KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient

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The Kidney Disease: Improving Global Outcomes (KDIGO) organization developed clinical practice guidelines on lipid management for all adults and children with chronic kidney disease (CKD). Thirteen recommendations were obtained from the available evidence outlining a three-step management including assessment in all, treatment in many, and follow-up measurements in few. A key element is the recommendation of statin or statin/ezetimibe treatment in adults aged ⩾50 years with estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 but not treated with chronic dialysis or kidney transplantation. In dialysis patients, the magnitude of any relative reduction in risk appears to be substantially smaller than in earlier stages of CKD and initiation of statin treatment is not recommended for most prevalent hemodialysis patients. In the past, clinical practice guidelines suggested the use of targets for LDL cholesterol, which require repeated measurements. Treatment escalation with higher doses of statin would be a consequence when LDL cholesterol targets are not met. The KDIGO Work Group did not recommend this strategy because higher doses of statins have not been proven to be safe in the setting of CKD. Since LDL cholesterol levels do not necessarily suggest the need to increase statin doses, follow-up measurement of lipid levels is not recommended.

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Kidney Disease: Improving Global Outcomes (KDIGO) developed the clinical practice guidelines on lipid management in 2013 to inform the management of dyslipidemia and the use of cholesterol-lowering medications in all adults and children with known CKD. All forms of CKD were included (non-dialysis-dependent, dialysis-dependent, and kidney transplant recipients). The KDIGO Lipid Guideline Development Work Group defined the scope of the guideline, gathered evidence, determined topics for systematic review, and graded the quality of evidence that had been summarized by an evidence review team. Searches of the English-language literature were conducted through August 2011 and supplemented by targeted searches through June 2013. The final modification of the guidelines was informed by the KDIGO Board of Directors and a public review process involving registered stakeholders. The full guideline including 13 recommendations was released on 7 November 2013 and is available at http: //www.kdigo.org/.[1]

Here we provide a quick summary of the KDIGO recommendations for lipid-lowering treatment separated into assessment of lipid status and pharmacological cholesterol- and triglyceride (TG)-lowering treatment in children and adults with CKD.

GUIDELINE DEVELOPMENT PROCESS, EVIDENCE GRADING, AND STAKEHOLDER AND PUBLIC CONSULTATION

The Work Group consisted of a truly international group of kidney specialists, diabetologists, cardiologists, epidemiologists, lipidologists, and a professional evidence review team. The Work Group formulated the scope of the guideline, and graded evidence on the basis of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[2]

The guideline updates the 2003 Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease.[3] The evidence review team carried out systematic reviews for six topics of interest. Systematic searches were last conducted in August 2011 and supplemented with additional evidence through June 2013. Further guideline development, evidence synthesis, and writing of the guideline itself was carried out

by the Work Group. Full details of the guideline development process, topic discussion, and consensus development can be found in the published guideline.[1] The draft guideline was reviewed by the KDIGO Board of Directors, and revisions were incorporated before a structured, Internet-based public review process. Feedback from this process was reviewed by the Work Group, and final revisions were incorporated before publication of the guideline. The order of recommendations in the guideline was based on the order used in the 2003 K/DOQI publication, and it presents recommendations on assessment of lipid status before those related to treatment.

RECOMMENDATIONS RELATING TO PHARMACOLOGICAL CHOLESTEROL-LOWERING TREATMENT IN ADULTS

Background

To maximize the ratio of benefits to harm, future coronary risk is considered an important potential determinant of the decision to prescribe statin treatment.[4] In people without kidney disease, low-density lipoprotein cholesterol (LDL-C) is often used as a proxy for future risk, as LDL-C levels are independently associated with the risk of atherosclerotic events.[5] However, the relative risk (RR) reduction associated with statin use is approximately constant across a broad range of baseline LDL-C levels, suggesting that absolute benefit from statin treatment is proportional to baseline coronary risk rather than baseline LDL-C.

