Clinical update

Lowering cholesterol in chronic kidney disease: is it safe and effective?

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The value of cholesterol lowering in preventing cardiovascular disease has now been established in patients with chronic kidney disease (CKD), who are intrinsically at high cardiovascular risk. While data from completed studies has clearly demonstrated substantive benefit of statins in early CKD, the effects in end-stage CKD remain controversial. Recent studies have also suggested that the effects of different statins on the kidney may be heterogeneous, and the safety of high-dose statins in this population remains uncertain. Communications from regulators such as the US Food and Drug Administration concerning potential side effects of statin therapy (particularly memory loss and the risk of diabetes) have created debate in the medical literature and unrest in the public mind about the value of long-term statin therapy for vulnerable patient populations. The evaluation of risks and benefits for this class of agents is critically dependent on baseline risk. This article will review current evidence for the benefits and risks of statin therapy for kidney and cardiovascular disease progression in the CKD population.

Keywords
Lipids • Statins • Chronic kidney disease

Introduction

Chronic kidney disease (CKD) affects up to 15% of the population and is increasing.1 It has been estimated that 2.6 million people received dialysis for end-stage kidney disease (ESKD) in 2010 and that this number would double by 2030.2 Cardiovascular disease (CVD) is the most common cause of death around the world, and CKD is associated with an increased risk of cardiac and vascular disease that becomes more severe as kidney function falls.3 The absolute risk of cardiovascular events in individuals with CKD is similar to that of patients with established coronary artery disease, and for individual with ESKD on dialysis, the risk of cardiovascular events and death is up to 40–50 times higher than the general population.4 The increase in risk is multifactorial: advanced kidney failure is associated with a higher prevalence of insulin resistance,5 high blood pressure, lipid abnormalities,6 vascular calcification,7 chronic inflammation,8 protein-energy wasting, and lack of regular exercise.8 Additionally, kidney failure is associated with a range of metabolic abnormalities, the so-called milieu of uraemic toxicity,7 and the role of neurohormonal axis including renin–angiotensin system,10 vitamin D receptors,11 fibroblast growth factor-23,12 etc., that may contribute to accelerated damage to the heart and vasculature, as well as the dialysis procedure itself, which may have a direct toxic effect on the myocardium13 (Figure 1). Ronco et al.14 classified the interaction of cardiac and renal pathophysiology into a clinical entity known as cardiorenal syndrome. Figure 1 shows the mechanisms by which different stages of CKD contribute to cardiac dysfunction, ventricular hypertrophy, and increased cardiovascular events in patients with CKD, although the exact mechanism remains unclear, and is beyond the scope of this review.

Long-term lowering therapy of LDL-cholesterol (LDL-C) has clear proven benefit for both primary and secondary prevention of CVD in the general population,15,16 with evidence suggesting earlier treatment with statins not only achieves CVD protection but also confers a survival benefit. Recent studies of cholesterol lowering would appear to confirm that these benefits are related to the degree of LDL-C reduction, rather than the pleotropic effects of statins.16 However, the clinical benefits of lipid lowering in patients with advanced CKD have been less certain. Initial observational studies in people with ESKD receiving dialysis failed to demonstrate any increase in the risk of cardiovascular (CV) events or death with higher cholesterol levels, but rather suggested an increased risk in individuals with lower levels.17 These cohort studies were likely...
confounded by coexistent wasting and/or inflammation that led to both lower lipid levels and an increased risk of events. Furthermore, there are conflicts in cholesterol-lowering guidelines by international bodies in this population. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not consider CKD as an indication to commence statin therapy as they see no trial evidence to justify such a recommendation, whereas the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines consider those with CKD [as defined by a glomerular filtration rate (GFR) \( \geq 60 \, \text{mL/min/1.73 m}^2 \)] a very high-risk group who require lipid management with a target LDL-C of \(<1.8 \, \text{mmol/L} \) or a 50% reduction in LDL-C. Stats in early stages of chronic kidney disease

