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KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

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KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

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Additional information in the form of supplementary materials can be found online at http://www.kdigo.org/home/guidelines/lipids

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Theodor Vogels, MSW
Angela Yee-Moon Wang, MD, PhD, FRCP
Christoph Wanner, MD
Elena Zakharova, MD, PhD

NKF-KDIGO GUIDELINE DEVELOPMENT STAFF

Kerry Willis, PhD, Senior Vice-President for Scientific Activities

Michael Cheung, MA, Guideline Development Director

Sean Slifer, BA, Guideline Development Manager

Reference Keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy-makers**
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	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.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding 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.

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.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

Parameter	Conventional unit	Conversion factor	SI units
Cholesterol (total, HDL-C, LDL-C)	mg/dl	0.0259	mmol/l
Creatinine (serum, plasma)	mg/dl	88.4	μmol/l
Triglycerides (serum)	mg/dl	0.0113	mmol/l

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Note: Conventional unit × conversion factor = SI unit.

Abbreviations and Acronyms

4D	Die Deutsche Diabetes Dialyse Studie
ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
AGREE	Appraisal of Guidelines for Research and Evaluation
ALERT	Assessment of Lescol in Renal Transplantation trial
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ALLIANCE	Aggressive Lipid Lowering Initiation Abates New Cardiac Events trial
ApoB	Apolipoprotein B
ASPEN	Atorvastatin as Prevention of Coronary Heart Disease Endpoints in Patients with Non-Insulin-Dependent Diabetes Mellitus trial
ASSIGN	ASSessing cardiovascular risk using SIGN guidelines
ATP	Adult Treatment Panel
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events trial
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children study
COGS	Conference on Guideline Standardization
CPG	Clinical practice guideline
CVD	Cardiovascular disease
DAIS	Diabetes Atherosclerosis Intervention Study
eGFR	Estimated glomerular filtration rate
ERT	Evidence review team
ESRD	End-stage renal disease
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes trial
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HD	Hemodialysis
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
IDEAL	Incremental Decrease in Endpoints Through Aggressive Lipid Lowering trial
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MI	Myocardial infarction
NKF	National Kidney Foundation
PDAY	Pathobiological Determinants of Atherosclerosis in Youth study
PICODD	Population, Intervention, Comparator, Outcome, study Design and Duration of follow-up
PREVEND IT	Prevention of REnal and Vascular ENdstage Disease Intervention Trial
PROCAM	Prospective Cardiovascular Münster
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk trial
PROVE IT	Pravastatin or Atorvastatin in Evaluation and Infection Therapy trial
QRISK2	QRISK cardiovascular disease risk algorithm version 2
RCT	Randomized controlled trial
RR	Relative risk
SCORE	Systematic Coronary Risk Evaluation Project
SCr	Serum creatinine
SEARCH	Study Evaluating Additional Reductions in Cholesterol and Homocysteine
SHARP	Study of Heart and Renal Protection trial
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial
TC	Total cholesterol
TG	Triglyceride
TLC	Therapeutic lifestyle changes
TNT	Treating to New Targets trial
VA-HIT	Veterans' Affairs high-density lipoprotein intervention trial

Notice

Kidney International Supplements (2013) **3,** 259; doi:10.1038/kisup.2013.27

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon systematic literature searches last conducted in August 2011, supplemented with additional evidence through June 2013. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirely at the end of this document in the Work Group members' Biographic and Disclosure Section, and is kept on file at KDIGO.

Foreword

Kidney International Supplements (2013) **3,** 260; doi:10.1038/kisup.2013.28

It is our hope that this document will serve several useful purposes. Our primary goal is to improve patient care. We hope to accomplish this, in the short term, by helping clinicians know and better understand the evidence (or lack of evidence) that determines current practice. By providing comprehensive evidence-based recommendations, this guideline will also help define areas where evidence is lacking and research is needed. Helping to define a research agenda is an often neglected, but very important, function of clinical practice guideline development.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence and the strength of recommendations. In all, there were 3 (27.3%) recommendations in this guideline for which the overall quality of evidence was graded 'A,' whereas 2 (18.2%) were graded 'B,' 4 (36.4%) were graded 'C,' and 2 (18.2%) were graded 'D.' Although there are reasons other than quality of evidence to make a grade 1 or 2 recommendation, in general, there is a correlation between the quality of overall evidence and the strength of the recommendation. Thus, there were 4 (36.4%) recommendations graded '1' and 7 (63.6%) graded '2.' There was 1 (9.1%) recommendation graded '1A,' 1 (9.1%) was '1B,' 2 (18.2%) were '1C,' and no '1D' recommendations. There were 2 (18.2%) recommendations graded '2A,' 1 (9.1%) were '2B,' 2 (18.2%) were '2C,' and 2 (18.2%) were '2D.' There were 2 (15.4%) statements that were not graded.

Some argue that recommendations should not be made when evidence is weak. However, clinicians still need to make decisions in their daily practice, and they often ask, "What do the experts do in this setting?" We opted to give guidance, rather than remain silent. These recommendations are often rated with a low strength of recommendation and a low quality of evidence, or were not graded. It is important for the users of this guideline to be cognizant of this (see Notice). In every case these recommendations are meant to be a place for clinicians to start, not stop, their inquiries into specific management questions pertinent to the patients they see in daily practice.

We wish to thank the Work Group Co-Chairs, Drs. Marcello Tonelli and Christoph Wanner, along with all of the Work Group members who volunteered countless hours of their time developing this guideline. We also thank the Evidence Review Team members and staff of the National Kidney Foundation who made this project possible. Finally, we owe a special debt of gratitude to the many KDIGO Board members and individuals who volunteered time reviewing the guideline, and making very helpful suggestions.

Bertram L Kasiske, MD
KDIGO Co-Chair

David C Wheeler, MD, FRCP
KDIGO Co-Chair

Work Group Membership

Kidney International Supplements (2013) **3,** 261; doi:10.1038/kisup.2013.29

WORK GROUP CO-CHAIRS

Marcello A Tonelli, MD, SM, FRCPC
University of Alberta
Edmonton, Canada

Christoph Wanner, MD
University of Würzburg
Würzburg, Germany

WORK GROUP

Alan Cass, MBBS, FRACP, PhD
Menzies School of Health Research
Darwin, Australia

Amit X Garg, MD, FRCPC, FACP, PhD
London Health Sciences Centre
London, Canada

Hallvard Holdaas, MD, PhD
Hospital Rikshospitalet
Oslo, Norway

Alan G Jardine, MBChB, MD, FRCP
BHF Cardiovascular Research Centre
Glasgow, United Kingdom

Lixin Jiang, MD, PhD
Chinese Academy of Medical Sciences and
Peking Union Medical College
Beijing, China

Florian Kronenberg, MD
Innsbruck Medical University
Innsbruck, Austria

Rulan S Parekh, MD, MS, FRCPC, FASN
Hospital for Sick Children
Toronto, Canada

Tetsuo Shoji, MD, PhD
Osaka City University
Osaka, Japan

Robert J Walker, MBChB, MD (Otago), FRACP, FASN, FAHA
University of Otago
Dunedin, New Zealand

EVIDENCE REVIEW TEAM

Tufts Center for Kidney Disease Guideline Development and Implementation, Tufts Medical Center, Boston, MA, USA:

Ashish Upadhyay, MD, Project Director

Ethan M Balk, MD, MPH, Program Director, Evidence Based Medicine

Amy Earley, BS, Project Coordinator

Shana Haynes, MS, DHSc, Research Assistant

Jenny Lamont, MS, Project Manager

Abstract

Kidney International Supplements (2013) **3,** 262; doi:10.1038/kisup.2013.30

The 2013 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease (CKD) provides guidance on lipid management and treatment for all patients with CKD (non-dialysis-dependent, dialysis-dependent, kidney transplant recipients and children). This guideline contains chapters on the assessment of lipid status and treatment for dyslipidemia in adults and children. Development of the guideline followed an explicit process of evidence review and appraisal. Treatment approaches are addressed in each chapter and guideline recommendations are based on systematic reviews of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE approach. Ongoing areas of controversies and limitations of the evidence are discussed and additional suggestions are also provided for future research.

Keywords: cholesterol; chronic kidney disease; clinical practice guideline; dyslipidemia; evidence-based recommendation; KDIGO; systematic review; triglycerides

CITATION

In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. *Kidney inter., Suppl.* 2013; **3**: 259–305.

Summary of Recommendation Statements

Kidney International Supplements (2013) **3,** 263–265; doi:10.1038/kisup.2013.31

Chapter 1: Assessment of lipid status in adults with CKD

1.1: In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). (*1C*)

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

Chapter 2: Pharmacological cholesterol-lowering treatment in adults

2.1.1: In adults aged $\geq$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*)

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

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

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

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

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

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

Chapter 3: Assessment of lipid status in children with CKD

3.1: In children with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). (*1C*)

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

Chapter 4: Pharmacological cholesterol-lowering treatment in children

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

Chapter 5: Triglyceride-lowering treatment in adults

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

Chapter 6: Triglyceride-lowering treatment in children

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

Quick summary of the KDIGO recommendations for lipid-lowering treatment in adults with CKD

(a) Rule out remediable causes of secondary dyslipidemia.
(b) Establish the indication of treatment (YES or NO) and select agent and dose.
(c) Treat according to a "fire-and-forget" strategy: do not measure LDL-C unless the results would alter management.

Upon first presentation to establish the diagnosis of CKD, the nephrologist will obtain a full lipid profile as part of routine care. In case of referral and to confirm the CKD diagnosis, a full lipid profile may already be available. Results of the lipid profile should be used together with other clinical data to rule out remediable causes of secondary dyslipidemia. If excluded, the nephrologist will establish whether statin treatment is indicated (YES or NO) based on underlying cardiovascular risk. If the level of risk suggests that statin treatment is indicated, she/he will select a dose of a statin (Table 4) that is available in her/his country and has been tested for safety in people with CKD.

Contemporary practice and other clinical practice guidelines emphasize the use of targets for LDL-C (e.g., 1.8 or 2.6 mmol/l [70 or 100 mg/dl]), which require repeated measurements of LDL-C and treatment escalation with higher doses of statin or initiation of combination lipid-lowering therapy ("treat-to-target" strategy) when the LDL-C target is not met. The KDIGO Work Group does not recommend the treat-to-target strategy because it has never been proven beneficial in any clinical trial. In addition, higher doses of statins have not been proven to be safe in the setting of CKD. Therefore, the Work Group recommends a "fire-and-forget" strategy for patients with CKD (see Rationale for Recommendation 1.2). Physicians may choose to perform follow-up measurement of lipid levels in patients for whom these measurements are judged to favorably influence adherence to treatment or other processes of care.

Introduction: The case for updating and context

Kidney International Supplements (2013) **3,** 266–267; doi:10.1038/kisup.2013.32

In 2003, the US-based KDOQI (Kidney Disease Outcomes Quality Initiative) group published Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease (CKD). In the absence of randomized controlled trials (RCTs), ATP III Guidelines (Adult Treatment Panel III) were considered to be generally applicable to patients with estimated glomerular filtration rate (eGFR) ≥ 15 ml/min/1.73 m^2 (GFR categories G1-G4, formerly CKD stages 1–4) with the exception that: (1) CKD was classified as a coronary heart disease (CHD) risk equivalent, (2) complications of lipid-lowering therapies may result from reduced kidney function, (3) indications for the treatment of dyslipidemias other than preventing acute cardiovascular disease (CVD) may be applicable, and (4) treatment of proteinuria might also be an effective treatment for dyslipidemias.[1] At that time the Work Group included children and adolescents with CKD (defined by the onset of puberty) in these guidelines, and recommended that they be managed in the same way as adults.

The 2003 publication anticipated that an update should be performed in about 3 years from the time of publication of major important trials in the general population and in patients with CKD, and recommended to review ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial), SEARCH (Study Evaluating Additional Reductions in Cholesterol and Homocysteine), TNT (Treating to New Targets), IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering), ALLIANCE (Aggressive Lipid Lowering Initiation Abates New Cardiac Events), PROVE IT (Pravastatin or Atorvastatin in Evaluation and Infection Therapy), PROSPER (Prospective Study of Pravastatin in the Elderly at Risk), FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), CARDS (Collaborative Atorvastatin Diabetes Study), ASPEN (Atorvastatin as Prevention of Coronary Heart Disease Endpoints in Patients with Non-Insulin-Dependent Diabetes Mellitus), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), and ACCORD (Action to Control Cardiovascular Risk in Diabetes). Several trials in patients with CKD that were ongoing included ALERT (Assessment of Lescol in Renal Transplantation), 4D (Die Deutsche Diabetes Dialyse Studie), PREVEND IT (Prevention of REnal and Vascular ENdstage Disease Intervention Trial), AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), and SHARP (Study of Heart and Renal Protection). Since that time, all these studies have been published and most have been synthesized in two recent meta-analyses in order to bring all information into context.

In 2007 KDOQI issued Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease and included a set of guidelines on Management of Dyslipidemia in Diabetes and Chronic Kidney Disease.[2] The guidelines adopted trends in treating people with very high risk and recommended treatment to target low-density lipoprotein cholesterol (LDL-C) of <2.6 mmol/l (<100 mg/dl) for people with diabetes and eGFR categories G1-G4. The target of <1.8 mmol/l (<70 mg/dl) was considered a therapeutic option. The guidelines included the results of the 4D study, which to the surprise of many, demonstrated that lowering LDL-C with atorvastatin in hemodialysis (HD) patients with type 2 diabetes did not produce statistically significant reductions in the primary outcome measure. The study had strong impact on a recommendation for HD patients which stated that "treatment with a statin should not be initiated in patients with type 2 diabetes on maintenance HD therapy who do not have a specific cardiovascular indication for treatment." Four years later, AURORA was hoped to provide clarification of whether LDL-C lowering with rosuvastatin would offer any benefit to HD patients. Like 4D, the main results of AURORA were negative. Since then, multiple hypotheses have been raised to explain these unexpected findings. A different cardiovascular pathology with vascular stiffness, calcification, structural heart disease, and sympathetic overactivity contributing to an increasing risk for cardiac arrhythmia and heart failure was deemed responsible. The results of SHARP, a very large international RCT, is highly relevant to this discussion. SHARP showed a significant decrease in major atherosclerotic events with simvastatin and ezetimibe compared with placebo in dialysis-dependent and non-dialysis-dependent patients.

The overall objective for the guideline is to advise about the management of dyslipidemia and use of cholesterol-lowering medications in adults and children with known CKD. Questions addressed by the guideline include how and when to assess lipid status, and how and when to prescribe lipid-lowering treatment in the target population. The target audience of the guideline includes nephrologists, primary care physicians, non-nephrology specialists (e.g., cardiologists, diabetologists, etc), clinical chemists and other practitioners caring for adults and children with CKD worldwide. The guideline is also expected to be suitable for use in public policy and other healthcare arenas. As a global guideline it is sensitive to issues related to ethnicity and geographical considerations and is written for use in different health care settings.

The Work Group included an international group of kidney specialists, diabetologists, cardiologists, epidemiologists, lipidologists and a professional evidence review team

(ERT) who provided support. Details of the methods used by the ERT are described in *Methods for Guideline Development* section, along with the systematic searches for areas identified by Work Group members and performed by the ERT.

Research recommendations are described to inform ongoing research agendas in the international community. The recommendations and statements created herein will serve to direct both care and research in the next decade. Several statements in this guideline have obtained a high grade according to the international system, Grading of Recommendations Assessment, Development and Evaluation (GRADE).

This document is not intended to serve as a textbook of medicine or nephrology. Unless otherwise stated, several aspects including drug dosing and interaction, especially in transplanted patients, are still valid with respect to the KDOQI 2003 guidelines.