LDL-C is not suitable for assessing coronary risk in people with CKD: although higher levels of LDL-C are associated with higher risk, dialysis patients with very low levels of LDL-C and total cholesterol are at a very high risk of all-cause and cardiovascular mortality,[5–9] likely because of coexisting malnutrition and inflammation.[10,11] Among people with CKD but without kidney failure, the excess risk associated with increased LDL-C decreases in parallel with estimated glomerular filtration rate (eGFR).[12] The weaker association between LDL-C and coronary risk among those with lower levels of eGFR (who are at the highest risk of myocardial infarction (MI) and other vascular events) suggest that it should not be used to identify the CKD patients who should receive statin treatment.

Future cardiovascular risk is often assessed using the 10-year incidence of coronary death or non-fatal MI, numerically equivalent to the rate of such events per 1000 patient-years. There is debate about the level of future coronary risk that is sufficient to justify statin treatment, but in the Work Group's judgment a rate of coronary death or non-fatal MI that exceed 10 per 1000 patient-years is a reasonable criterion. The rate of coronary death or incident MI among CKD patients aged >50 years (both men and women) is consistently >10 per 1000 patient-years, even in those without diabetes or prior MI. In contrast, the rate of coronary death or incident MI among CKD patients aged $\leqslant 50$ years is low in those without diabetes or prior MI (although it is substantially higher than in people with similar characteristics but without CKD). For comparison, the recent 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults suggests an estimated 10-year risk for a first hard atherosclerotic cardiovascular disease event of $>7.5\%$ (estimated using the new Pooled Cohort Equations in the CVD-free, non-pregnant US Population 40 to 79 years of age) as an indication to initiate statin therapy.[13]

Available evidence argues against the use of LDL-C to identify people with CKD who should receive statin treatment and suggests focusing on two other factors:[1] the absolute risk of coronary events and[2] the evidence that statin treatment is beneficial. This is the approach taken in the following KDIGO recommendations.

Chapter 1 | Assessment of lipid status in adults with CKD

Grade	
1C	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)
Not graded	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

Within each recommendation, the *strength of recommendation* is indicated as Level 1, Level 2, or Not graded, and the *quality of the supporting evidence* is shown as A, B, C, or D (see also Supplementary Appendix Tables S1 and S2 online). GRADE criteria were used for grade levels and letters in this guideline (2).
Level 1, 'We recommend'. Most patients should receive the recommended course of action.
Level 2, 'We suggest'. Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.
Not graded was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence.
Grade A quality of evidence is *high*, and we are confident that the true effect lies close to that of the estimate of the effect.
Grade B is *moderate*, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Grade C is *low* and the true effect may be substantially different from the estimate of the effect.
Grade D is *very low*. The estimate of effect is very uncertain, and often will be far from the truth.

WHY SHOULD WE OBTAIN A FULL LIPID PROFILE IN ALL CKD PATIENTS AT FIRST PRESENTATION?

The major factors predisposing to dyslipidemia in people with CKD are lower GFR, the presence of diabetes mellitus, more severe proteinuria, the use of immunosuppressive agents, modality of renal replacement, comorbidity, and nutritional status.[14] Initial evaluation of the lipid profile is intended to diagnose severe hypertriglyceridemia and/or hypercholesterolemia while ruling out any underlying secondary causes. Medical conditions that cause secondary dyslipidemias include hypothyroidism, excessive alcohol consumption, nephrotic syndrome, diabetes mellitus, and liver disease. Medications that may lead to dyslipidemias include corticosteroids, diuretics, 13-*cis*-retinoic acid,

anticonvulsants, oral contraceptives, highly active antiretroviral therapy, β-blockers, cyclosporine, and sirolimus.

The lipid profile should ideally be measured in patients who have been fasting. However, if this is not feasible, non-fasting values provide useful information as well.[15] Fasting specimens will be needed if significant lipid abnormalities are found on initial measurements, especially severe hypertriglyceridemia.[15–17] In the opinion of the Work Group, fasting TG levels above 11.3 mmol/l (1000 mg/dl) or LDL-C levels above 4.9 mmol/l (190 mg/dl) should prompt specialist referral for further evaluation.

