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REVIEW

Cardiovascular disease in patients with renal disease: the role of statins

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ABSTRACT

Objectives: Atherosclerosis is common in patients with chronic kidney disease (CKD), and cardiovascular disease (CVD) represents a major cause of death. The National Kidney Foundation guidelines favour the use of statin therapy for treatment of dyslipidaemia in patients with CKD. Much evidence supports statin therapy for reducing CVD and improving outcomes in the general population, but there is less evidence in patients with CKD. Consequently, prevention of CVD in CKD is based primarily on extrapolation from non-CKD trials. Significantly, in trials specifically designed to investigate patients with CKD, evidence is emerging for improved cardiovascular outcomes with statin therapy. This review describes available data relating to cardiovascular outcomes and the role of statins in patients with CKD, including predialysis, dialysis, and renal transplant patients.

Research design and methods: The PubMed database was searched (1998–present) to ensure comprehensive identification of publications (including randomised clinical trials) relevant to CKD patients, patterns of cardiovascular outcome in such patients and their relationship to lipid profile, and the role of statins for the prevention and treatment of cardiovascular complications.

Results: There are conflicting data on the relationship between dyslipidaemia and cardiovascular outcomes, with one major study of statin therapy (4D – Deutsche Diabetes Dialyse Studie) providing equivocal results. Further studies, including AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events; NCT00240331) in patients receiving haemodialysis, and SHARP (Study of Heart And Renal Protection; NCT00125593) in patients with CKD including those on dialysis, should help to clarify the role of statin therapy in these populations.

Conclusions: More studies are needed to elucidate the role of statins in improving cardiovascular outcomes for CKD patients. It is anticipated that ongoing clinical trials geared towards the optimal prevention and treatment of CVD in patients with CKD will help guide clinicians in the management of CKD.

Introduction

Chronic kidney disease (CKD) is a worldwide health problem[1]. The number of patients who develop end-stage renal disease (ESRD) requiring dialysis and/or transplantation continues to increase[2,3]. The recent revision of national guidelines towards the adoption of estimated glomerular filtration rate (eGFR) (based on the Modification of Diet in Renal Disease study equation) has focused attention on CKD, and increased the number of patients detected with low GFR. In the UK, approximately 15% of the population has CKD stage III (moderately decreased GFR; 30–59 mL/min per 1.73 m^2), IV (severely decreased GFR; 15–29 mL/min per 1.73 m^2), or V (kidney failure; GFR < 15 mL/min per 1.73 m^2 or dialysis). The US Renal Data System (USRDS) identified 339 cases per million population with ESRD requiring dialysis and transplantation and, in 2001, the number of patients in the US on renal replacement therapy exceeded 1 million[4]. In fact, with an increasing incidence of ESRD due to type 2 diabetes in particular, the number of patients with ESRD is expected to increase by approximately 7% per annum[5,6]. Similarly, the incidence of ESRD is increasing in Europe and Japan[3], posing an enormous social and economic burden.

This review summarises the available data relating to cardiovascular outcomes and the use of statins in patients suffering from CKD, including pre-dialysis, dialysis, and renal transplant patients. An extensive literature search was carried out on PubMed (1998–present) to ensure comprehensive identification of publications, including randomised clinical trials, relevant to these patient groups. We focused particularly on patterns of cardiovascular outcome in patients with CKD, the relationship of cardiovascular outcomes to the lipid profile, and the role of statins for the prevention and treatment of cardiovascular complications. Search terms comprised: chronic kidney disease, dialysis, renal transplant, cholesterol, dyslipidaemia, cardiovascular, coronary, statin (specifically atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin), and each article highlighted in the search was carefully considered and retrieved for possible inclusion if deemed potentially relevant.

CKD: risk factors for cardiovascular disease

A systematic review of 39 studies that followed over 1 million pre-dialysis CKD patients in total demonstrated that CKD was associated with an increased risk for all-cause (relative risk [RR] ranged from 0.94 to 5.0) and cardiovascular-related (RR ranged from 1.4 to 3.7; 14 studies) mortality[7]. Moreover, cardiovascular mortality is more than ten times higher in ESRD patients compared with the general population, and accounts for 50% of premature deaths in dialysis and renal transplant recipients[8,9]. It would seem logical to use strategies proven in the general population to treat patients with CKD. However, this assumes that the patterns of cardiovascular disease (CVD), and its determinants, in patients with CKD are similar to those observed in subjects without renal dysfunction. It seems likely that patients with early CKD are similar to the general population. However, with progression of CKD there is a progressive increase in the prevalence of conventional cardiovascular risk factors. As GFR declines, there is an increase in the prevalence of hypertension and left ventricular hypertrophy (LVH) – such that, in patients who reach ESRD, more than 50% have LVH[10]. The pattern of dyslipidaemia is not constant, and is dependent on both GFR and proteinuria[11]. Deteriorating renal function is also associated with some unique or novel cardiovascular risk factors including increased secretion of parathyroid hormone (PTH), increased production of calcium-phosphate products (markers of vascular calcification), and elevated inflammatory markers and markers of oxidative stress, including C-reactive protein (CRP), fetuin, and homocysteine[12–19].

