Danish Guidelines for Lipid-lowering Treatment in Patients with Chronic Renal Failure

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Erik Berg Schmidt was affiliated with the work group as a representative for the Danish Society of Cardiology. Thus the report has been approved by the Danish Society of Cardiology as well as the Danish Society of Nephrology.

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INTRODUCTION

The Danish Guidelines are mainly based on the recently published guideline: "KDIGO CLINICAL PRACTICE GUIDELINE FOR LIPID MANAGEMENT IN CHRONIC KIDNEY DISEASE" [1].

The KDIGO work group notes that several points in the guidelines are based on suboptimal data. Unfortunately, it is unlikely that important, new studies will appear within the next few years, and therefore decisions regarding lipid-lowering treatment in the individual patient or patient group must be made on the evidence available.

The present guideline has been made short and simple. For further detail and additional background literature, please see the KDIGO report [1]. In addition, the interested reader is referred to Kasiske's review of metaanalyses regarding risk reduction with cholesterol-lowering treatment in CKD patients [2].

The treatments mentioned below have been divided into recommendations and suggestions: a recommendation is based on a higher level of evidence than a suggestion [1].

The quality of the evidence will be given and graduated as follows: A (high evidence), B (moderate evidence), C (low evidence) and D (very low evidence).

BACKGROUND

In Denmark, the prevalence of chronic kidney disease (CKD), especially the milder stages CKD 0–3, is high, but the exact prevalence is -unknown. Reduced kidney function (elevated estimated glomerular filtration rate, eGFR) is strongly associated with cardiovascular disease (CVD) independent of other risk factors, and patients in chronic dialysis treatment have a marked 40-fold increased mortality compared with the background population. Thus chronic kidney disease is equivalent in risk to coronary artery disease.

MEASUREMENT OF THE LIPID PROFILE IN ADULTS WITH CKD 1–5

The lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) should be measured in all adults with CKD 1–5 (incl. patients receiving renal replacement therapy) at the time of diagnosis (1C).

The lipid profile is characterized by both quantitative and qualitative changes that increase with decreasing kidney function. Dyslipidaemias are typically seen in the form of increased triglycerides (Tg) and reduction of HDL cholesterol (HDL-C), whereas high LDL cholesterol (LDL-C) is less pronounced in CKD stages 1–2. Most patients with stages 3–5 have mixed forms of dyslipidaemia, and the lipid profile is atherogenic and consists of changes in all the lipoproteins.

Secondary causes of dyslipidaemia should always be considered in association with the evaluation of the lipid profile.

LDL-C > 4.0 mmol/l and/or Tg > 5 mmol/l should always give rise to additional examination in CKD patients (e.g. diabetes type 2).

MONITORING OF THE LIPID PROFILE IN ADULTS WITH CKD STAGES 1–5

KDIGO states:

In adults with CKD 1–5 follow-up measurement of lipids is not required (Not Graded).

KDIGO argues that in many cases it is not necessary to regularly monitor the lipid profile. This could be the case if, for example, a patient is being given a lipid-lowering drug without a pre-defined LDL-C treatment objective.

However, measuring LDL-C may be important for patient compliance or it may be of importance to know a patient's LDL-C in order to regulate medical treatment.

In the general population, intensification of treatment is recommended to achieve specific LDL-C goals. Low LDL-C, either without medical treatment or achieved with medical treatment, is associated with reduced morbidity and increased survival [3].

There is no major evidence for a similar strategy in patients with CKD, because even kidney patients with a low LDL-C have a greater CVD risk than does the general population. Thus CKD patients'

significant risk of CVD is the primary reason for lipid-lowering treatment.

Whereas scientific evidence indicates that cholesterol-lowering treatment in CKD-ND patients reduces the risk of CVD, there is no evidence that points to a specific treatment goal regarding LDL-C. The association between LDL-C and CVD and mortality is weaker in CKD patients than in the general population, but this should be considered in light of the fact that CKD patients' risk of CVD is greater than in the general population. Said in another way, a major part of the increased risk of CVD in CKD patients is independent of LDL-C. This does not mean, however, that one can assume that CKD patients do not achieve the same absolute reduction in risk, parallel with LDL-C reduction, as is seen in the general population. In the general population, CVD-related mortality is reduced proportionally with a reduction in LDL-C, also with LDL-C below 2 mmol/l [4].