No direct evidence indicates that measuring lipid status will lead to better clinical outcomes. However, measuring lipid status is noninvasive, inexpensive, and might improve the health of people with secondary dyslipidemia. In the judgment of the Work Group, these considerations justify a strong recommendation despite the low quality of the supporting evidence.

WHAT IS THE RATIONALE FOR NOT TAKING FREQUENT FOLLOW-UP MEASUREMENTS OF SERUM LIPIDS?

Prior guidelines have emphasized treatment escalation to achieve specific LDL-C targets by increasing the dose of statin and/or combination therapy.[1,18] Given the lack of data to support this approach,[19] the substantial variability in LDL-C measurements,[20] and the potential for comedication-related toxicity, this approach is not recommended for people with CKD (see guideline 1.2). As higher risk of future coronary events rather than elevated LDL-C is the primary indication to initiate lipid-lowering treatment in CKD patients, follow-up monitoring of LDL-C (after an initial measurement) will not usually be required for many patients—especially given normal variability in LDL-C over time, which reduces the clinical utility of follow-up measurements.[21]

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 the lipid profile in follow-up for people with CKD could include the following: assessment of adherence to statin treatment; change in renal replacement therapy modality or concern about the presence of a new secondary cause of dyslipidemia; 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 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 management. Similarly, as the link between LDL-C and adverse clinical outcomes is less robust in people with CKD than in people with normal GFR, the value of measuring LDL-C to assess prognosis is unclear.

There is no direct evidence that following on-treatment lipid levels will improve clinical outcomes or encourage adherence to statin therapy. However, some patients may prefer to know their lipid levels during follow-up, or may increase their adherence to statin treatment in response to feedback about these levels. In the judgment of the Work Group, these considerations favor an ungraded statement.

Chapter 2 | Pharmacological cholesterol-lowering treatment in adults

Grade	
1A	2.1.1: In adults aged $\geqslant 50$ years with eGFR <60 ml/min per 1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5), we recommend treatment with a statin or statin/ezetimibe combination
1B	2.1.2: In adults aged $\geqslant 50$ years with CKD and eGFR $\geqslant 60$ ml/min per 1.73 m^2 (GFR categories G1–G2), we recommend treatment with a statin
2A	2.2: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (2A): known coronary disease (myocardial infarction or coronary revascularization) diabetes mellitus prior ischemic stroke estimated 10-year incidence of coronary death or non-fatal myocardial infarction $>10\%$

THE SHARP STUDY HAD A LARGE IMPACT ON A STRONG RECOMMENDATION IN GFR CATEGORIES G3A–G5

As the absolute risk of future coronary events is consistently >10 per 1000 patient-years in people with non-dialysis-dependent CKD (eGFR <60 ml/min per 1.73 m^2) who are aged $\geqslant 50$ years, knowledge of LDL-C is not required to gauge average coronary risk in these people. Although multivariate prediction instruments might yield more precise estimates of risk for individuals, the Work Group felt that the simplicity of an age-based approach would enhance uptake of the guideline while allowing sufficiently accurate risk prediction.

The Study of Heart and Renal Protection (SHARP) indicated that simvastatin/ezetimibe combination therapy reduces the risk of major atherosclerotic events (coronary death, MI, non-hemorrhagic stroke, or any revascularization) compared with placebo in people with GFR categories G3a–G5.[22] These data are supported by *post hoc* analyses of randomized trials of statin versus placebo that focus on the subset of participants with CKD at baseline. In general, these analyses suggest that statins reduce the relative risk of cardiovascular events to a similar extent among patients with and without CKD, but that the absolute benefit of treatment is larger in CKD patients because of their higher baseline cardiovascular risk.[23]

The Work Group concluded that the combination of findings from SHARP, *post hoc* analyses of trials from the general population (focusing on the subset of participants with CKD), and the large body of evidence from the

general population trials collectively justify a strong recommendation.

