Analysis of Metabolic Parameters as Predictors of Risk in the RENAAL Study

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OBJECTIVE — Metabolic factors such as glycemic control, hyperlipidemia, and hyperkalemia are important considerations in the treatment of patients with type 2 diabetes and nephropathy. In the RENAAL (Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan) study, losartan reduced renal outcomes in the patient population. This post hoc analysis of the RENAAL study reports the effects of losartan on selected metabolic parameters and assesses the relationship between baseline values of metabolic parameters and the primary composite end point or end-stage renal disease (ESRD).

RESEARCH DESIGN AND METHODS — Glycemic control (HbA_{1c}) and serum lipid, uric acid, and potassium levels were compared between the losartan and placebo groups over time, and baseline levels were correlated with the risk of reaching the primary composite end point (doubling of serum creatinine, ESRD, or death) or ESRD alone.

RESULTS — Losartan did not adversely affect glycemic control or serum lipid levels. Losartan-treated patients had lower total (227.4 vs. 195.4 mg/dl) and LDL (142.2 vs. 111.7 mg/dl) cholesterol. Losartan was associated with a mean increase of up to 0.3 mEq/l in serum potassium levels; however, the rate of hyperkalemia-related discontinuation was similar between the placebo and losartan groups. Univariate analysis revealed that baseline total and LDL cholesterol and triglyceride levels were associated with increased risk of developing the primary composite end point. Similarly, total and LDL cholesterol were also associated with increased risk of developing ESRD.

CONCLUSIONS — Overall, losartan was well tolerated by patients with type 2 diabetes and nephropathy and was associated with a favorable effect on the metabolic profile of this population.

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Abbreviations: AIIA, angiotensin II receptor antagonist; ESRD, end-stage renal disease; Lp(a), lipoprotein a; RAAS, renin-angiotensin-aldosterone system; RENAAL, Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The significant socioeconomic burden of type 2 diabetic nephropathy associated with its eventual progression to end-stage renal disease (ESRD) has prompted the search for effective treatment (1,2). Within the last few years, three large clinical trials have addressed the role of angiotensin II receptor antagonists (AIIAs) and the therapeutic use of specific blockade of the renin-angiotensin-aldosterone system (RAAS) in these patients (3–5). The RENAAL (Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan) trial was a randomized double-blind study comparing the AIIA losartan with placebo, which were both taken in addition to conventional antihypertensive treatment. Losartan conferred a significant benefit on the primary renal end point, a composite of doubling of serum creatinine, ESRD, or all-cause death (risk reduction 16.1%, $P = 0.02$). In particular, losartan reduced the risk of progression to ESRD by 28.6% ($P = 0.002$) and ESRD or death by 19.9% ($P = 0.01$). The RENAAL study is the first to demonstrate that specific blockade of the RAAS reduces the incidence of ESRD in patients with type 2 diabetes and nephropathy.

Strict glycemic and lipid control has been associated with positive outcomes in patients with type 2 diabetes and nephropathy (6). Given the positive treatment effects of losartan in this patient population, it is important to assess the impact of losartan treatment on metabolic profile. This post hoc analysis investigated the effect of losartan versus placebo on long-term glycemic control and serum potassium, uric acid, and lipid levels, as well as the relationship between these baseline metabolic factors and the composite primary outcome or ESRD alone.

RESEARCH DESIGN AND METHODS

— The RENAAL study design, inclusion and exclusion criteria, treatment regimen, and baseline patient data have been reported elsewhere (3,7). Patients were stratified according to baseline proteinuria and, after a 6-week screening period, randomized to receive losartan (50 mg titrated to 100 mg once

daily) or placebo. Open-label antihypertensive medication (calcium channel blockers, diuretics, α- and β-blockers, and centrally acting agents) were added if trough sitting blood pressure did not reach the goal of <140/90 mmHg. The study population consisted of 1,513 patients of both sexes, aged 31–70 years.

Laboratory measurements

Clinical and laboratory evaluations were conducted at baseline and every 3 months. Laboratory measurements included (but were not limited to) HbA_{1c}, total, LDL, and HDL cholesterol, triglycerides, uric acid, and serum potassium. Lipoprotein a [Lp(a)] levels were measured only at baseline and at 1 year in 100% of the patients in the U.S., 25% of patients in Europe, and 15% of patients in Asia. Chemistry tests were performed after an overnight fast of ~8 h. A central laboratory analyzed blood and urinary specimens (albumin/creatinine levels).

