Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline

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Description: The Kidney Disease: Improving Global Outcomes (KDIGO) organization developed a clinical practice guideline in 2013 on lipid management and treatment of all adults and children with chronic kidney disease (CKD). All forms of CKD are included (non–dialysis-dependent, dialysis-dependent, and kidney transplant recipients).

Methods: 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. Final modification of the guidelines was informed by the KDIGO Board of Directors and a public review process involving registered stakeholders.

Recommendations: The full guideline includes 13 recommendations; a key element was the recommendation for statin or statin with ezetimibe treatment of adults aged 50 years or older with estimated glomerular filtration rates less than 60 mL/min/1.73 m^2 but not treated with long-term dialysis or kidney transplantation. This synopsis focuses on 8 recommendations pertinent to assessment of lipid status and treatment with a statin-based regimen in adults.

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* For a list of the members of the KDIGO Lipid Guideline Development Work Group, see the **Appendix** (available at www.annals.org).

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The publication of several landmark clinical trials led the Kidney Disease: Developing Global Guidelines (KDIGO) organization to develop an updated Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. The updated guideline applies to all adults and children with chronic kidney disease (CKD), including those treated with dialysis or kidney transplantation.

The overall objective for the guideline is to inform the management of dyslipidemia and use of cholesterol-lowering medications in all adults and children with known CKD (defined by reduced estimated glomerular filtration rate [eGFR] or markers of kidney damage, such as abnormal albuminuria). The target audience of the guideline includes nephrologists, primary care physicians, non-nephrology specialists (such as cardiologists and diabetologists), clinical chemists, and other practitioners caring for adults and children with CKD worldwide. Within the guideline, implications for clinical practice, future research, and implementation in international settings are highlighted. The full guideline is available at www.kdigo.org and includes 13 recommendations. This synopsis focuses on 8 key recommendations pertinent to assessment of lipid status and treatment with a statin-based regimen in adults.

See also:

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Guideline Development Process, Evidence Grading, and Stakeholder and Public Consultation

The work group consisted of an international group of clinicians and researchers, including an 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 as per KDIGO's usual practice (1) (**Appendix Tables 1** and **2**, available at www.annals.org).

This guideline updates the 2003 Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. The evidence review team did systematic reviews of randomized, controlled trials and systematic reviews for 6 topics of interest (**Appendix Table 3**, available at www.annals.org). Systematic searches were last conducted in August 2011 and supplemented with additional evidence through June 2013. Evidence from the systematic reviews was summarized into GRADE evidence tables; no primary decision analysis or economic analysis was done to inform the guideline. Guideline development, evidence synthesis, and writing of the guideline itself were done by the work group; recommendation statements were developed by the work group with all decisions made by consensus. Full

details of the guideline development process, topic discussion, and consensus development can be found in the published guideline. A summary of the classification scheme for CKD (on which the current recommendations are based) is found in the **Appendix Figure** (available at www.annals.org).

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 is based on the order used in the 2003 Kidney Disease Outcomes Quality Initiative publication and presents recommendations on assessment of lipid status before those related to treatment. Herein, we have presented recommendations related to treatment first to facilitate description of the chain of logic.

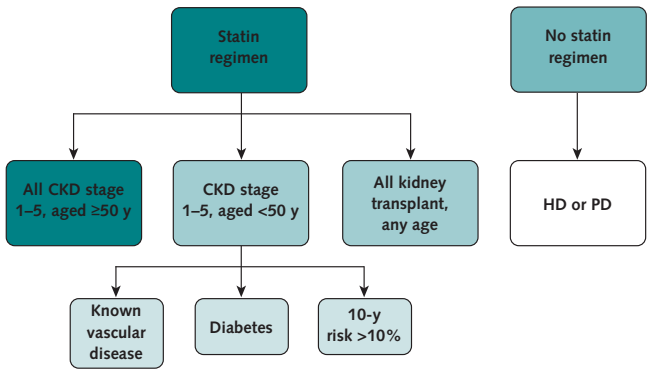
Recommendations Relating to Pharmacologic Cholesterol-Lowering Treatment in Adults

To maximize the ratio of benefits to harms and costs, future coronary risk is considered an important potential determinant of the decision to prescribe cholesterol-lowering treatment (2). In the general population, low-density lipoprotein (LDL) cholesterol is widely used as a proxy for future risk because LDL cholesterol levels are strongly and independently associated with risk for atherosclerotic events (3). However, the clinical benefits of statin treatment (including lower risk for myocardial infarction [MI], stroke, and peripheral vascular events) are proportional to baseline coronary risk rather than baseline LDL cholesterol.

