AJKD

KDOQI Commentary

KDOQI US Commentary on the 2013 KDIGO Clinical Practice Guideline for Lipid Management in CKD

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The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline for management of dyslipidemia in chronic kidney disease (CKD) was published in 2003. Since then, considerable evidence, including randomized controlled trials of statin therapy in adults with CKD, has helped better define medical treatments for dyslipidemia. In light of the new evidence, KDIGO (Kidney Disease: Improving Global Outcomes) formed a work group for the management of dyslipidemia in patients with CKD. This work group developed a new guideline that contains substantial changes from the prior KDOQI guideline. KDIGO recommends treatment of dyslipidemia in patients with CKD primarily based on risk for coronary heart disease, which is driven in large part by age. The KDIGO guideline does not recommend using low-density lipoprotein cholesterol level as a guide for identifying individuals with CKD to be treated or as treatment targets. Initiation of statin treatment is no longer recommended in dialysis patients. To assist US practitioners in interpreting and applying the KDIGO guideline, NKF-KDOQI convened a work group to write a commentary on this guideline. For the most part, our work group agreed with the recommendations of the KDIGO guideline, although we describe several areas in which we believe the guideline statements are either too strong or need to be more nuanced, areas of uncertainty and inconsistency, as well as additional research recommendations. The target audience for the KDIGO guideline includes nephrologists, primary care practitioners, and non-nephrology specialists such as cardiologists and endocrinologists. As such, we also put the current recommendations into the context of other clinical practice recommendations for cholesterol treatment.
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The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline for management of dyslipidemia in chronic kidney disease (CKD) was published in 2003.[1] This guideline defined CKD as a coronary heart disease (CHD) risk equivalent. For stages 1 to 4 CKD, the recommendation was to follow the National Cholesterol Education Program guideline for treatment goals, but with CKD as a CHD risk equivalent. Treatment was also recommended for both adults and adolescents with stage 5 CKD and dyslipidemia, defined by serum concentrations of low-density lipoprotein (LDL) cholesterol and/or triglycerides.

Since 2003, considerable evidence, including randomized controlled trials of statin therapy in adults with CKD, has helped better define medical treatments for dyslipidemia and the individuals most likely to benefit from treatment. In light of the new evidence, KDIGO (Kidney Disease: Improving Global Outcomes) formed a work group for the management of dyslipidemia in patients with CKD. This work group developed a new guideline that contains substantial changes from the prior NKF-KDOQI guideline. KDIGO recommends treatment of dyslipidemia primarily based on risk for CHD, which is driven in large part by age. Based on the results of 4D (Die Deutsche Diabetes Dialyse Studie)[2] and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events),[3] as well as the subgroup analysis of SHARP (Study of Heart and Renal Protection),[4] initiation of statin treatment is no longer recommended in dialysis patients.

The KDIGO guideline does not recommend using LDL cholesterol level as a guide for identifying individuals with CKD to be treated or as treatment

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targets. Previous use of LDL cholesterol levels for guiding treatment was based on achieved LDL cholesterol levels in statin trials. However, prior trials used fixed doses of statins and were not designed to test the benefits of achieving target LDL cholesterol levels. Current treatment recommendations are also primarily based on the use of statins (rather than alternative lipid-lowering agents) given that they have been shown in randomized controlled trials to reduce the risk for atherosclerotic events as both primary and secondary prevention.

The target audience for the KDIGO guideline includes nephrologists, primary care practitioners, and non-nephrology specialists such as cardiologists and endocrinologists. As such, it is important to put the current recommendations into the context of other clinical practice recommendations for cholesterol treatment (Table 1). The recently published American College of Cardiology/American Heart Association (ACC/AHA) guideline focused on atherosclerotic cardiovascular disease (CVD) risk and with a few exceptions, did not use LDL cholesterol level as a guide for the initiation of treatment.[5] For individuals aged 50 to 75 years, the KDIGO guideline recommends treating more individuals with statins than the ACC/AHA guideline. The KDIGO guideline recommendation for treating all individuals with CKD who are older than 50 years in many respects is similar to the recommendation for adults older than 40 years with diabetes mellitus, a variant of the prior CHD risk equivalent. The ACC/AHA risk calculator is based on cohort studies and does not include CKD in the calculations. Individuals who are female or white tend to have lower predicted risks for CHD using this calculator. Many white women with CKD and controlled blood pressure (systolic blood pressure $\leq$ 140 mm Hg) would not meet the ACC/AHA current threshold of $\geq$7.5% estimated 10-year risk of atherosclerotic CVD for the consideration of statin treatment initiation. However, prior studies have shown that individuals with CKD who are older than 50 years have on average a predicted risk $\geq$ 7.5%.[6-9] The discrepancy between the ACC/AHA risk calculator and the observed risk in CKD may reflect decreased accuracy of the calculators in patients with CKD, although results of studies addressing this question have been mixed.[10-14] In contrast to those aged 50 to 75 years, there are some individuals aged 40 to 49 years who would be more likely to be treated under the ACC/AHA guideline because the threshold for treatment used by the KDIGO guideline is based on a higher risk level ($\geq$10% estimated 10-year CHD risk compared to $\geq$7.5% estimated 10-year atherosclerotic cardiovascular risk in the ACC/AHA guideline). In KDIGO, CHD includes coronary death and nonfatal myocardial infarction. The definition of atherosclerotic CVD in the ACC/AHA guideline is broader and, in addition to CHD, includes stroke and peripheral vascular disease. Another area in which there is a difference in treatment recommendations between the guidelines is treatment in individuals older than 75 years. KDIGO does not have an upper age limit for treatment recommendations. In contrast, the ACC/AHA guidelines recommend treating individuals older than 75 years who have atherosclerotic disease (secondary prevention), but do not recommend the use of statin therapy for primary prevention due to the lack of both clinical trial data and validated risk calculators in individuals older than 79 years. For individuals older than 75 years without a history of atherosclerotic CVD, the ACC/AHA guideline recommends weighing patient preferences and the risks and benefits before initiating statin therapy.