CHOLESTEROL-LOWERING TREATMENT OF CKD PATIENTS

Focus should be on the absolute risk of CVD (and not just lipids) and on the evidence regarding the efficacy of treatment. In an evaluation of the combined risk of CVD, age, gender, blood pressure and smoking status should also be considered.

There are several scorings systems, but in Denmark and in the European (ESC) guidelines, the systematic coronary risk evaluation (SCORE) algorithm [5] is primarily used. Using the algorithm and information on age/gender/systolic blood pressure, total cholesterol and smoking status, a mean risk for CVD mortality over a 10-year period can be obtained. The algorithm cannot be used in patients with diabetes mellitus (DM), or with markedly increased single risk factors like familial hypercholesterolemia and severe hypertension. It should also be noticed that the SCORE algorithm does not take into account family history, severe overweight and glucose problems. The algorithm can be used to estimate the risk of CVD, but it must be noted that CKD is a serious risk factor in itself that is not part of the SCORE algorithm.

Several types of medicine reduce LDL-C, but only statins (and the combination statin/ezetimibe) have been shown to be effective in the treatment of CKD patients, and focus will be on these medicines in the following.

The point of departure for all treatment should be the same as in all the large studies, namely a patient's 10-year risk of CVD, which is usually given as, e.g., 20 major vascular events per 1000 patient years. A risk greater than 10 per 1000 patient years will normally indicate treatment. The risk of coronary death or AMI (acute myocardial infarction) in patients with CKD with an eGFR of 15–60 ml/min/1.73 m2 or heavy proteinuria is the same or higher than in patients with DM. This risk is, however, age-related, and in all patients > 50 years, the risk is > 10 per 1000 patient years, even in patients without DM or without previous AMI (Table 4 in reference 1). A risk of this magnitude usually indicates treatment.

In all CKD patients, it should be considered whether other factors suggest that treatment should not be started. Such conditions could be a patient's general physical and mental condition, short expected life expectancy or the presence of co-morbidities. In addition, side effects and possible drug interactions can contraindicate one or all LDL-C-lowering drugs.

PATIENTS ≥ 50 YEARS WITH CKD 1–5 NON-DIALYSIS (ND)

According to the above, it is recommended that these patients be treated with a statin (CKD 1-2, evidence level B), and in CKD patients in stage 3–5 ND the combination statin/ezetimibe (evidence level A) can also be used.

Rationale

In the SHARP study, 9270 high-risk patients with CKD were studied [6]. All grades of CKD (mean eGFR 27 ml/min/1.73 m2) were included: 3023 in dialysis and 6247 with lower grades of CKD. Median follow-up was 4.9 years. Major vascular events (non-fatal myocardial infarct, non- haemorrhagic stroke, arterial revascularisation) were reduced by 17% (95% CI: 0.74-0.94, p < 0.0021), but there was no effect on morality. Patients were treated with a combination of 10 mg ezetimibe + 20 mg simvastatin, and this combination was compared with placebo treatment. The treatment was monitored in relation to a decline in LDL-C (average fall in LDL-C 0.85 mmol/l). The Intention-to-treat analysis showed 21 fewer major vascular events per 1000 patients treated for 4.9 years (Christina Reith, personal communication). Among the 6247 patients who were not in dialysis at baseline, the active treatment had no effect on progression to terminal kidney failure. The greatest effect on endpoints seemed to be among patients who were not on dialysis, but the SHARP study did not have sufficient statistic power to determine the effect in individual sub-groups. The SHARP data are in agreement with post hoc analyses of random clinical trials (RCT) of statin versus placebo. These post hoc analyses have focused on patients who had CKD at inclusion, while reduced kidney function was not a criterion for inclusion. An example of such a post hoc analysis is "The Pravastatin Pooling Project (PPP)," in which 19,737 persons with a median follow-up of 64 months were studied [7]. Treatment had greatest advantage among patients with CKD and diabetes. A significant reduction in excess mortality of all types was shown (relative risk 0.81, 95% CI: 0.73–0.89.) In another post hoc analysis (The Heart Protection Study) the absolute risk reduction was 11% in a subgroup of patients with mild CKD compared with 5.4% in the total cohort [8]. These data do not suggest that the effect of statins is influenced by the degree of albuminuria [9] [10] [11].