Dyslipidaemia in CKD

Dyslipidaemia is a major cardiovascular risk factor. Studies consistently show that CKD is associated with compositional changes and metabolic abnormalities in plasma lipoproteins. The key features of dyslipidaemia in pre-dialysis patients are elevated triglycerides (TG), lowered high-density lipoprotein cholesterol (HDL-C), with normal (or low) total cholesterol (TC), and normal (or low) low-density lipoprotein cholesterol (LDL-C)[20–25].

Elevations in TG appear to correlate with decreasing GFR[20] and more than 70% of all patients who have reached ESRD, including transplant recipients, develop an atherogenic dyslipidaemic profile[26–28]. Patients on peritoneal dialysis typically demonstrate increased levels of TC, LDL-C (typically small-dense particles that are readily oxidised), apolipoprotein B, TG, and lipoprotein (a) (Lp[a]), and decreased HDL-C and apolipoprotein A[29–34]. In contrast, patients on haemodialysis have been reported to have near-normal LDL-C, increased oxidised LDL-C, TG, very-LDL-C (VLDL-C) and Lp(a), the presence of TG-rich VLDL-C, and decreased HDL-C [23,29,31,35–37].

Table 1. Dyslipidaemia in CKD patients (relative to the general population)

	Pre-dialysis	Haemodialysis	Peritoneal dialysis	Kidney transplant
TC	Normal[20]	Normal (or decreased)[31,37]	Increased[31]	Increased[39]
HDL-C	Decreased[20]	Decreased[37]	Decreased[31]	Decreased[39]
LDL-C	Normal (or decreased)[21]	Normal (or decreased)[37]	Increased[31]	Increased[39]
Small dense LDL-C	Increased[22]	Increased (triglyceride enriched)[37]	Increased[32]	–
VLDL-C	Increased[23]	Increased[37]	Increased[32]	Increased[39]
IDL-C	Increased[23]	Increased[37]	Increased[33]	–
TG	Increased[20]	Increased[37]	Increased[33]	Increased[39]
Lp (a)	Possibly increased[24,25]	Increased (or normal)[37]	Increased[34]	–
ApoAI	Decreased[24]	Decreased[31]	Decreased[31]	–
ApoAII	Decreased[23]	Decreased[31]	Decreased[31]	–
ApoB	Increased[24]	Normal[31]	Increased[31,32]	–
CRP	Increased[24]	–	–	–

ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII; ApoB, apolipoprotein B; CKD, chronic kidney disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IDL-C, intermediate-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein (a); TC, total cholesterol; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol; –, data not available

In renal transplant patients[38] the pattern of dyslipidaemia is again different and is characterised by elevated TC, LDL-C, VLDL-C, and TG, and markedly reduced HDL-C[39–41], reflecting the effects of immunosuppressant agents (Table 1).

Unlike the general population, the impact of dyslipidaemia on coronary artery disease (CAD), and wider cardiovascular outcomes in CKD patients, is unclear. The available evidence has been drawn from *post hoc* analyses of cardiovascular interventional trials with the caveat that these data reflect patients with CVD and co-existent CKD rather than patients with primary, progressive CKD[15]. In patients with ESRD, the relationship between TC, LDL-C, and cardiovascular outcomes is usually the reverse of that seen in the general population – patients with lower cholesterol levels are at greatest cardiovascular risk[42]. However, it is unlikely that high cholesterol levels have a protective effect in ESRD patients. It has been shown that hypercholesterolaemia is an independent risk factor for CVD mortality in a subgroup of dialysis patients without evidence of systemic inflammation and malnutrition[43]. The mechanism by which inflammation and malnutrition confounds the association between serum cholesterol and mortality has not been fully elucidated but it would appear that ill-health and poor nutrition cause both lower cholesterol levels and a higher risk of death[44], and it is important to take this into account when considering CVD risk in dialysis patients[43]. In renal transplant recipients there is, however, a progressive relationship between lipid levels and CAD events[41], although the relationship with other cardiovascular endpoints is less clear.

The nature and determinants of CVD in CKD

The situation is further complicated by the fact that the pattern of CVD in patients with ESRD differs from that found in the general population, with an excess risk of sudden death or heart failure, and fewer non-fatal ischaemic events. The pattern is more akin to that of patients with chronic heart failure (CHF) than CAD[45]. Table 2 shows the pattern of outcome in the 4S (Scandinavian Simvastatin Survival Study) of patients with ischaemic heart disease, compared to those of the 4D study (Deutsche Diabetes Dialyse Studie) of type 2 diabetes patients on haemodialysis and the ALERT (Assessment of Lescol in Renal Transplantation) study of renal transplant recipients[46–48]. These studies show that patients with ESRD, whether treated by haemodialysis or transplantation, have an increased cardiovascular event rate that is due to a greatly increased RR of fatal cardiac events[49]. Similar data reporting an increased risk of fatal cardiac events, presumed to be either primary arrhythmias or arrhythmias secondary to ischaemic events, have been reported in Registry data (e.g. USRDS) and also in patients with CKD[50,51].

The explanation for this atypical spectrum of CVD is probably a reflection of the severe LVH, with associated myocardial fibrosis[52], that accompanies progressive renal disease[53]. This, in turn, is likely to predispose to aberrant conduction and arrhythmias. In keeping with this hypothesis, increased QT dispersal (a marker for ventricular arrhythmias) and arrhythmias are associated with ESRD, specifically LVH in ESRD[54].

