

## Lipid abnormalities in kidney disease and management strategies

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### Abstract

Patients with kidney diseases continue to experience significant cardiovascular disease (CVD) morbidity and mortality. Although there are many important risk factors playing a role in the pathogenesis of CVD in chronic kidney disease (CKD) patients, dyslipidemia (elevated triglycerides, elevated oxidized low-density

lipoprotein and low/dysfunctional low high-density) represents one of the modifiable risk factors. Renal failure patients have unique lipid abnormalities which not only have complex role in pathogenesis of CVD but also cause relative resistance to usual interventions. Most of the randomized trials have been in hemodialysis population and data from CKD non-dialysis, peritoneal dialysis and renal transplant populations is extremely limited. Compared to general population, evidence of mortality benefit of lipid lowering medications in CKD population is scarce. Future research should be directed towards establishing long term benefits and side effects of lipid lowering medications, through randomized trials, in CKD population.

**Key words:** Chronic kidney disease; Dyslipidemia; Statins; Cardiovascular disease; Renal transplant recipients; Hemodialysis; Peritoneal dialysis

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**Core tip:** Burden of cardiovascular disease and dyslipidemia continues to be high among patients with kidney diseases. Our review includes unique lipid abnormalities specifically affecting patients with kidney diseases. We have included comprehensive review of the latest evidence of the dyslipidemia treatment for each subgroup [*i.e.*, chronic kidney disease (CKD) not on dialysis, CKD on dialysis and Kidney transplant recipients] and current guidelines from Kidney Diseases: Improving Global Outcomes.

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## INTRODUCTION

Chronic kidney disease (CKD) has become a public health problem with a global prevalence of around 8%-16%<sup>[1]</sup> and with an estimate of more than 10% (*i.e.*, > 20 million) prevalence in the adult United States population<sup>[2]</sup>. Data from National Health and Nutrition Examination Survey showed that CKD prevalence among ages 60 and above increased from 18.8% in 1988-1994 to 24.5% in 2003-2006<sup>[3]</sup>. According to United States Renal Data System (USRDS) a total of 112788 patients initiated dialysis in 2011<sup>[4]</sup>. Cardiovascular diseases (CVD) remain the number one cause of death among patients with kidney diseases<sup>[5,6]</sup>. USRDS 2013 Annual Data Report indicates that CKD patients not only have higher rates of congestive heart failure, acute myocardial infarction (MI) and cerebral vascular accident compared to non-CKD patients, but they also have lower survival rates compared to non-CKD patients. This survival further decreases with severity of CKD<sup>[7]</sup>. Similarly, renal transplant recipients (RTR) have elevated CVD mortality with estimated 10-year risk of 21.5%, due to effect of CKD, post-transplant allograft function and effects of various immunosuppressant medications<sup>[8,9]</sup>.

Dyslipidemia is a well-established risk factor for CVD in the general population but this relationship is not straightforward in CKD population. While dyslipidemia is associated with CVD in pre-dialysis CKD<sup>[10]</sup> and hemodialysis population<sup>[11]</sup>, data regarding its association in peritoneal dialysis patients is lacking<sup>[12]</sup>. With an ever increasing CKD burden worldwide, providing treatments for modifiable risk factors, like dyslipidemia, becomes an essential component for improving outcomes. In this review, we will examine various lipid abnormalities associated with kidney diseases and current evidence regarding various treatments.

### Reverse epidemiology

Relationship between dyslipidemia and survival has not been consistent among patients with kidney disease. "Reverse epidemiology", terminology first coined in 2003, refers to the findings of increase survival among dialysis patients with high body mass index, obesity and hypercholesterolemia<sup>[13]</sup>. Authors suggested that survival bias, presence of malnutrition and inflammation and time discrepancies of risk factors possibly explain these findings<sup>[13]</sup>. While some studies have shown that lower cholesterol was associated with an increase in mortality<sup>[13,14]</sup>, other studies have concluded that among dialysis patients without malnutrition/inflammation and among black dialysis patients, hypercholesterolemia is associated with an increase in cardiovascular mortality<sup>[15,16]</sup>. Chawla *et al.*<sup>[17]</sup> reported data from the cohort of non-diabetic CKD (non-dialysis) patients, cholesterol levels were not associated with CVD mortality.

### Lipid profile in kidney diseases

There are both qualitative and quantitative abnormali-

ties seen in the lipid profile of patients with kidney disease<sup>[18]</sup>. Some of these abnormalities also differ between spectrums of kidney diseases. With impaired renal function and reduced clearance, abnormal removal is major contributor of lipid abnormalities. Common initial abnormalities include hypertriglyceridemia and low high-density (HDL) cholesterol. Elevated triglyceride levels (TG) can be attributed to increased concentration of Apolipoprotein C-III<sup>[19]</sup> and also to the reduced activity of lipoprotein lipase<sup>[18]</sup>.

HDL cholesterol, generally considered as "good" cholesterol, usually plays a role in anti-inflammatory, anti-oxidation and reverse cholesterol transport processes in normal individuals. In CKD patients, these activities are severely affected due to variety of factors<sup>[20]</sup>. With advanced renal failure, there is decreased production of apolipoprotein A-1 (which leads to decreased HDL levels) and decreased production and activity of lecithin-cholesterol acyltransferase which further decreases HDL levels and maturation of HDL cholesterol<sup>[21]</sup>. There are functional changes noted in HDL cholesterol in patients with renal failure. Anti-oxidant and anti-inflammatory properties of HDL cholesterol are compromised due to reduced activities of paraoxonase and glutathione peroxidase in renal failure patients<sup>[20,21]</sup>. Furthermore, oxidative stress can result in dysfunctional HDL which has rather pro-inflammatory effects<sup>[22]</sup>. Studies in hemodialysis patients have shown that dysfunction of HDL is not only associated with multiple co-morbidities and poor quality of life<sup>[23]</sup>, but also with an increased risk of CVD events and CVD mortality<sup>[24]</sup>. In summary, patients with renal failure develop certain functional and structural abnormalities in HDL cholesterol which makes them prone to develop atherosclerosis and thus contributing to their CVD burden.