The data come primarily from the SHARP (Study of Heart And Renal Protection) study\(^2\), as well as subgroup analyses of participants with CKD from statin trials conducted in the general population. The SHARP trial is the largest study of lipid-lowering agents in patients with CKD, involving \( >9000 \) patients, randomized to placebo or a combination of low-dose simvastatin and ezetimibe, with a median follow-up of 4.9 years. CKD was defined as more than one previous measurement of serum or plasma creatinine of at least \( 150 \, \text{mmol/L} \) (1.7 mg/dL) in men or \( 130 \, \text{mmol/L} \) (1.5 mg/dL) in women, whether receiving dialysis or not. Overall, the study found that statin–ezetimibe therapy reduced the risk of major cardiovascular events by 17\% [95\% confidence interval (95\% CI): 6–26, \( P = 0.0021 \)], with no evidence of an increased risk of adverse events including myopathy. Six thousand two hundred and forty-seven of the participants in the study were not receiving dialysis at entry. In this population, statin therapy reduced the risk of major cardiovascular events by 22\% (95\% CI: 9–33), with no increase in the risk of adverse events.

Two large systematic reviews have reported the effects of statin therapy in patients with CKD who have not yet started on dialysis, pooling the results of SHARP with those from CKD subgroups of trials conducted in the general population. The largest review includes 50 studies (\( >45,000 \) participants) comparing statins with placebo or with two different statins in adults. Com pared with placebo, statin therapy consistently prevented major CV events [risk ratio (RR): 0.72, 95\% CI: 0.66–0.79], all-cause mortality (RR: 0.79, 95\% CI: 0.69–0.87), and myocardial infarction (RR: 0.55, 95\% CI: 0.42–0.72). This Cochrane review concludes that statins consistently lower death and major CV events by 20\% in people with CKD not requiring dialysis but have an uncertain effect on stroke. An earlier review by Upadhya et al.\(^3\) had similarly shown that lipid-lowering therapy lowers the risk for cardiac mortality (pooled RR: 0.82, 95\% CI: 0.74–0.91, \( P < 0.001 \)), cardiovascular events (including revascularization) (pooled RR: 0.78, CI: 0.71–0.86, \( P < 0.001 \)), and myocardial infarction (pooled RR: 0.74, CI: 0.67–0.81, \( P < 0.001 \)). Significant benefit was also seen for all-cause mortality but was limited by a high degree of heterogeneity.

**Figure 1** Known mechanisms behind various cardiovascular abnormalities seen in various stages of chronic kidney disease. (A) Cross section of the human heart. (B) Cross section of a human aorta with atherosclerosis. EPO, Erythropoietin; LVH, left ventricular hypertrophy; Vit D, vitamin D; FGF-23, fibroblast growth factor-23.
Hou et al.\textsuperscript{35} examined 31 trials that included at least one CV event, analysing data for >8000 patients with CKD who experienced 6690 major CV events and 6653 deaths. Statin therapy produced a 23\% relative risk reduction for major CV events ($P < 0.001$), an 18\% RR reduction for coronary events, and a 9\% reduction in cardiovascular or all-cause deaths but had no significant effect on stroke (21\%, 95\% CI: −12 to 44) and no clear effect on kidney failure events (5\%, 95\% CI: 21–10). Subgroup analysis demonstrated that the relative effects of statin therapy in CKD were significantly greater in people with early compared with advanced CKD and the number to treat increased as the stages of CKD progressed (Figure 2).

In summary, statins may have an important role in primary prevention of CV events and mortality in people with early CKD. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for lipid management in CKD\textsuperscript{36} recommends commencement of treatment with a statin or statin/ezetimibe in adults aged ≥50 years, patients with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m\textsuperscript{2} not receiving dialysis, or with functioning kidney transplants.