The current guideline synthesized all of the available evidence but is largely driven by a few large RCTs and *post hoc* analyses of patients with CKD from statin trials of the general population. This guideline proposes a new concept in the management of dyslipidemia in CKD in the hopes of stimulating discussion, generating substantial research, and influencing public policy and laboratory practice.

The requirement for an update will be assessed in five years from the publication date or earlier if important new evidence becomes available in the interim. Such evidence might, for example, lead to changes to the recommendations or may modify information provided on the balance between benefits and harms of a particular therapeutic intervention.

Chapter 1: Assessment of lipid status in adults with CKD

Kidney International Supplements (2013) **3,** 268–270; doi:10.1038/kisup.2013.33

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*)

RATIONALE

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

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

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

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

There is no direct evidence indicating that measurement of lipid status will improve clinical outcomes. However, such measurement is minimally invasive, relatively inexpensive, and has potential to improve the health of people with secondary dyslipidemia. In the judgment of the Work Group, patients with CKD place a high value on this potential benefit and are less concerned about the possibility of adverse events or inconvenience associated with baseline measurement of lipid levels. In the judgment of the Work Group, these considerations justify a strong recommendation despite the low quality of the available evidence.

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

RATIONALE

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

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

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

Table 1 | Secondary causes of dyslipidemias

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

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

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

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

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

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

Considerations for International Settings

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

Suggested Audit Criteria

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

KEY POINTS

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

RESEARCH RECOMMENDATIONS

Future studies should:

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

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

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

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

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

Chapter 2: Pharmacological cholesterol-lowering treatment in adults

Kidney International Supplements (2013) **3,** 271–279; doi:10.1038/kisup.2013.34

INTRODUCTION

Therapeutic lifestyle measures to reduce serum cholesterol levels have been broadly recommended by prior guidelines.[1,12] Although clinically appealing, such measures typically reduce serum cholesterol to only a small extent, and have not been shown to improve clinical outcomes (Supplemental Tables 1–5 online). The Work Group therefore chose to focus the recommendations for treatment on pharmacological interventions. However, it is important to note that many of these measures may improve general health (independent of any effect on lipid levels).

The primary rationale for pharmacological cholesterol-lowering treatment is to reduce morbidity and mortality from atherosclerosis. Although limited clinical data support a link between treatment of dyslipidemia and better renal outcomes,[13] more recent trials have not confirmed this hypothesis.[14]

Although several different medications lower LDL-C, only regimens including a statin (including statin/ezetimibe) have been convincingly shown to reduce the risk of adverse cardiovascular events in CKD populations. Therefore, the recommended approach for pharmacological cholesterol-lowering treatment in CKD focuses on the use of statins (with or without ezetimibe) in people at risk of future cardiovascular events.

BACKGROUND

LDL-C is not suitable for identifying CKD patients who should receive pharmacological cholesterol-lowering treatment

LDL-C is strongly and independently associated with risk of atherosclerotic events in the general population;[15] knowledge of this association facilitated the discovery that statins reduce coronary risk. Initially, statin use was limited to those with substantially elevated LDL-C (>4.5 mmol/l [>174 mg/dl]), but subsequent work indicated that the relative risk (RR) reduction associated with statin use is relatively constant across a broad range of baseline LDL-C levels, suggesting that absolute benefit from statin treatment is proportional to baseline coronary risk rather than baseline LDL-C.

Associations between LDL-C and coronary artery disease in dialysis patients. Observational data indicate that dialysis patients with the highest and lowest levels of LDL-C and TC are at the highest risk of adverse outcomes such as all-cause and cardiovascular mortality.[16–19] This paradoxical association between cholesterol and outcomes appears to be due to effect modification by protein energy wasting, inflammation and malnutrition,[20,21] which are all common in kidney failure and are themselves associated with a high risk of adverse outcomes. Put differently, patients with one of more of these three conditions are more likely to also have low cholesterol, which confounds the apparent association between cholesterol and the risk of cardiovascular death. Although cardiovascular risk is increased in dialysis patients with higher LDL-C and TC, elevated cholesterol seems unsuitable as the criterion for statin prescription in patients with kidney failure because it will fail to identify those with low cholesterol – who are also at high risk.

Associations between LDL-C and coronary artery disease in CKD patients with eGFR ≥ 15 ml/min/1.73 m^2. As eGFR declines, the magnitude of the excess risk associated with increased LDL-C decreases. For instance, the hazard ratio [HR] (95% confidence interval [CI]) of incident myocardial infarction (MI) associated with LDL-C >4.9 mmol/l [>190 mg/dl] (as compared to 2.6–3.39 mmol/l [100–131 mg/dl]) is 3.01 (2.46–3.69), 2.30 (2.00–2.65) and 2.06 (1.59–2.67) for people with eGFR of ≥ 90, 60–89.9 and 15–59.9 ml/min/1.73 m^2, respectively. Figure 1 shows the relation between LDL-C and the risk of hospitalization for MI for selected values of baseline eGFR.

The figure shows that the relation between LDL-C and the risk of MI appears linear at LDL-C above 2.6 mmol/l (100 mg/dl). The HR (95% CI) of MI associated with each 1 mmol/l (39 mg/dl) increase in LDL-C above 2.6 mmol/l (100 mg/dl) is 1.48 (1.43–1.54), 1.33 (1.27–1.40), 1.26 (1.18–1.35), 1.20 (1.09–1.30) and 1.13 (1.01–1.27) among people with eGFR of 90, 60, 45, 30 and 15 ml/min/1.73 m^2, respectively. The weaker and potentially misleading association between LDL-C and coronary risk among those with lower levels of kidney function (a group who is at the highest absolute risk) argue against its use for identifying CKD patients who should receive pharmacological cholesterol-lowering treatment.

Which CKD patients should receive pharmacological cholesterol-lowering treatment?

To maximize the ratio of benefits to harms and costs, contemporary clinical practice emphasizes three potential determinants of the decision to prescribe lipid-lowering treatment in people with normal kidney function: baseline coronary risk; case-fatality rate following MI; and evidence that lipid-lowering treatment is beneficial.[23]

Baseline coronary risk. The 10-year incidence risk of coronary death or non-fatal MI (numerically equivalent to the rate of such events per 1000 patient-years) is often used as

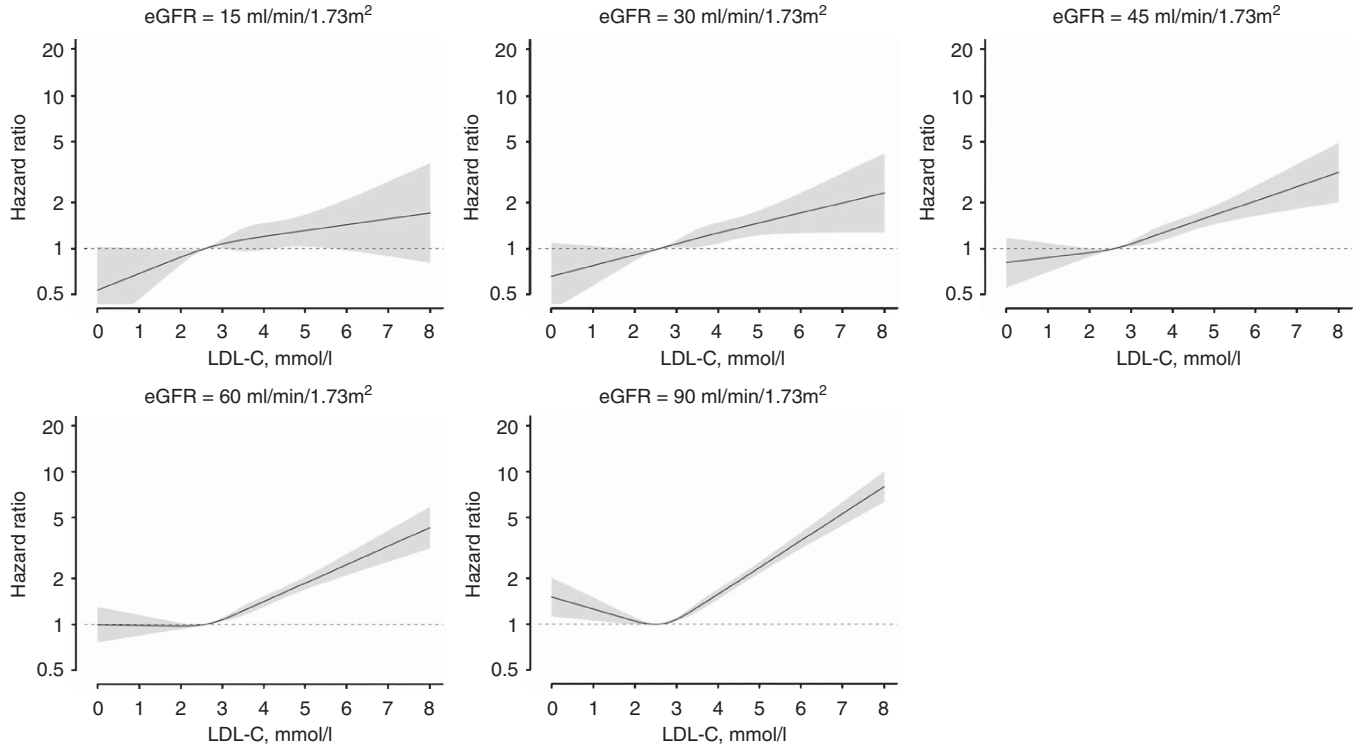

Figure 1 | Adjusted relation between LDL-C and HR of myocardial infarction by eGFR as a continuous variable. Data are adjusted hazard ratios for MI during a median follow-up period of 48 months. Data are from 836,060 participants in the Alberta Kidney Disease cohort and have been adjusted for age, sex, diabetes, hypertension, Aboriginal status, socioeconomic status, proteinuria categories, statin use, and the Charlson comorbidities (cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, metastatic solid tumor, MI, liver disease, hemiplegia/paraplegia, peptic ulcer disease, peripheral vascular disease, and rheumatic disease). eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction. Reproduced from Tonelli M, Muntner P, Lloyd A, *et al*. Association between LDL-C and Risk of Myocardial Infarction in CKD. *J Am Soc Nephrol* 2013; 24: 979–986 with permission from American Society of Nephrology[22] conveyed through Copyright Clearance Center, Inc; accessed http://jasn.asnjournals.org/content/24/6/979.long

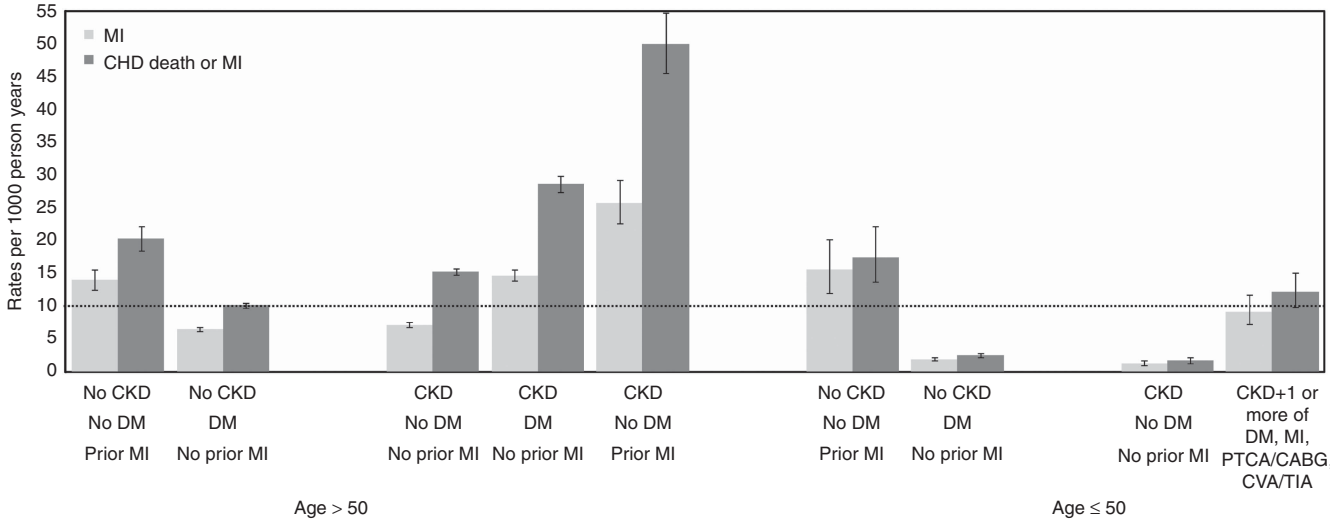

Figure 2 | Future 10-year coronary risk based on various patient characteristics. Data are unadjusted rates from 1,268,029 participants in the Alberta Kidney Disease cohort. CKD refers to eGFR 15-59.9 ml/min/1.73 m^2 or with proteinuria. CABG, coronary artery bypass grafting; CHD, coronary heart disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

Table 3 | Rate of coronary death or non-fatal MI (by age and eGFR)

	Rate (95% CI) of coronary death or non-fatal MI (per 1000 patient-years)		
	Overall	Male	Female
Age >40 years (eGFR G1-G4)	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 years (eGFR G1-G4)	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 years (eGFR G1-G4)	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)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.
Data are unadjusted rates from 1,268,029 participants in the Alberta Kidney Disease cohort. People with diabetes, MI, and other cardiovascular disease were included. Data do not apply to people with kidney transplants.

the benchmark for assessing future coronary risk; the risk in patients with prior MI (in whom the rate of new MI is 20 per 1000 patient-years) is generally considered as sufficiently high to clearly warrant ongoing statin treatment.[12] Most national guidelines for the general population also recommend universal or very liberal use of statin treatment among those with coronary risk that is lower than those with prior MI (but still substantially higher than average), such as those with diabetes or prior stroke.[12,24–26] There is no consensus on the level of future coronary risk that is sufficient to justify statin treatment, but in the judgment of the Work Group rates of coronary death or non-fatal MI <10 per 1000 patient-years are unlikely to be broadly accepted as an indication for treatment.

The rate of coronary death or incident MI among patients with CKD (defined by eGFR 15–59.9 ml/min/1.73 m^2 or with heavy proteinuria) is similar to or higher than those with diabetes (with or without CKD).[27] However, the risk associated with CKD is age-dependent. For example, the rate of coronary death or incident MI among CKD patients aged >50 years (both men and women) is consistently greater than 10 per 1000 patient-years, even in those without diabetes or prior MI) (Figure 2; Table 3). In contrast, the rate of coronary death or incident MI among CKD patients aged ≤50 years is low in those without diabetes or prior MI (Figure 2) – although it is higher than in otherwise comparable people without CKD. Further inspection of the absolute risks indicate that participants aged 40–50 years have average rates of CHD death or incident MI that are consistently less than 10 per 1000 patient-years.

Case-fatality rate following myocardial infarction. Multiple studies demonstrate that the risk of death following MI is increased among people with CKD, as compared to otherwise comparable people with normal kidney function.[27] The absolute risk of death is especially high in patients treated with chronic dialysis.[28]

Evidence that pharmacological cholesterol-lowering treatment is beneficial. The evidence supporting the clinical benefits of statin treatment in adults (alone or in combination with ezetimibe) differs substantially by severity of CKD. This evidence is presented in Supplemental Tables 6–18 online and summarized below.

Collectively, available evidence argues against the use of LDL-C to identify CKD patients who should receive cholesterol-lowering treatment and suggests focusing instead on two factors: the absolute risk of coronary events, and the evidence that such treatment is beneficial. This is the approach taken in the recommendations that follow. Prior studies convincingly demonstrate that treatments to prevent cardiovascular events are systematically underused in CKD populations despite their high baseline risk.[29–31] This suggests that a concerted attempt will be required to identify and treat CKD patients that are likely to benefit from lipid-lowering therapy.