The KDIGO guideline did not compare or harmonize their recommendations to other lipid guidelines, which may lead to some confusion among practitioners. The strongest evidence for advising primary care and non-nephrology specialists to use the KDIGO guideline comes from SHARP.[4] SHARP enrolled individuals older than 40 years with a serum creatinine level $\geq$ 1.7 mg/dL in men and $\geq$1.3 mg/dL in women and a mean estimated glomerular filtration rate (eGFR) of 27 $\pm$ 13 (SD) mL/min/1.73 m^2. There is less trial evidence for individuals with CKD who do not meet entry criteria for SHARP and who would not fit into the CKD subgroup analyses of trials in non-nephrology populations. However, we would anticipate that these individuals would behave more like SHARP and general population participants than dialysis patients. To help other practitioners, we would recommend reconciling the guidelines or perhaps adjustment of the risk calculators.

An additional difference between the KDIGO guideline and the ACC/AHA guidelines is that the KDIGO guideline recommends reducing the dose of statins in individuals with an eGFR $<$ 60 mL/min/1.73 m^2 (ie, avoiding high-intensity statins; Table 2). This recommendation is based on reduced renal excretion (true for some statins) and increased polypharmacy and comorbidity, as well as the dose of statin used in trials in CKD. In the absence of studies showing adverse effects with higher doses of statins, this recommendation may also lead to confusion on the management of individuals with CKD and a history of acute coronary syndrome, for whom the recommendation is to treat with a high-intensity statin. The prescribing information for atorvastatin says that dose adjustment for kidney disease is not required and prescribing information for rosuvastatin does not recommend dose adjustment until creatinine clearance is $<$30 mL/min/1.73 m^2.

Table 1. Comparison of Guidelines for Lipids

	KDIGO[9]	ACC/AHA[5] (not CKD specific)	2014 ADA[61] (not CKD specific)	AACE[62] (not CKD specific)
LDL level required for treatment decision	Does not consider LDL in treatment decision	If CVD history, do not consider LDL; if LDL ≥ 190, treat; if LDL 70-189, depends on risk	LDL not used for treatment initiation, though there are target LDL levels on treatment	As part of risk assessment, recommend treat all adults at risk for CAD to reach optimal lipid values
Target LDL on treatment?	No	Reasonable to target 50% reduction if LDL ≥ 190, otherwise no	Without CVD, LDL < 100; with CVD, LDL < 70 is an option; can use reduction by 30%-40% as alternative target if on maximum statin	LDL < 100 with goal < 70 for very high risk, also targets HDL and triglycerides
Support combination pharmacologic therapy?	No	No	No	Yes if cholesterol markedly elevated and target not achieved with monotherapy, for mixed dyslipidemia, or to use lower doses of ≥2 drugs to decrease toxicity risk
Treatment of adults with DM (non-ESRD)	Treat all adults with statin or statin/ezetimibe (age 18-49 y: statin; age ≥ 50 y: statin or statin/ezetimibe)	Age 40-75 y: treat with statin; age 21-39 or >75 y: evaluate benefit vs risk and patient preferences (moderate- or high-intensity statin depending on CVD/risk)	Age > 40 y: treat with statin; age 18-39 y with CVD: few data but consider statin; age 18-39 y, no CVD: consider statin in addition to lifestyle if LDL remains > 100 or multiple risk factors	Treat to target lipid levels; statins drug of choice
Treatment of adults without DM (non-ESRD)	Age ≥ 50 y: treat with statin/ezetimibe; age 18-39 y: statin suggested if estimated 10-y incidence of coronary death or nonfatal MI > 10%	Age ≥ 21 y with CVD: treat (high or moderate intensity depending on age/tolerance); age 40-75 y, no CVD: treat if LDL 70-189 and 10-y ASCVD risk ≥ 7.5% (moderate- or high-intensity statin depending on CVD/risk); age 18-39 or >75 y without CVD: benefit uncertain, consider risk/benefit and patient preferences	Not applicable	If history of or at risk for CVD, treat to target LDL
Treatment of adults on dialysis[a]	Do not initiate, but continue statins if receiving at time of initiation of dialysis	Stated no recommendation as there was insufficient information for or against	Not discussed	Not discussed
Treatment of children	Do not initiate	AHA recommendations for children not revised with current update; prior AHA statement for high-risk pediatric patients (including CKD) recommends therapeutic lifestyle intervention; if age > 10 and LDL > 100 despite therapeutic lifestyle, treat with statin[43]	Age < 10 y: do not use statin; age ≥ 10 y: reasonable to consider statin if after diet and lifestyle changes, LDL > 160 or >130 with multiple risk factors (note only relevant to DM)	Recommend pharmacotherapy for age > 8 if do not respond sufficiently to lifestyle modifications, particularly if LDL ≥ 190 or ≥160 with risk factors

Note: LDL levels are reported in mg/dL.

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACC/AHA, American College of Cardiology/American Heart Association; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HDL, high-density lipoprotein; KDIGO, Kidney Disease: Improving Global Outcomes; LDL, low-density lipoprotein; MI, myocardial infarction.

[a]KDIGO recommends statin for all transplant recipients; this population was not discussed in the other guidelines.

Table 2. Recommended Doses of Statins in Adults

	ACC/AHA Recommendations for eGFR > 60 mL/min/1.73 m^2		KDIGO Recommendations for eGFR < 60 mL/min/1.73 m^2
	High-Intensity Statin	Moderate-Intensity Statin	
Atorvastatin	40-80 mg	10-20 mg	20 mg
Fluvastatin	—	80 mg	80 mg
Lovastatin	—	40 mg	Not studied
Pravastatin	—	40-80 mg	40 mg
Rosuvastatin	20-40 mg	5-10 mg	10 mg
Simvastatin	—[a]	20-40 mg	40 mg
Simvastatin/ezetimibe	—	Not mentioned in ACC/AHA guidelines	20 mg/10 mg

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

[a]Simvastatin, 80 mg, would be high intensity, but this is no longer recommended by the US Food and Drug Administration.

To assist US practitioners in interpreting and applying the KDIGO guideline, the NKF-KDOQI convened a work group to write a commentary. The structure of this commentary lists each KDIGO statement followed by a commentary from the work group. (Numbered text within horizontal rules is quoted directly from the KDIGO document, using the same numbering scheme as in the original; all material is reproduced with permission of KDIGO.) In addition, we have summarized our additional research recommendations in Box 1. Each of the KDOQI statements was discussed via teleconferences to determine areas of agreement and controversy. Sections were subsequently written by groups of co-authors and discussed on teleconferences to achieve consensus.

