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MINIREVIEW

Treatment of dyslipidemia in chronic kidney disease: Effectiveness and safety of statins

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Abstract

Several cardiovascular (CV) risk factors may explain the high rate of CV death among patients with chronic kidney disease (CKD). Among them both traditional and uremia-related risk factors are implicated and, moreover, the presence of kidney disease represents "*per se*" a multiplier of CV risk. Plasma lipid and lipoprotein profiles are changed in quantitative, but above all in qualitative, structural, and functional ways, and lipoprotein metabolism is influenced by the progressive loss of renal function. Statin therapy significantly reduces cholesterol synthesis and both CV morbidity and mortality either directly, by reducing the lipid profile, or *via* pleiotropic effects; it is supposed to be able to reduce both the progression of CKD and also proteinuria. These observations derive from a post-hoc analysis of large trials conducted in the general population, but not in CKD patients. However, the recently published SHARP trial, including over 9200 patients, either on dialysis or pre-dialysis, showed that simvastatin plus ezetimibe, compared with placebo, was associated with a significant low-density lipoprotein cholesterol reduction and a 17% reduction in major atherosclerotic events. However, no benefit was observed in overall survival nor in preserving renal function in patients treated. These recent data reinforce the conviction among nephrologists to consider their patients at high CV risk and that lipid lowering drugs such as statins may represent an important tool in reducing atheromatous coronary disease which, however, represents only a third of CV deaths in patients with CKD. Therefore, statins have no protective effect among the remaining two-thirds of patients who suffer from sudden cardiac death due to arrhythmia or heart failure, prevalent among CKD patients. The safety of statins is demonstrated in CKD by several trials and recently confirmed by the largest SHARP trial, in terms of no increase in cancer incidence, muscle pain, creatine kinase levels, severe rhabdomyolysis, hepatitis, gallstones and pancreatitis; thus confirming the handiness of statins in CKD patients. Here we will review the latest data available concerning the effectiveness and safety of statin therapy in CKD patients.

Key words: Chronic kidney disease; Dyslipidemia; Statins; Hypercholesterolemia; Cardiovascular risk; Dialysis; 3-hydroxy-methyl-glutaryl-Coenzyme reductase; Hypertension; Inflammation; Renal disease; Kidney

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INTRODUCTION

The incidence of chronic kidney disease (CKD) is rapidly

increasing all over the world mainly driven by the ageing of the general population and by increased survival from cancer and major cardiovascular (CV) accidents (myocardial infarction or MI, major vascular surgery). The mortality rate from CV causes is highest in the general population, but in patients with CKD it is increasingly pronounced[1]. The reduction of CV risk factors remains a cornerstone of the treatment of patients affected by CKD who, up to 50% of the time, die of CV causes, before reaching the need for dialysis. Among CV causes only 20% are due to atherosclerotic coronary artery disease (CAD) while the majority of deaths depend on arrhythmia, sudden cardiac death (SCD) or heart failure, all conditions not related to atherosclerotic damage and not influenced by statin therapy[2]. Several traditional and uremia-related risk factors are responsible for this scenario and among them dyslipidemia plays an important role; in CKD it promotes atherosclerosis and, by the deposition of lipoprotein in glomerular structures, stimulates factors that excite inflammation and fibrogenesis. Therefore, as well as the correction of other CV risk factors, dyslipidemia has to be considered. Various dietetic suggestions are mandatory, but there are no randomized trials examining the safety and efficacy of a low-fat, low-cholesterol diet in CKD patients whether in reducing lipid profile or in reducing CV risk. Dietetic plans are reported to reduce only slightly low-density lipoprotein (LDL) levels in CKD patients[3,4] and, especially in the advanced stages of CKD, an unbalanced diet might favour malnutrition, a condition known to be related to increased mortality rate; so, lipid-lowering drugs must be added.

The amelioration of lipid profile with statins, namely a cutting-down of LDL-cholesterol, has clearly demonstrated a reduction in mortality rate, both in terms of primary and secondary prevention in the general, non-renal, population[5-11]. However, we, as clinicians, suffer from a lack of clear, irrefutable data in our renal patients. Why? Here we will review the latest data available on the effectiveness and safety of statin therapy in CKD patients.

DYSLIPIDEMIA IN PATIENTS WITH CKD

Dyslipidemia, as defined by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel Ⅲ)[12] represents a well-recognised important risk factor strictly associated with mortality. Simultaneously, in the earliest stages of primary kidney disease, dyslipidemia occurs, with a decline in renal function, and the lipid profile is altered initially in terms of reduced high-density-lipoprotein (HDL) (due to reduced plasma levels of ApoA- Ⅰ and ApoA Ⅱ, primary proteins forming HDL, higher concentrations of Apo-B and to lecithin-cholesterol-acyltransferase enzyme, LCAT, deficiency) and moderately increased tryglicerides (TG) serum concentrations, due to impaired clearance. However, this picture masks the real danger: the increase of very LDL (VLDL) and chylomicron remnants, accumulation of delipidated small dense LDL, post translational modification of lipoproteins, abnormal concentrations of Lp (a) and non-protective HDL[13].