How should the dose of pharmacological cholesterol-lowering treatment be determined in CKD patients?

Guidelines for the general population recommend that (among patients receiving statin treatment), the dose of statin is titrated to achieve the target level of LDL-C, which in turn is determined by each patient's presumed coronary risk.[12] This approach is widely accepted, although it has never been shown to lead to clinical benefit in a RCT. Instead, existing randomized trials have compared statin and placebo, or compared higher and lower doses of statin (regardless of achieved LDL-C). Taken together, these trials suggest that higher statin doses produce greater clinical benefits, but at the expense of an increased risk of adverse events.

CKD patients are at high risk of medication-related adverse events, perhaps because of the reduced renal excretion, frequent polypharmacy and high prevalence of comorbidity in this population. Therefore, reduced doses of statins are generally recommended for patients with advanced CKD. The SHARP trial addressed this issue by using lower dose simvastatin (20 mg/day) and adding ezetimibe (10 mg/day) to achieve an average LDL-C reduction of about 0.83 mmol/l (32 mg/dl), during a 4.9-year period of treatment.[14]

Subgroup analysis of the TNT trial reported that atorvastatin 80 mg/day reduced major cardiovascular events

to a greater extent than atorvastatin 10 mg/day, in 3107 patients with CKD defined by eGFR <60 ml/min/1.73 m^2 and pre-existing coronary artery disease (HR 0.68; 95% CI 0.55–0.84).[32] Serious adverse events and treatment discontinuation were increased in the high dose statin group for both people with and without CKD; the RRs of these adverse events were numerically higher in people with CKD as compared to those without, but no significance testing was performed. However, TNT participants were pretreated with 10 mg of atorvastatin during the run-in phase, and therefore were preselected for atorvastatin tolerance. In addition, the mean eGFR among TNT participants with CKD was approximately 53 ml/min/1.73 m^2, and patients with heavy proteinuria were excluded. Therefore, whether these findings apply to the broader population of people with CKD is uncertain.

Given the potential for toxicity with higher doses of statins and the relative lack of safety data, the Work Group suggests that prescription of statins in people with eGFR <60 ml/min/1.73 m^2 or RRT should be based on regimens and doses that have been shown to be beneficial in randomized trials done specifically in this population (Table 4). Patients with progressive renal dysfunction who are tolerating an alternative regimen do not necessarily need to be switched to a regimen described in Table 4, although dose reduction 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 eGFR ≥ 60 ml/min/1.73 m^2 (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-C target and thus adjusting the dose of statin regimens based on LDL-C levels is not required.

Safety data from large clinical trials suggest that the excess risk of adverse events associated with these regimens is similar among people with and without CKD. In the judgment of the Work Group, these considerations suggest that measurement of creatine kinase (CK) or liver enzyme assays is not required in asymptomatic patients.

Certain medications and grapefruit juice increase blood levels of statins (Supplemental Tables 19, 20 online). If such medications are required in patients who are otherwise good candidates for statin treatment, physicians may consider one of two strategies. For medications that will be required only for short periods (such as an antibiotic), the statin could be temporarily discontinued. For medications that will be required for more than a few days, a switch to an alternative statin or reducing the statin dose could be considered to reduce the risk of drug toxicity. Patients with CKD appear to be at increased risk of adverse events when statins and fibrates are used in combination (Supplemental Tables 21–28 online). For this reason, the Work Group recommends that fibrates not be used concomitantly with statins in patients with CKD. As mentioned earlier, given that evidence of clinical benefit is greater for statins than for fibrates, the Work Group recommends that statins be prescribed in preference to fibrates when clinicians are trying to choose between the two classes of medication.

Statins are contraindicated in pregnant or breast-feeding females; in people with active liver disease; and in people with transaminase levels that are three times or more the upper limit of normal. There is no evidence that the risk of liver dysfunction differs in people with CKD, as compared to those without. Regardless of CKD severity, the Work Group recommends that baseline levels of transaminases be measured before initiating statin treatment. Routine follow-up measurements of transaminases are not recommended, given the low frequency of abnormalities among people without abnormal values at baseline.[33] Similarly, the Work Group does not recommend measurement of CK levels at baseline or during follow-up, unless the patient develops symptoms suggestive of myopathy.

Table 4 | Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	nd
Fluvastatin	GP	80[1]
Atorvastatin	GP	20[2]
Rosuvastatin	GP	10[3]
Simvastatin/Ezetmibe	GP	20/10[4]
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, as it may increase the risk of adverse renal events. Cyclosporin inhibits the metabolism of certain statins resulting in higher blood levels. Data based on [1]ALERT, [2]4D, [3]AURORA, [4]SHARP. Abbreviations: eGFR, estimated glomerular filtration rate; GP, general population; nd, not done or not studied.

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*)

RATIONALE

Data on the effects of statins and statin/ezetimibe combination in non-dialysis dependent adults with eGFR <60 ml/min/1.73 m^2 are presented in Supplemental Tables 6–10, 15–17 online. The SHARP trial included 9270 participants with CKD (mean eGFR of 27 ml/min/1.73 m^2) to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo, and followed them for 5 years.[14] Thirty-three percent of participants ($n = 3023$) were receiving dialysis at randomization and 23% ($n = 2094$) had diabetes. Statin plus ezetimibe therapy led to a significant 17% reduction in the relative hazard of the primary outcome of major atherosclerotic

events (coronary death, MI, non-hemorrhagic stroke, or any revascularization) compared with placebo (HR 0.83; 95% CI 0.74–0.94), driven by significant reductions in non-hemorrhagic stroke and coronary revascularization. Among the 6247 patients with CKD not treated by dialysis at randomization, treatment with simvastatin plus ezetimibe did not reduce the risk of progression to end-stage renal disease (ESRD) requiring RRT. The risk of serious adverse events was similar in participants assigned to treatment and to control.

These data are supported by *post hoc* analyses of randomized trials of statin vs. placebo that focus on the subset of participants with CKD at baseline. In general, these analyses suggest that statins reduce the RR of cardiovascular events to a similar extent among patients with and without CKD but that the absolute benefit of treatment is larger in the former due to their higher baseline risk.[34] In addition, the risk of adverse events associated with statin treatment appeared similar in participants with and without CKD. However, most of the participants with CKD in these analyses had eGFR 45–59.9 ml/min/1.73 m^2 and very few had eGFR <30 ml/min/1.73 m^2.

Since the absolute risk in people who are non-dialysis-dependent with eGFR <60 ml/min/1.73 m^2 aged ≥ 50 years is consistently greater than 10 per 1000 patient-years, in the judgment of the Work Group, knowledge of LDL-C is not required to gauge average coronary risk in this population. Although multivariable prediction instruments might yield more precise estimates of risk for individuals, the Work Group judged that the increased simplicity of an age-based approach was defensible for patients aged ≥ 50 years based on the data presented above and would enhance uptake of the guideline.

There is no evidence that ezetimibe monotherapy will improve clinically relevant outcomes in patients with or without CKD. Therefore, ezetimibe monotherapy is not recommended.

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 collectively provide a strong rationale for this recommendation. In the judgment of the Work Group, these data warrant 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*)

RATIONALE

The risk of future coronary events in patients aged ≥ 50 years with CKD is markedly increased, as compared to those without CKD, and the rate of coronary death or non-fatal MI in this population exceeds 10 per 1000 patient-years even in the absence of prior MI or diabetes (Table 3). Most patients with CKD and eGFR ≥ 60 ml/min/1.73 m^2 have proteinuria and slightly reduced or normal eGFR; many such patients would have been included but not recognized in randomized trials of statins done in the general population, since many such trials did not assess proteinuria at baseline. On the other hand, this population was explicitly excluded from participation in SHARP, for which the primary inclusion criterion was elevated serum creatinine [SCr] (hence, reduced eGFR).

Existing data suggest that the relative benefit of statin treatment is not influenced by the presence of albuminuria: CARDS[35] and the Cholesterol and Recurrent Events (CARE) trial[36] both tested for an interaction between the presence of albuminuria and the effect of statin treatment on cardiovascular events. Both found no significant interaction ($p = 0.7$ and $p = 0.59$, respectively), suggesting that the benefit of statins is similar in people with and without albuminuria.

A randomized trial of pravastatin 40 mg daily vs. placebo in CKD patients with preserved GFR (i.e., eGFR categories G1-G2) but microalbuminuria found no significant risk reduction associated with pravastatin treatment on the risk of cardiovascular events (RR 0.87; 95% CI 0.49-1.57),[37] although the number of events was small ($n = 47$). A *post hoc* analysis of CARE participants with slightly more events ($n = 60$) found a significant reduction in the risk of the primary outcome (CHD death or non-fatal MI) among the subset of CKD patients with eGFR categories G1-G2 (HR of pravastatin vs. placebo 0.48; 95% CI 0.28–0.83).

Given these data, the high cardiovascular risk among people with CKD and eGFR categories G1-G2, the large body of evidence supporting the efficacy of statins in the general population, and the lack of an *a priori* reason why statins would be less effective in the presence of proteinuria (i.e., the lack of justification for a new trial done specifically in people with CKD and eGFR categories G1-G2), 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 non-fatal myocardial infarction $>10\%$**

RATIONALE

As mentioned, the risk of coronary events is age-dependent in people with CKD, just as it is in the general population. Although the absolute rate of such events is lower among people with CKD who are less than 50 years of age, the co-existence of other risk factors increases the rate of coronary death or non-fatal MI substantially. In the subset of CKD patients aged <50 years with diabetes or prior vascular disease (MI, coronary revascularization, stroke or transient ischemic attack), the rate of coronary death or incident MI

exceeds 10 per 1000 patient-years: 12.2 (95% CI 9.9–15.0) (Figure 2). In the judgment of the Work Group, this rate is sufficiently high to warrant statin treatment.

Similarly, some CKD patients aged 18–50 years may not have diabetes or prior vascular disease but yet have multiple cardiovascular risk factors that substantially increase their risk of future coronary events. In the judgment of the Work Group, an estimated 10-year incidence of coronary death or non-fatal MI is sufficiently high to warrant statin treatment. Since unequivocally elevated LDL-C does appear to confer an increased risk of coronary events in people with CKD (although to a lesser extent than in the general population), increased LDL-C levels should be considered when estimating coronary risk in CKD patients aged <50 years. The 10-year incidence of coronary death or non-fatal MI may be estimated using any validated risk prediction tool such as the Framingham risk score,[38] SCORE,[39] PROCAM,[40] ASSIGN,[41] or the QRISK2.[42] Overall, these instruments tend to overestimate future coronary risk and usually incorporate information on LDL-C. However, since most do not explicitly consider the presence of CKD, which would be expected to increase coronary risk for any given set of traditional cardiovascular risk factors, such overestimation should be less pronounced in CKD populations.

Patients whose 10-year risk of coronary death or non-fatal MI is $<10\%$ could choose to receive statin treatment if they placed relatively more value on a small absolute reduction in the risk of cardiovascular events, and relatively less value on minimizing the risks of polypharmacy and drug toxicity. On the other hand, patients valuing the potential benefits of statin treatment to a lesser extent than the potential harms might choose not to receive statin treatment even if their 10-year risk of coronary death or non-fatal MI is $>10\%$.

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

RATIONALE

There are three large-scale RCTs of statin treatment that enrolled dialysis patients. Data from these trials are presented in Supplemental Tables 11–13, 17 online.

The 4D Study (Die Deutsche Diabetes Dialyse Studie)

The 4D, a multicenter, double blind, randomized trial assigned 1255 HD patients with type 2 diabetes to receive 20 mg of atorvastatin daily or placebo.[43] After 4 weeks of treatment, atorvastatin reduced the median LDL-C level by 42%, and placebo by 1.3%. At least 1-mmol/l (39-mg/dl) difference in LDL-C level was maintained throughout the treatment period. During median follow-up of 4 years, 469 patients (37%) reached the primary endpoint (a composite of cardiac death, nonfatal MI, and fatal and nonfatal stroke): 226 assigned to atorvastatin and 243 assigned to placebo (RR 0.92; 95% CI 0.77–1.10; $p=0.37$). Atorvastatin had no effect on the single components of the primary endpoint with the exception of fatal stroke, in which RR was 2.03 (95% CI 1.05-3.93; $p=0.04$). The secondary endpoint of combined cardiac events (RR 0.82; 95% CI 0.68–0.99; $p=0.03$) was significantly reduced, but not all combined cerebrovascular events (RR 1.12; 95% CI 0.81–1.55; $p=0.49$) or total mortality (RR 0.93; 95% CI 0.79–1.08; $p=0.33$).

AURORA Study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Dialysis: an Assessment of Survival and Cardiovascular Events)

In this international double-blind randomized trial, 2776 HD patients were assigned to receive rosuvastatin 10 mg daily or placebo, and followed for a median of 3.8 years.[44] Despite the mean reduction in LDL-C of 43% in the intervention group, the combined primary endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was not reduced (HR 0.96; 95% CI 0.84–1.11; $p=0.59$). Rosuvastatin did not reduce the risk of individual components of the primary endpoint, nor of all-cause mortality (HR 0.96; 95% CI 0.86-1.07; $p=0.51$).

SHARP (Study of Heart and Renal Protection)

This international double-blind randomized trial assigned 9270 participants ≥ 40 years old with CKD to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo, and followed them for 4.9 years.[14] Thirty-three percent of the patients ($n=3023$) were receiving maintenance dialysis at randomization. The remaining 6247 CKD patients had a mean eGFR of 27 ml/min/1.73 m^2. Mean reduction in LDL-C among the treatment group was 0.83 mmol/l (32 mg/dl), compared to placebo. Statin plus ezetimibe therapy was associated with a significant 17% RR reduction of the primary outcome of major atherosclerotic events (coronary death, MI, non-hemorrhagic stroke, or any revascularization) compared with placebo (HR 0.83; 95% CI 0.74–0.94). SHARP indicated that risk for the primary outcome of major atherosclerotic events other than death was reduced by simvastatin/ezetimibe among a wide range of patients with CKD. Combination treatment did not significantly reduce the risk of the primary outcome in the subgroup of over 3000 patients treated with dialysis at baseline.

A systematic review pooling data from all available randomized trials done in CKD populations reported significant heterogeneity between dialysis and non-dialysis patients for the benefit of statins on major cardiovascular events (HR for dialysis 0.96; 95% CI 0.88–1.03; HR for non-dialysis 0.76; 95% CI 0.72–0.79; p for heterogeneity <0.001).[34] When findings from SHARP, 4D and AURORA are considered together, the clinical benefit of statins (alone or in combination with ezetimibe) in prevalent dialysis patients is uncertain. Another meta-analysis in essence confirmed the results, although the data were analyzed in a different manner.[45] Even if statins truly do prevent cardiovascular events in prevalent dialysis patients, it is clear that the magnitude of any relative reduction in risk is substantially

smaller than in earlier stages of CKD.[34] However, if this speculative benefit among dialysis patients is confirmed in future studies, the absolute benefit might be comparable to that in people with less severe CKD, due to the higher event rate among dialysis patients.[46]

The smaller RR reduction noted in SHARP could be due to lower compliance to study drug in the subgroup of dialysis patients. Dialysis patients showed on average a 0.60 mmol/l (23 mg/dl) LDL-C reduction in comparison to the non-dialysis CKD group which outlined a 0.96 mmol/l (37 mg/dl) LDL-C decrease.