### Statin use in advanced chronic kidney disease or end-stage kidney disease population

The role of statins in ESKD is less certain. Meta-analyses of results of randomized trials clearly demonstrate that relative risk reduction is less compared with people with preserved kidney function, although the absolute risk reduction is likely similar.\textsuperscript{33,35} A number of reports\textsuperscript{37} propose that a key CVD process in people with ESKD relates to cardiac hypertrophy and fibrosis (structural heart disease), with heart failure and arrhythmia, which would be largely unaffected by treatments targeted to atherosclerosis such as lipid lowering. If this is the case, then the reduction in absolute risk attributable to statin therapy may well be ‘drowned out’ by the larger number of the non-atherosclerotic cardiovascular events.

Reflecting this uncertainty, the KDIGO guidelines recommend that statins or statin/ezetimibe combination not be initiated in adults with dialysis-dependent CKD; however, if these patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, the treatment ought to be continued.\textsuperscript{36}

Along with SHARP, two multicentre, randomized double-blind, prospective trials specifically assessed the effects of statin therapy on major clinical outcomes in people with dialysis-dependent CKD.

The 4D study\textsuperscript{19} investigated 1255 subjects with Type 2 diabetes mellitus receiving maintenance haemodialysis who were randomly assigned to receive 20 mg of atorvastatin or matching placebo daily. During a median follow-up period of 4 years, atorvastatin had no significant effect on the primary endpoint, defined as composite of death from cardiac causes, fatal stroke, non-fatal myocardial infarction, or non-fatal stroke (relative risk, 0.92; 95\% CI: 0.77–1.10), except that there was an increase in the risk of fatal stroke (RR: 2.03, 95\% CI: 1.05–3.93) among those receiving atorvastatin. Atorvastatin reduced the rate of all cardiac events combined (RR: 0.82; 95\% CI: 0.68–0.99; $P = 0.03$, nominally significant) but not all cerebrovascular events or combined or total mortality.

In the AURORA study,\textsuperscript{20} 2776 participants on haemodialysis were randomized to rosuvastatin 10 mg or matching placebo daily and 804 patients developed major CV events during the follow-up period, of which 396 were in the rosuvastatin group and 408 were in the placebo group (9.2 and 9.5 events per 100 person-years of follow-up, respectively). There was no significant effect of treatment with rosuvastatin on the primary combined endpoint [hazards ratio (HR): 0.96; 95\% CI: 0.84–1.11]. The lack of efficacy of rosuvastatin on the primary endpoint was consistent among all subgroups including diabetes, high LDL-C levels, elevated C-reactive protein, hypertension, and pre-existing CV disease. There was a small but statistically significant increase in the incidence of haemorrhagic stroke in the diabetic patients who received rosuvastatin—an

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/36/43/2988/2293408)

**Figure 2** Effects of statin therapy on major cardiovascular events stratified by kidney function and the number needed to treat of statins in patients with chronic kidney disease. An decreased effects of statin therapy was observed with highest relative risk reduction seen in early chronic kidney disease, which becomes less pronounced as chronic kidney disease progressed. Chronic kidney disease stage 5: estimated GFR < 15 mL/min/1.73 m\textsuperscript{2}, stage 4: estimated glomerular filtration rate 15–30 mL/min/1.73 m\textsuperscript{2}, stage 3: estimated glomerular filtration rate 30–60 mL/min/1.73 m\textsuperscript{2}, and stage 2: estimated glomerular filtration rate 60–90 mL/min/1.73 m\textsuperscript{2}. NNT, number need to treat.
observation also reported in the 4D study. A post hoc analysis of the 731 diabetic patients receiving haemodialysis reported a 32% risk reduction of composite primary endpoints among patients with diabetes on haemodialysis in the treated arm (HR: 0.68; 95% CI: 0.51–0.90).10 The subgroup analyses of the SHARP study, comparing dialysis vs. non-dialysis patients and diabetic vs. non-diabetic, showed no good evidence that major atherosclerotic events differed between these groups, even after adjustment for the reduction in LDL-C. However, as the SHARP study was not powered to reliably assess these atherosclerotic events in these subgroups, they were only included as tertiary analyses.11 Furthermore, the increased CV risk in patients with ESKD is multifactorial and may be comparable to end-stage heart failure, in which disease progression is too advanced to be able to achieve significant disease regression.