Table 2. *Mortality and major cardiovascular outcomes in the 4S, 4D, and ALERT studies*

Outcome (% of patients)	4S[46] (IHD)			4D[47] (T2D on haemodialysis)			ALERT[48] (renal transplant)		
	Placebo ($n=2223$)	SMV 10, 20, or 40 mg od* ($n=2221$)	RR (95% CI)	Placebo ($n=636$)	ATV 20 mg od ($n=619$)	RR (95% CI)	Placebo ($n=1052$)	FLV 40 mg od† ($n=1050$)	RR (95% CI)
Fatal event									
All cardiac	9.3	6.1	0.65 (0.52–0.80)	23.4	19.5	0.81 (0.64–1.03)	5.1	3.4	0.62 (0.40–0.96)
All coronary	8.5	5.0	0.58 (0.46–0.73)	6.4	4.7	–	–	–	–
Definite MI	2.8	1.4	–	5.2	3.7	–	–	–	–
Cerebrovascular	0.5	0.6	–	2.0	4.4	2.03 (1.05–3.93)	1.3	1.5	–
Non-cardiac death	2.2	2.1	–	24.8	24.1	0.95 (0.76–1.18)	6.2	7.3	1.20 (0.86–1.67)
Non-fatal event									
All coronary	22.6	15.9	–	24.2	20.8	–	–	–	–
Definite MI	12.1	7.4	–	12.4	11.3	0.88 (0.64–1.21)	6.3	4.4	0.68 (0.40–1.00)
Cerebrovascular	4.3	2.7	–	5.0	5.3	1.04 (0.64–1.69)	5.5	4.7	–

4D, Deutsche Diabetes Dialyse Studie (median follow-up 4 years); 4S, Scandinavian Simvastatin Survival Study (median follow-up 5.4 years); ALERT, Assessment of Lescol in Renal Transplantation trial (median follow-up 5.1 years); ATV, atorvastatin; CI, confidence interval; FLV, fluvastatin; IHD, ischaemic heart disease; MI, myocardial infarction; RR, risk ratio; SMV, simvastatin; T2D, type 2 diabetes; –, data not available

*10, 20, or 40 mg daily (dose adjusted as appropriate); †40 mg daily, doubled to 80 mg daily after ~2 years

Table 3. National Kidney Foundation Guidelines for managing dyslipidaemias in adults with CKD[30]*

Dyslipidaemia	Goal	Initiate	Increase	Alternative
TG ≥500 mg/dL	TG < 500 mg/dL	TLC	TLC + fibrate or niacin	Fibrate or niacin
LDL-C 100–129 mg/dL	LDL-C < 100 mg/dL	TLC	TLC + low dose statin	Bile acid sequestrant or niacin
LDL-C ≥130 mg/dL	LDL-C < 100 mg/dL	TLC + low dose statin	TLC + max dose statin	Bile acid sequestrant or niacin
TG ≥200 mg/dL and non-HDL-C ≥130 mg/dL	Non-HDL-C < 130 mg/dL	TLC + low dose statin	TLC + max dose statin	Fibrate or niacin

CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TLC, therapeutic lifestyle changes

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The major determinants of LVH are hypertension and vascular stiffness. The latter is increased in CKD and ESRD, and may be particularly severe in this population because of the presence of vascular calcification in CKD.[55]

Statin therapy in patients with CKD

The few interventional trials that have been performed in patients with renal disease require careful assessment. There have been studies of patients with CKD recruited to statin trials, re-analysed by *post hoc* assessment of eGFR. These show that patients with pre-existing CVD (and CAD) specifically show a similar pattern to that seen in the general population with regard to lipid lowering and reduction of cardiovascular events[11,56]. An important observation in these trials is that low eGFR is often associated with clustering of conventional risk factors, suggesting that the benefits of statin therapy may reflect high conventional cardiovascular risk rather than risk due to CKD *per se*.

The only study of any significant size in patients with primary renal disease is the Dutch PREVEND IT (Prevention of REnal and Vascular ENdstage Disease Intervention Trial)[57]. This study failed to show a significant benefit on cardiovascular events overall with pravastatin 40 mg (the hazard ratio [HR] for the combined primary endpoint, cardiovascular mortality or hospitalisation for cardiovascular morbidity, was 0.87; 95% confidence interval [CI]: 0.49–1.57; $p = 0.649$). However, this study was underpowered for this endpoint and the overall event rate in the study was considerably lower than anticipated.

The National Kidney Foundation (NKF) guidelines favour drug therapy, including statins, for the treatment of dyslipidaemia in CKD, with treatment determined by the patient's lipid profile (Table 3)[30]. Randomised trials have provided very little information on the effects of statins in patients with CKD[58,59], and the NKF guidelines on dyslipidaemia treatment closely follow those recommended by the National Cholesterol Education Program Adult Treatment Program (NCEP ATPIII)[60]. *Post hoc* data analyses from large pivotal studies show that statins benefit both the lipid profile and renal function in CKD[58,61–63]; however, their effect on CVD remains unresolved.

