinuria (urine albumin:creatinine ratio) is the strongest risk factor for ESRD, followed by baseline serum creatinine (SCr) and baseline hemoglobin [4]. Current findings for the baseline factors associated with increased risk for ESRD and their role in different ethnic groups from the RENAAL study are presented here.

Baseline serum creatinine and the risk for ESRD

Assessment of renal function is critical in determining the rate of renal disease progression, and the most commonly used method is measurement of SCr. As expected, multivariate analyses of RENAAL data demonstrated that baseline SCr was highly predictive of increased risk of developing either a renal event (DSCr or ESRD) or ESRD alone [4, 5]. SCr was also a good predictor of ESRD in all ethnic groups (Fig. 1A). Losartan reduced the risk of ESRD regardless of baseline level of renal impairment (Fig. 1B). Patients with baseline SCr levels ≥2.0 mg/dL similarly benefited from losartan therapy to patients with baseline SCr levels <2.0 mg/dL. This would suggest that losartan treatment should be considered in patients with type 2 diabetes and nephropathy, even in those with more advanced renal disease.

Key words: end-stage renal disease, RENAAL, creatinine.

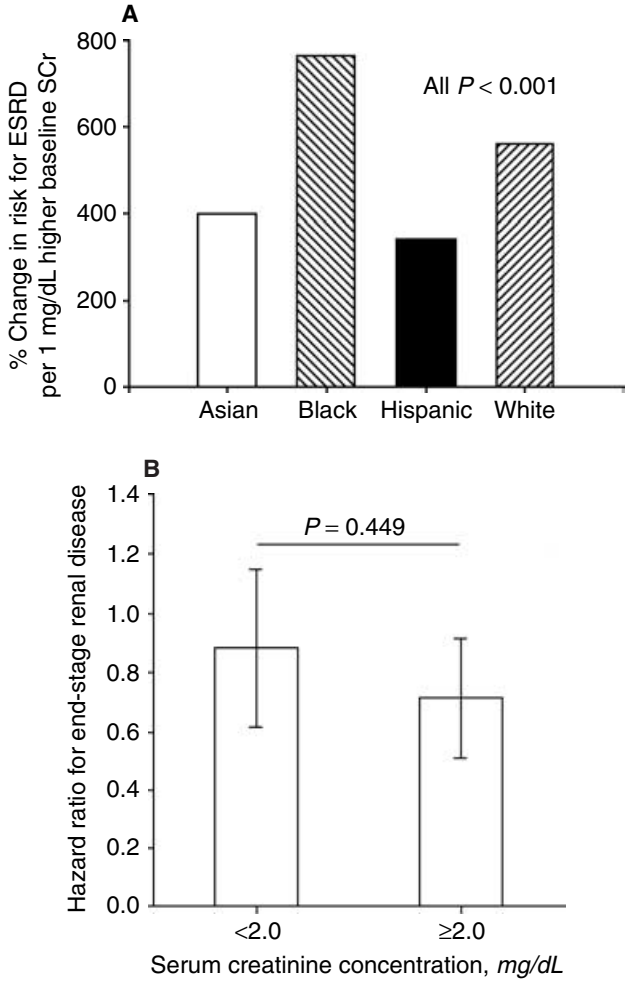

Fig. 1. Risk of end-stage renal disease associated with baseline serum creatinine. (*A*) For each 1 mg/dL increase in baseline serum creatinine the following risk increase was observed (univariate analysis). (*B*) Treatment effect of losartan vs. placebo by baseline serum creatinine.