Studies of statin therapy in kidney transplant recipients

The Assessment of LEscol in Renal Transplantation (ALERT) study examined the effect of fluvastatin (80 mg/day) vs. placebo in the high CVD risk renal transplant population.19 After a mean follow-up of 5.1 years, fluvastatin lowered LDL-C concentrations by 32%. Risk reduction with fluvastatin for the primary endpoint (the first occurrence of a major adverse cardiac event (MACE), i.e. cardiac death, non-fatal MI, or coronary revascularization procedure including both coronary artery bypass graft or percutaneous coronary intervention) (HR: 0.83; 95% CI: 0.64–1.06) was not significant, although there were fewer cardiac deaths or non-fatal MI (70 vs. 104, HR: 0.65; 95% CI: 0.48–0.88, P = 0.005) in the fluvastatin group than in the placebo group. Although cardiac deaths and non-fatal MI seemed to be reduced, fluvastatin did not reduce rates of coronary intervention procedures or mortality.

Of 1787 patients who completed ALERT randomized to fluvastatin or placebo for 5–6 years, 1652 (92%) were offered to participate in an open-label fluvastatin XL 80 mg/day 2-year extension study. The primary endpoint was the time to first MACE. The mean total follow-up was 6.7 years. Patients randomized to fluvastatin had a reduced risk of MACE (HR: 0.79, 95% CI: 0.63–0.99, P = 0.036) and a 29% reduction in cardiac death or definite non-fatal myocardial infarction (HR: 0.71, 95% CI: 0.55–0.93, P = 0.014). Total mortality and graft loss did not differ between groups. It appears that fluvastatin produces a safe and effective reduction in LDL-C and cardiovascular risk in kidney transplant recipient, comparable with those of statins in general population.

Should the use of cholesterol-lowering agents in chronic kidney disease be based on lipid levels?

Although LDL-C is widely used in estimating future CV risk in the general population, kidney function is not incorporated in current risk calculators despite the fact that reduced GFR confers increased CV risk.19 The prescription of statins using standard absolute risk algorithms may therefore result in many patients with renal impairment who would benefit from statins not receiving this therapy.

Among advanced-stage CKD patients, the magnitude of risk associated with LDL-C levels decreases with progression of the stage of CKD.28 For dialysis patients with the lowest level of LDL-C and total cholesterol, the all-cause and CV mortality remains high.29,30 Hence, the evidence argues against the use of LDL-C to identify patients requiring treatment, but rather suggests consideration of absolute risk for coronary events (such as history of known coronary disease, diabetes mellitus, prior ischaemic stroke or estimated 10-year incidence of coronary death or non-fatal MI >10%).31 As CKD itself is a risk factor for CV events, a reduced treatment threshold may be appropriate. The most recent KDIGO guidelines32 take this analysis into account in recommending the routine use of lipid lowering with a statin ± ezetimibe regimen in all people over the age of 50 with CKD.