Low-density lipoprotein cholesterol is not suitable for assessing coronary risk in persons with CKD: Although higher levels of LDL cholesterol are associated with higher risk, dialysis patients with the lowest levels of LDL cholesterol and total cholesterol are also at very high risk for all-cause and cardiovascular mortality (4–7), likely because of confounding by inflammation and malnutrition (8, 9). Among persons with non–dialysis-dependent CKD, the magnitude of the excess risk associated with increased LDL cholesterol levels decreases at lower eGFRs (10). The weaker and potentially misleading association between LDL cholesterol and coronary risk among those with lower levels of kidney function (who are at the highest absolute risk for coronary events) argues against the use of LDL cholesterol for identifying CKD patients who should receive pharmacologic cholesterol-lowering treatment.

Coronary risk is often assessed using the 10-year incidence of coronary death or nonfatal MI. There is no consensus on the level of future coronary risk that is sufficient to justify cholesterol-lowering treatment, but in the judgment of the work group, a 10-year risk for coronary death or nonfatal MI that exceeds 10% is a reasonable working definition. The 10-year risk for coronary death or nonfatal MI among CKD patients older than 50 years (both men and women) is consistently greater than 10%, even in those without diabetes or previous MI (**Appendix Table 4**, available at www.annals.org). In contrast, the 10-year risk for coronary death or nonfatal MI among CKD patients aged 50 years or younger is low in those without diabetes or previous MI—although it is higher than in otherwise similar persons without CKD.

Figure. **Algorithm for cholesterol-lowering treatment in persons with CKD.**



Boxes represent recommendations about whether to prescribe a statin regimen. Boxes with dark and medium green fill represent strong recommendations; lighter green and white boxes represent weak recommendations. Recommended statin regimens are shown in Table 1 and include statin monotherapy or statin/ezetimibe for those with CKD stage 3a to 5 and statin monotherapy for all other CKD populations. CKD = chronic kidney disease; HD = hemodialysis; PD = peritoneal dialysis.

Together, available evidence argues against the use of LDL cholesterol to identify patients with CKD who should receive cholesterol-lowering treatment and suggests focusing instead on 2 factors: the absolute risk for coronary events and evidence that such treatment is beneficial. This is the approach taken in the recommendations that follow (summarized in the **Figure**).

> 2.1.1: In adults aged ≥50 years with eGFR <60 ml/min/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)*

The 10-year risk for coronary death or nonfatal MI in persons who are non–dialysis-dependent, have eGFRs less than 60 mL/min/1.73 m^2, and are aged 50 years or older is consistently greater than 10%. Therefore, in the judgment of the work group, knowledge of LDL cholesterol is not required to gauge average coronary risk in this population. Although multivariable prediction instruments may yield more precise estimates of risk for patients, the work group judged that the increased simplicity of an age-based ap-

Table 1. **Recommended Doses of Statins in Adults With Chronic Kidney Disease***

Statin	eGFR G1–G2	eGFR G3a–G5, Including Patients Receiving Dialysis or Who Had a Kidney Transplant
Lovastatin	Any dose approved for GP	ND
Fluvastatin	Any dose approved for GP	80†
Atorvastatin	Any dose approved for GP	20‡
Rosuvastatin	Any dose approved for GP	10§
Simvastatin/ ezetimibe	Any dose approved for GP	20/10‖
Pravastatin	Any dose approved for GP	40
Simvastatin	Any dose approved for GP	40
Pitavastatin	Any dose approved for GP	2

eGFR = estimated glomerular filtration rate; GP = general population; ND = not done.
* All doses are mg/d. All statins may not be available in all countries. Lower doses than those used in major trials of statins in chronic kidney disease populations may be appropriate in Asian countries. Note that 40 mg of rosuvastatin daily is not recommended for use in patients with chronic kidney disease G1–G2 who did not have transplantation because it may increase the risk for adverse renal events. Cyclosporine inhibits the metabolism of certain statins, resulting in higher blood levels.
† Data based on Assessment of Lescol in Renal Transplantation trial.
‡ Data based on Die Deutsche Diabetes Dialyse Studie.
§ Data based on A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events.
‖ Data based on the Study of Heart and Renal Protection trial.

proach was defensible and would enhance uptake of the guideline.

