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# LDL-cholesterol lowering and renal outcomes

David D. Waters

## Purpose of review

Patients with chronic kidney disease (CKD) are at high risk for cardiovascular events. Statins reduce cardiovascular risk in a broad spectrum of patients. This article summarizes the evidence that statins reduce risk in CKD patients, and that statins have a small but favorable effect on renal function. Current guidelines for lipid management in patients with CKD are also reviewed.

## Recent findings

Two well conducted randomized trials showed no significant benefit for statins among patients receiving dialysis. One large trial demonstrated that simvastatin/ezetimibe reduced cardiovascular events in a broad spectrum of CKD patients. A recent meta-analysis concluded that CKD patients benefit from statins, and that the relevant benefit decreases as the severity of CKD worsens. In large trials, statin-treated patients have slightly less worsening of renal function overtime, and there are data to suggest that statins actually do not only preserve, but also increase renal function. Recent guidelines recommend a statin for CKD patients aged 50 years or older, for younger patients with known vascular disease, diabetes, or a 10-year risk greater than 10%, and for adult renal transplant recipients.

## Summary

Statins should be prescribed to older patients with CKD, and to younger patients with CKD who are at high CVD risk.

## Keywords

cardiovascular risk, cholesterol, chronic kidney disease, dialysis, statins

## INTRODUCTION

Cardiac disease and renal disease are closely linked. They often coexist, and each can cause or negatively influence the other. For example, patients with renal failure often develop heart failure, and severe heart failure induces important renal adaptations. Risk factors such as diabetes and hypertension are common to cardiac and renal disease.

Lipid lowering, documented mainly with statins, reduces cardiovascular events across a broad spectrum of patients at risk, including those with chronic kidney disease (CKD). The effects of lipid lowering on renal outcomes and renal function have been less well documented. These topics form the subject of this article.

## EFFECT OF STATINS ON CARDIOVASCULAR OUTCOMES IN PATIENTS WITH CHRONIC KIDNEY DISEASE

The effect of statins on cardiovascular outcomes in patients with CKD varies according to the stage of CKD. In two randomized, placebo-controlled trials statins did not reduce cardiovascular endpoints in

patients receiving hemodialysis. The German Diabetes and Dialysis Study (4D) randomized 1255 patients with type 2 diabetes on maintenance hemodialysis to atorvastatin 20 mg/day or placebo and followed them for a median of 4 years [1]. Atorvastatin lowered LDL-C by 42%, but the primary composite endpoint, comprising death from cardiac causes, nonfatal myocardial infarction (MI) and stroke, was not reduced (relative risk 0.92, 95% CI 0.77–1.10,  $P=0.37$ ). AQ2

In A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), 2776 patients receiving maintenance hemodialysis were randomized to receive rosuvastatin 10 mg/day or placebo, and were followed for a median of 3.8 years AQ3 AQ4

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## Lipid metabolism

### KEY POINTS

- Cholesterol lowering with statins reduces cardiovascular risk in patients with CKD and is recommended for all CKD patients aged 50 years and older, as well as for CKD patients aged 18–49 years with known cardiovascular disease, diabetes, or a 10-year risk greater than 10%.
- Relative risk reduction from cholesterol-lowering therapy decreases as the severity of CKD increases. Statin therapy is thus not recommended for patients on maintenance dialysis, although it is recommended that statins be continued in a patient beginning dialysis if previously prescribed.
- Statin treatment is recommended for adult renal transplant recipients.
- Ezetimibe may be used in combination with a statin for patients with CKD stages 3a-5, based upon the results of the Study of Heart and Renal Protection trial.

[2]. The primary endpoint was similar to that of German Diabetes and Dialysis Study. Rosuvastatin reduced LDL-C levels by 43% but did not reduce the primary endpoint (hazard ratio 0.96, 95% CI 0.84–1.11,  $P=0.51$ ).