CKD patients also have reduced levels of lipoprotein lipase, hepatic lipase and defective very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) receptors. This leads to accumulation of VLDL, intermediate-density lipoprotein and chylomicron remnants which are susceptible to oxidation. These oxidized products are usually atherogenic and play a role in CVD pathogenesis in this population<sup>[20]</sup>. CKD patients frequently develop secondary hyperparathyroidism which also has an impact on lipid abnormalities<sup>[25]</sup>. It has been postulated that this usually occurs due to an increase of intracellular calcium concentration in hepatocytes by elevated parathyroid hormone in CKD patients<sup>[26]</sup>. Studies have shown a role of parathyroidectomy in reducing triglyceride levels in CKD patients<sup>[26,27]</sup>.

Among renal transplant recipients, it has been seen that lipids and lipoprotein profile ratios were more beneficial when the TG levels were less than 150 mg/dL and apoA1 was greater than 150 mg/dL when compared to the opposite<sup>[28]</sup>. They are also on immunosuppressive medications, many of which affect the lipid profile adversely. In most renal transplant centers in the United States, kidney transplant patients receive induction

**Table 1 Common lipid profile in patients with kidney disease**<sup>[18,33,34]</sup>

|                   | CKD not on dialysis       | Hemodialysis  | Peritoneal dialysis | Transplant patients |
|-------------------|---------------------------|---------------|---------------------|---------------------|
| Total cholesterol | Normal or elevated        | Normal or low | Elevated            | Elevated            |
| Triglycerides     | Elevated                  | Elevated      | Elevated            | Elevated            |
| LDL cholesterol   | Normal or elevated or low | Normal or low | Elevated            | Elevated            |
| HDL cholesterol   | Low                       | Low           | Low                 | Normal              |

CKD: Chronic kidney disease; HDL: Low high-density; LDL: Low-density lipoprotein.

**Table 2 Brief summary of randomized clinical trials in patients with kidney diseases**<sup>[9,35,46,47]</sup>

| Trial         | Study population   | Intervention  | Follow-up     | Major findings  |
|---------------|--|---|---------------|---|
| ALERT (2003)  | Renal transplant recipients (n = 2102)   | Fluvastatin (40 mg/d) vs placebo                      | Mean 5.1 yr   | Fluvastatin group had reduced major cardiac events and cardiac death but this was not statistically significant<br>No effect seen on all-cause mortality  |
| 4D (2005)     | Hemodialysis patients with DM type II (n = 1255)   | Atorvastatin (20 mg/d)                                | Median 4 yr   | Atorvastatin did not have significant effect on CV death, non-fatal MI, non-fatal stroke and all-cause mortality  |
| AURORA (2009) | Hemodialysis patients aged 50-80 yr (n = 2776)   | Rosuvastatin (10 mg/d) vs placebo                     | Median 3.8 yr | Rosuvastatin had no significant effect on CV mortality, non-fatal MI, non-fatal stroke and all-cause mortality  |
| SHARP (2011)  | CKD not on dialysis (n = 6247)<br>Hemodialysis (n = 2527)<br>Peritoneal dialysis (n = 496) | Simvastatin 20 mg/d plus ezetimibe 10 mg/d vs placebo | Median 4.9 yr | Simvastatin plus ezetimibe significantly decreased major atherosclerotic event but had no major effect on CV mortality or all-cause mortality. Results were available for only entire population (both dialysis and non-dialysis) |

ALERT: Assessment of Ilescol in renal transplantation; AURORA: Assessment of survival and cardiovascular events; SHARP: Study of heart and renal protection; CKD: Chronic kidney disease; CV: Cardiovascular; MI: Myocardial infarction; DM: Diabetes mellitus.

immunosuppression followed by ongoing use of various combination of immunosuppression class of medications including corticosteroids, calcineurin inhibitors (tacrolimus, cyclosporine) and mammalian target of rapamycin (mTOR) antagonists (sirolimus, everolimus)<sup>[29]</sup>. Steroids commonly cause insulin resistance and hyperinsulinemia which is associated with hypercholesterolemia<sup>[30]</sup>. Cyclosporine has been noted to decrease hepatic clearance of LDL as well as increase the synthesis of VLDL and decrease the secretion of bile salts causing increase in cholesterol levels. Tacrolimus increases the incidence of new onset diabetes after transplant (NODAT) which in turn is associated with an increased risk of atherosclerotic cardiovascular events<sup>[31]</sup>. mTOR inhibitors inhibit the activity of lipases, thereby increasing the circulating lipoproteins; they also decrease the fatty acid uptake into the adipose tissue leading to a decrease in plasma lipid clearance adding to the dyslipidemia<sup>[32]</sup>.

Broadly, common lipid abnormalities among the patients with kidney diseases can be summarized in Table 1.