In summary, these data suggest that despite the exceedingly high cardiovascular risk in dialysis patients, it is uncertain whether statin regimens lead to clinical benefit in this population. Therefore, in the judgment of the Work Group, initiation of statin treatment is not recommended for most prevalent HD patients. However, patients might reasonably choose statin treatment if they are interested in a relatively small, uncertain reduction in cardiovascular events. Since very high LDL-C might increase the likelihood of benefit from statin in a dialysis patient,[47] patients who meet this criterion may be more inclined to receive a statin, recognizing that the benefit remains uncertain. Other factors that might influence a patient's decision to receive statin could include recent MI or greater life expectancy (both favoring treatment), and more severe comorbidity or higher current pill burden (both favoring non-treatment).

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*)

RATIONALE

SHARP, 4D and AURORA do not directly address the question of whether statins should be discontinued in patients initiating dialysis, who may be systematically different from prevalent dialysis patients. However, 2141 (34%) of SHARP patients without kidney failure at baseline commenced dialysis during the trial and were analyzed in the non-dialysis group – in which overall benefit was observed.[14] 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 dialysis patients 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/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 of polypharmacy and drug toxicity.

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

RATIONALE

The risk of future coronary events in kidney transplant recipients is markedly elevated: data from the placebo arm of the ALERT trial suggest that the rate of cardiovascular death or non-fatal MI is approximately 21.5 per 1000 patient-years.[48] Data on the rate of non-fatal MI by age are not available for kidney transplant recipients, but a population-based study from Australia and New Zealand suggests that the rate of cardiovascular death alone is approximately 5 per 1000 patient-years even among those aged 25–44 years.[49]

Data on the effect of statins in adult kidney transplant recipients are presented in Supplemental Tables 29–31 online. ALERT examined the effect of statin therapy on cardiovascular risk reduction in 2102 patients aged 30–75 years with functioning kidney transplants who were followed for 5–6 years. Fluvastatin therapy (40–80 mg/day) led to a non-significant 17% reduction in the primary outcome of coronary death or non-fatal MI, compared to placebo (RR 0.83; 95% CI 0.64–1.06). However, fluvastatin led to a significant 35% relative reduction in the risk of cardiac death or definite non-fatal MI (HR 0.65; 95% CI 0.48–0.88),[48] and an unblinded extension study found that randomization to 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 observed 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.

The age at which statin treatment should begin in kidney transplant recipients is uncertain: the risk of coronary events is age-dependent, and ALERT did not enroll participants younger than 30 years, However, ESRD treated by kidney transplantation is a chronic disease, with cardiovascular risk expected to increase over time even in the presence of optimal graft function. In the judgment of the Work Group, these considerations warrant treatment in all adult kidney transplant recipients. However, younger patients (for example, those <30 years and without traditional cardiovascular risk factors) could choose not to receive statin treatment if they placed relatively less value on a small absolute reduction in the risk of cardiovascular events, and relatively more value on minimizing the risks of polypharmacy and drug toxicity.

Considerations for International Settings

In some Asian countries, doses of statins tend to be lower than those used in Western countries, due to concern about drug toxicity and clinical trial data indicating that such doses safely reduce LDL-C[50,51] and improve clinical outcomes.[52,53] Therefore, physicians practicing in such countries may choose to prescribe lower doses than recommended in Table 4.

Suggested Audit Criteria

- One year before and after the publication of this guideline, assess the proportion of non-dialysis-dependent adults aged ≥ 50 years with eGFR < 60 ml/min/1.73 m^2 that receive treatment with a statin or statin/ezetimibe combination.
- One year before and after the publication of this guideline, assess the proportion of adults aged ≥ 50 years with CKD and eGFR > 60 ml/min/1.73 m^2 that receive treatment with a statin.
- One year before and after the publication of this guideline, assess the proportion of adult kidney transplant recipients that receive treatment with a statin.
- One year before and after the publication of this guideline, assess the prevalence of statin use among non-dialysis-dependent adults aged 18–49 years with CKD and at least one of the following risk factors: known coronary disease (MI or coronary revascularization), diabetes mellitus, previous ischemic stroke, or predicted 10-year risk of CHD death/non-fatal MI $> 10\%$.

KEY POINTS

- Coronary risk is sufficiently high to justify prescription of statins in people aged ≥ 50 with non-dialysis-dependent CKD or a kidney transplant.
- Coronary risk in people aged < 50 years with non-dialysis-dependent CKD is lower, but the presence of additional cardiovascular risk factors may increase risk to justify statin prescription. Given the evidence that treatment with statins improve vascular outcomes in this population, such treatment is suggested for patients aged < 50 years with non-dialysis-dependent CKD and known vascular disease (prior MI, coronary revascularization or stroke), diabetes, or other risk factors that increase the 10-year risk of coronary death or non-fatal MI (as estimated using a validated risk calculator) to $> 10\%$.
- Patients with dialysis-dependent CKD should not be initiated on statin or statin/ezetimibe treatment, given the lack of evidence that such treatment is beneficial. However, statin or statin/ezetimibe treatment should not necessarily be discontinued among existing users when dialysis treatment is initiated.
- Physicians should be alert to the possibility of toxicity resulting from substances that increase blood levels of statins (e.g., grapefruit juice, certain medications).

RESEARCH RECOMMENDATIONS

- An extended observational study should be undertaken of the SHARP study cohort to determine whether the reduction in major atherosclerotic events resulting from 5 years of LDL-C lowering persists in the long-term, and whether LDL-C lowering significantly delays renal disease progression in people with non-dialysis-dependent CKD and eGFR < 60 ml/min/1.73 m^2.
- Given that the majority of early CKD is managed in primary care, audits of pharmacological cholesterol-lowering treatment should be undertaken in this setting.
- Data from the AURORA, 4D and SHARP studies (dialysis cohort) should be pooled to undertake individual patient data meta-analysis to more comprehensively assess the benefits and risks of cholesterol-lowering treatment in people with dialysis-dependent CKD.

DISCLAIMER

SUPPLEMENTARY MATERIAL

Supplemental Table 1: Summary table of RCT examining the effect of exercise in CKD 5HD patients [continuous outcomes]

Supplemental Table 2: Summary table of RCT examining low vs. moderate protein diet in CKD patients without DM [categorical outcomes]

Supplemental Table 3: Summary table of RCT examining low vs. moderate protein diet in CKD patients without DM [continuous outcomes]

Supplemental Table 4: Summary table of RCT examining statin therapy vs. lifestyle modification in kidney transplant recipients without DM [categorical outcomes]

Supplemental Table 5: Summary table of RCT examining statin therapy vs. lifestyle modification in kidney transplant recipients without DM [continuous outcomes]

Supplemental Table 6: Summary table of RCT examining statin therapy vs. usual care in patients with CKD without DM [categorical outcomes]

Supplemental Table 7: Summary table of RCT examining statin therapy vs. usual care in patients with CKD without DM [continuous outcomes]

Supplemental Table 8: Summary table of RCTs of statins vs. placebo in patients with CKD with and without DM [categorical outcomes]

Supplemental Table 9: Summary table of RCTs of statins vs. placebo in various stages of CKD with and without DM [continuous outcomes]

Supplemental Table 10: Evidence profile of RCTs examining the effect of statins vs. placebo in patients with CKD with and without DM

Supplemental Table 11: Summary table of RCTs of statins vs. placebo in dialysis patients with and without DM [categorical outcomes]

Supplemental Table 12: Summary table of RCTs of statins vs. placebo in dialysis patients with and without DM [continuous outcomes]

Supplemental Table 13: Evidence profile of RCTs examining the effect of statins vs. placebo in dialysis patients with and without DM

Supplemental Table 14: Summary table of RCT examining statin vs. placebo in patients with ADPKD [continuous outcomes]

Supplemental Table 15: Summary table of RCT examining simvastatin/ezetimibe combination vs. simvastatin/placebo in CKD patients without DM [categorical outcomes]

Supplemental Table 16: Summary table of RCT examining simvastatin/ezetimibe combination vs. simvastatin/placebo in CKD patients without DM [continuous outcomes]

Supplemental Table 17: Summary table of RCT of statin + ezetimibe vs. placebo in CKD patients [categorical outcomes]

Supplemental Table 18: Summary table of RCT examining the effect of dose of atorvastatin in CKD patients with DM [categorical outcomes]

Supplemental Table 19: Drug interactions

Supplemental Table 20: Effects of grapefruit juice on statin pharmacokinetics and recommendations

Supplemental Table 21: Patients on statin + fibrate therapy reporting any adverse event

Supplemental Table 22: Patients receiving statin + fibrate therapy reporting other individual adverse events

Supplemental Table 23: Patients on statin + fibrate therapy reporting treatment related adverse events

Supplemental Table 24: Patients on statin + fibrate therapy discontinuing due to adverse events

Supplemental Table 25: Patients on statin + fibrate therapy with increased ALT or AST

Supplemental Table 26: Patients on statin + fibrate therapy with increased CK

Supplemental Table 27: Patients on statin + fibrate therapy with increased serum creatinine

Supplemental Table 28: Patients receiving statin + fibrate therapy reporting rhabdomyolysis

Supplemental Table 29: Summary table of RCTs of statin vs. placebo in kidney transplant patients [categorical outcomes]

Supplemental Table 30: Summary table of RCTs of statin vs. placebo in kidney transplant patients [continuous outcomes]

Supplemental Table 31: Evidence profile of RCTs examining the effect of statins vs. placebo in kidney transplant recipients

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/home/guidelines/lipids

Chapter 3: Assessment of lipid status in children with CKD

Kidney International Supplements (2013) **3,** 280–281; doi:10.1038/kisup.2013.35

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*)

RATIONALE

Young adults with eGFR <15 ml/min/1.73 m^2 have at least 10-fold higher risk for CVD mortality compared to the general population.[54] Many recent studies document the prevalence of CVD risk factors in children with CKD. However, due to limited follow-up, few studies demonstrate the association of dyslipidemia with clinical CVD events in adolescents or young adults, especially in the setting of CKD.

In the general pediatric population, lipid levels in childhood are predictive of future lipid levels and subsequent cardiovascular events.[55] The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study shows that initial fatty streaks seen in adolescents with normal kidney function develop into atheromatous plaques in young adults.[56] Over 50% of children 10-14 years old had early fatty streaks, and 8% had fibrous plaques, thus confirming that atherosclerosis begins in childhood.[56] Additional longitudinal studies demonstrate an association between childhood lipid levels and adult onset coronary artery disease.[57–59] Moreover, this atherosclerotic process is likely accelerated in nephrotic syndrome, proteinuric states and chronic kidney disease due to abnormal lipid metabolism and other atherogenic risk factors, thus putting children and adolescents at risk for developing CVD as they age into adulthood. In the Bogalusa Heart Study, body mass index, LDL-C, and systolic blood pressure were associated with atherosclerotic disease of the aorta and coronary vessels of children.[56,57] Recent studies of subclinical atherosclerotic CVD in children with familial hypercholesterolemia found an increase in intimal medial thickness of the aorta and carotid arteries compared to that of healthy young children.[60] Thus, atherosclerotic disease appears to begin in childhood, and dyslipidemia in children may play an important role in the early pathogenesis of atherosclerosis.

In children with CKD, the relationship between dyslipidemias and subsequent atherosclerotic clinical events is not known due to short follow-up in observational studies or clinical trials. Recently, the Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement from the American Heart Association Expert Panel on Population and Prevention Science stated that CVD prevention in many chronic pediatric conditions was warranted given the high risk of developing disease as adults.[61]

The recent National Institutes of Health Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents in 2011 addressed specific questions of screening for dyslipidemias in children and adolescents and also treatment of dyslipidemias.[7] Cholesterol and its metabolism are important in children as cholesterol is the basis of cell membranes, myelin formation, subcellular organelles and steroid hormones which are all key for natural growth and development. Based on growth and development, lipid levels vary depending on age, puberty, and gender.[62] Lipid levels are very low at birth and increase during the first year of life [mean TC of 3.9 mmol/l (150 mg/dl), LDL-C 2.6 mmol/l (100 mg/dl), and HDL-C 1.4 mmol/l (55 mg/dl)] where they remain fairly constant till age 12 and are slightly lower in girls than boys. During puberty, there is a decrease in TC, LDL-C, and a slight decrease in HDL-C in boys. After puberty, TC and LDL-C increase to adult levels in boys and girls. Boys continue to have a slightly lower HDL-C than girls. Due to these variations in levels, former guidelines used the 95th percentile for age and gender to determine the upper limit of acceptable values. More recently, age- and gender- specific curves for lipoproteins linked to CVD risk over 15-20 years[55,58] have been used instead. A simplified and more practical approach has been to define acceptable, borderline high and high lipid concentration for children and adolescents based on these curves[7] (see Table 5).

Many studies document the prevalence of dyslipidemias among children with CKD and ESRD.[63,64] As in adults, the pattern of dyslipidemias in children with CKD is greatly influenced by the underlying pathogenesis and duration of CKD, severity of proteinuria, and treatment.[63,64] Due to this variability, the prevalence of hypercholesterolemia ranges from 39% to 65% in children with CKD. Among 391 children from the North American observational cohort study, CKiD (Chronic Kidney Disease in Children), TG and non-HDL-C levels increased as the measured GFR declined in this cross sectional study population.[63] Conversely, HDL-C was lower for those with a lower GFR. Factors that impacted TG, HDL-C and non-HDL-C levels were primarily GFR, significant proteinuria and obesity by multivariate analyses.[63] Over half the population had no evidence of dyslipidemias and of the remainder, 25% had a single abnormal lipid level, and the other 25% had at least 2 abnormal lipid levels.[63] The most

Table 5 | Plasma lipid concentrations for children and adolescents[7]

Category	Acceptable	Borderline High (75%)	High (95%)
Total Cholesterol	<4.4 (<170)	4.4–5.2 (170–199)	>5.2 (≥200)
LDL-C	<2.8 (<110)	2.8–3.3 (110–129)	≥3.4 (≥130)
Non-HDL-C	<3.1 (<120)	3.1–3.7 (120–144)	≥3.8 (≥145)

Abbreviations: LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density-lipoprotein cholesterol.
Values given are in mmol/l (mg/dl). Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children. Non-HDL–C values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut points for LDL–C.

common abnormality was hypertriglyceridemia.[63] The frequency of these abnormalities suggests that clinicians should measure lipid levels at baseline in children with CKD to screen for underlying secondary causes of dyslipidemia.

As for adults, there is no direct evidence indicating that measurement of lipid status will improve clinical outcomes. However, such measurement is minimally invasive, relatively inexpensive, and has potential to improve the health of people with secondary dyslipidemia. In the judgment of the Work Group, children with CKD (and their families) place a high value on this potential benefit and are less concerned about the possibility of adverse events or inconvenience associated with baseline measurement of lipid levels. In the judgment of the Work Group, these considerations justify a strong recommendation despite the low quality of the available evidence.

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*)

RATIONALE

Few data document how frequently the clinical lipid status changes in children with CKD, although it is clear that abnormal levels (once documented) are likely to persist. Unlike adults, growth and development in children have potential to influence lipid levels over time. Therefore, the Work Group recommends that fasting lipid levels be followed in children with CKD to screen for underlying secondary causes of dyslipidemia.

The ideal frequency of follow-up for fasting levels of LDL-C, HDL-C and serum TGs is unknown. These levels could be assessed annually in most children with CKD. However, more frequent (or less frequent) follow-up measurements may be appropriate based on the clinical status of the patient, and the potential for such follow-up measurements to influence management.[65] Possible changes in management in response to such measurements could include therapeutic lifestyle measures (see Recommendation 6.1) or statin regimens for children with very high LDL-C levels (see Recommendation 4.1).

Considerations for International Settings

Similar to those for Chapter 1.