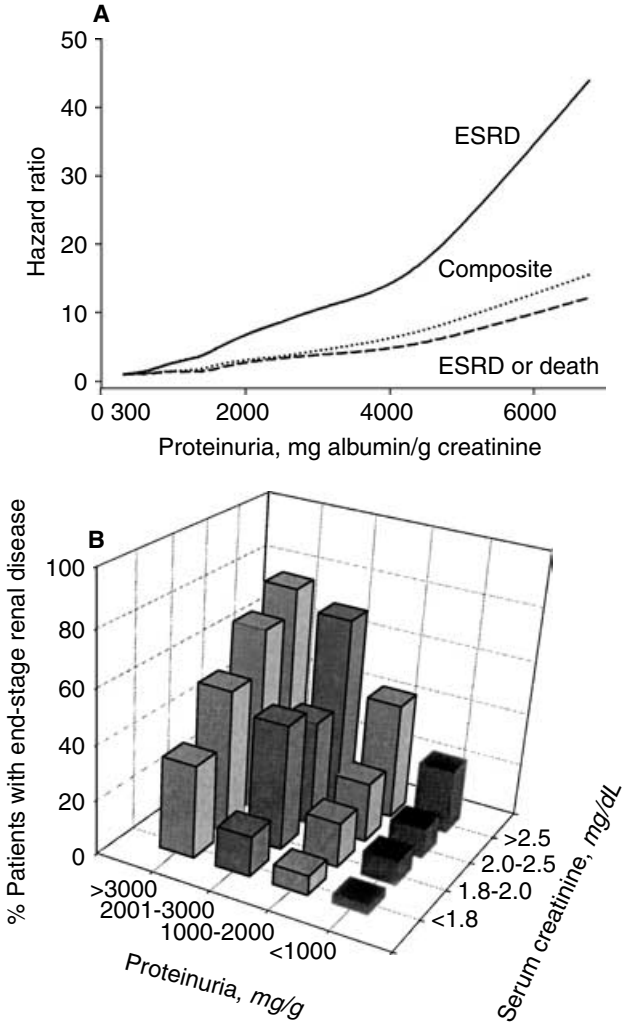

Fig. 2. Relationship between increasing baseline proteinuria and renal outcome (*A*). Independence of baseline proteinuria with serum creatinine in predicting the development of end-stage renal disease (*B*).

Baseline proteinuria and the risk for ESRD

The level of proteinuria at baseline was highly predictive of the primary composite end point, ESRD alone and ESRD or death (Fig. 2A). In addition, baseline proteinuria was shown to be the strongest risk predictor for ESRD in Asians, blacks, Hispanics, and whites (de Zeeuw, personal communication). In the RENAAL study, baseline proteinuria was as predictive of ESRD as was baseline SCr (Fig. 2B). To evaluate whether modification of this important risk factor by losartan was associated with changes in outcome, de Zeeuw et al [4] demonstrated that the reduction of proteinuria with losartan during the initial 6 months of therapy in RENAAL was a good predictor of ESRD outcome.

In the RENAAL study, losartan was associated with a 35% mean reduction in proteinuria ($P < 0.001$) [2]. The reduction of proteinuria was observed across all ethnic groups (de Zeeuw, personal communication), and was greater than the reduction in proteinuria observed for the placebo group. While reduction of proteinuria is associated with a decrease in risk of developing ESRD, it does not fully account for the treatment effect of losartan on reducing ESRD in the RENAAL study [6]. Only ~50% of the risk reduction for ESRD was attributable to a decrease in proteinuria [6], suggesting that additional factors contribute to ESRD.

Baseline hemoglobin and the risk of ESRD

Anemia is common among patients with type 2 diabetes and nephropathy. Small studies have shown that low hemoglobin levels are predictive of risk for progression of diabetic and nondiabetic nephropathy [7, 8]. In the RENAAL study, baseline hemoglobin concentrations ranged from 6.8 g/dL to 18.0 g/dL, with a mean and standard deviation of 12.5 ± 1.8 g/dL. Analysis of the

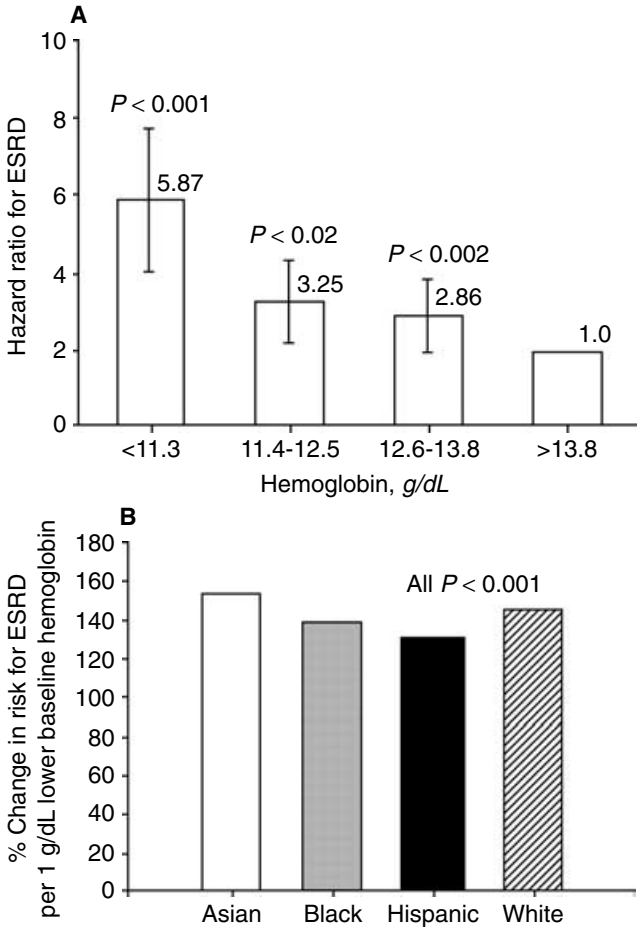

Fig. 3. Risk of end-stage renal disease (ESRD) associated with baseline hemoglobin (univariate analysis). (*A*) Risk of end-stage renal disease by baseline quartile of hemoglobin. (*B*) For each 1 g/dL decrease in hemoglobin the following increase in risk was observed for each ethnic group.