Effects of statins on progressive decline of kidney function

The data regarding the effects of statins on kidney function are conflicting. In a post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease (GREACE),23 800 participants randomized to receive atorvastatin, titrated to achieve a LDL-C target of <2.6 mmol/L, showed a modest improvement in eGFR over 4 years than subjects receiving standard care (lifestyle change and other pharmacological lipid-lowering agents at the discretion of the treating physicians) (12% increase vs. 4% decrease, P < 0.0001). A secondary analysis of the Cholesterol and Recurrent Events (CARE) trial suggested that pravastatin reduced the rate of kidney function loss to a greater extent in participants with dipstick-positive proteinuria (P < 0.001) and lower levels of eGFR at baseline (P = 0.04).24 It should be noted that it is unusual to see an improvement in eGFR in any study with CKD patients over time. A larger Pravastatin Pooling post hoc analysis from this group failed to show any effect of pravastatin on the risk of a 25% decline in eGFR from baseline (RR: 0.94, 95% CI: 0.88–1.01).19

In a sub-analysis of the Treating to New Target (TNT) study, Shepherd et al.26 compared atorvastatin 80 mg with atorvastatin 10 mg on kidney function in 10 001 patients with CVD. Baseline eGFR by MDRD was compared with eGFR at the end of follow-up in 9656 participants with complete renal data. Mean eGFR at baseline was 65.6 ± 11.4 mL/min/1.73 m² in the atorvastatin 10 mg group and 65.0 ± 11.2 mL/min/1.73 m² in the atorvastatin 80 mg group. At the end of ~5 years follow-up, mean change in eGFR showed an increase of 3.5 ± 0.14 mL/min/1.73 m² with atorvastatin 10 mg and 5.2 ± 0.14 mL/min/1.73 m² with atorvastatin 80 mg (P < 0.0001 for treatment difference), suggesting that this effect may be dose related. The expected 5-year decline in eGFR was not observed in the TNT study. Among the 6247 pre-dialysis patients at randomization in the SHARP study, simvastatin plus ezetimibe did not show significant reductions in any of the prespecified measures of kidney disease progression, namely doubling of baseline serum creatinine, ESKD, or death.29

Although a recent meta-analysis of nine randomized controlled trials (RCTs) focusing on atorvastatin did find a significant benefit on kidney function,27 a larger meta-analysis that included 50 trials...
and over 30 000 patients looking at the effects of a number of different statins in CKD found no renoprotective effect. Methodological issues related to the measurement of the key outcome measure (renal function) may have had an influence on these studies. Future studies should report the method of creatinine measurement and how the method used compares the reference standard (isotope dilution mass spectrometry). Change in methodology or renewal of platforms/machines in central laboratories can sometimes cause reported serum creatinine levels to change over time.

In summary, there is an insufficient evidence to support the use of statins to slow the rate of decline in kidney function in people with high cardiovascular risk with or without CKD.

Effects of statins on albuminuria and/or proteinuria

Albuminuria (or proteinuria) is a well-known predictor of kidney failure as well as CVD. However, the evidence regarding statin effects on albuminuria/proteinuria remains controversial. A meta-analysis examined 27 RCTs involving 39 704 participants and reported that statin therapy seemed to modestly and heterogeneously reduce urinary protein excretion, only when pooled data on albuminuria and proteinuria were considered together [-0.58 units of standard deviation (SD); 95% CI: −0.98 to −0.17; I² = 89%]. These findings are consistent with pooled data from 18 studies involving 1323 participants with mixture of renal diagnoses including glomerulonephritis, diabetes, and hypertension, using a variety of indices for protein excretion, where statin therapy was found to reduce protein excretion by 0.6 SD (P < 0.005). However, both of these analyses found substantial heterogeneity and had short median follow-up (mostly <6 months).

A potential mechanism for an increase in proteinuria due to direct statin effects on tubular inhibition of protein uptake has been proposed, which may be partially related to the type and dose of statin used. Some studies have identified an association between statin use and the prevalence of proteinuria; however, these are highly prone to confounding and therefore unreliable. Nevertheless, a large body of evidence has shown that statins do not seem to be deleterious for kidney function.

On the other hand, the data looking at statin efficacy according to baseline albuminuria or proteinuria status are very limited. The most convincing data came from the SHARP study.

Are statins safe?