Statistical analyses

Selected baseline characteristics were compared between the placebo and losartan groups using a χ^2 test (for discrete variables) or a *t* test (for continuous variables). The relationship between baseline metabolic variables and the primary composite end point or ESRD alone was examined by pooling the data from both arms of the study. The composite end point was examined using the time-to-first-event principle, and only the first event was counted in the analysis. A univariate analysis was performed on each baseline variable using a Cox regression model that was adjusted for region. The hazard ratio for each baseline variable and its 95% CI were calculated. A hazard ratio >1 indicates increasing risk of reaching the end point with increasing values of the variable. A *P* value <0.05 was considered statistically significant. All statistical tests were two sided. For the variables found to be significant in the univariate analysis, the hazard ratios were examined graphically by quartile. For this analysis, the first quartile served as the base of comparison. Serum triglycerides were log transformed for the hazard ratio analysis.

RESULTS

Baseline characteristics

At baseline, no differences were observed between the losartan and placebo groups for age, BMI, sex, or smoking (3). At baseline, similar percentages of patients in the losartan and placebo groups were receiving insulin (61.4 vs. 58.9%, *P* = NS), oral antidiabetic agents (48.1 vs. 50.0%, *P* = NS), and lipid-lowering agents (36.5 vs. 36.1%, *P* = NS). Most patients in both treatment groups had poor glycemic control, with ~81% of patients in both groups having HbA_{1c} levels >7% (8) (Table 1). About one-third of patients had baseline total cholesterol levels within the recommended range of <200 mg/dl, whereas one-third of patients had baseline total cholesterol levels >240 mg/dl (Table 1). Only 13.8% of patients taking losartan and 12.5% of patients on placebo had HDL cholesterol levels >60 mg/dl, as recommended by the Adult Treatment Panel III (9) (Table 1). Approximately half of the patients had high LDL cholesterol (>130 mg/dl; losartan 49.9% and placebo 50.7%) and one-third triglyceride levels >200 mg/dl (losartan 35.6% and placebo 38.7%) (Table 1).

Table 1—*Analysis of baseline metabolic status and the number of patients in predefined ranges*

Laboratory characteristic	Losartan (*n* = 751)	Placebo (*n* = 762)
HbA_{1c} (%)		
<7	132 (17.6)	138 (18.1)
7–9	375 (49.9)	374 (49.1)
9–12	213 (28.4)	224 (29.4)
>12	22 (2.9)	18 (2.4)
Total cholesterol (mg/dl)		
<200	253 (33.7)	248 (32.5)
200–240	242 (32.2)	236 (31.0)
>240	248 (33.0)	271 (35.6)
HDL cholesterol (mg/dl)		
<40	337 (44.9)	345 (45.3)
40–60	298 (39.7)	312 (40.9)
>60	104 (13.8)	95 (12.5)
LDL cholesterol (mg/dl)		
<130	301 (40.1)	297 (39.0)
130–160	186 (24.8)	175 (23.0)
160–190	104 (13.8)	116 (15.2)
>190	85 (11.3)	95 (12.5)
Triglycerides (mg/dl)		
<200	476 (63.4)	460 (60.4)
200–500	230 (30.6)	254 (33.3)
>500	37 (4.9)	41 (5.4)

Data are *n* (%). Ranges predefined by American Diabetes Association (8) and Adult Treatment Panel III (9) guidelines.

Changes in metabolic profile during RENAAL

Table 2 shows the mean levels of HbA_{1c}, lipids, serum uric acid, and serum potassium over the course of the RENAAL study. Neither treatment group showed significant changes in HbA_{1c} values. In both groups, total cholesterol levels were elevated at baseline and decreased at the last follow-up. At 12 and 36 months, total cholesterol was significantly lower in the losartan group compared with the placebo group despite equivalent use of lipid-lowering medication (Table 2). Although LDL cholesterol levels decreased in both treatment groups, the losartan group showed greater numerical decreases and the difference between groups was statistically significant at 12 months (losartan 126.07 mg/dl vs. placebo 134.01 mg/dl, $P < 0.05$). At baseline, HDL cholesterol levels were almost identical for the losartan and placebo groups, and modest but similar decreases were observed in both groups (Table 2). Baseline triglyceride levels were also similar between the two groups, and no significant change was observed over time (Table 2). Baseline Lp(a) levels were significantly higher in the losartan group than in the placebo group ($P < 0.05$), and there was no significant change in the levels of Lp(a) in either group at the final 1-year analysis (Table 2). Although losar-