## MANAGEMENT STRATEGIES

### CKD patients not on dialysis

**Statins:** In general population, statins are clearly associated with decreasing CVD events and mortality, however results in CKD population have been variable. Most of the data regarding statins in CKD (not on dialysis) comes from subgroup/post hoc analysis and meta-analysis. Only one randomized trial, Study of Heart and Renal Protection (SHARP) trial, evaluated

statin therapy with major cardiovascular events<sup>[35]</sup>. SHARP trial included 6247 patients with CKD not on dialysis, with mean glomerular filtration rate (GFR) of 26.6 mL/min per 1.73 m<sup>2</sup>. Patients were randomly assigned to simvastatin 20 mg daily plus ezetimibe 10 mg daily vs placebo. The primary outcome was first major atherosclerotic event with median follow up of 4.9 years. Final results were available for the entire study group (both non-dialysis and dialysis), and it showed a significant reduction in the risk of major atherosclerotic event (RR = 0.83, *P* = 0.0021); non-hemorrhagic stroke (RR = 0.75, *P* = 0.01) and reduction for the need for revascularization procedure (RR = 0.79, *P* = 0.0036) in simvastatin/ezetimibe group. There was no significant difference between the two groups for major coronary events and it did not show any significant difference in progression to end-stage renal disease (ESRD) among non-dialysis patients (Table 2).

A 2014 meta-analysis by Palmer *et al.*<sup>[36]</sup>, which included 50 studies and 45285 patients, showed that statins consistently reduced CVD events and death rates in CKD patients not on dialysis. It showed that, when compared to placebo, statins reduced overall mortality (RR = 0.79 with 95%CI: 0.69-0.91 in 10 studies and 28276 patients), cardiovascular (CV) mortality (RR = 0.77, 95%CI: 0.69-0.87 in 7 studies and 19059 patients), CV events (RR = 0.72, 95%CI: 0.66-0.79 in 13 studies and 36033 patients), and myocardial infarction (RR = 0.55, 95%CI: 0.42-0.72 in 8 studies and 9018 patients). This meta-analysis did not show any consistent effect of statin on progression of CKD.

Post hoc analyses of three randomized trials

**Table 3** Kidney diseases: improving global outcomes recommended doses of commonly used statins, based on doses used in trials, in patients with estimated glomerular filtration rate < 60<sup>[9,35,45-47]</sup>

|                       | Dose (mg/d) |
|-----------------------|-------------|
| Fluvastatin           | 80          |
| Atorvastatin          | 20          |
| Rosuvastatin          | 10          |
| Simvastatin/ezetimibe | 20/10       |
| Pravastatin           | 40          |
| Simvastatin           | 40          |
| Pitavastatin          | 2           |

(CARE, LIPID and WOSCOPS) have also shown that pravastatin reduced cardiovascular event rates (HR = 0.77, 95%CI: 0.68-0.86) in patients with moderate CKD; and this was similar to the patients without CKD<sup>[37]</sup>. Interestingly, subgroup analysis of JUPITER trial showed that rosuvastatin decreased cardiovascular event rates as well as overall mortality in patients with moderate CKD even in the absence of hyperlipidemia (LDL < 130). However, this study originally excluded patients with diabetes and advanced CKD<sup>[38]</sup>. Other meta-analyses of trials (randomized trials in CKD population plus sub-group analysis of trials of general population) have persistently shown the beneficial effect of statins<sup>[39-41]</sup>.

There has been a suggestion that statins might have been associated with decreased decline in renal function<sup>[42]</sup>. However, not only majority of data is from secondary analysis; the results have been contradictory as well<sup>[43]</sup>. As stated above, SHARP trial (only randomized trial in this population) did not show any effect of statin on renal progression. Recent meta-analysis by Nikolic *et al*<sup>[44]</sup> showed improvement in GFR with statin use with the most benefit observed between year 1 and year 3 of statin therapy.

**Recommendations for use:** Kidney diseases: improving global outcomes (KDIGO) 2013 guidelines<sup>[45]</sup> recommend treatment with statins for CKD patients (not on chronic dialysis or had transplantation)  $\geq$  50 years of age who have estimated GFR (eGFR) below or above 60 mL/min per 1.73 m<sup>2</sup>. For patients between ages of 18-49, KDIGO currently recommends statin therapy if they have known coronary disease, diabetes, prior history of ischemic stroke and if their cumulative 10-year risk of coronary death or non-fatal MI is greater than 10%. Statins are generally well tolerated; main side effects include hepatotoxicity and muscle toxicity including myopathy, myalgia and rhabdomyolysis. The incidence of these side effects has not been higher in CKD population compared to general population. For patients with eGFR  $\geq$  60 mL/min per 1.73 m<sup>2</sup>, there is no dose adjustments required for CKD patients. KDIGO recommends using doses, used in randomized trials for particular statins, for the patients with eGFR below 60

(Table 3).

**Fibrates:** Fibrates mainly have effects on reducing triglyceride levels and increasing HDL cholesterol levels. Fibrates can decrease triglyceride levels by 18%-45%<sup>[48]</sup> and increase HDL cholesterol by 10%<sup>[49]</sup>. However in patients with CKD, their overall effect on cardiovascular risk has not been proven consistently. K/DOQI guidelines in 2003 recommended use of fibrates for the prevention of pancreatitis in patients with hypertriglyceridemia but in their latest 2013 guidelines, this recommendation has been removed<sup>[50]</sup>.