In summary: there is a qualitative highly atherogenic lipemic picture that significantly affects patients with CKD and a changed dyslipidemic picture occurring in different renal scenarios (Table 1). The teaching point is that the usual target point at which statin therapy is started, such as total cholesterol and LDL, are not expressed sufficiently in CKD patients, resulting in these lipid levels appearing to be normal or low[14]. To aggravate the lipidic profile in CKD there is also an association with a marked decrease of anti-oxidant properties of HDL-cholesterol that results in an increased promotion of atherosclerosis[15]. HDL cholesterol, which has a protective role in the general population, is highly different in uremic patients in whom, during acute inflammation, HDL particles incorporate serum amyloid A, therefore acting not as protective, but paradoxically, as pro-atherogenic particles[14].

We recently observed that in patients affected by AA amyloidosis in Muckle-Wells Syndrome[16], a rare hereditary disease characterized by increased levels of C-reactive protein (CRP) and impressively high levels of serum amyloid levels, up to hundreds of times greater than baseline values, the pathogenetic trigger to renal damage was the inflammatory state, namely the excessive and inappropriate interleukin (IL)-1β release, that mediates progressive renal injury. We demonstrate that, over a 1-year follow up, IL-1 blocked with human anti-IL-1β monoclonal antibody canakinumab reverses renal damage, ameliorating estimated glomerular filtration rate (eGFR) and significantly reducing proteinuria.

In summary, in CKD patients rather than a CV protective role, serum HDL, the so-called "good" cholesterol, is transformed into inflammatory HDL[17].

In addition, a significant change in lipidic shape occurs in CKD patients resulting in accumulation of small, dense highly atherogenic LDL, decreased metabolism of chylomicrons and remnants of chylomicrons, reduced catabolism of Lp (a); such modifications interfere with uptake of LDL by classic LDL receptors.

ApoA-I level, reduced in CKD, is also the principal cofactor of the LCAT enzyme and LCAT is required for maximum cholesterol uptake by the cholesterol ester (CE) of poor discoid-shaped HDL-3 to the CV protective CE-rich spherical HDL-2. Serum LCAT activity is markedly reduced in end-stage renal disease (ESRD) patients and may impact dramatically on the increased risk of premature atherosclerosis in familial LCAT deficiency, as previously reported[18]. Approximately 75% of plasma LCAT activity is associated with HDL, but LCAT may also produce cholesteryl esters in LDL and other ApoB-containing lipoproteins[19] (Figure 1).

Similar to LCAT-deficient patients[20], LCAT-knockout mice on a high-fat diet develop proteinuria and glomerulosclerosis, characterized by mesangial cell proliferation, sclerosis, and lipid accumulation[21].

Table 1 Different dyslipidemic patterns at various stages of chronic kidney disease

	Patients with CKD but NOT nephrotic syndrome	Patients with nephrotic syndrome	Patients on hemodialysis	Patients on peritoneal dialysis	Transplanted patients
Total CHL	‹—› or ↑	↑↑	‹—› or ↓	↑↑	↑↑
HDL	↓	↓	↓	↓	‹—›
LDL	‹—› or ↑	↑↑↑	‹—› or ↓	↑	↑↑
TG	↑	↑↑	↑	↑↑↑	‹—› or ↑

CKD: Chronic kidney disease; CHL: Chlorophyll; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides.

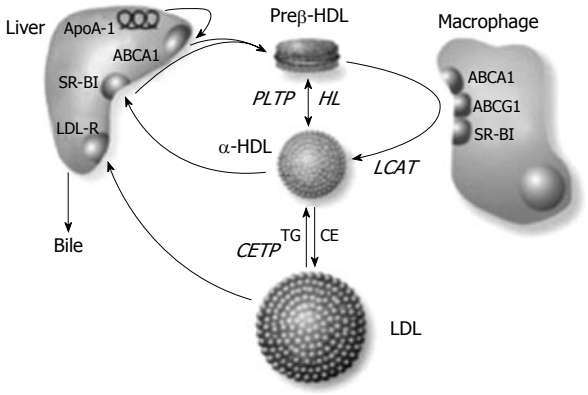

Figure 1 Diagram of the lecithin: cholesterol acyltransferase reaction[18]. Cholesterol acyltransferase (LCAT) cleaves the fatty acid (R2) from the sn-2 position of phosphatidylcholine and then transesterifies it to the A-ring of cholesterol, producing lysophosphatidylcholine and cholesteryl ester. CE: Cholesteryl ester; CETP: Cholesteryl ester transfer protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; SR-BI: Scavenger receptor class B type I.

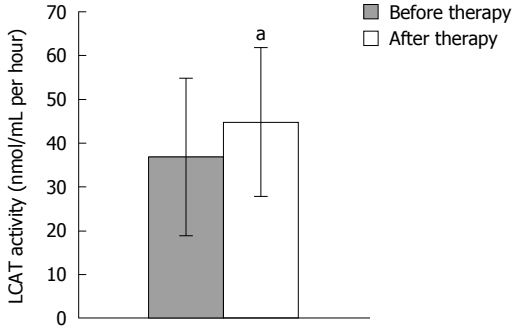

Figure 2 The impact of atorvastatin on the activity of lecithin: Cholesterol acyltransferase enzymes of high-density-lipoprotein remodelling[21]. LCAT: Cholesterol acyltransferase. $^{a}P < 0.05$.