Potential pleiotropic effects of statins in CKD

Impact on renal function

Hyperlipidaemia may exacerbate pre-existing kidney disease and accelerate kidney disease progression[64]. Whether statins have a beneficial effect on renal function is, however, controversial. The available data is shown in Table 4[44,57,64–76]. Several statin trials in pre-dialysis CKD patients have shown benefit towards renal function from either their lipid-lowering or pleiotropic effects[67–75], with only a few notable exceptions[57,76]. Notably, several meta-analyses[44,64,77] have shown that statin therapy results in a modest reduction in proteinuria. Although the meta-analysis by Strippoli *et al.*[44] failed to show a concomitant improvement in GFR, other meta-analyses and studies[64–66,78] have shown a significant but modest reduction in the rate of kidney function loss (Table 4). However, significant heterogeneity of results has been demonstrated and clinically important endpoints e.g. doubling of creatinine, requirement of chronic dialysis, or death have rarely been included in studies to date. Moreover, further studies are required to confirm the benefit of statins in specific populations, particularly those with differing stages of CKD. It is also unclear whether the potential beneficial effect of statins on renal function

Table 4. *Impact of statin therapy on renal function in pre-dialysis CKD patients*

Study	Design	Patient type	Key findings	Comments
Meta-analyses				
Fried *et al.*[65]	Meta-analysis of 13 pc trials Most patients treated with statins	Glomerulonephritis and/or diabetic nephropathy ($n=362$)	GFR decline significantly slowed by 1.9 mL/min per year in treatment group vs. placebo ($p=0.008$) No difference regarding proteinuria	
Sandhu *et al.*[64]	Meta-analysis of 27 controlled or crossover trials of statins that reported assessment of kidney function	Glomerulonephritis, cardiovascular disease, diabetes, hypertension, hyperlipidaemia, or general ($n=39\,704$)	GFR decline slowed by 1.22 mL/min per year in statin recipients	In subgroup analysis, the benefit of statins remained significant in cardiovascular disease but not in diabetic or hypertensive kidney disease or glomerulonephritis
Vidt *et al.*[66]	Meta-analysis of 13 RSV studies with serum creatinine measured at baseline and 6–8 weeks after RSV initiation	Baseline proteinuria Baseline eGFR < 60 mL/min/1.73 m^2, hypertension, and/or diabetes ($n=3956$)	GFR increased significantly ($p<0.01$) across all doses of RSV (5–40 mg) compared with baseline (by 0.9–3.2 mL/min/1.73 m^2)	In five blinded, PI-controlled studies, GFR increased by a mean of 0.8 mL/min/1.73 m^2 in the RSV group compared with a decrease of 1.5 mL/min/1.73 m^2 in the Pl group ($p<0.001$)
Strippoli *et al.*[44]	Meta-analysis of 50 randomised, controlled studies of statins	Chronic kidney disease ($n=30\,144$)	Significant reduction in 24-h urinary protein excretion in pre-dialysis patients treated with a statin compared with Pl (weighted mean difference: –0.73 g/24 h [95% CI: –0.95 to –0.52]) (6 studies; 311 patients)	No difference in creatinine clearance between groups
Studies showing a positive impact of statins on renal function				
Bianchi *et al.*[67]	Controlled, open-label, then pc 1 year with ACEi and/or ARB before randomisation for 1 year to additional ATV or placebo	Hypercholesterolaemia Mean GFR 50 mL/min Proteinuria 2.2 g/24 h ($n=56$)	Slower decline in CrCI with ATV (−1.2 mL/min) vs. placebo (−5.8 mL/min, $p<0.01$) CrCl 49.8 mL/min (statin) vs. 44.2 mL/min (Pl) 57% reduction in proteinuria with statin vs. 31% with placebo ($p<0.01$) Mean proteinuria 1.5 g/day for statin vs. 2.2 g/day for placebo	Only statin trial to date of reasonable size and duration in a population of patients with CKD Small unblinded study Statins may reduce proteinuria and rate of progression of CKD, but larger randomised, controlled studies are necessary to confirm

(*continued*)

Table 4. *Continued*

Study	Design	Patient type	Key findings	Comments
van Dijk *et al.*[68]	Double-blind, crossover 4 weeks SMV and 4 weeks placebo	ADPKD Normocholesterolaemia ($n=10$)	Significant rise in GFR by 8 mL/min with SMV ($p<0.05$)	SMV can ameliorate renal function in ADPKD patients, by increase in renal plasma flow Based on only 10 patients and 4 weeks of therapy
Tonolo *et al.*[69]	Crossover, 10 months SMV and 10 months CHL in random order	Type 2 diabetes Hypertension Microalbuminuria ($n=26$)	SMV and CHL equally effective in reducing cholesterol levels Significant reduction in albumin excretion with SMV, but not with CHL No effect on renal function as measured by serum creatinine and GFR	More evidence for a small benefit from pleiotropic statin effects, independent of cholesterol lowering
Lee *et al.*[70]	3 months Pl then randomised to Pl ± ARB or PVT ± ARB for 6 months	Proteinuria Normolipidaemia ($n=63$)	Significant reduction in proteinuria vs. baseline excretion for PVT ± ARB ($p<0.0001$)	No correlation between lipids and reduction in proteinuria – possible pleiotropic benefit of statins
Tonelli *et al.*[71] (subgroup analysis of the CARE study)	*Post hoc* analysis of double-blind, pc study of PVT vs. Pl	Previous MI and moderate CKD (GFR < 60 mL/min/1.73 m^2) ($n=690$)	Overall, there was no significant difference in GFR decline between groups, but there was a benefit in patients with lower GFR at baseline. Rate of change in MDRD-GFR was 0.6 mL/min/1.73 m^2/y (95% CI: –0.1 to 1.2; $p=0.07$) slower in the PVT than Pl group in those with MDRD-GFR < 50 mL/min, and 2.5 mL/min/1.73 m^2/y (95% CI: 1.4–3.6; $p=0.0001$) slower in those with MDRD-GFR < 40 mL/min per 1.73 m^2/y	PVT also reduced rates of renal loss to a greater extent in subjects with proteinuria at baseline compared with those without proteinuria ($p=0.006$)
Athyros *et al.*[72] (subgroup analysis of the GREACE study)	Randomised, open-label trial; patients received usual care with or without a statin, or structured, dose-titrated ATV	Established coronary heart disease	Patients not treated with statins ($n=704$) showed a 5.2% decrease in creatinine clearance, whereas patients receiving structured care on atorvastatin ($n=783$) had a 12% increase in creatinine clearance ($p<0.0001$)	

