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Acronyms and Abbreviations

4-D	Die Deutsche Diabetes Dialyse Studie
4S	Scandinavian Simvastatin Survival Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACVD	Atherosclerotic Cardiovascular Disease
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
AHA	American Heart Association
AJKD	American Journal of Kidney Diseases
ALERT	Assessment of Lescol in Renal Transplantation
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ALLIANCE	Aggressive Lipid Lowering Initiation Abates New Cardiac Events
ASPEN	Atorvastatin as Prevention of Coronary Heart Disease
	Endpoints in Patients with Non-Insulin-Dependent Diabetes Mellitus
AST	American Society of Transplantation
ATP III	Adult Treatment Panel III
AUC	Area under the (concentration-time) curve
AZA	Azathioprine
BIP	Bezafibrate Infarction Prevention
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CHD	Coronary Heart Disease
CHOL	Cholesterol
CK	Creatinine phosphokinase
CKD	Chronic kidney disease
CMV	Cytomegalovirus
Cr	Creatinine (serum)
CsA	Cyclosporine A
CVD	Cardiovascular disease
DOQI	Dialysis Outcomes Quality Initiative
EDTA	European Dialysis and Transplantation Association
EPA	Eicosapentaenoic acid (20:n-3)
ESRD	End-stage renal disease
EXCEL	Expanded Clinical Evaluation of Lovastatin
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FMC	Fresenius Medical Care
GFR	Glomerular filtration rate
HD	Heart disease
HDL	High-density lipoprotein
HPS	The Heart Protection Study
IDEAL	Incremental Decrease in Endpoints Through Aggressive Lipid Lowering
IDL	Intermediate-density lipoproteins
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low-density lipoprotein
LIPID	Long-Term Intervention with Pravastatin in Ischaemic Disease
LMWH	Low molecular weight heparin
Lp(a)	Lipoprotein (a)
MI	Myocardial infarction
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
MMF	Mycophenolate mofetil
MRC	Medical Research Council
N	Number (of data points)

NCEP	National Cholesterol Education Program
NCEP-C	National Cholesterol Education Program-Children
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
NKF	National Kidney Foundation
NKF-K/DOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NS	Nephrotic syndrome
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
PREVEND IT	Prevention of REnal and Vascular ENdstage Disease Intervention Trial
PRINCE	Pravastatin Inflammation/C-Reactive Protein Evaluation
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PROVE IT	Pravastatin or Atorvastatin in Evaluation and Infection Therapy
SEARCH	Study Evaluating Additional Reductions in Cholesterol and Homocysteine
SHARP	The Study of Heart and Renal Protection
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
TG, TRIG	Triglycerides
TLC	Therapeutic lifestyle changes
TNT	Treating to New Targets
USFDA	United States Food and Drug Administration
VA-HIT	Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial
VLDL	Very low-density lipoprotein
WOSCOPS	West of Scotland Coronary Prevention Study

K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease

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Foreword

IN MARCH 1995, the National Kidney Foundation (NKF) launched the Dialysis Outcomes Quality Initiative (DOQI), supported by an unrestricted educational grant from Amgen, Inc, to develop clinical practice guidelines that would improve outcomes of patients on maintenance dialysis. Since their publication in 1997, the DOQI guidelines have had a significant and documented impact on the care and outcomes of dialysis patients.[1] In the course of developing the DOQI guidelines, it became evident that in order to actually improve dialysis outcomes it was necessary to improve the health status of those who reach end-stage renal disease (ESRD), and that therein existed an even greater opportunity to improve outcomes for all individuals with chronic kidney disease (CKD), from its earliest onset through its various stages of progressive loss of kidney function, when the complications of CKD develop resulting in an increasing number of comorbidities with which patients with kidney failure present for dialysis. It was on this basis that, in the fall of 1999, the board of directors of the NKF approved a proposal to move the clinical practice guidelines initiative into a new phase, in which its scope would be enlarged to encompass the entire spectrum of CKD. To reflect this expanded scope, the reference to "dialysis" in DOQI was changed to "disease" and the new initiative was termed Kidney Disease Outcomes Quality Initiative (K/DOQI).

To provide a unifying focus for this new initiative, it was decided that its centerpiece would be a set of clinical practice guidelines on the evaluation, classification, and stratification of CKD, which would provide a basis for the continuous care and appropriate management of patients throughout the course of progressive kidney disease. Work on the Chronic Kidney Disease: Evaluation, Classification, and Stratification guidelines began in January 2000 and the final guidelines were published in February 2002.[2]

It was decided from the outset that interventional guidelines for the management of the specific problems that affect patients with CKD would follow and be based on the staging and classification developed by Chronic Kidney Disease: Evaluation, Classification, and Stratification guidelines. Three such guidelines are now under various stages of development. We are proud to present the first of these interventional guidelines for the management of dyslipidemias.

Work on these guidelines began in November 2000. The Work Group appointed to develop these guidelines screened 10,363 relevant abstracts and selected 258 articles for formal structured review of content and methodology.

As detailed in the introductory comments of the Rationale for these Guidelines, they are meant to supplement the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel, ATP III) published in 2001.[3] Since its launch in 1985 by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH), NCEP has made significant strides towards its stated goal of reducing the prevalence of high blood cholesterol in the United States. However, ATP III and its older component in children (NCEP-C), without excluding or including patients with CKD, make few specific recommendations for the evaluation

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and treatment of dyslipidemias in CKD. Given the recommendations of the NKF Task Force on Cardiovascular Disease in Chronic Renal Disease[4] that patients with CKD should be considered in the highest risk group for cardiovascular disease, it was decided from the outset of K/DOQI that management of dyslipidemias in patients with kidney disease would be one of the first interventional guidelines that would be developed. The differences of the present set of guidelines from those of the ATP III and NCEP-C are given in Tables 5 and 6 of the guidelines, respectively.

On behalf of the NKF, we would like to acknowledge the considerable effort and contributions of all those who made these guidelines possible. In particular, we wish to acknowledge the following: the members of the Work Group charged with developing the guidelines, without whose tireless effort and commitment these guidelines would not have been possible; the members of the Support Group, whose input at monthly conference calls was instrumental in resolving the problems encountered in the course of the many months that it has taken to bring the guidelines to their present stage; the members of the K/DOQI Advisory Board, whose insights and guidance were essential in refining and expanding the applicability of the guidelines; to Amgen, Inc, which had the vision and foresight to appreciate the merits of K/DOQI and provided the unrestricted grant support for its launching and continued work since 2000; to Fujisawa Healthcare, Inc, which shared the K/DOQI objective to improve the management and care of this important problem which affects patients with CKD and transplantation, and as the Primary Sponsor of the present set of guidelines provided the unrestricted funds necessary for their development; and to the K/DOQI staff in New York, who worked diligently in attending to the innumerable details that needed attention on a daily basis, for coordinating and facilitating the work of everyone who has contributed to the guidelines, and in meeting the nearly impossible deadlines that have to be met in a project such as this.

A special debt of gratitude goes to Bertram L. Kasiske, MD, Chair of the Work Group, who, the perfect gentleman that he is, in his inimitable efficient and accommodating manner made the task for everyone who worked on these guidelines not only easier but a pleasant experience. His leadership, intellectual rigor, and expertise were the driving force that brought these guidelines to fruition. Special thanks are due also to Joseph Lau, MD, Director of the Evidence Review Team, for providing methodological rigor and staff support in developing the evidentiary basis of the guidelines. As the individual in charge of the review team of CKD and the present guidelines, as well as two other sets now under development, he has been the model patient and effective teacher who has helped train and graduate the members of the different Work Groups into the experts they have become in evidentiary medicine.

In a voluntary and multidisciplinary undertaking of the magnitude of K/DOQI, numerous others have made important contributions to these guidelines but cannot be individually acknowledged here. On behalf of all the patients and providers who will become the ultimate beneficiaries of these guidelines, we would like to extend our sincerest appreciations to each and every one of them.

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Abstract

THE INCIDENCE OF cardiovascular disease (CVD) is very high in patients with chronic kidney (CKD) disease. Indeed, available evidence for patients with Stage 5 CKD, and kidney transplant recipients, suggests that the 10-year cumulative risk of coronary heart disease is at least 20%, or roughly equivalent to the risk seen in patients with previous CVD. The Work Group concluded that the National Cholesterol Education Program Guidelines are applicable to patients with Stages 1-4 CKD. Therefore, these K/DOQI guidelines target adults and adolescents with Stage 5 CKD, and kidney transplant recipients. Dyslipidemias are very common in this population, but no randomized controlled trials have examined the effects of dyslipidemia treatment on CVD. Nevertheless, evidence from the general population suggests that treatment of dyslipidemias reduces CVD, and evidence in patients with Stage 5 CKD suggests that judicious treatment can be safe and effective in improving dyslipidemias. Therefore, guidelines were developed to aid clinicians in the management of dyslipidemias, until the needed randomized trials are completed. These guidelines are divided into four sections. The first section (Introduction) provides the rationale for the guidelines, and describes the target population, scope, intended users, and methods. The second section presents guidelines on the assessment of dyslipidemias (Guidelines 1-3), while the third section offers guidelines for the treatment of dyslipidemias (Guidelines 4-5). The key guideline statements are supported by data from studies in the general population, but there is an urgent need to confirm these study results in patients with CKD. Therefore, a fourth section outlines recommendations for research. The overall strength of each guideline statement was rated according to the table below.

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Rating the Strength of Recommendations.

Grade	Recommendation
A	It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves net health outcomes.
B	It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderate evidence that the practice improves net health outcomes.
C	It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence, poor evidence or on the opinions of the Work Group and reviewers, that the practice might improve net health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving net health outcomes implies that benefits outweigh any adverse effects.

I. INTRODUCTION

THE RATIONALE FOR THESE GUIDELINES

THE NUMBER OF patients with chronic kidney disease (CKD) is increasing. Unfortunately, the survival of CKD patients remains poor.[5] This is, in large part, due to premature cardiovascular disease (CVD) that manifests itself as coronary heart disease (CHD), cerebrovascular disease, and/or peripheral vascular disease (Table 1). There are 2 major overlapping categories of CVD: (1) disorders of cardiovascular perfusion, which include atherosclerotic CVD (ACVD); and (2) disorders of cardiac function, such as heart failure and left ventricular hypertrophy. Some risk factors are unique to each category of CVD, and some risk factors are shared by both categories of CVD.

The National Kidney Foundation (NKF) Task Force on CVD concluded that the incidence of ACVD is higher in patients with CKD compared to the general population (Fig 1).[4] The Task Force concluded that patients with CKD should be considered to be in the highest risk category, ie, a CHD risk equivalent, for risk factor management. In response to recommendations of the NKF Task Force on CVD, the NKF Kidney Disease Outcomes Quality Initiative (K/DOQI) convened a Work Group to develop guidelines for the management of dyslipidemias, one of the risk factors for CHD in CKD. The Work Group first met on November 27, 2000.

During the development of these guidelines, the NKF K/DOQI also completed guidelines on CKD.[2] These CKD guidelines defined CKD, and reiterated that CKD should be considered a CHD risk equivalent and that risk factors should be managed accordingly (Fig 1). In the CKD guidelines, CKD is defined according to the presence, for at least 3 months, of either of the following:

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Table 1. Definitions of Some Terms Used in These Guidelines

Term	Definition
Chronic Kidney Disease (CKD)	At least 3 months of either: 1) structural or functional abnormalities of the kidney that can lead to kidney failure; or 2) GFR <60 mL/min/1.73m^2
Cardiovascular Disease (CVD)	Coronary heart disease, cerebrovascular disease, renal artery stenosis, peripheral vascular disease, congestive heart failure, or left ventricular hypertrophy
Atherosclerotic Cardiovascular Disease (ACVD)	Coronary heart disease, cerebrovascular disease, renal artery stenosis, or peripheral vascular disease
Coronary Heart Disease (CHD)	Atherosclerotic disease of the coronary arteries that causes myocardial ischemia
Cerebrovascular Disease	Atherosclerotic disease of the cerebral arteries that causes strokes and transient ischemic attacks
Peripheral Vascular Disease	Atherosclerotic disease of arteries that causes ischemia of the extremities
Dyslipidemia	Any abnormality in plasma lipoprotein concentration or composition that is associated with an increased risk for atherosclerotic cardiovascular disease
Lipid Profile	Plasma levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides
Adults	Individuals ≥18 years old
Adolescents	Individuals <18 years old, but after the onset of puberty

Abbreviation: GFR, glomerular filtration rate.

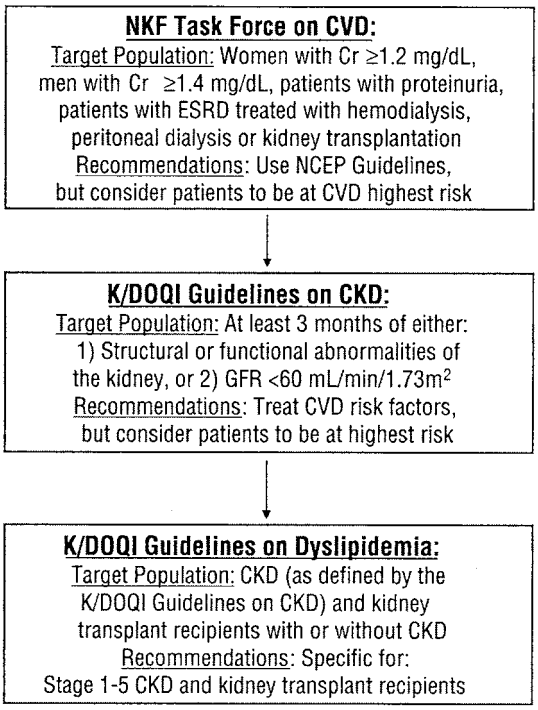


Fig 1. The evolution of National Kidney Foundation guidelines for the management of dyslipidemias in patients with chronic kidney disease. To convert serum creatinine from mg/dL to mmol/L, multiply by 88.4. Abbreviations: Cr, serum creatinine; ESRD, end-stage renal disease; NCEP, National Cholesterol Education Program; CVD, cardiovascular disease; GFR, glomerular filtration rate; CKD, chronic kidney disease; K/DOQI, Kidney Disease Outcomes Quality Initiative.

(1) Structural or functional abnormalities of the kidney, with or without decreased GFR. These abnormalities are manifested by either pathological abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in radiographic imaging tests.

(2) GFR <60 mL/min/1.73 m^2 (Table 1).

The definitions of Stages 1-5 CKD are based on measured or estimated GFR (Table 2), where the GFR is estimated from the serum creatinine using an established formula, as described in the K/DOQI CKD Guidelines.[2] Stage 1 CKD is defined by estimated GFR $\geq$90 mL/ min/1.73 m^2, with evidence of kidney damage (as defined above). Stage 2 CKD is defined as evidence of kidney damage with mildly decreased GFR of 60-89 mL/min/1.73 m^2. The level of estimated GFR, with or without kidney damage, defines Stages 3-4. Stage 5 (kidney failure) is defined as GFR <15 mL/min/1.73 m^2, or the clinical indication for kidney replacement therapy with maintenance hemodialysis, peritoneal dialysis, or transplantation (Table 2). Thus, some Stage 5 patients may need kidney replacement therapy because of uremic symptoms, even when, based solely on GFR, they would be classified in Stage 4 (GFR 15-29 mL/min/1.73 m^2) (Table 2).

Of the traditional risk factors for ACVD in patients with CKD, dyslipidemias may play a major role. In developing these guidelines, the Work Group was greatly aided by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III),[3] and the National Cholesterol Expert Panel on Children (NCEP-C).[6] The definitions of dyslipidemias adopted by the Work Group were those of ATP III (Table 3). In the end, the major task of the Work Group was to decide how the ATP III and NCEP-C guidelines should be applied to patients with CKD.

Table 2. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 or dialysis

From the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification.
Abbreviation: GFR, glomerular filtration rate.

Table 3. Dyslipidemias As Defined in the Adult Treatment Panel III Guidelines.[3]

Dyslipidemia	Level (mg/dL)
Total cholesterol	
Desirable	<200
Borderline high	200-239
High	≥240
Low-density lipoprotein (LDL) cholesterol	
Optimal	<100
Near optimal	100-129
Borderline	130-159
High	160-189
Very high	≥190
Triglycerides	
Normal	<150
Borderline high	150-199
High	200-499
Very high	≥500
High-density lipoprotein (HDL) cholesterol	
Low	<40

To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and cholesterol by 0.02586.

There is evidence from observational studies that, in addition to dyslipidemias, some "non-traditional" risk factors such as calcium, phosphorus, and parathyroid hormone,[7,8] homocysteine,[9-16] and systemic inflammation[17-21] may also play a role in the pathogenesis of CVD in patients with CKD. However, unlike dyslipidemias, there are no intervention trials from patients in the general population (or in those with CKD) demonstrating that the modification of these non-traditional risk factors reduces CVD. Therefore, these guidelines focus on the assessment and treatment of dyslipidemias in patients with CKD. Unfortunately, there are no randomized controlled intervention trials in CKD patients showing that the treatment of dyslipidemias reduces the incidence of ACVD. Moreover, it is possible that trial results from the general population may not be applicable to all patients with CKD. It is also possible that in some subpopulations of CKD patients, treatment of dyslipidemias may not be as safe—or as effective—in reducing the incidence of ACVD, as it is in the general population. This may be due to the unique complications of CKD (eg, anemia, calcium and phosphorus metabolic abnormalities) that may contribute to the risk of ACVD in CKD. Therefore, the Work Group concluded that additional, randomized, placebo-controlled trials are urgently needed in patients with CKD, and that the use of a placebo is justified in the context of an appropriately designed trial, even when lipid levels fall within the treatment thresholds recommended by these guidelines (see *IV. Research Recommendations*).

TARGET POPULATION

One of the first tasks of the Work Group was to define the target population for guidelines on the management of dyslipidemia. It was decided to include all patients with Stage 5 CKD, as well as kidney transplant recipients, irrespective of whether kidney transplant recipients were classified as having CKD according to the K/DOQI CKD Guidelines. Some kidney transplant pa-

tients who have normal kidney function (GFR ≥90 mL/min/1.73 m^2) may not have CKD according to the K/DOQI Guidelines defining CKD. Similarly, some patients with GFR ≥60 mL/min/1.73 m^2 may not fit the K/DOQI definition of CKD, because they do not have evidence of kidney damage, ie, they may have normal urine protein excretion, urine sediment, histology, and radiographic imaging. However, the CKD guidelines consider such patients at increased risk for CKD. As such, the Work Group decided to consider that all kidney transplant recipients have CKD, or are at increased risk for CKD, and to include kidney transplant recipients in the target population.

The Work Group considered whether the guidelines should include patients with Stages 1-4 CKD (GFR ≥15 mL/min/1.73 m^2). These patients have a very high prevalence of dyslipidemias and ACVD,[22-25] and it was concluded that the recently updated guidelines of the ATP III[3] were generally applicable to patients with Stages 1-4 CKD. Specifically, it was concluded that it is unlikely that the recommendations of the ATP III would need to be modified for patients with Stages 1-4 CKD, except to:

(1) Classify CKD as a CHD risk equivalent;
(2) Consider complications of lipid-lowering therapies that may result from reduced kidney function;
(3) Consider whether there might be indications for the treatment of dyslipidemias other than preventing ACVD; and
(4) Determine whether the treatment of proteinuria might also be an effective treatment for dyslipidemias.

Classification of CKD as a CHD risk equivalent has already been recommended by two NKF Work Groups.[2,4] Therefore, for Stage 1-4 CKD patients, the Work Group focused its attention on the latter three issues, and otherwise recommended that the ATP III Guidelines be followed in all patients with Stages 1-4 CKD.