Lipid Measurement 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)*

Commentary

We agreed that this is a reasonable recommendation. In the KDIGO guideline, lipid levels are not intended to be used in guiding the decision to initiate pharmacologic treatment. The foundation for this recommendation is that dyslipidemia is common among patients with CKD and an initial evaluation will allow for the identification of hypercholesterolemia and hypertriglyceridemia. Additionally, measuring lipids provides information on secondary causes of dyslipidemia, including nephrotic syndrome, hypothyroidism, and diabetes mellitus. For patients with CKD younger than 50 years, lipids provide information on overall CVD risk that can be used to guide the decision to initiate statins. While this appears to contradict the statements above regarding LDL cholesterol level as a guide for treatment, it should be recognized that many risk calculators use lipid levels in determining risk for primary prevention. In addition, very high LDL cholesterol levels may be an indication for treatment with statins. While not commented on in the KDIGO guideline, LDL cholesterol $\geq$ 190 mg/dL is an indication for statins in the ACC/AHA guideline. The KDIGO guideline acknowledges the lack of evidence that measuring lipids will improve clinical outcomes. However, the harm associated with lipid measurement is low and the risk-benefit of lipid measurement is favorable. Routine measurement of lipoprotein(a), apolipoprotein B, and other lipid markers is not recommended as the value of these markers for guiding clinical decisions requires further study in patients with CKD.

Follow-up Lipid Measurements in Adults With CKD

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)*

Commentary

Although follow-up cholesterol measurements are not recommended in the KDIGO guideline, important caveats are provided. For example, the KDIGO guideline states that follow-up measurements of lipids may be useful for identifying low statin adherence. Low statin adherence is common and has been reported to occur in more than half the patients with CKD.[15] We agree that monitoring of LDL cholesterol following the initiation of statin therapy to identify individuals with low adherence is warranted. Alternate approaches (eg, validated questionnaires and confirming refills from the pharmacy) may also be used to monitor adherence both after initiation of statin therapy and for long-term statin users.[16,17]

Box 1. Additional Research Recommendations

Adults

- Evaluate accuracy of current risk calculators for CVD in CKD
- Evaluate whether calculators should incorporate albuminuria, estimated GFR, or both
- Develop CVD risk calculators for individuals aged 18-40 y with CKD
- Evaluate the utility of measuring lipoprotein(a), apolipoprotein B, and other markers of dyslipidemia in CKD
- Evaluate the degree to which low adherence prevents the expected reduction in LDL cholesterol associated with statin initiation among individuals with CKD
- Assess LDL cholesterol response to statins among patients with CKD
- Evaluate whether follow-up lipid measurements provide useful information
- Evaluate whether duration of disease, particularly pediatric onset, should be overtly considered in risk assessment and lipid treatment guidelines
- Randomized trials of fibrates in patients with CKD to clarify the benefits and risks of fibrates in this population
- Studies assessing the incidence of hypertriglyceridemia-induced pancreatitis and the burden of pancreatitis due to triglycerides > 1,000 mg/dL among both hemodialysis and peritoneal dialysis patients
- Observational studies and randomized trials of lipid treatment in peritoneal dialysis patients
- Randomized controlled trial of statin vs no statin in a representative US kidney transplant recipient population with primary end point of cardiovascular mortality and secondary end points of major adverse cardiovascular event, administered from time of transplantation
- Randomized controlled study of statin vs no statin in a representative US kidney transplant recipient population, stratified by level of cardiovascular risk factors, with primary end point of cardiovascular mortality and secondary end points of major adverse cardiovascular event, administered from time of transplantation

Pediatric

- Determine the association between lipids in childhood CKD with development of CVD many years later
- Develop risk calculators for CVD in pediatric CKD
- Obtain short-term primary pharmacokinetic/dynamic and drug safety data in children with reduced GFR, those with significant proteinuria, and those with kidney transplants
- Develop and validate surrogate outcomes for CVD in the pediatric population

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein.

However, there are additional reasons to consider measuring lipids following the initiation of statin therapy. Based on meta-analyses, moderate-intensity statins (ie, the intensity recommended by KDIGO) are associated with an average reduction in LDL cholesterol of 30%.[5,18] Therefore, many patients do not have a ≥30% reduction in LDL cholesterol following the initiation of statin therapy. As described in our discussion of KDIGO guideline recommendations 2.1.1 and 2.1.2 below, physicians may consider high-intensity statins for patients with CKD who already have (or are at very high risk for) atherosclerotic CVD and who are at lower risk of adverse side effects. An example of the latter may be the large group of patients with CKD with eGFRs of 45 to 59 mL/min/1.73 m^2, a subgroup who received a benefit from high-dose atorvastatin in the TNT (Treating to New Targets) trial.[19] In order to identify patients with a small response to moderate-intensity statin who may have their dose uptitrated, we believe that measuring LDL cholesterol 6 weeks to 3 months following the initiation of statin therapy should be considered. Once an adequate (≥30%) decline in LDL cholesterol is observed following the initiation of statin therapy, monitoring cholesterol will not discern within-person variability over time from true changes.[20] From this perspective, annual follow-up measurements of lipid levels are not useful.

For patients younger than 50 years with CKD, a high atherosclerotic CVD risk (Framingham risk > 10%) based on risk calculators is a key consideration in the decision to initiate statin therapy. Most CVD risk calculators incorporate total and high-density lipoprotein (HDL) cholesterol levels, necessitating the measurement of lipids.[21] Given the substantial within-person variation in components of risk scores, including total and HDL cholesterol, the value of updating a patient's CVD risk using follow-up lipid measurements is unclear. However, it is important to recognize that lipid levels may experience real changes over time in CKD due to disease progression or remission, introduction of immunosuppressive drugs, and development of malnutrition. Therefore, remeasurement of lipids may be warranted for some patients with CKD younger than 50 years.

We agreed with the research recommendations provided in the KDIGO report. Additionally, research is needed to evaluate the degree to which low adherence prevents the expected reduction in LDL cholesterol level associated with statin initiation among individuals with CKD. Other areas of research that may warrant future investigation are studies assessing LDL cholesterol response to statins among patients with CKD and studies of whether follow-up lipid measurements provide useful information (Box 1).