There are ongoing debates in the general community about the safety of statins. The Food and Drug Administration (FDA) has recently issued safety warnings for statins, centred around the risk of diabetes and short-term memory loss (but not dementia). This has been accompanied by a fierce debate in the medical literature and the press, in which some physicians have suggested that statins have been overprescribed. These controversies have the effect of raising doubts in the mind of patients about whether the risks of statin therapy are outweighed by the benefits. The SHARP study found that the risk of myopathy was only two additional cases per 10 000 patients per year of treatment with the combination of simvastatin and ezetimibe compared with the placebo (9 (0.2%) vs. 5 (0.1%), without any evidence of excess risks of hepatitis, gallstones, or cancer. However, the active run-in period employed in this trial could potentially lead to underestimation of this risk. In the Cochrane meta-analysis on pre-dialysis CKD patients, the potential harms from statin therapy (elevated creatinine kinase, liver function abnormalities, withdrawal due to side effects, and cancer) were limited by lack of systematic reporting and were uncertain in analyses due to small numbers. Hou et al. reported no difference in adverse events in statins groups compared with the control groups. Even for the high-risk groups (dialysis and renal transplant patients), there was no increase in the incidence of rhabdomyolysis or liver disease in the statin groups compared with the placebo group in the AURORA, 4D, and ALERT study. Hence, FDA has recommended against routine monitoring of liver function tests that were once considered standard procedure for statin users for it has not been effective in predicting or preventing the rare occurrences of serious liver injury associated with statin use (Table 1).

In addition, reports from administrative data have suggested the possibility that high-intensity statins may be associated with an increased risk of admission for acute kidney injury. These findings were not confirmed in analyses of RCT data.

Indeed, a recent pooled analysis of 24 statin placebo-controlled trial specifically looked at renal-associated serious adverse event (SAE). The authors used search term ‘Renal impairment’, ‘Renal disorder’, ‘Renal failure’, ‘Renal failure acute’, ‘Nephritis’, ‘Nephropathy’, ‘Renal tubular disorder’, or ‘Renal tubular necrosis’. This study showed no difference in the incidence of renal-associated adverse event at 120 days after drug initiation (0.04 vs. 0.10%, P = 0.162) between atorvastatin [10 345 patients on atorvastatin (10–80 mg/day)] and placebo (8945 patients on placebo) or in the high-dose vs. low-dose statin trials. Results were similar for renal-related SAEs after 120 days.

In a review article by Maj et al. on the safety of statins, agents that modulate CYP-450 isoenzymes, isoprenoid deficiency, coenzymes Q inhibition, selenoproteins and dolichols deficiency, etc. that are more common in patients with CKD have been proposed as potential pathways behind statin toxicity. Hence, a clinical assessment of risk factors and awareness of drug-to-drug interaction seems like a more sensible approach in predicting risk of adverse effects.

Current evidence suggests that the benefit of statin outweigh the risks in individuals with CKD, even if they are members of these high-risk and vulnerable populations.

Are all approaches to lipid lowering equal?