Suggested Audit Criteria

Similar to those for Chapter 1.

KEY POINTS

- Dyslipidemia is common in children with CKD.
- All children with CKD should be screened for dyslipidemias at presentation.
- Because growth and development as well as modality switches may influence lipid metabolism, lipids could be regularly evaluated during follow-up and when children initiate dialysis or receive a kidney transplant.

RESEARCH RECOMMENDATION

- Future studies should be conducted to determine the prevalence of dyslipidemias among children initiating dialysis or receiving a kidney transplant.

Chapter 4: Pharmacological cholesterol-lowering treatment in children

Kidney International Supplements (2013) **3,** 282–283; doi:10.1038/kisup.2013.36

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*)

RATIONALE

Clinical trials of dyslipidemias are limited in the pediatric CKD population given the rapid transitions from CKD to dialysis and/or transplant, which complicates trial design, recruitment and analyses (Supplemental Table 32 online). Accurately predicting CVD risk is also not possible in the pediatric CKD population given the limited data available; scores commonly used in adults have not been validated in the pediatric population. Nonetheless, young adults ages 20–24 treated with dialysis or kidney transplantation have significantly lower expected survival compared to an age-matched group in the general population.[66]

Treatment for dyslipidemia in children should first include nutrition and dietary counseling, and address obesity with weight loss regimens if necessary. Recent studies in the general population have shown that dietary fat restriction is safe in children.[67–70] In particular, there have been no adverse effects on growth and development, or nutrition.[67–70] Diets, however, should be used judiciously, or not at all, in children who are malnourished. Secondary causes of dyslipidemias should also be treated first (Table 1). Therapeutic lifestyle changes (TLC) should be adopted among all children with CKD.

Statin therapy has been shown to reduce LDL-C in children and adolescents ages 8–18 years with no adverse effects on growth, development or sexual maturation reported.[7] However, the follow-up time of the studies was quite variable and safety data in children with CKD are very limited. Data on the benefits of treating LDL-C in children aged <10 years are extremely limited, and chiefly include patients with severe familial hypercholesterolemia or cardiac allografts. In the US, statins are approved for use among adolescent boys and post-menarchal girls ages 10–18 years (age 8 and older for pravastatin) for treatment of elevated LDL-C among those with familial dyslipidemias, family history of premature heart disease and 2 or more cardiovascular risk factors.[7]

Four randomized trials have examined drug treatment of dyslipidemia in children with CKD, primarily in children with nephrotic syndrome.[71–74] The trials demonstrate that statins lower LDL-C over 7 months to 5 years. No randomized trials have studied clinically relevant outcomes such as cardiovascular events or mortality.

There have been 13 statin trials in 1683 children with dyslipidemias and normal kidney function. These trials have demonstrated that statins lower LDL-C by 17-50% (depending on dose) and have modest effects on TGs or HDL-C.[75–87] There were only two studies that studied statins in combination with a second drug such as colestipol or ezetimibe.[81,85]

This is a weak recommendation that reflects the lack of evidence for benefit and safety associated with long-term use. As for all weak recommendations, practitioners should consider the clinical circumstances and the patient's preferences when considering an individual patient. The Work Group further suggests that the patient's age could also be considered when applying this recommendation.

Due to the very limited available data, the Work Group does not recommend the use of statins in children with CKD aged <10 years. Patients (boys aged >10 years and post-menarchal girls, together with their parents) with severely elevated LDL-C who place a higher value on the potential for preventing cardiovascular events and are less concerned about adverse events from statin use might be candidates for statin use – especially those with multiple additional risk factors such as family history of premature coronary disease, diabetes, hypertension, smoking and ESRD.

If a statin is prescribed, the Work Group suggests the lowest dose available. There are no data on the appropriate target for LDL-C in children (with or without CKD), extremely limited long-term safety data in pediatric CKD populations, and no dose escalation studies in children with CKD to confirm the safety of higher statin doses even over the short term.

Given the lack of evidence for the benefit and safety of combination therapy with bile acid resins, colestipol and ezetimibe in pediatric CKD populations, the Work Group does not recommend the use of such multi-drug regimens even in children with severely elevated LDL-C.

Suggested Audit Criteria

- Determine the number of children treated with statins (and statin type) and other lipid-lowering therapies by CKD severity.
- Document the number of children with intolerance and/or non-compliance to statins or other lipid-lowering treatment.
- Document the number of children that receive statin therapy for primary prevention.

KEY POINTS

- TLC should be recommended to all children with CKD and dyslipidemia.
- Statins are not recommended for children with CKD and dyslipidemia.

RESEARCH RECOMMENDATIONS

Future studies should be conducted to assess short- and long-term association between lipids and CVD, using surrogate outcomes such as carotid intima-media thickness and clinically relevant outcomes such as MI and stroke.

DISCLAIMER

SUPPLEMENTARY MATERIAL

Supplemental Table 32: Summary table of RCTs of statins vs. placebo in children with CKD without DM [continuous outcomes]

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/home/guidelines/lipids

Chapter 5: Triglyceride-lowering treatment in adults

Kidney International Supplements (2013) **3,** 284–285; doi:10.1038/kisup.2013.37

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*)

RATIONALE

Non-pharmacological treatment of high triglycerides

TLC includes dietary modification, weight reduction, increased physical activity, reducing alcohol intake, and treatment of hyperglycemia (if present). Evidence that TLC will reduce serum TGs in patients with CKD is weak. However, the elements of TLC are unlikely to lead to harm and may improve general health. In the opinion of the Work Group, it is reasonable to advise patients with high fasting levels of serum TGs (> 5.65 mmol/l [> 500 mg/dl]) to adopt TLC. Dietary changes that may reduce serum TGs include a low-fat diet (< 15% total calories), reduction of monosaccharide and disaccharide intake, reducing the total amount of dietary carbohydrates, and use of fish oils to replace some long-chain TGs. Dietary modification should be used judiciously, if at all, in individuals who are malnourished. This is a weak recommendation that is based on very low quality evidence.

Pharmacological treatment of high triglycerides: effects on risk of pancreatitis

Although previous guidelines have suggested the use of fibric acid derivatives for preventing pancreatitis from severe hypertriglyceridemia,[1] the evidence supporting the safety and efficacy of this approach is extremely weak, especially in patients with CKD. Therefore, the Work Group no longer recommends this approach, especially since statins appear to prevent pancreatitis in people with normal or mildly elevated TGs.[88]

Fibric acid derivatives could be considered for the rare patients with CKD and markedly elevated fasting levels of serum TG (> 11.3 mmol/l [> 1000 mg/dl]). If such therapy is prescribed, fibric acid derivatives must be dose-adjusted for kidney function. There is limited evidence to recommend one fibric acid derivative over another in the setting of CKD and therefore any of the alternatives may be used. As mentioned in Chapter 2, concomitant therapy with both a fibric acid derivative and a statin is not recommended in patients with CKD due to the potential for toxicity.

Nicotinic acid has not been well studied in advanced CKD and therefore is not recommended for treatment of severe hypertriglyceridemia, given the risk of toxicity (especially flushing and hyperglycemia).

The Work Group considered a weak recommendation against the use of fibric acid derivatives in people with CKD. However, in the judgment of the Work Group, there is insufficient evidence to recommend for or against the use of fibric acid derivatives in this population. Treatment with fibric acid derivatives might be warranted in patients who place a relatively high value on preventing pancreatitis, and a relatively low value on the risks of polypharmacy and drug toxicity.

Pharmacological treatment of high triglycerides: effects on cardiovascular risk

A meta-analysis of data from 18 randomized trials involving 45,058 participants drawn from the general population (i.e., not specific to CKD) demonstrated a modest 10% RR reduction (95% CI 0–18; $p = 0.048$) in major cardiovascular events and a 13% RR reduction in coronary events (95% CI 7–19; $p < 0.0001$) for fibrate therapy. But such benefits are smaller than the 20% reduction in vascular events and 10% reduction in mortality demonstrated by statins per mmol/l reduction in LDL-C.[14,89,90]

As mentioned in Chapter 1, the dyslipidemia associated with CKD appear particularly suited to therapy with fibric acid derivatives, which alter triglyceride-rich lipoproteins more than LDL-C, the main target of statins. This observation has raised the hypothesis that fibrates might be especially effective for preventing vascular events in CKD populations.

Randomized treatment trials that examined the effect of fibrates relative to placebo in patients with diabetes and CKD are summarized below. The Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) found evidence that gemfibrozil reduces risk of major cardiovascular events (i.e., fatal CHD, nonfatal MI, and stroke) by 42% compared with placebo (RR 0.58; 95% CI 0.38–0.89) in a *post hoc* analysis of 297 individuals with low eGFR (GFR < 75 ml/min/1.73 m^2) and diabetes.[91]

The Diabetes Atherosclerosis Intervention Study (DAIS)[92] and the FIELD study[93] reported that fenofibrate treatment significantly lowered the risk of developing new-onset microalbuminuria compared with placebo (RR 0.87 in patients with type 2 diabetes; 95% CI 0.77-0.97). In a pooled analysis of these two trials, fenofibrate also promoted regression from microalbuminuria to normoalbuminuria (RR1.15; 95% CI 1.04–1.28; $n = 2260$). None of the other trials of fibrate therapy in diabetes reported CVD or kidney disease outcomes for the subgroup of patients with CKD.

The FIELD study was a large randomized double-blind trial in which 9795 participants aged 50–75 years with type 2

diabetes were allocated to micronized fenofibrate 200 mg daily or matching placebo, and followed for a median of 5 years.[93] Patients were eligible if there was no clear indication for, or treatment with, lipid-modifying therapy at study entry, and patients with renal impairment, defined as a plasma creatinine $>130\,\mu mol/l$ ($>1.47\,mg/dl$), were excluded. There was a significant difference in the proportion of participants with progression of albuminuria, analyzed categorically to/from normo-, micro-, and macro-albuminuria (466 [9.5%] progressing and 462 [9.4%] regressing in the fenofibrate group vs. 539 [11.0%] progressing and 400 [8.2%] regressing in the placebo group; i.e., 2.6% more patients were regressing or not progressing in those allocated fenofibrate than placebo, $p=0.002$). Importantly, only 5% (519 of 9795) of the randomized participants had a baseline eGFR below 60 ml/min/1.73 m^2, so only 117 cardiovascular events occurred in this subgroup. The significant treatment effects presented for those with eGFR below 60 ml/min/1.73 m^2 (for the outcomes of coronary revascularization, cardiovascular mortality, and total cardiovascular events) were based on too few events to be reliable. Hence, there was not good evidence that the treatment effects on vascular outcomes differed between those with and without lower baseline eGFR.

Ting and colleagues also considered whether allocation to fenofibrate affected renal function but were unable to conclusively address this issue due to lack of statistical power.[94] Another paper, which provides more detailed renal analyses from FIELD, suggested that after excluding the 10–12 μmol/l (0.11–0.14 mg/dl) step-rise in creatinine on commencing fenofibrate, allocation to fenofibrate was in fact associated with a slower rate of change in eGFR (-1.19 vs. -2.03, absolute difference ~ 1 ml/min/1.73 m^2 per year; $p<0.001$).[95] But the inaccuracy of eGFR above 60 ml/min/1.73 m^2 and the use of surrogate outcomes such as rate of change in eGFR and albuminuria remain important caveats. Furthermore, allocation to fenofibrate was also associated with an increased risk of doubling of plasma creatinine (148 [3.0%] vs. 90 [1.8%], $p<0.001$), which cannot simply be explained by the small step-rise in creatinine.

ACCORD Lipid, the other large randomized trial which investigated the effect of fibrates in type 2 diabetic patients, assessed the addition of fenofibrate 160 mg daily to simvastatin 10–40 mg daily (dose modified over time in response to changing guidelines) in 5518 participants.[96] Again, this study excluded patients with impaired kidney function, creatinine $>133\,\mu mol/l$ ($>1.5\,mg/dl$), such that only 141 participants had baseline eGFR below 50 ml/min/1.73 m^2. Ultimately too few participants with eGFR <60 ml/min/1.73 m^2 were included in either FIELD or ACCORD Lipid to provide reliable information on either the safety or efficacy of fenofibrate in this group.

A recent large observational study in patients aged ≥ 66 years demonstrated a clear association between new prescriptions for fibric acid derivatives and increased SCr levels, as well as a small increase in the risk of hospitalization and nephrologist consultation.[97] These findings contribute to the uncertainty that fibric acid derivatives would yield net clinical benefit in people with CKD.

For these reasons, use of fibric acid derivatives to reduce cardiovascular risk is not recommended in patients with CKD.

Suggested Audit Criteria

Given the lack of evidence to support this recommendation, no audit criteria are suggested.

KEY POINTS

- TLC should be recommended to adults with CKD and hypertriglyceridemia.
- Fibric acid derivatives are not recommended to prevent pancreatitis or reduce cardiovascular risk in adults with CKD and hypertriglyceridemia.

RESEARCH RECOMMENDATIONS

- There are currently no published randomized trials of fibric acid derivatives in CKD populations and too few participants with CKD were included in previous trials to provide reliable information. Other agents, such as niacin and the cholesteryl ester transfer protein inhibitor anacetrapib are currently being investigated in clinical trials in the general population and deserve investigation in CKD patients.
- CKD registries should report hypertriglyceridemia-induced pancreatitis to identify true incidence.
- Studies should be conducted to confirm that pancreatitis due to TG levels above 11.3 mmol/l (1000 mg/dl) is infrequent in HD patients.

DISCLAIMER

Chapter 6: Triglyceride-lowering treatment in children

Kidney International Supplements (2013) **3,** 286; doi:10.1038/kisup.2013.38

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

RATIONALE

Non-pharmacological treatment of high triglycerides

TLC includes dietary modification, weight reduction, increased physical activity, reducing alcohol intake, and treatment of hyperglycemia (if present). As for adults, the evidence that TLC will reduce serum TG levels and/or improve clinical outcomes is weak. Nonetheless, in the opinion of the Work Group, it is reasonable to advise children with high fasting levels of serum TGs (>5.65 mmol/l [>500 mg/dl]) to adopt TLC based on similar considerations as mentioned in Guideline 5.1. Dietary changes that may reduce serum TGs include a very low-fat diet ($<15\%$ total calories), medium-chain TGs, and fish oils to replace some long-chain TGs. Dietary modification should be used judiciously, if at all, in children who are malnourished. Input from a social worker may be helpful if there are concerns that the patient or his/her parents are unable to safely implement TLC.

Pharmacological treatment of high triglycerides: effects on risk of pancreatitis

Although previous guidelines have suggested the use of fibric acid derivatives for preventing pancreatitis from severe hypertriglyceridemia, the evidence supporting the safety and efficacy of this approach is extremely weak – especially in children with CKD. Therefore, the Work Group no longer recommends this approach.

Evidence that very high TGs can cause pancreatitis in children comes from case reports and small series of patients with familial dyslipidemias.[98,99] The safety and efficacy of lowering TGs with fibrates and niacin have not been established in adolescents; studies have been of extremely short duration and with very small sample sizes.[100–102] There have been 4 trials of fish oil completed in children with glomerular causes of CKD and one trial among children on dialysis; fish oil appears to lower serum TGs after as little as 12 weeks of therapy,[103–106] but the longer-term benefits, harms, and tolerability of such treatment is unclear.

Therefore, pharmacological treatment of hypertriglyceridemia is not recommended in children with CKD. This is a weak recommendation that reflects the lack of evidence on clinical benefit and safety. Treatment could be considered in children with very severely increased hypertriglyceridemia (>11.3 mmol/l [>1000 mg/dl]); such children should be referred to a pediatric lipid specialist for management and to rule out familial hypertriglyceridemia or rare, inherited disorders such as lipoprotein lipase deficiency or apolipoprotein C-II deficiency.