Statins and Adults Aged 50 or Older With CKD

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)*

Commentary

On average, individuals older than 50 years with CKD have a 10-year CHD risk > 10%, which suggests

that this is a high-risk population.[6,7] The recommendation to treat with a statin would be consistent with recommendations for high-risk individuals in the general population. In general, we agree with the recommendations but believe that a 1A grade is too strong. If we follow the practice of other guidelines, a 1A grade is not appropriate given the lack of multiple randomized studies or meta-analyses. SHARP is the only large randomized trial that focused on individuals with CKD, with a mean eGFR of 27 mL/min/1.73 m^2 in that population.[4] There are subgroup analyses evaluating CKD in a number of other large treatment trials[22]; however, because of the inclusion criteria in these trials, most individuals with CKD had stage 3a (eGFR of 45-59 mL/min/1.73 m^2). Given that only one randomized controlled trial has included adults with stages 3 and 4 CKD, we believe a 1B grade is more consistent with ACC/AHA guideline criteria, as well as the current level of data. We agree with the recommendation that either a statin or a statin/ezetimibe combination can be used. Although the combination was used in SHARP, the totality of evidence from general population studies suggests that it is the statin that is primarily providing benefit. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), an ongoing study comparing simvastatin and simvastatin/ezetimibe in individuals with acute coronary syndrome, might help clarify the question of whether LDL cholesterol lowering with statin plus ezetimibe reduces risk versus statin monotherapy.

In individuals with CKD and eGFR $<$ 60 mL/min/1.73 m^2 who are not kidney transplant recipients, the KDIGO work group suggests using doses of statins recommended in the general population (Table 2). In the general population, a high-intensity statin is recommended in individuals with CVD or at very high risk for CVD. Due to concerns of increased toxicity, dose reduction of statins was recommended by KDIGO for individuals with an eGFR $<$ 60 mL/min/1.73 m^2. Given the positive benefit of high-dose atorvastatin in individuals in the TNT Trial,[19] one might consider using general population doses for individuals with GFR category G3a (45-59.9 mL/min/1.73 m^2) or even a high-intensity statin in individuals with acute coronary syndrome and lower eGFR unless there are significant drug interactions with concomitant medications.

Statins and Adults in GFR Categories G1-G2

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)*

Commentary

This guideline refers to both individuals with albuminuria as the marker of kidney damage and individuals with other manifestations of CKD, including polycystic kidney disease and nonurologic hematuria. Treatment recommendations should be based on both the underlying risk and published evidence that treatment decreases this risk.

Individuals older than 50 years with albuminuria, the most common marker identifying structural CKD in those with eGFR ≥ 60 mL/min/1.73 m^2, are at increased risk of CHD events.[7,23] However, there are no randomized trials indicating that statin treatment of this population decreases the risk of CHD. Albuminuria is not typically identified in clinical lipid trials and these individuals are generally incorporated into the general population. In the CARE (Cholesterol and Recurrent Events) Study, individuals with proteinuria (protein excretion ≥ 1+, which would correspond to albuminuria with albumin excretion $>$ 300 mg/g or albuminuria classification A3 in the new KDIGO classification[24]) had a greater risk of cardiovascular events, but data were not provided on the treatment effect of statins on the event rate in this subgroup.[25] In CARDS (Collaborative Atorvastatin Diabetes Study), treatment with atorvastatin in individuals with albuminuria decreased the risk of cardiovascular events (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.36-0.99)[26]; however, the report did not stratify the group with albuminuria by baseline eGFR and it is not appropriate to extrapolate directly to those with eGFR $>$ 60 mL/min/1.73 m^2. Furthermore, CARDS took place in individuals with diabetes mellitus who would meet criteria for therapy in the ACC/AHA guideline irrespective of level of albuminuria. PREVEND IT (Prevention of Renal and Vascular Endstage Disease Intervention Trial) was a 2 × 2 study of fosinopril/placebo and pravastatin/placebo in individuals with moderately increased albuminuria (albumin-creatinine ratio of 30-300 mg/g; category A2) and preserved creatinine clearance.[27] Pravastatin did not decrease the risk of cardiovascular events (HR, 0.87; 95% CI, 0.49-1.57). Without trial data for those with preserved eGFR and albuminuria, we would recommend that this population be treated according to the guidelines for the general population. Many of these individuals would meet treatment criteria using the current ACC/AHA guidelines. What is less clear is what proportion of individuals older than 50 years with eGFR ≥ 60 mL/min/1.73 m^2 with albuminuria would not meet general population criteria for treatment. In the absence of trial data, one would need to be cautious in extrapolating benefit of treatment: therefore, we would favor using the general population recommendations for those older than 50 years with CKD and eGFR ≥ 60 mL/min/1.73 m^2. A research recommendation would be the development of a risk predictor

that assesses whether albuminuria should be incorporated into the risk assessment (Box 1).

In individuals with CKD that is not due to albuminuria, we also favor using general population recommendations given the lack of randomized controlled data in these populations.

Statins and Adults Younger Than 50 With CKD

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%

Commentary

Adults with clinical atherosclerotic CVD should receive a moderate- or high-intensity statin regardless of age or CKD status. KDIGO includes known CHD or prior ischemic stroke, though one could also consider the broader definition of the ACC/AHA guidelines that includes angina, other atherosclerotic revascularization (eg, lower extremity), transient ischemic attack, or atherosclerotic peripheral arterial disease. Among diabetic patients, statins decrease the risk of cardiovascular events in those older than 40 years; in the ACC/AHA guideline, this group is identified as one of the major subgroups for which the benefit of statin clearly outweighed the risk. The treatment benefit in adults with diabetes mellitus younger than 40 years without clinical atherosclerotic disease is less clear, though generally recommended, especially if other risk factors are present. Therefore, the treatment recommendation in KDIGO is reasonable.

The age cutoff used in KDIGO guideline recommendations 2.1 and 2.2 is 50 years. However, there may be significant differences in risk between age 40 to 50 and younger than 40 years. SHARP[4] enrolled individuals 40 years and older and it would be most consistent with that trial to treat individuals with CKD between 40 and 49 years who have an eGFR < 60 mL/min/1.73 m^2 with a statin or statin/ezetimibe. KDIGO suggested treatment in individuals younger than 50 years if the 10-year risk estimate for CHD is >10%. We agree that this is a reasonable approach, but clinical application of this recommendation may be difficult. A practical question is whether there are accurate prediction equations for estimating risk in individuals with CKD, especially those younger than 40 years (including those with childhood onset of CKD, as discussed below). The current ACC/AHA risk calculator has not been validated in individuals younger than 40 years. We therefore would suggest an additional research recommendation of development of validated risk calculators in CKD for younger individuals, though we recognize that such studies would require a very large sample size and there are no treatment studies in this population. We recognize that we have not mentioned risk calculators for patients older than 50 years. This is for 2 reasons. First, although there are risk calculators for those older than 50 years, their accuracy in CKD is controversial. Second, use of the calculator would not affect therapy if one follows the KDIGO recommendation.