Table 2—*Changes in metabolic parameters from baseline values over time*

	Treatment time (months)				
	Baseline	12	24	36	Last
HbA_{1c} [% (*n*)]					
Losartan	8.53 (742)	8.54 (629)	8.55 (498)	8.33 (285)	8.36 (171)
Placebo	8.43 (754)	8.53 (604)	8.51 (465)	8.36 (238)	8.47 (129)
Total cholesterol [mg/dl (*n*)]					
Losartan	227.42 (743)	213.50 (644)*	205.32 (523)	196.39 (310)*	195.42 (74)
Placebo	228.69 (755)	225.43 (637)	211.47 (500)	207.33 (271)	205.17 (52)
HDL [mg/dl (*n*)]					
Losartan	45.20 (739)	45.91 (639)	45.19 (521)*	42.40 (311)	41.36 (74)
Placebo	44.92 (752)	47.60 (633)	47.31 (499)	44.10 (271)	41.60 (50)
LDL [mg/dl (*n*)]					
Losartan	142.15 (676)	126.07 (588)*	120.18 (484)	115.47 (298)	111.67 (69)
Placebo	142.31 (683)	134.01 (573)	124.81 (463)	122.22 (248)	119.13 (46)
Triglycerides [mg/dl (*n*)]					
Losartan	212.80 (743)	212.11 (643)	205.10 (523)	197.72 (310)	219.78 (74)
Placebo	225.17 (755)	226.93 (637)	205.77 (500)	211.75 (271)	223.64 (50)
Lp(a) [mg/dl (*n*)]					
Losartan	41.35 (482)*	43.52 (309)	ND	ND	ND
Placebo	35.91 (481)	42.20 (321)	ND	ND	ND
Serum K^+ [mEq/l (*n*)]					
Losartan	4.59 (751)	4.77 (635)*	4.80 (504)*	4.78 (288)*	4.78 (226)*
Placebo	4.62 (762)	4.55 (616)	4.55 (483)	4.53 (244)	4.49 (187)
Uric acid [mg/dl (*n*)]					
Losartan	6.70 (751)	6.95 (635)	7.24 (509)*	7.51 (288)	7.59 (226)
Placebo	6.71 (762)	7.09 (620)	7.57 (485)	7.59 (244)	7.68 (187)

*$P < 0.05$, losartan vs. placebo. ND, not determined.

tan was associated with increased serum potassium at all time points, the mean rise never exceeded 0.3 mEq/l. Increased serum potassium levels led to similar discontinuation rates (losartan 1.1% vs. placebo 0.5%, P = NS). Baseline uric acid levels were similar in the two groups, and, in the losartan group, uric acid tended to be lower at all measured points and was significantly lower at 24 months (losartan vs. placebo, $P < 0.05$).

Relationship between baseline metabolic profile and the primary composite end point

Total cholesterol (risk increase 67% per 100 mg/dl, $P < 0.001$), LDL cholesterol (risk increase 32% per 50 mg/dl, $P < 0.001$), and triglycerides (risk increase 47% per log-transformed mg/dl, $P = 0.011$) were associated with increased risk of developing the primary composite outcome (Fig. 1*A*). Hazard ratios for the primary composite end point showed no significant relationship with baseline serum potassium, HbA_{1c}, and HDL cholesterol. Baseline total cholesterol levels >220 mg/dl (third and fourth quartiles) were associated with an increased risk of reaching the primary composite end point compared with levels in the first quartile (Fig. 1*B*). Similarly, an increased risk of reaching the primary composite end point was related to baseline LDL cholesterol >167 mg/dl (fourth quartile) (Fig. 1*C*) and baseline triglyceride levels >245 mg/dl (fourth quartile) (Fig. 1*D*).

