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Commentary

KHA-CARI commentary on the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

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Due to the markedly accelerated risks of cardiovascular disease for people who have chronic kidney disease (CKD),[1] lipid-lowering treatment represents a potentially effective intervention to reduce cardiovascular events, including death from cardiovascular disease. However, existing randomized trials have been inconsistent about whether statin therapy is beneficial for all patients with CKD, particularly those who are treated with dialysis,[2–4] while data for recipients of a kidney transplant and children with CKD are sparse. Given the extensive trial data that have become available over recent years and in particular, information from the Study of Heart and Renal Protection (SHARP) trial of simvastatin/ezetimibe which involved more than 9000 adults with advanced kidney disease,[3] lipid management is a highly relevant guideline for development by the Kidney Disease Improving Global Outcomes (KDIGO) group.[5] The KDIGO 'Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease' was published in November 2013 and makes 13 recommendations.[6] In this commentary, we consider the recommendations made in the KDIGO guideline with particular reference to the New Zealand and Australian context. Overall, the KDIGO guideline recommendations are suitable for Australasian clinical practice.

GUIDELINE SUMMARY

This KDIGO guideline provides guidance on lipid management in adults and children who have CKD, including those with eGFR categories G1-G5 and CKD treated with dialysis or kidney transplantation.[6] The guideline is designed to address how and when to assess lipid status, and how and when to prescribe lipid-lowering interventions in the setting of CKD. The assessment of lipid profiles, management of hypertriglyceridaemia and cholesterol-lowering treatment for children are similar across all stages of CKD, whereas cholesterol-lowering treatment in adults is different, based on CKD severity. The key recommendations of the KDIGO guideline are shown in Box 1.

COMMENTARY

The KDIGO guideline substantially updates earlier clinical guidance on lipid management in CKD following the release of numerous randomized trials and *post hoc* analyses of trial data since 2004. The KDIGO guideline is described by the guideline Working Group as a 'new concept' in the management of dyslipidaemia in CKD and appears to deliberately diverge from previous guidelines in both the interpretation of the evidence and through greater simplicity aimed at enhancing implementation. The key three-step summary for clinical care of adults with CKD from KDIGO is to: (i) rule out remediable secondary causes of elevated lipids; (ii) establish whether treatment is indicated; and (iii) treat without monitoring lipid levels unless monitoring would change clinical management. For children, the clinical process could be considered as simply ruling out remediable secondary causes.

Choosing lipid levels to initiate treatment

Randomized trials supporting lipid-lowering therapy for specific low-density lipoprotein (LDL-C) thresholds in CKD are

Box 1 Summary of recommendation statements

- In adults and children with newly identified chronic kidney disease, evaluation with a lipid profile is recommended. Consider secondary causes and specialist evaluation if severely elevated fasting lipid levels (LDL-cholesterol >4.9 mmol/L or triglycerides >11.3 mmol/L). (*1C*)
- In adults, follow-up measurement of lipid levels is not required for the majority of patients. (*Not graded*)
- In children, annual follow-up measurement of fasting lipid levels is suggested. (*Not graded*)
- Treat adults who are aged ≥50 years with a statin when the eGFR is above 60 mL/min per 1.73 m^2 (*1B*) and treat with a statin or statin/ezetimibe combination when the eGFR is below 60 mL/min per 1.73 m^2. (*1A*)
- Treat adults younger than 50 years (with eGFR categories G1 to G5) with a statin if presence of one or more of: coronary disease, previous ischaemic stroke, diabetes or estimated 10-year incidence of fatal or non-fatal myocardial infarction above 10%. (*2A*)
- Treat adult recipients of a kidney transplant with a statin. (*2B*)
- Treatment with a statin or statin/ezetimibe combination is not recommended in adults being treated with dialysis. (*2A*)
- Treatment with a statin or statin/ezetimibe treatment is not recommended in children with CKD. (*2C*)
- Treat adults and children with CKD who have hypertriglyceridaemia with lifestyle advice. (*2D*)

lacking. To recognize this, KDIGO now departs from earlier guidelines and recommends that lipid levels are measured once only in people with CKD and that LDL-C thresholds are not used to guide commencement of lipid-lowering therapy. This approach is consistent with a systematic review of randomized trials[7] showing that statin therapy has similar effects in patients irrespective of baseline total and LDL-cholesterol. Notably, despite a lack of evidence, the approach to measure lipid levels at identification of CKD is given a strong recommendation based on the Working Group's judgement that patients would place high value on this approach in order to receive treatment for secondary causes of dyslipidaemia. It is unclear to what extent this strong recommendation applies to the Australian and New Zealand context, as specific data on patient preferences for heart disease treatment in Australia and New Zealand are absent and vary widely in other regions.[8]