As mentioned earlier, while the recent ACC/AHA guidelines do not focus on LDL cholesterol, they recommend treatment with a statin if LDL cholesterol level is ≥190 mg/dL regardless of other risk factors. This is not addressed in the current KDIGO lipid guideline. This may be most relevant to younger adults with nephrotic syndrome. Individuals with significant proteinuria often have high levels of LDL cholesterol and increased cardiovascular risk.[28] Given the lack of clinical trials of lipid-lowering agents in individuals with nephrotic syndrome, it might be prudent to follow the ACC/AHA guidelines and treat individuals with a statin if they have LDL cholesterol ≥ 190 mg/dL, especially if nephrotic syndrome is not responsive to therapy and the course is prolonged. This could lead to treatment of younger individuals with CKD who do not currently meet treatment recommendations based on risk calculators.

Initiation of Statin Treatment in Dialysis Patients

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

Commentary

Given that CVD is the leading cause of death in dialysis patients and statins have been shown to lower the risk of CVD in the general population, use of statin therapy in patients treated by dialysis has been of considerable interest. However, several large studies such as AURORA and 4D have not shown a benefit of statin therapy in reducing cardiovascular events in hemodialysis patients.[2,3] It needs to be acknowledged that the follow-up period of these trials was relatively short and benefits in theory may take a longer time to accrue. SHARP showed a benefit of statin/ezetimibe therapy in the overall study population, but not in the subgroup of patients receiving dialysis.[4] Given the totality of evidence (2 negative trials in dialysis) and the absence of benefit in the

dialysis subgroup in SHARP, we agree that for most hemodialysis patients, initiation of statin or statin/ezetimibe therapy is not indicated.

There are also several caveats that need to be considered in the implementation of this guideline. First, patients with a recent acute coronary event were typically excluded from clinical trials and may be considered for statin therapy. Similarly, patients who are young, are on a kidney transplant list, and have long life expectancy should be considered for statin use. The guidelines create some inconsistency as a clinician takes care of an individual: first recommending statin therapy during CKD, not recommending initiation during dialysis, and then recommending it again after the patient receives a kidney transplant. Finally, previous trials in dialysis patients have focused on hemodialysis patients. Additional research is needed in peritoneal dialysis patients, and individual decision making, incorporating risks and benefits, needs to be evaluated in peritoneal dialysis patients (Box 1).

Continuation of Statin Treatment in Dialysis Patients

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)*

Commentary

This recommendation is weak given the lack of data regarding statin therapy in incident dialysis patients. We agree that it is reasonable to continue statins in incident dialysis patients given that a significant percentage of patients in SHARP reached end-stage renal disease (ESRD) and those randomly assigned to a statin/ezetemibe had a benefit. It would be informative to know the events pre- and post-dialysis by randomly assigned group in SHARP, but these data have not been published.

However, it is important to recognize that neither guideline statement 2.3.1 nor 2.3.2 specifically addresses whether statin use should be continued in prevalent dialysis patients. In principle, these patients may have started statin treatment during an earlier stage of CKD or alternatively when they were already on dialysis therapy. Should these 2 groups of patients be treated differently? Clearly, we do not have the data to answer these questions, but we would recommend continuing therapy in those who are already on it. The guideline appropriately discusses personalizing treatment decisions based on the risk-benefit estimation and including patient preferences into individual decision making. Given the paucity of data in this setting, this seems to be a reasonable approach.

Statin Treatment for Kidney Transplant Recipients

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

Commentary

The incidence and prevalence of dyslipidemia is high in kidney recipients, partly due to immunosuppressive agents such as mammalian target-of-rapamycin inhibitors (sirolimus and everolimus), corticosteroids, and calcineurin inhibitors (cyclosporine A and tacrolimus), as well as other factors, including proteinuria, transplant dysfunction, and the comorbidities of obesity, diabetes mellitus, and metabolic syndrome.[29-31] Observational studies suggest that dyslipidemia is independently associated with cardiovascular events in this population.[29,31]

NKF-KDOQI initially published a guideline[32] for evaluating and treating dyslipidemia in kidney transplant recipients in 2004; these recommendations were largely endorsed by the KDIGO clinical practice guideline for care of the kidney transplant recipient, published in 2009.[33] The KDIGO guideline recommended treatment of dyslipidemia to reduce cardiovascular risk based on strong evidence in general population studies with little reason to believe that treatment would not be safe and effective in kidney recipients, as well as the fact that the dyslipidemia prevalence is high enough to warrant screening and intervention. The major study underpinning this recommendation was the ALERT (Assessment of Lescol in Renal Transplantation) trial[34] and its extension component.[35]

ALERT, a randomized controlled trial, noted that treatment with fluvastatin nonsignificantly reduced major adverse cardiac events, the primary end point. Secondary end points, including mortality, were decreased by fluvastatin, and an unblinded extension study suggested that major adverse cardiac events were attenuated in the long term. The KDIGO lipid guideline work group considered that the apparent benefits observed in ALERT are consistent with the effects of statins in the general population and suggests that statins offer benefit to kidney transplant recipients with a functioning transplant. We agree with this weakly graded recommendation and the underlying rationale.

We also considered that among its shortcomings, ALERT: (1) was underpowered for a primary prevention study (n = 2,106 compared, eg, to n = 6,605 in a general population study such as the Air Force/Texas Coronary Atherosclerosis Prevention Study)[36]; (2) was conducted in patients in Western Europe, Scandinavia, and Canada with a relatively low cardiovascular risk profile (eg, 13% with diabetes mellitus as a cause of ESRD), limiting generalizability to more ethnically and racially heterogeneous US kidney

recipients (23% with diabetes mellitus as cause of ESRD[37]); and (3) excluded many patients with preexisting CHD because of preceding statin use or recent myocardial infarction, so that only 3% of study participants had a history of myocardial infarction. Taking these important limitations into consideration, we believe that US kidney recipients are a higher cardiovascular risk group overall than ALERT participants and that it is very possible that statins would reduce cardiovascular events if a randomized controlled trial with this drug class was conducted in this population (Box 1). Unfortunately, it is unlikely that this will take place in the foreseeable future.