(*continued*)

Table 4. *Continued*

Study	Design	Patient type	Key findings	Comments
Kano *et al.*[73]	Controlled, randomised to FVS + dipyridamole, or dipyridamole alone for 1 year	Normocholesterolaemia Paediatric patients with mild IgA nephropathy ($n = 30$)	Significant reduction from baseline after 1 year in urinary protein, haematuria and serum creatinine levels in the combined treatment group	FVS + dipyridamole yields an antiproteinuric effect and amelioration of renal function
Kano *et al.*[74]	Controlled, randomised to FVS or dipyridamole for 2 years	Normocholesterolaemia Paediatric patients with mild minimal change glomerulonephritis ($n = 36$)	2 years following study end, proteinuria, haematuria and creatinine significantly lower for FVS both vs. baseline and vs. dipyridamole	Confirms Kano *et al.*[73] findings
Shepherd *et al.*[75] (subanalysis of TNT study)	Double-blind, randomised study of ATV 10 mg vs. ATV 80 mg	Coronary heart disease and LDL-C <130 mg/dL ($n = 9656$)	At median follow-up of 59.5 months, mean GFR increased from baseline by 3.5 ± 0.14 mL/min/1.73 m^2 with 10 mg ATV and by 5.2 ± 0.14 mL/min/1.73 m^2 with 80 mg ($p < 0.0001$ for treatment difference)	The expected 5-year decline in renal function was not observed with ATV treatment
Studies showing no impact of statins on renal function				
Asselbergs *et al.*[57] (PREVEND IT)	Double-blind trial with patients randomised to PVT 40 mg or Pl and fosinopril 20 mg or PI	Persistent microalbuminuria ($n = 864$)	PVT had no effect on 24 h urinary albumin excretion during the 4-year follow-up	Urinary albumin excretion was reduced in the fosinopril group compared with the placebo group during the entire study period ($p < 0.05$)
Rahman *et al.*[76] (report from ALLHAT)	*Post hoc* analysis of randomised clinical trial of PVT 40 mg vs. usual care	Hypertensive, dyslipidaemic patients stratified according to baseline eGFR ($n = 10\,060$)	No difference in the 6-year rates of ESRD was seen between the PVT and usual care groups (1.36/100 vs.1.45/100 patients; $p = 0.9$)	These findings were similar when patients were stratified according to GFR at baseline (≥90, 60–89 or < 60 mL/min/1.73 m^2)

ACEi, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin AT1 receptor antagonist; ATV, atorvastatin; CARE, Cholesterol and Recurrent Events; CHL, cholestyramine; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; e-GFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FVS, fluvastatin; GREACE, GREek Atorvastatin and Coronary heart disease Evaluation study; IgA, immunoglobulin A; LDL-C, low-density lipoprotein cholesterol; MDRD-GFR, Modification of Diet in Renal Disease GFR; MI, myocardial infarction; pc, placebo-controlled; Pl, placebo; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PVT, pravastatin; RSV, rosuvastatin; SMV, simvastatin; TNT, Treating to New Targets study

results from their direct renal effects, or improved renal perfusion associated with improved endothelial or cardiac function and/or decreased exposure to events associated with acute renal failure; again, further studies are warranted to address this question.

Other lipid-lowering therapies have also been investigated for their impact on renal function. In the LRC CPP (Lipid Research Clinics Coronary Primary Prevention) trial, renal function was examined in 3603 middle-aged men, with TC levels > 265 mg/dL and baseline eGFR of ≥60 mL/min/1.73 m^2 treated with cholestyramine 24 g daily or placebo[79]. During almost 8 years of follow-up, TC and LDL-C were significantly reduced in the cholestyramine versus the placebo group ($p < 0.0001$). Although renal function improved slightly in both groups over the course of the study, neither the GFR nor serum creatinine concentrations were significantly different between the cholestyramine and placebo groups. Thus, decreasing lipid levels alone may not be sufficient to protect renal function, although it should be noted that the magnitude of lipid lowering attainable with cholestyramine is lower than that of the statins.