Relationship between baseline metabolic profile and ESRD

Similar to the relationships between reaching the primary end point and baseline levels of metabolic factors, the risk of reaching ESRD was strongly related to baseline total cholesterol (risk increase 96% per 100 mg/dl, $P < 0.001$) and LDL cholesterol (risk increase 47% per 50 mg/dl, $P < 0.001$) (Fig. 2*A*). No significant relationship was observed for HbA_{1c} or HDL cholesterol, and triglycerides were borderline significant. Hazard ratios by quartile of baseline total cholesterol showed a significant relationship with the risk of developing ESRD at the two highest quartiles (>220 mg/dl) (Fig. 2*B*). Baseline LDL cholesterol in the fourth quartile (>167 mg/dl) was also strongly associated with the risk of developing ESRD (Fig. 2*C*).

CONCLUSIONS — Diabetic nephropathy has reached near-epidemic proportions worldwide, and its incidence continues to rise. It is the leading cause of ESRD in the U.S., and ~50% of new patients starting dialysis have type 2 diabetes (1,2). Among patients with ESRD, those with diabetes have the highest rates of morbidity and mortality. Given these data, any treatment that reduces the progression of diabetic nephropathy to ESRD should have significant effects on morbidity, mortality, and the cost of ESRD. In addition, the importance of strict maintenance of glycemic control and serum lipid profile necessitates that these parameters should not be adversely affected by the treatment. Recently, the RENAAL trial documented the role of losartan, an angiotensin II blocker, in the reduction of progression to renal failure in patients with type 2 diabetes and clinical nephropathy (3). This post hoc analysis demon-