Although not addressed by the KDIGO work group, we also believe it is necessary to emphasize that calcineurin inhibitors may potentiate the toxicity of statins by slowing their metabolism via the cytochrome P450 system. Both tacrolimus and cyclosporine are known to inhibit the CYP3A4 enzyme in vitro; however, studies suggest that cyclosporine has a stronger inhibitory effect compared to tacrolimus.[38,39] Cyclosporine also has a dominant inhibitory effect on OATP1B1, a liver-specific statin transporter.[40] By blocking entry into hepatocytes, it results in higher systemic levels of statins. Because the potential for adverse drug interaction is greater with cyclosporine than with tacrolimus, this has implications when considering the starting statin dose and especially when converting from one calcineurin inhibitor to another. Because there are no studies to guide statin dosing in these specific settings, we recommend initiating statin therapy at low doses, with cautious uptitration both as indicated and as tolerated, especially in cyclosporine-treated patients. When switching from tacrolimus to cyclosporine, we would suggest reducing the statin dose at the time of conversion, followed by lipid monitoring and appropriate statin-dose adjustment over the next several months. Dyslipidemia frequently complicates mammalian target-of-rapamycin inhibitor use, and lipid-lowering therapy is required in most patients receiving these agents.[41]

Lipid Measurement 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)*

Commentary

We agree with this statement and note that it agrees in large part with recommendations from the American Academy of Pediatrics, National Heart, Lung, and Blood Institute (NHLBI), and AHA.[42,43] Routine lipid screening is recommended even for healthy children by age 9 to 11 years and again at age 18 to 21 years. Lipid screening is used to identify primary or familial dyslipidemia (which could co-exist with CKD), additional secondary causes of dyslipidemia, or extreme dyslipidemia in children with CKD, most typically in children with nephrotic syndrome. The statement is also consistent with the adult guideline recommendation 1.2.

Follow-up Lipid Measurements in Children With CKD

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)*

Commentary

Noting that the statement is not consistent with the adult guideline 1.2, we agree there is insufficient evidence to make a graded statement on this matter and there are points both for and against this approach. As discussed with respect to the adult guideline recommendation, we believe there are frequently clinical reasons to recheck the lipid profile. Examples include extreme levels at a previous check, significant change in eGFR or proteinuria, or if medication changes have been made that are likely to alter the lipid profile. However, we acknowledge that for most individuals, the risk profile is unlikely to change over short periods. Further, the short-term risk of atherosclerotic CVD events remains exceptionally low throughout childhood (even in the setting of ESRD) and indications for treatment have not been defined in younger individuals with CKD with dyslipidemia (see below). Thus, the argument against yearly measurement would seem most salient if a screening evaluation of lipids does not reveal values that would lead to treatment.

Statins and Children With CKD

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)*

Commentary

We agree with this statement with minor modification. While the guidelines state that therapeutic lifestyle changes should be advised for all children with CKD, we note that children with CKD often experience poor growth and we therefore suggest that therapeutic lifestyle changes specifically directed to reduce cholesterol intake should be reserved for children with non-HDL cholesterol $>$ 145 mg/dL or LDL cholesterol $>$ 130 mg/dL or those who are overweight. Adequate physical activity and attention to a healthy diet is a recommendation that is

congruent with the previously mentioned general pediatric recommendations for healthy children.

For the more difficult issue of statin/ezetimibe treatment in children, there are a number of unanswered questions. The most important issue relates to the likelihood of CKD progression and the lifetime risk of CVD. It may also not be correct to group all pediatric CKD together because children and teens with CKD due to chronic glomerular disease face a greater degree of risk factors (proteinuria, dyslipidemia, and hypertension) for any given GFR.[44]

In children with CKD, progression is likely, and considering atherosclerosis as a long-term complication, it may be appropriate to visualize the lifetime trajectory of the particular child, teen, or young adult and assess cumulative risk exposures as they age. Half the children with eGFR < 75 mL/min/1.73 m^2 reach ESRD in only 5 years, and 70%, in 10 years.[45,46] Likewise, most children with ESRD "progress" to transplantation: by 1 year after identification of ESRD, >50% of children receive a kidney transplant.[46] Thus, pediatric CKD should be regarded as a disease sequence "CKD-ESRD" in which long-term complications develop while moving through the stages of CKD and renal replacement therapies.

While children with CKD are low risk during childhood, they can be anticipated to have many years of exposure to the adverse cardiovascular effects of CKD. Thus, while severe complications take many years to develop, they occur at relatively young ages in the individuals who had childhood CKD. The expected remaining lifetime after ESRD in the 0- to 14-year age group is only about 30 years, and total life expectancy is similar for those who reach ESRD as young adults (Fig 1), with the leading cause of death being CVD.[46-51] The life expectancy of the youngest individuals with ESRD is less than the age cut point used in recommendations 2.1.1 and 2.1.2.

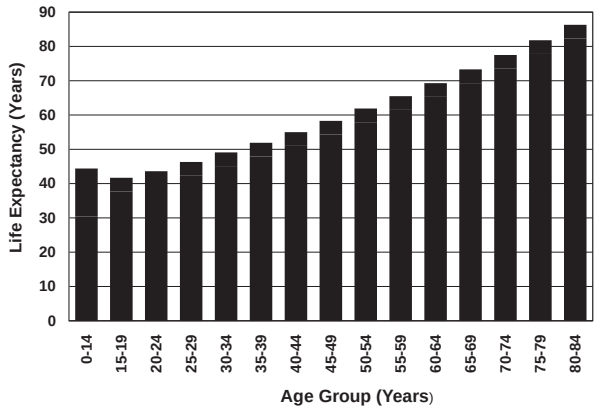

Figure 1. Life expectancy after development of end-stage renal disease by age. Derived from US Renal Data System data.[48]

Accordingly, we suggest a research recommendation evaluation of whether duration of disease, particularly pediatric onset, should be overtly considered in risk assessment and lipid treatment recommendations (Box 1).

