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Do statins protect the kidney as well as the heart?

By MARCELLO TONELLI, MD, SM, FRCPC

Statins are widely prescribed for the primary and secondary prevention of cardiovascular disease, based on evidence indicating that they reduce mortality and the risk of vascular events in a variety of populations.¹ Chronic kidney disease (CKD) is a common condition that is associated with variable rates of kidney function loss and often with dyslipidemia,^{2,3} and CKD by itself may promote progressive kidney disease. This issue of *Cardiology Rounds* outlines the data linking dyslipidemia and progressive kidney disease and focuses on studies examining the ability of statins to improve renal outcomes in people with coronary disease.

Nature of dyslipidemia in kidney disease

Both qualitative and quantitative dyslipidemia are common in people with CKD, especially in patients with the nephrotic syndrome. From a quantitative standpoint, both hypercholesterolemia and hypertriglyceridemia (by definition) are common in the nephrotic syndrome.⁴ Typically, nephrotic patients have significantly elevated levels of all apolipoprotein (apo)B-containing lipoproteins including very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL), as well as normal or slightly depressed high-density lipoprotein (HDL). This is perhaps due, in part, to enhanced lipoprotein synthesis, although more recent studies suggest an important role for decreased catabolism and clearance.

The dyslipidemia of non-nephrotic CKD is characterized by an increase in serum triglycerides and triglyceride-rich lipoproteins (eg, VLDL), as well as by low HDL-cholesterol (C); however, mean LDL-C levels are similar to those observed in the general population. Besides the well-known bidirectional relation between dyslipidemia and proteinuria, lipoprotein metabolism also appears to be influenced by the severity of renal dysfunction.⁵ HDL-C and LDL-C levels decrease in parallel with estimated glomerular filtration rate (GFR) and, on average, are similar or lower in people with stages 3 to 5 CKD than levels in the general population. These changes are accompanied by increased serum triglyceride levels and atherogenic triglyceride-rich apoB containing lipoproteins (eg, VLDL and IDL), perhaps due to decreased activity of hepatic triglyceride lipase and peripheral lipoprotein lipase.

Link between dyslipidemia and progressive kidney function loss

Experimental data

A considerable body of experimental data indicates that dyslipidemia mediates progressive kidney function loss.

- First, dietary cholesterol loading induces glomerulosclerosis, mesangial proliferation, and modest proteinuria in animals with normal kidney function, and exacerbates histologic injury and proteinuria in those with pre-existing renal disease.^{6,7}
- Renal biopsy specimens obtained from patients with glomerular disease show lipoprotein deposition in endothelial and mesangial cells and, in some cases, foam cells (reminiscent of those seen in atherosclerotic blood vessels) are apparent.⁸ These observations suggest that intrarenal



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lipid deposition may mediate some types of renal disease.

- Finally, renal mesangial cells bind both LDL-C and oxidized LDL-C.⁹ Several studies have shown that mesangial proliferation *in vivo* occurs in response to oxidized LDL-C and LDL-C is toxic to rat mesangial cells in a dose-dependent fashion, suggesting that cholesterol may be directly toxic to renal tissues.

Human data

Relevant epidemiologic data from humans include several large prospective cohort studies. The Physicians' Health Study examined the risk of developing renal insufficiency (defined as serum creatinine >132 $\mu\text{mol/L}$) in 4483 apparently healthy men with levels less than this threshold at baseline in over a 13-year period. After adjustments for potential confounders, lower levels of HDL-C and higher levels of baseline LDL-C, total cholesterol, and total cholesterol to HDL-C ratio were all associated with a significantly increased risk of new renal dysfunction. However, this study did not include data on proteinuria, which is a relevant potential confounder.¹⁰ Data from the Atherosclerosis Risk in Communities Study also demonstrate an apparently independent association between dyslipidemia and declining renal function.¹¹

Effects of statins

Lipid-dependent effects

Statins compete with the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) molecule for binding at the active site of the enzyme, HMG-CoA reductase. Binding blocks the rate-limiting step of hepatic cholesterol biosynthesis, leading to enhanced surface expression and subsequent recycling of LDL receptors with a 30% to 60% reduction in serum LDL-C. Statins also shift the LDL profile away from the more atherogenic, small, dense form towards the larger, less dense, and less atherogenic subtype. The effect of statins on other lipids such as HDL-C and serum triglycerides is less marked.