Suggested Audit Criteria

- Audit the number of pediatric CKD patients treated with TLC, diet, and weight loss for lowering TGs.
- Audit the number of pediatric CKD patients treated with pharmacological TG-lowering therapy.
- Record the number of pediatric CKD patients with drug intolerance and/or non-compliance.

KEY POINTS

- TLC should be recommended to children with CKD and hypertriglyceridemia.
- Fibric acid derivatives are not recommended to prevent pancreatitis or reduce cardiovascular risk in children with CKD and hypertriglyceridemia.

RESEARCH RECOMMENDATIONS

Future studies should be conducted to:

- Determine prevalence of hypertriglyceridemia in pediatric kidney transplant recipients.
- Determine the effect of diet and weight loss in lowering TG among pediatric CKD patients.

DISCLAIMER

Methods for guideline development

Kidney International Supplements (2013) **3,** 287–296; doi:10.1038/kisup.2013.39

AIM

The overall aim of this project was to develop an evidence-based CPG for the management of dyslipidemia and CKD. The guideline consists of recommendation statements, rationales, and a summary of systematically generated evidence on relevant pre-defined clinical topics. The general guideline development method is described at http://www.kdigo.org/home/guidelines/development as well as below.

OVERVIEW OF PROCESS

The development process for the *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease* included the following steps:

- Appointing Work Group members and the evidence review team (ERT)
- Discussing process, methods, and results
- Developing and refining topics
- Identifying populations, interventions or predictors, and outcomes of interest
- Selecting topics for systematic evidence review
- Standardizing quality assessment methodology
- Developing and implementing literature search strategies
- Screening abstracts and retrieving full-text articles on the basis of pre-defined eligibility criteria
- Creating data extraction forms
- Extracting data and performing critical appraisal of the literature
- Grading the methodology and outcomes in individual studies
- Tabulating data from individual studies into summary tables
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles
- Grading the strength of recommendations on the basis of the quality of evidence and other considerations
- Finalizing guideline recommendations and supporting rationales
- Sending the guideline draft for peer review to the KDIGO Board of Directors in August 2012 and for public review in November 2012
- Editing the guideline
- Publishing the final version of the guideline

The Work Group Co-Chairs, KDIGO Co-Chairs and ERT met for a two-day meeting to go over the guideline development process, evidence review topics, and systematic review findings. Following this, the Work Group, KDIGO Co-Chairs and KDIGO support staff met held a two-day meeting to revisit the available evidence, formulate recommendation statements, deliberate on rationale for recommendations, and to develop consensus.

Commissioning of Work Group and ERT

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group of domain experts, including individuals with expertise in internal medicine, adult and pediatric nephrology, cardiology, hypertension, pharmacology, epidemiology, and endocrinology. The Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA, was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician–methodologists with expertise in nephrology and evidence-based clinical practice guideline development, a project coordinator, a research assistant, and a project manager/medical writer.

Defining Scope and Topics

The Work Group Co-Chairs and the ERT defined the overall scope and goals of the guideline (including a list of critical and important outcomes) and then drafted a preliminary list of topics and key clinical questions. They also reviewed the topics in the KDOQI guideline,[1] which the ERT also had helped to develop. The Work Group and ERT further developed and refined each topic and specified screening criteria, literature search strategies, and data extraction forms (Table 6).

Establishing the Process for Guideline Development

The ERT performed systematic literature searches and organized abstract and article screening. The ERT also coordinated the methodological and analytical processes, and defined and standardized the methodology for performing literature searches, data extraction, and summarizing the evidence. The Work Group took the primary role of writing the recommendation statements and rationales and retained final responsibility for their content. The Work Group Co-Chairs and the ERT prepared the first draft of the scope of work document as a series of open-ended questions to be considered by Work Group members.

Formulating Questions of Interest

Questions of interest were formulated according to the PICODD (Population, Intervention, Comparator, Outcome, study Design and Duration of follow-up) criteria. Details of the PICODD criteria are presented in Table 6.

Table 6 | Systematic review topics and screening criteria

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, halving of GFR Continuous: changes in TC, LDL-C, or HDL-C or TGs
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 weeks for continuous lipid outcomes; 1 year for clinical outcomes; if general population study, 1 year
Minimum *N* of Subjects	≥100 per arm for adults, ≥25 per arm for children; if general population study, ≥500 per arm for adults or ≥100 per arm 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, halving of GFR Continuous: changes in TC, LDL-C, or HDL-C or TGs
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 weeks for continuous lipid outcomes; 1 year for clinical outcomes; if general population study, 1 year
Minimum *N* of subjects	≥25 per arm
Drug interactions (update of Tables 32-37 in KDOQI 2003 guideline)	
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 *N* of subjects	NA
Change in LDL-C level by statin	
Population	General population
Intervention	Any statin
Comparator	Other agent or placebo
Outcomes	Change in LDL-C
Design	Systematic review or meta-analysis, 2006-2011
Minimum duration of follow-up	NA
Minimum *N* of subjects	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 owing to drug, AKI, cancer, rhabdomyolysis, myalgia, increased creatine kinase, increased creatinine, increased ALT or AST, any other specified; in children, also measures of growth, development, cognitive function
Design	Any
Minimum duration of follow-up	Any
Minimum *N* of Subjects	Any
Frequency of lipids testing	
Population	Any
Intervention	Any regimen with variable timing of measurement: e.g., more vs. less testing, 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 months
Minimum *N* of subjects	≥50 per arm

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; RCT, randomized controlled trial; SCr, serum creatinine; TC, total cholesterol; TG, triglyceride.

Ranking of Outcomes

The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table 7). Mortality, cardiovascular mortality, cardiovascular or cerebrovascular events, ESRD, and graft failure were considered to be of critical importance; doubling of SCr and halving of GFR, high importance; and change in TC, LDL-C, or HDL-C or TG, moderate importance. The importance of adverse events was considered to depend on the event severity.

Literature Searches and Article Selection

Systematic search strategies were developed by the ERT with input from the Work Group Co-Chairs. Modules were created for RCTs, kidney disease, dyslipidemia, and lipid-lowering agents. For the primary search, search terms were limited to the year 2000 and later to capture trials that would affect current clinical practice and because the KDOQI dyslipidemia guideline covered through 2000. Five new topics were added to the KDOQI systematic review for studies in the general population: effect of diet or lifestyle modification; an update of drug interactions with statins and fibrates; changes in LDL-C levels associated with various statins; adverse events from statin and fibrate use; and frequency of lipid-level testing. These searches were not restricted to 2000 and later. The text words or medical subject headings (MeSH) that were included are provided in the Supplemental Appendix 1. In addition, the ERT searched for existing relevant systematic reviews. The final searches were conducted in August 2011. The ERT searched MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. The ERT also relied on Work Group members to identify large, general population RCTs reporting on CKD subgroups. The search yield was also supplemented by articles provided by Work Group members through June 2013.

For selection of studies, all members of ERT independently and manually screened the abstracts using the computerized screening program Abstrackr. To establish relevance and consensus among reviewers, the entire team screened and achieved consensus on an initial batch of 500 abstracts. A total of 11,337 citations were initially screened. Journal articles reporting original data, meta-analyses, and systematic reviews were selected for evidence review, based on *a priori* criteria for eligible evidence. Editorials, letters, abstracts, unpublished reports, and articles published in non–peer-reviewed journals were not included. The Work Group also decided to exclude publications from journal supplements because of potential differences in the process of how they are solicited, selected, reviewed, and edited compared to peer-reviewed publications. The overall search yield along with the number of abstracts identified and articles reviewed for each topic are presented in Table 8.

Data Extraction

Data extraction was done by an ERT member. Although no duplicate extraction was independently performed, data from each study was examined by another reviewer to confirm accuracy. The ERT, in consultation with the Work Group Co-Chairs, designed forms to capture data on design, methodology, sample characteristics, interventions, comparators, outcomes, results, and limitations of individual studies. Methodology and outcomes were also systematically graded (see the section on grading below) and recorded during the data extraction process.

Summary Tables

Summary tables were developed for each comparison of interest. Summary tables contain outcomes of interest, relevant population characteristics, description of intervention and comparator, results, and quality grading for each outcome. Categorical outcomes and continuous lipid outcomes were tabulated separately. For studies not exclusively examining CKD populations, only those reporting analysis by CKD subgroups were tabulated.

Work Group members proofed all summary table data and quality assessments. Summary tables are available at http://www.kdigo.org/home/guidelines/lipids.

Table 7 | Hierarchy of outcomes

Hierarchy	Outcome
Critical importance	Mortality, cardiovascular mortality, cardiovascular or cerebrovascular events, ESRD, graft failure
High importance	Doubling of SCr or halving of GFR
Moderate importance	Change in TC, LDL-C, or HDL-C or TGs
Importance dependent on severity	Adverse events

Abbreviations: ESRD, end-stage renal disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SCr, serum creatinine; TC, total cholesterol; TG, triglyceride

Table 8 | Literature yield for RCTs*

				Studies included in Summary Tables						
Intervention	Abstracts identified	Articles retrieved	Studies with data extracted	Statin vs. Placebo	Atorvastatin vs. Placebo, kidney transplant recipients	Statin vs. Lifestyle	Statin vs. Placebo, ADPKD	Atorvastatin 80 mg vs. 10 mg	Low vs. Moderate Protein Diet	Ezetimibe vs. Placebo
Agent or Diet/Lifestyle	11,337	120	16	9	2	1	1	1	1	1
Adverse Events	11,337	89	11	11 (across all comparisons)						

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; RCT, randomized controlled trial.
*Counts not listed for the four other topics for various reasons: no RCTs were found for frequency of testing and existing systematic reviews were used for change in LDL-C by statin and drug interactions.

Evidence Profiles

Evidence profiles were constructed to assess the quality and record quality grades and descriptions of effect for each outcome across studies, as well as the quality of overall evidence and description of net benefits or harms of the intervention or comparator across all outcomes. These profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based on data from the primary studies listed in corresponding summary tables and on judgments of the ERT and Work Group. When the body of evidence for a particular comparison of interest consisted of only one study, the summary table provided the final level of synthesis and an evidence profile was not generated. Each evidence profile was initially constructed by the ERT and then reviewed, edited, and approved by the Work Group. The work products created by the ERT for summarizing the evidence base are listed in Table 9.

Grading of Quality of Evidence for Outcomes of Individual Studies

Methodological quality (internal validity) refers to the design, conduct, and reporting of outcomes of a clinical study. A previously devised three-level classification system for quality assessment was used to grade the overall study quality and quality of all relevant outcomes in the study (Table 10). Grading of individual studies was done by one of the reviewers, then confirmed by another, and finalized in a group meeting. Variations of this system have been used in most KDOQI and all KDIGO guidelines and have been recommended by the US Agency for Healthcare Research and Quality Evidence-based Practice Center program.[107]

Each study was given an overall quality grade based on its design, methodology (randomization, allocation, blinding, definition of outcomes, appropriate use of statistical methods, etc.), conduct (dropout percentage, outcome assessment methodologies, etc.) and reporting (internal

Table 10 | Classification of study quality

Good quality	Low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective. If study of intervention, must be RCT.
Fair quality	Moderate risk of bias, but problems with study or paper are unlikely to cause major bias. If study of intervention, must be prospective.
Poor quality	High risk of bias or cannot rule out possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

Abbreviation: RCT, randomized controlled trial.

Table 9 | Work products for the guideline*

Topic	Summary table of RCTs	Evidence profile
Lipid-lowering agents or diet/lifestyle modification		
Atorvastatin vs. atorvastatin	+	– (single study)
Ezetimibe vs. placebo (simvastatin+ezetimibe vs. simvastatin)	+	– (single study)
Statin vs. placebo in ADPKD	+	– (single study)
Statin vs. placebo in CKD	+	+ (8 studies)
Statin vs. usual care	+	– (single study)
Low vs. moderate protein diet	+	– (single study)
Statin + ezetimibe vs. placebo	+	– (single study)
Statin vs. placebo in kidney transplant recipients	+	+ (2 studies)
Statin vs. lifestyle in kidney transplant recipients	+	+ (2 studies)
Statin vs. placebo in children	+	– (single study)
Statin vs. placebo in CKD with dialysis	+	+ (2 studies)
Exercise vs. control	+	– (single study)
Drug interactions (update of Tables 32–37 in KDOQI 2003 guideline)		
Drug interactions	+	– (single pre-existing systematic review)
Adverse events from statin+fibrate therapy		
Any adverse event	+	– (no evidence profiles prepared re adverse events)
Serious adverse event	+	– (no evidence profiles prepared re adverse events)
Treatment-related adverse event	+	– (no evidence profiles prepared re adverse events)
Discontinuation due to adverse event	+	– (no evidence profiles prepared re adverse events)
Increased ALT or AST	+	– (no evidence profiles prepared re adverse events)
Increased creatine kinase	+	– (no evidence profiles prepared re adverse events)
Increased SCr	+	– (no evidence profiles prepared re adverse events)
Rhabdomyolysis	+	– (no evidence profiles prepared re adverse events)
Other adverse event	+	– (no evidence profiles prepared re adverse events)
Frequency of lipids testing		
Frequency of lipids testing	–	– (0 studies)
Change in LDL-C by statin		
Change in LDL-C by statin	+	– (single pre-existing systematic review)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; SCr, serum creatinine.
Coding: +: work product is indicated for the topic of interest; –: work product is not indicated for the topic of interest.
General population studies with a CKD subgroup are included.

consistency, clarity, thoroughness and precision, etc.). Each reported outcome was then evaluated and given an individual grade depending on the quality of reporting and methodological issues specific to that outcome. However, the quality grade of an individual outcome could not exceed the quality grade for the overall study.

Grading the Quality of Evidence and the Strength of a Guideline Recommendation

A structured approach, based on GRADE[108–110] and facilitated by the use of evidence profiles, was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Co-Chairs. The "strength of a recommendation" indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The "quality of a body of evidence" refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.[109]

Grading the quality of evidence for each outcome across studies. Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized on the basis of study design. For questions of interventions, the initial quality grade was 'High' if the body of evidence consisted of RCTs, 'Low' if it consisted of observational studies, and 'Very Low' if it consisted of studies of other study designs. For questions of interventions, the Work Group decided to use only RCTs. The grade for the quality of evidence for each intervention–outcome pair was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate [0 or 1 event] in either arm or a CI spanning a range >1) or sparse (only 1 study or total $N<500$), or if there was thought to be a high likelihood of bias. Once consensus is reached in a group meeting, the final grade for the quality of the evidence for an intervention–outcome pair could be one of the following four grades: 'High', 'Moderate', 'Low' or 'Very Low' (Table 11).

CKD subgroup analyses. The following criteria were devised to grade the quality of CKD-subgroup analyses of RCTs that were not specifically designed for or limited to individuals with CKD. CKD subgroups were graded only if they were of an acceptable size for the topic of interest (e.g., 50 per arm with CKD for lipid guideline). These criteria will be considered along with the assessment of whether the putative subgroup effect is plausible with regard to direction and size of effect.