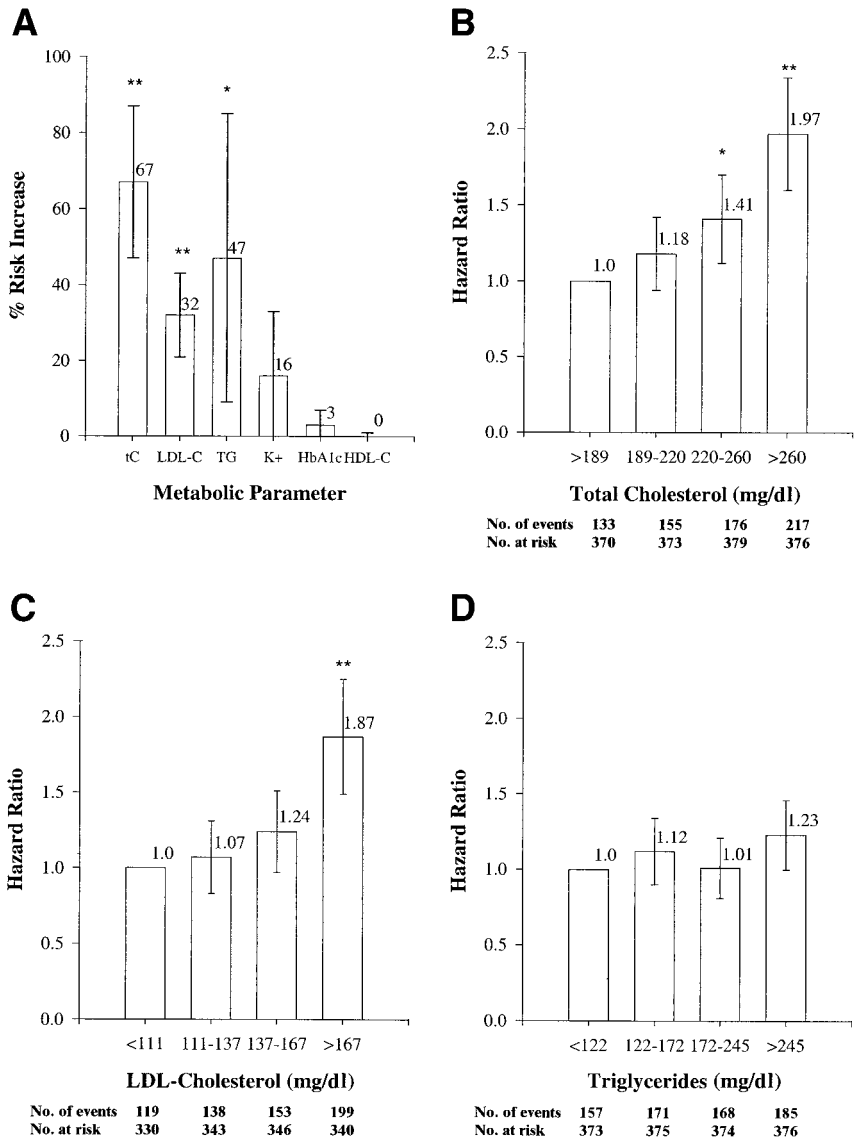

Figure 1—*Relationship between selected metabolic parameters and the primary composite end point.* A*: Percentage of increased risk for the primary composite end point associated with elevated values of selected baseline metabolic factors.* B–D*: Hazard ratios by quartile of those selected metabolic parameters that were statistically significant: total cholesterol (tC)* (B)*, LDL cholesterol (C), and triglycerides (TG)* (D)*.* *P < *0.05;* **P < *0.001.*

strates that losartan is not associated with adverse effects on metabolic parameters such as glycemic control and lipid profile.

Achieving optimal glycemic control in patients with type 2 diabetes is often challenging. In the current study, with usual care from the patients' physicians, baseline HbA_{1c} levels were well above the guidelines recommended by the American Diabetes Association (8). These levels did not decrease significantly throughout the study despite consistent monitoring by a clinical management committee. It is possible, and even likely, that tighter glycemic control may have benefitted the patients long term. In contrast to prior studies (6), baseline HbA_{1c} levels did not correlate with the primary composite outcome in this population. This may simply reflect the difficulty of maintaining optimal glycemic control in the RENAAL patient population. Importantly, unlike ACE inhibitors, for which there is conflicting data (10–12), losartan was not associated with adverse effects on glycemic control or with any significant difference in the incidence of hyper- or hypoglycemia in patients in the RENAAL study. Similar findings have been reported for irbesartan (5).

Few studies have dealt with the relationship between hyperlipidemia and progression to renal failure. In the RENAAL study, total and LDL cholesterol were elevated at baseline and a strong correlation for total and LDL cholesterol and triglycerides was observed for the primary composite end point. In addition, both total and LDL cholesterol were associated with an increased risk of developing ESRD. The association between lipids and renal disease has attracted significant interest, especially because half of the deaths in dialysis patients are of cardiovascular origin (13). Several studies in experimental animal models support a causal relationship between elevated lipid levels and the development of glomerular damage (14); in addition, pharmacologic lowering of lipids by a variety of classes of antihyperlipidemic medications has been reported to ameliorate renal damage (15–18). In humans, high serum cholesterol in conjunction with obesity has been reported to induce structural glomerular changes (19), and some prospective studies in humans have shown that hyperlipidemia may exacerbate progressive renal disease (6,20–24). Elevated cholesterol levels and low HDL cholesterol levels have been identified as independent risk factors for progressive renal disease (6), and smaller trials support elevations of LDL cholesterol or apolipoprotein B as predictors of renal progression (20–22). The role of individual lipid fractions in promoting renal dysfunction in humans is unclear; however, the data presented here suggest that elevated total and LDL cholesterol are important predictors of the development of ESRD in patients with type 2 diabetic nephropathy and are in agreement with prior studies in patients with impaired renal function with or without diabetes (6,20–24). Whether this is due to a primary role of hyperlipidemia or a correlation with proteinuria and other risk factors for renal progression remains to be proven. As such, further prospective studies are required; however, aggressive lipid lowering should clearly be an important consideration in treating patients with type 2 diabetes and clinical nephropathy.

Hyperkalemia is a clinically relevant adverse event associated with agents that block the renin-angiotensin system. In six clinical trials involving over 1,500 pa-