RESULTS FROM TRIALS IN THE GENERAL POPULATION AND COMORBIDITY HAD IMPACT ON A STRONG RECOMMENDATION IN YOUNGER AGE AND EARLIER STAGES OF CKD

Most patients with CKD and eGFR $\geqslant 60$ ml/min per 1.73 m^2 have albuminuria and slightly reduced or normal eGFR; most of these would have been included but not recognized in trials of statins performed in the general population. The benefit of statin monotherapy appears similar in people with and without albuminuria.[24,25]

Given these data, the high cardiovascular risk among people with CKD and eGFR categories G1–G2, the large body of evidence supporting the efficacy of statins in the general population, and the lack of justification for a new trial performed specifically in people with CKD and eGFR categories G1–G2, the Work Group judged that a strong recommendation was appropriate.

Chapter 2 | continued: Pharmacological cholesterol-lowering treatment in adults

Grade	
2A	2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated
2C	2.3.2: In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued
2A	2.4: In adult kidney transplant recipients, we suggest treatment with a statin

WHY DID THE WORK GROUP NOT RECOMMEND INITIATION OF STATIN TREATMENT IN DIALYSIS PATIENTS?

Three large trials[22,26,27] have failed to show a conclusive benefit of statin treatment (alone or in combination) among prevalent dialysis patients—raising the hypothesis that inadequate statistical power was responsible for the apparent lack of benefit. Nonetheless, it is clear that even if statins do prevent cardiovascular events in prevalent dialysis patients, the magnitude of any relative reduction in risk is substantially smaller than in earlier stages of CKD.[23] Therefore, in the judgment of the Work Group, initiation of statin treatment is not recommended for most prevalent hemodialysis patients. However, patients might decide to receive statin treatment if they are interested in a relatively uncertain and small reduction in cardiovascular events. As high LDL-C might increase the likelihood of benefit from statin in a dialysis patient,[28] patients who meet this criterion may be more interested in receiving statin treatment, recognizing that the benefit remains speculative. Other factors that might influence a patient's decision to receive statin treatment could include a recent cardiovascular event (MI or stroke) or longer anticipated life expectancy (both of which would favor treatment), and more severe comorbidity or higher current medication burden (both of which would favor lack of treatment).

WHY SHOULD STATIN TREATMENT NOT BE STOPPED WHEN THE PATIENT NEW ON DIALYSIS HAS RECEIVED TREATMENT IN EARLIER STAGES OF CKD?

Available evidence does not directly address whether statins should be discontinued in incident dialysis patients, who may be systematically different from those who are already prevalent on dialysis (such as those included in the major trials of lipid-lowering treatment in dialysis patients). However, 2141 (34%) of SHARP patients without kidney failure at baseline commenced dialysis during the trial and were considered as'non-dialysis' patients; overall benefit was observed in this latter group.[22] The Work Group judged that it is reasonable to continue statins in patients who are already receiving them at the time of dialysis initiation, recognizing that they may lead to less clinical benefit than in patients without kidney failure. Physicians should consider periodically reviewing the clinical status of dialysis patients and revisiting the decision to prescribe statins as required.

As there is no direct evidence that statin treatment improves cardiovascular outcomes in patients who require dialysis treatment, this is a weak recommendation. Discontinuing statin or statin/ezetimibe treatment is reasonable in patients who place a relatively lower value on a small potential relative reduction in vascular events, and a relatively higher value on the risks of polypharmacy, drug–drug interactions, and drug toxicity.

SHOULD WE TREAT PATIENTS WITH A STATIN AFTER KIDNEY TRANSPLANTATION?

The risk of future cardiovascular events in kidney transplant recipients is substantially elevated compared with people without CKD: the rate of cardiovascular death or non-fatal MI is approximately 21.5 per 1000 patient-years.[29] The Assessment of LEscol in Renal Transplantation (ALERT) trial showed that fluvastatin (40–80 mg per day) nonsignificantly reduces the risk of coronary death or non-fatal MI, compared with placebo (RR: 0.83; 95% confidence interval: 0.64–1.06). However, fluvastatin led to a significant 35% relative reduction in the risk of cardiac death or definite non-fatal MI (hazard ratio: 0.65; 95% confidence interval: 0.48–0.88)[29] in an unblinded extension study. A significant reduction in the original primary outcome was found after 6.7 years of follow-up. The Work Group judged that the apparent benefits observed in ALERT are consistent with the effects of statins in the general population, suggesting that statins will improve cardiovascular outcomes in kidney transplant recipients. However, the lack of statistical significance in the primary analysis and the fact that only one randomized trial was available both favor a weak recommendation.