A total of 9270 patients with CKD were enrolled in the Study of Heart and Renal Protection, of whom 3023 were on maintenance hemodialysis [3]. Randomization was to simvastatin 20 mg along with ezetimibe 10 mg/day or to placebo, and median follow-up was 4.9 years. The key prespecified outcome was first major atherosclerotic event, defined as nonfatal MI or coronary death, nonhemorrhagic stroke, or any arterial revascularization procedure. This outcome occurred in 11.3% of drug-treated and 13.4% of placebo-treated patients (RR 0.83, 95% CI 0.74–0.94,  $P=0.0021$ ). The 17% event reduction in Study of Heart and Renal Protection was accompanied by a 0.85 mmol/l difference in LDL-C between the treatment groups. This relationship is in line with the effects of statins in other patient

populations, in which, on average, a 1 mmol/l difference in LDL-C is associated with about a one-fifth reduction in events [4].

Do higher doses of statins, and the more aggressive LDL-C lowering that comes with this, yield greater CVD risk reduction? This question can be answered in the affirmative from studies that compare intensive versus moderate dose statin therapy [5], and for patients with CKD, can be answered affirmatively from a subgroup analysis of the Treating to New Targets (TNT) trial [6]. In TNT, among 10001 patients with stable coronary disease randomized to 10 or 80 mg of atorvastatin, 3107 had CKD at baseline, defined as an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m<sup>2</sup>. During a median follow-up of 5 years, major cardiovascular events occurred in 11.3% of CKD patients compared with 8.6% of patients with a normal eGFR (hazard ratio 1.35, 95% CI 1.18–1.54,  $P<0.0001$ ). In patients with CKD, atorvastatin 80 mg compared with 10 mg reduced the risk of a major cardiovascular event by 32% (hazard ratio 0.68, 95% CI 0.55–0.84,  $P=0.0003$ ).

### META-ANALYSES OF THE EFFECTS OF STATINS ON CARDIOVASCULAR OUTCOMES IN CHRONIC KIDNEY DISEASE

A recent comprehensive systematic review and meta-analysis of the effects of statin therapy in patients with CKD included 31 trials with 48 429 CKD patients, with 6690 major cardiovascular events and 6653 deaths [7<sup>■</sup>]. Overall, statin treatment produced a 23% reduction in the risk of cardiovascular events (RR 0.77, 95% CI 0.70–0.85) or an 18% reduction per mmol/l reduction in LDL-C (RR 0.82, 95% CI 0.74–0.91).

Importantly, the effect of statin therapy on major cardiovascular events was dependent on baseline kidney function, as shown in Table 1. RR reduction progressively declined as eGFR declined. For patients with stage 5 CKD, most of who were on

**Table 1.** Cardiovascular event reduction with statins according to chronic kidney disease stage

CKD stage	Events/patients statin	Events/patients placebo	Relative risk (95% CI)
5 – Dialysis	866/3639	934/3650	0.93 (0.86–1.00)
5 – Nondialysis	67/614	81/607	0.82 (0.60–1.11)
4	134/1263	179/1335	0.78 (0.63–0.96)
2–3	504/6194	764/6211	0.69 (0.63–0.77)
Overall <sup>a</sup>	2727/20 492	3418/20 578	0.77 (0.70–0.85)

Adapted with permission Hou *et al.* [7<sup>■</sup>].  $P$  for heterogeneity between different CKD stages less than 0.001. CKD, chronic kidney disease.

<sup>a</sup>Includes patients from trials in whom stage was not reported.

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maintenance hemodialysis, RR reduction was 8% (95% CI 1–14%). For stage 4 CKD, RR reduction was 22% (95% CI 4–37%) and for stages 2–3 it was 31% (23–37%). Absolute risk was higher in higher CKD stages, and number needed to treat to prevent one major cardiovascular event was 46 for stage 5, 36 for stage 4, and 24 for CKD stages 2–3. Stages 2 and 3 were combined in all of these analyses because the number of patients known to be in stage 2 was small.

### STATINS IN RENAL TRANSPLANT RECIPIENTS

Dyslipidemia is common in renal transplant recipients, worsened by immunosuppressive therapy, and resistant to treatment; additionally, statins and immunosuppressive drugs are metabolized by the same hepatic enzyme system [8]. Cardiovascular disease is the commonest cause of death in renal transplant recipients.