There have been reports that statins (particularly high-dose rosuvastatin) increase proteinuria[80,81]. An independent analysis of risks of rosuvastatin concluded that this proteinuria was mild, of tubular origin, observed most frequently at the highest approved doses, and tended to be transient. Notably, no negative effects on renal function have been detected for rosuvastatin or other statins at recommended doses[81,82].

Impact on cardiovascular events

Statin-related pleiotropic effects are increasingly considered important in reducing cardiovascular events[83], perhaps through improved endothelial function[84,85] and reduction of the pro-inflammatory marker CRP[86]. Much evidence suggests that beneficial pleiotropic effects occur independently of LDL-C-lowering[87], although a recent meta-analysis suggested that 89–98% of CRP change was related to LDL-C-lowering[88]. Outcomes data relating to the cardiovascular benefits of reducing CRP are awaited[86].

Pre-dialysis patients. A number of trials involving pre-dialysis CKD patients with CHD have demonstrated a beneficial effect of statin therapy. In a subanalysis of the TNT (Treating to New Targets) study of patients ($n = 3107$) with CHD and pre-existing CKD (eGFR < 60 mL/min/1.73 m^2), atorvastatin 80 mg was shown to reduce the risk of major cardiovascular events significantly compared with atorvastatin 10 mg after a median follow-up of 5 years (HR 0.68; 95% CI: 0.55–0.84; $p = 0.0003$)[89]. Similar risk reduction with atorvastatin 80 mg was observed in a further subanalysis of the TNT study of patients ($n = 546$) with diabetes and CKD (HR 0.65; 95% CI: 0.43–0.98; $p = 0.04$)[90].

Moreover, in the CARE (Cholesterol and Recurrent Events) study of patients ($n = 159$) with mild CKD (creatinine clearance ≤75 mL/min), a history of acute myocardial infarction (MI), and total plasma cholesterol <240 mg/dL, pravastatin 40 mg significantly reduced the incidence of death from coronary disease or symptomatic non-fatal MI compared with placebo[91]. After a median follow-up of 58.9 months, the adjusted HR for this primary outcome was 0.72 (95% CI: 0.55–0.95; $p = 0.02$).

However, there have been very few studies carried out in CKD patients who have not had a previous vascular event (primary prevention)[44]. Patients in the HPS (Heart Protection Study) were stratified according to the presence of diabetes; approximately half of the patients with diabetes had evidence of vascular disease and 5% had elevated blood creatinine concentrations (≥ 110 μmol/L for women and ≥ 130 μmol/L for men)[92]. In diabetes patients who did not have a diagnosis of occlusive artery disease at study entry, there was a 33% reduction in first major vascular event with simvastatin versus placebo (95% CI for the reduction: 17–46; $p = 0.0003$). Moreover, the risk reduction with simvastatin was greater in diabetes patients with elevated creatinine (34.5% of simvastatin-treated vs. 44.6% of placebo patients experienced a first major cardiovascular event) than in those without elevated creatinine (19.5 vs. 23.9%, respectively)[92]. Also of note, the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm) evaluated atorvastatin 10 mg in the primary prevention of CHD in 10 305 hypertensive patients who were not deemed conventionally dyslipidaemic (TC ≤6.5 mmol/L). Overall, atorvastatin produced a significant reduction in major cardiovascular events (non-fatal MI plus fatal CHD) relative to those treated with placebo (HR 0.64; 95% CI: 0.50–0.83; $p = 0.0005$), despite the relatively short follow-up time of 3.3 years, with similar results observed in the cohort of patients with renal dysfunction at baseline[62].

Dialysis patients. Statin-related beneficial effects towards risk factors for CVD in dialysis patients are evident[56,93,94]. In a secondary observational data analysis relating to 3716 patients on dialysis from the USRDS Dialysis Morbidity and Mortality Wave-2 study[56], statin use was independently associated with

a reduced risk of total mortality (RR 0.68; 95% CI: 0.54–0.87), as well as cardiovascular-specific mortality (RR 0.64, 95% CI: 0.45–0.91); this was in contrast to the use of fibrates (RR 1.29, 95% CI: 0.85–1.95). However, significant limitations of this study, characteristic of registry-based assessments, meant that the authors could not confirm whether the reduced mortality was related to changes in lipid levels (i.e. 83% of the HDL-C and LDL-C values were missing).

Data from the multinational DOPPS I (Dialysis Outcomes and Practice Patterns Study) have also suggested that statins reduce the risk of mortality in haemodialysis patients. In this observational study of 7365 prevalent dialysis patients, statins were prescribed for 11.8% of patients. Statin-prescribed patients had a 31% lower RR for death compared with those not prescribed statins (HR 0.69; 95% CI: 0.60–0.79; $p<0.0001$)[95]. Statin therapy was also associated with a 44% reduction in non-cardiovascular mortality (HR 0.56; 95% CI: 0.46–0.69; $p<0.0001$), though – since this is an observational study – there is the potential that this could at least partially reflect treatment selection bias[95].