Monitoring of lipid levels during treatment

The KDIGO guideline emphasizes the high cardiovascular risk associated with CKD regardless of LDL-C levels, in an effort to reduce guideline complexity and to increase implementation. The guideline suggests (in an ungraded statement) that lipid levels should not be measured during follow-up of statin or statin/ezetimibe therapy in line with the relative lack of trial data. This is in contrast to the earlier 2007 KDOQI guidelines for adults with diabetes, which recommended specific LDL-C targets[9] and the 2003 KDOQI guidelines, which suggested lifestyle changes and pharmacological interventions titrated in response to lipid levels for all CKD patients.[10] The recent ACC/AHA guideline on this topic has also moved away from targeting a cholesterol level and changed focus to statin use being linked to overall CVD risk. The guideline states 'The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-C treatment targets. The appropriate intensity of statin therapy should be used to reduce atherosclerotic CVD risk in those most likely to benefit.'[11] The current KDIGO statement is appropriate for Australian and New Zealand practice, consistent with the 2013 KHA-CARI guideline stating that no large-scale RCT have examined the optimal target lipid levels to which patients who have eGFR categories G1-G3 should be treated.[12] Although some discomfort with this approach has been voiced, (e.g. missed opportunities for patients to respond to monitoring as motivation for adherence or to check for poor responses to treatment), specific LDL-C targets are not supported by high-quality evidence due to the large within-person variation in total cholesterol levels that occur (estimated at ±0.8 mmol/L) that may obscure true changes in lipid levels or be misinterpreted as a treatment response.[13]

Cholesterol-lowering treatment for adults with chronic kidney disease

Patients with CKD are less likely to receive statin therapy for the secondary prevention of cardiovascular events, and treatment is associated with better outcomes.[14] In light of this relative under-treatment of coronary risk in patients who have eGFR G1-G5[14] and the lack of evidence supporting specific LDL-C treatment targets to modify risks of adverse cardiovascular events, the KDIGO Working Group provides a pragmatic guideline for cholesterol-lowering treatment in practice. The guideline does not consider lifestyle advice to be an appropriate initial strategy for adults with CKD due to lack of evidence for efficacy. The KDIGO framework provides two key considerations that, if present, should trigger consideration of statin therapy for adults with CKD. These are: (i) is the risk of coronary death or non-fatal myocardial infarction (MI) above 10% over 10 years?; and (ii) is there evidence of treatment efficacy? Low density lipoprotein-C levels are not considered.

The KDIGO guideline strongly recommends statin treatment for adults with eGFR G1-G5 when their 10-year risk of coronary death or non-fatal MI is above 10%. To simplify this recommendation for practice and recognizing that

standard cardiovascular risk tables may not necessarily include CKD within risk algorithms, the KDIGO guideline uses an age cut-off to categorize cardiovascular risk and make treatment recommendations. KDIGO strongly recommends universal statin therapy in patients older than 50 years with CKD, and statin treatment in those younger than 50 years who have additional comorbidities (i.e. coronary disease, diabetes, stroke or other) that raise their risk above the 10% threshold over 10 years.

Although an age cut-point to identify a 10% 10-year cardiovascular risk to initiate statin therapy enhances guideline simplicity, the absolute cardiovascular risks are based on data from a Canadian population and may not necessarily be generalizable to Australasian settings. In addition, although the KDIGO guideline is simple, it diverges from cardiovascular guidelines for Australia[15] and New Zealand[16] and with the KHA-CARI guideline which recommends treatment of all patients with mild-moderate CKD with a statin or statin/ezetimibe combination regardless of cardiovascular risk.[12] Australian cardiovascular guidelines consider the presence of CKD eGFR category G3b or microalbuminuria as automatic indicators of high cardiovascular risk (>15% over 5 years) and for these patients, advise frequent and sustained specific advice and support regarding diet in addition to lipid-lowering therapy to cholesterol targets (LDL-C below 2 mmol/L).[15] New Zealand guidelines also recommend drug treatment of risk factors when the 5-year risk is >15% and considers adults who have diabetic nephropathy as being in the highest cardiovascular risk category (>20% at 5 years) and that diabetes with microalbuminuria increases the baseline risk by 5%.[16] Australian guidelines do not specifically address lipid treatment for adults with eGFR categories G1-G3b and New Zealand guidelines do not consider eGFR in risk considerations or albuminuria in patients without diabetes. Both guidelines have risk thresholds that are considerably less intensive than those of KDIGO.