In post-hoc subgroup analysis of VA-HIT trial, gemfibrozil was evaluated for secondary prevention of cardiovascular events in patients with CKD<sup>[51]</sup>. Gemfibrozil therapy reduced the composite outcome of coronary death, non-fatal MI and stroke but overall mortality was unchanged. Gemfibrozil group had higher incidence of increase in serum creatinine compared to placebo. Other major trials, evaluating effects of fibrates on cardiovascular risk, either had a very small proportion of patients with kidney disease<sup>[52]</sup> or CKD patients were entirely excluded<sup>[53]</sup>. At present KDIGO recommends against use of combination of statin and fibrates in CKD patients due to increased adverse events.

KDIGO recommends therapeutic life style changes in patients with hypertriglyceridemia, although the evidence for this is weak. These include weight reduction, dietary modification, increase physical activity, reduced alcohol intake and treatment of hyperglycemia. KDIGO recommends that fibrates can be considered in patients with triglycerides > 1000 mg/dL<sup>[50]</sup>.

### CKD patients on dialysis

**Statins:** There have been three major randomized clinical trials evaluating effect of statins in dialysis population. First one to be reported was Die Deutsche Diabetes Dialyse study, commonly known as 4D study. In this study, effect of atorvastatin on cardiovascular disease and death was evaluated among 1255 diabetic patients who were receiving maintenance hemodialysis<sup>[47]</sup>. Groups were assigned to receive atorvastatin 20 mg or matching placebo. At median follow-up of 4 years, despite decrease in LDL cholesterol by 42% within first four weeks, atorvastatin use did not significantly impact the primary endpoints of cardiovascular death, non-fatal MI and non-fatal stroke. Interestingly, atorvastatin group had higher incidence of fatal stroke. Atorvastatin also did not have significant effect on all-cause mortality. Various factors have been attributed to these findings, including the fact that the entire patient population was diabetic, had significant cardiovascular disease burden at baseline, relatively lower dose of atorvastatin, and probable limited role of statin once ESRD occurs. Subsequent post hoc analysis of 4D trial by März *et al*<sup>[54]</sup> showed that atorvastatin reduced fatal and non-fatal cardiac event and all-cause mortality in the particular group when pre-

**Table 4** Kidney disease: Developing global guidelines recommendations for dyslipidemia treatment among chronic kidney disease groups

| CKD groups                   | KDIGO recommendations for dyslipidemia  |
|------------------------------|---|
| CKD patients not on dialysis | In adults $\geq 50$ yr with eGFR $\geq 60$ mL/min per $1.73\text{ m}^2$ , treatment with statins is recommended<br>In adults $\geq 50$ yr with eGFR $\leq 60$ mL/min per $1.73\text{ m}^2$ , treatment with statins or statins/ezetimibe combination is recommended<br>In adults 18-49 yr, treatment with statins is recommended if they have one or more of the following risk factors:<br>Known coronary disease<br>Diabetes mellitus<br>Prior ischemic stroke<br>Estimated 10-yr incidence of coronary death or non-fatal myocardial infarction $> 10\%$ |
| CKD patients ON dialysis     | In adult CKD patients on dialysis, initiation of statin or statin/ezetimibe combination is not recommended<br>In adult dialysis patients who are already on statin or statin/ezetimibe combination at the initiation of dialysis, these agents should be continued  |
| Kidney transplant patients   | In adult patients with kidney transplant, treatment with statin is recommended  |

Adapted from Tonelli *et al*<sup>[45]</sup>. CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate.

treatment LDL is  $> 145$  mg/dL<sup>[54]</sup>.

A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) trial tried to investigate effects of rosuvastatin in hemodialysis patients<sup>[46]</sup>. This trial included 2776 hemodialysis patients randomly assigned to rosuvastatin 10 mg daily or matching placebo. Primary end-point was composite of death from cardiovascular cause, non-fatal MI and non-fatal stroke. At median follow up of 3.8 years, rosuvastatin did not have any significant association with primary end-point (HR = 0.96, 95%CI: 0.84-1.11,  $P = 0.59$ ). As seen in the 4D study, rosuvastatin group in this study had a 43% reduction in their LDL levels from baseline at 3 mo. No significant effect on all-cause mortality was seen either. Authors suggested several possibilities contributing to these findings which include exclusion of patients  $< 50$  years of age and those who have been on statin, high percentage of patients leaving the study, and lower than expected yearly cardiovascular event rates. In post hoc analysis of this trial among diabetics ( $n = 731$ ), rosuvastatin did not have significant effect on primary end-point although rosuvastatin group had significant decrease in cardiovascular events (HR = 0.68, 95%CI: 0.51-0.90)<sup>[55]</sup>.

SHARP trial<sup>[35]</sup> included CKD patients on dialysis as well as not on dialysis. It also included patients on both hemodialysis and peritoneal dialysis. Out of 9270 patients, 3023 were on dialysis and among them 2527 were on hemodialysis and 496 were on peritoneal dialysis. As mentioned earlier, there was a 17% reduction in major atherosclerotic event with the use of simvastatin and ezetimibe but the data on individual components of primary endpoints were only available for whole (dialysis + non-dialysis) population, and not separately. The authors suggested that proportional effect on major atherosclerotic event did not differ between dialysis and non-dialysis patients. The results showed that simvastatin and ezetimibe did not have any significant effect on cardiovascular mortality and all-

cause mortality. In sub-group of dialysis patients, there were similar numbers of major atherosclerotic events in simvastatin plus ezetimibe group (15%) as in the placebo group (16.5%) with RR = 0.9 with 95%CI: 0.75-1.08, although this trial did not have sufficient power to see any effect in subgroup analysis. Interestingly, lesser number of dialysis patients used lipid lowering therapy and had lower LDL cholesterol levels at baseline compared to non-dialysis patients (Table 2).