SHARP (Study of Heart and Renal Protection) showed that simvastatin-and-ezetimibe combination therapy reduced the risk for major atherosclerotic events (coronary death, MI, nonhemorrhagic stroke, or any revascularization) compared with placebo in persons with GFR categories G3a to G5 (11). 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 for cardiovascular events to a similar extent among patients with and without CKD but that the absolute benefit of treatment is larger in the former because of the greater baseline risk (12).

The work group concluded that the combination of findings from SHARP, post hoc analyses of randomized trials from the general population (focusing on the subset with CKD), and the large body of evidence from the general population trials (including persons with and without a baseline history of coronary disease) collectively justify a strong recommendation.

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

Most patients with CKD and eGFRs of 60 mL/min/1.73 m^2 or greater have albuminuria and slightly reduced or normal eGFRs; many such patients would have been included but not recognized in randomized trials of statins done in the general population because many such trials did not assess the presence of albuminuria at baseline. The benefit of statin monotherapy seems to be similar in persons with and without albuminuria (13, 14).

Given these data, the high cardiovascular risk among persons with CKD and eGFR categories G1 to G2, and the large body of evidence supporting the efficacy of statins in the general population, the work group judged that a strong recommendation was appropriate.

> 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 nonfatal myocardial infarction >10%

Although the absolute rate of such events is lower among persons with CKD who are younger than 50 years, the coexistence of other risk factors substantially increases the rate of coronary death or nonfatal MI. In the subset of CKD patients younger than 50 years with diabetes or previous vascular disease (MI, coronary revascularization, stroke, or transient ischemic attack), the 10-year risk for coronary death or nonfatal MI is 12.2% (95% CI, 9.9% to 15.0%).

Similarly, some CKD patients aged 18 to 50 years may not have diabetes or previous vascular disease but yet have several cardiovascular risk factors that substantially increase their risk for future coronary events. Because unequivocally elevated LDL cholesterol levels are associated with increased risk for coronary events in persons with CKD (although to a lesser extent than in the general population), increased LDL cholesterol levels should be considered when estimating coronary risk in CKD patients younger than 50 years. The 10-year incidence of coronary death or nonfatal MI may be estimated by using any validated risk prediction tool (15–19). Although these instruments tend to overestimate future coronary risk, most do not explicitly consider the presence of CKD and thus such overestimation should be less pronounced in CKD populations.

Patients whose 10-year risk for coronary death or nonfatal MI is less than 10% could choose to receive statin treatment if they place relatively more value on a small absolute reduction in the risk for cardiovascular events and relatively less value on minimizing the risks for polypharmacy and drug toxicity. However, patients valuing the potential benefits of statin treatment to a lesser extent than

the potential harms may choose not to receive statin treatment even if their 10-year risk for coronary death or nonfatal MI is greater than 10%.

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

Three large randomized trials (11, 20, 21) have not shown a conclusive benefit of statin treatment (alone or in combination) among prevalent dialysis patients—leading to speculation that inadequate statistical power is responsible for the apparent lack of benefit. Even if statins truly do prevent cardiovascular events in prevalent dialysis patients, the magnitude of any relative reduction in risk seems substantially smaller than in earlier stages of CKD (12), although this may still translate into a clinically meaningful absolute benefit (22). Therefore, in the judgment of the work group, initiation of statin treatment is not recommended for most prevalent hemodialysis patients. However, patients may reasonably choose statin treatment if they are interested in a relatively small, uncertain reduction in cardiovascular events. Because high LDL cholesterol levels may increase the likelihood of benefit from a statin in a patient receiving dialysis (albeit to a lesser extent than in someone with normal kidney function) (23), patients who meet this criterion may be more inclined to receive a statin, recognizing that the benefit remains uncertain. Other factors that may influence a patient's decision to receive a statin could include recent MI or greater life expectancy (both favoring treatment) and more severe comorbidity or higher current pill burden (both favoring nontreatment).