For the complete set of subgroup grading criteria, see Figure 3. Briefly, the study quality was graded according to

Table 11 | GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence and definition
Randomized trials = High	*Study quality* −1 level if serious limitations −2 levels if very serious limitations	*Strength of association* +1 level if strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity	High = Further research is unlikely to change confidence in the estimate of the effect
	Consistency −1 level if important inconsistency	*Other* +1 level if evidence of a dose–response gradient	Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Observational study = Low	*Directness* −1 level if some uncertainty −2 levels if major uncertainty	+1 level if all residual plausible confounders would have reduced the observed effect	Low = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate
Any other evidence = Very Low	Other −1 level if sparse or imprecise data[c] −1 level if high probability of reporting bias		Very Low = Any estimate of effect is very uncertain

Abbreviation: GRADE, Grading of Recommendations Assessment, Development and Evaluation.
[a]Strong evidence of association is defined as 'significant relative risk of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.
[b]Very strong evidence of association is defined as 'significant relative risk of >5 (<0.2)' based on direct evidence with no major threats to validity.
[c]Sparse if there is only one study or if total $N<500$. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range >1.
Adapted by permission from Macmillan Publishers Ltd: *Kidney International*. Uhlig K, Macleod A, Craig J *et al*. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 70: 2058–2065;[110] accessed http://www.nature.com/ki/journal/v70/n12/pdf/5001875a.pdf

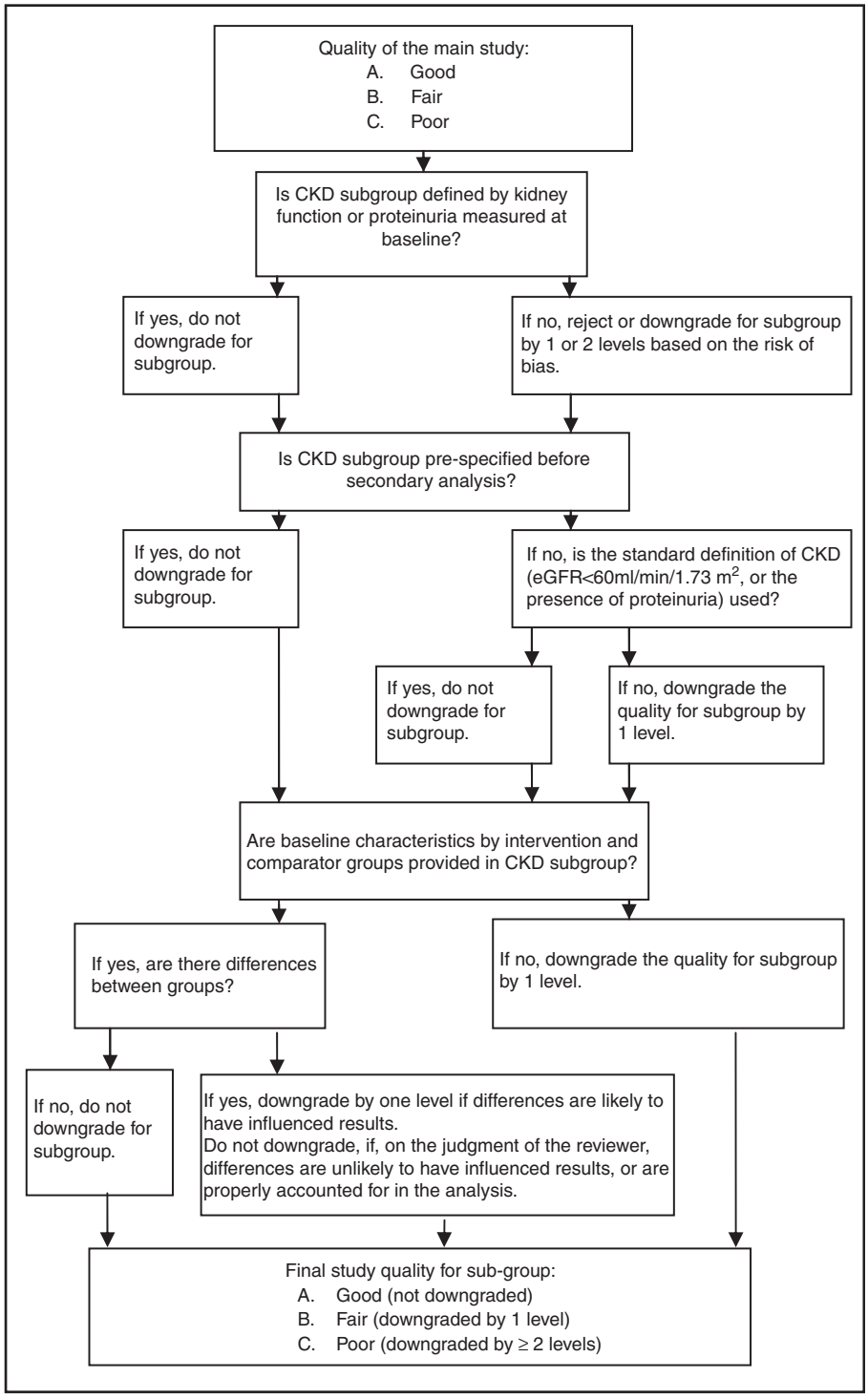

Figure 3 | Grading the quality of CKD subgroups of non-CKD trials. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

whether the CKD subgroup defined by kidney function or proteinuria measured at baseline (rather than after the start of treatment), whether or not analyses of subgroups were pre-specified before randomization, whether or not intervention and comparator groups were balanced within the CKD subgroup. The directness of the CKD subgroup analysis was graded on the basis of whether or not the CKD subgroup results of trials that were not specifically designed for CKD were applicable to patients with CKD and also whether or not a test for interaction by baseline kidney function (or the level of proteinuria) was performed.

Grading the overall quality of evidence. The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: 'A', 'B', 'C' or 'D' (Table 12).

Assessment of the net health benefit across all important clinical outcomes. The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table 13). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

Developing the recommendations. Draft recommendation statements were developed by the Work Group Co-Chairs and Work Group members with input from all Work Group members. The health benefits, side effects, and risks associated with each recommendation were considered when formulating the guideline, as well as information on patient preferences when available. Recommendation statements were revised in a multi-step process during teleconferences and a face-to-face meeting, as well as in subsequent drafts by email. All Work Group members provided feedback on initial and final drafts of the recommendation. The final draft was sent for internal and external peer review, and was further revised by the Work Group Co-Chairs and members. All Work Group members approved the final version of the guideline.

Grading the strength of the recommendations. The strength of a recommendation is graded as level 1 or level 2. Table 14 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy-makers. Recommendations can be for or against doing something. Each recommendation includes an explicit link between the quality of the

Table 12 | Final grade for overall quality of evidence

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.

Table 13 | Balance of benefits and harms

When there was evidence to determine the balance of medical benefits and harms of an intervention to a patient, conclusions were categorized as follows:

- For statistically significant benefit or harm, report as 'benefit [or harm] of drug X.'
- For non–statistically significant benefit or harm, report as 'possible benefit [or harm] of drug X.'
- In instances where studies are inconsistent, report as 'possible benefit [or harm] of drug X.'
- 'No difference' can only be reported if a study is not imprecise.
- 'Insufficient evidence' is reported if imprecision is a factor.

Table 14 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade*	Patients	Clinicians	Policy-makers
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	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.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding 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.

Table 15 | Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature where possible or were assessed in the judgment of the Work Group where robust evidence was not identified.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Table 16 | The Conference on Guideline Standardization (COGS)[112] checklist for reporting clinical practice guidelines

Topic	Description	Discussed in KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	*Abstract* and *Methods for Guideline Development*.
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	Management of elevated levels of TC, LDL-C, or HDL-C or TGs and lipid-lowering agents in adults and children with CKD (non-dialysis-dependent or dialysis) or a kidney transplant.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This CPG is intended to assist the practitioner caring for patients with CKD and dyslipidemia and to prevent deaths, CVD events, and progression to kidney failure while optimizing patients' quality of life.
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	Target audience is practicing nephrologists and other healthcare providers for adults and children with CKD and dyslipidemia.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Adults and children with CKD and dyslipidemia.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO Names/credentials/potential conflicts of interest of individuals involved in the guideline's development are disclosed in the Biographic and Disclosure Information.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	KDIGO is supported by the following consortium of sponsors: Abbott, Amgen, Bayer Schering Pharma, Belo Foundation, Bristol-Myers Squibb, Chugai Pharmaceutical, Coca-Cola Company, Dole Food Company, Fresenius Medical Care, Genzyme, Hoffmann-LaRoche, International Society of Nephrology, JC Penney, Kyowa Hakko Kirin, NATCO—The Organization for Transplant Professionals, NKF-Board of Directors, Novartis, Pharmacosmos, PUMC Pharmaceutical, Robert and Jane Cizik Foundation, Shire, Takeda Pharmaceutical, Transwestern Commercial Services, Vifor Pharma, and Wyeth. No funding is accepted for the development or reporting of specific guidelines. All stakeholders could participate in open review.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic reviews on treatment with different lipid-lowering agents or lifestyle modifications, we searched for RCTs in MEDLINE, Cochrane Central Registry for trials, and Cochrane database of systematic reviews. Screening criteria are outlined in the *Methods for Guideline Development* chapter. The search was updated through August 2011 and supplemented by articles identified by Work Group members through June 2013. We also searched for pertinent existing guidelines and systematic reviews.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a three-tiered grading system (see Table 10). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 12 and 14). The Work Group could provide general guidance in unngraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	For systematic review topics, summary tables and evidence profiles were generated. For recommendations on treatment interventions, the steps outlined by GRADE were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline had undergone internal review by the KDIGO Board in August 2012 and external public review in November 2012. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.	The requirement for an update will be assessed in five years from the publication date or earlier if important new evidence becomes available in the interim. Such evidence might, for example, lead to changes to the recommendations or may modify information provided on the balance between benefits and harms of a particular therapeutic intervention.

Table 16 | Continued

Topic	Description	Discussed in KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	*Abbreviations and Acronyms*.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9.	Each guideline chapter contains recommendations for lipid management in CKD patients. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation.
15. Potential benefits and harms	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each comparison of interventions are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Recommendations that are level 2 or ''discretionary'' indicate a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	No overall algorithm.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are intended for a global audience. Review criteria were not suggested because implementation with prioritization and development of review criteria have to proceed locally. Furthermore, most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria. Suggested audit criteria were provided to assess impact of guideline after publication. Research recommendations were also outlined to address current gaps in the evidence base.

Abbreviations: CKD, chronic kidney disease; CPG, clinical practice guideline; CVD, cardiovascular disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HDL-C, high-density lipoprotein cholesterol; KDIGO, Kidney Disease: Improving Global Outcomes; LDC-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; TC, total cholesterol; TG, triglyceride.

available evidence and the strength of that recommendation. However, Table 15 shows that the strength of a recommendation is determined not only by the quality of the evidence but also by other, often complex judgments regarding the size of the net medical benefit (potential risks versus benefit), values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Ungraded statements. This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense, it provides reminders of the obvious, and it is not sufficiently specific to allow for application of evidence to the issue and therefore it is not based on systematic evidence review. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme, with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, as well as the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took on the primary role of writing the recommendations and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Format for guideline recommendations. Each chapter contains one or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2 and the quality of the supporting evidence is shown as A, B, C, or D. The recommendation statements and grades are followed by the rationale text summarizing the key points of the evidence base and the judgments supporting the recommendation. In relevant sections, considerations of the guideline statements in international settings and suggested audit criteria are also provided where applicable. Important key points and research recommendations suggesting future research to resolve current uncertainties are also outlined at the conclusion of each chapter.

Limitations of Approach

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was

the only database searched. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, any important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

Review of Guideline Development Process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE 2) criteria,[111] the Conference on Guideline Standardization (COGS) checklist,[112] and the Institute of Medicine's recent *Standards for Systematic Reviews*[113] and *Clinical Practice Guidelines We Can Trust*.[114] Table 16 and Supplemental Appendix 2 online show, respectively, the criteria which correspond to the COGS checklist and the Institute of Medicine standards, and how each one of them is addressed in this guideline.

SUPPLEMENTARY MATERIAL

Supplemental Appendix 1: Online search strategies.

Supplemental Appendix 2: Concurrence with Institute of Medicine standards for systematic reviews and for guidelines.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/home/guidelines/lipids

Biographic and disclosure information

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Marcello A Tonelli, MD, SM, FRCPC (Work Group Co-Chair), received an MD from the University of Western Ontario, specialist certification in nephrology (FRCPC) at Dalhousie University, and an SM in epidemiology from Harvard University. He is a nephrologist and Associate Professor at the University of Alberta. He serves as Associate Editor of *American Journal of Kidney Diseases*, the Cochrane Renal Group and the *Journal of Nephrology*, and is a member of the Editorial Board for *Journal of the American Society of Nephrology*. Dr. Tonelli is the President of the Canadian Society of Nephrology, a Councillor of the International Society of Nephrology and a past member of the Minister's Expert Committee for Drug Evaluation for the Province of Alberta. In March 2010, Dr. Tonelli was named the chair of the Canadian Task Force for Preventive Health Care, a national panel of experts that will make recommendations about preventive health services to Canada's more than 36,000 family physicians.

Dr. Tonelli holds a Health Scholar award from the Alberta Heritage Foundation for Medical Research (AHFMR) and a Canada Research Chair in the optimal care of people with CKD. He is a founding member of the Alberta Kidney Disease Network and co-leader of the AHFMR Interdisciplinary Chronic Disease Collaboration (ICDC) research team. Since 2005, Dr. Tonelli has been the co-leader of a joint initiative between the University of Alberta and the Hospital Civil de Guadalajara, aimed at prevention of kidney failure among the poor of Jalisco, Mexico.

Consultant: Merck (honorarium donated to charity)
Speaker: Merck (honorarium donated to charity)

Christoph Wanner, MD (Work Group Co-Chair), is Head of Nephrology, Department of Medicine at University of Würzburg, where he also obtained his MD. He then trained in Internal Medicine and subsequently Nephrology, in Freiburg, Germany. Dr Wanner has maintained an active research interest in the role of lipids in progression of kidney disease, having participated in two major trials conducted in this area: 4D and SHARP. His research also includes the elucidation of the inflammatory response syndrome in diabetic nephropathy, CKD and ESRD; pathogenesis and treatment for Fabry disease; and identification of risk factors for CKD progression and CVD in large study cohorts. Dr. Wanner has authored over 400 publications, including serving presently as Editor-in-Chief of *Journal of Renal Nutrition* and editorial board member for *Clinical Nephrology*, *Current Opinion in Nephrology & Hypertension*, *Kidney International*, and *Nephrology Dialysis Transplantation*. He is also President of the International Society of Renal Nutrition and Metabolism and Chairman of ERA-EDTA Renal Registry. In recognition of his contributions to nephrology, he was awarded the International Distinguished Medal from the US NKF in 2007 and nominated as honorary member of the Polish Society of Nephrology in 2011. In 2012 he obtained a doctor honoris causa from the Charles University of Prague.

Advisory Board: Boehringer Ingelheim; Keryx; Reata
Consultant: AMAG; Baxter; Boehringer Ingelheim; Reata
Development of Educational Materials: Mitsubishi
*Grant/Research Support: Genzyme**
Speaker: Abbott; Amgen; Astellas; AstraZeneca; Bristol-Myers Squibb; Fresenius Medical Care; Genzyme; Merck Sharp & Dohme; Mitsubishi; Roche
**monies paid to institution*

Alan Cass, MBBS, FRACP, PhD, is Director of the Menzies School of Health Research in Darwin, Australia and previously served as Senior Director, Renal and Metabolic Division, The George Institute for Global Health in Sydney, Australia. Dr Cass completed his nephrology training and PhD studies at the University of Sydney where he investigated the social determinants of ESRD. His current research encompasses the use of rigorous quantitative and qualitative methods to foster the development, implementation and evaluation of strategies to address the growing burden of CKD. He also conducts primary care intervention research aiming to reduce barriers to necessary care for Indigenous Australians and enhance access to renal services in remote areas, thereby improving their health outcomes. Dr Cass is President-Elect for the Australian and New Zealand Society of Nephrology (ANZSN), a member of the Executive of the Australasian Kidney Trials Network and International Society of Nephrol-

ogy (ISN) CKD Policy Task Force. An author of over 150 publications, he recently received the 2012 NSW Aboriginal Health Award for Closing the Gap through Excellence in Chronic Care, and the 2013 T J Neale Award for Outstanding Contribution to Nephrological Science from ANZSN.