Interestingly, some authors recorded a beneficial effect on LCAT reduction by atorvastatin in 33 dyslipidemic patients[22], suggesting an adjunctive protective role of statins in atherosclerosis prevention, beyond LDL level reduction (Figure 2).

To complicate matters even further, increased parathyroid hormone (PTH) secretion is also involved. Hyperparathyroidism, frequently occurring in CKD patients, may further impact upon this dyslipidemic picture by increasing calcium accumulation within liver and adipose tissue cells. In experimental animals with renal insufficiency, either parathyroidectomy or the administration of calcium-blocker verapamil[23] can normalize plasma TG levels and hepatic lipase activity. On the other hand, normal parathyroid function is necessary for normal lipid metabolism. PTH infusion in hypocalcemic rats was found to be related to reduced total cholesterol and TG levels, and such events may be prevented by the parathyroidectomy[24]. Moreover, hyperparathyroidism induces a deficiency in enzymes involved in lipid metabolism, such as lipoprotein lipase, hepatic lipase and VLDL deficiency[25-27].

In summary: the prevalence of dyslipidemia in CKD is higher than in the general population varying in: (1) type of lipids; (2) type of population studied [CKD patients not on dialysis, patients with nephrotic syndrome, patients on hemodialysis (HD) or in peritoneal dialysis (PD), transplanted patients]; (3) primary cause of kidney failure; and (4) stage of kidney disease.

STATINS AND RENAL FUNCTION

The decline in glomerular filtration rate (GFR) may be accelerated by dyslipidemia and statins have clearly demonstrated an ameliorating effect on the dyslipidemic profile, but there is no clear consensus on ameliorating renal function too.

Several post-hoc analyses of large interventional trials[28] seem to indicate a benefit in ameliorating renal function from lipid-lowering therapy. The Physicians' Health Trial[29] enrolled 4483 subjects with increased serum creatinine levels > 1.5 mg/dL and reduced eGFR (defined as < 55 mL/min) among dyslipidemic patients (defined as serum total cholesterol > 240 mg/dL or reduced serum HDL < 40 mg/dL). After 14 years 134/4483 patients (3%) had increased serum creatinine and 244/4483 (5.4%) had reduced eGFR. The authors concluded that dyslipidemia was significantly associated with increased risk of developing renal insufficiency.

A meta-analysis of 13 small RCT studies involving 384 patients was published in 2000. In 7 studies patients were affected by diabetes, in three studies by glomerulonephritis while in the other 2 studies at least three-quarters had glomerulonephritis. The authors examined the effects of statins on GFR and proteinuria in patients with renal disease, and concluded that statin treatment reduced the rate of decline in GFR with a trend toward proteinuria reduction, despite not being statistically significant[30].

In another large trial, the Cholesterol And Recurrent Events (CARE)[31], 690 patients with reduced GFR, less than 60 mL/min, were treated with pravastatin or placebo. No difference in the rate of decline of GFR in patients with moderate renal disease was observed, while a slight difference in favour of treatment was observed in patients with severe renal disease (GFR < 40 mL/min). In the post-hoc analysis of Treating to New Targets[32], the effects of intensive statin treatment (atorvastatin 80 mg compared with 10 mg) in 10 000 patients with coronary heart disease (CHD) were studied.

After 5 years of follow-up, a mean eGFR increase was observed in both groups, greater among the 80 mg group compared with the 10 mg (increase of 5.2 mL/min *vs* 3.5 mL/min), suggesting a dosage-related statin protective role.

In another large trial, the JUPITER[33], the effect of rosuvastatin in primary CV disease prevention was studied in more than 17 000 apparently healthy individuals with levels of LDL < 130 mg/dL and increased inflammatory state. A subgroup analysis of 3267 patients with CKD, as defined by eGFR < 60 mL/min, was carried out. Treated patients were shown to have a reduced incidence of CV events, compared with placebo. Patients with CKD exhibited a worse lipid profile as well as increased CRP levels compared with those with normal renal function. At the end of the study renal function was marginally improved in treated patients, compared with placebo (eGFR 66.8 mL/min *vs* 66.6 mL/min, $P = 0.02$). This benefit was not evident in subjects with eGFR < 60 mL/min at baseline. All-cause mortality was reduced more by rosuvastatin in moderate CKD subjects compared with subjects with normal renal function (44% *vs* 12%, P for interaction = 0.048). In the recently published SHARP trial[34], the largest one involving more than 9000 CKD patients, the treatment with simvastatin 20 mg added to ezetimibe 10 mg was compared with placebo. Thirty-three percent of patients were on dialysis treatment (27% on HD, 6% on PD) and another 20% had a eGFR less than 15 mL/min. Patients with CKD not on dialysis had baseline serum creatinine at least 1.7 mg/dL (1.5 in women) with an average eGFR of 26.6 ± 13.0 mL/min by MDRD formula, with mean LDL-cholesterol levels of 108 mg/dL.