PATIENTS AGED 18–49 YEARS MED CKD 1–5 ND

It is recommended that these patients be treated with a statin if they also have one or more of the following conditions (evidence level A):

- -known CVD
- -DM
- -prior ischemic stroke
- -estimated 10-year risk of coronary death or non-fatal AMI > 10% (reference [1] Figure 2) or
- risk of fatal cardiovascular disease > 5% (SCORE [9])

Rationale

The risk of coronary disease is age-dependent in patients with CKD, as it is in the general population. In patients with CKD < 50 years, the risk is less but the presence of other risk factors markedly increases the risk of coronary death and non-fatal AMI.

In general, many of these patients will have an estimated 10-year risk of coronary death or non-fatal AMI > 10% because of the presence of other risk factors. Several prediction models can be used as an alternative to SCORE, for example the Framingham risk score, PROCAM [12], ASSIGN [13] or QRISK [14]. It should be noted that according to the European Society of Cardiology and a number of other societies' guidelines [9], patients with an eGFR < 30 ml/min/1.73 m^2 are considered at high risk with goal LDL-C < 1.8 mmol/l and patients with eGFR 30-60 ml/min/1.73 m^2 as at

high risk with a goal LDL-C < 2.5 mmol/l. Thus, these guidelines have treatment goals for LDL-C. If a scoring system is not used, lipid-lowering treatment can be started in patients with hypertension and in those who smoke.
Note that the Danish working committee's guidelines are identical with KDIGO, whereas the cardiologic guidelines recommend LDL-C-lowering treatment to all with known CVD.

PATIENTS WITH CKD STADIUM 5D
It is recommended that these patients are not started on statin or statin/ezetimibe treatment as standard treatment (evidence level A).
Rationale
There are three large randomised multicentre studies of a statin in which dialysis patients were included.
In Die Deutsche Diabetes Dialyse Studie (4D) Trial [15] and AURORA study [16], it was not possible to document an effect of statin treatment on cardiovascular endpoints. SHARP is mentioned above.
In a systematic review of the data from all studies in which CKD patients were randomised to a statin or a placebo, a significant heterogeneity between dialysis and non-dialysis patients was found with regard to the effect of statins on major cardiovascular endpoints. (hazard ratio for dialysis patients 0.96; 95% CI: 0.88–1.03; hazard ratio for non-dialysis patients 0.76; 95% CI: 0.72–0.79, p for heterogeneity < 0.001) [17]. If SHARP, 4D and AURORA are analysed together, the effect of statin treatment is uncertain in dialysis patients [18]. Even if statin had an effect on cardiovascular endpoints, it seems clear that the *relative* risk reduction is markedly less than in CKD patients in the early stages [17]. This, however, does not rule out that the absolute reduction in CVD could be the same as in the general population. This clinical situation can, however, mean that statin treatment could be considered in patients newly started on dialysis under special circumstances – especially co-morbidities such as -CVD or diabetes as well as relative young age.
Note that this guideline is identical with KDIGO, whereas the cardiologic guidelines recommend LDL-C-lowering treatment to all with known CVD.

PATIENTS WHO START DIALYSIS AND ARE ALREADY IN STATIN/EZETIMIBE TREATMENT
Recommendation: Treatment should be continued (evidence level C).
Rationale
SHARP, AURORA and 4D did not examine whether statin treatment should be discontinued in patients that start dialysis and are already in statin treatment.
In a sub analysis among 2141 patients (34%) who were not in dialysis at the inclusion of SHARP but who started dialysis during the study, some effect of statin treatment was found [6]. Except for this analysis, documentation regarding whether to continue or discontinue treatment is lacking.