Palmer *et al*<sup>[56]</sup> presented review of statins in dialysis population in 2013. Their review included 25 studies and 8289 patients. Authors reported that at the dose of simvastatin 20 mg/d or equivalent, statin reduced total cholesterol by 46 mg/dL. But they had no significant effect on major cardiovascular events (RR = 0.95 with CI: 0.88-1.03 in 4 studies with  $n = 7084$ ), cardiovascular mortality (RR = 0.94 with CI: 0.84-1.06 in 13 studies with  $n = 4627$ ), and all-cause mortality (RR = 0.96 with CI: 0.90-1.02 in 13 studies with  $n = 4705$ ). They further noted that the data regarding risk of adverse events were not conclusive and there was not enough information to evaluate difference between hemodialysis and peritoneal dialysis population. It was concluded that statins could not be recommended for the prevention of cardiovascular events among dialysis patients.

**Recommendations for use:** KDIGO 2013 guidelines<sup>[45]</sup> recommend not to initiate statin or statin plus ezetimibe in dialysis population based on the results of the above mentioned clinical trials. For the patients who are already on statin or statin plus ezetimibe at the initiation of dialysis, there is no conclusive data available. Nevertheless, at this time, KDIGO recommends to continue these agents and periodically review them (Table 4).

**Fibrates:** There are no specific randomized trials of the use of fibrates in dialysis population. At present, KDIGO recommendations for hypertriglyceridemia and use of

fibrates remain same for both non-dialysis and dialysis populations.

### Kidney transplant patients

Kidney transplant patients are unique in that they are not only on multiple long term immunosuppressive medications but are also prone for infections and malignancy therefore one need to be extremely cautious in adding medications in this unique population. Use of any combination of medication in RTR entails one to be vigilant of the side effect profile as well as the drug interactions. Guidelines are developed based on input from several landmark trials; however paucity of trials in managing lipid abnormalities in RTR does pose a challenge.

Assessment of LEscal in renal transplantation (ALERT) Study was a well conducted multicenter randomized double-blind, placebo controlled trial which included 2102 renal transplant recipient who were treated with fluvastatin or placebo and followed for 5-6 years. At the end of the study Fluvastatin group had a significant lowering of their mean LDL cholesterol, total cholesterol and triglyceride levels compared to placebo, with no significant change in the HDL cholesterol level. Even though the study showed a reduction in the primary endpoint of major adverse cardiac events, it was not statistically significant. However the treatment with fluvastatin led to a reduction in the risk of cardiac death by about 38% and non-fatal Myocardial Infarction by about 32% without any significant difference in the adverse events related to the medication dose. Of note, the power of the trial (to achieve its primary end point) was low; along with that there was increased use of statin in the placebo arm towards the end of the study, both of which could have limited the evidence of the full benefits of the statin drug<sup>[9,57-59]</sup>. An Extension of the ALERT study reinforced the effective reduction of LDL-Cholesterol as well as the major adverse cardiac events without any safety or tolerability issues even in the cyclosporine treated patients<sup>[58]</sup>.

Another multicenter randomized trial looking into the effect of fluvastatin on acute rejection involved 364 RTR who were given fluvastatin 40 mg and were compared to placebo. Individuals receiving fluvastatin had a reduction in LDL cholesterol level by 18%, total cholesterol (TC) by 10% and an augmented increase in the HDL cholesterol by 6%. There was no increase in adverse events from the use of statin and no reduction in the acute rejection rates in RTR<sup>[60]</sup>. A recent meta-analysis of statin use in RTR included 22 studies and found the inconclusive effects of statin on all-cause mortality and kidney function. However it did show the significant reduction of TC, LDL cholesterol and concluded the possible benefit of statin in reducing cardiovascular events<sup>[61]</sup>.

As mentioned above, various immunosuppressive combinations are used in RTR and fluvastatin appears to have a less lipid lowering effect in everolimus treated

patients which is an mTOR antagonist. Given this information alternative statin therapy or a combination of medication may have to be instituted to better optimize the dyslipidemia. A small study involving 12 RTR on everolimus, when switched from fluvastatin to rosuvastatin showed an additional significant improvement in the lipid panel without affecting the safety and tolerability<sup>[62]</sup>.

Smaller trials have assessed the safety and tolerability of various statins in RTR and some have highlighted the pleiotropic effects of statin on graft survival and improving endothelial dysfunction. Atorvastatin and Simvastatin in spite of their involvement in the cytochrome P450 pathway have been shown to be relatively safe overall in RTR<sup>[63]</sup>.

Based on available data, KDIGO recommends (weak recommendation with moderate quality of evidence) use of statin in renal transplant recipients<sup>[45]</sup>.

## CONCLUSION

In summary, patients with kidney diseases have unique lipid abnormalities when compared to general population and they have different clinical implications associated with these abnormalities. Over the time, our understanding has evolved regarding dyslipidemia in CKD patients. Statins remain the first line of treatment for dyslipidemia. Majority of current evidence comes from subgroup/post hoc analysis and meta-analysis, especially in CKD (pre-dialysis), peritoneal dialysis and renal transplant population. Prospective interventional studies are needed in this population to identify subsets of patients who will benefit most and also to assess long term toxicity of statins. KDIGO recommendations provide general principles regarding treatment of dyslipidemia but it should be individualized for each patient.

