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Metabolic alterations in dialysis patients

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CHAPTER

Evidence based management of lipid disorders

**What are the consequences of renal insufficiency
or the nephrotic syndrome for lipid levels?**

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An introduction to chronic kidney disease

Chronic kidney disease is characterized by the failure of the kidneys to remove waste products and excess fluid from the body. It is defined by a sustained impairment of kidney function, as reflected by an abnormal excretion of urinary protein or a reduction of the glomerular filtration rate (GFR). When the glomerular filtration rate reaches levels below 15 ml/min (corresponding to a reduction in kidney function by approximately 90%), patients require renal replacement therapy, which is provided in the form of dialysis or transplantation. The etiology of chronic kidney disease (CKD) is heterogeneous, involving both primary kidney diseases, and a variety of non-renal diseases, which affect the kidneys. The main causes among primary kidney diseases are glomerulonephritis and renal vascular diseases, while diabetes mellitus, hypertension, and atherosclerosis are the most frequent non-renal causes potentially leading to a loss of kidney function.

The National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) workgroup has defined CKD by a glomerular filtration rate <60 ml/min/1.73m², or the presence of a marker of kidney damage.^{1,2} Based upon these definitions, a classification of CKD by stages has been recommended and internationally accepted (Table 1).

Chronic kidney disease represents a large public health problem. Its prevalence in the United States currently is about 13%^{3,4}, with an increasing trend in the recent decade. Data from the United States Renal Data System (USRDS) furthermore show an increase in the incidence rate of end-stage renal disease, reaching 360 per million population in 2006. Accordingly, the number of patients entering the end-stage renal disease (ESRD) program rose from 106.912 in 2005 to 110.854 patients in 2006^{3,5}. The costs of treatment, which in the form of dialysis represents one of the most expensive chronic therapies, put an enormous burden on health care resources. Prevention of disease progression and associated complications therefore is highly important, requiring the knowledge of risk factors and appropriate treatment.

Table 1. Stages of chronic kidney disease

Stage		GFR (ml/min/1.73m ²)	Prevalence
1	Kidney damage with normal or increased GFR	≥ 90	3.3%
2	Kidney damage with mild decreased GFR	60 – 89	3.0%
3	Moderately decreased GFR	30 – 59	4.3%
4	Severely decreased GFR	15 – 29	0.2%
5	Kidney failure	< 15 (or dialysis)	0.1%

GFR = glomerular filtration rate.

Dyslipidemia in the patient with kidney disease

Proteinuria induced dyslipidemia

Abnormal lipid metabolism is common in patients with renal disease, and most prominent in the nephrotic syndrome. Studies have shown that about half of the patients with nephrotic syndrome (proteinuria > 3g/day) had total cholesterol concentrations above 300 mg/dL^{6,7}, and 80% of the patients had LDL cholesterol levels above 130 mg/dL⁸.

The main abnormalities of lipid metabolism in the nephrotic syndrome include increases in total cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol, apolipoproteins B (Apo B), C-III and triglycerides, while Apo A-I is reduced. Furthermore, the high-density lipoproteins are distributed abnormally (increased HDL₃ fraction and decreased HDL₂ fraction). Hyperlipidemia in the nephrotic syndrome results from increased hepatic synthesis and decreased catabolism of lipoproteins, whereby the contribution of each to establishing blood lipid levels has not been characterized in detail. Increased triglyceride rich lipoprotein concentration, VLDL and intermediate density lipoprotein (IDL) primarily results from decreased clearance⁹, partly due to a reduced lipoprotein lipase (LPL) activity. Lipoprotein lipase is necessary for endothelial binding of VLDL and for normal lipolysis. The loss of the cofactor apoCII (a lipoprotein lipase activator), which is especially common in proteinuric renal disease, and a depletion of the endothelial bound lipoprotein lipase (LPL)

pool¹⁰ may contribute to the reduced LPL-activity. In addition, both LDL and lipoprotein(a) [Lp(a)] synthesis are increased^{9,11}, whereby evidence exists that LDL synthesis may be augmented through a mechanism bypassing its normal precursor VLDL. Finally, due to decreased activity of lecithin:cholesterol acyltransferase (LCAT) in proteinuric renal disease¹², mature, the number of spherical HDL particles are decreased. These particles are important carriers for several cofactors, amongst which apoCII, affecting LPL activity and VLDL level.

The impact of CKD on serum lipids and lipoproteins

Dyslipidemia in patients with CKD and no nephrotic syndrome can be characterized by high triglyceride levels and low HDL concentrations, while total and LDL cholesterol are normal or even low^{13,14}. Although the lipid abnormalities captured by routine laboratory measurements may not be impressive, more sophisticated analyses reveal profound disturbances in lipid metabolism. Mainly as a result of decreased catabolism, the concentration of triglyceride-rich lipoproteins (VLDL, IDL) is increased, in particular in the post prandial phase. Lipolysis of the highly atherogenic VLDL and chylomicron (CM) remnants is impaired partly due to the decreased lipoprotein lipase (LPL) on the vascular endothelium, and partly due to increased levels of the major LPL inhibitory apolipoprotein apo CIII. Furthermore, kidney failure is associated with a shift in the size distribution of LDL to increased content of small dense LDL. A reduction in LDL size, resulting in increased levels of small dense LDL, results from increased TG concentration, which via the action of cholesterol ester transfer protein (CETP) and hepatic lipase (HL)¹⁵ result in the formation of small dense LDL. Due to the increased oxidative stress in patients with CKD and the reduced clearance, the fraction of highly atherogenic oxidized LDL is increased.

Disorders in HDL maturation and catabolism add to the dyslipidemic profile in CKD patients. Processes favoring HDL maturation are associated with a greater abundance of large mature HDL and greater HDL levels. The adenosine triphosphate binding cassette 1 (ABCA 1) is responsible for initial lipidation of apoAI and transfer of cholesterol and small (native) HDL particles. The formation of large, mature HDL particles is mediated by LCAT -resulting in the esterification

of cholesterol- as well as by LPL. As previously mentioned, functional deficiencies in LCAT and LPL activity may therefore affect HDL maturation.