More than 2000/6247 of the patients who were not on dialysis treatment at the start of the study, despite a significant reduction of LDL compared with placebo, progressed to ESRF during the trial. Simvastatin plus ezetimibe did not show any evidence of a renal protective effect defined as starting of chronic dialysis or doubling of baseline serum creatinine [1190 (38.2%) *vs* 1257 (40.2%); relative risk (RR) = 0.93, 0.86-1.01; $P = 0.09$] or transplantation.

In the ezetimibe/simvastatin group, fewer patients reached the end point "ESRD": 1057 (33.9%) *vs* 1084 (34.6%), but the difference was not significant ($P = 0.41$), similar to the end point "ESRD or death", which was reached with ezetimibe/simvastatin by 47.4% *vs* 48.3% ($P = 0.34$) and for the end point "ESRD or doubling of baseline serum creatinine" by 38.2% *vs* 40.2% ($P = 0.10$). These results were comparable in all the CKD stages and subgroups. In summary, because CKD may be considered a chronic inflammatory disease, and it is known that higher baseline C-RP and soluble tumor necrosis factor receptor Ⅱ levels are independently associated with more rapid kidney function loss in CKD[35], the attenuation induced by statin therapy of the inflammatory response to renal injury on vascular structures might be considered another possible explanation for the renoprotective actions of statin therapy.

STATINS IN DIALYSIS PATIENTS

On account of the very high CV risk among patients on dialysis, two large trials published in recent years valued the effects of statins in reducing CV risk in HD patients. The first one, the Die Deutsche Diabetes Dialyse Study (4D)[36], detected no mortality reduction from atorvastatin in 1255 type 2 diabetic patients on HD randomly treated with either atorvastatin or placebo and followed over 3.9 years. Despite a median 42% reduction in LDL from baseline, atorvastatin 20 mg compared with placebo, had no significant effect on CV death, non-fatal MI and stroke, or on all-cause mortality, leading to a non-significant 8% decrease in the primary composite end-point.

4D study included only diabetic patients and, apart from a consideration that the study may have been underpowered, it might be questioned whether these results can be generalized also in non-diabetic patients on HD.

Four years later another large trial was published, AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)[37], which enrolled 2776 patients on HD, from 50 to 80 years of age, randomly assigned to 10 mg of rosuvastatin or placebo and followed over a mean of 3.2 years. Rosuvastatin permitted a mean reduction in LDL levels of 43%, remarkably similar to that obtained from 4D. At the end of the AURORA study 396 patients on rosuvastatin and 408 in the placebo group reached the primary end point (death from CV causes, non-fatal MI, or non-fatal stroke), indicating a lack of therapeutic effect both on all-causes mortality or in the combined end points. Several observations were made on the results of these large trials. Firstly the lower-than-expected event rates (9.5% *vs* 11% anticipated in the placebo group in AURORA), the study might not have had sufficient statistical power. Secondly, at baseline in AURORA either patients who had already been on statin therapy or younger patients, at higher CV risk of death, were excluded from the study. AURORA[37] and 4D[36] studies showed that the hope of a successful intervention with simply a drug to reduce CV events in patients undergoing HD had no success.

Even the more recently published SHARP trial[34], studied 9270 patients with CKD, 3023 of whom on dialysis, randomized to receive simvastatin 20 mg plus

ezetimibe 10 mg daily and followed over 4.9 years. The treatment caused a mean reduction of LDL levels, lower in patients on dialysis than in those who were not, a third smaller among the first one on dialysis (101.4 mg/dL *vs* 115.1 mg/dL, $P < 0.0001$).

At advanced stage of CKD, several confounder factors are operating in assessing the real effect of dyslipidemia, and consequently the possible protective role of statins on CV events. One of the most important confounder factors is the role of malnutrition/inflammation in the link between cholesterol levels and mortality[13].

The results from 4D and AURORA suggest that CV disease in HD patients differs from that in the general population, namely the confounder effect of malnutrition/inflammation and the non-atherosclerotic CV causes of death, mainly due to arrhythmia or SCD, that are not influenced by statin therapy; while an atherosclerotic coronary cause of death was reported to occur only in one-quarter, as in SHARP trial. In a recently published post-hoc analysis of 4D[38] the authors found 196 patients who had wasting, described as body mass index, albumin, and creatinine values less than the median, and less or increased median CRP levels, and compared them with other 1059 patients without wasting. Patients with severe wasting had significantly increased risks of SCD [adjusted hazard ratio (HR), 1.8; 95%CI: 1.1-3.1], all-cause mortality (adjusted HR, 1.8; 95%CI: 1.4-2.4), and deaths due to infection (adjusted HR, 2.3; 95%CI: 1.2-4.3).

In contrast, MI was not affected. The authors concluded that the increased risk of CV events (adjusted HR, 1.5; 95%CI: 1.0-2.1) observed in 4D trial was mainly explained by the effect of wasting on SCD.