Finally, the Work Group considered whether to include children and adolescents in these guidelines (Fig 2). Although the ATP III covers only individuals ≥20 years of age,[3] it was concluded that CKD individuals 18-20 should also be included and considered as adults. Much has changed in the decade since the report of the NCEP-C.[6] However, there are still very few studies of dyslipidemias in children and adolescents, either in the general population or in persons with CKD. In the end, it was concluded that adolescents (defined by the onset of puberty), in any stage of CKD or with a kidney transplant, should be included in these guidelines. Children (before the onset of puberty) should be managed according to existing guidelines, such as the NCEP-C.[6]

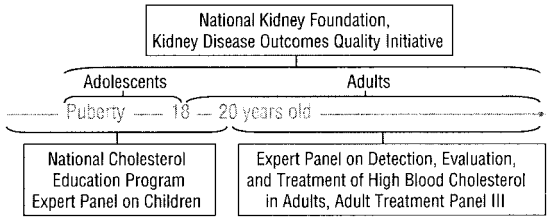


Fig 2. Ages covered by the current guidelines, and those covered by previous guidelines developed for use in the general population.

SCOPE

The Work Group also considered the recommendations of the NKF Task Force on CVD concerning the management of risk factors other than dyslipidemias.[4] There are 2 potential reasons to assess other risk factors for ACVD: (1) to categorize overall risk for the purpose of making decisions regarding the management of dyslipidemia; and (2) to identify modifiable risk factors other than dyslipidemia that should also be treated. The first reason was considered unnecessary (for the purpose of these guidelines) by accepting the recommendation that a patient with CKD should be considered to have a CHD risk equivalent when deciding the appropriate management of dyslipidemia. However, the Work Group acknowledged that other risk factors are also important in the pathogenesis of ACVD and should be treated. Therefore, the Work Group concluded that for patients with CKD:

- Dyslipidemia management should be undertaken in conjunction with all other available measures to reduce the overall risk of ACVD.
- Modifiable, conventional, risk factors (including hypertension, cigarette smoking, glucose intolerance or diabetes control, and obesity) should be assessed at initial presentation and at least yearly thereafter.

Table 4. Some Government-Sponsored Web Sites with Information Useful in Risk Factor Management.

Risk Factor	Web Site Address
Diet	www.nutrition.gov
Body weight	www.nhlbi.nih.gov/subsites/index.htm (click on Healthy Weight)
Exercise	www.fitness.gov/aboutpcpfs/aboutpcpfs.html
Cholesterol*	www.nhlbi.nih.gov/chd
Blood pressure	www.nhlbi.nih.gov/hbp
Hormone replacement	www.nhlbi.nih.gov/whi/hrtupd/index.htm
Smoking	www.cdc.gov/tobacco/sgr_tobacco_use.htm

*National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III. All web addresses were as of October 30, 2002.

- Modifiable risk factors should be managed according to existing guidelines (Table 4), including, but not limited to:

—The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[26]

—The American Diabetes Association Clinical Practice Recommendations[27]

—Hormone replacement therapy and cardiovascular disease: A statement for health-care professionals from the American Heart Association[28]

—Aspirin for the primary prevention of cardiovascular events[29]

—A statement for health-care professionals from the Nutrition Committee of the American Heart Association[30]

—Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD: National Heart, Lung, and Blood Institute; 1998

—The American Heart Association/American College of Cardiology guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease[31]

—Primary prevention of ischemic stroke: A statement for health-care professionals from the Stroke Council of the American Heart Association[32]

—A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report[33]

The task of the Work Group was greatly facilitated by the ATP III,[3] and the NCEP-C for children and adolescents.[6] However, the ATP III and NCEP-C make few specific recommendations for the evaluation and treatment of dyslipidemias in CKD, and none of the guideline statements includes or excludes patients with CKD. The ATP III notes that nephrotic syndrome is a cause of secondary dyslipidemia, and suggests consideration be given to the use of cholesterol-lowering drugs if hyperlipidemia persists despite specific treatment for kidney disease. The ATP III also notes that various dyslipidemias have been reported in persons with kidney failure. However, the ATP III suggests that a cautious approach be taken, since these persons are prone to drug side-effects, eg, they are at increased risk for myopathy from both fibrates and statins. In fact, the ATP III suggests that chronic kidney failure is a contraindication to fibrates.

The Work Group concluded that, in most areas, the ATP III and NCEP-C were applicable to adults and adolescents, respectively. It considered its principal task to define areas where the ATP III and NCEP-C needed modification and refinement for patients with CKD. In the end, relatively few modifications were needed (Tables 5 and 6).

INTENDED USERS

These guidelines are intended for use by physicians, nurses, nurse practitioners, pharmacists, dietitians, and other health-care professionals who care for patients with CKD. The information contained in these guidelines can and should be conveyed to patients and their families in an understandable manner by their physician and/or

Table 5. Key Features of the NKF-K/DOQI Guidelines That Differ from Those of the National Cholesterol Education Program Adult Treatment Panel III

NKF-K/DOQI Guidelines	Adult Treatment Panel III Guidelines
1. CKD patients should be considered to be in the highest risk category.	1. CKD patients are not managed differently from other patients.
2. Evaluation of dyslipidemias should occur at presentation with CKD, after a change status, and annually.	2. Evaluation of dyslipidemias should occur every 5 years.
3. Drug therapy should be used for LDL 100-129 mg/dL after 3 months of TLC.	3. Drug therapy is considered optional for LDL 100-129 mg/dL.
4. Initial drug therapy for high LDL should be with a statin.	4. Initial drug therapy for high LDL should be with a statin, bile acid sequestrant, or nicotinic acid.
5. Recommendations are made for patients <20 years old.	5. No recommendations are made for patients <20 years old.
6. Fibrates may be used in Stage 5 CKD a) for patients with triglycerides ≥500 mg/dL; and b) for patients with triglycerides ≥200 mg/dL with non-HDL cholesterol ≥130 mg/dL, who do not tolerate statins.	6. Fibrates are contraindicated in Stage 5 CKD.
7. Gemfibrozil may be the fibrate of choice for treatment of high triglycerides in patients with CKD.	7. No preferences are indicated for which a fibrate should be used to treat hypertriglyceridemia.

To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and cholesterol by 0.02586.
Abbreviations: NKF-K/DOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; CKD, chronic kidney disease; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TLC, therapeutic lifestyle changes.

Table 6. Key Features of the NKF-K/DOQI Guidelines That Differ from Those of the National Cholesterol Expert Panel on Children.

NKF-K/DOQI Guidelines	Expert Panel on Children
1. Adolescents with CKD should be considered to be in the highest risk category.	1. Adolescents with CKD are not managed differently from other patients.
2. Evaluation of dyslipidemias should occur after presentation with CKD, after a change in kidney failure treatment modality, and annually.	2. Evaluation of dyslipidemias should occur every 5 years.
3. If LDL is 130-159 mg/dL, start TLC diet (if nutritional status is adequate), followed in 6 months by a statin[a] if LDL ≥130 mg/dL.	3. If LDL >130 mg/dL, start TLC Step I AHA diet, followed in 3 months by Step II AHA diet if LDL >130 mg/dL
4. If LDL ≥160 mg/dL, start TLC plus a statin.	4. If LDL ≥160 mg/dL and family history of CHD or two or more CVD risk factors, start drug therapy.

To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and cholesterol by 0.02586.
[a]Currently, atorvastatin is the only statin approved by the U.S. Food and Drug administration for use in children.
Abbreviations: NKF-K/DOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; CKD, chronic kidney disease; AHA, American Heart Association; LDL, low-density lipoprotein cholesterol; TLC, therapeutic lifestyle changes; CVD, cardiovascular disease.

other health-care professionals. The development of educational support materials designed specifically for patients and their families should be part of the implementation of these guidelines.

ANTICIPATED UPDATES

All guidelines should be updated whenever new, pertinent information becomes available. To anticipate when these guidelines may need to be updated, the Work Group discussed ongoing clinical trials in the general population and in patients with CKD, as those results may be pertinent to some recommendations. Late in the course of development of these guidelines, the results of the Heart Protection Study were published.[34] This study randomly allocated 20,536 adults with coronary artery disease to simvastatin 40 mg versus matching placebo. Patients treated with simvastatin had an 18% reduction in coronary deaths. Importantly, the reduction in mortality was seen irrespective of the baseline level of cholesterol. This raised the possibility that all patients with known coronary artery disease should be treated with a statin, regardless of the serum cholesterol level. Ultimately, these and other results from ongoing trials could conceivably change the recommended approach to treatment of dyslipidemias. Some other important ongoing trials in patients from the general population include:

—Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [35]
—Study Evaluating Additional Reductions in Cholesterol and Homocysteine (SEARCH)[36]
—Treating to New Targets (TNT)[37]
—Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL)[38]
—Aggressive Lipid Lowering Initiation Abates New Cardiac Events (ALLIANCE)[39]
—Pravastatin or Atorvastatin in Evaluation and Infection Therapy (PROVE IT)[40]
—Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)[41]
—Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)[42]
—Collaborative Atorvastatin Diabetes Study (CARDS)[38;42]
—Atorvastatin as Prevention of Coronary Heart Disease Endpoints in Patients with Non-Insulin-Dependent Diabetes Mellitus (ASPEN)[38]
—Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)[38]
—Action to Control Cardiovascular Risk in Diabetes (ACCORD)

Some important, ongoing trials being conducted in patients with CKD include:

—Assessment of Lescol in Renal Transplantation (ALERT)[43]
—Die Deutsche Diabetes Dialyse Studie (4D)[44]
—Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT)[45]
—The Study of Heart and Renal Protection (SHARP) study

Thus, a number of potentially important trials will be completed within the next 3-5 years. Given the potential for these and other studies to provide information pertinent to the assessment and treatment of dyslipidemias in patients with CKD, it was concluded that these guidelines should be updated in about 3 years from the time of publication, and sooner if new, pertinent information becomes available before then. The Work Group will monitor the progress of these trials and recommend updating these guidelines as indicated.

METHODS

Guideline Development

These guidelines were developed using 4 basic principles set forth by the K/DOQI:

(1) The guidelines were developed using a scientifically rigorous process, and the rationale and evidentiary basis for each guideline is clearly explained.
(2) A multidisciplinary Work Group, with expertise in the management of CKD, dyslipidemias, and ACVD developed the guidelines.
(3) The Work Group members worked independently from any organizational affiliations and had final responsibility for determining guideline content.
(4) The guidelines underwent widespread critical review before being finalized.

The guidelines were developed using an evidence-based approach similar to that endorsed by the Agency for Health-Care Research and

Rating the Strength of Recommendations.

Grade	Recommendation
A	It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves net health outcomes.
B	It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderate evidence that the practice improves net health outcomes.
C	It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence, poor evidence or on the opinions of the Work Group and reviewers, that the practice might improve net health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving net health outcomes implies that benefits outweigh any adverse effects.

Quality. The Work Group reviewed all pertinent, published evidence, and critically appraised the quality of studies and the overall strength of evidence supporting each recommendation.

Rating the Strength of Guidelines and Evidence

The overall strength of each guideline statement was rated by assigning either "A," "B," or "C" (Table 7). An "A" rating indicates "it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves net health outcomes, and benefits substantially outweigh harms." There were no guidelines that were assigned an "A" level recommendation. The "B" rating indicates "it is recommended that clinicians routinely follow the guideline for eligible patients. There is moderate evidence that the practice improves net health outcomes." A "C" rating indicates "it is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence, poor evidence or on the opinions of the Work Group and reviewers, that the practice might improve net health outcomes."

The strength of evidence was assessed using a rating system that takes into account (1) methodological quality of the studies; (2) whether or not the study was carried out in the target population, ie, patients with CKD, or in other populations;

Table 8. Rating the Strength of Evidence.

		Methodological Quality		
Outcome(s)	**Population**	**Well designed and analyzed (little, if any, potential bias)**	**Some problems in design and/or analysis (some potential bias)**	**Poorly designed and/or analyzed (large potential bias)**
Health outcome(s)	**Target population**	Strong[a]	Moderate[b]	Weak[h]
Health outcome(s)	**Other than the target population**	Moderate[c]	Moderate[d]	Weak[h]
Surrogate measure for health outcome(s)	**Target population**	Moderate[e]	Weak[f]	Weak[h]
Surrogate measure for health outcome(s)	**Other than the target population**	Weak[g]	Weak[g]	Weak[g,h]

Strong- [a]Evidence includes results from well-designed, well-conducted study/studies in the target population that directly assess effects on net health outcomes.
Moderate- [b]Evidence is sufficient to determine effects on net health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; *OR* [c]evidence is from a population other than the target population, but from well-designed, well-conducted studies; *OR* [d]evidence is from studies with some problems in design and/or analysis; *OR* [e]evidence is from well-designed, well-conducted studies on surrogate endpoints for efficacy and/or safety in the target population.
Weak- [f]Evidence is insufficient to assess the effects on net health outcomes because it is from studies with some problems in design and/or analysis on surrogate endpoints for efficacy and/or safety in the target population; *OR* [g]the evidence is only for surrogate measures in a population other than the target population; *OR* [h]the evidence is from studies that are poorly designed and/or analyzed.

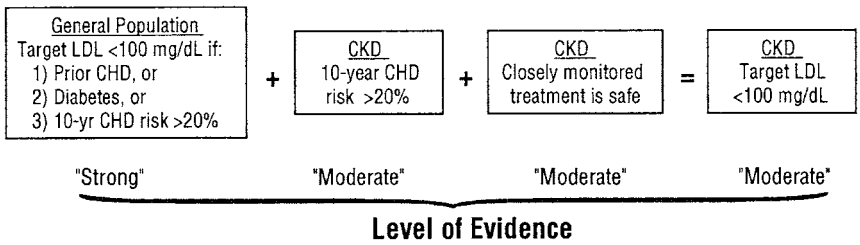


Fig 3. The chain of logic for evidence supporting the treatment of low-density lipoprotein cholesterol in patients with chronic kidney disease. See text for details. Abbreviations: LDL, low-density lipoprotein; CHD, coronary heart disease; CKD, chronic kidney disease.

and (3) whether the studies examined health outcomes directly, or examined surrogate measures for those outcomes, eg, improving dyslipidemia rather than reducing CVD (Table 8). These 3 separate study characteristics were combined in rating the strength of evidence provided by pertinent studies.

Literature Retrieval and Review

The Work Group collaborated with a professional Evidence Review Team to identify and summarize pertinent literature (see Appendix 1). The Work Group and the Evidence Review Team first identified the topics to be searched, and the Evidence Review Team conducted the literature search. The topics that were selected for search included the incidence or prevalence of dyslipidemia, the association of dyslipidemia with ACVD, and the treatment of dyslipidemia in patients with Stage 5 CKD (including kidney transplant recipients). For patients with Stages 1-4 CKD, topics for the literature retrieval were limited to adverse effects of dyslipidemia treatment, the effects of dyslipidemia treatment on kidney disease progression, and the effects of therapies that reduce proteinuria on dyslipidemias. Systematic searches for all studies on dyslipidemia prevalence, association with ACVD, and treatment for patients with Stages 1-4 CKD were not conducted. As described above, the Work Group concluded a priori that the ATP III Guidelines were generally applicable to patients with Stages 1-4 CKD.

Briefly, the literature search included only full, peer-reviewed, journal articles of original data. Review articles, editorials, letters, case studies, and abstracts were excluded. Studies were identified primarily through MEDLINE searches of the English language literature up to May 2001.

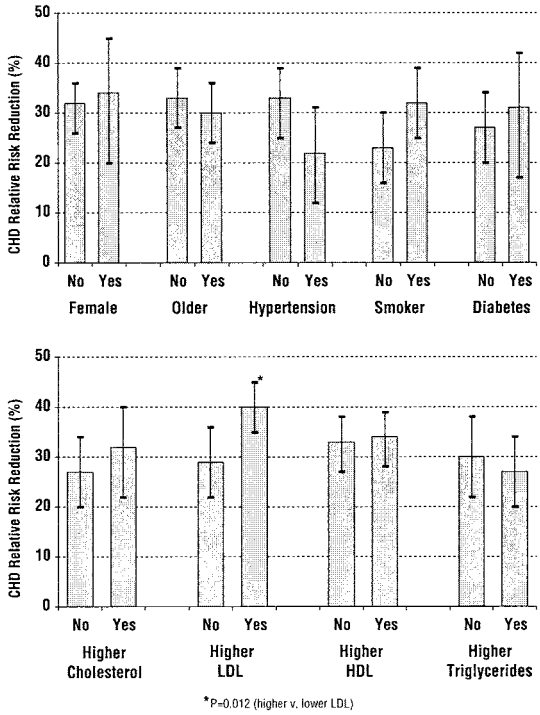


Fig 4. The relative coronary heart disease risk reduction in subgroups of patients from major lipid-lowering trials in the general population. The bars indicate the mean relative risk reduction (compared to a reference level of 0% reduction), with a higher number indicating a proportionally greater reduction in risk. The error bars represent 95% confidence intervals. There were at least 20,000 patients in each category (divided between "no" and "yes"). The only category where the risk reduction was statistically different was for baseline LDL (lower panel), where patients with a higher baseline LDL had a greater reduction in risk, although patients with lower and higher baseline cholesterol had significant risk reductions. Data are from Table II.2-3 of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (www.nhlbi.nih.gov/guidelines/cholesterol/index.htm).

Table 9. Exclusion of CKD Patients in Some Recent, Large, Pivotal, Lipid-Lowering Trials.

Study	N	CKD Exclusions
Heart Protection Study,[34] 2002	20,536	"Cr ≥2.26 mg/dL"
MIRACL Study,[51] 2001	3,086	"renal failure requiring dialysis"
BIP,[52;53]2000	3,090	"Cr ≥1.5 mg/dL or NS"
AVERT,[54] 1999	341	"Significant renal dysfunction"
LIPID,[55;56]1998	9,014	"renal disease"
AFCAPS/TexCAPS,[57;58]1998	5,615	"secondary hyperlipoproteinemia, NS"
CARE,[59;60]1996	1,283	"NS or other renal disease"
ALLHAT,[35]1996	20,000	"Cr ≥ 2 mg/dL"
LCAS,[61], 1996	572	"Any kidney disease"
WOSCOPS,[62;63]1995	6,595	"Cr >1.75 mg/dL"
REGRESS,[64] 1995	885	"NS, Cr ≥ 2.5 mg/dL"
PLAC-1,[65], 1995	480	"Cr ≥ 2.5 mg/dL, urine protein > 2+"
4S,[66;67]1994	4,444	Not reported, but only 72 had Cr ≥1.5 mg/dL
CCAIT,[68] 1994	331	"Impaired kidney function"
EXCEL,[69;70]1991	8,245	"NS" Baseline Cr = 1.1±0.2 mg/dL (mean ± SD) "4% had elevated Cr"
Helsinki Heart Study,[71-73]1987	18,966	"Cr ≥1.3 mg/dL"

To convert mg/dL to μmol/L multiply by 88.4.
A number of trials did not report on whether there were any exclusions based on kidney disease.[74-83]
Abbreviations: CKD, chronic kidney disease; Cr, serum creatinine; NS, nephrotic syndrome; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; BIP, Bezafibrate Infarction Prevention; AVERT, Atorvastatin Versus Revascularization Treatments; LIPID, Long Term Intervention with Pravastatin in Ischaemic Disease; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE, Cholesterol and Recurrent Events; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; LCAS, Lipoprotein and Coronary Atherosclerosis Study; WOSCOPS, West of Scotland Coronary Prevention Study; REGRESS, The Regression Growth Evaluation Statin Study; PLAC-1, Pravastatin Limitation in Atherosclerosis in the Coronary Arteries; 4S, Scandinavian Simvastatin Survival Study; CCAIT, Canadian Coronary Atherosclerosis Intervention Trial ; EXCEL, Expanded Clinical Evaluation of Lovastatin.

Studies published between May 2001 and November 2002, that were identified through means other than the systematic literature searches, were included if appropriate.

Separate search strategies were developed for each topic. The text words or MeSH headings for all topics included kidney or kidney diseases, hemodialysis, peritoneal dialysis, or kidney transplant. The searches were limited to human studies, but included both adult and pediatric populations. Potential articles for retrieval were identified from printed abstracts and titles, based on study population, relevance to the topic, and article type. These were screened by clinicians on the Evidence Review Team. Overall, 10,363 abstracts were screened, 642 articles were retrieved, and 258 articles were subjected to structured review by members of the Work Group. Although systematic, manual searches were not conducted, members of the Work Group supplied a number of articles that were not located by the MEDLINE searches.