In addition, elevated levels of Lp(a) have been found in CKD.¹⁶⁻²⁰, partly due to the diminished renal clearance¹⁷. Lp(a) is an LDL-like particle which has an additional protein, apolipoprotein(a), and constitutes an important risk factor for atherosclerosis. The mechanisms of lipid metabolism and alterations in renal failure are shown in Figure 1.

Lipid disorders in dialysis

The lipid abnormalities in CKD stages 2-4 as characterized by an increase in plasma triglycerides, VLDL and IDL, along with a reduction in HDL cholesterol, generally also apply for dialysis patients. Dyslipidemia becomes more pronounced as kidney failure advances to CKD stage 5 requiring dialysis.

Hemodialysis and peritoneal dialysis can both provide an adequate relief of uremic symptoms, but the two techniques appear to have different effects on uremic dyslipidemia^{21,22}. Patients on peritoneal dialysis (PD) show higher cholesterol, triglyceride, LDL and Lp(a) levels than patients on maintenance hemodialysis (HD). Possible reasons may be a considerable loss of protein (7-14g/day) into the peritoneal dialysate, and the absorption of glucose (150-200g/day) from the dialysis fluid. Plasma concentrations of apoB100 were shown to be increased in peritoneal dialysis patients, whereas normal concentrations of apoB100 were found in hemodialysis patients²¹. The increase in apoB100 thereby was most markedly in the VLDL fraction, and only to a minor extent in IDL and LDL. An overproduction of VLDL-1 and VLDL-2 apoB100 has been suggested secondary to reduced insulin sensitivity and increased free fatty acid availability in PD patients. This leads to an increase in the poolsize of triglycerides and apoB100 in the VLDL fraction of PD patients. Although lipid profiles differ between PD and HD patients, abnormalities in lipid metabolism qualitatively have similarities regarding the pathogenesis of atherosclerosis and endothelial dysfunction in these groups.

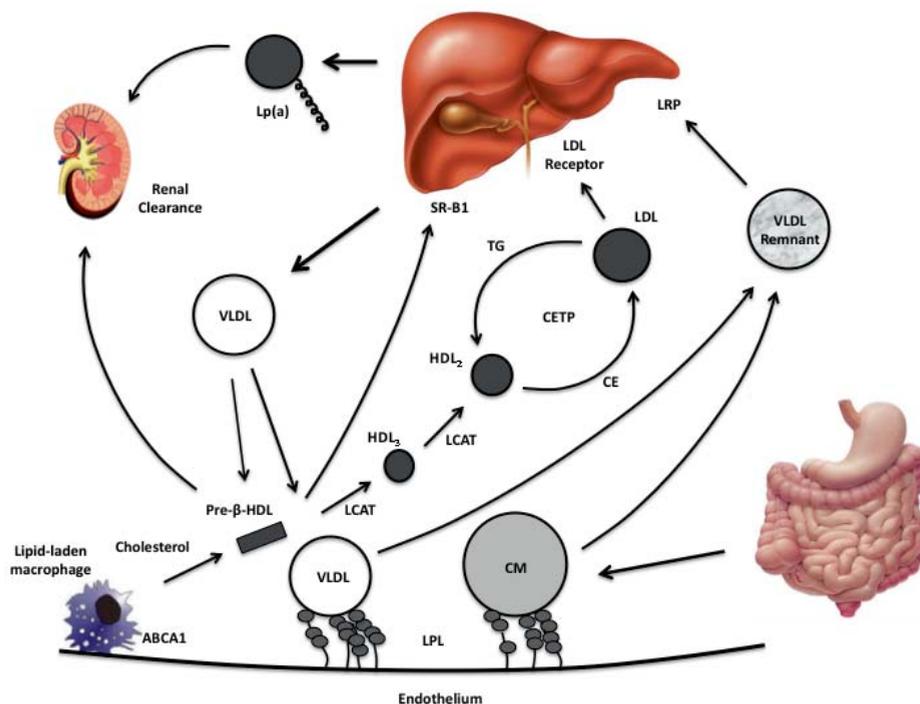


Figure 1. Triglyceride-rich lipoproteins are secreted by the gut (chylomicrons) or liver (VLDL) and then are processed on the vascular endothelium by lipoprotein lipase (LPL), yielding remnant particles. LPL is activated by apo CII and inhibited by apo CI and apo CIII. Apo CI and apo CIII are increased in chronic kidney disease (CKD). HDL formation is initiated by the combination of apo AI with cholesterol and phospholipids through interaction with the adenosine triphosphate binding cassette 1 (ABCA1). The nascent pre- β -HDL is then matured by cholesterol esterification through lecithin cholesterol ester transfer protein (LCAT), first to HDL₃ and then to HDL₂. HDL₂ is taken up by the liver by the scavenger receptor B1 (SR-B1). Alternatively, it transfers its cholesterol ester-rich core to VLDL, creating LDL (via CETP activity). LCAT protein mass and activity are both reduced in CKD. This results in accumulation of pre- β or discoidal HDL and HDL₃, which are subject to accelerated degradation in part by the kidney. While HDL₃ is usually rich in the antioxidant enzyme paraoxonase 1 (PON1), this is not the case in HDL₃ in patients having CKD. Lipoprotein(a) levels are increased in CKD as a result of decreased clearance.

Abbreviations: TG = triglyceride, VLDL = very low density lipoprotein, LPL = lipoprotein lipase, CKD = chronic kidney disease, HDL = high density lipoprotein, ABCA1 = adenosine triphosphate binding cassette 1, LCAT = lecithin cholesterol ester transfer protein, SR-B1 = scavenger receptor B1, CETP = cholesterol ester transfer protein, Lp(a) = lipoprotein (a), LRP = lipoprotein like receptor, CE = cholesteryl ester.

Lipid disorders after kidney transplantation

Lipid abnormalities in kidney transplant recipients are common, occurring in 60% to 70% of renal transplant recipients receiving immunosuppressive therapy ^{23,24}. Major characteristics are the increases in levels of LDL, VLDL and triglycerides, while HDL is usually normal.