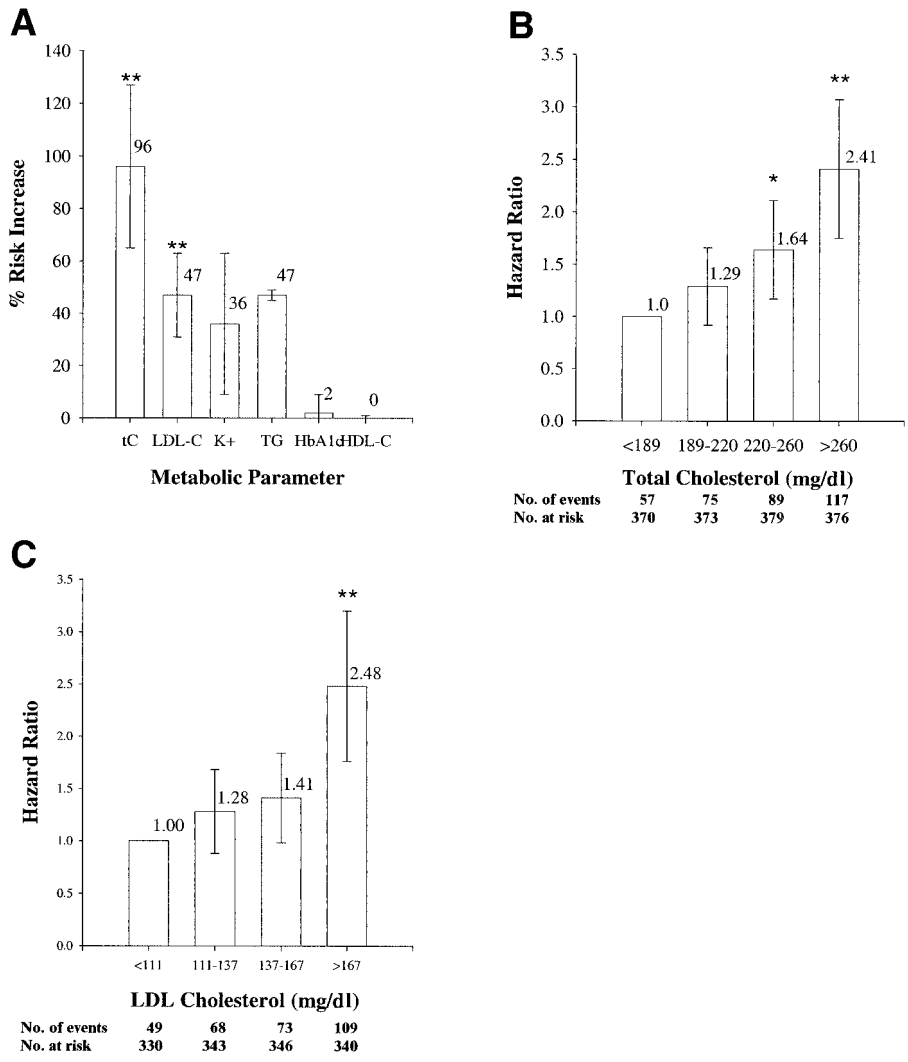

Figure 2—*Relationship between selected metabolic parameters and ESRD.* A*: Percentage of increased risk for ESRD associated with the elevated values of selected baseline metabolic factors.* B *and* C*: Hazard ratios by quartile of those selected metabolic parameters that were statistically significant: total cholesterol (tC)* (B) *and LDL cholesterol* (C)*. *P < 0.05; **P < 0.001. TG, triglycerides.*

tients with renal insufficiency, increases in serum potassium (mean 0.3–0.6 mEq/l) occurred in patients randomized to ACE inhibitors (25–30). Additionally, it has been reported that in patients with moderate renal impairment, less hyperkalemia was observed in the AIIA-treated group when compared with patients receiving an ACE inhibitor (31). In the current study, serum potassium levels were elevated at all study points in the losartan group; however, the mean increase never exceeded 0.3 mEq/l. A small number of patients, 1.1% in the losartan group and 0.5% in the placebo group, had to discontinue therapy because of hyperkalemia, which demonstrates that hyperkalemia associated with losartan is clinically manageable in this patient population.

It should be noted that the analyses described herein are post hoc, and as such the data should be interpreted with this limitation in mind. Further analysis of the RENAAL database is required to examine the role of baseline variables of predictors of outcome in this trial.

In the RENAAL study, losartan therapy in patients with type 2 diabetes and nephropathy provided renal protection by delaying the time to the composite end point of doubling of serum creatinine, ESRD, or death. In this post hoc analysis, losartan had no adverse effect on glycemic control, lipid profile, or serum uric acid. Overall, losartan was generally well tolerated in these patients.

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