

# Chapter 1: Assessment of lipid status in adults with CKD

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**1.1: In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). (IC)**

## RATIONALE

Dyslipidemia is common but not universal in people with CKD. The major determinants of dyslipidemia in CKD patients are glomerular filtration rate (GFR), the presence of diabetes mellitus, severity of proteinuria, use of immunosuppressive agents, modality of renal replacement therapy [RRT] (treatment by HD, peritoneal dialysis, or transplantation), comorbidity and nutritional status.<sup>3</sup>

Initial evaluation of the lipid profile mainly serves to establish the diagnosis of severe hypercholesterolemia and/or hypertriglyceridemia and potentially rule out a remediable (secondary) cause if present. Major causes of secondary dyslipidemia should be considered (Table 1). The precise levels of serum or plasma lipids that should trigger specialist referral are not supported by evidence, but in the opinion of the Work Group, fasting triglyceride (TG) levels above 11.3 mmol/l (1000 mg/dl) or LDL-C levels above 4.9 mmol/l (190 mg/dl) should prompt consideration of (or specialist referral for) further evaluation.

Previous guidelines have emphasized the potential value of LDL-C as an indication for pharmacological treatment with lipid-lowering agents;<sup>1</sup> the KDIGO Work Group no longer recommends this approach (see Chapter 2.1). Isolated low high-density lipoprotein cholesterol (HDL-C) does not imply specific therapy in people with CKD; the Work Group suggests that HDL-C be measured as part of the initial lipid panel because it may help to assess overall cardiovascular risk. Measurement of lipoprotein(a) [Lp(a)] and other markers of dyslipidemia require further research before it can be routinely recommended in CKD patients.

The lipid profile should ideally be measured in the fasting state; if not feasible, nonfasting values provide useful information as well.<sup>4</sup> Fasting will mainly affect TG values and to a lesser extent LDL-C values as estimated from the Friedewald formula. Fasting status does not affect HDL-C.<sup>4–6</sup>

There is no direct evidence indicating that measurement of lipid status will improve clinical outcomes. However, such measurement is minimally invasive, relatively inexpensive, and has potential to improve the health of people with secondary dyslipidemia. In the judgment of the Work Group, patients with CKD place a high value on this potential benefit

and are less concerned about the possibility of adverse events or inconvenience associated with baseline measurement of lipid levels. In the judgment of the Work Group, these considerations justify a strong recommendation despite the low quality of the available evidence.

**1.2: In adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow-up measurement of lipid levels is not required for the majority of patients. (Not Graded)**

## RATIONALE

Prior guidelines have emphasized treatment escalation to achieve specific LDL-C targets by increasing the dose of statin and/or combination therapy.<sup>1,7</sup> Given the lack of data to support this approach in populations with and without CKD,<sup>8</sup> the substantial within-person variability in LDL-C measurements<sup>9</sup> and the potential for medication-related toxicity, this approach is no longer recommended for CKD populations (see guideline 2). Since higher cardiovascular risk and not elevated LDL-C is now the primary indication to initiate or adjust lipid-lowering treatment in CKD patients, follow-up monitoring of LDL-C (after an initial measurement) may not be required for many patients – especially given normal variability in LDL-C over time, which reduces the clinical utility of follow-up measurements.<sup>10</sup>

In the judgment of the Work Group, follow-up measurement of lipid levels should be reserved for instances where the results would alter management. Potential reasons to measure LDL-C (or the lipid profile) in people with CKD after their initial presentation might include: assessment of adherence to statin treatment; change in RRT modality or concern about the presence of new secondary causes of dyslipidemia (Table 1); or to assess 10-year cardiovascular risk in patients aged <50 years and not currently receiving a statin (because knowledge of LDL-C in this case might suggest that a statin was required – see Recommendation 2.2).

In the judgment of the Work Group, it is unnecessary to measure LDL-C in situations where the results would not (or likely would not) change management. For example, patients already receiving a statin (or in whom statin treatment is clearly indicated/not indicated based on changes in their cardiovascular risk profile or clinical status) would not require follow-up LDL-C measurements because the results would not alter treatment. Similarly, since the association

**Table 1 | Secondary causes of dyslipidemias**

Medical Conditions	
Nephrotic syndrome	Excessive alcohol consumption
Hypothyroidism	Liver disease
Diabetes	
Medications	
13- <i>cis</i> -retinoic acid	Androgens
Anticonvulsants	Oral contraceptives
Highly active anti-retroviral therapy	Corticosteroids
Diuretics	Cyclosporine
Beta-blockers	Sirolimus

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between LDL-C and adverse clinical outcomes is weaker in people with CKD than in the general population, the value of measuring LDL-C to assess prognosis is uncertain.

Since low HDL-C and elevated apolipoprotein B (apoB) or non-HDL-C associated with excess risk of future cardiovascular events,<sup>11</sup> clinicians might choose to measure these parameters in patients not receiving a statin but in whom estimated cardiovascular risk is close to the threshold for initiating statin treatment. Put differently, clinicians could choose to measure HDL-C, apoB and/or non HDL-C if the finding of these tests would influence their decision to prescribe statin treatment.

Few data document how frequently CKD patients develop severely elevated fasting TGs >11.3 mmol/l (>1000 mg/dl). Since clinical experience suggests that this event is rare, routine measurement of fasting TG levels is not recommended. However, clinicians may consider following serum TG levels in patients with known severe hypertriglyceridemia.