RENAAL study revealed that baseline hemoglobin was an independent predictor of ESRD [9] and of renal events (DScR or ESRD) [5]. Patients with lower baseline hemoglobin concentrations had a greater prevalence of ESRD events, independent of their renal function and proteinuria levels, and the risk associated with hemoglobin levels increased as hemoglobin concentration decreased (Fig. 3A) [9]. In addition, baseline hemoglobin was a good predictor of ESRD in all ethnic groups (Fig. 3B).

Additional risk factors associated with ESRD

Reduction of blood pressure (BP) is recognized as an important mechanism in delaying the progression of renal disease [10]. The RENAAL study adopted a BP goal of ≤140/90 mm Hg based on current, applicable guidelines at the time of study inception. Multivariate analysis demonstrated that baseline BP was not an independent risk factor for the development of ESRD in the RENAAL study. However, baseline BPs of ≤140/90 mm Hg were associated with decreased risk of ESRD, lending support to a relationship between lower BP and reduced ESRD risk [11].

Losartan was demonstrated to reduce the risk of ESRD regardless of whether goal BP was achieved (risk reduction 28%, $P = 0.002$) [11]. Nonetheless, in those patients who achieved a goal systolic BP of <140 mm Hg, losartan treatment was associated with a 34% risk reduction ($P = 0.03$) [11]. These data highlight that achieving goal BP is important; however, blockade of angiotensin II by losartan provides additional benefit over blood pressure reduction alone.

Studies in animal models suggest a relationship between hyperlipidemia and progression of renal disease [12]. In addition, small studies in humans allude to a potential role for hyperlipidemia in progressive renal disease [13, 14]. Baseline low-density lipid cholesterol (LDL) was associated with an increased risk of developing ESRD in the RENAAL study [15]. This effect was most apparent in patients whose baseline LDL was >167 mg/dL (HR 2.48, $P < 0.001$) [15]. While these data are tantalizing, further elucidation of the role of hyperlipidemia, either as a primary risk or as a correlated factor with proteinuria, in the progression of renal disease is required.

CONCLUSION

RENAAL is the first study to demonstrate that angiotensin II antagonism with losartan is renal protective by delaying the onset of ESRD in patients with type 2 diabetes and nephropathy. Baseline proteinuria, serum creatinine, and hemoglobin were identified as independent predictors of increased risk of ESRD in all patients, regardless of ethnic origin. The similar risks seen in ethnically diverse patients, and the positive treatment effect of losartan, suggest that losartan therapy may be an important part of the treatment strategy for patients with type 2 diabetes and nephropathy. Additionally, the projected delay in the need for dialysis or transplantation, and the reduction in patient treatment costs associated with losartan, has major socioeconomic importance, particularly in countries were renal replacement therapies are limited.

Reprint requests to Dr. Shahnaz Shahinfar, P.O. Box 4, BLX-21, West Point, PA 19486.
E-mail: shahnaz_shahinfar@merck.com

REFERENCES

1. World Health Organization Statistics: 2000 report.
2. Brenner BM, Cooper ME, de Zeeuw D, *et al*, for the Renaal Study Investigators: 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. Herman WH, Shahinfar S, Carides GW, *et al*: Losartan reduces the costs associated with diabetic end-stage renal disease: The RENAAL study economic evaluation. *Diabetes Care* 26:683–687, 2003
4. de Zeeuw D, Remuzzi G, Parving H-H, *et al*: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65:2309–2320, 2004
5. Keane WF, Brenner BM, de Zeeuw D, *et al*: 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
6. Shahinfar S, Dickson TZ, Ahmed T, *et al*, for the RENAAL Study Investigators: Losartan in patients with type 2 diabetes and proteinuria: Observations from the RENAAL Study. *Kidney Int* 62:S64–S67, 2002
7. 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
8. The US Recombinant Human Erythropoietin Predialysis Study Group: Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients. *Am J Kidney Dis* 18:50–59, 1991
9. Mohanram A, Zhang Z, Shahinfar S, *et al*: Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. *Kidney Int* 66:1131–1138, 2004
10. 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. *BMJ* 321:412–419, 2000
11. Bakris GL, Weir MR, Shanifar S, *et al*: Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAAL study. *Arch Intern Med* 163:1555–1565, 2003
12. Wheeler DC: Lipids: What is the evidence for their role in progressive renal disease? *Nephrol Dial Transplant* 12:19–21, 1997
13. Sammuelson O, Attman P, Knight-Gibson C, Alaupovic P: Complex apolipoprotein B containing lipoprotein particles are associated with a higher rate of progression of human chronic renal insufficiency. *Am J Soc Nephrol* 9:1482–1488, 1998
14. Washiio M, Okuda S, Ikeda M, *et al*: Hypercholesterolemia and the progression of renal dysfunction in chronic renal failure patients. *J Epidemiol* 6:172–177, 1996
15. Appel GB, Radhakrishnan J, Avram MM, *et al*, for the RENAAL Study Investigators: Analysis of metabolic parameters as predictors of risk in the RENAAL study. *Diabetes Care* 26:1402–1407, 2003