Finally, in uremic patients a circulating lipase inhibitor pre-β-HDL was reported[39], a form of apo A-I found in the non-lipoprotein fraction of normal plasma, that could explain the influence of dialysis modality on lipid profile, often improved with high-flux HD in some[40,41] but not all[42] studies.

STATINS AND PROTEINURIA

The correlation among blood pressure, proteinuria reduction and renal failure is clearly demonstrated by a large body of evidence and proteinuria alone, independently of any effect upon intraglomerular pressure, may aggravate renal damage[43]. Moreover, proteinuria is recognised as an independent risk factor for cardio-vascular disease[44].

3-hydroxy-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase expression is increased in rats with renal impairment, heavy proteinuria and hypercholesterolemia[45] and this provides potential explanation for the use of statins in hypercholesterolemic CKD patients. Although statins usually appear to reduce proteinuria and slow the rate of GFR decline, discrepant findings have been reported in some studies. Short-term therapy with statins, particularly at high doses, has been reported to induce proteinuria. During the clinical development of rosuvastatin, the highest dose studied of 80 mg was associated with a 2 + dipstick-positive proteinuria (in 13.2% among 1129 subjects treated compared with the 3.4% among 997 subjects treated with 40 mg and 1.6% among 1258 in those treated with 10 mg/d). In many cases, rosuvastatin-treated patients had normal urine dipstick findings when testing was repeated, even when rosuvastatin was continued[46]. Most of the protein excreted, analysed by urinary protein electrophoresis, were indicated at a lower molecular weight than albumin[47], suggesting that the proteinuria was induced by reduced reabsorption of normally filtered protein in renal tubule cells rather than by glomerular leakage of albumin and other larger proteins.

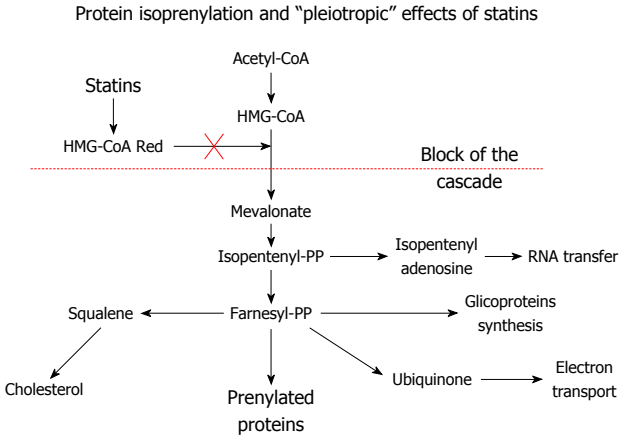

Figure 3 Protein isoprenylation and "pleiotropic" effects of statins[63-65]. HMG-CoA: 3-hydroxy-methyl-glutaryl-Coenzyme A.

Statin-induced proteinuria would be induced probably *via* an effect in reducing receptor-mediated endocytosis (RME) in proximal tubular cells[48]. RME is reported to be the process responsible for albumin uptake in proximal tubular cells occurring *via* megalin and cubulin receptors, in the presence of prenylated GTP binding proteins[49]; this effect was found to be dose-dependent[50].

Statins reduce the activity of mevalonate, a key step for the generation of isoprenoid pyrophosphates, that are required for prenylation of GTP binding proteins (Figure 3). Experimentally, statins reduced RME by reducing prenylation of GTP binding proteins in cell cultures of proximal tubular cells derived from the opossum kidney: the same authors demonstrated that inhibition of HMG-CoA reductase was related to the lipophilicity of the statin[50].

Moreover, the addition of cholesterol did not correct the impairment in RME, providing evidence that RME was not impaired due to reduction in cholesterol synthesis, but as a direct result of prenylation of GTP-binding proteins.

The National Lipid Association Statin Safety Assessment Task Force reported that "statin-induced proteinuria is more likely to be seen with statins that are potent inhibitors of HMG-CoA reductase, but it is not associated with either renal impairment or renal failure"[51]. In a sub-analysis of the PREVEND-IT[52] subjects (788 with a urinary albumin excretion, UAE, 15-300 mg/d) who received pravastatin 40 mg/d *vs* placebo and/or fosinopril 20 mg/d *vs* placebo in a RCT design, pravastatin

did not change UAE or GFR over a 4-year follow-up, nor in fosinopril yes/no subgroups. In the observational cohort, statin use was neither associated with a rise in UAE (+12.1%), compared with statin non-users, nor was it associated with a significant change in GFR. Another systematic review of 15 randomized studies[53] (1384 participants) showed that statins reduced albuminuria by 47% (95%CI: 26-67) and 48% (95%CI: 25-71) in people with > 300 mg/d and 30-300 mg/d of UAE at baseline, respectively, but no influence on UAE for baseline levels less than 30 mg/24 h[52] was observed.

Other authors[54], in reviewing 6 RCT including 311 patients with CKD, reported a reduction in UAE of 0.73 g/d (95%CI: 0.95-0.52) in patients treated with statins.

In another study[55] it was reported that, among 120 hypercholesterolemic patients on simvastatin therapy of 40 mg/d, 8% of them developed proteinuria and, after resolution, proteinuria recurred in 2 patients when 40 mg/d of simvastatin was resumed.