Work Group members used forms that were developed by the Evidence Review Team to extract information from each article that was reviewed. The Evidence Review Team used the information from these forms to construct the Evidence Tables. The Evidence Review Team then used the Evidence Tables to construct the Summary Tables that are included with the guidelines in this report. The Summary Tables describe the information in the Evidence Tables according to 4 study dimensions: size, applicability, results, and methodological quality.

The study (sample) size was used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. Applicability (generalizability or external validity) addresses the issue of whether the study population is sufficiently broad

so that the results can be generalized to the population of interest. The applicability of each article was determined using a three-level scale:

(1) the study sample is representative of the target population;
(2) the sample is representative of a relevant subgroup; or
(3) the sample is representative of a narrow subgroup of patients.

Methodological quality (internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of designs were evaluated, a broad classification system to rate the quality of individual studies was used:

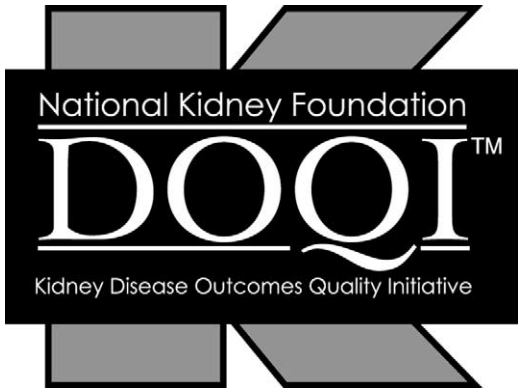
(a) least bias, most valid, ie, a study that meets most generally accepted criteria for high quality;
(b) susceptible to some bias, but not sufficient to invalidate the results; and
(c) significant bias that may invalidate the results.

GUIDELINES, EVIDENCE, AND RESEARCH RECOMMENDATIONS

There were no guidelines that were assigned an "A" level recommendation. The key guideline statements in this document were graded "B" or "C." Some would argue that no guideline statements should be made in the absence of evidence from randomized trials in patients with CKD (yielding level "A" recommendations). However, it was decided that when the strength of evidence for treatment efficacy was strong—based on trials in the general population—this evidence might be reasonably extrapolated to patients with CKD (Fig 3). Specifically, it was assumed that similar treatment efficacy as reported in the general population would be found if the trials were carried out in patients with CKD. This also assumes, of course, that treatment is safe and effective in ameliorating dyslipidemias in patients with CKD.

The principal results of large multicenter trials in the general population have generally been applicable to most, if not all, major subgroups of patients that have been examined (Fig 4). For example, the benefit of reducing LDL cholesterol extends to men and women[3,46,47]; old and middle-aged[3,46,47]; smokers and non-smokers[3,47]; hypertensive and non-hypertensive patients[47]; diabetics and nondiabetics[48]; and individuals with higher or lower LDL,[3,47] higher or lower total cholesterol,[3,47] higher or lower triglycerides,[3,47] and higher or lower HDL.[3,47,49,50] In other words, the results of lipid-lowering trials are usually generalizable to population subgroups. Therefore, it was reasonable to assume that the major findings from randomized trials in the general population are applicable to patients with CKD, until proven otherwise.

Nevertheless, there are reasonable doubts as to whether trial results from the general population can be extrapolated to all patients with CKD, and most major trials in the general population have excluded patients with elevated serum creatinine and Stage 5 CKD (Table 9). It is possible that, in some subpopulations of CKD patients, dyslipidemias may not play as large a role in the pathogenesis of CVD as they do in the general population. Therefore, it was concluded that additional studies are needed in patients with CKD (see *IV. Research Recommendations*). However, pending the results of these trials, the recommendations were based on the evidence from the general population.



II. ASSESSMENT OF DYSLIPIDEMIAS

IN EACH OF the following guideline statements, kidney transplant recipients are included along with other patients with CKD, whether or not they have other evidence of CKD. Each guideline statement is followed by a letter grade (in parentheses) indicating the strength of the recommendation (Table 7).

GUIDELINE 1

1.1. All adults and adolescents with CKD should be evaluated for dyslipidemias. (B)

1.2. For adults and adolescents with CKD, the assessment of dyslipidemias should include a complete fasting lipid profile with total cholesterol, LDL, HDL, and triglycerides. (B)

1.3. For adults and adolescents with Stage 5 CKD, dyslipidemias should be evaluated upon presentation (when the patient is stable), at 2-3 months after a change in treatment or other conditions known to cause dyslipidemias; and at least annually thereafter. (B)

Associations Between Dyslipidemias and ACVD in CKD

The incidence of ACVD is very high in patients with CKD (Fig 5). Therefore, the NKF Task Force on CVD and the K/DOQI Work Group on CKD both concluded that, in the management of risk factors such as dyslipidemia, patients with CKD should be considered to be in the highest risk category, ie, equivalent to that of patients with known CHD.[2,4] There is very strong evidence from the general population that dyslipidemias cause ACVD, and this evidence has led to the ATP III guidelines for evaluation and treatment.[3] It is conceivable that the pathogenesis of ACVD is different in patients with CKD, and that dyslipidemias do not contribute to ACVD in CKD. However, the relationship between dyslipidemias and ACVD in the general population is robust, ie, it is valid in men and women[3,46,47]; old and middle-aged[3,46,47]; smokers and nonsmokers[3,47]; hypertensive and non-hypertensive patients[47]; diabetics and nondiabetics[3,48]; and individuals with higher or lower LDL,[3,47] higher or lower total cholesterol,[3,47] higher or lower triglycerides,[3,47] and higher or lower HDL (Fig 4).[3,47,49,50] There are no compelling reasons to assume that dyslipidemias do not contribute to ACVD in patients with CKD as well.

There are no randomized, controlled, intervention trials testing the hypothesis that dyslipidemias cause ACVD in patients with CKD. However, in an observational study of 3,716 patients initiating treatment for Stage 5 CKD in 1996, the use of statins in 362 (9.7%) was independently associated with lower all-cause mortality and a reduction in CVD deaths during follow-up.[84] Unfortunately, it is likely that the patients using statins had other favorable characteristics that were not accounted for in the adjusted analysis, but may have explained their reduced risk for CVD independent of their use of statins. Therefore, these study results are consistent with, but do not prove, the hypothesis that dyslipidemias contribute to ACVD in patients with CKD.

Associations Between Dyslipidemias and ACVD in Hemodialysis Patients

There are no large, prospective, observational studies examining the relationship between ACVD and dyslipidemias in hemodialysis patients. A number of retrospective, cross-sectional studies found no relationship, or—in some cases—even paradoxical correlations between dyslipidemias and ACVD in hemodialysis patients (Table 10). However, there are a number of reasons that studies have failed to find a positive association between dyslipidemias and ACVD. None of these studies was a long-term, prospective, cohort study, and it is likely that illness, inflammation, and poor nutrition confounded the relationships between dyslipidemias and ACVD. Support for this notion comes from studies that have found that at least some of the seemingly paradoxical associations between dyslipidemias and ACVD are, in part, explained by statistical adjustment for markers of malnutrition and systemic inflammation.[85-87]

More than a decade ago, it was reported that the association between cholesterol and mortality (much of which was presumably due to CVD) in hemodialysis patients took the form of a U-shaped curve.[85,86] Moreover, the association between low cholesterol and increased mortality

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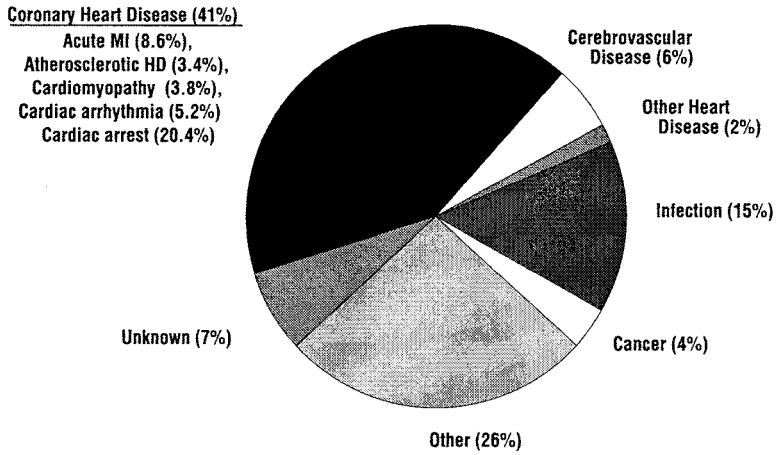


Fig 5. Causes of death among period prevalent patients 1997–1999, treated with hemodialysis, peritoneal dialysis, or kidney transplantation. Data are from the USRDS 2001 Annual Data Report (www.usrds.org). Abbreviations: MI, myocardial infarction; HD, heart disease.

was reduced after adjusting for levels of serum albumin.[85,86] Similarly, in a recent prospective study of 1,167 hemodialysis patients, low serum cholesterol levels were associated with all-cause mortality in patients with low serum albumin.[87] However, in patients with normal serum albumin, the opposite was true; high serum cholesterol predicted mortality.[87] C-reactive protein, a marker of inflammation, has been associated with lower serum cholesterol levels.[87] Other markers of inflammation, eg, interleukin-6 and tumor necrosis factor-α, are also associated with

Table 10. Associations between Dyslipidemias and Cardiovascular Disease in Hemodialysis Patients.

Study	N	Quality[a]	Applicability[b]	Adjusted[c]	Cardiovascular Disease Risk with Worsening Dyslipidemia[d] CHOL	LDL	HDL	TG
Cheung,[89] 2000	936	●	↑↑↑	Yes	⇔			
Kronenberg,[90] 1999	440	●	↑↑↑	Yes	⇔	⇔	⇩	⇔
Zimmerman,[18] 1998	280	●	↑↑↑	Yes	⇔	⇔	⇓	⇔
Cressman,[91] 1992	129	●	↑↑↑	Yes	⇔	⇔	⇔	⇔
Stack,[92] 2001	3,925	❍	↑↑↑	Yes	⇔	⇔	⇔	⇔
Degoulet,[94] 1982	1,453	❍	↑↑↑	Yes	⇔			⇩
Iseki,[95] 1996	1,491	❍	↑↑	Yes	⇔			⇔
Goldwasser,[96] 1993	125	❍	↑↑	No	⇑		⇔	
Kimura,[97] 1996	195	❍	↑↑	Yes	⇔			
Fujisawa,[98] 2000	51	❍	↑↑	No	⇔	⇔		⇔
Yeun,[20] 2000	91	○	↑↑	Yes	⇔			

[a]Study quality was graded: ● least bias, results are valid; ❍ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.

[b]Applicability was rated: ↑↑↑ representative of a wide spectrum of patients; ↑↑ representative of a relevant subgroup; or ↑ representative of a narrow subgroup.

[c]Indicates whether results were statistically adjusted for covariates.

[d]⇔ indicates no association between dyslipidemia and cardiovascular disease; ⇓ indicates that dyslipidemia was associated with less cardiovascular disease or there was a trend that was not statistically significant (⇩); and ⇑ indicates that dyslipidemia was associated with more cardiovascular disease or there was a trend that was not statistically significant (⇧).

Abbreviations: N, number of subjects in the study; CHOL, cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TRIG, triglycerides.

low serum cholesterol levels in hemodialysis patients.[88]

Altogether, these data demonstrate a seemingly paradoxical association between low serum cholesterol and increased mortality in hemodialysis patients. They should not be interpreted to mean that dyslipidemias do not contribute to the pathogenesis of ACVD. Rather, it is more likely that the opposite is true, ie, that high cholesterol contributes to ACVD in hemodialysis patients as it does in the general population, and that other conditions accompanying low cholesterol (such as inflammation) account for the increased mortality of patients with low cholesterol.

Non-Traditional Lipid Abnormalities and ACVD in Hemodialysis Patients

Several observational studies have reported a positive association between lipoprotein(a) [Lp(a)] and ACVD in hemodialysis patients.[18,90,91,93,96,98] In 4 of these studies, the association was statistically significant.[18,91,93,98] Interestingly, apolipoprotein(a) low molecular weight phenotypes, which correlate with higher levels of Lp(a), were recently shown to be associated with ACVD in 440 hemodialysis patients.[90] In contrast, a small study (n = 75) of peritoneal dialysis patients[99] and a small study (n = 79) of transplant patients both failed to find an association between Lp(a) and ACVD. Although other studies have noted elevated Lp(a) in CKD patients as well,[100,101] there are no studies in patients with CKD, or in the general population, examining the effect of reducing Lp(a) on CVD. Thus, it is difficult to recommend routine measurement of Lp(a) in clinical practice.

It is also possible that other, non-traditional, atherogenic lipoprotein abnormalities may cause or contribute to ACVD in hemodialysis patients. For example, some,[102-105] but not all,[106] case control studies examining oxidized lipoproteins in hemodialysis patients have reported higher levels compared to matched controls. In addition, a randomized, controlled trial found that supplementation with vitamin E reduced recurrent ACVD events in 196 hemodialysis patients ($P = 0.014$).[107] However, this trial was small, and much larger trials in the general population have failed to show benefit from vitamin E supplementation.[108-115]

Evidence from observational studies in the general population has suggested that lipoprotein remnants may contribute to ACVD, especially in patients with high triglycerides.[3] There are also cross-sectional studies reporting that hemodialysis patients have higher levels of remnant lipoproteins, eg, triglyceride-enriched lipoproteins and/or small dense LDL, compared to controls.[104,116-123] However, none of these studies reported correlations between levels of remnant lipoproteins with ACVD, and the significance of these abnormalities is unknown.

Associations Between Dyslipidemias and ACVD in Peritoneal Dialysis Patients

Only 2 studies that examined the relationship between dyslipidemias and ACVD in peritoneal dialysis patients were identified (Table 11). Both of these studies had major design limitations, and both were too small to rigorously examine the relationship between dyslipidemias and ACVD in the peritoneal dialysis patient population.

Associations Between Dyslipidemias and ACVD in Kidney Transplant Recipients

Several studies have reported a positive association between total cholesterol and ACVD in kidney transplant recipients (Table 12). Unfortunately, few of these studies examined the relationship between LDL and ACVD. Lower levels of HDL were associated with ACVD in 3 of 4 studies. In 3 of 6 studies, higher levels of triglycerides were associated with ACVD. Altogether these studies suggest that the relationship between ACVD and dyslipidemias in kidney transplant recipients is similar to that observed in the general population. However, each of these studies had design limitations; in particular, none was truly prospective. Kidney transplant recipients may also have non-traditional lipoprotein abnormalities that could theoretically contribute to ACVD.[125-127] However, the role of these lipoprotein abnormalities in the pathogenesis of ACVD in CKD, as in the general population, is unclear.

The Evaluation of Dyslipidemias in CKD

Measurements of total cholesterol, HDL, and triglycerides are readily available in most major

Table 11. Associations between Dyslipidemias and Cardiovascular Disease in Peritoneal Dialysis Patients.

Study	N	Quality[a]	Applicability[b]	Adjusted[c]	Cardiovascular Disease Risk with Worsening Dyslipidemia[d] CHOL	LDL	HDL	TG
Webb,[99] 1993	75	⊙	↑↑	Yes	↑	↑	⇔	⇔
Olivares,[124] 1992	102	○	↑↑	No	⇔	⇔	⇔	⇔

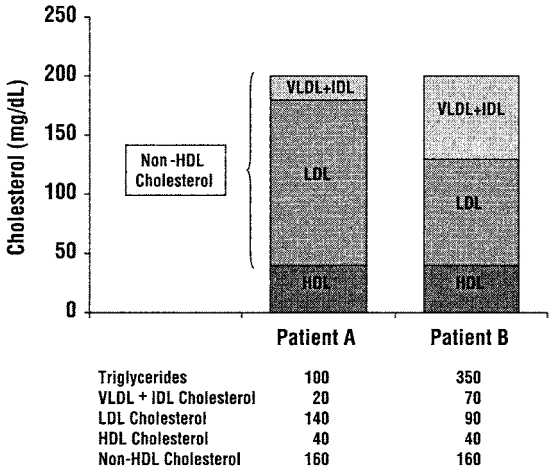
[a]Study quality was graded: ● least bias, results are valid; ⊙ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.
[b]Applicability was rated: ↑↑↑ representative of a wide spectrum of patients; ↑↑ representative of a relevant subgroup; or ↑ representative of a narrow subgroup.
[c]Indicates whether results were statistically adjusted for covariates.
[d]⇔ indicates no association between dyslipidemia and cardiovascular disease; ↓ indicates that dyslipidemia was associated with less cardiovascular disease or there was a trend that was not statistically significant (⇩); and ↑ indicates that dyslipidemia was associated with more cardiovascular disease or there was a trend that was not statistically significant (⇧).
Abbreviations: N, number of subjects in the study; CHOL, cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TRIG, triglycerides.

clinical laboratories. The LDL that forms the foundation for treatment decisions in the ATP III Guidelines[3] is generally calculated from total cholesterol, HDL, and triglycerides using the Friedewald formula. The ATP III Guidelines also recommend treatment of some dyslipidemias that may occur with normal or low LDL. These dyslipidemias—often seen in association with the metabolic, or insulin resistance syndrome (the syndrome of obesity, hypertension, insulin resistance, and hyperlipidemia) and characterized by increases in circulating lipoprotein remnants—can be most readily measured as non-HDL cholesterol, ie, total cholesterol minus HDL (Fig 6).[3] All of the major treatment decisions for dyslipidemia in these guidelines, as in the ATP III Guidelines, are based on levels of triglycerides, LDL, and non-HDL cholesterol.

Table 12. Associations between Dyslipidemias and Cardiovascular Disease in Kidney Transplant Recipients.

Study	N	Quality[a]	Applicability[b]	Adjusted[c]	Cardiovascular Disease Risk with Worsening Dyslipidemia[d] CHOL	LDL	HDL	TG
Kasiske,[128] 1996	675	●	↑↑↑	Yes	⇔	⇔	↓	↑
Aker,[129] 1998	427	●	↑↑	Yes	↑	↑	↓	⇔
Aakus,[130] 1999	406	●	↑	No	↑		⇔	
Kasiske,[131] 2000	1,124	⊙	↑↑	Yes	↑	⇧	⇔	↑
Ong,[132] 1994	192	⊙	↑↑	No	↑		⇔	⇔
Barbagallo,[133] 1999	57	⊙	↑↑	Yes	⇔	⇩	⇧	⇔
Roodnat,[134] 2000	676	○	↑↑	Yes	⇧			
Massy,[135] 1998	79	○	↑↑	Yes	↑		⇧	⇔
Biesenbach,[136] 2000	21	○	↑	No	⇔			⇩

[a]Study quality was graded: ● least bias, results are valid; ⊙ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.
[b]Applicability was rated: ↑↑↑ representative of a wide spectrum of patients; ↑↑ representative of a relevant subgroup; or ↑ representative of a narrow subgroup.
[c]Indicates whether results were statistically adjusted for covariates.
[d]⇔ indicates no association between dyslipidemia and cardiovascular disease; ↓ indicates that dyslipidemia was associated with less cardiovascular disease or there was a trend that was not statistically significant (⇩); and ↑ indicates that dyslipidemia was associated with more cardiovascular disease or there was a trend that was not statistically significant (⇧).
Abbreviations: N, number of subjects in the study; CHOL, cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TRIG, triglycerides.



	Patient A	Patient B
Triglycerides	100	350
VLDL + IDL Cholesterol	20	70
LDL Cholesterol	140	90
HDL Cholesterol	40	40
Non-HDL Cholesterol	160	160

Fig 6. Example demonstrating the relative contributions of VLDL and IDL remnants to non-HDL cholesterol in two hypothetical patients with normal and high triglycerides, respectively. Although both patients A and B have the same total and HDL cholesterol levels, for patient A with normal triglycerides, most of the non-HDL cholesterol is LDL. However, for Patient B with high triglycerides, much of the non-HDL cholesterol is VLDL and IDL remnants. Units are in mg/dL. To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and total, LDL, HDL and non-HDL cholesterol by 0.02586. Abbreviations: VLDL, very low-density lipoproteins; IDL, intermediate density lipoproteins; LDL, low-density lipoproteins; HDL, high-density lipoproteins.