Risk factors contributing to the development of dyslipidemia after transplantation are age, male gender, proteinuria, obesity, pretransplant hyperlipidemia and diabetes mellitus. Furthermore, dyslipidemia following kidney transplantation is associated with the use and dose of immunosuppressive agents such as corticosteroids, calcineurin-inhibitors, and inhibitors of the mammalian target of rapamycin (mTOR). The cumulative dose of corticosteroids thereby appears to be the most significant risk factor. Among calcineurin-inhibitors, a higher incidence of hyperlipidemia was shown with the use of ciclosporine as compared to tacrolimus. Sirolimus and everolimus however, both mTOR inhibitors, seem to even more impact on lipid metabolism with significant increases in triglyceride and cholesterol levels ²⁵. Mycophenolate mofetil is the only available immunosuppressive agent with no adverse effects on lipids.

Dyslipidemia and progression of kidney disease

Dyslipidemia, partly explained by its association with proteinuria, predicts progressive loss of kidney function ²⁶. This was seen particularly in early stages of diabetic nephropathy ^{27,28}. Elevated levels of triglycerides seem to contribute to the progression of albuminuria ²⁹, diabetic nephropathy ³⁰, and retinopathy.

They were furthermore associated with a higher risk of end-stage renal disease requiring renal replacement therapy ³¹. In contrast, higher levels of HDL were found to be protective of albuminuria in type 1 diabetes ³².

Dyslipidemia, cardiovascular risk and mortality

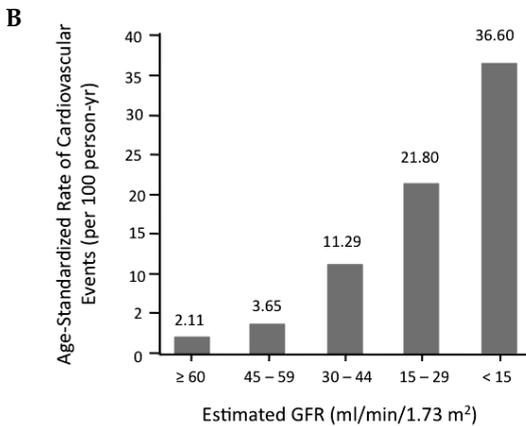
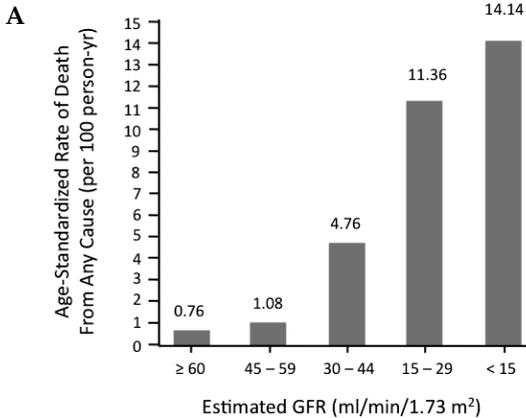
Chronic kidney disease per se has been shown to be a strong risk factor for cardiovascular morbidity and mortality ³³. Patients with a moderately impaired kidney function already have a high risk to develop cardiovascular complications ³⁴. Cardiovascular risk further increases inversely proportionate to the decline in kidney function (Figure 2), and the majority of patients with chronic kidney disease die of cardiac and vascular events before reaching end-stage renal disease.

In patients on long-term dialysis, cardiac and vascular disease is the leading cause of death, accounting for 43% of all-cause mortality ³. Compared to the general population, mortality from cardiovascular disease is excessively high: it ranges from a 500 fold increased risk in young patients aged 25-35 years to a 5-fold increased risk in individuals of a high age of 85 years or more ³⁵. Possible reasons may involve the increased prevalence of traditional risk factors as known from the general population, and further uremia-related risk factors. Lipid abnormalities, being common in patients with kidney disease, have been suggested to play a major role. Therefore, it is tempting to propose a general need for treatment of lipid disorders in this patient group.

However, while a loglinear relation between blood cholesterol levels and cardiovascular risk is well established in the general population, this is not the case in renal patients. Many studies in patients with CKD, mainly stage 5, have failed to show a similar, clear pattern of high plasma total cholesterol, LDL cholesterol and triglycerides being associated with increased cardiovascular mortality. In fact, a number of studies have even found that low (not high) serum total cholesterol was associated with increased mortality ³⁶⁻³⁹. U-shaped curves, and

recently, J-shaped curves have been described for the relationship between serum cholesterol and mortality. This probably reflects the influence of malnutrition and chronic inflammation, resulting in the phenomenon known as reverse causation. Concomitant illnesses accompanied by inflammation are associated with an increased risk of death; when they furthermore induce a decrease in cholesterol synthesis, the result may be artifactually negative associations between cholesterol and mortality. Supporting this hypothesis, hypercholesterolemia was shown to be an independent risk factor for cardiovascular and all-cause mortality in dialysis patients without, but not in those with evidence of malnutrition or inflammation

40.



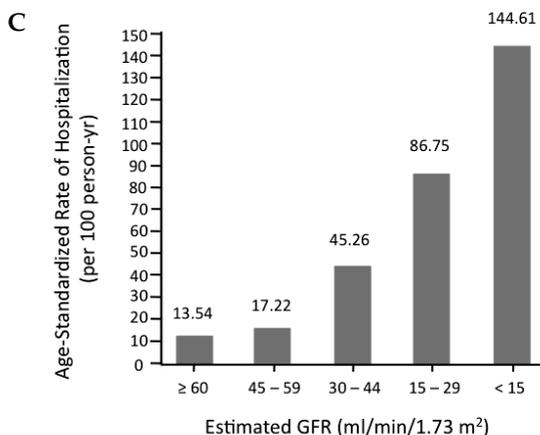


Figure 2. Age-standardized rates of death from any cause (A), cardiovascular events (B), and hospitalization (C), according to the estimated glomerular filtration rate (GFR).[©]

In general, caution is required on translating observational findings into possible therapeutic treatments. Furthermore, concern is also justified when applying recommendations for the treatment of lipid disorders from the general population –which are based upon many prospective randomized placebo-controlled trials– to patients with chronic kidney disease. Extrapolation of data from the general population may not meet the special disease pattern of kidney disease patients:

Despite cardiovascular deaths being a major cause of mortality in dialysis patients, the proportion of myocardial infarctions in cardiac deaths is much lower in patients with chronic kidney disease as compared to the general population. Only 25 per cent of the cardiac deaths in hemodialysis patients can be attributed to myocardial infarctions, while the majority of events constitutes of sudden cardiac deaths³. Although sudden cardiac death may to some extent also result from infarctions and arrhythmias, other reasons such as structural heart diseases presumably play an important role. Whether these may be modifiable with cholesterol lowering treatment, is unlikely.