In the previously mentioned SHARP trial[34], with the use of simvastatin plus ezetimibe *vs* placebo among more than 9000 CKD patients, on or not on dialysis, in 3021 patients who had not reached the ESRD end-point, the UACr ratio was the same for either treatment or placebo group (167 and 154 mg/g, respectively, $P = 0.2$) thus resulting in no influence on proteinuria from simvastatin plus ezetimibe.

However, as a result of inhibition of HMG-CoA reductase by blocking isoprenoid synthesis, statins produce an array of anti-inflammatory and vascular effects that are independent of cholesterol reduction, the so-called pleiotropic effects, that have been considered as responsible for a protective role on CV events.

STATINS AND CV DISEASE IN CKD

A grade association between lower levels of the estimated GFR and the risks of death, CV events, and hospitalization was reported in a large observational trial among 1 120 295 adults, between 1996 and 2000, and who had not undergone dialysis[1]. Despite continued improvements in therapies, CV risk remains high in CKD patients and death due to a cardiac cause represents the major risk in CKD patients, much more than the risk of reaching the need for dialysis.

The association between increasing plasma cholesterol and coronary risk in the general population is well-known[56] and the K/Dialysis Outcome Quality Initiative guidelines[57], which were published some years before publications of large trials in CKD patients were available, recommended a goal LDL-cholesterol of less than 100 mg/dL (< 2.6 mmol/L) in patients with CKD. Statins have been demonstrated by several large randomized trials to be able to reduce serum total cholesterol levels (from -22% up to -42%), LDL cholesterol (from -27% up to -55%), and TG (from -10% up to -35%), but also to increase serum HDL levels (from +4% up to 8%), so reducing CV risk both in primary and secondary prevention in the non-renal population[6-9,31].

No RCT has demonstrated to apply, to renal patients, the clear positive results of statins in reducing CV mortality as obtained in the general population. From these considerations it would seem that the pathogenesis of atherosclerosis in patients with renal disease may be considerably different from that in the general population, so, as a result, the role of statins in reducing CV death among CKD patients remains uncertain.

The limited data available came only from post-hoc analysis of large trials conducted in the general population, because renal patients with advanced renal failure are rarely enrolled in RCT. In the analysis of the Pravastatin Pooling Project[58], a database from 3 randomized trials of pravastatin (40 mg daily) *vs* placebo, studying 19 700 subjects, 22.8% of them had moderate CKD, with an eGFR of 30 to 59.99 mL/min per 1.73 m^2.

The authors found that moderate CKD was independently associated with an increased risk at the time of MI, coronary death, or percutaneous/surgical coronary revascularization compared with those with normal renal function.

Among the 4491 subjects with moderate CKD, pravastatin significantly reduced the incidence of the primary outcome (HR 0.77, 95%CI: 0.68-0.86), similar to the effect of pravastatin on the primary outcome in subjects with normal kidney function (HR 0.78, 95%CI: 0.65-0.94) and pravastatin also appeared to reduce the total mortality rate in those with moderate CKD (adjusted HR 0.86, 95%CI: 0.74-1.00, $P = 0.045$). The authors concluded that pravastatin reduces CV event rates in people with, or at risk of, CAD and concomitant moderate CKD. A similar effect was also observed in the sub-group of patients affected by diabetes. Also, in the previously reported CARE trial[59] the authors found significant benefit from statin therapy in lowering CV events in patients with CKD and eGFR < 40 mL/min.

In another post-hoc analysis of the 4S study[6] among patients with CHD the authors[60] studied 52.1% of 4444 patients who had mild chronic renal insufficiency, defined as eGFR < 75 mL/min. At the end of the study simvastatin-treated patients had decreased all-cause mortality (adjusted HR 0.69; 95%CI: 0.54-0.89) and also had significantly lower rates of major coronary events and coronary revascularization.

Other authors[61] analyzing USRDS data, found a lower mortality rate in a relatively small group of 362 patients on dialysis, treated with statins, compared with 3354 patients on dialysis not using statins (143/1000 person-years, *vs* 202/1000 person-years for patients (RR = 0.68, 95%CI: 0.54-0.87). In contrast, the use of fibrates was not associated with reduced mortality (RR = 1.29).

Among patients with early stages of CKD, in a sub-analysis of the CARE trial[31], in the 1711 patients with eGFR ⩽ 70 mL/min at entry, patients treated with pravastatin, after a median follow-up of 58.9 mo, had significantly lower HRs for coronary events (HR 0.72; 95%CI: 0.50-0.83; P 1⁄4 0.001) and coronary revascularization (HR 0.65; 95%CI: 0.0-0.83; P1⁄40.001), compared with placebo-treated patients, but not for total mortality and

stroke. The authors did not report excess side-effects. However, in the large RC trials among HD patients 4D[35] and AURORA[36], previously reported, statins failed to demonstrate their effectiveness as observed in the general population or in post-analysis of patients with mild stages of CKD. The unfavourable trials results with the use of statins in reducing CV risks among dialysis patients found in the 4D and AURORA studies were surprising. Great expectation has been placed on the results from the largest trial, the SHARP[34], which studied over 9000 CKD patients, with no known history of myocardial infarction or coronary revascularization, assigned to be treated with ezetimibe plus simvastatin *vs* a placebo.