Lipid-independent effects

In addition to directly improving the lipid profile, statins also exert a number of lipid-independent ("pleiotropic" effects), including improvement in endothelial dysfunction by reducing endothelial permeability to LDL and enhancing vasodilatory response, blunting local and perhaps systemic inflammatory responses, providing antioxidant effects, reducing the expression of endothelial adhesion molecules, and stabilizing atherosclerotic plaques.^{9,12} Some of these pleiotropic effects might theoretically influence the course of renal disease, since the lipid-independent actions of statins have been documented on several different types of kidney cells (including mesangial, podocytes, endothelium, and tubular epithelium). However, the clinical significance of these effects remains to be determined.

Effects of statins on cardiovascular events in renal populations

The risk of recurrent atherosclerotic events in people with known vascular disease is high, especially in those with superimposed CKD, diabetes mellitus, or both. Recent studies demonstrate that statins reduce the relative risk to a similar extent in patients with normal and with moderately impaired kidney function, especially when diabetes mellitus is present. In contrast to patients with kidney failure,¹³ the absolute benefit of treatment is substantially higher in individuals with mild-to-moderate impairment in kidney function than in those without renal insufficiency.^{14,15}

Effects of statins on renal outcomes

Meta-analysis

A recent systematic review identified 22 placebo-controlled trials that studied the renal benefits of statins. Although there was considerable between-trial heterogeneity, the pooled estimate suggested that statins reduced the rate of decline in GFR by approximately 1.2 mL/min/1.73 m²/year, compared with placebo.¹⁶ Statins also appeared to modestly reduce urinary protein excretion, although this outcome was evaluated in a smaller number of studies. Many of the reviewed trials did not stipulate that participants have a known vascular disease for inclusion.

Studies of patients with, or at high risk of, coronary events

Several large trials studying the effects of statins on cardiovascular events, have also examined the effects of these agents on the rate of change in estimated GFR (Table 1; Figure 1). The Heart Protection Study (HPS) was conducted in nearly 20,000 individuals at very high risk for cardiovascular events and found that serum creatinine (SCr) increased to a significantly lesser extent in participants randomized to receive simvastatin (40 mg) daily, compared with those receiving placebo.¹⁷ However, detailed analyses on kidney function were not reported and the clinical magnitude of the effect in the entire study population was small (Figure 1).

Similar findings were reported by the Greek Atorvastatin and Coronary Heart Disease (GREACE) study of structured dyslipidemia management vs standard care in patients with documented coronary disease.¹⁸ Participants (n=1600) were randomized to receive atorvastatin, titrated to achieve an LDL-C target of <2.6 mmol/L, or usual care, which could include pharmacological lipid-lowering treatment at the discretion of the patient's own physician. In intention-to-treat analyses, the GREACE investigators reported a modest improvement in kidney function among the 800 atorvastatin recipients (12%) that was significantly different than the slight decrease in kidney function (4%) observed in the 800 placebo recipients during the follow-up period (up to 4 years). Structured-care participants, who

Table 1: Randomized trials of statin therapy in people with or at high risk for coronary disease

Study	Statin	Dose (mg)	Years of follow-up	Sample size	Mean age (year)	Baseline mean GFR (mL/min)	Cholesterol (mmol/L)	Δ Chol (mmol/L)	Percent lost to follow-up
ALLIANCE 2005	Atorva	10-80	2.0	2442	61	88	–	-1.34	21
GREACE 2004	Atorva	10-80	4.0	1600	58	77	–	-2.38	1
HPS 2003	Simva	40	4.6	15696	64	–	5.84	–	24
WOSCOPS 1995	Prava	40	4.9	6248	55	77	7.03	–	30
CARE 1996	Prava	40	5.0	4079	59	71	5.40	-	0
LIPID 1998	Prava	40	6.1	8246	62	71	5.64	-1.00	0