Chapters 3 and 4 | Assessment of lipid status and pharmacological cholesterol treatment in children with CKD

Grade	
1C	3.1: In children 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)
Not graded	3.2: In children with CKD (including those treated with chronic dialysis or kidney transplantation), we suggest annual follow-up measurement of fasting lipid levels
2C	4.1: In children <18 years of age with CKD (including those treated with chronic dialysis or kidney transplantation), we suggest that statins or statin/ezetimibe combination not be initiated

THE ATHEROSCLEROTIC PROCESS BEGINS IN CHILDHOOD

Many studies document the prevalence of dyslipidemia among children with CKD and end stage renal disease.[30,31] As in adults, the pattern of dyslipidemias in children with CKD is greatly influenced by the underlying pathogenesis and duration of CKD, severity of proteinuria, and treatment.[30,31]

In children or adolescents with CKD, the relationship between dyslipidemias and subsequent atherosclerotic clinical events is not known owing to short follow-up in observational studies or clinical trials. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study shows, in adolescents with normal kidney function, that atherosclerosis begins in childhood.[32] This atherosclerotic process is likely accelerated in nephrotic syndrome, proteinuric states, and chronic kidney disease (CKD) owing to abnormal lipid metabolism and other atherogenic risk factors.

The frequency of lipid abnormalities suggests that clinicians should measure lipid levels at baseline in children with CKD to screen for underlying secondary causes of dyslipidemia.

Children with CKD (and their families) 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.

Children with very severely increased hypertriglyceridemia (>11.3 mmol/l (>1000 mg/dl)) should be referred to a pediatric lipid specialist for management and to rule out familial hypertriglyceridemia or rare, inherited disorders such as lipoprotein lipase deficiency or apolipoprotein C-II deficiency.

UNLIKE ADULTS, GROWTH AND DEVELOPMENT IN CHILDREN HAVE THE POTENTIAL TO INFLUENCE LIPID LEVELS OVER TIME

The ideal frequency of follow-up for fasting levels of LDL-C, HDL-C, and serum TGs is unknown. More frequent (or less frequent) follow-up measurements may be appropriate based on the clinical status of the patient, and the potential for such follow-up measurements to influence management.[33] Possible changes in management in response to such measurements are likely.

LACK OF EVIDENCE FOR BENEFIT AND SAFETY PRECLUDES STATIN TREATMENT IN CHILDREN OR ADOLESCENTS

Clinical trials of dyslipidemias in children are limited given the rapid transitions from CKD to dialysis and/or transplant, which complicates trial design, recruitment, and analyses. Four randomized trials have examined drug treatment of dyslipidemia primarily in children with nephrotic syndrome, but no trials have studied clinically relevant outcomes.[34–37] These trials demonstrate that statins lower LDL-C over 7 months to 5 years, but no dose escalation has been carried out. There have been 13 placebo-controlled trials of statins in 1683 children with dyslipidemias and normal kidney function.

This recommendation does not apply to children with severely elevated LDL-C, and therapeutic lifestyle changes should be adopted among all children with CKD. As for all weak recommendations, practitioners should consider the clinical circumstances, patient's age, and preferences when considering an individual patient and his lifetime risk for atherosclerotic cardiovascular disease events with potential exposure to high LCL-C. Treatment strategies based on lifetime risk are problematic because of the lack of data on the long-term follow-up of randomized clinical trials >15 years in the general population, the safety, and event reduction when statins are used for periods >10 years, especially in individuals <40 years of age.