The end point was first major atherosclerotic event, an end point considered not so "hard" as death. This population included 33% on dialysis plus another 20% of patients with an eGFR equal or less than 15 mL/min, so resulting in 53% of the patients at an advanced stage 5 CKD. Among non-dialysis patients 80% had micro- (37%) or macro- (43%) albuminuria, a well-known condition associated with increased CVD. Notably, 46% of the patients enrolled were diabetics and, as expected, mean LDL cholesterol levels were lower in HD patients (101.4 mg/dL *vs* 113.1 mg/dL, $P < 0.0001$).

SHARP's authors concluded that simva plus ezetimibe permitted a reduction in first-major atherosclerotic event of 11.3% in drug allocated treatment group, compared with 13.4% in placebo group, corresponding to a significant 17% proportional reduction (RR = 0.83, 95%CI: 0.74-0.94; $P = 0.0021$), and that treatment with simva + ezetimibe was associated with non-significantly fewer first major coronary events (4.6% *vs* 0.0%; RR = 0.92, 95%CI 0.76-1.11; $P = 0.37$) but, notably, no significant difference in coronary mortality (2 *vs* 1.9) was found. Interestingly SHARP demonstrated that there was no good evidence that major atherosclerotic events differed between patients on dialysis or not: LDL reduction was about a third less in patients on HD (23.20 mg/dL) than in those not on HD (37.12 mg/dL).

Another result of this trial was that the primary end point in dialysis patients was similar between treated or untreated patients (15.2% *vs* 15.9%, respectively). This might reflect an underpowered study for the comparison by dialysis. Another explanation may be that SCD, due to heart failure or arrhythmia, favoured by electrolyte disturbances, largely prevails in ESRD patients over non-fatal atherosclerotic coronary disease or myocardial infarction, so frustrating the possible helpful role of statins, unable to work in non-atherosclerotic problems. To confirm this, in the SHARP trial coronary deaths were attributed to 181/749 patients (24%) of the total CV deaths and to 181/2257 (8%) of all the deaths. The SHARP authors remarked that the absolute benefit of treatment would be greater in renal patients with a previous history of CAD and with a higher absolute risk of major atherosclerotic event, but who were excluded from the study.

Finally, despite the undeniable efficacy of the association simvastatin plus ezetimibe, it was not compared with simvastatin only treatment, so leaving in abeyance whether the association with ezetimibe really confers additional benefit to simvastatin alone.

Table 2 Cardiovascular risk factors in chronic kidney disease patients

Traditionals (Framingham-like)	Non-traditionals uremia-related
Age	Anemia
Male gender	Hyperomocysteinemia
Diabetes	Chronic inflammation
Obesity	Oxidative stress
Hypertension	Hyperparathyroidism and
Smoking	vascular calcifications
Insulin levels	Accumulation of metabolic
Family history	products (advanced glycation
Dyslipidemia	end-products, asymmetric
↑ Total cholesterol	dimethyl arginine…)?
↑ LDL	
↑ Apolipoprotein a1	
↑ TG	
↑ Apolipoprotein B	
↓ HDL	
↑ Lipoprotein (a)	
↑ Oxidized LDL	

HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides.

However, as previously discussed in another paper[13], these results in ESRD patients are not easily transferable to patients with early-stage CKD. One of the major confounder factors is, as previously described, the role of malnutrition/inflammation which is characterized by low serum cholesterol levels, a condition present in approximately 33% of maintenance dialysis patients, and known for some time to be associated with increased mortality[62]. The conclusions from the more recent large trial on statins in CKD do not allow us to clarify the effectiveness of treating dyslipidemia in renal patients and leave us undecided as to the actual role of statins in CKD.

In our opinion it is important to remember that CV risks in CKD patients depend not only on dyslipidemia, but on several other factors, each important in its own way, depending both on traditional (the so-called Framingham-like) and on the uremia-related ones (Table 2).

Therefore, effectiveness in the reduction of CV death in CKD patients depends on the contemporaneous correction of all, or at least the majority, of CV risk factors. Notably, the importance of real prevention and the repeated therapeutic correction of CV risk factors before irreparable damage occurs to the vascular system must be emphasized because data seem to indicate that giving statins in the early stages of CKD may have a favourable impact.

WHAT ABOUT SAFETY OF STATINS IN CKD?

The major side-effects potentially attributable to statin therapy are listed in Table 3, datasourced from references[51,63,64].