In the Assessment of Lescol in Renal Transplantation (ALERT) study, 2102 renal transplant recipients with total cholesterol from 4.0 to 9.0 mmol/l were randomized to fluvastatin 40 mg/day or placebo and were followed for a mean of 5.1 years [9]. Fluvastatin lowered LDL-C by 32%. The primary endpoint, a composite of cardiac death, nonfatal MI, or coronary intervention procedure, was reduced by 17%, but this difference was not statistically significant (risk ratio 0.83, 95% CI 0.64–1.06). However, cardiac death or nonfatal MI was significantly reduced (70 versus 104, risk ratio 0.65, 95% CI 0.48–0.88,  $P=0.005$ ). The authors noted that the trial was underpowered for the primary endpoint because the event rate was lower than anticipated, attributed in part to crossover of placebo patients to statin treatment.

After a 2-year extension of ALERT, in which all patients were offered open-label fluvastatin 80 mg/day, a significant reduction in the primary endpoint was seen (hazard ratio 0.79, 95% CI 0.63–0.99,  $P=0.036$ ) among patients who had originally been randomized to fluvastatin [10]. Mean LDL-C was 98 mg/dl (2.5 mmol/l) at this point, compared with a prestudy level of 159 mg/dl (4.1 mmol/l).

The effect of statins in renal transplant patients has not been well defined because too few such patients have been included in clinical trials. A recent Cochrane meta-analysis on the effect of statins in renal transplant recipients included 22 studies; however, approximately 2 of 3 of the patients were from ALERT [11]. This meta-analysis concluded that statins may reduce cardiovascular events in these patients, but that the treatment effects are imprecise because of a lack of data. No effect was observed for all-cause mortality or stroke.

### EFFECTS OF STATINS ON RENAL FUNCTION

The effects of statins on renal function are subtle. Most of the positive data come from large, long-term trials that were designed to assess cardiovascular outcomes, in which measures of renal function were usually limited to eGFR. Head-to-head comparisons of the renal effects of different statins are rare.

The Lipid lowering and Onset of Renal Disease trial randomized 132 patients with stages 2–4 CKD to atorvastatin 10 mg/day or to placebo and followed them for a mean of 2.5 years [12]. The primary outcomes were both the rate of Modification of Diet in Renal Disease (MDRD) eGFR and Cockcroft–Gault creatinine clearance decline. In the atorvastatin group, MDRD eGFR declined 29% less, and Cockcroft–Gault creatinine clearance declined 20% less than in the placebo group; however, neither of these differences approached statistical significance.

Differences of this magnitude were statistically significant in clinical trials with much larger numbers of patients and longer follow-up. In a pooling of three trials in which pravastatin 40 mg/day was compared with placebo over a follow-up period of about 5 years, pravastatin reduced the decline in adjusted MDRD eGFR by 34% ( $P=0.001$ ) among 3402 patients with baseline eGFR between 30 and 60 ml/min/1.73 m<sup>2</sup> [13]. However, the absolute difference between the groups was small 0.24 ± 0.08 ml/min/1.73 m<sup>2</sup>/year.

Change in kidney function could be calculated for 3842 of the 4444 patients in a post-hoc analysis of the Scandinavian Simvastatin Survival Study [14]. During 5.5 years of follow-up, simvastatin 20–40 mg/day reduced the frequency of an at least 25% decline in kidney function (adjusted odds ratio 0.68, 95% CI 0.50–0.92,  $P=0.01$ ). The adjusted annualized decline in eGFR was lower in the simvastatin group than in the placebo group (0.34 versus 0.41 ml/min/1.73 m<sup>2</sup>,  $P=0.02$ ).

Atorvastatin appears to improve eGFR, instead of slowing its decline, based upon post-hoc analyses from several long-term trials [15–18]. In TNT, eGFR improved by 3.5 ± 0.14 and by 5.2 ± 0.14 ml/min/1.73 m<sup>2</sup> in atorvastatin 10 mg and 80 mg/day groups ( $P<0.0001$ ) over 5 years of follow-up [15]. In the Collaborative Atorvastatin Diabetes Study, treatment with atorvastatin 10 mg/day was associated with a modest improvement in eGFR of 0.18 ml/min/1.73 m<sup>2</sup>/year (95% CI 0.04–0.32,  $P=0.01$ ) [16]. In the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events study, eGFR increased slightly in atorvastatin-treated patients and decreased slightly in usual care patients over a median follow-up of 54.3 months, with the difference being statistically significant [17]. In the Stroke

## Lipid metabolism

Prevention by Aggressive Reduction in Cholesterol Levels trial [18], eGFR increased more over 60 months in patients randomized to atorvastatin 80 mg/day compared with placebo ( $3.46 \pm 0.33$  versus  $1.42 \pm 0.34$  ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ ).