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

Available trials do not directly address the question of whether statins should be discontinued in patients initiating dialysis, who may be systematically different from patients with kidney failure receiving dialysis. However, 2141 of SHARP patients (34%) without kidney failure at baseline commenced dialysis during the trial and were analyzed in the nondialysis group—in which overall benefit was observed (11). Therefore, SHARP could be interpreted as demonstrating that initiating a statin regimen in patients without kidney failure (and continuing treatment if kidney failure occurs) is beneficial, whereas initiating statin treatment in prevalent patients receiving dialysis is of uncertain benefit. In the judgment of the work group, it is reasonable to continue statins in patients who are already receiving them at the time of dialysis initiation, recognizing that the magnitude of clinical benefit may be lower than in patients with non–dialysis-dependent CKD. Physicians should consider periodically reviewing the clinical status of patients receiving dialysis (to assess the factors favoring treatment and nontreatment, noted previously) and revisiting the decision to prescribe statins as required.

Given the lack of direct evidence that statin treatment is beneficial in dialysis patients, this recommendation is graded as weak. Discontinuation of statin or statin with ezetimibe may be warranted in patients who place a relatively low value on a small potential relative reduction in cardiovascular events and a relatively high value on the risks for polypharmacy and drug toxicity.

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

The risk for future coronary events in kidney transplant recipients is markedly elevated: The 10-year risk for coronary death or nonfatal MI is approximately 21.5% (24). The ALERT (Assessment of Lescol in Renal Transplantation) study showed a benefit of fluvastatin therapy (40 to 80 mg/d) on the risk for coronary death or nonfatal MI compared with placebo (relative risk, 0.83 [CI, 0.64 to 1.06]) that was not statistically significant. However, fluvastatin led to a significant 35% relative reduction in the risk for cardiac death or nonfatal MI (hazard ratio, 0.65 [CI, 0.48 to 0.88]) (24), and an unblinded extension study found that receiving fluvastatin was associated with a significant reduction in the original primary outcome after 6.7 years of follow-up. In the judgment of the work group, the apparent benefits seen in ALERT are consistent with the effects of statins in the general population and suggest that statins are beneficial in patients with a functioning kidney transplant. However, the nominal lack of statistical significance in the primary analysis and the existence of a single randomized trial favor a weak recommendation.

Recommendations Relating to the 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)*

Dyslipidemia is common but not universal in persons with CKD. The major determinants of dyslipidemia in CKD patients are GFR, the presence of diabetes mellitus, severity of proteinuria, use of immunosuppressive agents, method of renal replacement, comorbidity, and nutritional status (25).

Initial evaluation of the lipid profile mainly serves to establish the diagnosis of severe hypercholesterolemia or hypertriglyceridemia and potentially rule out a remediable (secondary) cause if dyslipidemia is present (**Table 2**). The lipid profile should ideally be measured in the fasting state; if not feasible, nonfasting values provide useful informa-

Table 2. **Secondary Causes of Dyslipidemia***

Medical Conditions
The nephrotic syndrome
Hypothyroidism
Diabetes
Excessive alcohol consumption
Liver disease
Medications
13-cis-retinoic acid
Anticonvulsants
Highly active antiretroviral therapy
Diuretics
β-Blockers
Androgens
Oral contraceptives
Corticosteroids
Cyclosporine
Sirolimus

* Reproduced from reference 30.

tion as well (26), but fasting specimens will be needed if significant lipid abnormalities are found, especially severe hypertriglyceridemia (26–28). 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 levels greater than 11.3 mmol/L (1000 mg/dL) or LDL cholesterol levels greater than 4.9 mmol/L (190 mg/dL) should prompt consideration of (or specialist referral for) further evaluation.