## REFERENCES

- 1 **Jha V**, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; **382**: 260-272 [PMID: 23727169 DOI: 10.1016/S0140-6736(13)60687-X]
- 2 **Centers for Disease Control and Prevention (CDC)**. National Chronic Kidney Disease Fact Sheet: General Information and National Estimates on Chronic Kidney Disease in the United States. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2014. Available from: URL: [http://www.cdc.gov/diabetes/pubs/pdf/kidney\\_factsheet.pdf](http://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf)
- 3 **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**. Kidney Disease Statistics for the United States. Bethesda, MD. US Department of Health and Human Services, National Institutes of Health, 2012. Available from: URL: [http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/KU\\_Diseases\\_Stats\\_508.pdf](http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/KU_Diseases_Stats_508.pdf)
- 4 **US Renal Data System**. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, 2013. Available from: URL: [http://www.usrds.org/2013/pdf/v2\\_ch1\\_13.pdf](http://www.usrds.org/2013/pdf/v2_ch1_13.pdf)
- 5 **Foley RN**, Parfrey PS, Sarnak MJ. Clinical epidemiology of

- cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32**: S112-S119 [PMID: 9820470]
- 6 **Sarnak MJ**, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; **108**: 2154-2169 [PMID: 14581387 DOI: 10.1161/01.CIR.0000095676.90936.80]
- 7 **US Renal Data System**. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013. Available from: URL: [http://www.usrds.org/2013/pdf/v1\\_ch4\\_13.pdf](http://www.usrds.org/2013/pdf/v1_ch4_13.pdf)
- 8 **Israni AK**, Snyder JJ, Skeans MA, Peng Y, Maclean JR, Weinhandl ED, Kasiske BL. Predicting coronary heart disease after kidney transplantation: Patient Outcomes in Renal Transplantation (PORT) Study. *Am J Transplant* 2010; **10**: 338-353 [PMID: 20415903 DOI: 10.1111/j.1600-6143.2009.02949.x]
- 9 **Holdaas H**, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhammar-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambühl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003; **361**: 2024-2031 [PMID: 12814712 DOI: 10.1016/S0140-6736(03)13638-0]
- 10 **Muntner P**, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 2005; **16**: 529-538 [PMID: 15625072 DOI: 10.1681/ASN.2004080656]
- 11 **Shoji T**, Masakane I, Watanabe Y, Iseki K, Tsubakihara Y. Elevated non-high-density lipoprotein cholesterol (non-HDL-C) predicts atherosclerotic cardiovascular events in hemodialysis patients. *Clin J Am Soc Nephrol* 2011; **6**: 1112-1120 [PMID: 21511840 DOI: 10.2215/CJN.09961110]
- 12 **Krediet RT**, Balafoutis O. Cardiovascular risk in the peritoneal dialysis patient. *Nat Rev Nephrol* 2010; **6**: 451-460 [PMID: 20567248 DOI: 10.1038/nrneph.2010.68]
- 13 **Kalantar-Zadeh K**, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003; **63**: 793-808 [PMID: 12631061 DOI: 10.1046/j.1523-1755.2003.00803.x]
- 14 **Iseki K**, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int* 2002; **61**: 1887-1893 [PMID: 11967041 DOI: 10.1046/j.1523-1755.2002.00324.x]
- 15 **Liu Y**, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, Tracy RP, Powe NR, Klag MJ. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004; **291**: 451-459 [PMID: 14747502 DOI: 10.1001/jama.291.4.451]
- 16 **Kilpatrick RD**, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K. Association between serum lipids and survival in hemodialysis patients and impact of race. *J Am Soc Nephrol* 2007; **18**: 293-303 [PMID: 17167113 DOI: 10.1681/ASN.2006070795]
- 17 **Chawla V**, Greene T, Beck GJ, Kusek JW, Collins AJ, Sarnak MJ, Menon V. Hyperlipidemia and long-term outcomes in nondiabetic chronic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**: 1582-1587 [PMID: 20558558 DOI: 10.2215/CJN.01450210]
- 18 **Keane WF**, Tomassini JE, Neff DR. Lipid abnormalities in patients with chronic kidney disease: implications for the pathophysiology of atherosclerosis. *J Atheroscler Thromb* 2013; **20**: 123-133 [PMID: 23095239 DOI: 10.5551/jat.12849]