Also, as described earlier, despite showing a marked reduction in LDL-C, studies such as 4D (in which LDL-C levels were lowered by 42% with atorvastatin)[47] have failed to show beneficial effects of statins on cardiovascular outcomes in patients on haemodialysis and with type 2 diabetes mellitus. The 4D study assessed the benefits of atorvastatin 20 mg per day (vs. placebo) for approximately 4 years in this patient population. The composite primary cardiovascular endpoint (death from cardiac causes, fatal stroke, non-fatal MI, or non-fatal stroke, whichever occurred first) was reduced by 8%, a non-significant finding, and the incidence of MI was reduced by 7%. However, more cases of fatal stroke occurred with atorvastatin (27 cases in 619 patients) than with placebo (13 cases in 636 patients; RR 2.03; 95% CI: 1.05–3.93; $p=0.04$), contributing to the reduced treatment effect on the primary endpoint. The opposite was found for all cardiac events combined (RR 0.82; 95% CI: 0.68–0.99; $p=0.03$, nominally significant), and statin therapy was well tolerated overall. The authors of the 4D study considered these disparate and unexpected results to be related to the advanced stage of atherosclerosis and complex pathogenesis of vascular lesions in patients with diabetes[47].

Renal transplant patients. While treatment that is effective in reducing CVD-related morbidity and mortality in the general population may also be effective in high-risk renal transplant patients, few interventional trials have been performed in these patients. The ALERT study was one of the first placebo-controlled trials evaluating the effect of fluvastatin on risk of a major adverse cardiac event (i.e. cardiac death, non-fatal MI, or coronary intervention procedure) in transplant recipients[48]. ALERT compared fluvastatin 40–80 mg per day to placebo on cardiovascular outcomes in 2100 renal transplant recipients[48,96]. Notably, fluvastatin is not metabolised by CYP 3A4 and thus presents advantages in transplant recipients receiving calcineurin inhibitors that inhibit this enzyme.

Fluvastatin was well tolerated and produced lipid-lowering benefits comparable to other statins in other populations – 40 mg per day lowered LDL-C by >30%[48] and significantly reduced the risk of cardiac death and non-fatal MI by up to 56% in patients starting fluvastatin <4.5 years after renal transplantation (RR 0.44; 95% CI: 0.26–0.74; $p=0.002$)[96]. However, as in the 4D study (which investigated atorvastatin 20 mg in patients on haemodialysis), fluvastatin treatment over a median follow-up of 5.1 years produced a non-significant risk reduction in the composite primary cardiovascular endpoint (cardiac death, non-fatal MI, or coronary revascularisation procedure) (RR 0.83; 95% CI: 0.64–1.06; $p=0.139$)[48]. The failure of the primary composite cardiovascular endpoint to achieve significance was a reflection of lack of effect on other cardiovascular endpoints, as the incidence of cardiac death or non-fatal MI in the overall study population was significantly reduced by 35% with fluvastatin (RR 0.65; 95% CI: 0.48–0.88; $p=0.005$)[48]. This was due to inadvertent underpowering of the study, but further analysis of the ALERT cohort confirmed that early initiation of statin therapy provides markedly greater reduction in cardiac risk versus later initiation[96]. Moreover, a 2-year open-label extension to the ALERT study, during which patients received fluvastatin 80 mg/day, showed effective reduction in LDL-C comparable with other statins, a sustained reduction in risk of major adverse cardiac event (HR 0.79; $p=0.036$), and a 29% reduction in cardiac death or definite non-fatal MI (HR 0.71; $p=0.014$)[97]. The ALERT study yielded additional interpretations of the link between cardiovascular risk factors and individual cardiovascular events. Thus, all lipid subfractions were associated with conventional risk of MI, which was not dependent on blood pressure or the level of renal dysfunction. However, cardiac death was more dependent on blood pressure and the presence of LVH (particularly with ischaemic changes), and GFR[41].

When considering the use of statins in transplant patients it is important to bear in mind that immunosuppressant therapy, particularly cyclosporine, has the

potential to increase plasma concentrations of these agents[30].

Taken together, these data – from statin trials, epidemiological data, and observational studies – suggest that CVD in patients with primary CKD may differ from the general population at least in later stages of CKD. There is an increased risk of fatal cardiovascular events rather than MI. This is likely to be due to the presence of LVH and myocardial fibrosis that predispose to the development of arrhythmias. The challenge is to identify ways of combating the excess risk of cardiac death. The most likely approach is to produce regression of LVH (or prevent its development) by tighter control of blood pressure and by treating its non-haemodynamic mechanisms.

Although conclusive evidence for improved cardiovascular outcomes with statin therapy in CKD is not yet available, strong support is provided by a recent meta-analysis of 30 placebo-controlled trials, which showed that fluvastatin significantly reduced the combined incidence of cardiac death and non-fatal MI in patients with normal renal function–mild impairment (−30%; $p = 0.009$) and moderate–severe renal impairment (–41%; $p = 0.007$)[98]. Furthermore, a recent meta-analysis of 50 randomised, controlled studies involving > 30 000 patients has examined the effects of statins in pre-dialysis, dialysis, or renal transplant patients, most of whom had established occlusive arterial disease[44]. In 43 studies involving 10 894 patients treated with a statin and 10 993 patients receiving placebo or no treatment, fatal cardiovascular events were found to be reduced by 19% with statin therapy (RR 0.81; 95% CI: 0.73–0.90). Similarly, in eight studies (statin therapy, $n = 11\,361$; placebo/no treatment, $n = 11\,502$) non-fatal cardiovascular events were reduced by 22% (RR 0.78; 95% CI: 0.73–0.84). The magnitude of benefit appeared to be similar in pre-dialysis, dialysis, and renal transplant patients. In contrast, no effect on all-cause mortality was established (44 studies, 23 665 patients in total; RR 0.92; 95% CI: 0.82–1.03), although this may reflect inadequate statistical power for this endpoint[44]. In addition, *post hoc* analysis of data from patients with mild renal insufficiency from the 4S study showed a beneficial effect of simvastatin on cardiovascular outcomes[99]. Conflicting data have been reported[57], however, along with negative data following dietary supplementation with n-3 polyunsaturated fatty acids, known to have potentially protective effects towards the vasculature[100]. It is anticipated that large ongoing prospective statin trials with cardiovascular endpoints may support the adjunctive use of these agents in high-risk CKD patients[101].