Therefore, it is obvious that the classical guidelines, such as the national cholesterol education program adult panel III cannot generally be applied to renal patients. In particular, treatment indications may differ according to the severity of chronic kidney disease. In the subsequent chapter, we therefore present the available evidence for lipid lowering therapy according to the stages of chronic kidney disease as defined by K/DOQI (Kidney Disease Outcomes Quality Initiative) (Tab. 1)^{2,41}.

Lipid lowering therapy in patients with the nephrotic syndrome

Studies have shown that patients with persistent nephrotic syndrome and hyperlipidemia are at increased risk for atherosclerotic disease, particularly if other risk factors are present.^{7,42,43} Furthermore, it has been suggested from animal experiments and observations in humans that hyperlipidemia may also enhance the rate of progressive glomerular injury, possibly by promoting an intraglomerular equivalent of atherosclerosis. Thus, it appears reasonable that lowering lipid levels may both protect against systemic atherosclerosis and slow the progression of the underlying kidney disease. Studies have shown that statins can efficiently lower total and LDL cholesterol concentrations by 20 to 45%, and to a lesser extent triglyceride levels and Lp(a) levels⁴³⁻⁴⁷. Despite the lack of studies using “hard” endpoints, statins are suggested as the treatment of choice for persistent hyperlipidemia in the nephrotic syndrome (IV/C). Due to side effects, other lipid lowering medication as nicotinic acid, fibric acid, probucol or bile acid sequestrants are not generally recommended. Instead, additional therapeutic options include dietary modification⁴⁸ and angiotensin inhibition (IV/C), the latter being associated with a 10 to 20% decline in the plasma levels of total and LDL-cholesterol and Lp(a)⁴⁹.

Statins in patients with chronic kidney disease

Early renal disease: CKD stage 1-3 (GFR ≥ 30 ml/min/1.73m²)

The effects of a lipid lowering therapy on cardiovascular, cerebrovascular and renal endpoints were investigated in a subgroup analysis of the *Pravastatin Pooling Project*, including 12333 patients with mild CKD (stage 2) and 4491 patients with moderate CKD (stage 3). Pravastatin 40mg/day resulted in a significant 23% relative risk reduction in the combined endpoint of non-fatal myocardial infarction, cardiac death, percutaneous or surgical revascularizations in patients with moderate CKD. A similar effect was seen in patients with mild CKD, among whom even total mortality was reduced. The achieved relative risk reduction corresponds to the effect, which would have been expected in the general population without kidney disease. The corresponding absolute risk reduction was - due to the higher event rate - even more than twice as high compared to patients with normal kidney function (6.3 vs 2.9%)⁵⁰ **(IIb/B)**.

Furthermore, a prespecified subgroup analysis of 6.517 patients with kidney dysfunction was performed among the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), including 19.000 hypertensive patients with at least 3 other risk factors for coronary artery disease, and non-fasting cholesterol levels ≤ 6.5 mmol/l. It showed that patients receiving 10mg atorvastatin per day had a significantly lower risk of reaching the composite primary endpoint, consisting of nonfatal myocardial infarction and cardiac death, compared to patients receiving placebo⁵¹ **(IIb/B)**.

Similar results were obtained from analyses of 1.329 patients with slightly elevated creatinine (110 to 200 μ mol/L) participating in the Heart Protection Study (HPS). A total of 268 of the patients receiving placebo experienced a vascular event vs. 182 of the simvastatin treated patients, This corresponds to a 25% relative risk reduction in the simvastatin group⁵² **(IIb/B)**. Recent findings from the Treatment to New Targets (TNT) study confirmed that treatment of patients having less severe CKD does reduce the cardiovascular risk⁵³ **(IIb/B)**.

Finally, there are data suggesting that statins may also slow the rate of decline in kidney function and lower urinary protein excretion. One subanalysis within the GRACE-study showed that in untreated patients with coronary heart disease, dyslipidemia and normal baseline creatinine, the glomerular filtration rate (GFR) decreased over a period of 3 years. Treatment with a statin could prevent this decline and lead to a significant improvement in kidney function⁵⁴. In the TNT study, patients on 80mg atorvastatin per day had a significantly lower rate of decline of renal function than did patients receiving 10mg/day⁵⁵ (**IIb/B**). Similarly, a post-hoc subgroup analysis of the CARE study had shown a lower GFR decline in pravastatin as compared to placebo treated patients⁵⁶ (**IIb/B**). The reduction of GFR decline as achieved by statins (reduction of 0.1 ml/min/1.73m² per year in the latter study) however is relatively small (in comparison: reductions of 3 to 4 ml/min/1.73m² by the control of hypertension and ACE-inhibitor therapy in proteinuric patients^{57,58}).

Although some data also exist for fibrates suggesting beneficial effects on the rate of progression of renal disease and cardiovascular risk^{59,60} (**IIb/B**), these drugs have been considered with caution in patients with CKD. This is mainly because most fibrates or their active metabolites accumulate in renal failure and occasionally cause rhabdomyolysis.

In conclusion, despite the absence of direct evidence from randomized controlled trials in patients with CKD, these data provide indirect evidence that patients with CKD stages 2 and 3 may benefit from a lipid lowering intervention. Based on the above post hoc analyses of past statin trials on subcohorts of patients with early CKD, data are sufficiently suggestive to justify the administration of statins in these patients (**IIb/B**).