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 the potential to improve the health of persons with secondary dyslipidemia. 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)*

Previous guidelines have emphasized treatment escalation to achieve specific LDL cholesterol targets by increasing the dose of statin or combination therapy (29, 30). The implicit but unproven hypothesis associated with these recommendations is that more intensive regimens will reduce cardiovascular risk without increasing adverse events. An additional weakness of this approach is that it will lead to underutilization of statins in CKD patients with low LDL cholesterol, who are at very high cardiovascular risk (31). Given the lack of data to support this approach in populations with and without CKD (32), the substantial within-person variability in LDL cholesterol measurements (33) and the potential for medication-related toxicity (including direct effects on muscle and liver, and indirect effects mediated through drug interactions), this approach is no longer recommended for CKD populations and the decision to prescribe statins is based on 10-year risk for coronary events (see the Recommendations Relating to Pharmacologic Cholesterol-Lowering Treatment in Adults section). Because higher cardiovascular risk rather than elevated LDL cholesterol levels is now the primary indication to initiate or adjust lipid-lowering treatment in CKD patients, follow-up monitoring of LDL cholesterol (after an initial measurement) may not be required for many patients—especially given normal variability in LDL cholesterol levels over time, which reduces the clinical utility of follow-up measurements (34).

In the judgment of the work group, follow-up measurement of lipid levels should be reserved for instances in which the results would alter management. Potential reasons to measure LDL cholesterol (or the lipid profile) in persons with CKD after their initial presentation may include assessment of adherence to statin treatment, change in renal replacement method or concern about the presence of new secondary causes of dyslipidemia (**Table 2**), or assessment of 10-year cardiovascular risk in patients younger than 50 years who are not currently receiving a statin (because knowledge of LDL cholesterol in this case may suggest that a statin was required—see recommendation 2.2).

In the judgment of the work group, it is unnecessary to measure LDL cholesterol in situations in which the results would not (or likely would not) change management (**Table 3**). For example, patients already receiving a statin (or in whom statin treatment is clearly indicated or not indicated based on changes in their cardiovascular risk profile or clinical status) would not require follow-up LDL cholesterol measurements because the results would not alter treatment. Likewise, because the association between LDL cholesterol and adverse clinical outcomes is weaker in persons with CKD than in the general population, the value of measuring LDL cholesterol to assess prognosis is uncertain.

There is no direct evidence that routine follow-up of lipid levels improves clinical outcomes or adherence to lipid-lowering therapy. In fact, random within-patient variation in serum cholesterol levels is substantial (± 0.8 mmol/L [± 30 mg/dL] for total cholesterol)—and therefore, such follow-up measurements may not reliably indicate good or poor compliance (34). 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.

Discussion

The evidence highlights the limitations of LDL cholesterol as a marker of cardiovascular risk in persons with

Table 3. **Examples of Situations in Which Measuring Cholesterol Levels May or May Not Change Patient Management**

Patient Characteristics	Is the Patient Already Receiving Statin?	Would Measuring Cholesterol Levels Change Management?
Man aged 55 y with eGFR of 35 mL/min/1.73 m^2	Yes	No; patient is already receiving a statin
Man aged 55 y with eGFR of 35 mL/min/1.73 m^2	No	No; statin is already indicated based on recommendation 2.1.1
Man aged 55 y with eGFR of 75 mL/min/1.73 m^2 and ACR of 1100 mg/g	No	No; statin is already indicated based on recommendation 2.1.2
Man aged 45 y with eGFR of 35 mL/min/1.73 m^2 who is a smoker and has diabetes and hypertension	No	No; statin is already indicated based on recommendation 2.1.3 because predicted 10-y risk for coronary death or MI is >10% regardless of cholesterol level
Man aged 45 y with eGFR of 35 mL/min/1.73 m^2 who is a nonsmoker without diabetes or hypertension	Yes	No; patient is already receiving a statin
Man aged 45 y with eGFR of 35 mL/min/1.73 m^2 who is a nonsmoker without diabetes or hypertension	No	Yes; patient's predicted 10-y risk for 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.
Man aged 35 y with eGFR of 35 mL/min/1.73 m^2 who is a nonsmoker without diabetes or hypertension	No	No; patient's predicted 10-y risk for coronary death or MI is <10% regardless of cholesterol level

ACR = albumin–creatinine ratio; eGFR = estimated glomerular filtration rate; MI = myocardial infarction.