Recommendations for treatment of adults rest on the evidence for CVD prevention. Vascular disease events are uncommon in children, there are no clinical CVD prevention studies in this age group, and the evidence to support aggressive interventions is weak. If dyslipidemia led more quickly to adverse outcomes or there were adequate surrogate markers for clinical outcomes, treatment studies would be easier and the evidence for or against treatment could be strengthened. For example, treatment of hypertension in children is well accepted, likely because changes in cardiac structure are clearly related to hypertension and treatment of hypertension reduces these surrogates.[42,43,52,53] While there are data suggesting an association of lipids with increased carotid intima media thickness in a subset of children in the CKiD (CKD in Children Cohort) Study,[54] there have been no trials of lipid treatment with either clinical outcomes or surrogate outcomes in this population. Therefore, additional trials incorporating both accepted surrogates and clinical outcomes are needed (Box 1).

Besides the weaker foundation for the benefit of treatment, there are important considerations that prohibit a recommendation to treat with statins or ezetimibe, beginning with the lack of simple pharmacokinetic and safety studies of these agents in this population. There are virtually no data for children younger than 10 years. Pediatric labeling in the United States is based on short-term studies in children older than 10 years with heterozygous familial hypercholesterolemia (HeFH). However, multiple pathophysiologic differences exist between HeFH with its singular issue of hypercholesterolemia in comparison to CKD with its multiplicity of abnormalities and complications, including low GFR, heavy proteinuria, and polypharmacy, which might affect pharmacologic parameters.[55] HeFH is the only subgroup for whom the American Diabetes Association, American Association of Clinical Endocrinologists, AHA, NHLBI, and American Academy of Pediatrics recommend treatment with a statin in individuals as young as 8 years. We would also recommend caution in assuming that dosing and safety can be inferred from adult patients with CKD. An additional concern that does not appear to have been addressed is whether there is a safe lower limit for cholesterol during growth and puberty, and whether short-term studies in teens with HeFH (with much higher cholesterol levels than seen in most with CKD) can be extrapolated to those with CKD. Finally, the work group is not aware of studies

evaluating whether the beneficial effects of statins or ezetimibe increase over time or reach a plateau at some point. For example, for an individual whose cardiovascular events are likely to occur 25 to 30 years in the future, it is not known whether treatment for 25 years is "better" than treatment for 10 or 15 years.

Therapeutic Lifestyle Changes in Adults With CKD

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)*

Commentary

We agreed that it is a reasonable recommendation to advise therapeutic lifestyle changes for adults with CKD and hypertriglyceridemia. While the benefits of therapeutic lifestyle changes on outcomes for individuals with CKD and hypertriglyceridemia are not clear, they may improve overall health, and the risk for harm with therapeutic lifestyle changes is minimal.

Additionally, we agreed with the recommendation that fibrates not be used in the population with high triglyceride levels and CKD. Most randomized trials have excluded individuals with more advanced CKD (eg, eGFR < 45 mL/min/1.73 m^2) and thus data about the risks and benefits of fibrates in patients with CKD are limited. Where fibrates may have a role is in patients who do not tolerate statins. In a meta-analysis of 2 studies with 918 individuals with eGFR of 30 to 59 mL/min/1.73 m^2, a reduced risk for CVD events and CVD death but not all-cause mortality was observed for those randomly assigned to fibrate treatment versus placebo.[56] However, fibrates were associated with an acute reduction in eGFR in this meta-analysis. Additionally, the concurrent use of statins and fibrates raises the risk for rhabdomyolysis, and the combination should not be used in CKD.[57] Also, in a large observational study, fibrate use was associated with an increased risk for hospitalization due to an increase in serum creatinine level and nephrologist consultation within 90 days of initiation.[58] This excess risk was magnified for patients with CKD. If fibrates are used in patients with CKD who are intolerant of statins, dosing to avoid myalgia is important. Fenofibrate is contraindicated in individuals with eGFR < 30 mL/min/1.73 m^2, and there are not much data about the safety of gemfibrozil in patients with advanced CKD.

We agree with the research recommendations provided in the KDIGO guideline. Randomized trials of fibrates in patients with CKD are needed to clarify the benefits and risks of fibrates in this population. Other areas of research that may warrant future investigation are studies assessing the incidence of hypertriglyceridemia-induced pancreatitis and the burden of pancreatitis due to triglycerides $>$ 1,000 mg/dL among both hemodialysis and peritoneal dialysis patients (Box 1).

Therapeutic Lifestyle Changes in Children With CKD

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

Commentary

The work group agrees with this statement and notes it is consistent with adult guideline recommendation 5.1. It is valuable to point out that therapeutic lifestyle changes in both adults and children should not imply that hypertriglyceridemia is limited to the overweight in CKD. While obesity and insulin resistance exacerbate hypertriglyceridemia, this derangement in CKD is likely related as much or more to impaired metabolism of triglycerides as to dietary excess.[59,60]

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REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis*. 2003;41(4)(suppl 3):I-IV, S1-S91.

2. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353(3):238-248.

3. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360(14):1395-1407.

4. 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(9784):2181-2192.

5. 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: a report of the

American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2): S1-S45.

6. Debella YT, Giduma HD, Light RP, Agarwal R. Chronic kidney disease as a coronary disease equivalent—a comparison with diabetes over a decade. *Clin J Am Soc Nephrol*. 2011;6(6): 1385-1392.

7. Tonelli M, Muntner P, Lloyd A, et al. Impact of age on the association between CKD and the risk of future coronary events. *Am J Kidney Dis*. 2014;64(3):375-382.

8. Wanner C, Tonelli M. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85(6): 1303-1309.

9. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid managment in chronic kidney disease. *Kidney Int Suppl*. 2013;3: 259-305.

10. Chang A, Kramer H. Should eGFR and albuminuria be added to the Framingham risk score? Chronic kidney disease and cardiovascular disease risk prediction. *Nephron Clin Pract*. 2011;119(2):c171-c177; discussion c177-c178.

11. Drawz PE, Baraniuk S, Davis BR, et al. Cardiovascular risk assessment: addition of CKD and race to the Framingham equation. *Am Heart J*. 2012;164(6):925-931, e922.

12. Nishimura K, Okamura T, Watanabe M, et al. Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the Framingham risk score: the Suita Study. *J Atheroscler Thromb*. 2014;21(8):784-798.

13. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol*. 2007;50(3):217-224.

14. Weiner DE, Tighiouart H, Griffith JL, et al. Kidney disease, Framingham risk scores, and cardiac and mortality outcomes. *Am J Med*. 2007;120(6):552.e1-552.e8.

