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Review Article

Managing dyslipidaemia in patients with chronic kidney disease

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ABSTRACT

Patients with CKD are at increased risk for cardiovascular events. Clinical studies suggest statins reduce all-cause mortality and cardiovascular events in patients with CKD. Lipid lowering therapy with statin with or without ezetemibe is recommended for most of the patients in patients with eGFR <60 mL/min and also in those who have an increased urinary albumin-to-creatinine ratio (≥3 mg/mmol) for at least 3 months. Evidence suggests that it should not be started for hemodialysis patients without evidence of ASCVD. Patients who were already taking statins or statin/ezetimibe combination at the time of dialysis should consider continuing these medications, especially if they have ASCVD. Fibrates should not be used in conjunction with statins in patients with CKD, and ezetimibe monotherapy is also not recommended. The role of PCSK9 inhibitors is evolving suggests that it is effective in lowering LDL cholesterol without affecting the renal outcomes.

Chronic kidney disease (CKD) is a medical condition characterized by lasting structural or functional abnormalities in the kidneys, persisting for a duration of over three months and significantly impacting an individual's health. The classification of CKD is based on various factors, including the underlying cause, glomerular filtration rate (GFR), and the category of albuminuria.[1] The presence of CKD in patients with established CVD is associated with a substantially higher mortality rate compared to those with CVD but normal kidney function. In addition to other cardiovascular risk factors, the decline in GFR itself is strongly associated with an increased risk of cardiovascular disease (CVD) among adults.[2,3] Both vascular disease and structural heart disease are more prevalent in individuals with chronic kidney disease. It is crucial to recognize the heightened risk of cardiovascular complications in individuals with CKD. By understanding this association, healthcare professionals can implement appropriate preventive measures and treatment strategies to mitigate the impact of CVD in patients with CKD.[4,5] Consequently, patients with CKD, particularly those in stage 3 CKD, or at a more advanced stage (stage 4–5 CKD) requiring dialysis, are considered to be at a high or very-high risk of developing CVD. The evidence of use of statin in these patients has been explored in many trials.[6]

1. Lipid abnormalities in chronic kidney disease

In patients with chronic kidney disease (CKD), it is commonly observed that triglyceride levels are elevated, while levels of high-density lipoprotein cholesterol (HDL-C) are decreased,additionally, there is an increase in the concentration of small dense low-density lipoprotein (LDL) particles. Furthermore, kidney dysfunction leads increased levels of LP(a) due to impaired catabolism of lipoprotein(a) [Lp(a)], resulting in elevated Lp(a) levels. These lipid abnormalities along with other factors are the important reason of increased cardiovascular morbidity and mortality. However, these acquired lipid abnormalities can be reversed through kidney transplantation or the remission of nephrosis.[3–5]

2. Management of lipid abnormalities in CKD patients

The management of lipid abnormalities in CKD patients involves a multifaceted approach aimed at reducing the risk of cardiovascular morbidity and mortality. Lifestyle modifications by adopting a healthy diet which is low in saturated and trans fats. This is also to be complemented by engaging in regular physical activity, and smoking cessation. Pharmacological interventions are often necessary to achieve lipid control along with the life style changes in CKD patients.

The use of statins, which inhibit cholesterol synthesis and promote LDL receptor expression, is the cornerstone of lipid-lowering therapy. The use of statins in managing the dyslipdemia in CKD patients has been extensively studied and investigated in trials.It is important to consider the specific statin dosage adjustments which may be required in patients with CKD due to altered drug metabolism and potential drug–drug interactions. Other lipid-lowering agents, such as fibrates or ezetimibe, may also be considered as adjunctive therapy in certain cases, although their use should be individualized based on patient characteristics and

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potential side effects.

Evidence from trials suggest despite the high CV risk among haemodialysis patients the statin therapy may not offer significant benefits. Several early trials, including the Die Deutsche Diabetes Dialyse Studie (the 4D study) [6] and the An Assessment of Survival and Cardiovascular Events (AURORA) trial [7] found no benefit in haemodialysis patients. The studies done later such as the Study of Heart and Renal Protection (SHARP) study, simvastatin and ezetimibe combination therapy reduced the risk of major atherosclerotic events in people with CKD stage 3A–5,[8,9]

A meta analysis investigated the effect of statins on renal outcomes in CKD patients. Ten studies from 142 full-text papers were included in this meta-analysis. Their findings suggest that statin use in CKD patients can delay the progression of kidney disease and that statins may have a dose-dependent effect on kidney function, but only high-intensity statins significantly improved renal function as measured by estimated GFR.[10]

Statin therapy consistently provided beneficial effects in a retrospective cohort study of adult patients with end stage renal disease (ESRD) who were on maintenance haemodialysis,. These beneficial effects were more pronounced in patients who received statin on a continuous basis throughout the study periodand also patients who received statin/ezetimibe combination therapy. After adjusting for age, gender, and Charlson Comorbidity Index (CCI), the benefits of statin therapy remained significant. Sensitivity analysis revealed that statin therapy provided consistent benefits across various subgroups, including older (aged >75 years) and younger (aged 40 years) patients.[11]

Statin therapy is clearly effective in mild-to-moderate CKD, but a major question that remained after the publication of the 4D, AURORA, and SHARP studies was whether statin therapy is effective in more advanced CKD, particularly in dialysis patients.