Chapters 5 and 6 | Triglyceride-lowering treatment in adults and in children

Grade	
2D	5.1: In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised
2D	6.1: In children with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised

NO RECOMMENDATION FOR PHARMACOLOGICAL TREATMENT OF HIGH TGS IN ADULTS COULD BE MADE

A meta-analysis of data from 18 randomized trials involving 45,058 participants drawn from the general population (i.e., not specific to CKD) demonstrated a modest 10% relative risk reduction in major cardiovascular events and a 13% relative risk reduction in coronary events for fibrate therapy.[38]

Too few participants with eGFR <60 ml/min per 1.73 m^2 were included in either FIELD (The Fenofibrate Intervention and Event Lowering in Diabetes) or ACCORD-Lipid (Action to Control Cardiovascular Risk in Diabetes-Lipid) to provide reliable information on either the safety or efficacy of fenofibrate in this group.

Allocation to fenofibrate in the FIELD study was associated with an increased risk of doubling of plasma creatinine, which cannot simply be explained by the small step-rise in creatinine due to fenofibrate.

A recent large observational study in patients aged >66 years demonstrated a clear association between new

prescriptions for fibric acid derivatives and increased serum creatinine levels, as well as a small increase in the risk of hospitalization and nephrologist consultation.[39]

These findings contribute to the uncertainty that fibric acid derivatives would yield net clinical benefit in people with CKD. For these reasons, the use of fibric acid derivatives to reduce cardiovascular risk is not recommended in patients with CKD.

Fibric acid derivatives could be considered for the rare patients with CKD and markedly elevated fasting levels of serum TGs (>11.3 mmol/l (>1000 mg/dl)). If such therapy is prescribed, fibric acid derivatives must be dose-adjusted for kidney function. Concomitant therapy with both a fibric acid derivative and a statin is not recommended in patients with CKD owing to the potential for toxicity.

Non-pharmacological treatment of high TGs (>500 mg/dl; 5.65 mmol/l) includes therapeutic lifestyle changes such as dietary modification, weight reduction, increased physical activity, reducing alcohol intake, and treatment of hyperglycemia (if present). Evidence that lifestyle changes will reduce serum TGs in patients with CKD is weak, but the elements of lifestyle changes are unlikely to lead to harm and may improve general health.

TREATMENT FOR HYPERTRIGLYCERIDEMIA IN CHILDREN AND ADOLESCENTS SHOULD FOCUS ON SEVERE CASES

As for adults, the evidence that lifestyle changes will reduce serum triglyceride levels and/or improve clinical outcomes is weak. Nonetheless, it is reasonable to advise children with high fasting levels of serum TGs (>5.65 mmol/l (>500 mg/dl)) to adopt lifestyle changes, but dietary modification should be used judiciously, if at all, in children who are malnourished.

The safety and efficacy of lowering TGs with fibrates and niacin have not been established in adolescents; fish oil appears to lower serum TGs after as little as 12 weeks of therapy,[40–43] but the longer-term benefits, harms, and tolerability of such treatment is unclear.

DISCLOSURE

MT, Advisor/Consultant: Merck (honoraria donated to charity).
CW, Speaker: Astellas-Pfizer (Japan); Merck & Merck Sharp Dohme.