Advisory Board: Abbott; Merck
Consultant: Baxter
Expert Testimony: Merck
Grant/Research Support: Amgen; Baxter;* Merck;* Novartis**
Speaker: Fresenius Medical Care
**monies paid to institution*

Amit X Garg, MD, FRCPC, FACP, PhD, is a Professor of Medicine, Epidemiology and Biostatistics at the University of Western Ontario. He practices nephrology at the London Health Sciences Centre and cares for patients with CKD, acute kidney injury (AKI) and individuals wishing to donate a kidney to a loved one. Dr. Garg conducts clinical and health services research to improve health outcomes for patients with kidney diseases including those receiving dialysis or a kidney transplant. He also aims to improve the efficiency by which renal care is delivered. He currently holds a Clinician Scientist Award from the Canadian Institutes of Health Research. He is the current Director of the London Kidney Clinical Research Unit and Scientific Director of the Institute for Clinical Evaluative Sciences at Western Facility.

Dr Garg reported no relevant financial relationships

Hallvard Holdaas, MD, PhD, is senior consultant in Nephrology at Department of Transplant Medicine, Oslo University Hospital, Rikshospitalet, Norway, where he also received his training in transplant medicine. His primary research interests are immunosuppression, dyslipidemia, and CVD in renal transplant recipients. He was the PI in the ALERT trial (fluvastatin) and co-PI in the AURORA and SHARP trials. Dr Holdaas is a member of numerous professional organizations including American Society of Nephrology, American Society of Transplantation, European Dialysis and Transplant Association and European Society for Organ Transplantation. He has published more than 170 original articles, reviews and book chapters in the fields of nephrology, dialysis and transplantation.

Speaker: Abbott; Astellas; AstraZeneca; Novartis

Alan G Jardine, MBChB, MD, FRCP, graduated in Physiology (1981) and Medicine (1984) from the University of Glasgow. He undertook postgraduate research training as a Clinical Training Fellow in the MRC Blood Pressure Unit, where he pursued studies on the physiology, pharmacology and therapeutic potential of natriuretic peptides. He trained initially in Endocrinology and subsequently Nephrology, in Glasgow and Aberdeen, UK. Since 1994 he has been on the staff of the University of Glasgow, where he has been Professor of Renal Medicine since 2006. He has pursued a variety of research themes that center on accelerated vascular disease and long-term adverse outcomes in patients with renal disease and transplantation, their pathophysiological and genetic determinants, and their management. His current research combines laboratory work, clinical research and clinical trials, and he is the leader of the Renal Research Group in the BHF Glasgow Cardiovascular Research Centre. Since 2010 he has been the Head of the Undergraduate Medical School in Glasgow. He is a member of the Council of the European Society for Transplantation.

Consultant: Abbott; Novartis; Pfizer; Opsona**
*Development of Educational Materials: Pfizer**
Expert Testimony: Commission on Human Medicines (UK); European Medicines Agency; US Food and Drug Administration
*Speaker: Astellas; Bristol-Myers Squibb; Genzyme (Sanofi); Merck Sharp & Dohme; Pfizer**
**monies paid to institution*

Lixin Jiang, MD, PhD, is the Director for National Cardiovascular Bio-bank Centre, Co-Director for China Oxford Centre for International Health Research, and Deputy Director for Center of Dyslipidemia and Cardiovascular Disease of Fuwai Hospital. She is also Editor-in-Chief for *The Lancet* Chinese Edition, Editorial Board Member for the journal *Circulation: Cardiovascular Quality and Outcomes* and a Doctoral mentor at Chinese Academy of Medical Sciences and Peking Union Medical College.

Dr. Jiang obtained her medical degree from the Chinese Academy of Medical Sciences and Peking Union Medical College. Her main research interests involve large RCTs, epidemiological studies, pharmacogenomics studies and outcomes research. She serves as the Executive Member in the Young and Middle-Aged Scholar Committee of Stroke Screening and Prevention, National Health and Family Planning Commission of China, and the Advisory Expert on the Panel on Cardiovascular Disease, Committee of Experts on Rational Drug Use, National Health and Family Planning Commission of China.

As the Steering Committee member and site PI in China, Dr. Jiang has successfully run several international large-scale clinical trials including: ISCHEMIA, HPS3/TIMI55: REVEAL, HPS2-THRIVE, COMMIT/CCS-2, SHARP, TRACER, and INTER-HEART. Moreover, she is the PI of four national key research projects funded by Chinese government, including China Patient-centered Evaluative Assessment of Cardiac Events (China PEACE) (2012–2014), The Study on Hereditary Susceptibility to Statin-related Myopathy (2011–2015), Establishment of the Bio-bank of Chinese Cardiovascular & Cerebrovascular Disease (2011–2015), and China PEACE-stent (2013–2014).

Dr. Jiang started her international collaboration with the Oxford University in the 1980 s and since then she has been cooperating with different top research institutions worldwide. Presently, her collaborative partners include Oxford University, Yale University, NHLBI, NIH, University of Edinburgh, Duke University, Merck Research Laboratories, etc. Through years of research operation, Dr. Jiang has set up a reliable and stable national cooperation network of over 200 hospitals within 31 provinces in China.

Her achievements in the field of evidence-based medicine have attracted international recognition and acclaim. Sir Richard Peto, Co-Director of Clinical Trials Service Unit and Epidemiological Studies Unit at Oxford University, once said that she has been a "whirlwind force for evidence" and *The Lancet* commented that "she is at the heart of China's evidence base."

Dr Jiang reported no relevant financial relationships

Florian Kronenberg, MD, received his MD from the University of Innsbruck, Austria. After specializing in Medical Genetics he worked two years each at the University of Utah, Salt Lake City, USA and the Institute of Epidemiology at the Helmholtz Center, Munich, Germany. In 2004, he became Full Professor for Genetic Epidemiology at the Innsbruck Medical University where he presently heads the Department of Medical Genetics, Molecular and Clinical Pharmacology. Dr. Kronenberg served as PI in several studies on genetic risk factors for atherosclerosis and biomarkers for the progression of CKD including the ″Mild to Moderate Kidney Disease Study″ (MMKD). He served as a workgroup member of the NKF K/DOQI Guidelines on Cardiovascular Disease in Dialysis Patients and is Associate Editor of *Atherosclerosis* and Academic Editor of *PLoS One*.

Advisory Board: Genzyme, Keryx
Speaker: Amgen; Genzyme

Rulan S Parekh, MD, MS, FRCP(C), FASN, is a Clinician Scientist and Associate Professor of Medicine and Paediatrics at the University of Toronto, The Hospital for Sick Children and University Health Network. The focus of Dr. Parekh's research is to study risk factors both clinically and genetically leading to progression of CKD and CVD. She has published over 80 peer reviewed manuscripts and book chapters, and has mentored over 25 postdoctoral fellows and students. She leads the NIH-NIDDK sponsored "Predictors in Arrhythmic and Cardiovascular Disease in End Stage Renal Disease (PACE)", a new cohort study in dialysis patients to identify risk factors for sudden cardiac death. She is currently the chair of the American Kidney Fund Clinical Scientist Committee and on the Board of Trustees of the American Kidney Fund. She has recently been inducted into the American Society of Clinical Investigation and Society for Pediatric Research and has received awards for Advising, Teaching and Mentoring Award from the Johns Hopkins Bloomberg School of Public Health. She is presently an Associate Editor for *BMC Nephrology* and on the editorial board of the *Clinical Journal of the American Society of Nephrology*.

Trustee: American Kidney Fund (no compensation)
*Grant/Research Support: Physician Services Inc**
**monies paid to institution*

Tetsuo Shoji, MD, PhD, is affiliated with the Department of Geriatrics and Vascular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan. He studied medicine in the medical school of Osaka City University and then worked at the Second Department of Internal Medicine, Osaka City University Hospital. He is interested in dyslipidemia, and other metabolic and endocrine alterations as factors affecting CVD in patients with CKD. He is a member of the Japanese Society for Dialysis Therapy (JSDT), the Japanese Society of Nephrology (JSN), the Japan Atherosclerosis Society (JAS), the Japan Diabetes Society (JDS) and others. He was the recipient of the Society Award from JSDT and a Work Group Member for the following guideline groups: 2011 JSDT Guidelines for the Evaluation and Treatment of Cardiovascular Complications in HD Patients; 2012 JSDT Guideline for CKD-Mineral Bone Disorder; 2012 JAS Guidelines for Prevention of Atherosclerotic CVD; and 2013 JSN Guideline for the Treatment of CKD.

Grant/Research Support: Astellas; Daiichi Sankyo;* Dainippon Sumitomo;* Mochida;* Shionogi**
Speaker: Astellas; Daiichi Sankyo; Kowa; Kyowa Hakko Kirin; Merck Sharp & Dohme; Mochida; Pfizer; Shionogi
**monies paid to institution*

Robert J Walker, MBChB, MD (Otago), FRACP, FASN, FAHA, is Professor of Medicine and Head of the Department of Medicine at Dunedin School of Medicine, University of Otago, New Zealand. He is also a Consultant Nephrologist and Head of Nephrology at Healthcare Otago. Dr Walker has a broad base of translational renal research with interests in renal pharmacology, renal pathophysiology and drug nephrotoxicity, linked to the ongoing clinical research interests in the regulation of renal and cardiovascular hemodynamics and AKI. His clinical research program addresses a long-standing interest in renal hemodynamics, drug-induced alterations in renal function and nephrotoxicity, the role of renovascular hormones in the control of hypertension and renal disease, and cardiovascular risk factors in kidney disease. Dr Walker has also participated in a number of pivotal trials including IDEAL, SHARP, ASFAST, and PERFECT, and authored over 180 publications. Until 2011, he was actively involved in the Scientific Programme and Education Committee for the ANZSN, responsible for the scientific program of its annual scientific meeting as well as overseeing the society's education program. Professor Walker is a member of the ISN Nexus and Forefronts Committees, as well as serving on the Caring for Australasians with Renal Impairment guideline committees for cardiovascular risk factors in renal disease and dialysis adequacy. He is also an Executive Council member of Asian Pacific Society of Nephrology and has a strong interest in developing links between Australia & New Zealand with South East Asia and the Pacific to further advance the scientific knowledge and research in all aspects of nephrology.

Advisory Board: Fresenius SE Asia (no compensation)

KDIGO CHAIRS

Bertram L Kasiske, MD, is Professor of Medicine at the University of Minnesota, USA. He received his medical degree from the University of Iowa and completed his Internal Medicine residency and fellowship training in Nephrology at Hennepin County Medical Center where he is currently Director of Nephrology. Dr Kasiske is former Deputy Director of the United States Renal Data System and former Editor-in-Chief of *American Journal of Kidney Diseases*. He has served as Secretary/Treasurer and on the Board of Directors of the *American Society of Transplantation*, and on the Organ Procurement and Transplantation Network/United Network of Organ Sharing Board of Directors, and the Scientific Advisory Board of the US NKF. He is currently serving on the Board of Councilors of the ISN and he is the PI for a National Institutes of Health-sponsored, multicenter study of long-term outcomes after kidney donation. Dr Kasiske is the Director of the Scientific Registry of Transplant Recipients and has over 160 scientific publications in major peer-reviewed journals, and 230 review articles, editorials and textbook chapters. Dr Kasiske is also a recipient of the US NKF's Garabed Eknoyan Award in 2003.

Advisory Board: Litholink/Labcorp
Speaker: Merck Japan

David C Wheeler, MD, FRCP, holds an academic position in Nephrology (Reader) at University College London, UK and is an Honorary Consultant Nephrologist at the Royal Free Hospital. His research is focused on the cardiovascular complications of CKD and the role of vascular risk factors in progression of kidney damage. Dr Wheeler is a member of the International Steering Committee of SHARP and was UK National Coordinator for the trial. He is involved in several other randomized trials and observational studies involving patients with CKD. Dr Wheeler is Co-Chair of KDIGO, having served previously on its Executive Committee and Board. He received an International Distinguished Medal from the US NKF in recognition of his contribution to guideline development. In the UK, he has been elected President of the Renal Association for the term 2012-2014. Dr Wheeler has served on the editorial boards of *American Journal of Kidney Diseases* and *Journal of the American Society of Nephrology* and is presently Co-Editor for *Nephrology Dialysis Transplantation*.

Consultant: Amgen; Astellas; Baxter; Merck Sharp & Dohme; Otsuka; Vifor
Grant/Research Support: Abbott; AstraZeneca;* Genzyme**
Speaker: Abbott; Amgen; Astellas; Fresenius Medical Care; Genzyme; Otsuka; Shire
**monies paid to institution*

EVIDENCE REVIEW TEAM

Ashish Upadhyay, MD, is Assistant Professor, Renal Section and Associate Director, Internal Medicine Residency Program at Boston University School of Medicine, Boston, MA, USA. Dr Upadhyay was previously Assistant Professor at Tufts University School of Medicine and staff physician in the William B Schwartz, MD, Division of Nephrology at Tufts Medical Center. He joined the ERT in July 2009 and served as the Assistant Project Director for the KDIGO Management of Blood Pressure in CKD and Anemia in CKD Guidelines. In the role as lead project director for this guideline, Dr Upadhyay coordinated and assisted in the collection, evaluation, grading, and synthesis of evidence, and played a critical role in the revisions of the final evidence report. He also provided methodological guidance and training of Work Group members on topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. Dr Upadhyay's past research involved studying kidney disease epidemiology in the Framingham Heart Study. He has published in areas ranging from arterial stiffness in CKD and inflammation in kidney

disease to dialysis complications and epidemiology of hyponatremia.

Dr Upadhyay reported no relevant financial relationships

Ethan M Balk, MD, MPH, is Director, Evidence-based Medicine at the Tufts Center for Kidney Disease Guideline Development and Implementation, in Boston, MA, USA, Associate Director of the Tufts Evidence-based Practice Center, and Associate Professor of Medicine at Tufts University School of Medicine. Dr Balk graduated from Tufts University School of Medicine and completed a fellowship in Clinical Care Research. As Program Director for this guideline, he played a role in providing methodological expertise in the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence and the revisions of the final evidence report. Dr Balk also provided methodological guidance and training of Work Group members regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal.

Dr Balk reported no relevant financial relationships

Amy Earley, BS, is a project coordinator at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She is key in coordinating the guideline development activities within the ERT, especially in the development of the evidence reports for all guidelines. Ms Earley also heads the actual evidence review, which includes running searches, screening, data extraction, drafting of tables and methods sections, proofing of guideline drafts, and critical literature appraisals. She participates in the conduct of research projects at the Center and actively collaborates with other members of the Center on independent research topics and manuscript submissions.

Ms Earley reported no relevant financial relationships

Shana Haynes, MS, DHSc, is a research assistant at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development. She screens abstracts and articles, extracts data, and assists in the drafting and editing of evidence tables. Dr Haynes also assists in the development of clinical practice guidelines and conducts systematic reviews and critical literature appraisals.

Dr Haynes reported no relevant financial relationships

Jenny Lamont, MS, is a project manager and medical writer at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development, assists in the preparation of talks and manuscripts, and edits KDIGO draft guidelines currently in progress.

Ms Lamont reported no relevant financial relationships.

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Marcello A Tonelli, MD, SM, FRCPC
Christoph Wanner, MD
Work Group Co-Chairs

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