Advanced renal disease: CKD stage 4-5 and dialysis patients

Unfortunately, patients with more advanced CKD (stage 4) were either absent in the above described subgroup analyses, or their numbers were too small to be

analyzed. There is a complete lack of controlled studies addressing the effect of lipid lowering medication on outcome in patients at CKD stage 4. These patients represent a population with advanced kidney failure, where all-cause mortality markedly increases and the pattern of cardiovascular disease may change, compared to CKD stages 2 and 3. One open study has been performed in a small group of patients (n=143) over 20 months, and showed that atorvastatin decreased the primary cardiac endpoint in patients with pre-end stage renal disease, while this was not the case in dialysis patients ⁶¹.

More definite evidence has been provided by the prospective, randomized controlled 4D study (The German Diabetes and Dialysis Study). This study evaluated the effect of 20 mg atorvastatin / day vs placebo in 1255 hemodialysis patients with type 2 diabetes mellitus during 4 years of follow-up ⁶². Although Atorvastatin effectively lowered LDL cholesterol by 42%, the composite primary cardiovascular endpoint, consisting of death from cardiac causes, non-fatal myocardial infarction and stroke, was only reduced by 8%, which was not statistically significant (RR 0.92, 95%CI 0.77-1.10, p=0.37) **(Ib/A)**. Similarly, all-cause mortality was not significantly reduced (RR 0.93, 95%CI 0.79-1.08, p=0.33). There was a positive result however for the secondary endpoint of all cardiac events combined, which were lowered by 18% in the atorvastatin group as compared to the placebo group (RR 0.82, 95%CI 0.86-0.99, p=0.03). Further evidence was contributed by AURORA: A study to evaluate the Use of Rosuvastatin in subjects On Regular Dialysis: an Assessment of survival and cardiovascular events⁶³. In this international prospective randomized controlled trial, 2776 hemodialysis patients were assigned to receive rosuvastatin 10mg daily or placebo, and followed for a median of 3.8 years. Despite the mean reduction in LDL cholesterol of 43% in the intervention group, the combined primary endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke could not be reduced (HR 0.96, 95%CI 0.84-1.11, p=0.59) **(Ib/A)**. Rosuvastatin neither had an effect on individual components of the primary endpoint, nor on all-cause mortality (HR 0.96, 95%CI 0.86-1.07, p=0.51). It remains unclear whether these data can be generalized to peritoneal dialysis patients. This will be clarified by the ongoing

Study of Heart and Renal Protection (SHARP), which is a large-scale randomized controlled trial comparing the use of simvastatin and ezetimibe vs. placebo in 9489 patients in CKD stage 4 and on dialysis – the results are awaited in 2011 ⁶⁴.

In conclusion, the 4D and AURORA studies do not provide a rationale to start statin treatment in hemodialysis patients (**Ib/A**). Treatment aiming at primary prevention in the absence of signs and symptoms of coronary heart disease presumably comes too late once the patient has advanced to end-stage renal disease. It has been suggested however that patients who are already on statins when entering chronic dialysis should be left on the medication ¹⁴.

Patients after kidney transplantation

Recipients of kidney transplants had been investigated in the ALERT study, which was a randomized controlled trial comparing fluvastatin (40-80 mg/day) vs. placebo in 2,102 patients with long-term stable graft function. Despite a mean reduction in LDL cholesterol of 1 mmol/l during 5.1 ± 1.1 years, there was no significant risk reduction for the combined primary endpoint, consisting of cardiac death, non-fatal myocardial infarction and coronary revascularization (RR 0.83 (95% CI 0.64-1.06), $p=0.139$) (**Ib/A**). Furthermore, total mortality and graft loss did not differ significantly between the groups (In the fluvastatin and placebo groups there were 143 deaths compared with 138, and 146 graft losses compared with 137, respectively.) Rates in two of the three subcomponents of the primary endpoint - cardiac death and non-fatal myocardial infarction- were observed to be lower in the intervention group (RR 0.65 (0.48-0.88), $p=0.005$). The authors suggested that the trial may have been too small to detect a significant effect on the primary endpoint because the event rate was lower than expected. ⁶⁵.

A post hoc analysis of the ALERT trial showed that the success of a lipid lowering therapy in kidney transplant recipients is dependent on when treatment is initiated. Indeed, a significant reduction in cardiac endpoints was observed in patients who started fluvastatin treatment within the first 4.5 years after renal transplantation (4.6% in fluvastatin group vs 9.2% in placebo group)⁶⁶ (**Ib/B**).

Despite the lack of direct evidence it can therefore be suggested that renal transplant recipients with hyperlipidemia should be treated with a statin so that target LDL cholesterol levels can be achieved (**IIb/B**). Importantly, for any statin therapy in renal transplant recipients, potential interactions with other medication and changes of immunosuppressive regimens should be taken into account. All statins, except Pravastatin, primarily undergo metabolism by the CYP 450 isoenzymes in the liver. The CYP 2C9 isoenzyme is responsible for the metabolism of fluvastatin and rosuvastatin, whereas atorvastatin, lovastatin, and simvastatin are metabolized by the CYP 3A4 isoenzyme. Concomitant intake of further drugs being metabolized by the CYP 3A4 system – such as the immunosuppressant Cyclosporine in renal transplant recipients, macrolide antibiotics or calcium channel blockers like verapamil - may dramatically increase the plasma concentration of the statin, placing patients at risk for adverse events like myopathy or rhabdomyolysis. Pravastatin and Rosuvastatin are less likely to induce drug-drug interactions and considered as more safe.

In summary, results from the 4D and ALERT trials do not necessarily doubt the validity of the subgroup analyses done for patients with CKD stages 2 and 3, in whom lipid lowering therapy appears to be just as effective as in patients with normal kidney function. It remains less clear whether lipid lowering therapy is still effective when started in patients with more advanced stages of chronic kidney disease.