- 19 **Arnadottir M**, Thysell H, Dallongeville J, Fruchart JC, Nilsson-Ehle P. Evidence that reduced lipoprotein lipase activity is not a primary pathogenetic factor for hypertriglyceridemia in renal failure. *Kidney Int* 1995; **48**: 779-784 [PMID: 7474664 DOI: 10.1038/ki.1995.350]
- 20 **Epstein M**, Vaziri ND. Statins in the management of dyslipidemia associated with chronic kidney disease. *Nat Rev Nephrol* 2012; **8**: 214-223 [PMID: 22349484 DOI: 10.1038/nrneph.2012.33]
- 21 **Moradi H**, Vaziri ND, Kashyap ML, Said HM, Kalantar-Zadeh K. Role of HDL dysfunction in end-stage renal disease: a double-edged sword. *J Ren Nutr* 2013; **23**: 203-206 [PMID: 23611547 DOI: 10.1053/j.jrn.2013.01.022]
- 22 **Navab M**, Reddy ST, Van Lenten BJ, Anantharamaiah GM, Fogelman AM. The role of dysfunctional HDL in atherosclerosis. *J Lipid Res* 2009; **50** Suppl: S145-S149 [PMID: 18955731 DOI: 10.1194/jlr.R800036-JLR200]
- 23 **Kalantar-Zadeh K**, Kopple JD, Kamranpour N, Fogelman AM, Navab M. HDL-inflammatory index correlates with poor outcome in hemodialysis patients. *Kidney Int* 2007; **72**: 1149-1156 [PMID: 17728705 DOI: 10.1038/sj.ki.5002491]
- 24 **Honda H**, Ueda M, Kojima S, Mashiba S, Michihata T, Takahashi K, Shishido K, Akizawa T. Oxidized high-density lipoprotein as a risk factor for cardiovascular events in prevalent hemodialysis patients. *Atherosclerosis* 2012; **220**: 493-501 [PMID: 22119537 DOI: 10.1016/j.atherosclerosis.2011.10.038]
- 25 **Akmal M**, Kasim SE, Soliman AR, Massry SG. Excess parathyroid hormone adversely affects lipid metabolism in chronic renal failure. *Kidney Int* 1990; **37**: 854-858 [PMID: 2313975]
- 26 **Liang K**, Oveisi F, Vaziri ND. Role of secondary hyperparathyroidism in the genesis of hypertriglyceridemia and VLDL receptor deficiency in chronic renal failure. *Kidney Int* 1998; **53**: 626-630 [PMID: 9507207 DOI: 10.1046/j.1523-1755.1998.00786.x]
- 27 **Lacour B**, Rouillet JB, Liagre AM, Jorgetti V, Beyne P, Dubost C, Drüeke T. Serum lipoprotein disturbances in primary and secondary hyperparathyroidism and effects of parathyroidectomy. *Am J Kidney Dis* 1986; **8**: 422-429 [PMID: 3812471 DOI: 10.1016/S0272-6386(86)80169-X]
- 28 **Kimak E**, Halabiš M, Baranowicz-Gaszczyk I. Relationships between serum lipid, lipoprotein, triglyceride-rich lipoprotein, and high-density lipoprotein particle concentrations in post-renal transplant patients. *J Zhejiang Univ Sci B* 2010; **11**: 249-257 [PMID: 20349521 DOI: 10.1631/jzus.B1000012]
- 29 **Corsini A**, Holdaas H. Fluvastatin in the treatment of dyslipidemia associated with chronic kidney failure and renal transplantation. *Ren Fail* 2005; **27**: 259-273 [PMID: 15957541 DOI: 10.1081/JDI-56623]
- 30 **Spinelli GA**, Felipe CR, Park SI, Mandia-Sampaio EL, Tedesco-Silva H, Medina-Pestana JO. Lipid profile changes during the first year after kidney transplantation: risk factors and influence of the immunosuppressive drug regimen. *Transplant Proc* 2011; **43**: 3730-3737 [PMID: 22172836 DOI: 10.1016/j.transproceed.2011.08.074]
- 31 **Wissing KM**, Pipeleers L. Obesity, metabolic syndrome and diabetes mellitus after renal transplantation: prevention and treatment. *Transplant Rev (Orlando)* 2014; **28**: 37-46 [PMID: 24507957 DOI: 10.1016/j.tre.2013.12.004]
- 32 **Kaplan B**, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. *Transplant Rev (Orlando)* 2014; **28**: 126-133 [PMID: 24685370 DOI: 10.1016/j.tre.2014.03.002]
- 33 **Scarpioni R**, Ricardi M, Albertazzi V, Melfa L. Treatment of dyslipidemia in chronic kidney disease: Effectiveness and safety of statins. *World J Nephrol* 2012; **1**: 184-194 [PMID: 24175258 DOI: 10.5527/wjn.v1.i6.184]
- 34 **Kassimatis TI**, Goldsmith DJ. Statins in chronic kidney disease and kidney transplantation. *Pharmacol Res* 2014; **88**: 62-73 [PMID: 24995940 DOI: 10.1016/j.phrs.2014.06.011]
- 35 **Baigent C**, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairitichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhammar-Riska C, Dasgupta T, Lewis D, Herrington