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SUPPLEMENTARY MATERIAL

Table S1. GRADE Criteria Used for Grade Levels in the KDIGO Lipid Guideline.
Table S2. GRADE Criteria Used for Letter Grades in the KDIGO Lipid Guideline.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. *Kidney Int Suppl* 2013; **3**: 259–305.
2. Uhlig K, Macleod A, Craig J *et al.* Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; **70**: 2058–2065.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis* 2003; **41**: S1–92.
4. Grundy SM. Diabetes and coronary risk equivalency: what does it mean? *Diabetes Care* 2006; **29**: 457–460.
5. Lewington S, Whitlock G, Clarke R *et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007; **370**: 1829–1839.
6. Chiang CK, Ho TI, Hsu SP *et al.* Low-density lipoprotein cholesterol: association with mortality and hospitalization in hemodialysis patients. *Blood Purif* 2005; **23**: 134–140.
7. Coresh J, Longenecker JC, Miller ER 3rd *et al.* Epidemiology of cardiovascular risk factors in chronic renal disease. *J Am Soc Nephrol* 1998; **9**(Suppl): S24–S30.
8. Iseki K, Yamazato M, Tozawa M *et al.* Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int* 2002; **61**: 1887–1893.
9. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 1990; **15**: 458–482.
10. Krane V, Winkler K, Drechsler C *et al.* Association of LDL cholesterol and inflammation with cardiovascular events and mortality in hemodialysis patients with type 2 diabetes mellitus. *Am J Kidney Dis* 2009; **54**: 902–911.
11. Liu Y, Coresh J, Eustace JA *et al.* Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *J Am Med Assoc* 2004; **291**: 451–459.
12. Tonelli M, Muntner P, Lloyd A *et al.* Association between LDL-C and risk of myocardial infarction in CKD. *J Am Soc Nephrol* 2013; **24**: 979–986.
13. Stone NJ, Robinson J, Lichtenstein AH *et al.* 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *J Am Coll Cardiol* 2013; doi:10.1016/j.jacc.2013.11.002.
14. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis* 1998; **32**(Suppl 3): S142–S156.
15. Bachorik PS, Ross JW. National Cholesterol Education Program recommendations for measurement of low-density lipoprotein cholesterol: executive summary. The National Cholesterol Education Program Working Group on Lipoprotein Measurement. *Clin Chem* 1995; **41**: 1414–1420.
16. Stein EA, Myers GL. National Cholesterol Education Program recommendations for triglyceride measurement: executive summary. The National Cholesterol Education Program Working Group on Lipoprotein Measurement. *Clin Chem* 1995; **41**: 1421–1426.
17. Warnick GR, Wood PD. National Cholesterol Education Program recommendations for measurement of high-density lipoprotein cholesterol: executive summary. The National Cholesterol Education Program Working Group on Lipoprotein Measurement. *Clin Chem* 1995; **41**: 1427–1433.
18. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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). *J Am Med Assoc* 2001; **285**: 2486–2497.
19. Kilpatrick RD, McAllister CJ, Kovesdy CP *et al.* Association between serum lipids and survival in hemodialysis patients and impact of race. *J Am Soc Nephrol* 2007; **18**: 293–303.
20. Glasziou PP, Irwig L, Heritier S *et al.* Monitoring cholesterol levels: measurement error or true change? *Ann Intern Med* 2008; **148**: 656–661.
21. Takahashi O, Glasziou PP, Perera R *et al.* Lipid re-screening: what is the best measure and interval? *Heart* 2010; **96**: 448–452.
22. Baigent C, Landray MJ, Reith C *et al.* The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; **377**: 2181–2192.
23. Palmer SC, Craig JC, Navaneethan SD *et al.* Benefits and harms of statin therapy for persons With chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 263–275.