The Cholesterol Treatment Trialists' (CTT) Collaboration investigators by combining data from the three CKD trials with other trials in the existing database, discovered a trend toward smaller relative reductions in major atherosclerotic events per mmol/l reduction in LDL-C as eGFR declines (with little evidence of benefit among dialysis patients).[12] This decrease in relative risk reduction as GFR decreases implies that more intensive LDL-lowering regimens are required to achieve the same benefit, at least in non-dialysis patients.

3. Initial lipid assessment and follow-up measurements

For all adults recently diagnosed with chronic kidney disease (CKD), it is advisable to conduct initial evaluation of lipid profile. This should encompass measurements of total cholesterol, LDL-C, HDL-C, and triglycerides. The primary goal of this assessment is not only to assist in determining when to start statin treatment for CKD patients under the age of 50 but also to identify potential underlying causes of abnormal lipid levels, such as nephrotic syndrome, and to detect hypertriglyceridemia, a common lipid issue in CKD patients. In patients have fasting triglyceride levels exceeding 1000 mg/dL or LDL-C levels surpassing 190 mg/dL, it is recommended to involve specialists.

4. Safety of lipid lowering drugs in patients with chronic kidney disease

Safety issues and dose adjustments are important in advanced stages of CKD (stages 3–5), as adverse events are commonly dose-related and due to increased accumulation in blood. According to the CTT meta-analysis, the goal in patients without CKD should be to achieve the greatest absolute reduction in LDL-C while remaining safe.[12]

Although the 4D, AURORA, and SHARP trials raised no specific safety concerns. Some concerns regarding use of statins metabolised by CYP3A4 causing adverse effects due to drug–drug interactions are there. The routine testing of transaminase levels is as per the usual statin use baseline levels and also at 3 months and 1 year is recommended. No additional monitoring of transaminase amd CK levels is required until there are any symptoms suggestive of toxicity.

5. Current status of lipid lowering therapies in CKD

Each CKD patient should be assessed and receive an individualised treatment plan. The presence of severe comorbidity, a recent myocardial infarction, or a longer life expectancy all favour statin treatment in these patients.

The kidney disease: Improving Global Outcomes (KDIGO) clinical practice guideline for lipid management in CKD patients and the ESC 2019guidelines have based the recommendations based on the available evidence. They emphasise statin medication for dyslipidaemia management instead of specific LDL targets. Based on their recommendations treatment with a statin alone or in combination with ezetimibe is recommended for this age group with more advanced stages of CKD (Stage 3–5, eGFR 60 ml/min/1.73 m2)-.[13] Moderate-intensity statins including atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 40 mg and pitavastatin 2 mg daily are recommended.[14] It is recommended that all patients with CKD stage 3 or worse receive lipid-lowering therapy to reach a LDL target value < 70 mg/dl irrespective of their baseline levels and/or clinical conditions preferably with a statin or statin/ezetimibe combination.

We also recommend statin initiation to all patients with a GFR <60 mL/min/1.73 m2 and with a preserved GFR but who have an increased urinary albumin-to-creatinine ratio (≥3 mg/mmol) for at least 3 months. Statins should be continued with or without ezetimibe in patients treated with hemodialysis who are already on statins.In view of conflicting evidence new statin initiation is not recommended until the patient is suffering from ASCVD.[14,15]

6. Use of non statin drugs in patients of CKD

Fibrates should not be used in conjunction with statins in patients with CKD, and ezetimibe monotherapy is not recommended. Patients with Stage 1 or 2 CKD (eGFR >60 ml/min/1.73 m2) can be treated in the same way as the general population because drug toxicity is reduced with improved renal excretion. All CKD patients should have their baseline transaminase levels checked before starting statin therapy, but routine transaminase for CK levels is not recommended unless there is clinical evidence of hepatotoxicity or myopathy.[15]

The PCS K9 inhibitor studies such as ODYSSEY COMBO I and ODYSSEY COMBO II found that alirocumab was significantly superior to placebo and ezetimibe in lowering LDL cholesterol when combined with statins in CKD sub-group analysis, and case reports have suggested efficacy in nephrotic syndrome.[16]

Bempedoic acid is well-tolerated and the incidence and type of adverse events is not affected by the degree of renal impairment. It is safe in patients with mild or moderate renal impairment. No dose adjustments is necessary for patients with mild or moderate renal impairment.[17]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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