Effect of LDL Cholesterol and Treatment With Losartan on End-Stage Renal Disease in the RENAAL Study

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Renal pathology and dyslipidemia commonly coexist. Treatments that lower albuminuria/proteinuria may lower lipids, but it is not known whether lipid lowering independent of lessening albuminuria/proteinuria slows progression of kidney disease. We examined the association between LDL cholesterol levels and treatment with losartan on end-stage renal disease (ESRD). Lipid levels and albuminuria measurements were obtained at baseline and at year 1 in a post hoc analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, which compared the effects of losartan- versus placebo-based antihypertensive therapy in patients with type 2 diabetes and nephropathy. LDL cholesterol lowering was associated with a lower risk of ESRD; however, this seemed to be largely an association with the reduction in albuminuria.

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Approximately 60% of patients with chronic kidney disease (CKD) have dyslipidemia (1,2). Elevated LDL cholesterol may be associated with CKD progression (2); however, patients with normal renal function and dyslipidemia do not develop renal insufficiency (3). Treatments that reduce albuminuria and slow CKD progression commonly lower lipids. It is unclear whether lipid lowering itself, rather than as a result of reduced albuminuria, slows CKD progression.

We investigated the relationship of LDL cholesterol and albuminuria at baseline and/or year 1 and treatment with losartan on end-stage renal disease (ESRD) in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study.

RESEARCH DESIGN AND METHODS

— The RENAAL study evaluated losartan- versus placebo-based therapy in 1,513 patients with type 2 diabetes and nephropathy (4). This post hoc analysis included LDL cholesterol (5) and albuminuria measurements at baseline and year 1 before ESRD. Patients were encouraged to control protein and salt intake, but there were no instructions regarding lipid management.

Changes from baseline to year 1 are reported as the absolute difference for LDL cholesterol and as the percentage of change in the geometric mean ratio for albuminuria. Stratification for LDL cholesterol at baseline (<2.59, >2.59 to ≤3.10, >3.10 to ≤3.62, >3.62 to ≤4.14, >4.14 to ≤4.65, and >4.65 mmol/l) was based on clinical judgment and sample size/stratum. Event rates were calculated as number of endpoints per 1,000 patient-years of follow-up. Cox regression models were used to calculate hazard ratios (HRs), 95% CIs, and *P* values with LDL cholesterol <2.59 mmol/l as reference with/without adjustments for baseline albuminuria (log transformed), serum creatinine, serum albumin, and hemoglobin (6) and with/without additional adjustment for albuminuria at year 1. Similar analyses were done when treatment group was incorporated into the model with the placebo-administered LDL cholesterol increase group as reference. Change in albuminuria by group and by LDL cholesterol < and ≥3.10 mmol/l was assessed with adjustment for baseline albuminuria (log transformed), serum creatinine, serum albumin, and hemoglobin. A two-sided *P* value <0.05 defined statistical significance.

RESULTS

— There were 1,061 patients (70% of the overall population) included. Baseline characteristics were similar between the losartan (n = 540) and placebo (n = 521) groups; the placebo group was somewhat older and had somewhat higher triglycerides. Baseline LDL cholesterol and albuminuria were positively associated. Decreases in LDL cholesterol (losartan baseline 3.63, year 1 3.39 mmol/l; placebo 3.64, year 1 3.50 mmol/l) and albuminuria (losartan 1,054.8, year 1 696.6 g/mmol, ratio 0.7; placebo 1,058.1, year 1 1,032.4 g/mmol, ratio 1.0) were greater in the losartan group. Changes in LDL cholesterol and albuminuria were positively associated. The decrease in albuminuria with losartan was greater in those with baseline LDL cholesterol <3.10 mmol/l compared with those with LDL cholesterol ≥3.10 mmol/l, a relationship that was not evident with placebo.