Associations Between Dyslipidemias and Kidney Disease Progression

The principal reason to evaluate dyslipidemias in patients with CKD is to detect abnormalities that may be treated to reduce the incidence of ACVD. However, there may be other reasons to evaluate and treat dyslipidemias in CKD. A number of observational studies have reported that various dyslipidemias are associated with decreased kidney function in the general population and in patients with CKD (Table 13). It is impossible to determine from these studies whether dyslipidemias cause reduced kidney function, result from reduced kidney function, or whether other conditions such as proteinuria cause both reduced kidney function and dyslipidemias. Each of these explanations is plausible, and only randomized, controlled trials can adequately test the hypothesis that dyslipidemias cause a decline in kidney function.

Unfortunately, there are no large, adequately powered, randomized, controlled trials testing the hypothesis that treatment of dyslipidemia preserves kidney function. However, there have been several small studies,[137-148] and a meta-analysis of these studies.[149] This meta-analysis included prospective, controlled trials published before July 1, 1999. Three trials published only in abstract form were included in this meta-analysis[137,138,148]; one of these studies has subsequently been published in a peer-reviewed journal.[148] All patients were followed for at least 3 months, but in only 5 studies were patients followed for at least 1 year. Statins were used in 10 studies, gemfibrozil in 1 study, and probucol in 1 study. Altogether, 362 patients with CKD were included in the meta-analysis. The results suggested that the rate of decline in GFR was significantly less in patients treated with a cholesterol-lowering agent compared to placebo.[149] No significant heterogeneity in treatment effect was detected between the studies. However, the quality of the studies was generally low, and their small sample sizes and relatively short duration of follow-up make it difficult to conclude that lipid-lowering therapies reduce the rate of decline in GFR in CKD. Therefore, the primary or secondary prevention of ACVD remains the principal reason to evaluate and treat dyslipidemias in patients with CKD.

The Prevalence of Dyslipidemias in Hemodialysis Patients

The prevalence of dyslipidemias in patients with CKD is high (Tables 14, 15, 16, and 17). Dyslipidemias in hemodialysis patients are most often characterized by normal LDL, low HDL, and high triglycerides. From the published literature, it is difficult to discern the prevalence of dyslipidemia in hemodialysis patients, since most studies are relatively small and use varying definitions for dyslipidemia. Therefore, the Work Group examined the prevalence of dyslipidemia in a large cross-section of 1,047 hemodialysis patients in the Dialysis Morbidity and Mortality Study (Table 16). The definitions of the ATP III Guidelines, as well as those adopted in these guidelines, were used. According to ATP III definitions, only 20.2% of hemodialysis patients had normal lipid levels, ie, LDL $<$130 mg/dL ($<$3.36 mmol/L), HDL $>$40 mg/dL ($>$1.03 mmol/L), and triglycerides $<$150 mg/dL ($<$1.69 mmol/L). Using the definitions of the present guidelines, 61.1% would require treatment of a

Table 13. Relationship between Dyslipidemias and Kidney Disease Progression.

Study	N	Kidney Diseases Examined	Quality[a]	Applicability[b]	GFR Range[c] (mL/min/1.73 m²) 0 30 60 90 120	Results[d] (Univariate)	Results[e] (Multivariate)
Cholesterol							
Walker,[150] 1993	5,524	DM, HTN	●	↑↑	S_{Cr} 1.1±0.14 mg/dL	⇔	⇔
Hunsicker,[151] 1997	826	No IDDM	● (<3)	↑↑		⇔	
Ravid,[152] 1998	574	DM	●	↑↑	ND		↑
Klein,[153] 1999	555	IDDM	●	↑↑		↑	
Hovind,[154] 2001	301	IDDM	●	↑↑		↑	↑
Massy,[155] 1999	138	All	○	↑↑↑		⇔	
Samuelsson,[156] 1996	49	All	○	↑↑↑		⇔	
Yokoyama,[157] 1997	182	DM	○ (<3)	↑↑		↑	⇔
Samuelsson,[158] 1997	73	No DM	○	↑↑			↑
Nielsen,[159] 1997	32	DM	○	↑↑			⇔
Gall,[160] 1993	26	DM	○	↑↑		⇔	⇔
Locatelli,[161] 1991	456	No DM	○ (<3)	↑↑	S_{Cr} 1.3–7.0 mg/dL		⇔
Dillon,[162] 1993	59	DM	○ (<3)	↑↑		↑	↑
Biesenbach,[163] 1994	32	DM	○	↑↑			⇔
Toth,[164] 1994	100	Membranous GN	○	↑			↑

Table 13. Relationship between Dyslipidemias and Kidney Disease Progression, continued.

Triglycerides							
Walker,[150] 1993	5,524	DM, HTN	●	↑↑	S_{Cr} 1.1±0.14 mg/dL	⇔	
Massy,[155] 1999	138	All	○	↑↑↑		↑	⇧
Samuelsson,[156] 1996	49	All	○	↑↑↑		⇔	
Yokoyama,[157] 1997	182	DM	○(<3)	↑↑		↑	⇔
Samuelsson,[158] 1997	73	No DM	○	↑↑			⇔
Nielsen,[159] 1997	32	DM	○	↑↑			⇔
Biesenbach,[163] 1994	32	DM	○	↑↑			⇔
Low HDL							
Hunsicker,[151] 1997	826	No IDDM	●(<3)	↑↑		↑	↑
Ravid,[152]1998	574	DM	●	↑↑	ND		↑
Klein,[153] 1999	555	IDDM	●	↑↑		↑	↑
Massy,[155] 1999	138	All	○	↑↑↑		↑	⇔
Samuelsson,[156] 1996	49	All	○	↑↑↑		⇔	
Yokoyama,[157] 1997	182	DM	○(<3)	↑↑		⇔	
Samuelsson,[158] 1997	73	No DM	○	↑↑			⇔
Nielsen,[159] 1997	32	DM	○	↑↑			⇔
Gall,[160] 1993	26	DM	○	↑↑		⇔	⇔
LDL							
Hunsicker,[151] 1997	826	No IDDM	●(<3)	↑↑		⇔	

Table 13. Relationship between Dyslipidemias and Kidney Disease Progression, continued.

Ravid,[152] 1998	574	DM	●	↑↑	ND	↑
Samuelsson,[156] 1996	49	All	O	↑↑↑		↑
Samuelsson,[158] 1997	73	No DM	O	↑↑		↑

[a]Study quality was graded: ● least bias, results are valid; O susceptible to some bias, but not sufficient to invalidate the results; or O significant bias that may invalidate the results. "<3" superscript indicates a mean or median duration of follow-up <3 years.
[b]Applicability was rated: ↑↑↑ representative of a wide spectrum of patients; ↑↑ representative of a relevant subgroup; or ↑ representative of a narrow subgroup.
[c]At baseline
[d,e]↑ = dyslipidemia measurement associated with faster GFR decline (statistically significant);
⇧ = dyslipidemia measurement associated with faster GFR decline;
⇳ = dyslipidemia measurement *not* associated with rate of GFR decline.

dyslipidemia; 55.7% would require treatment based on LDL ≥100 mg/dL (≥2.59 mmol/L), while another 5.4% with normal LDL would require treatment based on triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L) (Table 16).

The Prevalence of Dyslipidemias in Peritoneal Dialysis Patients

The prevalence of dyslipidemia in patients treated with peritoneal dialysis is high, and differs somewhat from that in hemodialysis patients (Tables 14, 15, 16, and 17). In a cross-section of 317 peritoneal dialysis patients from the Dialysis Morbidity and Mortality Study (Table 17), only 15.1% had normal lipid levels according to the ATP III Guidelines, ie, LDL <130 mg/dL (<3.36 mmol/L), HDL >40 mg/dL (>1.03 mmol/L), and triglycerides <150 mg/dL (<1.69 mmol/L). Using the definitions of the present guidelines, 78.6% would require treatment of a dyslipidemia; 73.2% would require treatment based on LDL ≥100 mg/dL (≥2.59 mmol/L), while another 5.4% with normal LDL would require treatment based on triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L) (Table 17).

The Prevalence of Dyslipidemias in Kidney Transplant Recipients

The prevalence of dyslipidemias in kidney transplant recipients is very high (Table 14 and Table 15). Particularly common are increases in total cholesterol and LDL. Triglycerides are often increased, but HDL is usually normal.

The Frequency of Dyslipidemia Evaluation in CKD

Many factors influence the prevalence of dyslipidemias in CKD. Changes in proteinuria, GFR, and treatment of CKD may alter lipoprotein levels. Therefore, it is prudent to evaluate dyslipidemias more often than is recommended in the general population. Lipoprotein levels may change during the first 3 months of hemodialysis, peritoneal dialysis, and kidney transplantation. On the other hand, waiting 3 months to measure the first lipid profile may needlessly delay effective treatment for patients who present with dyslipidemia. For patients whose lipid profile is normal at presentation, it is reasonable to repeat

Table 14. The Prevalence of Dyslipidemias in Adults.

Study	Modality	N	Age (years)	Quality[a]	Applicability[b]	Time After Initiation of Treatment	Mean Values (mg/dL) and Percent Elevated[c] CHOL >200	LDL >100	HDL <40	TG
Senti, [165] 1992	HD	101	57.7	○	🧍	4.49 mo.	14.8% 16% est. (159±41)	34% est. (88±28.6)	75% est. (32±12)	(136±70)
Shoji, [120] 1998	HD	210	55	○	🧍🧍	5.3 years	23% est. (170±40.6)			(119±57)
Hernandez,[166] 1996	HD	40	52.4	○	🧍	93.6 mo.	44% est. (194±42)	81% est. (145±52)	59% est. (40±12)	(167±105)
Avram,[167] 1988	HD	63	55	○	🧍	63±7 mo.	36% est. (183±47.6)		60% est (38±7.9)	(172±143)
Parra, [168] 1988	HD	76	48	○	🧍	—	60% est. (214±55)			(173±93)
Aakhus,[169] 1996	Transplant	403	47	◎	🧍🧍	48 mo.	94% est. (281±52.5)		18% (55.5±17)	
Gonyea, [170] 1992	Transplant	100	—	◎	🧍🧍	1 year	83% est. (250±53)	90% est. (167±53)	21% est. (51±14)	
Brown, [171] 1997	Transplant	100	41.8	◎	🧍🧍	CsA 36 mo. AZA+P 98 mo.	83% est. (258±61) 87% est. (262±55)	93% est. (168±47) 92% est. (167±48)	30% est. (48±15) 14% est. (55±14)	[163 (11-1912)] [159 (61-687)]
Moore, [172] 1993	Transplant	214	44.7	○	🧍	>1 year	90% est. (278±62)	97% est. (213±58)	48% est. (46±123)	(195±106)

[a]Study quality was graded: ● least bias, results are valid; ◎ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.
[b]Applicability was rated: 🧍🧍🧍 representative of a wide spectrum of patients; 🧍🧍 representative of a relevant subgroup; or 🧍representative of a narrow subgroup.
[c]Shown is the percent of patients with dyslipidemia at the threshold indicated (if available), the percent with dyslipidemia estimated (est.) from the mean and standard deviation, and (in parentheses) the mean and standard deviation.
To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and cholesterol by 0.02586.

Table 15. The Prevalence of Dyslipidemias in Children and Adolescents.

Study	Modality	N	Age (years)	Quality[a]	Applicability[b]	Time After Initiation of Treatment	Mean Values (mg/dL) and Percent Elevated[c] CHOL >200	LDL >100	HDL <40	TG
Querfeld,[173] 1991	PD	20	13.9	◉	🧍🧍	2.1 years	33 est. (184±36)	78 est. (125±33)	48 est. (39±16)	(154±62)
Querfeld,[174] 1993	PD	16	11.1	◉	🧍🧍	1.7 years	69 est. (234±68.8)	87 est. (154±47.2)	39 est. (37±10)	(182±93)
Scolnik,[175] 1993	PD	53	<5	○	🧍🧍	2 years	63% est. (216±48)		31% est. (46±.12)	(244±174)
Querfeld,[176] 1988	PD	68	12.6	○	🧍🧍	16.1 months	71% est. (240±74.2)			(236±115)
Broyer,[177] 1983	PD	15	9.2	○	🧍	—	86% est. (251±47.6)			(256±85)
Bakkaloglu,[178] 2000	PD	18	12.9	○	🧍	1.5-54 months	14 est. (196±47)	29 est. (119±38)	45 est. (38±16)	(193±114)
Querfeld,[174] 1993	Transplant	23	14.8	◉	🧍🧍	3.6 years	61% est. 213.8±47.2	84% est. 141.9±42.2	67% est. 44.9±10.8	154±73
Silverstein,[179] 2000	Transplant	62	15.4	◉	🧍🧍	6.7 years	51.6% 55% est. (206±44)			(157±88)
Goldstein,[180] 1984	Transplant	30	9.9	○	🧍🧍	2.5-5.0 years	66% est. (218±44)			(109.5)
Van Gool,[181] 1991	Transplant	20	13.6	○	🧍	—	63% est. (218±57)	72% est. (129±50)	84% est. (55±15)	(156±77)
Milliner,[182] 1994	Transplant	69	14.4	○	🧍	1 year	66% est. (219±45)	81% est. (130±34)	19% est (53±15)	(142±98)
Singh,[183] 1998	Transplant	29	14.5	○	🧍	—	242	148	59	167

[a]Study quality was graded: ● least bias, results are valid; ◉ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.
[b]Applicability was rated: 🧍🧍🧍 representative of a wide spectrum of patients; 🧍🧍 representative of a relevant subgroup; or 🧍representative of a narrow subgroup.
[c]Shown is the percent of patients with dyslipidemia at the threshold indicated, the percent with dyslipidemia estimated (est.) from the mean and standard deviation, and (in parentheses) the mean and standard deviation.
To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and cholesterol by 0.02586.

Table 16. Prevalence of Dyslipidemias among 1,047 Hemodialysis Patients.

Treatment Thresholds in These Guidelines				
LDL ≥100	Non-HDL Chol. ≥130	TG ≥200	Percent	Treatment Required?
Yes	—	—	5.4	Yes - 55.7%
Yes	Yes	—	32.5	
Yes	—	Yes	0.5	
Yes	Yes	Yes	17.3	
—	—	—	32.2	No - 38.9%
—	Yes	—	1.8	
—	—	Yes	4.9	
—	Yes	Yes	5.4	Yes - 5.4%

Values for LDL, HDL ant TG are in mg/dL. To convert to mmol/L multiply LDL and HDL values by 0.02586 and multiply TG values by 0.01129. Data are from the Dialysis Morbidity and Mortality Study and were provided by Rulan Parekh (personal communication).
Abbreviations: LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; non-HDL, non-HDL cholesterol; TG, triglycerides.

the lipid profile 3 months later, to confirm that the initial values were not low due to malnutrition or systemic disease. During the course of kidney disease treatment, lipid levels may change. Therefore, the Work Group recommends measuring subsequent levels at least annually. Reasons to repeat lipid measurements after 2-3 months include changes in kidney replacement therapy modality, treatment with diet or lipid-lowering agents, immunosuppressive agents that affect lipids (eg, prednisone, cyclosporine, or sirolimus) or other changes that may affect plasma lipids.

Table 17. Prevalence of Dyslipidemias among 317 Peritoneal Dialysis Patients.

Treatment Thresholds in These Guidelines				
LDL ≥100	Non-HDL Chol. ≥130	TG ≥200	Percent	Treatment Required?
Yes	—	—	5.1	Yes - 73.2%
Yes	Yes	—	41.0	
Yes	—	Yes	0.0	
Yes	Yes	Yes	27.1	
—	—	—	18.0	No - 21.5%
—	Yes	—	1.9	
—	—	Yes	1.6	
—	Yes	Yes	5.4	Yes - 5.4%

Values for LDL, HDL ant TG are in mg/dL. To convert to mmol/L multiply LDL and HDL values by 0.02586 and multiply TG values by 0.01129. Data are from the Dialysis Morbidity and Mortality Study and were provided by Rulan Parekh (personal communication).
Abbreviations: LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; non-HDL, non-HDL cholesterol; TG, triglycerides.

Table 18. Serum Total Cholesterol Levels in U.S. Children and Adolescents.

		Cholesterol Values for Mean and Percentiles (mg/dL)							
Category	N	Mean	5th %-tile	10th %-tile	25th %-tile	50th %-tile	75th %-tile	90th %-tile	95th %-tile
Males									
0-4	238	159	117	129	141	156	176	192	209
5-9	1,253	165	125	134	147	164	180	197	209
10-14	2,278	162	123	131	144	160	178	196	208
15-19	1,980	154	116	124	136	150	170	188	203
Females									
0-4	186	161	115	124	143	161	177	195	206
5-9	1,118	169	130	138	150	168	184	201	211
10-14	2,087	164	128	135	148	163	179	196	207
15-19	2,079	162	124	131	144	160	177	197	209

Values were converted from plasma to serum (plasma value × 1.03 = serum value). Insufficient data were available for children ages 0-4 years. To convert mg/dL to mmol/L multiply values by 0.02586. Data are from the Lipid Research Clinics Program.[190]
Abbreviation: %-tile, percentile.

Dyslipidemias in Adolescents

Young adults (20-40 years old) with Stage 5 CKD have at least a 10-fold higher risk for CVD mortality compared to the general population.[184] There are limited data on ACVD in children with CKD. However, CVD accounts for approximately 23% of deaths in children and adults <30 years old who started treatment for stage 5 CKD as children.[185] Recent data from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study provide compelling evidence in the general pediatric population, that initial fatty streaks seen in adolescents develop into atheromatous plaques in young adults.[186] Moreover, this atherosclerotic process is believed to be accelerated in uremia, thus putting children with Stage 5 CKD at high risk for developing ACVD. Indeed, studies of arteries from children with Stage 5 CKD have demonstrated early ACVD changes.[187,188]

It is important to note that lipid levels in the general population change with age and puberty, and differ by gender (Tables 18, 19, 20, and 21).[189] Very low levels at birth increase rapidly in the first year of life to a mean total cholesterol of 150 mg/dL (3.88 mmol/L), LDL 100 mg/dL (2.59 mmol/L), and HDL 55 mg/dL (1.42 mmol/L). From ages 1-12, lipid levels remain fairly constant, and are slightly lower in girls than boys. During puberty, there is a decrease in total cholesterol, LDL, and a slight decrease in HDL in boys. After puberty, ie, by age 17, cholesterol and LDL increase to adult levels in boys and girls. Boys continue to have a slightly lower HDL than girls. These changes dictate that the definitions of dyslipidemias be different in children and adults. These guidelines define dyslipidemias for children using lipid levels greater than the 95th percentile for age and gender (Tables 18, 19, 20, and 21). Treatment thresholds for children do not differ by age and gender, but these thresholds are different from those of adults.

There are few data documenting the prevalence of dyslipidemias in children and adolescents with CKD. A search was conducted for studies published after 1980 that included at least 15 patients and reported data on the prevalence of dyslipidemia in unselected patients with CKD. There were no studies of hemodialysis patients. Children and adolescents on peritoneal dialysis appeared to have a very high prevalence of dyslipidemias (Table 15). Indeed, 29% to 87% of pediatric peritoneal dialysis patients had LDL >100 mg/dL (>2.59 mmol/L). Similarly, 72% to

Table 19. Serum LDL Levels in U.S. Children and Adolescents.

		LDL Values for Mean and Percentiles (mg/dL)							
Category	N	Mean	5th %-tile	10th %-tile	25th %-tile	50th %-tile	75th %-tile	90th %-tile	95th %-tile
White Males									
5-9	131	95	65	71	82	93	106	121	133
10-14	284	99	66	74	83	97	112	126	136
15-19	298	97	64	70	82	96	112	127	134
White Females									
5-9	114	103	70	75	91	101	118	129	144
10-14	244	100	70	75	83	97	113	130	140
15-19	294	99	61	67	80	96	114	133	141

Values were converted from plasma to serum (plasma value × 1.03 = serum value). Insufficient data were available for children ages 0-4 years. To convert mg/dL to mmol/L multiply values by 0.02586. Data are from the Lipid Research Clinics Program.[190]
Abbreviations: %-tile, percentile; LDL, low-density lipoprotein cholesterol

84% of pediatric kidney transplant recipients had LDL >100 mg/dL (>2.59 mmol/L) (Table 15). In a longitudinal study of pediatric transplant patients, the prevalence of hypercholesterolemia declined from 70.4% to 35% at 10 years, with a decrease in hypertriglyceridemia from 46.3% to 15%.[182] This decline in prevalence may reflect reductions in immunosuppressive medications and improved kidney function. Unfortunately, no longitudinal studies have defined the long-term risk of dyslipidemias in children with CKD, particularly as they survive into young adulthood.