Further therapeutic concepts for lipid-lowering in CKD

Nutritional interventions and physical activity

Nutritional interventions and physical activity play an important role as lipid lowering treatments in the general population. They presumably have similar importance in patients with chronic kidney disease in early stages 1-3 (**IV/C**).

In stage 4, reduction in nutrient intake without sufficient physical activity may lead to a catabolic state with reduction of muscle mass. Therefore, nutritional interventions should not generally be applied to patients in advanced stages of CKD, but carefully considered individually.

Antiproteinuric therapy

Any intervention leading to a reduction of urinary protein excretion also leads to a reduction in LDL-cholesterol and Lp(a). ACE-inhibitors and AT1-receptor-blockers have antiproteinuric properties, and thus result in a reduction of the – microalbuminuria or proteinuria-induced- dyslipidemia.

Treatment guidelines

Guidelines including the European Best Practice guidelines (EBPG) ⁶⁷ and the US National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) ^{68,69} have been difficult to define due to the lack of randomized controlled trials addressing dyslipidemia in chronic kidney disease. Kidney transplant recipients are represented by the Kidney Disease Improving Global Outcomes (KDIGO)⁷⁰ guideline, which for the treatment of dyslipidemia refers to K/DOQI. Table 2 summarizes guideline treatment recommendations, and –as the randomized controlled studies were still ongoing once the guidelines were developed- reflects that they are mainly based on *opinion*.

It is to be expected that further ongoing randomized controlled trials will add reliable evidence for the treatment of dyslipidemia especially in advanced chronic kidney disease (stages 4-5 and dialysis), so that new treatment guidelines with higher evidence levels may be established in the near future.

Table 2. Recommendations for the treatment of dyslipidemia according to the K/DOQI guidelines for patients with CKD and the KDIGO guidelines for kidney transplant recipients

Treatment of patients with CKD stage 1-4

In general, the K/DOQI working group recommended that the *NCEP/ATP III guidelines*⁷¹ were applicable to patients with CKD stages 1-4, with some specific aspects deserving further consideration:

- 1) CKD should be classified as a CVD risk equivalent.
- 2) Complications of lipid-lowering therapies resulting from reduced kidney function should be anticipated.
- 3) It should be considered whether there may be indications for the treatment of dyslipidemia other than preventing CVD.
- 4) It should be determined whether the treatment of proteinuria may also be an effective treatment for dyslipidemias.

Supporting the treatment of dyslipidemia, assessment and treatment of other modifiable traditional risk factors as hypertension, smoking, obesity and diabetes should be performed.

Treatment of patients with CKD stage 5

1. For adults with Stage 5 CKD and fasting triglycerides ≥ 500 mg/dL (≥ 5.65 mmol/L) that cannot be corrected by removing an underlying cause, treatment with therapeutic lifestyle changes (TLC) and a triglyceride-lowering agent should be considered. (C)
 2. For adults with Stage 5 CKD and LDL ≥ 100 mg/dL (≥ 2.59 mmol/L), treatment should be considered to reduce LDL to < 100 mg/dL (< 2.59 mmol/L). (B)
 3. For adults with Stage 5 CKD and LDL < 100 mg/dL (< 2.59 mmol/L), fasting triglycerides ≥ 200 mg/dL (≥ 2.26 mmol/L), and non-HDL cholesterol (total cholesterol minus HDL) ≥ 130 mg/dL (≥ 3.36 mmol/L), treatment should be considered to reduce non-HDL cholesterol to < 130 mg/dL (< 3.36 mmol/L). (C)
-

Treatment of patients after kidney transplantation

1. For patients with fasting triglycerides ≥ 500 mg/dL (≥ 5.65 mmol/L) that cannot be corrected by removing an underlying cause, we suggest therapeutic lifestyle changes and a triglyceride-lowering agent. [Based on KDOQI Recommendation 4.1 for patients with CKD stage 5, Evidence Level C]
 2. For patients with elevated low-density lipoprotein (LDL) cholesterol, we suggest: If LDL ≥ 100 mg/dL (≥ 2.59 mmol/L), treat to reduce LDL to < 100 mg/dL (< 2.59 mmol/L) [Based on KDOQI Guideline 4.2 for patients with CKD stage 5, Evidence Level B]
 3. For patients with normal LDL cholesterol, elevated triglycerides and elevated non-HDL cholesterol, we suggest: If LDL < 100 mg/dL (< 2.59 mmol/L), fasting triglycerides ≥ 200 mg/dL (≥ 2.26 mmol/L), and non-HDL ≥ 130 mg/dL (≥ 3.36 mmol/L), treat to reduce non-HDL to < 130 mg/dL (< 3.36 mmol/L) [Based on KDOQI Guideline 4.3 for patients with CKD stage 5, Evidence Level C]
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Conclusions

In conclusion, disturbances in lipid metabolism are common in patients with the nephrotic syndrome, patients with chronic kidney disease (CKD) and patients after kidney transplantation. The classical guidelines on lipid lowering therapy –such as the national cholesterol education program adult panel III- however cannot generally be applied to renal patients, as extrapolation of data from the general population may not meet the special disease pattern of patients with CKD. Although post-hoc analyses of statin trials support the administration of statins in patients with early stages of CKD (stages 1-3), patients with advanced chronic kidney disease do not benefit to the same extent from lipid-lowering therapy. In particular, there is no rationale to start statin treatment in patients, once they require maintenance hemodialysis.

Key points

Lipid abnormalities in the nephrotic syndrome and in renal insufficiency

- Abnormal lipid metabolism is common in patients with the nephrotic syndrome and in patients with chronic kidney disease (CKD) or after kidney transplantation.
- Main abnormalities of lipid metabolism in the nephrotic syndrome include increases in total cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol, apolipoproteins B, C-III and triglycerides, while apo-A1 is reduced.
- The profound disturbances in lipid metabolism in patients with chronic kidney disease include increased concentrations of triglyceride-rich lipoproteins, small dense and oxidized LDL, and impaired HDL maturation and catabolism. These alterations are not captured by routine laboratory measurements.
- Immunosuppressive therapy importantly contributes to the development of dyslipidemia after kidney transplantation.
- Chronic kidney disease per se is a strong risk factor for cardiovascular morbidity and mortality. Cardiovascular risk and mortality increase inversely proportionate to the decline in kidney function.