In the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin trial [19], median eGFR decreased between baseline and 1 year by 6.5 and 7.0 ml/min/1.73 m<sup>2</sup> in the rosuvastatin and placebo groups, respectively. Median eGFR was higher at 1 year in the rosuvastatin group ( $P = 0.02$ ). The large decrease in eGFR in both groups appeared to be accounted for mainly by declines in patients with eGFR values in the normal range [20].

Limited data are available comparing the renal effects of different statins head-to-head. In the Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease (PLANET 1), the effects on renal function of rosuvastatin 10 mg and 40 mg/day were compared with atorvastatin 80 mg/day in 353 diabetic patients receiving a stable dose of an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker [21]. The primary endpoint, change in urine protein:creatinine ratio between baseline and 52 weeks, improved by 13% ( $P = 0.033$ ) in the atorvastatin group but did not change significantly in the rosuvastatin groups. eGFR decreased in both rosuvastatin groups but did not change significantly in the atorvastatin group. Either acute renal failure or a doubling of serum creatinine level was observed in 9 of 123 patients in the high-dose rosuvastatin group, but in only one atorvastatin patient, and in no patients in the rosuvastatin 10 mg group. These findings suggest that high-dose rosuvastatin should be avoided in patients with diabetes and CKD.

### CHOLESTEROL TREATMENT GUIDELINES FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

The 2013 ACC/AHA guidelines for the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults do not specifically address patients with CKD [22]. However, the Kidney Disease: Improving Global Outcomes (KDIGO) organization has recently released guidelines for lipid management of adults and children with CKD [23<sup>24</sup>]. These guidelines include 13 recommendations, the key one being the recommendation for statin or statin with ezetimibe treatment for adults aged 50 years or older with an eGFR less than 60 ml/min/1.73 m<sup>2</sup> but not treated with long-term dialysis or kidney transplantation.

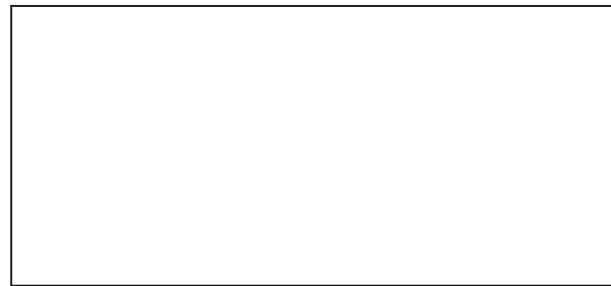


FIGURE 1.

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The KDIGO guidelines make the point that LDL-C is not an accurate predictor of cardiovascular risk in CKD patients and should not be used to determine who should receive pharmacologic cholesterol-lowering treatment. Instead, the level of risk and evidence that treatment will reduce risk are the criteria that should inform the treatment decision. In addition to treating patients aged 50 and older with an eGFR less than 60 ml/min/1.73 m<sup>2</sup>, the KDIGO guidelines recommend treatment for those aged 18–49 years with a 10-year risk greater than 10%. This group includes patients with known coronary disease, previous stroke, or diabetes. Treatment is not recommended for patients receiving dialysis; however, if dialysis is being initiated in a patient receiving a statin, the guidelines recommend that it be continued. A statin is recommended for adult transplant recipients. These guidelines are depicted in Fig. 1.

Measurement of a lipid profile is recommended for patients with newly diagnosed CKD mainly to establish the diagnosis of severe hypercholesterolemia or hypertriglyceridemia and potentially rule out a remediable cause if dyslipidemia is present, for example, hypothyroidism. But routine measurement of lipids during follow-up is not recommended unless the result would alter management. Dose titration to achieve a specific LDL-C goal is not recommended because no evidence supports such an approach.

### CONCLUSION

Statins should be prescribed to older patients with CKD, and to younger patients at high risk, as recommended by the KDIGO guidelines.

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## Conflicts of interest

The author has received remuneration for participating in clinical trial committees from Merck Schering-Plough, Pfizer, and Sanofi, and has received honoraria for lectures and consulting fees from Pfizer.

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- of special interest
- of outstanding interest

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