Use of the Friedewald Formula to Calculate LDL

The Friedewald formula appears to be the most practical, reliable method for determining LDL cholesterol in clinical practice:

Table 20. Serum HDL Levels in U.S. Children and Adolescents.

		HDL Values for Mean and Percentiles (mg/dL)							
Category	N	Mean	5th %-tile	10th %-tile	25th %-tile	50th %-tile	75th %-tile	90th %-tile	95th %-tile
White Males									
5-9	142	57	39	43	50	56	65	72	76
10-14	296	57	38	41	47	57	63	73	76
15-19	299	48	31	35	40	47	54	61	65
White Females									
5-9	124	55	37	39	48	54	63	69	75
10-14	247	54	38	41	46	54	60	66	72
15-19	295	54	36	39	44	53	63	70	76

Values were converted from plasma to serum (plasma value × 1.03 = serum value). Insufficient data were available for children ages 0-4 years. To convert mg/dL to mmol/L multiply values by 0.02586. Data are from the Lipid Research Clinics Program.[190]
Abbreviations: %-tile, percentile; HDL, high-density lipoprotein cholesterol.

Table 21. Serum Triglycerides in U.S. Children and Adolescents.

		Triglyceride Values for Mean and Percentiles (mg/dL)							
Category	N	Mean	5th %-tile	10th %-tile	25th %-tile	50th %-tile	75th %-tile	90th %-tile	95th %-tile
Males									
0-4	238	58	30	34	41	53	69	87	102
5-9	1,253	30	31	34	41	53	67	88	104
10-14	2,278	68	33	38	46	61	80	105	129
15-19	1,980	80	38	44	56	71	94	124	152
Females									
0-4	186	66	35	39	46	61	79	99	115
5-9	1,118	30	33	37	45	57	73	93	108
10-14	2,087	78	38	45	56	72	93	117	135
15-19	2,079	78	40	45	55	70	90	117	136

Values were converted from plasma to serum (plasma value × 1.03 = serum value). Insufficient data were available for children ages 0-4 years. To convert mg/dL to mmol/L multiply values by 0.01129. Data are from the Lipid Research Clinics Program.[190]
Abbreviations: %-tile, percentile; HDL, high-density lipoprotein cholesterol.

$$\text{LDL} = \text{Cholesterol} - \text{HDL} - (\text{triglycerides} \div 5), \text{ in mg/dL,}$$

or

$$\text{LDL} = \text{Cholesterol} - \text{HDL} - (\text{triglycerides} \div 2.19), \text{ in mmol/L.}[191]$$

Two recent studies found the Friedewald formula to be reliable in dialysis patients,[192,193] although other investigators reported that the percentage error for the formula is higher in patients with CKD compared to the general population.[194] No studies have examined the accuracy of the Friedewald formula in transplant recipients, or studies in other CKD patients, eg, those with nephrotic syndrome.

Recent data from a study in the general population suggest that the Friedewald formula may underestimate LDL in patients with low LDL levels.[31] Data from the general population also suggest that the Friedewald formula is not accurate when triglycerides are ≥400 mg/dL (≥4.52 mmol/L). Direct measurement of LDL with ultracentrifugation or immunoprecipitation techniques is reasonably accurate when triglycerides are 400-800 mg/dL (4.52-9.03 mmol/L), but there are no reliable techniques for determining LDL when triglycerides are ≥800 mg/dL (≥9.03 mmol/L). Fasting triglycerides ≥800 mg/dL (≥9.03 mmol/L) generally indicate the presence of hyperchylomicronemia, and the role of hyperchylomicronemia in ACVD is unknown.

There are few studies in children, and none included children with CKD. However, in 1 study of children from the general population, calculating LDL using the Friedewald formula was more reliable in correctly classifying patients with high LDL than was the direct measurement of LDL.[195]

Dyslipidemias in Acute Medical Conditions

Some acute medical conditions may transiently alter plasma lipid levels (Table 22). For example, severe infections, surgery and acute myocardial infarction are often associated with lower-than-normal lipid levels. Other conditions, for example acute pancreatitis, may be associated with higher levels. In general, it is best to wait until acute conditions that may alter lipid levels have resolved before assessing dyslipidemias for possible ACVD risk. It should be noted, however, that the lipid profile is not significantly altered within the first 24 hours after a myocardial infarction, and a lipid profile can be measured during this time.[196-198]

Table 22. Transient Effects of Some Acute Conditions on Lipid Levels.

Acute Condition	Total Cholesterol	LDL	HDL	Triglycerides
Myocardial infarction [196-198]	↓	↓	↓	NC
Stroke [199]	↓	↓	NC	NC
Bacterial sepsis[200-202]	↓	↓	↓	↑
Surgery[203-205]	↓	↓	↓	↓
Acute pancreatitis [206;207]	↑	NC	NC	↑
Transplant acute rejection[208]	↓	↓	NC	↓/NC
Transplant CMV infection[208]	↓	↓	NC	↓

Abbreviations: LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; NC, no change; CMV, cytomegalovirus.

The Influence of Immunosuppressive Agents

Immunosuppressive medications, eg, prednisone, cyclosporine, and sirolimus are among the several potential remediable causes of dyslipidemias in patients with CKD and after kidney transplantation (Table 23). It is not clear how soon these agents exert their effects on lipoprotein metabolism, and when lipid levels reach a new steady state. However, the effects of diet and lipid-lowering agents may not be fully manifest for 2-3 months, and—by analogy—it may be best to measure a lipid profile 2-3 months after starting or stopping an immunosuppressive agent that is known to have a major effect on lipoprotein levels, eg, prednisone, cyclosporine, or sirolimus.

The present guidelines are consistent with those of the American Society of Transplantation (AST), which recommend that a lipid profile should be measured during the first 6 months post-transplant, at 1 year after transplantation, and annually thereafter.[209] The AST guidelines also suggest that changes in immunosuppressive therapy, graft function, or CVD risk warrant additional testing.[209]

GUIDELINE 2

2.1. For adults and adolescents with Stage 5 CKD, a complete lipid profile should be measured after an overnight fast whenever possible. (B)

2.2. Hemodialysis patients should have lipid profiles measured either before dialysis, or on days not receiving dialysis. (B)

Fasting

Eating raises plasma triglycerides, carried mostly in chylomicrons and very low-density lipoprotein (VLDL), and, as a result, total cholesterol levels also increase. The post-prandial increases in triglycerides and cholesterol are quite variable, depending on the type of food ingested. In addition, substantial variability in post-prandial lipid levels is attributable to inherited and acquired differences between individuals. Although these differences affect the risk for ACVD, the relationship between post-prandial lipid levels and ACVD is not as well established as the relationship between fasting lipid levels and ACVD.[3] Practical considerations may make non-fasting measurements the only alternative for some patients. While fasting lipid profiles are best, it is better to obtain non-fasting lipid profiles than to forgo evaluation altogether. If the lipid profile obtained in a non-fasting patient is normal, then no further assessment is needed at that time. However, an abnormal lipid profile in a non-fasting patient is an indication to obtain a fasting lipid profile.

Effects of Hemodialysis and Peritoneal Dialysis on Plasma Lipids

There is some evidence that the hemodialysis procedure acutely alters plasma lipid levels.[217] This may be due to hemoconcentration and/or effects of the dialysis membrane or heparin on lipoprotein metabolism. Therefore, assessment should be done prior to the hemodialysis procedure. There are few data describing how quickly

Table 23. Randomized Trials Evaluating the Effects of Immunosuppressive Agents on Dyslipidemias after Kidney Transplantation.

Study	N	Quality[a]	Applicability[b]	Treatment	Change Compared To Baseline (%)[c] CHOL	LDL	HDL	TG
Johnson,[210] 2000	223	●	↑↑↑	Tacrolimus+azathioprine vs.	+14	+18		
				CsA+MMF vs.	+25*	+30*		
				Tacrolimus+MMF	+12	+1		
McCune,[211] 1998	53	●	↑↑↑	Tacrolimus vs.	-16*	-25*	NC	
				CsA	NC	NC	NC	
Vanrenterghem,[212] 2000	500	●	↑↑	MMF+CsA+half dose corticosteroid (low stop) vs.	+6			-3
				MMF+CsA+full dose corticosteroid (control)	+29*			+10*
Curtis,[213] 1982	28	○	↑↑	Alternate day vs.	-12			-28
				daily prednisone	~+4[d]			~-7[d]
Hollander, [214] 1997	84	○	↑↑	Prednisone continuation vs.	-10	-12	-7	-17
				withdrawal	-8	-7	-14	-4
Hilbrands,[215] 1995	122	○	↑↑	Azathioprine+prednisone vs.	-4	+2	-15	-12*
				CsA monotherapy	-0	-0	-19	+24
John,[216] 1999	208	○	↑↑	High dose CsA vs.	-13			+9
				low dose CsA	-19			+3

[a]Study quality was graded: ● least bias, results are valid; ○ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.
[b]Applicability was rated: ↑↑↑ representative of a wide spectrum of patients; ↑↑ representative of a relevant subgroup; or ↑representative of a narrow subgroup.
[c]The percent change within each group is indicated. "*" indicates a statistically significant difference between treatment and control.
[d]Results were estimated from figures.
Abbreviations: CsA, cyclosporine A; MMF, mycophenolate mofetil; NC, the study reported "no change."

Table 24. 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

lipoprotein levels change during the course of peritoneal dialysis exchanges. However, it is probably most practical to draw blood in the morning, after an overnight fast (whenever possible), and with whatever peritoneal dialysis fluid is dwelling in the peritoneal cavity when the blood is drawn.

GUIDELINE 3

Stage 5 CKD patients with dyslipidemias should be evaluated for remediable, secondary causes. (B)

Rationale

Causes of secondary dyslipidemias include nephrotic syndrome,[218-223] hypothyroidism,[224-226] diabetes,[227-229] excessive alcohol ingestion,[230-234] and chronic liver disease (Table 24).[235-237] Medications that can cause dyslipidemias include 13-*cis*-retinoic acid,[238-240] anticonvulsants,[241-243] highly active anti-retroviral therapy,[244-246] beta-blockers,[247] diuretics,[247] androgens/anabolic steroids,[248-251]oral contraceptives,[252-254] corticosteroids,[212,255,256] cyclosporine,[210,215,257] and sirolimus[258,259] (Table 24). The assessment of these secondary causes with history, physical examination, and appropriate laboratory testing is recommended for any patient with dyslipidemia, since effective correction of these disorders may improve the lipid profile.

Urine protein excretion, especially if >3 g per 24 hours, can also cause or contribute to dyslipidemias.[218-223] Therefore, CKD patients who still produce urine should have protein excretion measured, if this has not been done recently. In some cases, the underlying cause(s) of the proteinuria can be treated and effectively reversed. In other cases, angiotensin II converting enzyme inhibitors or angiotensin II receptor blockers may help reduce protein excretion, and may thereby improve the lipid profile in some patients. Clinical hypothyroidism can cause dyslipidemia,[224-226] and even subclinical hypothyroidism may cause mild changes.[225,260] Some of the signs and symptoms of hypothyroidism may resemble those of uremia, which may make the clinical diagnosis of hypothyroidism more difficult in patients with CKD. Glucose intolerance can also cause dyslipidemias.[227-229] Therefore, patients with dyslipidemia and CKD (but without known diabetes) should be assessed with fasting blood glucose and possibly glycosylated hemoglobin. Glycemic control can improve lipid profiles.

Secondary causes of dyslipidemia in children and adolescents, in addition to those listed in Table 24, include lipodystrophy[261,262]; idiopathic hypercalcemia[263,264]; glycogen storage diseases[265-268]; cystine storage disease; Gaucher disease; Juvenile Tay-Sachs disease; Niemann-Pick Disease; sphingolipidoses; obstructive liver disease such as biliary atresia[269,270]; biliary cirrhosis; intrahepatic cholestasis; nephrotic syndrome; anorexia nervosa[271,272]; progeria[273,274]; systemic lupus erythematosus[275,276]; Werner syndrome; and Klinefelter syndrome. These conditions are fortunately rare, and require referral to appropriate tertiary care specialists.

III. TREATING DYSLIPIDEMIAS

THE APPROACH adopted for adults (Guideline 4) closely parallels that recommended by the ATP III Guidelines,[3] and is summarized in Fig 7 and Table 25. For the rare adult patient with markedly elevated serum triglyceride levels, triglyceride reduction is the principal focus of treatment in order to prevent pancreatitis. Otherwise, high levels of LDL are the focus of treatment. Patients with normal LDL, but high triglycerides, frequently have high levels of remnant lipoproteins. In general, the level of non-HDL cholesterol can be used as a surrogate for increased remnant lipoproteins, and elevated levels of non-HDL cholesterol should be considered for treatment.[3] Non-HDL cholesterol is the total cholesterol minus HDL cholesterol (Fig 6).

The approach adopted for adolescents (Guideline 5) is similar to that for adults, but uses higher thresholds for treating LDL and non-HDL cholesterol (Fig 8). These higher thresholds are in deference to the relative lack of evidence for safety and efficacy of treatment in adolescents, and the likelihood that the benefit-to-risk ratio is higher at higher levels of LDL and non-HDL cholesterol.

TREATMENT OF ADULTS WITH DYSLIPIDEMIAS

GUIDELINE 4

4.1. For adults with Stage 5 CKD and fasting triglycerides ≥500 mg/dL (≥5.65 mmol/L) that cannot be corrected by removing an underlying cause, treatment with therapeutic lifestyle changes (TLC) and a triglyceride-lowering agent should be considered. (C)

4.2. For adults with Stage 5 CKD and LDL ≥100 mg/dL (≥2.59 mmol/L), treatment should be considered to reduce LDL to <100 mg/dL (<2.59 mmol/L). (B)

4.3. For adults with Stage 5 CKD and LDL <100 mg/dL (<2.59 mmol/L), fasting triglycerides ≥200 mg/dL (≥2.26 mmol/L), and non-HDL cholesterol (total cholesterol minus HDL) ≥130 mg/dL (≥3.36 mmol/L), treatment should be considered to reduce non-HDL cholesterol to <130 mg/dL (<3.36 mmol/L). (C)

Rationale for Treating Very High Triglycerides

The general approach to treating dyslipidemia in adults with CKD closely follows the approach adopted by the ATP III (Fig 7 and Table 25). For rare patients with very high triglycerides, treatment of hypertriglyceridemia to reduce the risk for pancreatitis takes precedence over treatment of LDL cholesterol. The ATP III guidelines classify very high fasting triglycerides as ≥500 mg/dL (≥5.65 mmol/L).[3] Very high triglycerides are unusual and are generally due to an inherited abnormality in lipoprotein metabolism. For individuals with very high triglycerides, the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. Only when triglycerides are <500 mg/dL (<5.65 mmol/L) should attention be focused on LDL cholesterol reduction.

Rarely, severe hypertriglyceridemia can cause pancreatitis in the general population. The incidence of pancreatitis caused by hypertriglyceridemia in patients with CKD is unknown, but it is probably also very low. In 1 observational study, the overall incidence of acute pancreatitis in patients with kidney failure was 2.3% (23/1,001),[277] but probably few, if any, of these cases of pancreatitis were caused by dyslipidemias. In another study of 716 patients with kidney failure, 46 (6.4%) were identified as having pancreatitis, while 31 (4.3%) had their first episode of pancreatitis after starting treatment for kidney failure.[278] Of 13 patients in whom a first episode of pancreatitis developed after starting hemodialysis, in only 1 was the pancreatitis felt to be caused by hyperlipidemia, and this patient also had cholelithiasis.[278] Of 217 patients who received a kidney transplant, pancreatitis developed in 12 (5.5%), but in none of these cases was the pancreatitis believed to be caused by hyperlipidemia. Thus, these limited data suggest that hyperlipidemia is a rare cause of pancreatitis among patients with kidney failure. However, additional studies are needed to better ascertain the incidence of pancreatitis in CKD, and the

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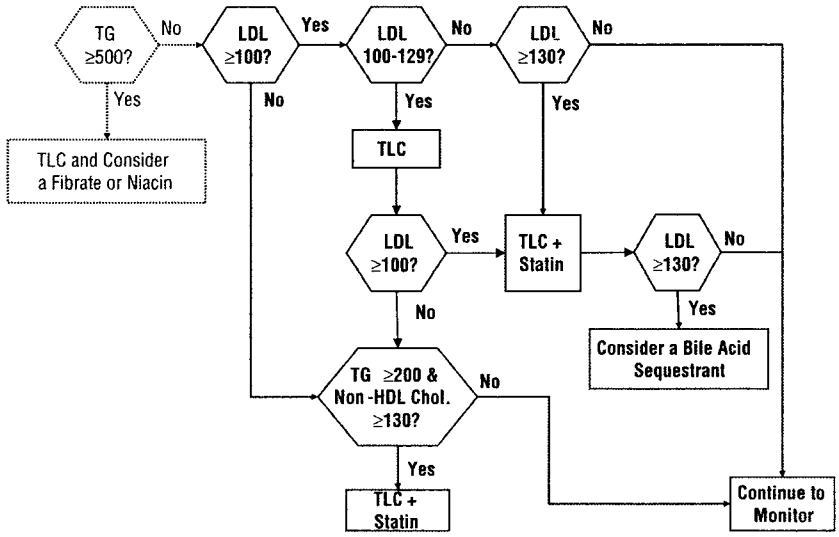


Fig 7. The approach to treatment of dyslipidemias in adults with chronic kidney disease used in these guidelines. Units are in mg/dL. To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and LDL or non-HDL cholesterol by 0.02586. Abbreviations: TG, triglycerides; TLC, therapeutic lifestyle changes; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

possible role of dyslipidemias in its pathogenesis.

Treating Very High Triglycerides With Therapeutic Lifestyle Changes

The ATP III guidelines suggest that triglycerides ≥500 mg/dL (≥5.65 mmol/L) should be treated with TLC. In the absence of data on the risk of acute pancreatitis from very high triglycerides in patients with kidney failure, it is reasonable to follow the ATP III guidelines. The ATP III guidelines recommend that TLC include diet, weight reduction, increased physical activity, abstinence from alcohol, and treatment of hyperglycemia (if present). For patients with fasting triglycerides ≥1,000 mg/dL (≥11.29 mmol/L), the ATP III diet recommendations include a very low-fat diet (<15% total calories), medium-chain triglycerides, and fish oils to replace some long-chain triglycerides. Diet should be used judiciously, if at all, in individuals who are malnourished.

Drug Treatment of Very High Triglycerides

If TLC is not sufficient to reduce triglycerides to <500 mg/dL (<5.65 mmol/L), then treatment with a fibrate or nicotinic acid should be considered (Table 25). Studies from the general population suggest that fibrates and nicotinic acid lower triglycerides by 20% to 50% (Fig 9). Statins cause less triglyceride lowering, and bile acid sequestrants may actually increase triglyceride levels. Therefore, when triglycerides continue to be ≥500 mg/dL (≥5.65 mmol/L) despite TLC and/or withdrawal of causative agents, drug treatment should be considered. In general, fibrates are better tolerated than nicotinic acid. In any case, the benefits of drug therapy for hypertriglyc-

Table 25. The Management of Dyslipidemias in Adults with Chronic Kidney Disease.

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG ≥500 mg/dL	TG <500 mg/dL	TLC	TLC + Fibrate or Niacin	Fibrate or Niacin
LDL 100-129 mg/dL	LDL <100 mg/dL	TLC	TLC + low dose Statin	Bile acid seq. or Niacin
LDL ≥130 mg/dL	LDL <100 mg/dL	TLC + low dose Statin	TLC + max. dose Statin	Bile acid seq. or Niacin
TG ≥200 mg/dL and non-HDL ≥130 mg/dL	Non-HDL <130 mg/dL	TLC + low dose Statin	TLC + max. dose Statin	Fibrate or Niacin

To convert mg/dL to mmol/L, multiply triglycerides by 0.01129, and cholesterol by 0.02586.
Abbreviations: TG, triglycerides; LDL, low-density lipoprotein cholesterol; TLC, therapeutic lifestyle changes.