CKD, as well as the high baseline cardiovascular risk in this population. These considerations argue against the use of LDL cholesterol as the primary determinant of statin prescription in CKD populations. How then should statin regimens be selected and adjusted in persons with CKD?

Guidelines for management of dyslipidemia in the general population recommend that the statin dose is titrated to achieve the target level of LDL cholesterol, which in turn is determined by each patient's presumed coronary risk (35). This approach (often termed "treat-to-target") is widely accepted, although it is not directly supported by the results of clinical trials. Instead, existing randomized trials have compared statin and placebo or compared higher and lower doses of statin (regardless of achieved LDL cholesterol). Taken together, available evidence suggests that higher statin doses produce greater clinical benefits but at the expense of an increased risk for adverse events.

Whether the treat-to-target strategy is the optimal way to reduce cardiovascular risk in the general population is a topic of intense debate. Data to assess the safety of more intensive lipid-lowering treatment in persons with CKD is insufficient. However, it is known that CKD patients are at high risk for adverse events attributable to other medications, perhaps because of the reduced renal excretion, frequent polypharmacy, and high prevalence of comorbidity in this population.

Given the potential for toxicity with higher doses of statins and the relative lack of data evaluating the safety of these regimens in advanced CKD, the work group suggests that prescription of statins in persons with eGFR less than 60 mL/min/1.73 m^2 or renal replacement therapy should be based on regimens and doses that have been shown to be beneficial in randomized trials done specifically in this population (**Table 1**). Patients with progressive renal dysfunction who are tolerating an alternative regimen do not necessarily need to be switched to a regimen described in **Table 1**, although dose reduction based on eGFR may be prudent in patients with severe kidney dysfunction who are receiving very aggressive regimens. Given less concern about drug toxicity in the setting of better kidney function, patients with eGFRs of 60 mL/min/1.73 m^2 or greater (and no history of kidney transplantation) may be treated with any statin regimen that is approved for use in the general population. In the judgment of the work group, existing evidence does not support a specific on-treatment LDL cholesterol target and thus adjusting the dose of statin regimens based on LDL cholesterol levels is not required. This type of strategy has been termed "fire-and-forget". Potential advantages of a fire-and-forget strategy in persons with CKD include simplicity, lower resource consumption (due to less unnecessary use of LDL cholesterol testing and high-dose statin regimens), and reduced risk for side effects (due to the lower statin doses suggested in **Table 1**) (32).

Previous studies convincingly demonstrated that the prevalence of statin use among persons with CKD who were at risk for cardiovascular events was lower than among otherwise similar persons with normal kidney function (36–38). We are optimistic that the current guideline will help to close this quality gap by emphasizing the high cardiovascular risk associated with CKD (regardless of LDL cholesterol levels) while also reducing complexity for practitioners and enhancing implementation.

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Appendix: Members of the Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group

Members of the Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group were: Marcello Tonelli and Christoph Wanner (co-chairs), Alan Cass, Amit X. Garg, Hallvard Holdaas, Alan G. Jardine, Lixin Jiang, Florian Kronenberg, Rulan S. Parekh, Tetsuo Shoji, and Robert J. Walker.

Appendix Table 1. **GRADE Criteria Used for Grading the Strength of Recommendation in the KDIGO Lipid Guideline**

Grade Level*	Implications		
	Patients	Clinicians	Policymakers
1 ("We recommend")	Most persons in this situation would—and only a small proportion would not—want the recommended course of action.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
2 ("We suggest")	Most persons in this situation would—but many would not—want the recommended course of action.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with his or her values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

GRADE = Grading of Recommendations Assessment, Development and Evaluation; KDIGO = Kidney Disease: Improving Global Outcomes.
* Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded. The additional category "Not Graded" was used to provide guidance on the basis of common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations about monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger recommendations than level 1 or 2 recommendations.

Appendix Table 2. **GRADE Criteria Used for Grading the Overall Quality of Evidence in the KDIGO Lipid Guideline**

Letter Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain and often will be far from the truth.