The safety of statins was recently highlighted in a very

Table 3 The major side effects potentially attributable to statin therapy

Hepatic toxicity
Muscle toxicity including:
Myopathy (general term referring to any disease of muscles)
Myalgia (muscle ache or weakness without creatine kinase increase) in 1%-3%
Myositis (muscle symptoms with increase creatine kinase levels) in 0.1%
Rhabdomyolysis (muscle symptoms with increase > 10 × the upper limit of normal CK and creatinine elevation, usually associated with brown urine and urinary mioglobina in 0.0005%

large RCT[64] involving more than 20 500 high-risk patients, where the authors found a very low incidence (less than 0.1%) of myopathy during 5 years treatment with simvastatin 40 mg daily. The risk of hepatitis, if any, was undetectable, prompting the authors to exclude routine monitoring of liver function tests during treatment with simvastatin 40 mg. Statin-related toxicity may be more common in elderly or frail people, or in patients with previous liver or renal disease, and toxicity may be increased by other drugs such as gemfibrozil, verapamil, amiodarone, macrolide antibiotics, cyclosporine, HIV protease inhibitors, certain anti-depressant such as nefazodone, large quantities of grapefruit juice or alcohol abuse[65]. Serum transaminase elevation, defined as increased up to 3 fold, generally occurs with all statins and depends on dosage. Incidence at lower doses is < 1% and 2%-3% at higher doses and it is almost always reversible with removal of therapy. Liver failure is extremely rare, similar in frequency to that of the general population and causality from statins is not clearly established[51]. Recently some papers drew attention to vitamin D deficiency, a very sensitive issue among patients with renal disease, as an aggravating factor in statin myopathy.

Vitamin D serum levels in statin-treated patients were reported to be lower among the 128 patients with myalgia than in the 493 asymptomatic ones ($P < 0.0001$). Vitamin D-deficient myalgic patients, when supplemented with vitamin D while continuing statins, found after 12 wk the serum vitamin D increased and resolution of myalgia occurred in 92% of them[66].

To confirm this finding other authors[67] recently reported symptomatic myalgia in hypercholesterolemic statin-treated patients, with concurrent serum 25 (OH) vitamin D deficiency. Of the 150 patients, 131 (87%), were free of myositis-myalgia over a median of 8.1 mo after vitamin D supplementation. Given the quality and paucity of studies on this topic and the lack of a placebo-controlled group, additional studies are needed to examine the potential role of vitamin D deficiency in statin myopathy and it is premature at present to recommend vitamin D supplementation indiscriminately as treatment for statin-associated myalgia, in the absence of low vitamin D levels[68].

Finally, the exact mechanism of statin-induced myopathy is not clear but some mechanisms suggested include decreased production of ubiquinone or coenzyme Q10 involved in mitochondrial energy production. Mitochondrial function may be impaired by statin therapy, and statins are reported by some authors to reduce circulating CoQ10 levels by 16%-54% and this effect may be exacerbated by exercise. However, there is insufficient evidence to prove the etiological role of CoQ10 deficiency in statin-associated myopathy and data on the effect of CoQ10 supplementation on myopathic symptoms are scarce and contradictory[69].

STATINS AND *DE-NOVO* DIABETES

Particular attention has recently been focused on the incidence of *de-novo* diabetes during statin therapy. In JUPITER trial an increased incidence of the development of diabetes was noted in rosuvastatin-treated subjects compared with placebo-treated subjects (270 and 216 reports, respectively, $P = 0.01$); also a minimal increase in glycosylated haemoglobin was observed in the rosuvastatin group (5.9% *vs* 5.8%, $P < 0.001$)[70].

A similar trend was also noted in a recent meta-analysis among five statin trials involving 32 752 participants without diabetes at baseline. During the study 2749 subjects developed diabetes, 1449 were assigned intensive-dose therapy, while 1300 subjects were assigned moderate-dose therapy.

The authors concluded that intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate dose statin therapy (OR 1.12, 95%CI: 1.04-1.22; $I^2 = 0\%$) for new-onset diabetes[71]. Similar results indicating increased risk of developing diabetes was reported in another meta-analysis among 13 statin trials with 91 140 participants, 4278 of whom (2226 assigned statins and 2052 control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (OR 1.09; 95%CI: 1.02-1.17), with little heterogeneity ($I^2 = 11\%$) between trials. Meta-regression showed that risk of developing diabetes with statins was highest in trials with older participants[72]. In accordance with these data, particular attention to glycemic control during statin therapy is recommended.

CONCLUSION

We can assume that in CKD patients we lack a clear target for drug therapy, unlike in the general non-renal population, in which LDL-cholesterol is a well-defined target of statin therapy. Given the lack of clear, conclusive results from large randomized controlled trials on the benefits of statin therapy in retarding CKD progression or reducing CV mortality in ESRD patients, it is not advisable to give statin.

Despite the uncertainty of results in delaying the progression of renal disease in CKD patients not on dialysis, especially in the earliest stages of CKD, it seems reasonable to use statins. Our personal opinion is that, due to the high risk of cardiac death and the safety pro-

file, statins can be suggested in CKD patients: (1) early-mid stage at high risk of coronary or peripheral vascular disease; (2) with nephrotic syndrome, in order to ameliorate lipid profile; (3) already on dialysis with a previous history of coronary or peripheral vascular disease or at high risk of CVD; (4) irrespective of the stage of CKD, at high risk of developing CV complications, even if the presumed atherosclerotic coronary risk involves only a minor, but important increased rate; and (5) on dialysis previously treated with statins in view of the benefit on atherosclerotic complications.

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