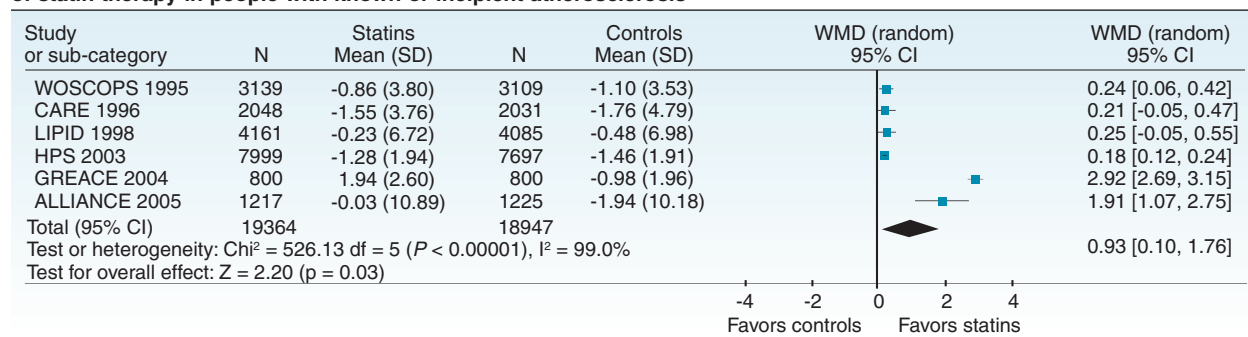
GFR = glomerular filtration rate. To convert cholesterol from mmol/L to mg/dL, divide by 0.02586.

discontinued atorvastatin, had outcomes similar to usual-care participants, who did not receive a statin. Similarly, usual-care participants, who received statins other than atorvastatin, had a slight improvement in kidney function (4.9%) that was less pronounced than the improvement in the atorvastatin recipients in the structured-care group (Figure 2). Subgroup analysis suggested that higher doses of atorvastatin and lower levels of kidney function at baseline were associated with greater renal benefits from statin treatment.

The Cholesterol and Recurrent Events (CARE) trial was a trial of pravastatin (40 mg) daily vs placebo in survivors of myocardial infarction (MI) with average cholesterol levels. A post hoc analysis of the CARE trial found no evidence that pravastatin reduced the rate of kidney function loss compared with placebo when all 3384 eligible participants were considered.¹⁹ However, statistical tests for interaction suggested that pravastatin reduced the rate of kidney function loss to a greater extent in participants with lower levels of renal function at baseline ($p=0.04$) and with dipstick positive proteinuria ($p<0.001$). For example, in patients with an estimated baseline GFR of <50 mL/min/1.73 m² in CARE, the benefit of pravastatin was nonsignificant (0.6 mL/min/1.73 m² per year, 95% CI, -0.1 –1.2, $p=0.07$). However, the benefit of pravastatin was significant in patients whose estimated GFR was

<40 mL/min/1.73 m² (2.5 mL/min/1.73 m² per year, 95% CI, 1.4-3.6, $p=0.0001$). However, the small number of participants in the latter subgroup ($n=32$) suggests that caution is required when interpreting these findings.

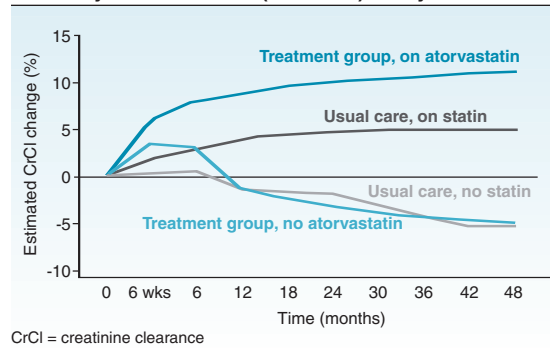
An analysis from the Pravastatin Pooling Project (PPP) extended these findings by including results from subjects in the CARE, West of Scotland Coronary Prevention (WOSCOPS), and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) studies, which together constituted a population with, or at high risk of, coronary disease. When all PPP subjects were considered, pravastatin exerted a small beneficial effect on the rate of change in MDRD-GFR (the formula from the Modification of Diet in Renal Disease Study) of 7%, or approximately 0.1 mL/min/1.73 m²/year. It also modestly reduced the risk of acute renal failure (RR 0.60; 95% CI, 0.41-0.86), but did not significantly reduce the risk of a 25% decline in kidney function from baseline (RR 0.94; 95% CI, 0.88-1.01).²⁰ In the group with lower baseline kidney function (GFR <60 mL/min/1.73 m²) and proteinuria on dipstick urinalysis ($n=249$), pravastatin recipients were significantly less likely to experience a $\geq 25\%$ decrease in GFR (12.5% vs 19.9%; RR 0.63; 95% CI, 0.41-0.96) or acute renal failure (3.2% vs 8.7%; RR 0.37; 95% CI, 0.17-0.82) during follow-up (Figure 3). Interestingly, results appeared even more robust when the Cockcroft-Gault equation

Figure 1: Change in estimated glomerular filtration rate (mL/min per year) for statins versus controls in randomized trials of statin therapy in people with known or incipient atherosclerosis

WMD = weighted mean difference.