In support of the safety of statins in patients with CKD, the meta-analysis by Strippoli and colleagues found no significant difference in the risk of withdrawal from the study owing to adverse events for statins relative to placebo (20 studies, 4887 patients; RR 1.03; 95% CI: 0.84–1.25)[44]. Moreover, there was no significant increase in the risk of abnormalities in liver function tests or raised creatinine phosphokinase (which is a risk factor for rhabdomyolysis) (29 studies, 6829 patients; RR 1.5; 95% CI: 0.86–2.59)[44].

Ongoing and future trials

These observations suggest that we require further larger-scale outcome studies of cardiovascular endpoints in patients with CKD, including pre-dialysis, dialysis, and renal transplant patients. Whether statin therapy is beneficial in these populations has yet to be fully established, given the fact that neither the 4D study (in haemodialysis patients)[47] nor the ALERT trial (in renal transplant patients)[48] achieved statistical significance in their primary aims, and that the beneficial effects in early CKD are reliant on *post hoc* analyses of non-renal trials. Two statin trials in patients with primary renal disease currently underway, SHARP (Study of Heart and Renal Protection)[102], and AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events)[103,104], should provide answers to these questions.

The inclusion criteria for AURORA and SHARP differ in that AURORA (rosuvastatin) includes patients with ESRD on chronic haemodialysis (< 25% with type 2 diabetes mellitus, and approximately 50% with a history of CVD)[104]. In contrast, SHARP (simvastatin and ezetimibe) includes patients with CKD, approximately 70% pre-dialysis and without established CHD[102]. It is anticipated that results from both AURORA and SHARP will help determine the best preventative treatments for patients with CKD, particularly as both have clearly defined baseline criteria (relative to CKD) and thus should help to clarify the benefits of statins at different stages of CKD.

It should be noted that despite recent reports of a potential increased risk of cancer in patients taking a combination of simvastatin and ezetimibe[105], further analyses of three ezetimibe trials concluded that the results did not provide credible evidence of any adverse effect of ezetimibe on rates of cancer[106]. Therefore, the Independent Data and Safety Monitoring committee of SHARP has recommended that the trial continues to its scheduled end date of 2010.

Two other trials that concern the potential renoprotective properties of statins are also ongoing. The

LORD (Lipid lowering and Onset of Renal Disease) trial aims to assess the effectiveness of atorvastatin 10 mg on slowing the progression of kidney disease in a population of patients with CKD (serum creatinine > 120 μmol/L)[107]. The requirement for ESRD management will also be assessed. Furthermore, ESPLANADE (Statins in Proteinuric Nephropathies – NCT00199927) will soon report on whether fluvastatin 40 or 80 mg in combination with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers can reduce proteinuria in patients with diabetic nephropathy (creatinine clearance > 20 mL/min/1.73 m^2). The results of these trials, together with those from AURORA and SHARP, should help to further elucidate the role of statins in the treatment of patients with CKD.

Limitations of this review

This review provides a broad summary of the current information on the impact and therapy of CVD in CKD patients, but there are some limitations in the information presented concerning the lack of high-quality, randomised, controlled trials currently available, and this makes definitive conclusions difficult. To date, most results stem from *post hoc* assessment of patients recruited to statin trials and stratified according to baseline eGFR, with few prospective studies specifically in patients with CKD. Whilst the data presented are generally supportive of the role of statins in the secondary prevention of CVD in patients with CKD, the role of statins for primary prevention is something that remains largely unanswered.

A further limitation concerns the search strategies utilised for this review. The literature search concentrated on the PubMed database. Although we also examined the reference sections of those papers considered to be relevant to the topic, the use of a single database presents the possibility that not all relevant literature on the subject may have been captured.

Conclusions

There is abundant evidence to support the efficacy and tolerability of statins for reducing the burden of CVD and improving outcomes in the general population. There are sound theoretical and mechanistic reasons why these benefits should also apply to the growing population with CKD. Appreciation that individual cardiovascular events may have different determinants, and that the pattern of CVD in patients with CKD may differ from that found in the general population, will help to clarify the impact of specific interventions, such as statin therapy, on overall cardiovascular endpoints. Thus, statin therapy may be primarily effective in preventing cardiac events dependent on lipid levels rather than sudden cardiac death dependent on arrhythmia or LVH. Optimal preventative management of CVD in ESRD may therefore consist of combination therapy involving statin administration together with other treatments of hypertension, inflammation, vascular calcification etc. The results of ongoing studies, such as AURORA and SHARP, should help to confirm the role of statin treatment in CKD patients.

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