Baseline LDL cholesterol level was predictive of ESRD but not after adjusting for baseline albuminuria (Table 1). Baseline statin use was not predictive of ESRD. Change in LDL cholesterol (decrease vs. increase) predicted ESRD (HR 0.71) after adjustment. Predictivity for ESRD was

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Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

Table 1—*HRs for ESRD*

	LDL cholesterol at year 1	Combined		Losartan		Placebo	
		n	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)
Adjusted by							
Baseline[a]	Increase	409	1.00	180	0.70 (0.44–1.11)	229	1.00
	Decrease	652	0.71 (0.53–0.96)*	360	0.50 (0.34–0.75)*	292	0.76 (0.52–1.13)
Baseline + year 1[b]	Increase	409	1.00	180	0.88 (0.55–1.39)	229	1.00
	Decrease	652	1.11 (0.81–1.53)	360	0.93 (0.61–1.41)	292	1.18 (0.79–1.76)

*$P < 0.05$. [a]Adjusted by baseline albuminuria (log transformed), serum creatinine, serum albumin, hemoglobin, and LDL cholesterol. [b]Adjusted by the above and albuminuria at year 1.

lost when adjusting for baseline risk factors and year 1 albuminuria (Table 1). Losartan therapy and decreasing LDL cholesterol at year 1 were associated with reduced ESRD risk. Much of the reduced risk was accounted for when year 1 albuminuria was added to the model.

CONCLUSIONS — In univariate analysis in the RENAAL study, risk for the primary endpoint increased by 32% per 50 mg/dl (1.29 mmol/l) in LDL cholesterol, 67% per 100 mg/dl (2.59 mmol/l) in total cholesterol, and 47% per log-transformed mg/dl (0.01 mmol/l) in triglycerides, with no relationship between HDL cholesterol and the primary composite endpoint (7). Total (risk increase 96% per 100 mg/dl [2.59 mmol/l]) and LDL (risk increase 47% per 50 mg/dl [1.29 mmol/l]) cholesterol increased risk for ESRD. Our data suggest that these associations are mediated by changes in albuminuria associated with losartan therapy, and lipid level changes are secondary effects of losartan treatment. LDL cholesterol decreased in both groups at year 1, considerably more in the losartan group. Decreases in the placebo group may have been related to diet or lipid-lowering agents.

Kidney function may be improved by agents that lower lipids (8–10). In the Cholesterol and Recurrent Events (CARE) study (10), patients with previous myocardial infarction, total cholesterol <240 mg/dl (6.21 mmol/l), and CKD had reduced rates of decline in renal function with pravastatin versus placebo. In the Diabetes Atherosclerosis Intervention Study (DAIS) (11) and in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (12) in patients with type 2 diabetes, fenofibrate therapy reduced progression of albuminuria. Simvastatin in the Heart Protection Study (HPS) significantly decreased decline in glomerular filtration rate in diabetic subjects (13).

Several hypotheses regarding relationships among albuminuria, CKD, and lipid abnormalities exist (14,15). In CKD, increased total cholesterol, LDL cholesterol, and lipoprotein (a) could be secondary to urinary protein loss and subsequent increased hepatic production of lipoproteins (16–19). Lipoproteins may play a role in renal injury in CKD in a way that is analogous to their involvement in atherosclerosis (20–22), such as promoting renal vascular dysfunction (22) and inflammation (12,23).

The analysis showed a greater decrease in albuminuria with losartan and in those with lower baseline LDL cholesterol, which was not found with placebo. It is difficult to interpret these findings because lower baseline LDL cholesterol was at least partially due to use of statins in those with lower baseline LDL cholesterol. However, it is possible that lower baseline LDL cholesterol and/or statin therapy interacts with losartan to induce a greater decrease in proteinuria, which in turn leads to further lowering in LDL cholesterol.

LDL cholesterol lowering was associated with lower risk of ESRD in the RENAAL study. Losartan reduced albuminuria and LDL cholesterol after 1 year of treatment. The association between LDL cholesterol and ESRD seems to be largely mediated by changes in albuminuria. Additional data are needed to clarify the role of lipid lowering in the progression of type 2 diabetic nephropathy. However, given the cardioprotective effects of lipid lowering in this high-risk group, lipid-lowering therapy should remain a mainstay of the management of diabetic patients, even without a renoprotective effect.

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