Positive differences in per year rates of change indicate slower decline in renal function in the statin group, as compared to the placebo group. The Figure shows that statin recipients in these trials had average rates of kidney function loss that were 0.9 mL/min/1.73 m²/year slower than placebo recipients (95% CI, 0.1-1.8).

Figure 2: Findings from the Greek Atorvastatin and Coronary Heart Disease (GREACE) study¹⁸



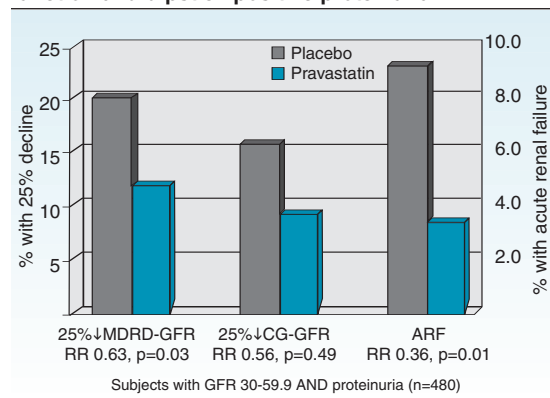
rather than MDRD-GFR was used to estimate kidney function. Although these findings are provocative, they require confirmation in additional trials.

Studies of patients with hypertension

Lee et al studied the renal effects of pravastatin in 2 separate groups of hypertensive patients with 0.3 to 3.0 g/day of proteinuria. In the first study, subjects were randomized to pravastatin (10 mg) daily or placebo, and were required to continue their baseline anti-hypertensive regimen.²¹ During the 6-month follow-up, kidney function was stable in both groups and pravastatin significantly reduced proteinuria compared with placebo (54% vs 8%, respectively, $p < 0.001$). A statistical test for interaction suggested that the reduction in proteinuria due to pravastatin use was more pronounced in subjects who received an angiotensin receptor blocker during the study (Figure 4).

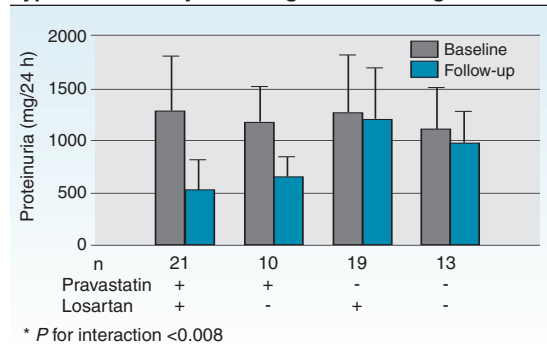
The second randomized trial by Lee et al extended these findings by including only subjects with > 0.3 g/d of proteinuria who were receiving losartan for hypertension.²² During the 6-month follow-up, kidney function was stable in both groups, and prava-

Figure 3: Findings from the Pravastatin Pooling Project: effects of pravastatin on change in kidney function among participants with reduced kidney function and dipstick-positive proteinuria²⁰



MDRD-FR = Modification of Diet in Renal Disease Study - Glomerular Filtration Rate
 CG-GFR = Cockcroft-Gault - Glomerular Filtration Rate
 ARF = Acute Renal Failure

Figure 4: Effect of pravastatin on proteinuria in hypertensive subjects using and not using losartan²¹