ADULT KIDNEY-TRANSPLANTED PATIENTS
Recommendation: These patients should be treated with a statin (evidence level B).
Rationale
Mortality due to CVD is high also after a kidney transplantation. Data from the placebo arm in "Assessment of Lescol in Renal Transplant" (ALERT) study showed that prevalence of cardiovascular death or non-lethal AMI was 22 per 1000 patient years. Age-related data are not available. In addition, cyclosporin A and rapamycin are associated with an increase in serum lipids.
In ALERT, 2102 transplanted patients (age 30–75 years) were randomised to receive fluvastatin or placebo and treated for 5-6 years [19]. A non-significant 17% reduction was seen in the primary endpoint, which was a combination of coronary death or non-lethal AMI. However, a significant 35% relative reduction in the risk of cardiac death or non-lethal AMI was found. A post-hoc analysis of a continuation of the study for 6.7 years documented a significant reduction, also in the primary endpoint [20].
Special attentions should be given to the interactions that may appear between lipid-lowering drugs and those used for immunosuppressive treatment, including treatment with calcineurin inhibitors, mTOR inhibitors, etc.

TREATMENT CHOICES IN PATIENTS WITH CKD
With regard to dosage and choice of preparations, the statin treatment of patients with more pronounced CKD (stages 3–5) should be based on the regimens and dosages that have been used in the clinically controlled studies, because of the potential risk of increased toxicity in patients with reduced kidney function. Table 4 in reference [1] summarises the recommended preparations and dosages to be used with the various stages of CKD and in kidney transplanted patients. Note that the recommendations regarding choice of preparation and dosages in patients with CKD stages 1–2 are the same as those for the general population.
In addition, several special conditions should be kept in mind.

- The treatment algorithm should be based on kidney function
- Drugs that are primarily eliminated via the liver should be given preference (fluvastatin, atorvastatin and ezetimibe, also in combination med simvastatin).
- Use of statins metabolised by CYP3A4 can lead to serious side effects because of interaction with other drugs
- For the same reason, fluvastatin should be used in transplanted patients being treated with calcineurin inhibitors.

From an economic point of view, note that rosuvastatin is still under patent protection and is therefore an expensive drug choice.
Regarding treatment of patients with the late stages of CKD, one should be aware that lipid-regulating treatment is just one of many treatment modalities and that multifactorial intervention aimed at many risk factors is necessary. Attention should also be given to adequate management of the following:
- Blood pressure
- Calcium-phosphate metabolism
- Malnutrition
- Compliance with the general treatment
- Dialysis quality (if CKD 5D patients are treated)

PATIENTS WITH DIABETES AND CKD
These patients like all other patients with diabetes with reduced kidney function should be treated with multifactorial intervention, including treatment with statins. Thus all DM patients with

microalbuminuria or later stages should be treated with a statin in a maximally tolerated dose.

SUMMARY

Measurement of lipid profile in adults with CKD 1–5
We recommend measuring the lipid profile (T cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) in all adults with newly diagnosed CKD 1–5 (including patients in renal replacement therapy).
Monitoring of lipid profile in adults with CKD 1–5
In many cases it is not necessary to regularly monitor the lipid profile.
Patients ≥ 50 years with CKD 1–5 ND
We recommend that these patients be treated with a statin (CKD 1–2, evidence level B), and in CKD patients in stages 3–5 ND that a statin or the combination statin/ezetimibe be used (evidence level A).
Patients aged 18-49 years with CKD 1–5 ND
We suggest treating these patients with a statin if they also have one or more of the following conditions (evidence level A):
- known CVD
- DM
- Prior ischaemic stroke
- Estimated 10-year risk of coronary death or non-fatal AMI > 10 % or risk of fatal cardiovascular disease > 5% (SCORE [9])

Patients with CKD stage 5D
We suggest that these patients not be given a statin or started on statin/ezetimibe treatment (evidence level A).
Patients who start dialysis and are already being treated with a statin or statin/ezetimibe
We suggest that treatment be continued (evidence level C).
Adult kidney transplanted patients
We suggest that these patients be treated with a statin (evidence level B).

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