The available data strongly suggest that the cardiovascular benefits of lipid-lowering therapy with statins and/or ezetimibe are directly related to the degree of LDL-C lowering achieved. This observation
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<th>Study</th>
<th>Intervention</th>
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<th>CKD stage</th>
<th>Benefits</th>
<th>Kidney function</th>
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<td>(A) RCTs</td>
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<td><strong>SHARP</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
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<td>Simvastatin 20 mg + ezetimibe 10 mg</td>
<td>9270 (3023 on dialysis)</td>
<td>All stages of CKD including dialysis (peritoneal dialysis and HD)</td>
<td>RR: 0.83 (0.74–0.94) on major atherosclerotic events</td>
<td>No effect on progression to ESKD or doubling of serum creatinine or death</td>
<td>No difference in stroke, rhabdomyolysis, hepatitis, gallstones, or cancer</td>
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<td>4D&lt;sup&gt;25&lt;/sup&gt;</td>
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<td>Atorvastatin 20 mg daily vs. placebo</td>
<td>1255</td>
<td>Stage 5 CKD on HD (Type 2 diabetic only)</td>
<td>No effect on composite of death from cardiac causes, fatal stroke, non-fatal MI, or non-fatal stroke</td>
<td>HR: 0.92 (0.77–1.10)</td>
<td>Increased fatal stroke, RR: 2.03 (1.05–3.93), P = 0.04</td>
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<td><strong>AURORA</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>Rosuvastatin 10 mg daily vs. placebo</td>
<td>2776</td>
<td>Stage 5 CKD on HD</td>
<td>No difference in major CV event.</td>
<td>HR: 0.96 (0.84–1.11)</td>
<td>No difference in rhabdomyolysis, myopathy, liver dysfunction, withdrawal, or cancer</td>
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<td><strong>ALERT</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
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<td>Fluvastatin vs. placebo</td>
<td>2102</td>
<td>Renal transplant recipient</td>
<td>No difference in major CV event.</td>
<td>RR: 0.83 (0.6–1.06)</td>
<td>Increase in haemorrhagic strokes in the diabetic subgroup (12 vs. 2 events), P = 0.03</td>
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<td>(B) Systematic review</td>
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<td>Cochrane meta-analysis&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Statins vs. placebo or no treatment or other statins</td>
<td>45 285 (50 studies)</td>
<td>All stages of CKD not on dialysis</td>
<td>RR: 0.72 (0.66–0.79) on major cardiovascular events</td>
<td>No effect on Creatinine clearance</td>
<td>No difference in rhabdomyolysis, liver dysfunction, withdrawal, or cancer</td>
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<tr>
<td>Meta-analysis, Hou et al.&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Statins vs. placebo or conventional therapy</td>
<td>48 429 (31 studies)</td>
<td>All stages CKD of including dialysis</td>
<td>RR: 0.77 (0.70–0.84) for major cardiovascular events</td>
<td>No effect on a composite of 25% declined in eGFR, doubling of serum creatinine, or ESRD, RR: 0.95 (0.90–1.01)</td>
<td>No difference in rhabdomyolysis, liver dysfunction, withdrawal, or cancer</td>
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CKD, chronic kidney disease; RR, risk ratio; HR, hazard ratio; MI, myocardial infarction; ESKD, end-stage kidney disease; CV, cardiovascular; HD, haemodialysis; RCTs, randomized controlled trials.
provides support for the use of the highest safe dose of an appropriate agent in individuals at risk.

There are questions about whether all agents are the same and what the preferred statin dose should be used in people with CKD. Subgroup analyses of trials comparing high vs. low intensity statins in the general population suggest that people with CKD had at least equivalent benefit to those with normal kidney function when high-dose agents were used, without reported differences in the rates of adverse effects.

A more recently reported trial raises questions about the equivalence of different agents in people with kidney disease. In this combined data analysis from two concurrent studies (PLANET I and PLANET II) conducted in proteinuric diabetic (Type 1 and Type 2) and proteinuric non-diabetic CKD, respectively, individuals were randomized to atorvastatin 80 mg, rosuvastatin 10 mg, or rosvastatin 40 mg daily with the primary aim of assessing effects on albuminuria. Not only did the participants treated with atorvastatin have lower levels of proteinuria by the end of the 12-month study, but they also had significantly less decline in kidney function. It is not possible to be certain whether this might reflect a protective effect of atorvastatin or a harmful effect of rosvastatin, but it does suggest that agents shown at least to be safe from a renal perspective (such as simvastatin–ezetimibe and perhaps atorvastatin) might be preferred in people with CKD.

Promising newer cholesterol-lowering agents

With a better understanding of the biological and molecular mechanisms underlying the atherosclerotic process and its interface with lipoprotein metabolism, a number of novel agents for the treatment of dyslipidemia have emerged.