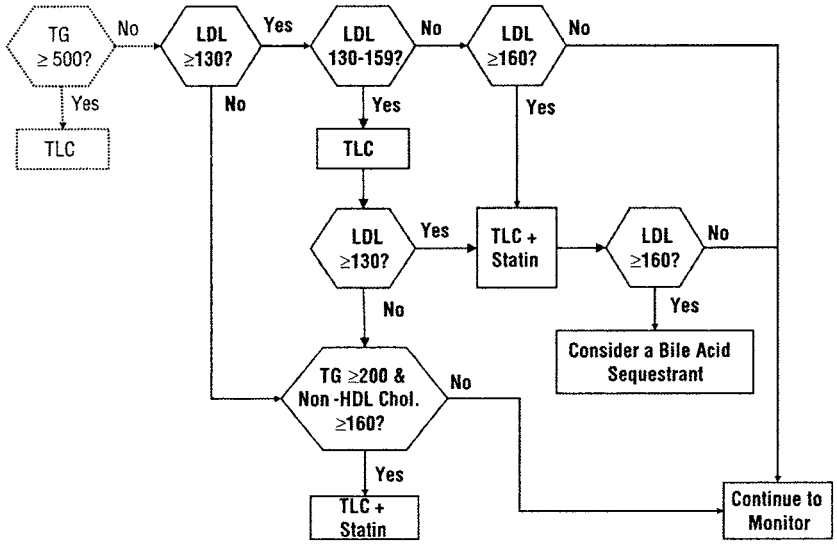


Fig 8. The approach to treatment of dyslipidemias in adolescents with chronic kidney disease used in these guidelines. Units are in mg/dL. To convert mg/dL to mmol/L, multiply triglycerides by 0.01129 and LDL or non-HDL cholesterol by 0.02586. Abbreviations: TG, triglycerides; TLC, therapeutic lifestyle changes; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

eridemia should be weighed against the risks, and the risk of complications (particularly myositis and rhabdomyolysis) is increased in CKD.

Rationale for Treating High LDL Cholesterol

The ATP III Guidelines were developed using rigorous, evidence-based methods. In the absence of data from randomized trials conducted in patients with CKD, it is reasonable to assume that the interventions recommended by the ATP III will similarly reduce ACVD in patients with CKD. However, randomized trials proving that treatment of dyslipidemias reduce the incidence of ACVD ultimately need to be conducted.

The risk of CHD events is markedly increased in patients with CKD.[2,4] Therefore, patients with CKD should be considered to have a risk equivalent to that of CHD. This risk category in the ATP III Guidelines includes patients with known ACVD, patients with diabetes, and patients with an expected 10-year risk of CHD >20%. Evidence suggests that patients with CKD have an expected 10-year CHD risk >20%,[2,4] thereby justifying their inclusion in this highest risk category.

Treating Proteinuria

Nephrotic-range proteinuria increases total and LDL cholesterol.[218-223] In patients with severe proteinuria, triglycerides may also be increased. It may be possible to induce a remission in the nephrotic syndrome by treating the underlying glomerular disease. If not, it may be possible to reduce the level of proteinuria, and thereby improve the patient's lipid profile. Unfortunately, few randomized controlled trials have documented the lipid-lowering effects of therapies that reduce urine protein excretion, eg, angiotensin II converting enzyme inhibitors, angiotensin II receptor antagonists, and/or low-protein diets.

In a randomized, controlled trial, treatment of 17 nephrotic patients with an angiotensin II converting enzyme inhibitor reduced urine protein excretion from a mean of 5.56 to 4.28 g per day, and decreased mean total cholesterol from 247 to 225 mg/dL (6.39 to 5.82 mmol/L).[279] There were no changes in protein excretion or cholesterol levels in 9 placebo-treated controls.[279] In a randomized trial of 94 type II diabetic patients with microalbuminuria, treatment with an angiotensin II converting enzyme inhibitor reduced total cholesterol from 245 ± 24 mg/dL (6.34 ± 0.62 mmol/L) to 239 ± 29 mg/dL (6.18 ± 0.75 mmol/L), while cholesterol increased slightly in the placebo group.[280] However, in other randomized trials of microalbuminuric type II diabetic patients, angiotensin II converting enzyme inhibitors had little effect on lipid levels.[281,282] There are few data on the effects of low-protein diets on lipid levels. In the feasibility phase of the Modification of Diet in Renal Disease study, serum total and LDL cholesterol levels tended to decrease with reduced dietary protein intake.[283]

There is substantial evidence that angiotensin

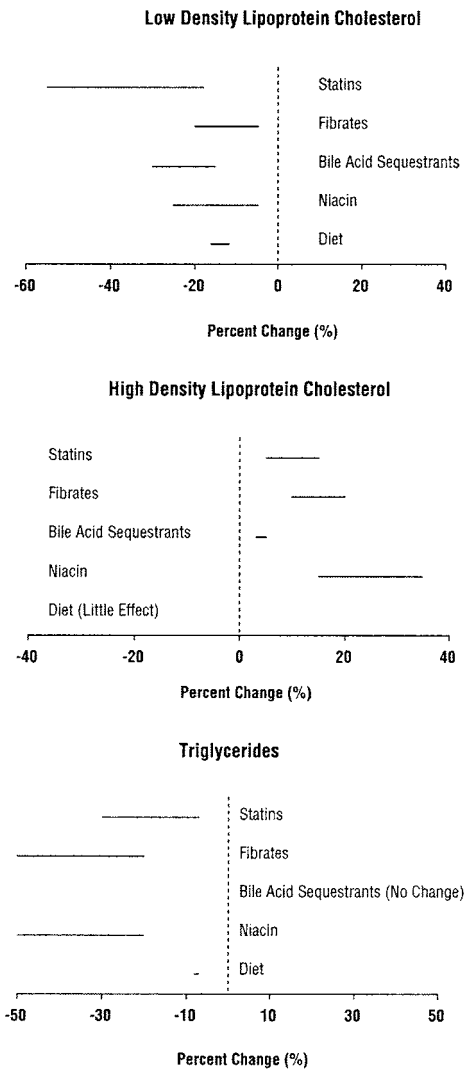


Fig 9. Expected responses to treatment of low-density lipoprotein (upper panel), high-density lipoprotein (middle panel), and triglycerides (lower panel), based on studies in the general population.[3]

II converting enzyme inhibitors reduce the rate of kidney disease progression in patients with proteinuria. Therefore, proteinuric patients with CKD should generally be treated with an angiotensin II converting enzyme inhibitor or angiotensin II receptor antagonist, regardless of plasma lipids.[2]

Treating High LDL With Therapeutic Lifestyle Changes: Diet

There are no randomized trials examining the safety and efficacy of a low-fat, low-cholesterol diet in patients with CKD. However, evidence from the general population suggests that a lipid-lowering diet can reduce LDL.[3,30,284] Diet should be used judiciously, if at all, when there is evidence of protein-energy malnutrition. The diet should include <7% of calories as saturated fat, up to 10% of calories as polyunsaturated fat, up to 20% of calories as monounsaturated fat, and a total fat of 25% to 35% of total calories (Table 26 and Appendix 2). The diet should also contain complex carbohydrates (50% to 60% of total calories), and fiber (20-30 g per day). Dietary cholesterol should be <200 mg/day. There are few, if any, adverse effects from this dietary regimen. Some patients with LDL 100-129 mg/dL (2.59-3.34 mmol/L) may achieve the goal of LDL <100 mg/dL (<2.59 mmol/L) with TLC alone.[284] Thus, for patients with LDL 100-129 mg/dL (2.59-3.34 mmol/L), it is reasonable to attempt dietary changes for 2-3 months before beginning drug treatment. However, patients with CKD often have a number of other nutritional concerns,[285] and it is important to consult a dietitian experienced in the care of patients with CKD.

Treating High LDL With Therapeutic Lifestyle Changes: Exercise and Weight Reduction

Controlled trials in the general population suggest that exercise training produces small, but significant improvements in dyslipidemias.[284,289] Exercise has a number of beneficial effects, independent of those on dyslipidemias, and the lack of adverse effects makes a compelling case for recommending exercise in patients at risk for ACVD.[3] At least one small, randomized, controlled trial demonstrated that exercise improved cardiovascular function in hemodialysis patients.[290] However, few studies have examined the effects of exercise and/or weight reduction on dyslipidemias in patients with CKD. One randomized, controlled trial examining dyslipidemias in a small number of patients with CKD found that exercise caused a significant decrease only in triglycerides (Table 27).[291] Clearly, additional, controlled trials are needed to study the effects of exercise on dyslipidemias and other ACVD risk factors in patients with CKD. Meanwhile, it is recommended that exercise be encouraged in patients with CKD, based on data from studies in the general population.

Table 26. Therapeutic Lifestyle Changes (TLC) for Adults with Chronic Kidney Disease.

Diet (Consult a dietitian with expertise in chronic kidney disease)
Emphasize reduced saturated fat:
Saturated fat: <7% of total calories
Polyunsaturated fat: up to 10% of total calories
Monounsaturated fat: up to 20% of total calories
Total fat: 25%-35% of total calories
Cholesterol: <200 mg per day
Carbohydrate: 50%-60% of total calories
Emphasize components that reduce dyslipidemia
Fiber: 20-30 g per day emphasize 5-10 g per day viscous (soluble) fiber
Consider plant stanols/sterols 2 g per day
Improve glycemic control
Emphasize total calories to attain/maintain standard NHANES body weight
Match intake of overall energy (calories) to overall energy needs
Body Mass Index 25-28 kg/m^2
Waist circumference
Men <40 inches (102 cm)
Women <35 inches (88 cm)
Waist-Hip Ratio (Men <1.0; women <0.8)
Physical Activity
Moderate daily lifestyle activities
Use pedometer to attain/maintain 10,000 steps per day
Emphasize regular daily motion and distance (within ability)
Moderate planned physical activity
3-4 times per week 20-30 minute periods of activity
Include 5-minute warm-up and cool-down
Choose walking, swimming, supervised exercise (within ability)
Include resistance exercise training
Emphasize lean muscle mass and reducing excess body fat
Habits
Alcohol in moderation: limit one drink per day with approval of physician
Smoking cessation

References[3;30;284;286-288] See also Appendix 2.
Abbreviation: NHANES, National Health and Nutrition Examination Survey.

There are also very few controlled trials examining the effects of weight reduction, with diet and/or exercise, on dyslipidemias in CKD patients. The role of weight reduction, in CKD patients that often have a number of nutritional concerns,[285] is unclear. Again, additional studies are needed to define the role of diet, exercise, and weight reduction in dyslipidemic patients with CKD.

Treating High LDL With a Statin

The reduction in LDL that can be achieved with TLC is generally modest. Therefore, TLC alone is usually insufficient to reduce the LDL to

the goal of <100 mg/dL (<2.59 mmol/L). In patients who cannot reduce LDL to <100 mg/dL (<2.59 mmol/L) by diet, a statin (3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitor) should be added, provided that there is no evidence of acute or chronic liver disease. Diet should be continued as an adjunct to the statin. The dose of statin needed to reach the goal of LDL <100 mg/dL (<2.59 mmol/L) varies from patient to patient. Therefore, starting at a low dose and titrating the dose upwards is the best strategy for finding the lowest dose that achieves the goal. This approach will also minimize the frequency and severity of adverse effects. Statins reduced LDL by 18% to 55% in studies in the general population (Fig 9). Statins that are currently approved for use in the United States include atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.

There is strong evidence from studies in the general population that statins reduce CHD events and all-cause mortality. The reduction in mortality and in CHD events is proportional to the reduction in LDL. The literature search identified only 2 small, controlled trials of simvastatin in hemodialysis patients (Table 27), and only 2 randomized trials demonstrating the efficacy of statins in peritoneal dialysis patients (Table 28). There is substantial evidence that statins are safe and effective in reducing LDL in kidney transplant recipients (Table 29). In the absence of strong evidence to the contrary, it is reasonable to assume that statins will reduce LDL and thereby ACVD in most patients with CKD. Statins are clearly the most effective class of antilipemic agents for reducing LDL.

Elevated hepatic transaminases occur in 0.5% to 2.0% of patients treated with statins in the general population.[325] Therefore, many recommend that baseline alanine and aspartate transferase levels should be obtained, although this is controversial.[325] Indeed, whether statins cause hepatotoxicity is controversial. Statins have not been shown to worsen outcomes in patients with chronic transaminase elevations due to hepatitis B or C.[325]

Patients should also be monitored for signs and symptoms of myopathy. The risk of myopathy from statins is increased by CKD, advanced age, small body frame, and concomitant medications (eg, fibrates, nicotinic acid, cyclosporine, azole antifungals, macrolide antibiotics, protease inhibitors, nefazodone, non-dihydropyridine calcium antagonists, and amiodarone).[325] Most experts recommend obtaining a baseline creatinine phosphokinase (CK) level to help in the interpretation of subsequent CK levels. Monitoring statin therapy with routine CK levels is probably not helpful. Patients who develop muscle pain or tenderness should discontinue statin therapy immediately and have a CK level drawn. Elevations greater than 10 times the upper limit of normal are indicative of myositis and require at least temporary cessation of statin therapy.[325] For patients with muscle soreness and either normal or mildly elevated CK, levels should be measured weekly, and the patient's symptoms monitored closely. Often symptoms may improve with a reduction in the dose of the statin. However, if symptoms worsen, the statin should be discontinued. Other causes of myopathy should also be considered, eg, strenuous exercise or hypothyroidism.

There are limited data on blood levels of statins in patients with CKD (Table 30). In 19 patients with calculated creatinine clearances 13-143 mL/min, the level of kidney function did not affect the blood levels of atorvastatin.[326] Pravastatin blood levels were not altered by the level of kidney function in 20 patients with creatinine clearance 15-112 mL/min (0.25-1.87 mL/s),[327] or in 12 patients on chronic hemodialysis.[328] Lovastatin blood levels were significantly higher in 6 patients with CKD (creatinine clearance 12-39 mL/min [0.20-0.65 mL/s]).[329] Therefore, the dose of lovastatin should probably be reduced by 50% in patients with Stages 4 or 5 CKD (GFR <30 mL/min/1.73 m^2) (Table 31). The doses of atorvastatin and pravastatin probably do not need to be altered for reduced kidney function per se. Since there are few published data on blood levels for fluvastatin or simvastatin in patients with CKD, we recommend that the doses of these agents be reduced by approximately 50% in patients with Stages 4 or 5 CKD (GFR <30 mL/min/1.73 m^2).

Pleiotropic Effects of Statins

Recent data from studies in the general population have indirectly suggested that some of the reduction in ACVD from statins may be independent of their effects on plasma lipids.[341,342] Although statins may have favorable effects on endothelial function, coagulation, and plaque sta-

Table 27. Randomized Trials Evaluating the Treatment of Dyslipidemias in Hemodialysis Patients.

Study	N	Quality[a]	Applicability[b]	Treatment	Change Compared To Baseline (%)[c]			
					CHOL	LDL	HDL	TG
Soroka,[292] 1998	15	⊙	🧍	Animal-based low-protein diet vs.	-5	-6	-10	+8
				Soy-based vegetarian diet	-5	-3	-16	-4
Khajehdehi,[293] 2000	84	○	🧍	Vitamin E vs.	—	-5	+15	—
				Vitamin D_3 vs.	-4	-23	+3	-10
				Vitamin C vs.	-13*	-16*	—	-2
				Placebo	—	+5	+4	-1
Khajehdehi,[294] 2000	60	○	🧍	Fish oil (1.5 g/d) vs.	-10	-16	+138*	-11
				Corn oil (4.5 g/d) vs.	-2	-18	+42*	-10
				Sesame oil (4.5 g/d) vs.	-5	-1	+28	-2
				Placebo	+4	-13	+5	-1
Seri,[295] 1993	28	○	🧍	Fish oil vs.	-1	-24	+35	-4
				Blackcurrant seed oil vs.	—	-22	+10	-9
				Mixed oils vs.	—	+15	+39	-11
				Placebo	—	+5	+2	+3
Schrader,[296] 1988	70	⊙	🧍🧍	LMWH vs.	+5	+18	—	—
				Standard heparin	+2	+38	+5	+36
Kronenberg,[297] 1995	48	○	🧍🧍	LMWH vs.	+6*	+13*	+6*	—*
				Standard heparin	-3	-4	+22	+18
Saltissi,[298] 1999	36	○	🧍🧍	LMWH vs.	—	+1	—	-9
				Unfractionated heparin	—	—	-3	+4
Blankenstijn,[299] 1995	28	⊙	🧍	High-flux vs.	-9	-3	+8	-28
				Low-flux dialysis membrane	+2	+5	+3	+2
Golper,[300] 1990	82	⊙	🧍🧍	L-carnitine vs.	—	-7	-3	
				Placebo	-3	-2	-3	
Weschler,[301] 1984	10	⊙	🧍🧍	L-carnitine vs.	+17			+22
				Placebo	+15			—
Nilsson-Ehle,[302] 1985	28	⊙	🧍	L-carnitine vs.	—	—	+5	+5
				Placebo	+1	+2	—	-1
Giorcelli,[303] 1980	84	○	🧍🧍	L-carnitine vs.				-41
				Thiadenol				-42
Casciani,[304] 1982	15	○	🧍	L-carnitine vs.			+23	
				Placebo			+7	
Saltissi,[305] 2002	33	●	🧍🧍🧍	Simvastatin (n=22) vs.	-21*	-25*	-6	-18
				Placebo (n=11)	-12	-14	-3	-14

Table 27. Randomized Trials Evaluating the Treatment of Dyslipidemias in Hemodialysis Patients, continued.

Chang, [306] 2002	62	●	🧍🧍🧍	Simvastatin (n=31) vs. No treatment (n=31)	-16 * +2	-41* +3	+3 -3	-17* +2
Chertow,[307] 1997	36	●	🧍🧍🧍	Sevelamer hydrochloride vs. Placebo	-10* +4	* 	+5 +2	
Chertow,[308] 2002	200	●	🧍🧍🧍	Sevelamer hydrochloride vs. Placebo	-22* -1	-36* +1	-2 —	-7 +8
Park,[309] 2000	65	◎	🧍🧍	Estrogen/medroxprogesterone vs. No treatment	+1 +0	-9 +1	+12 -2	+20 +2
Goldberg,[291] 1983	25	○	🧍	Exercise vs. Control	-3 -3	NC NC	+16 -7	-33 -3

[a]Study quality was graded: ● least bias, results are valid; ◎ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.
[b]Applicability was rated: 🧍🧍🧍 representative of a wide spectrum of patients; 🧍🧍 representative of a relevant subgroup; or 🧍 representative of a narrow subgroup.
[c]The percent change within each group is indicated. "*" indicates a statistically significant difference between treatment and control groups.
Abbreviations: LMWH, low molecular weight heparin; NC, no change (as stated by the authors, without reporting data).

Table 28. Randomized Trials Evaluating the Treatment of Dyslipidemias in Peritoneal Dialysis Patients.

					Change Compared To Baseline (%)[c]			
Study	**N**	**Quality[a]**	**Applicability[b]**	**Treatment**	**CHOL**	**LDL**	**HDL**	**TG**
Saltissi,[305] 2002	23	●	🧍🧍🧍	Simvastatin (n=16) vs. Placebo (n=7)	-22* -2	-25* -4	0 +5	-2 +4
Harris,[310] 2002	130	●	🧍🧍🧍	Atorvastatin vs. Placebo	-29* -6	-40* -9	+7* -4	-14* +11

[a]Study quality was graded: ● least bias, results are valid; ◎ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.
[b]Applicability was rated: 🧍🧍🧍 representative of a wide spectrum of patients; 🧍🧍 representative of a relevant subgroup; or 🧍 representative of a narrow subgroup.
[c]The percent change within each group is indicated. "*" indicates a statistically significant difference between treatment and control.

Table 29. Randomized Trials Evaluating the Treatment of Dyslipidemia in Kidney Transplant Recipients.