Treatment recommendations

Evidence level

- The classical guidelines on lipid lowering therapy –such as the national cholesterol education program adult panel III- cannot generally be applied to renal patients, as extrapolation of data from the general population may not meet the special disease pattern of patients with chronic kidney disease.
- Patients with the nephrotic syndrome should be treated with a statin. Additional therapeutic options include dietary modification and inhibition of the renin-angiotensin system (angiotensin-converting enzyme inhibitors). IV/C
- Post-hoc analyses of statin trials support the administration of statins in patients with early stages of chronic kidney disease (CKD stage 1-3) IIb/B
- Patients with advanced chronic kidney disease do not benefit to the same extent from lipid-lowering therapy as do patients with early stages of CKD. In particular, there is no rationale to start statin treatment in patients, once they require maintenance hemodialysis. Ib/A
- Despite the lack of direct evidence, it is suggested that renal transplant recipients with hyperlipidemia should be treated with a statin. IIb/B
Importantly, potential interactions with immunosuppressants and other medication should be taken into account.
- The present guidelines (EBPG and K/DOQI) on the treatment of lipid disorders in patients with chronic kidney disease do not reflect the current evidence.

References

- (1) National Kidney Foundation. K/DOQI Clinical Practice Guidelines for chronic kidney disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 2002; 39:S1.
- (2) Levey AS, Eckardt KU, Tsukamoto Y et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2005;67:2089-2100.
- (3) U.S. Renal Data System, USRDS: 2006 Annual Report. National Institutes of Health, Bethesda, 2006.
- (4) Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007;298:2038-2047.
- (5) U.S. Renal Data System, USRDS: 2005 Annual Report. National Institutes of Health, Bethesda, 2005.
- (6) Kronenberg F, Lingenhel A, Lhotta K et al. Lipoprotein(a)- and low-density lipoprotein-derived cholesterol in nephrotic syndrome: Impact on lipid-lowering therapy? *Kidney Int.* 2004;66:348-354.
- (7) Radhakrishnan J, Appel AS, Valeri A, Appel GB. The nephrotic syndrome, lipids, and risk factors for cardiovascular disease. *Am J Kidney Dis.* 1993;22:135-142.
- (8) Weiner DE, Sarnak MJ. Managing dyslipidemia in chronic kidney disease. *J Gen Intern Med.* 2004;19:1045-1052.
- (9) de Sain-van der Velden MG, Reijngoud DJ, Kaysen GA et al. Evidence for increased synthesis of lipoprotein(a) in the nephrotic syndrome. *J Am Soc Nephrol.* 1998;9:1474-1481.
- (10) Attman PO, Samuelsson O, Alaupovic P. Lipid abnormalities in progressive renal insufficiency. *Contrib Nephrol.* 1997;120:1-10.
- (11) de Sain-van der Velden MG, Kaysen GA, Barrett HA et al. Increased VLDL in nephrotic patients results from a decreased catabolism while increased LDL results from increased synthesis. *Kidney Int.* 1998;53:994-1001.
- (12) Kaysen GA, de Sain-van der Velden MG. New insights into lipid metabolism in the nephrotic syndrome. *Kidney Int Suppl.* 1999;71:S18-S21.

- (13) Prinsen BH, de Sain-van der Velden MG, de Koning EJ, Koomans HA, Berger R, Rabelink TJ. Hypertriglyceridemia in patients with chronic renal failure: possible mechanisms. *Kidney Int Suppl.* 2003;S121-S124.
- (14) Ritz E, Wanner C. Lipid abnormalities and cardiovascular risk in renal disease. *J Am Soc Nephrol.* 2008;19:1065-1070.
- (15) Kaysen GA. New insights into lipid metabolism in chronic kidney disease: what are the practical implications? *Blood Purif.* 2009;27:86-91.
- (16) Cressman MD, Heyka RJ, Paganini EP, O'Neil J, Skibinski CI, Hoff HF. Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. *Circulation.* 1992;86:475-482.
- (17) Frischmann ME, Kronenberg F, Trenkwalder E et al. In vivo turnover study demonstrates diminished clearance of lipoprotein(a) in hemodialysis patients. *Kidney Int.* 2007;71:1036-1043.
- (18) Kronenberg F, König P, Neyer U et al. Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol.* 1995;6:110-120.
- (19) Levine DM, Gordon BR. Lipoprotein(a) levels in patients receiving renal replacement therapy: methodologic issues and clinical implications. *Am J Kidney Dis.* 1995;26:162-169.
- (20) Longenecker JC, Klag MJ, Marcovina SM et al. High lipoprotein(a) levels and small apolipoprotein(a) size prospectively predict cardiovascular events in dialysis patients. *J Am Soc Nephrol.* 2005;16:1794-1802.
- (21) Attman PO, Samuelsson OG, Moberly J et al. Apolipoprotein B-containing lipoproteins in renal failure: the relation to mode of dialysis. *Kidney Int.* 1999;55:1536-1542.
- (22) Deighan CJ, Caslake MJ, McConnell M, Boulton-Jones JM, Packard CJ. Atherogenic lipoprotein phenotype in end-stage renal failure: origin and extent of small dense low-density lipoprotein formation. *Am J Kidney Dis.* 2000;35:852-862.
- (23) Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. *Transplantation.* 1997;63:331-338.