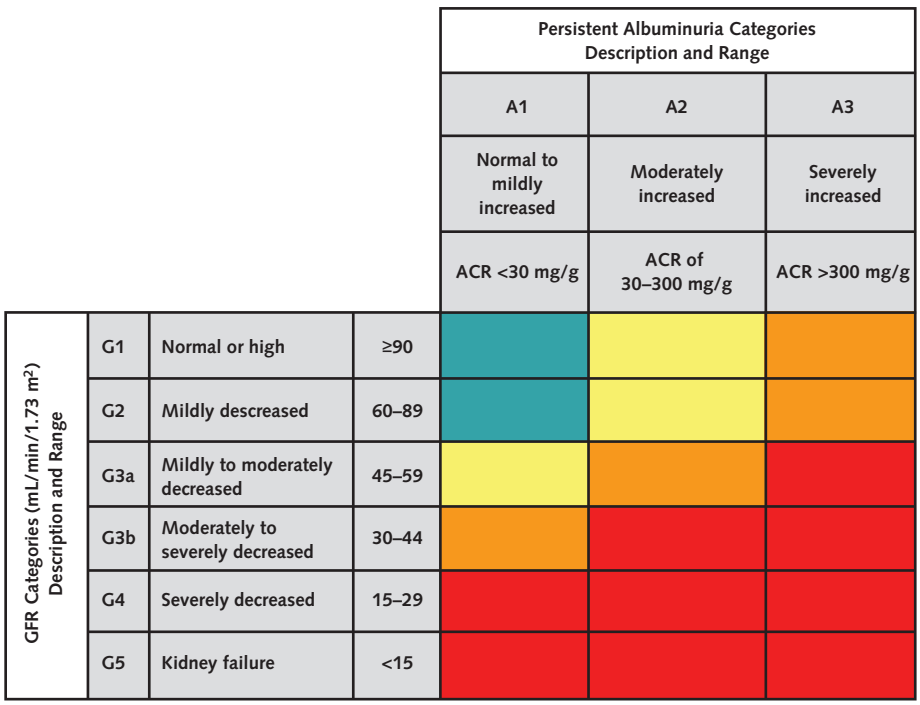
GRADE = Grading of Recommendations Assessment, Development and Evaluation; KDIGO = Kidney Disease: Improving Global Outcomes.

Appendix Table 3. Topics Chosen for Systematic Review and Screening Criteria

Topic	Definition
Lipid-lowering agents	
Population	Adults and children with CKD of any severity, with or without dyslipidemia and diabetes; kidney transplant recipients; CKD subgroups in large studies of the general population
Intervention	≥1 lipid-lowering agent (typically statin, niacin, colestipol, or cholestyramine). Excluded dietary supplements, phosphate binders, apheresis, stanols, and sterols.
Comparator	Active or control
Outcome	Categorical: All-cause mortality, cardiovascular mortality, clinical cardiovascular events, ESRD, graft failure, doubling of SCr level, halving of GFR Continuous: changes in total cholesterol, LDL cholesterol, or HDL cholesterol or TG levels
Study design	RCTs with parallel-group design; systematic reviews, CKD subgroup analyses of general population RCTs if no evidence of selection bias and of sufficient size
Minimum duration of follow-up	4 wk for continuous lipid outcomes; 1 y for clinical outcomes; if general population study, 1 y
Minimum number of participants	≥100 per group for adults, ≥25 per group for children; if general population study, ≥500 per group for adults or ≥100 per group for children in full study
Diet or lifestyle modification	
Population	Adults and children with CKD of any severity, with or without dyslipidemia and diabetes; kidney transplant recipients; CKD subgroups in large studies of the general population
Intervention	Weight loss, special diet, or exercise; also structured care vs. usual care
Comparator	Different diet or lifestyle modification or agent or placebo
Outcome	Categorical: All-cause mortality, cardiovascular mortality, clinical cardiovascular events, ESRD, graft failure, doubling of SCr level, halving of GFR Continuous: changes in total cholesterol, LDL cholesterol, or HDL cholesterol or TG levels
Design	RCTs with parallel-group design; systematic reviews, CKD subgroup analyses of general population RCTs if no evidence of selection bias and of sufficient size
Minimum duration of follow-up	4 wk for continuous lipid outcomes; 1 y for clinical outcomes; if general population study, 1 y
Minimum number of participants	≥25 per group
Drug interactions (update of Tables 32–37 in KDOQI 2003 guideline) (30)	
Population	General population
Intervention	Any statin and any other drug
Comparator	NA
Outcomes	Change in bioavailability of statin
Design	Systematic reviews
Minimum duration of follow-up	NA
Minimum number of participants	NA
Change in LDL cholesterol level by statin	
Population	General population
Intervention	Any statin
Comparator	Other agent or placebo
Outcomes	Change in LDL cholesterol
Design	Systematic review or meta-analysis, 2006–2011
Minimum duration of follow-up	NA
Minimum number of participants	NA
Adverse events from statin + fibrate therapy	
Population	General population (typically focused on familial hypercholesterolemia or mixed dyslipidemia)
Intervention	Any statin or statins + any fibrate or fibrates
Comparator	Statin or statins alone (also captured data vs. fibrate alone or placebo)
Outcomes	Any adverse event, any serious adverse event, discontinuation because of drug, AKI, cancer, rhabdomyolysis, myalgia, increased creatine kinase level, increased creatinine level, increased ALT or AST level, any other specified serious adverse event; in children, also measures of growth, development, cognitive function
Design	Any
Minimum duration of follow-up	Any
Minimum number of participants	Any
Frequency of lipids testing	
Population	Any
Intervention	Any regimen with variable timing of measurement (e.g., more vs. less testing and some vs. no testing)
Comparator	Active or placebo
Outcomes	Measures of compliance, cardiovascular outcomes, mortality
Design	RCTs or systematic reviews
Minimum duration of follow-up	6 mo
Minimum number of participants	≥50 per group