15. Chang TI, Desai M, Solomon DH, Winkelmayer WC. Kidney function and long-term medication adherence after myocardial infarction in the elderly. *Clin J Am Soc Nephrol*. 2011;6(4):864-869.

16. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. *Curr Opin Cardiol*. 2004;19(4):357-362.

17. Dunbar-Jacob J, Sereika SM, Houze M, Luyster FS, Callan JA. Accuracy of measures of medication adherence in a cholesterol-lowering regimen. *West J Nurs Res*. 2012;34(5): 578-597.

18. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.

19. Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) Study. *J Am Coll Cardiol*. 2008;51(15):1448-1454.

20. Glasziou PP, Irwig L, Heritier S, Simes RJ, Tonkin A. Monitoring cholesterol levels: measurement error or true change? *Ann Intern Med*. 2008;148(9):656-661.

21. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2935-2959.

22. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2014;5: CD007784.

23. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012;308(22):2349-2360.

24. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1-150.

25. Tonelli M, Jose P, Curhan G, Sacks F, Braunwald E, Pfeffer M. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ*. 2006;332(7555):1426.

26. 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(5):810-819.

27. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation*. 2004;110(18):2809-2816.

28. Kronenberg F. Dyslipidemia and nephrotic syndrome: recent advances. *J Ren Nutr*. 2005;15(2):195-203.

29. Diaz JM, Gich I, Bonfill X, et al. Prevalence evolution and impact of cardiovascular risk factors on allograft and renal transplant patient survival. *Transplant Proc*. 2009;41(6):2151-2155.

30. Phillips S, Heuberger R. Metabolic disorders following kidney transplantation. *J Ren Nutr*. 2012;22(5):451-460. e451.

31. Vanrenterghem YF, Claes K, Montagnino G, et al. Risk factors for cardiovascular events after successful renal transplantation. *Transplantation*. 2008;85(2):209-216.

32. Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant*. 2004;(4)(suppl 7):13-53.

33. Kasiske BL, Zeier MG, Craig JC, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(suppl 3):S1-S155.

34. 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(9374):2024-2031.

35. Jardine AG, Fellstrom B, Logan JO, et al. Cardiovascular risk and renal transplantation: post hoc analyses of the Assessment of Lescol in Renal Transplantation (ALERT) Study. *Am J Kidney Dis*. 2005;46(3):529-536.

36. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615-1622.

37. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). *OPTN/SRTR 2011 Annual Data Report*. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012.

38. Lemahieu WP, Maes BD, Verbeke K, Vanrenterghem Y. CYP3A4 and P-glycoprotein activity in healthy controls and transplant patients on cyclosporin vs. tacrolimus vs. sirolimus. *Am J Transplant*. 2004;4(9):1514-1522.

39. Lemahieu WP, Hermann M, Asberg A, et al. Combined therapy with atorvastatin and calcineurin inhibitors: no interactions with tacrolimus. *Am J Transplant*. 2005;5(9):2236-2243.

40. Shitara Y, Takeuchi K, Nagamatsu Y, Wada S, Sugiyama Y, Horie T. Long-lasting inhibitory effects of cyclosporin A, but not tacrolimus, on OATP1B1- and OATP1B3-mediated uptake. *Drug Metab Pharmacokinet*. 2012;27(4):368-378.

41. Sayin B, Karakayali H, Colak T, et al. Conversion to sirolimus for chronic allograft nephropathy and calcineurin inhibitor toxicity and the adverse effects of sirolimus after conversion. *Transplant Proc*. 2009;41(7):2789-2793.

42. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213-S256.

43. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114(24):2710-2738.

44. Wilson AC, Schneider MF, Cox C, et al. Prevalence and correlates of multiple cardiovascular risk factors in children with chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(12):2759-2765.

45. Ardissino G, Dacco V, Testa S, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. *Pediatrics*. 2003;111(4, pt 1):e382-e387.

46. Smith JM, Stablein DM, Munoz R, Hebert D, McDonald RA. Contributions of the Transplant Registry: the 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). *Pediatr Transplant*. 2007;11(4):366-373.

47. Collins AJ, Foley RN, Chavers B, et al. US Renal Data System 2013 annual data report. *Am J Kidney Dis*. 2014;63(1)(suppl 1):e1-e420.

48. US Renal Data System. USRDS 2007 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (includes Special Request, Table H.13 Combined Transplant and Dialysis Groups). USRDS Coordinating Center UR. http://www.usrds.org. Accessed August 7, 2008.

49. Groothoff JW, Gruppen MP, Offringa M, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. *Kidney Int*. 2002;61(2):621-629.

50. Gruppen MP, Groothoff JW, Prins M, et al. Cardiac disease in young adult patients with end-stage renal disease since childhood: a Dutch cohort study. *Kidney Int*. 2003;63(3):1058-1065.

51. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. *N Engl J Med*. 2004;350(26):2654-2662.

52. Kupferman JC, Aronson Friedman L, Cox C, et al. BP control and left ventricular hypertrophy regression in children with CKD. *J Am Soc Nephrol*. 2014;25(1):167-174.

53. Kupferman JC, Paterno K, Mahgerefteh J, et al. Improvement of left ventricular mass with antihypertensive therapy in children with hypertension. *Pediatr Nephrol*. 2010;25(8):1513-1518.

54. Brady TM, Schneider MF, Flynn JT, et al. Carotid intima-media thickness in children with CKD: results from the CKiD Study. *Clin J Am Soc Nephrol*. 2012;7(12):1930-1937.

55. Appel-Dingemanse S, Smith T, Merz M. Pharmacokinetics of fluvastatin in subjects with renal impairment and nephrotic syndrome. *J Clin Pharmacol*. 2002;42(3):312-318.

56. Jun M, Zhu B, Tonelli M, et al. Effects of fibrates in kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2012;60(20):2061-2071.

57. Molitch ME. Management of dyslipidemias in patients with diabetes and chronic kidney disease. *Clin J Am Soc Nephrol*. 2006;1(5):1090-1099.

58. 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(8):560-569.

59. Vaziri ND. Causes of dysregulation of lipid metabolism in chronic renal failure. *Semin Dial*. 2009;22(6):644-651.

60. Saland JM, Ginsberg HN. Lipoprotein metabolism in chronic renal insufficiency. *Pediatr Nephrol*. 2007;22(8):1095-1112.

61. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

62. Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis: executive summary. *Endocr Pract*. 2012;18(2):269-293.