- (24) Ong CS, Pollock CA, Caterson RJ, Mahony JF, Waugh DA, Ibels LS. Hyperlipidemia in renal transplant recipients: natural history and response to treatment. *Medicine (Baltimore)*. 1994;73:215-223.
- (25) Kasiske BL, de MA, Flechner SM et al. Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients. *Am J Transplant*. 2008;8:1384-1392.
- (26) Ozsoy RC, van der Steeg WA, Kastelein JJ, Arisz L, Koopman MG. Dyslipidaemia as predictor of progressive renal failure and the impact of treatment with atorvastatin. *Nephrol Dial Transplant*. 2007;22:1578-1586.
- (27) Earle KA, Harry D, Zitouni K. Circulating cholesterol as a modulator of risk for renal injury in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2008;79:68-73.
- (28) Ficociello LH, Perkins BA, Silva KH et al. Determinants of progression from microalbuminuria to proteinuria in patients who have type 1 diabetes and are treated with angiotensin-converting enzyme inhibitors. *Clin J Am Soc Nephrol*. 2007;2:461-469.
- (29) Misra A, Kumar S, Kishore VN, Kumar A. The role of lipids in the development of diabetic microvascular complications: implications for therapy. *Am J Cardiovasc Drugs*. 2003;3:325-338.
- (30) Hadjadj S, Duly-Bouhanick B, Bekherras A et al. Serum triglycerides are a predictive factor for the development and the progression of renal and retinal complications in patients with type 1 diabetes. *Diabetes Metab*. 2004;30:43-51.
- (31) Cusick M, Chew EY, Hoogwerf B et al. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Report No. 26. *Kidney Int*. 2004;66:1173-1179.
- (32) Molitch ME, Rupp D, Carnethon M. Higher levels of HDL cholesterol are associated with a decreased likelihood of albuminuria in patients with long-standing type 1 diabetes. *Diabetes Care*. 2006;29:78-82.
- (33) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-1305.
- (34) Anavekar NS, McMurray JJ, Velazquez EJ et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285-1295.

- (35) Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32:S112-S119.
- (36) Habib AN, Baird BC, Leygoldt JK, Cheung AK, Goldfarb-Rumyantzev AS. The association of lipid levels with mortality in patients on chronic peritoneal dialysis. *Nephrol Dial Transplant.* 2006;21:2881-2892.
- (37) 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.
- (38) 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.
- (39) Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition-inflammation-cachexia syndrome. *J Am Soc Nephrol.* 2007;18:304-311.
- (40) Liu Y, Coresh J, Eustace JA et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA.* 2004;291:451-459.
- (41) Levey AS, Coresh J, Balk E et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003;139:137-147.
- (42) Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. *Kidney Int.* 1993;44:638-642.
- (43) Wheeler DC, Bernard DB. Lipid abnormalities in the nephrotic syndrome: causes, consequences, and treatment. *Am J Kidney Dis.* 1994;23:331-346.
- (44) Brown CD, Azrolan N, Thomas L et al. Reduction of lipoprotein(a) following treatment with lovastatin in patients with unremitting nephrotic syndrome. *Am J Kidney Dis.* 1995;26:170-177.
- (45) Massy ZA, Ma JZ, Louis TA, Kasiske BL. Lipid-lowering therapy in patients with renal disease. *Kidney Int.* 1995;48:188-198.
- (46) Rabelink AJ, Hene RJ, Erkelens DW, Joles JA, Koomans HA. Effects of simvastatin and cholestyramine on lipoprotein profile in hyperlipidaemia of nephrotic syndrome. *Lancet.* 1988;2:1335-1338.

- (47) Thomas ME, Harris KP, Ramaswamy C et al. Simvastatin therapy for hypercholesterolemic patients with nephrotic syndrome or significant proteinuria. *Kidney Int.* 1993;44:1124-1129.
- (48) Gentile MG, Fellin G, Cofano F et al. Treatment of proteinuric patients with a vegetarian soy diet and fish oil. *Clin Nephrol.* 1993;40:315-320.
- (49) Keilani T, Schlueter WA, Levin ML, Battle DC. Improvement of lipid abnormalities associated with proteinuria using fosinopril, an angiotensin-converting enzyme inhibitor. *Ann Intern Med.* 1993;118:246-254.
- (50) Tonelli M, Isles C, Curhan GC et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation.* 2004;110:1557-1563.
- (51) Sever PS, Dahlof B, Poulter NR et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;361:1149-1158.
- (52) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7-22.
- (53) Shepherd J, Kastelein JJ, Bittner V et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol.* 2008;51:1448-1454.
- (54) Athyros VG, Mikhailidis DP, Papageorgiou AA et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol.* 2004;57:728-734.
- (55) Shepherd J, Kastelein JJ, Bittner V et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. *Clin J Am Soc Nephrol.* 2007;2:1131-1139.
- (56) Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol.* 2003;14:1605-1613.

- (57) Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet*. 1997;349:1857-1863.
- (58) Klahr S, Levey AS, Beck GJ et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330:877-884.
- (59) Nagai T, Tomizawa T, Nakajima K, Mori M. Effect of bezafibrate or pravastatin on serum lipid levels and albuminuria in NIDDM patients. *J Atheroscler Thromb*. 2000;7:91-96.
- (60) 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.
- (61) Stegmayr BG, Brannstrom M, Bucht S et al. Low-dose atorvastatin in severe chronic kidney disease patients: a randomized, controlled endpoint study. *Scand J Urol Nephrol*. 2005;39:489-497.
- (62) Wanner C, Krane V, Marz W et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238-248.
- (63) Fellström BC, Jardine AG, Schmieder RE et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395-1407.
- (64) Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl*. 2003;S207-S210.
- (65) Holdaas H, Fellstrom B, Jardine AG et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet*. 2003;361:2024-2031.
- (66) Holdaas H, Fellstrom B, Jardine AG et al. Beneficial effect of early initiation of lipid-lowering therapy following renal transplantation. *Nephrol Dial Transplant*. 2005;20:974-980.
- (67) European Best practice guidelines for hemodialysis (part 1). Section VII. Vascular disease and risk factors. *Nephrol Dial Transplant* 2002; 17(Suppl 7): 88-109.

- (68) National Kidney Foundation. K/DOQI Clinical Practice Guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis* 2003; 41 (4suppl 3):I-IV, S1-S91.
- (69) National Kidney Foundation. K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis* 2007; 49 (Suppl 2): S88-S95.
- (70) National Kidney Foundation. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients, Public Review Draft, March 9, 2009; http://www.kdigo.org/clinical_practice_guidelines
- (71) Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Jama* 2001; 285: 2486-2497.