The KDIGO approach is reasonable for the Australasian setting because of its simplicity and acknowledgement of evidence. However, the presence of several differing guidelines for lipid management in the local context may increase clinical decision complexity and reduce guideline implementation. Notably, the age cut-point in CKD for decisions about cardiovascular risk suggested by KDIGO based on age are unlikely to be appropriate for indigenous populations in Australasia who experience the complications of heart disease a decade younger than non-Indigenous people.[17] In New Zealand and Australia, the threshold risk at which to consider statin therapy in CKD (>10% at 10 years) for indigenous patients might need to be lowered to 40 years of age.

The KDIGO guideline recommends a statin or statin/ezetimibe combination for adults over 50 years who have eGFR categories G3a-G5 but only statin treatment for those over 50 years with milder kidney disease (eGFR categories G1-G2) and those who are younger than 50 years. The rationale for differences in recommended treatment strategies (statin or statin/ezetimibe combination) in the different treatment groups is unclear. Similar treatment benefits are observed in trials irrespective of ezetimibe co-therapy, and considerably more data for statins compared with ezetimibe generally[18] indicates statin therapy alone might be appropriate for all treatment groups, consistent with the KHA-CARI guidelines.[7]

While the large SHARP trial[3] suggested that treatment efficacy was similar across all stages of CKD including those receiving dialysis for renal replacement therapy, two meta-analyses in 2012 showed that statin treatment offers little or no benefit in relation to cardiovascular and all-cause death for patients treated with dialysis.[7,19] Although patients are likely to experience small or nil reductions in cardiovascular endpoints while being treated with dialysis, they might reasonably wish to accept this small and uncertain treatment benefit for preventing cardiovascular events and death in exchange for an additional pill-burden and potential treatment toxicity. In addition, benefits and harms of statin therapy for patients who are already on a statin when they start dialysis and for those who are treated with dialysis as a planned bridge to transplantation are not adequately addressed by current trials and these patients might reasonably consider to either have or decline statin therapy.

There is considerably lower confidence in the estimated harms and benefits of statin therapy for kidney transplant recipients because of inconsistency between trial results, limitations in study methodologies and imprecision in treatment effects. Despite these limitations, statin therapy may proportionally reduce risks of cardiovascular death and non-fatal MI by 10–30%.[7] Australian and New Zealand-specific data suggest transplant recipients experience a risk of cardiovascular mortality approaching 9 per 1000 patient-years, close to the KDIGO threshold for routine statin therapy (>10% 10-year risk) and that this risk is present for those older than 45 years.[20] These local data support the KDIGO guideline recommendation to consider statin therapy for adults treated with a kidney transplant.

Triglyceride-lowering in adults with chronic kidney disease

Although triglyceride levels are inversely associated with eGFR for adults, the confidence in the relevant evidence is very low that the benefits of fibric acid derivatives (lower cardiovascular events and death) outweigh the harms (hospitalization and worsening kidney function). This is largely based on the fact that meta-analyses for effects of fibrates on cardiovascular events in eGFR categories G1-G3b are reliant on few events in predominantly post-hoc subgroup analyses in CKD and that potential hazards of treatment are poorly understood.[21]

Lipid assessment and treatment for children with chronic kidney disease

The KDIGO guideline makes statements about the management of lipid abnormalities in children with CKD, taking into consideration the lack of long-term data for both cardiovascular risks associated with elevated serum lipids and safety data for treatment in children. As for adults, the KDIGO Working Group considers baseline assessment of lipid levels to be appropriate given the minimally invasive risk of the blood test and that children with CKD and their families would place high value on the potential to improve the health of children who have secondary dyslipidaemias. However, this strong recommendation may not necessarily be appropriate in Australia and New Zealand, as patient preferences for investigations and management in CKD may vary widely and Australasian data for children's preferences for cholesterol management are absent.

While interventions such as nutrition and dietary counselling are suggested for children with CKD by the KDIGO guideline, the absence of evidence of both efficacy and safety of dietary modifications in children with CKD suggests that no recommendation is possible and choosing not to have specific treatment or make lifestyle changes might be a reasonable choice for children who have CKD and their families.

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