* P for interaction < 0.008

Adapted from Lee, *Hypertension* 2002

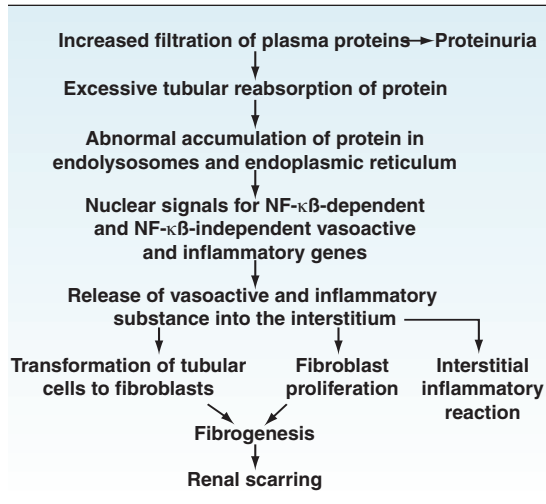
statin again reduced proteinuria compared with placebo (58% reduction vs 5% increase in placebo recipients, $p < 0.001$). A second randomization step blindly allocated subjects in the treatment group to continue receiving pravastatin or to begin receiving placebo. Subjects in whom pravastatin was withdrawn returned to their baseline levels of proteinuria; in contrast, a stable reduction was observed in those who continued on pravastatin. Levels of blood pressure were similar between groups throughout the study. Reduction in proteinuria was significantly associated with a change in urinary endothelin-1 (ET-1), but not to changes in plasma LDL-C or total cholesterol. The authors concluded that pravastatin reduced proteinuria independent of its lipid-lowering effects, perhaps by suppression of renal ET-1 production. However, since ET-1 production in proximal cells *in vitro* is directly proportional to albumin concentrations, it is unclear whether the apparent renal benefits of pravastatin in this study were due to direct effects on ET-1, or rather to some other factor that reduced both proteinuria and ET-1.

Potential mechanisms for the putative renoprotective effects of statins

How does proteinuria cause progressive kidney dysfunction?

Proteinuria is a powerful predictor of rapid kidney function loss and appears to mediate progressive renal disease via the mechanisms outlined in Figure 5.²³ Diseases that cause glomerular damage lead to additional filtration of plasma proteins into the glomerular space, leading to an increased concentration of protein in the lumen of the proximal tubule. This leads to increased endocytosis of protein by the specific receptors, megalin and cubulin, which requires prenylation of guanine nucleotide binding (GTP) proteins.²⁴ Increased protein uptake, in turn, causes abnormal accumulation of protein (especially albumin) in organelles of the proximal tubular cells, with secondary initiation of interstitial inflammation and fibrosis.

Figure 5: Mechanism of progressive kidney function loss²³



How might statins abrogate the deleterious effects of proteinuria?

Statins may reduce protein traffic across proximal tubular cells by 2 mechanisms: by decreasing proteinuria directly and by blocking receptor-mediated endocytosis of filtered protein.²⁵ In addition, statins may mitigate the damage ensuing from residual protein traffic by inhibiting the inflammatory response that usually follows.²⁶

Do statins reduce proteinuria or cause proteinuria?

This discussion of the putative antiproteinuric effects of statins may require clarification in light of recent reports that higher doses of rosuvastatin cause a dose-dependent risk of hematuria and proteinuria.²⁷ It appears that the excess proteinuria is tubular rather than glomerular in origin, possibly because of the inhibited receptor-mediated endocytosis described above.²⁸ Processes that cause tubular proteinuria (ie, due to lower reabsorption of filtered protein rather than to transglomerular protein loss resulting from glomerular damage) do not appear to be associated with the same risk of renal loss, probably because endocytosis and protein traffic are reduced rather than increased. However, this hypothesis does not explain the increased risk of hematuria observed with rosuvastatin.

Do statins protect the kidney through effects on the cardiovascular system?

Since statins improve endothelial function,²⁹ some or all of their apparent benefits on GFR may relate to improved renal perfusion, especially in patients with known vascular disease. Further investigation is required to determine whether the apparent renal effects of statins are mediated by the same or different mechanisms in different study populations (eg, people

with glomerulonephritis vs those with coronary disease). Finally, the apparent beneficial effect of statins on the risk of acute renal failure might relate to prevention of acute vascular events (eg, potential triggers for acute renal failure such as coronary angiography) or, alternatively, to specific pleiotropic effects.³⁰

Conclusions

Statins appear to reduce the rate of kidney function loss in humans with, or at risk of, coronary heart disease, although the clinical significance of this effect is unclear. Trials consistently show a statistically significant, but clinically small, overall effect on the rate of kidney function loss, especially in patients with proteinuria at baseline. Whether this effect translates into a clinically relevant renal benefit remains to be shown and, since such patients often receive statins anyway for prevention of atherosclerosis, these data may not influence management. Future studies (preferably in patients with heavy proteinuria) are required before statins can be recommended solely for renal indications. In the meantime, prescribing statins to patients with kidney disease according to existing guidelines for the prevention of atherosclerosis does not appear to increase renal risk and it would be expected to improve clinical outcomes, at least in patients with no overt kidney failure.

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