24. Colhoun HM, Betteridge DJ, Durrington PN *et al.* Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis* 2009; **54**: 810–819.
25. Tonelli M, Jose P, Curhan G *et al.* Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ* 2006; **332**: 1426.
26. 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.
27. Fellstrom BC, Jardine AG, Schmieder RE *et al.* Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; **360**: 1395–1407.
28. Marz W, Genser B, Drechsler C *et al.* Atorvastatin and low-density lipoprotein cholesterol in type 2 diabetes mellitus patients on hemodialysis. *Clin J Am Soc Nephrol* 2011; **6**: 1316–1325.
29. 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.
30. Saland JM, Ginsberg H, Fisher EA. Dyslipidemia in pediatric renal disease: epidemiology, pathophysiology, and management. *Curr Opin Pediatr* 2002; **14**: 197–204.
31. Saland JM, Ginsberg HN. Lipoprotein metabolism in chronic renal insufficiency. *Pediatr Nephrol* 2007; **22**: 1095–1112.
32. Strong JP, Malcom GT, McMahan CA *et al.* Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA* 1999; **281**: 727–735.
33. National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. *Am J Kidney Dis* 2009; **53**: S1–124.
34. Coleman JE, Watson AR. Hyperlipidaemia, diet and simvastatin therapy in steroid-resistant nephrotic syndrome of childhood. *Pediatr Nephrol* 1996; **10**: 171–174.
35. Garcia-de-la-Puente S, Arredondo-Garcia JL, Gutierrez-Castrellon P *et al.* Efficacy of simvastatin in children with hyperlipidemia secondary to kidney disorders. *Pediatr Nephrol* 2009; **24**: 1205–1210.
36. Sanjad SA, al-Abbad A, al-Shorafa S. Management of hyperlipidemia in children with refractory nephrotic syndrome: the effect of statin therapy. *J Pediatr* 1997; **130**: 470–474.
37. Yoshimura N, Oka T, Okamoto M *et al.* The effects of pravastatin on hyperlipidemia in renal transplant recipients. *Transplantation* 1992; **53**: 94–99.
38. Jun M, Foote C, Lv J *et al.* Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010; **375**: 1875–1884.
39. Zhao YY, Weir MA, Manno M *et al.* New fibrate use and acute renal outcomes in elderly adults a population-based study. *Ann Intern Med* 2012; **156**: 560–569.
40. Cerkauskiene R, Kaminskas A, Kaltenis P *et al.* Influence of omega-3 fatty acids on lipid metabolism in children with steroid sensitive nephritic syndrome]. *Medicina* 2003; **39**(Suppl 1): 82–87.
41. Chongviriyaphan N, Tapaneya-Olarn C, Suthutvoravut U *et al.* Effects of tuna fish oil on hyperlipidemia and proteinuria in childhood nephritic syndrome. *J Med Assoc Thai* 1999; **82**(Suppl 1): S122–S128.
42. Goren A, Stankiewicz H, Goldstein R *et al.* Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. *Pediatrics* 1991; **88**: 265–268.
43. Hogg RJ, Lee J, Nardelli N *et al.* Clinical trial to evaluate omega-3 fatty acids and alternate day prednisone in patients with IgA nephropathy: report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol* 2006; **1**: 467–474.

APPENDIX 1
SUMMARY OF RECOMMENDATION STATEMENTS

Chapter 1: ASSESSMENT OF LIPID STATUS IN ADULTS WITH CKD

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). (*1C*)

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*)

CHAPTER 2: PHARMACOLOGICAL CHOLESTEROL-LOWERING TREATMENT IN ADULTS

2.1.1: In adults aged $\geqslant$50 years with eGFR $<$60 ml/min per 1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5), we recommend treatment with a statin or statin/ezetimibe combination. (*1A*)

2.1.2: In adults aged $\geqslant$50 years with CKD and eGFR $\geqslant$60 ml/min per 1.73 m^2 (GFR categories G1–G2), we recommend treatment with a statin. (*1B*)

2.2: In adults aged 18-49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (*2A*):

- known coronary disease (myocardial infarction or coronary revascularization)
- diabetes mellitus
- prior ischemic stroke
- estimated 10-year incidence of coronary death or non-fatal myocardial infarction $>$10%.

2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (*2A*)

2.3.2: In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued. (*2C*)

2.4: In adult kidney transplant recipients, we suggest treatment with a statin. (*2B*)

CHAPTER 3: ASSESSMENT OF LIPID STATUS IN CHILDREN WITH CKD

3.1: In children 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). (*1C*)

3.2: In children with CKD (including those treated with chronic dialysis or kidney transplantation), we suggest annual follow-up measurement of fasting lipid levels. (*Not Graded*)

CHAPTER 4: PHARMACOLOGICAL CHOLESTEROL-LOWERING TREATMENT IN CHILDREN

4.1: In children less than 18 years of age with CKD (including those treated with chronic dialysis or kidney transplantation), we suggest that statins or statin/ezetimibe combination not be initiated. (*2C*)

CHAPTER 5: TRIGLYCERIDE-LOWERING TREATMENT IN ADULTS

5.1: In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised. (*2D*)

CHAPTER 6: TRIGLYCERIDE-LOWERING TREATMENT IN CHILDREN

6.1: In children with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised. (*2D*)