AKI = acute kidney injury; ALT = alanine aminotransferase; AST = aspartate aminostransferase; CKD = chronic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HDL = high-density lipoprotein; KDOQI = Kidney Disease Outcomes Quality Initiative; LDL = low-density lipoprotein; NA = not applicable; RCT = randomized, controlled trial; SCr = serum creatinine; TG = triglyceride.

Appendix Figure. **Prognosis of CKD chronic kidney disease by GFR and albuminuria categories: KDIGO 2012.**



Chronic kidney disease is defined as abnormalities of kidney structure or function, present for >3 mo, with implications for health. Chronic kidney disease is classified based on cause, GFR category (G1–G5), and albuminuria category (A1–A3), abbreviated as CGA. Green means low risk (if no other markers of kidney disease, no CKD), yellow means moderately increased risk, orange means high risk, and red means very high risk. ACR = albumin–creatinine ratio; GFR = glomerular filtration rate.

Appendix Table 4. **Risk for Coronary Death or Nonfatal MI, by Age and eGFR***

Characteristic	10-Year Probability of Coronary Death or Nonfatal MI (95% CI), %		
	Overall	Men	Women
Age >40 y	14.9 (14.6–15.3)	17.4 (16.9–17.9)	12.7 (12.3–13.1)
eGFR G3a–G4	19.3 (18.8–19.8)	23.4 (22.6–24.2)	16.4 (15.8–17.0)
eGFR G1–G2	9.7 (9.3–10.0)	12.0 (11.4–12.6)	6.7 (6.3–7.2)
Age >50 y	17.3 (17.0–17.7)	20.2 (19.6–20.8)	14.8 (14.3–15.3)
eGFR G3a–G4	19.9 (19.4–20.4)	24.3 (23.4–25.2)	16.9 (16.3–17.5)
eGFR G1–G2	12.9 (12.4–13.4)	15.2 (14.5–16.0)	9.7 (9.0–10.5)
Age 40–50 y	3.2 (2.9–3.6)	4.7 (4.2–5.4)	1.6 (1.2–2.0)
eGFR G3a–G4	4.7 (3.7–6.0)	5.9 (4.3–8.1)	3.6 (2.5–5.3)
eGFR G1–G2	3.0 (2.6–3.3)	4.6 (4.0–5.3)	1.2 (0.9–1.6)

eGFR = estimated glomerular filtration rate; MI = myocardial infarction.
* Data are unadjusted rates from 1 268 029 participants in the Alberta Kidney Disease Network cohort. Persons with diabetes, MI, and other cardiovascular disease were included. Data do not apply to persons who had kidney transplantation.