Study	N	Quality[a]	Applicability[b]	Treatment	Change Compared To Baseline (%)[c] CHOL	LDL	HDL	TG
Bennett, [311] 1995	90	◐	🧍	High-dose EPA vs.		+6	-10	
				Low-dose EPA		+6*	-5	
Urakaze, [312] 1989	30	◐	🧍	Fish oil vs.			-25*	
				Placebo			+4	
Maachi, [313] 1995	80	○	🧍	Fish oil vs.	—	—	—	—
				Placebo	—	—	—	—
Holdaas, [314] 2001	364	●	🧍🧍🧍	Fluvastatin vs.	-18*	-41*	+5	-25*
				Placebo	+28	+26	+29	+44
Kasiske, [315] 2001	141	◐	🧍🧍🧍	Simvastatin vs.	*	*	—	—
				Gemfibrozil vs.	—	—	—	—
				Placebo	—	—	—	—
Arnadottir,[316] 1994	37	◐	🧍🧍	Simvastatin vs.	-22*	-32*	+13*	-12
				Placebo	-3	-4	—	+4
Martinez-Hernandez, [317] 1993	21	◐	🧍🧍	Simvastatin vs.	-16*	-20*	+7	-15
				Placebo	+5	+1	+4	+8
Castro,[318] 1997	36	◐	🧍🧍	Simvastatin vs.	-16	-18	-3	-26
				Fish oil	-10	-2	-16	-23
Katznelson ,[319] 1996	48	◐	🧍🧍	Pravastatin vs.	-15*	*		*
				Control	+30	—		—
Kliem,[320] 1996	44	◐	🧍🧍	Pravastatin vs.	-16	-21	—	-6
				Lovastatin	-26	-31	-6	-25
Sahu,[321] 2001	65	◐	🧍🧍	Lovastatin vs.	*	*		*
				Placebo	—	—		—
Kasiske,[322] 1990	11	◐	🧍🧍	Lovastatin vs.	-20	-27	+4	-17
				Diet				
Renders,[323] 2001	10	◐	🧍🧍	Atorvastatin vs.	-30	-43	+16	-23
				Cerivastatin	-32	-35	+6	-23
Santos,[324] 2001	67	○	🧍🧍	Simvastatin vs.	-23*	-35*	+7	-10
				Placebo	-2	-2	-8	+2

[a]Study quality was graded: ● least bias, results are valid; ◐ susceptible to some bias, but not sufficient to invalidate the results; or ○ significant bias that may invalidate the results.

[b]Applicability was rated: 🧍🧍🧍 representative of a wide spectrum of patients; 🧍🧍 representative of a relevant subgroup; or 🧍 representative of a narrow subgroup.

[c]The percent change within each group is indicated. "*" indicates a statistically significant difference between treatment and control.

Abbreviation: EPA, eicosapentaenoic acid (20:n-3).

Table 30. Lipid-Lowering Medication Dose Adjustments for Reduced Kidney Function.

	Adjust for Reduced GFR (mL/min/1.73 m²)			
Agent	60-90	15-59	<15	Notes
Atorvastatin[326]	No	No	No	
Cerivastatin[330]	No	↓ to 50%	↓ to 50%	Withdrawn
Fluvastatin	?	?	?	
Lovastatin[329]	No	↓ to 50%	↓ to 50%	
Pravastatin[327;328]	No	No	No	
Simvastatin	?	?	?	
Nicotinic acid[331]	No	No	↓ to 50%	34% kidney excretion
Cholestipol	No	No	No	Not absorbed
Cholestyramine	No	No	No	Not absorbed
Colesevelam	No	No	No	Not absorbed
Bezafibrate[332-334]	↓ to 50%	↓ to 25%	Avoid	May ↑ serum creatinine
Clofibrate[335-337]	↓ to 50%	↓ to 25%	Avoid	May ↑ serum creatinine
Ciprofibrate	?	?	?	May ↑ serum creatinine
Fenofibrate[338]	↓ to 50%	↓ to 25%	Avoid	May ↑ serum creatinine
Gemfibrozil[339;340]	No	No	No	May ↑ serum creatinine

Abbreviations: GFR, glomerular filtration rate; USFDA, United States Food and Drug Administration.

bility,[343] it has been hypothesized that the effects of statins on systemic inflammation is one of the most important of these pleiotropic effects.[343,344] If true, this observation could be important for patients with CKD, who appear to have a high prevalence of elevated C-reactive protein and other markers of systemic inflammation.[17-21] On the other hand, analysis of the data from multiple clinical trials in the general population suggests that most, but not all, of the reduction in ACVD from statins can be explained by reductions in LDL.[345]

The Use of Statins in Patients Receiving Cyclosporine or Tacrolimus

Cyclosporine has been shown to increase the blood levels of virtually every statin that has been investigated (Table 32). The degree that levels are altered may depend on differences in the metabolic pathways of the different statins. The mechanisms for this interaction are not proven, but calcineurin inhibitors may compete with some of the same enzymes responsible for the metabolism of statins. For example, the cyto-

Table 31. Recommended Daily Statin Dose Ranges. [a]

	Level of GFR (mL/min/1.73 m²)		With
Statin	≥30	<30 or dialysis	Cyclosporine
Atorvastatin	10-80 mg	10-80 mg	10-40 mg
Fluvastatin	20-80 mg	10-40 mg	10-40 mg
Lovastatin	20-80 mg	10-40 mg	10-40 mg
Pravastatin	20-40 mg	20-40 mg	20-40 mg
Simvastatin	20-80 mg	10-40 mg	10-40 mg

[a]Adult Treatment Panel III recommendations for GFR ≥30 mL/min/1.73 m².(Ref 3) Most manufacturers recommend once daily dosing, but consider giving 50% of the maximum dose twice daily.

Table 32. Effects of Cyclosporine on Blood Levels of Statins in Kidney Transplant Recipients.

Statin	Increase in the Statin's AUC
Atrovastatin[346]	8-fold
Cerivastatin[a347]	5-fold
Simavastatin[348]	3-fold
Simavastatin[349]	8-fold
Lovastatin[350]	2-fold
Lovastatin[351]	3-fold
Lovastatin[352]	20-fold
Pravastatin[352]	5-fold
Fluvastatin[353]	2-fold[b]

[a]Withdrawn, [b]P>0.05
Abbreviation: AUC, area under the concentration-time curve.

chrome P450 3A4 enzyme, which is thought to be important in the metabolism of lovastatin, simvastatin, and atorvastatin, is inhibited by cyclosporine. Fluvastatin is metabolized through the cytochrome P-450 2C9 pathway. Pravastatin does not rely on the cytochrome P-450 system for metabolism, but is instead metabolized by sulfation. Nevertheless, increased levels of fluvastatin and pravastatin have been reported in patients treated with cyclosporine, although the increases in fluvastatin were not statistically significant (Table 32).

There have been few comparison trials to determine if the increase in statin blood levels from cyclosporine is different for various statins.[352] Moreover, the literature search identified only 1 study that examined blood levels of statins in patients treated with tacrolimus. In this study, 4 patients treated with tacrolimus had similar simvastatin blood levels compared to 4 controls who were treated with simvastatin alone.[349] However, since the number of patients in this study was very small, and the metabolism of tacrolimus is very similar to that of cyclosporine, it should be assumed (until proven otherwise) that tacrolimus may cause elevations in statin blood levels.

Accumulating evidence suggests that statins can be used safely with cyclosporine if the dose of the statin is reduced (Table 29). It is recommended that the maximum doses of statins be reduced in patients receiving either cyclosporine or tacrolimus (Table 31). The addition of a third agent that is also metabolized by the cytochrome P450 system increases the risk of myositis and rhabdomyolysis, and therefore such combinations should be avoided. The new immunosuppressive agent everolimus had minimal effects on the blood levels of atorvastatin and pravastatin.[354] The effects of sirolimus on statins are unknown.

Avoiding Agents That Increase the Blood Levels of Statins

A number of medications may interact with the metabolism of statins and thereby increase statin blood levels. Medications known to increase statin blood levels should either be avoided, or, if necessary, the statin should be reduced or stopped. While this is true for all patients, it is especially true for patients with CKD Stages 4-5, since some statin levels tend to be high in Stage 4-5 CKD patients (Table 26). It is even more critical for interactions to be avoided among kidney transplant patients receiving cyclosporine (and possibly tacrolimus), since cyclosporine often increases statin levels through mechanisms that may be exacerbated by the addition of a third interacting agent.

Most medications that are well documented to increase statin blood levels are also metabolized by the hepatic cytochrome P450 enzyme super-

Table 33. Effects of the Macrolide Antibiotic Erythromycin on Blood Levels of Statins in Normal Individuals.

Statin (Change in Blood Levels)		Macrolide Antibiotic	
Statin	**P450 Isoenzyme**	**Agent**	**P450 Isoenzyme**
Atorvastatin (↑)[355]	3A4	Erythromycin	3A4
Simvastatin (↑↑)[356]	3A4	Erythromycin	3A4

Shown are the effects of macrolide antibiotics on blood levels of statins. NC, no change (P>0.05); ↑ less than a 2-fold increase; and ↑↑ greater than a 2-fold increase in the area under the plasma concentration-time curve. 3A4 indicates the subfamily of cytochrome P450 hepatic oxygenase enzyme superfamily felt to be important in the metabolism of the statin (1st column) or erythromycin (3rd column).

Table 34. Effects of Azole Antifungal Agents on Blood Levels of Statins in Normal Individuals.

Statin (Change in Blood Levels)		Azole Antifungal	
Statin	**P450 Isoenzyme**	**Agent**	**P450 Isoenzyme**
Atorvastatin (↑↑)[357]	3A4	Itraconazole	3A4
Atorvastatin (↑↑)[358]	3A4	Itraconazole	3A4
Lovastatin (↑↑)[359]	3A4	Itraconazole	3A4
Lovastatin (↑↑)[360]	3A4	Itraconazole	3A4
Simvastatin (↑↑)[361]	3A4	Itraconazole	3A4
Fluvastatin (↑)[362]	2C9	Fluconazole	2C9
Fluvastatin (NC)[360]	2C9	Itraconazole	3A4
Pravastatin (↑)[358]	None	Itraconazole	3A4
Pravastatin (NC)[362]	None	Fluconazole	2C9
Pravastatin (NC)[361]	None	Itraconazole	3A4

Shown are the effects of azole antifungal agents on blood levels of statins. NC, no change (P>0.05); ↑ less than a 2-fold increase; and ↑↑ greater than a 2-fold increase in the area under the plasma concentration-time curve. 3A4 or 2C9 indicates the subfamily of cytochrome P450 hepatic oxygenase enzyme superfamily felt to be important in the metabolism of the statin (1st column) or azole antifungal agent (3rd column).

family. These include macrolide antibiotics (Table 33), azole antifungal agents (Table 34), calcium-channel blockers (Table 35), fibrates, and nicotinic acid (Table 36). Other agents that may also increase statin levels include the serotonin reuptake inhibitors (Table 36), warfarin (Table 36), and grapefruit juice (Table 36).

Adding a Second LDL-Lowering Agent to a Statin

There are very few data on the safety and efficacy of combination therapies in patients with CKD. In general, it is probably wise to avoid the use of a fibrate together with a statin, at least until additional studies are conducted in patients with CKD to establish the safety of this combination. Fibrates lowered LDL by only 5% to 20% in normotriglyceridemic patients in the general population. They may actually increase LDL in patients with high triglycerides. Fibrates may increase the blood levels of statins (Table 37). The mechanisms for the interactions between fibrates and statins are not well understood. It was recently reported that gemfibrozil is a potent inhibitor of the cytochrome P450 2C9 isoform, but had minimal effect on 3A4 in vitro.[375]

For patients who continue to have LDL ≥100 mg/dL (≥2.59 mmol/L) despite TLC and optimal treatment with a statin, consideration should be given to adding a bile acid sequestrant, if triglycerides are <400 mg/dL (<4.52 mmol/L) (Fig 7 and Table 25). Evidence from studies in the general population indicate that bile acid sequestrants are safe and effective in lowering LDL by 15% to 30% (Fig 9). Bile acid sequestrants can be used in combination with a statin.[380] However, there are few studies of the safety and efficacy of bile acid sequestrants in patients

Table 35. Effects of Calcium-Channel Blockers on Blood Levels of Statins in Normal Individuals.

Statin (Change in Blood Levels)		Calcium-Channel Blockers	
Statin	**P450 Isoenzyme**	**Agent**	**P450 Isoenzyme**
Lovastatin (↑↑)[363]	3A4	Diltiazem	3A4
Simvastatin (↑↑)[364]	3A4	Diltiazem	3A4
Simvastatin (↑↑)[356]	3A4	Verapamil	3A4
Simvastatin (↑)[365]	3A4	Lacidipine	3A4
Pravastatin (NC)[363]	None	Diltiazem	3A4

Shown are the effects of calcium-channel blockers on blood levels of statins. NC, no change (P>0.05); ↑ less than a 2-fold increase; and ↑↑ greater than a 2-fold increase in the area under the plasma concentration-time curve. 3A4 indicates the subfamily of cytochrome P450 hepatic oxygenase enzyme superfamily felt to be important in the metabolism of the statin (1st column) or calcium-channel blocker (3rd column).

Table 36. Agents That May Alter Statin Blood Levels.

Statin (Effect)	Agent	Possible Mechanism
Simvastatin (↑)	Nefazodone	P450 3A4[366]
Pravastatin (↑)	Nefazodone	P450 3A4[367]
Atorvastatin (↑)	Grapefruit juice	P450 3A4[368]
Lovastatin (↑)	Grapefruit juice	P450 3A4[369]
Simvastatin (↑)	Grapefruit juice	P450 3A4[370]
Atorvastatin (↓)	Troglitazone[a]	P450 3A4[371]
Simvastatin (↓)	Troglitazone[a]	P450 3A4[372]
Simvastatin (↓)	Rifampin	P450 3A4[373]
Simvastatin (↓)	Cholestyramine	↓ Absorption[374]

Arrows indicate the direction, but not the magnitude, of change. 3A4 indicates the subfamily of cytochrome P450 hepatic oxygenase enzyme superfamily felt to be important in the interaction.
[a]Troglitazone is no longer available in the U.S.; other thizolidinediones are metabolized by the cytochrome P450 3A4 pathway and may have similar effects of statin levels.

with CKD. Cholestyramine, colestipol, and colesevelam hydrochloride are approved for use in the United States (Table 38). Bile acid sequestrants are contraindicated in patients with triglycerides ≥400 mg/dL (≥4.52 mmol/L), since they may increase triglycerides in some patients. They are relatively contraindicated for triglycerides ≥200 mg/dL (≥2.26 mmol/L). It should be noted that the new phosphate-binding agent sevelamer hydrochloride appears to lower lipid levels by mechanisms similar to those of bile acid sequestrants.[308]

For patients who have triglycerides that preclude the use of a bile acid sequestrant, or for patients who do not tolerate a bile acid sequestrant, nicotinic acid can be considered as an alternative second agent in combination with a statin. Studies in the general population indicate that nicotinic acid reduces LDL by 5% to 25%, reduces triglycerides by 20% to 50%, and raises HDL by 15% to 35% (Fig 9). There are no data on the use of combination therapy with a statin and nicotinic acid in patients with CKD. Adverse effects of nicotinic acid include flushing, hyperglycemia, and hepatotoxicity. Contraindications to nicotinic acid include liver disease, severe gout, and active peptic ulcer disease.

Treating High LDL in Patients Who Cannot Take a Statin

Patients who develop minor adverse effects from a statin may be able to tolerate a reduced dose, or a different statin. However, for patients who do not tolerate a reduced dose or another statin, a second-line agent can be used. Either a bile acid sequestrant or nicotinic acid can be used

Table 37. The Effects of Fibrates on Blood Levels of Statins in Normal Individuals.

Statin (Change in Blood Levels)		Fibrate	
Statin (Effect)	P450 Isoenzyme	Interaction Agent	P450 Isoenzyme
Simvastatin (↑↑)[376]	3A4	Gemfibrozil	2C9
Pravastatin (NC)[377]	None	Fenofibrate	None
Lovastatin (NC)[378]	3A4	Bezafibrate	None
Lovastatin (↑↑)[378]	3A4	Gemfibrozil	2C9
Fluvastatin (NC)[379]	2C9	Gemfibrozil	2C9

Shown are the effects of fibrates on blood levels of statins. NC, no change (P>0.05); ↑ a less than a 2-fold increase; and ↑↑ a greater than a 2-fold increase in the area under the plasma concentration-time curve. P450 indicates the subfamily of cytochrome -P450 hepatic oxygenase enzyme superfamily (3A4, 2C9, or none) felt to be important in the metabolism of the statin (2nd column) or fibrate (4th column).

Table 38. Bile Acid Sequestrant Dose.

Agent	Dose Range (g per day)
Cholestyramine	4-16
Colestipol	5-20
Colesevelam	2.6-3.8

to effectively reduce LDL cholesterol. For patients who cannot afford the cost of a statin, nicotinic acid offers a cheaper alternative. The phosphate-binding agent sevelamer hydrochloride may also lower total and LDL cholesterol. There have been 2 randomized, controlled trials in CKD patients.[307,381] In these studies, sevelamer hydrochloride caused significant reductions in total cholesterol (Table 27).

The Use of Bile Acid Sequestrants in Kidney Transplant Recipients

Bile acid sequestrants may interfere with the absorption of immunosuppressive medications, particularly immunosuppressive agents that bind to lipids. However, some small, uncontrolled studies suggest that a bile acid sequestrant can be used safely, without interfering with the absorption of cyclosporine. In 1 uncontrolled study, co-administration of cholestyramine and cyclosporine in 5 heart transplant recipients did not reduce the area under the concentration-time curve of cyclosporine.[382] In another study of 6 kidney transplant patients, administration of cholestyramine 4 hours after a dose of cyclosporine did not reduce the area under the concentration-time curve of cyclosporine.[383] Based on these very limited data, it appears that bile acid sequestrants may not have a major effect on cyclosporine absorption. However, it may be prudent to avoid administering a bile acid sequestrant from 1 hour before to 4 hours after the dose of cyclosporine, and to monitor blood levels of cyclosporine.

Unfortunately, there are no published data on the effects of bile acid sequestrants on other immunosuppressive agents. In general, the risks and benefits of adding a bile acid sequestrant to an oral immunosuppression regimen should be carefully weighed. For many patients, the risk of transplant rejection resulting from poor absorption of immunosuppressive medication may outweigh the benefits of a further reduction in LDL from adding a bile acid sequestrant. However, for some patients (eg, patients with severe coronary artery disease), the benefit of a further reduction in LDL may exceed the small risk of adding a bile acid sequestrant.

Similarly, bile acid sequestrants could theoretically interfere with the absorption of statins.[374] Therefore, it is probably best to avoid taking the bile acid sequestrant at the same time as any other medication, if this is possible.

Optimizing Immunosuppressive Agents in Kidney Transplant Recipients

For kidney transplant recipients who have LDL $\geq$100 mg/dL ($\geq$2.59 mmol/L), despite maximal medical management, consideration should be given to changing the immunosuppression protocol to one that is less likely to exacerbate high LDL levels, if this can be done without causing undue risk to the allograft. Options to consider include: (1) tapering and discontinuing prednisone,[212,214,255,256] with or without adding or increasing the dose of azathioprine or mycophenolate mofetil; (2) replacing cyclosporine with tacrolimus[210,211,215]; (3) tapering and discontinuing cyclosporine,[215] with or without adding or increasing the dose of azathioprine or mycophenolate mofetil; or (4) discontinuing or replacing sirolimus with an alternative immunosuppressive agent.[258,259]

Evidence suggests that discontinuing or replacing prednisone, cyclosporine, or sirolimus may reduce the prevalence and severity of dyslipidemias and other ACVD risk factors such as hypertension and glucose intolerance (Table 23). However, in deciding to change or not to change immunosuppressive agents, the risk of rejection should be weighed against the risk of ACVD. Transplant recipients who are diabetic and/or have known ACVD may have more to gain from changing immunosuppressive agents than patients at lower risk for ACVD. Moreover, the effects of immunosuppression on overall ACVD risk should be taken into account, not just their effects on dyslipidemias (Table 39). For example, different immunosuppressive agents have different effects on blood pressure and post-transplant diabetes, both of which can affect the incidence of ACVD. In any case, the decision to alter immunosuppression should be made only

Table 39. Relative Effect of Different Immunosuppressive Agents on Cardiovascular Disease Risk Factors after Kidney Transplantation.