- W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; **377**: 2181-2192 [PMID: 21663949 DOI: 10.1016/S0140-6736(11)60739-3]
- 36 **Palmer SC**, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2014; **5**: CD007784 [PMID: 24880031]
- 37 **Tonelli M**, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, Craven T, West M. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2004; **110**: 1557-1563 [PMID: 15364796 DOI: 10.1161/01.CIR.0000143892.84582.60]
- 38 **Ridker PM**, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol* 2010; **55**: 1266-1273 [PMID: 20206456 DOI: 10.1016/j.jacc.2010.01.020]
- 39 **Upadhyay A**, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 251-262 [PMID: 22910936 DOI: 10.7326/0003-4819-157-4-201208210-00005]
- 40 **Palmer SC**, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 263-275 [PMID: 22910937 DOI: 10.7326/0003-4819-157-4-201208210-00007]
- 41 **Hou W**, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, Cass A, Zhang H, Wang H. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J* 2013; **34**: 1807-1817 [PMID: 23470492 DOI: 10.1093/eurheartj/ehd065]
- 42 **Elisaf M**, Mikhailidis DP. Statins and renal function. *Angiology* 2002; **53**: 493-502 [PMID: 12365855 DOI: 10.1177/000331970205300501]
- 43 **Heymann EP**, Kassimatis TI, Goldsmith DJ. Dyslipidemia, statins, and CKD patients' outcomes - review of the evidence in the post-sharp era. *J Nephrol* 2012; **25**: 460-472 [PMID: 22641572 DOI: 10.5301/jn.5000154]
- 44 **Nikolic D**, Banach M, Nikfar S, Salari P, Mikhailidis DP, Toth PP, Abdollahi M, Ray KK, Pencina MJ, Malyszko J, Rysz J, Rizzo M. A meta-analysis of the role of statins on renal outcomes in patients with chronic kidney disease. Is the duration of therapy important? *Int J Cardiol* 2013; **168**: 5437-5447 [PMID: 24016544 DOI: 10.1016/j.ijcard.2013.08.060]
- 45 **Tonelli M**, Wanner C. Lipid management in chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. *Ann Intern Med* 2014; **160**: 182 [PMID: 24323134 DOI: 10.7326/M13-2453]
- 46 **Fellström BC**, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; **360**: 1395-1407 [PMID: 19332456 DOI: 10.1056/NEJMoa0810177]
- 47 **Wanner C**, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238-248 [PMID: 16034009 DOI: 10.1056/NEJMoa043545]
- 48 **Brunzell JD**. Clinical practice. Hypertriglyceridemia. *N Engl J Med* 2007; **357**: 1009-1017 [PMID: 17804845 DOI: 10.1056/NEJMcip070061]
- 49 **Birjmohun RS**, Hutten BA, Kastelein JJ, Stroes ES. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005; **45**: 185-197 [PMID: 15653014 DOI: 10.1016/j.jacc.2004.10.031]
- 50 Chapter 5: Triglyceride-lowering treatment in adults. *Kidney Int Suppl* (2011) 2013; **3**: 284-285 [PMID: 25019003 DOI: 10.1038/kisup.2013.37]
- 51 **Tonelli M**, Collins D, Robins S, Bloomfield H, Curhan GC. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004; **66**: 1123-1130 [PMID: 15327407 DOI: 10.1111/j.1523-1755.2004.00862.x]
- 52 **Keech A**, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366**: 1849-1861 [PMID: 16310551 DOI: 10.1016/S0140-6736(05)67667-2]
- 53 **Ginsberg HN**, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1563-1574 [PMID: 20228404 DOI: 10.1056/NEJMoa1001282]
- 54 **März W**, Genser B, Drechsler C, Krane V, Grammer TB, Ritz E, Stojakovic T, Scharnagl H, Winkler K, Holme I, Holdaas H, Wanner C. Atorvastatin and low-density lipoprotein cholesterol in type 2 diabetes mellitus patients on hemodialysis. *Clin J Am Soc Nephrol* 2011; **6**: 1316-1325 [PMID: 21493741 DOI: 10.2215/CJN.09121010]
- 55 **Holdaas H**, Holme I, Schmieder RE, Jardine AG, Zannad F, Norby GE, Fellström BC. Rosuvastatin in diabetic hemodialysis patients. *J Am Soc Nephrol* 2011; **22**: 1335-1341 [PMID: 21566054 DOI: 10.1681/ASN.2010090987]
- 56 **Palmer SC**, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Nigwekar SU, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev* 2013; **9**: CD004289 [PMID: 24022428]
- 57 **Holdaas H**, Fellström B, Jardine AG. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: lessons to be learnt from the assessment of Lescol in renal transplantation (ALERT) trial. *Am J Transplant* 2005; **5**: 1574-1575 [PMID: 15888072 DOI: 10.1111/j.1600-6143.2005.00909.x]
- 58 **Holdaas H**, Fellström B, Cole E, Nyberg G, Olsson AG, Pedersen TR, Madsen S, Grönhagen-Riska C, Neumayer HH, Maes B, Ambühl P, Hartmann A, Staffler B, Jardine AG. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant* 2005; **5**: 2929-2936 [PMID: 16303007 DOI: 10.1111/j.1600-6143.2005.01105.x]
- 59 **Holdaas H**, Fellström B, Holme I, Nyberg G, Fauchald P, Jardine A, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Weinreich T, Olsson AG, Pedersen TR, Benghozi R, Hartmann A. Effects of fluvastatin on cardiac events in renal transplant patients: ALERT (Assessment of Lescol in Renal Transplantation) study design and baseline data. *J Cardiovasc Risk* 2001; **8**: 63-71 [PMID: 11324372 DOI: 10.1097/00043798-200104000-00002]
- 60 **Holdaas H**, Jardine AG, Wheeler DC, Brekke IB, Conlon PJ, Fellström B, Hammad A, Holme I, Isoniemi H, Moore R, Rowe PA, Sweny P, Talbot DA, Wadström J, Østraat Ø. Effect of fluvastatin on acute renal allograft rejection: a randomized multicenter trial. *Kidney Int* 2001; **60**: 1990-1997 [PMID: 11703619 DOI: 10.1046/j.1523-1755.2001.00010.x]
- 61 **Palmer SC**, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev* 2014; **1**: CD005019 [PMID: 24470059]

62 **Robertson I**, Asberg A, Granseth T, Vetthe NT, Akhlaghi F, Ghareeb M, Molden E, Reier-Nilsen M, Holdaas H, Midtvedt K. More potent lipid-lowering effect by rosuvastatin compared with fluvastatin in everolimus-treated renal transplant recipients. *Transplantation* 2014; **97**: 1266-1271 [PMID: 24521776 DOI: 10.1097/01.TP.0-

000443225.66960.7e]

63 **Hermann M**, Asberg A, Christensen H, Reubsæet JL, Holdaas H, Hartmann A. Atorvastatin does not affect the pharmacokinetics of cyclosporine in renal transplant recipients. *Eur J Clin Pharmacol* 2005; **61**: 59-62 [PMID: 15711834 DOI: 10.1007/s00228-004-0874-5]

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