A Phase III clinical trial using fortnightly subcutaneous injection of alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor vs. placebo (n = 2341), in participants at high CV risk (with or without therapy) included some participants with moderate CKD (i.e. eGFR >30 and < 60 mL/min/1.73 m^2). Alirocumab significantly reduced LDL cholesterol by 62% when compared with placebo, and this effect persisted over a treatment period of 78 weeks. Some increase in adverse effects (injection site reaction, myalgia, ophthalmological events, and neurocognitive events including amnesia, memory impairment, and confusional state) was reported in the alirocumab-treated groups. There was evidence of a reduction in the rate of cardiovascular events in a post hoc analysis.

Another large long-term study (n = 4465) examining monthly subcutaneously evolocumab injection plus standard therapy, compared with standard therapy alone, showed similar efficacy for LDL reduction (mean 61%) and a lower incidence of cardiovascular events (HR: 0.47, 95% CI: 0.28–0.78, P = 0.003).

However, neither of these studies has published data on subgroup analyses by kidney function to date. This may be important as patients with advanced CKD have lower serum PCSK9 levels, but retain a positive correlation with LDL-C, suggesting that PCSK9 inhibitors may still play a role in LDL lowering in patients with advanced CKD.

Future perspectives

Recent evidence confirms the large residual CV risk in patients with CKD. Treatment with lipid-lowering agents only moderately reduce atherosclerotic events in these individuals without being proven to alter the mortality outcomes. Therefore, agents that could be used in combination with statins, such as some fibrates (use with caution as increased risk of rhabdomyolysis and reversible GFR decline), or that are more potent than statins, such as PCSK9 inhibitors, or cholesteryl ester transfer protein inhibitors such as anacetrapib or evacetrapib, or apoA-I mimetic peptides, that can raise HDL levels and/or to enhance HDL functionality may have a potential role in altering the high inherent CV risk of this population. As it is generally agreed that high-dose or high-intensity treatment should be prescribed with caution once the GFR falls below 60 mL/min, the window of opportunity is open for controlled trials of new and safer agents, especially in proteinuric patients and also in ESKD.

Conclusion

Current evidence provides convincing data that statin therapy reduces the risk of major CV events in patients with CKD across a broad range of kidney function with some uncertainty persisting for patients receiving dialysis. Although the relative CV protection of statins is significantly modified by kidney function, meaningful reductions in absolute risk would be expected in all stages of CKD, likely including those receiving renal replacement therapy. These data, along with some evidence of varying renal effects with different statins, suggest that those agents proven to be beneficial should be routinely used in CKD patients. Additional protective strategies are urgently required to address the large excess of CV events in the population with ESKD, and novel lipid-lowering approaches offer additional promise in that regard for this high-risk population. Well-designed trials utilizing novel approaches, and/or targeted specifically to proteinuric and advanced kidney failure patients, are required to address the current gaps in the evidence base.

Authors’ contributions

C.W. and V.P. handled funding and supervision; M.G.W. and V.P. acquired the data; M.G.W., C.W., J.K., and V.P. conceived and designed the research; M.G.W. and V.P. drafted the manuscript; M.G.W., C.W., J.K., and V.P. made critical revision of the manuscript for key intellectual content.

Conflict of interest: M.G.W. has received fees for scientific lectures from AstraZeneca. J.K. is a former employee of Johnson & Johnson Pharmaceutical Research and Development and a former consultant to Amgen. He has no current conflicts of interest. V.P. has received honoraria for scientific lectures from Boehringer Ingelheim, Merck, AbbVie, Roche, AstraZeneca, and Servier; he serves on Steering Committees and/or advisory boards supported by Abb-Vie, Astellas, Baxter, Boehringer Ingelheim, BMS, GSK, Janssen, and Pfizer. His employer, the George Institute for Global Health, holds research contracts for trials in cardiovascular and/or kidney disease with a range of commercial organizations. C.W. has received...
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