The ideal frequency of follow-up of LDL-C, HDL-C and serum TGs is unknown. Since any benefits of lipid-lowering treatment are likely to accrue over years rather than months or weeks, the Work Group suggests that cardiovascular risk be assessed annually in most patients with CKD. However, more frequent (or less frequent) follow-up measurements may be appropriate based on the clinical status of the patient.

There is no direct evidence that routine follow-up of lipid levels improves clinical outcomes or adherence to lipid-lowering therapy. In fact, evidence indicates that random within-patient variation in serum cholesterol levels is substantial ( $\pm 0.8$  mmol/l [31 mg/dl] for total cholesterol [TC]) and therefore that such follow-up measurements may not reliably indicate good or poor compliance.<sup>10</sup> However, some patients may prefer to know their lipid levels during follow-up, or may respond favorably to such knowledge (for example, with better adherence to recommended statin use). In the judgment of the Work Group, these considerations favor an ungraded statement. Physicians may choose to perform follow-up measurement of lipid levels in patients for

whom these measurements are judged to favorably influence processes of care.

### Considerations for International Settings

If resources are limited, priority should be given to prescribing statins to patients at risk based on clinical criteria, rather than to measuring lipid profiles at baseline or in follow-up. In the opinion of the Work Group, the frequency of pancreatitis due to severe hypertriglyceridemia among CKD patients is sufficiently low that measuring fasting TG levels can be omitted in low-resource settings. Conversely, in settings where documentation of hypercholesterolemia is required to justify prescription of statins (e.g., Japan), more liberal or more frequent measurement of serum lipids may be necessary.

### Suggested Audit Criteria

- Proportion of adults who had a lipid profile measured within 1 month of referral.
- Frequency of specialist referral for further evaluation of abnormal lipid abnormalities (e.g., fasting TG levels above 11.3 mmol/l (1000 mg/dl) or LDL-C levels above 4.9 mmol/l (190 mg/dl)).

### KEY POINTS

- Dyslipidemia is common in people with CKD but LDL-C does not reliably discriminate between those at low or high risk of cardiovascular events.
- Clinicians should measure the lipid profile at initial presentation with CKD. Follow-up of the lipid profile or LDL-C is not required unless the results would change management. Examples of patients in whom knowledge of LDL-C might change management are given in Table 2.

### RESEARCH RECOMMENDATIONS

Future studies should:

- Assess the clinical effectiveness and economic merits of interventions to improve adherence to these recommendations, particularly those which are level 1. This includes better understanding of physician and patient barriers to guideline adoption and the contribution of polypharmacy.
- Examine secular trends in adherence to recommendations in this clinical practice guideline (CPG) and any secular changes in patient outcomes.
- Confirm real practice safety of statin use (outside of restrictive eligibility criteria used in RCTs). Specifically the frequency and severity of clinically relevant statin-drug interactions should be studied in this population to improve the safety of statin prescribing.
- Assess the cost implications of less frequent or avoidance of cholesterol measurements, and confirm that less frequent measurements do not adversely affect the clinical benefits of treatment (compared to more frequent measurements).

**Table 2 | Examples of situations in which measuring cholesterol level might or might not change the management implied by Recommendation 1.2**

	Already receiving statin?	Would measuring cholesterol level change management?
55-year old man with eGFR 35 ml/min/1.73 m <sup>2</sup>	Y	No; patient is already receiving statin
55-year old man with eGFR 35 ml/min/1.73 m <sup>2</sup>	N	No; statin is already indicated based on Recommendation 2.1.1
55-year-old man with eGFR 75 ml/min/1.73 m <sup>2</sup> and ACR of 110 mg/mmol (1100 mg/g)	N	No; statin is already indicated based on Recommendation 2.1.2
45-year-old man with eGFR 35 ml/min/1.73 m <sup>2</sup> , who is a smoker and has diabetes and hypertension	N	No; statin is already indicated based on Recommendation 2.1.3 because predicted 10-year risk of coronary death or MI > 10% regardless of cholesterol level
45-year-old man with eGFR 35 ml/min/1.73 m <sup>2</sup> , who is a non-smoker without diabetes or hypertension	Y	No; patient is already receiving statin
45-year-old man with eGFR 35 ml/min/1.73 m <sup>2</sup> , who is a non-smoker without diabetes or hypertension	N	Yes; patient's predicted 10-year risk of coronary death or MI could vary from 5 to 20% based on cholesterol level. This would change the decision to prescribe a statin based on Recommendation 2.1.3
35-year-old man with eGFR 35 ml/min/1.73 m <sup>2</sup> , who is a non-smoker without diabetes or hypertension	N	No; patient's predicted 10-year risk of coronary death or MI is < 10% regardless of cholesterol level

Abbreviations: ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

- Perform time-dependent analysis of lipid values for risk prediction. Since lipid levels show considerable changes during the various stages of CKD, it might be interesting to see whether a data analysis considering all measured values during the entire observation period is more predictive than the classical analysis with one measurement at baseline of a certain CKD stage.
- Investigate whether the association between serum TGs and risk varies meaningfully as a function of fasting status.
- Investigate the independent association between Lp(a), apoB and cardiovascular outcomes in large prospective studies of people with CKD. It should further be investigated whether knowledge of high Lp(a), non-HDL-C, and/or apoB values has any influence on the management of other risk factors and whether this has an influence on outcomes.

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