	AZA or MMF	Prednisone	Cyclosporine	Tacrolimus	Sirolimus
Hypertension	—	↑↑	↑↑	↑	—
Dyslipidemia	—	↑↑	↑↑	—	↑↑↑
Diabetes	—	↑	↑	↑↑	—

Arrows offer a crude, semiquantitative comparison of the relative effect of each agent on cardiovascular disease risk factors.
Abbreviations: AZA, azathioprine; MMF, mycophenolate mofetil.

after fully informing the patient of the risks and benefits that are involved.

Rationale for Treating Non-HDL Cholesterol in Patients With High Triglycerides

Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol. No evidence has directly linked low HDL, high fasting triglycerides, and increased non-HDL cholesterol to ACVD in patients with CKD. However, a growing body of evidence from the general population has suggested that this lipid profile is part of a metabolic syndrome (insulin resistance, obesity, hypertension, and dyslipidemia) that is associated with ACVD.[3] Measures that safely and effectively improve this lipid profile should be considered to help reduce the incidence of ACVD in patients with CKD. Indeed, several cross-sectional studies have reported that hemodialysis patients have higher levels of remnant lipoproteins than comparable patients in the general population.[104,116-123]

Studies in the general population have implicated increased triglycerides as an independent risk factor for ACVD.[384,385] It is considered most likely that the risk of high triglycerides is a result of atherogenic, remnant lipoproteins. These include small VLDL and intermediate density lipoproteins (IDL). Since VLDL cholesterol is highly correlated with remnant lipoproteins, VLDL can be combined with LDL cholesterol to enhance risk prediction when triglycerides are high. Non-HDL cholesterol is calculated as total cholesterol minus the HDL cholesterol. In persons with high triglycerides, eg, 200-499 mg/dL (2.26-5.63 mmol/L), most of the cholesterol in non-HDL cholesterol is contained in remnant VLDL. Recent data suggest that non-HDL cholesterol may actually be a better predictor of coronary mortality than LDL.[386] Non-HDL cholesterol is also a reasonable surrogate marker for apolipoprotein B, the major apolipoprotein of all atherogenic lipoproteins.[387]

Studies in the general population suggest that in individuals with triglycerides <200 mg/dL (<2.26 mmol/L) VLDL is not particularly elevated, and non-HDL cholesterol correlates best with LDL cholesterol (Fig 6).[387] Therefore, using non-HDL cholesterol as the threshold and target for treatment makes little sense for individuals who do not have high triglycerides. Most clinical trials in the general population have not used non-HDL cholesterol as a target of therapy. Moreover, it is difficult to attribute the risk reduction in these trials to non-HDL cholesterol (compared to VLDL or LDL), because percentage changes in non-HDL cholesterol, VLDL, and LDL closely parallel each other.

Since a normal VLDL cholesterol is usually defined as <30 mg/dL (0.78 mmol/L),[388] a reasonable goal for non-HDL cholesterol is one that is 30 mg/dL (0.78 mmol/L) higher than the LDL cholesterol goal of 100 mg/dL (2.59 mmol/L), ie, <130 mg/dL (<3.36 mmol/L).[3] The ATP III does not target triglycerides per se for therapy, since triglyceride levels have more day-to-day variability than non-HDL cholesterol, and targeting the latter allows more flexibility in the choice of therapies.[3] The ATP III does not target apolipoprotein B for therapy, since (1) standardized measures of apolipoprotein B are not readily available; (2) measures of apolipoprotein B have not been shown to have greater predictability than non-HDL cholesterol in individuals with high triglycerides; and (3) measurement of apolipoprotein B adds to the expense of the usual lipoprotein profile.[3]

Limited data from studies in hemodialysis

patients suggest that, in this population, remnant lipoproteins are elevated even in patients with normal or near-normal triglycerides. In one study, hemodialysis patients showed higher levels of VLDL and IDL, and lower HDL, than age- and sex-matched controls at similar levels of plasma triglycerides.[389] This suggests that the triglyceride threshold for treating non-HDL cholesterol in hemodialysis patients should be lower. However, the Work Group concluded that, in the absence of data from randomized trials in hemodialysis patients, it is prudent to use the higher threshold of triglycerides recommended in the ATP-III. Using a triglyceride threshold 200-499 mg/dL (2.26-5.63 mmol/L) for treating non-HDL cholesterol in patients with low LDL means that only patients with very high VLDL and IDL will be treated. Clearly, additional studies are needed to establish whether therapy targeting lower levels of VLDL and IDL is safe and effective in patients with CKD.

Removing Causes of Hypertriglyceridemia and Elevated Non-HDL Cholesterol

Potentially remediable causes of hypertriglyceridemia include obesity, physical inactivity, excessive alcohol intake, high carbohydrate diet, type 2 diabetes, nephrotic syndrome, and some medications such as estrogens and beta-blockers. Corticosteroids are often used in patients with CKD, and corticosteroid withdrawal may decrease plasma cholesterol and triglycerides.[212,214,255,256] Similarly, the immunosuppressive agents cyclosporine,[210,215] and especially sirolimus,[258,259] cause dyslipidemias, and may occasionally cause triglycerides ≥500 mg/dL (≥5.65 mmol/L). For patients who have triglycerides ≥500 mg/dL (≥5.65 mmol/L), consideration should be given to reducing the dose or withdrawing the offending agent. Anabolic steroids can cause dyslipidemia.[248-251] The widespread adoption of erythropoietin to treat anemia in patients with CKD has greatly diminished the use of anabolic steroids. However, in some countries, anabolic steroids may still be used when cost precludes the use of erythropoietin. In some cases, the benefits of anemia treatment may outweigh the risks of dyslipidemia induced by anabolic steroids.

Therapeutic Lifestyle Changes for High Triglycerides and Non-HDL Cholesterol

Moderate alcohol consumption (1-2 ounces of alcohol per day) has been linked to a reduced risk for ACVD in the general population. However, excessive alcohol consumption increases the risk for hypertension, dyslipidemias, and ACVD in the general population. There are virtually no studies on the effects of alcohol consumption in patients with CKD.

Studies in the general population have shown that glycemic control with diet, oral hypoglycemic agents, and insulin are effective in raising HDL and lowering fasting triglycerides. However, studies from the general population have produced conflicting results as to whether intensive (versus usual) glycemic control reduces the risk for ACVD.[390-392] In addition, patients with diabetes and CKD may be more likely to have adverse effects from intensive glycemic control measures than diabetic patients in the general population. Nevertheless, patients with low HDL and/or high triglycerides should be assessed for diabetes, and diabetic patients with this lipid profile should have as good glycemic control as possible without causing excessive hypoglycemia.

Obesity is also associated with low HDL and/or high triglycerides. Nutritionally sound diets that restrict calories and increased physical activity help to reduce weight in obese patients in the general population. However, there are few studies demonstrating successful weight reduction in obese patients with CKD.

Low-fat diets and increased physical activity have both been shown to raise HDL and reduce triglycerides in the general population. A limited number of studies suggest that these measures may also be effective in patients with CKD.

Dietary fish oil supplements have been shown to reduce triglycerides in studies in the general population. Few studies have examined the effects of fish oil supplements on lipoproteins in patients with CKD, and their results have been inconclusive (Tables 27 and 29).

Drug Therapy for High Triglycerides and Non-HDL Cholesterol

Observational studies in the general population suggest that high triglycerides are indepen-

dent risk factors for ACVD.[384,385] Intervention trials have shown that statins, fibrates, and nicotinic acid reduce the risk of CHD, and indirect evidence suggests that not all of the benefit in these trials is the result of LDL reductions. However, few studies in patients with CKD have examined the relationships between low HDL, high triglycerides, and ACVD, and the results of these studies have been inconclusive (Tables 10, 11, and 12).

Patients who are not already receiving a statin for treatment of LDL, who have fasting triglycerides ≥200 mg/dL (≥2.26 mmol/L), non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L), and who do not have liver disease, should be started on a statin along with TLC. In studies in the general population, statins lowered triglycerides by 7% to 30% and increased HDL by 5% to 15% (Fig 9). Furthermore, statins reduced the incidence of major coronary events, CHD mortality, and stroke and all-cause mortality in studies in the general population. Statins are contraindicated in patients with liver disease. A lipid profile and liver enzymes should be obtained within 2-3 months after starting a statin, and 2-3 months following any adjustment in the dose. The Work Group considered whether a statin or a fibrate should be the first-line agent for treatment of non-HDL cholesterol. Although there are compelling theoretical reasons for considering fibrates in this setting, the Work Group concluded that the safety and efficacy of statins for preventing CVD has been more conclusively established in randomized trials in the general population. Clearly, randomized trials examining both statins and fibrates are needed in patients with CKD.

If the statin is tolerated, no further treatment of non-HDL cholesterol is indicated. If the statin is not tolerated at a reduced dose or after switching to another statin, then consider discontinuing the statin and treating instead with a fibrate.

Only 4 randomized, controlled trials of lipid-lowering agents in hemodialysis patients were identified (Table 27). In 1 study of sevelamer hydrochloride, the effects on triglycerides were not statistically significant, and in a small study of simvastatin the effects on triglycerides were reduced compared to placebo (Table 27). Only 2 trials of lipid-lowering agents in peritoneal dialysis patients were identified, and in these studies statins caused a modest reduction in triglycerides (Table 28). Most randomized trials of lipid-lowering agents in kidney transplant patients were with statins, which generally caused a 15% to 25% reduction in triglycerides (Table 29).

The blood levels of bezafibrate, clofibrate, and fenofibrate are increased in patients with decreased kidney function, compared to controls with normal kidney function (Table 30). In contrast, blood levels of gemfibrozil do not appear to be altered by decreased kidney function (Table 30). Bezafibrate,[334,393-401] ciprofibrate,[401,402] fenofibrate,[401-410] and gemfibrozil[410] have been reported to cause increased serum creatinine and blood urea nitrogen levels.[334,393,394,399,401,402,404,410] The mechanism for this effect is not known. Since both serum creatinine and blood urea nitrogen are affected, the mechanism presumably involves a reduction in GFR. Indeed, in 1 study, tubular secretion of creatinine was not altered by bezafibrate.[395] However, in a study of 13 patients with normal, or mild to moderate kidney disease, fenofibrate increased serum creatinine without altering GFR or plasma flow.[408] Gemfibrozil was not thought to cause increased serum creatinine,[401,402] but recently there was a report of 2 cases where this occurred.[410] Nevertheless, since dose modification for decreased kidney function is not required for gemfibrozil, unlike other fibrates (Table 40), gemfibrozil should probably be considered the fibrate of choice for most CKD patients.

Nicotinic acid can be used in place of fibrates for patients with elevated triglycerides. However, there are almost no data on blood levels of nicotinic acid in patients with CKD. In 1 study, only 34% of a dose of nicotinic acid was excreted in the urine, suggesting that major dose modification may not be necessary in patients with reduced kidney function (Table 41). The incidence of adverse effects from nicotinic acid, eg, flushing and hyperglycemia, is high.[411,412] However, there are few studies examining whether the incidence of adverse effects of nicotinic acid is higher in patients with CKD compared to the general population.[413] Insulin resistance is common in patients with CKD, and a higher than expected incidence of hyperglycemia from nicotinic acid would not be surprising in CKD patients.

Table 40. Maximum Doses of Fibrates in Patients with Reduced Kidney Function.

	Dose (mg) by Level of GFR (mL/min/1.73 m²)			
Fibrate	**>90**	**60-90**	**15-59**	**<15**
Bezafibrate	200 tid	200 bid	200 qd	Avoid
Clofibrate	1,000 bid	1,000 qd	500 qd	Avoid
Ciprofibrate	200 qd	?	?	?
Fenofibrate	201 qd	134 qd	67 qd	Avoid
Gemfibrozil	600 bid	600 bid	600 bid	600 bid

Abbreviation: GFR, glomerular filtration rate.

Isolated, Low HDL Cholesterol

Patients with isolated HDL ≥40 mg/dL (≥1.03 mmol/L) should be treated with TLC. However, the pharmacological treatment of isolated low HDL cholesterol is not recommended. There are few data defining the risk of ACVD attributable to isolated, low HDL in the general population or in patients with CKD (Tables 10, 11, and 12). The effects of pharmacological agents on HDL are modest, and the incidence of adverse effects is probably higher in patients with CKD than in the general population. Therefore, the risks of pharmacological therapy to raise HDL (in the absence of high LDL or high triglycerides) probably outweigh the benefits.

TREATMENT OF ADOLESCENTS WITH DYSLIPIDEMIAS

GUIDELINE 5

5.1. For adolescents with Stage 5 CKD and fasting triglycerides ≥500 mg/dL (≥5.65 mmol/L) that cannot be corrected by removing an underlying cause, treatment with therapeutic lifestyle changes (TLC) should be considered. (C)

5.2. For adolescents with Stage 5 CKD and LDL ≥130 mg/dL (≥3.36 mmol/L), treatment should be considered to reduce LDL to <130 mg/dL (<3.36 mmol/L). (C)

5.3. For adolescents with Stage 5 CKD and LDL <130 mg/dL (<3.36 mmol/L), fasting triglycerides ≥200 mg/dL (≥2.26 mmol/L), and non-HDL cholesterol (total cholesterol minus HDL) ≥160 mg/dL (≥4.14 mmol/L), treatment should be considered to reduce non-HDL cholesterol to <160 mg/dL (<4.14 mmol/L). (C)

Table 41. Nicotinic Acid Dose.

Agent	Dose Range (g per day)
Immediate release	1.5-3.0
Extended release	1-2
Sustained release	1-2

Rationale for Treating Very High Triglycerides

Evidence that very high triglycerides can cause pancreatitis in children comes from case reports and small series of patients with familial dyslipidemias.[414,415] The incidence of pancreatitis caused by hypertriglyceridemia in adolescents with CKD is unknown. However, it seems prudent to treat very high triglycerides with TLC, if nutrition is otherwise adequate (Fig 8). The safety and efficacy of lowering triglycerides with fibrates and niacin have not been established in adolescents.

Isolated hypertriglyceridemia in adolescents should be treated with TLC. Cases of triglycerides persistently ≥500 mg/dL (≥5.65 mmol/L) are rare, and they are generally due to an inherited metabolic disorder. Drug therapy, eg, low-dose fibrates or nicotinic acid,[416] may be warranted. The use of fibrates or nicotinic acid in adolescents has not been well studied[417-419]; therefore, routine use of these agents cannot be recommended at this time. Patients should be referred, however, 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.[420]

Rationale for Treating High LDL and High Non-HDL Cholesterol

Atherosclerosis in young adults was first described in 1953.[421] Most recently, the PDAY study found that 50% of children 10-14 years old had early fatty streaks, and 8% had fibrous plaques, thus confirming that atherosclerosis begins in childhood.[186] Risk factors associated with ACVD in adults are also associated with atherosclerosis in children.[186,422] In the Bogalusa Heart Study, body mass index, LDL, and systolic blood pressure were associated with atherosclerotic disease of the aorta and coronary vessels of children.[423] Moreover, hypercholesterolemia in children and adolescents persists into adulthood.[423] Recent studies of subclinical ACVD 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.[424] Thus, these and other studies in the general population suggest that ACVD begins in childhood, and that dyslipidemia in children may play an important role in the pathogenesis of ACVD. However, in children with CKD, the relationship between dyslipidemia and subsequent ACVD is unknown.

Approach to Treating High LDL and High Non-HDL Cholesterol

Secondary causes of dyslipidemias should be treated first (Guideline 3). Thereafter, for LDL 130-159 mg/dL (3.36-4.11 mmol/L), TLC should be used first (Fig 8). If, after 6 months of TLC, LDL is ≥130 mg/dL (≥3.36 mmol/L), then consider pharmacological management. If LDL is ≥160 mg/dL (≥4.14 mmol/L), then consider starting atrovastatin at the same time as TLC (Fig 8).

Therapeutic Lifestyle Changes

TLC for children are similar to those recommended for adults (Table 26). Recent studies in the general population have shown that dietary fat restriction is safe in children.[425-428] In particular, there have been no adverse effects on growth and development, or nutrition.[425-428] However, TLC should be used judiciously, or not at all, in children who are malnourished. If TLC has failed after 6 months, and potential secondary causes of dyslipidemia have been ruled out, drug therapy should be considered.

Drug Therapy

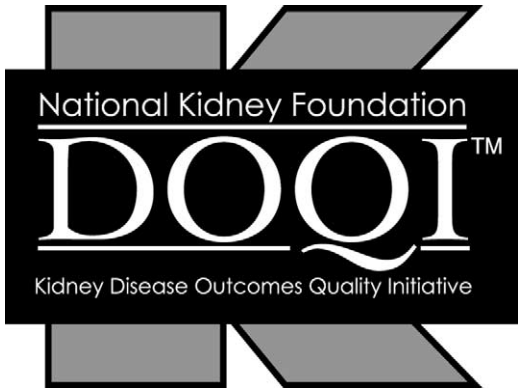
There are few studies examining drug treatment of dyslipidemia in children with CKD. However, a limited number of small, randomized, controlled trials in children and adolescents from the general population have found that statins are safe and effective in lowering LDL.[429-432] In particular, statins do not appear to have adverse effects on growth and development.[433] A few, very small, uncontrolled trials have likewise reported that statins are safe and effective in patients with nephrotic syndrome.[434-436] Thus, although statins are not approved for use in children and adolescents, and additional studies are needed, preliminary data suggest they are safe and effective. Therefore, statins should be considered for therapy in adolescents with CKD and elevated LDL, or in hypertriglyceridemic adolescents with CKD and increased non-HDL cholesterol. Currently, the only statin approved by the United States Food and Drug Administration (USFDA) for use in children and adolescents is atorvastatin.

For adolescents who do not achieve the desired target with a statin, addition of a bile acid sequestrant can be considered (Fig 8). Bile acid sequestrants appear to be safe and effective in improving dyslipidemias in children. Cholestyramine is approved for use in children by the USFDA. Although bile acid resins are safe in children of all ages, adherence to therapy is often poor due to the high incidence of adverse effects.[437-439] No dosage adjustment is required in patients with CKD. However, pediatric dosages have not been established. In children 6-12 years of age, doses of anhydrous cholestyramine 80 mg/kg 3 times a day, not to exceed 8 g per day, can be used (Product Information Questran, 2000; Product Information Questran Light, 2000). Adverse effects are common and include constipation, abdominal discomfort, nausea, flatulence, vomiting, diarrhea, heartburn, anorexia, and indigestion. In children and adults treated with cyclosporine, bile acid sequestrants should probably be administered between cyclosporine doses. Bile acid sequestrant powders are generally mixed with 4-6 ounces of fluid, and several glasses of water between doses are recommended. The fluid recommended with bile acid powders may limit

their use in dialysis or CKD patients who have been prescribed strict fluid restrictions. The newer bile acid sequestrant colesevelam has not yet been studied in children, and thus cannot be recommended at this time. Similarly, the phosphate-binding (and lipid-lowering) agent sevelamer hydrochloride has not been studied in children.

Bile acid sequestrants can increase triglycerides, and hypertriglyceridemia is common in children with CKD. Bile acid resins are relatively contraindicated in patients with triglycerides ≥200 mg/dL (≥2.26 mmol/L), and definitely contraindicated in patients with triglycerides ≥500 mg/dL (≥5.65 mmol/L). Other potential, long-term adverse effects of bile acid resins include deficiencies of vitamins A, E, and folic acid. In studies with long-term follow-up, a folic acid supplement was required; however, anemia from folate deficiency was not observed.[440,441] In CKD patients, hyperhomocysteinemia is more common than in the general population, and therefore the potential for adverse effects from folate deficiency caused by bile acid sequestrants is potentially greater. Taken together, these considerations suggest that bile acid resins should be used with caution in children, and close monitoring for adverse effects such as vitamin deficiencies are warranted.

Currently, atorvastatin is the only USFDA-approved statin for children, and it is approved for post-pubertal males with familial hypercholesterolemia. However, more recent data in boys with familial hypercholesterolemia suggest that lovastatin 10-40 mg can safely decrease LDL by 21% to 36%.[442,443] Similar results were reported with pravastatin 5-20 mg.[444] Additional data on long-term safety, especially with respect to growth and nutrition, are needed before statins can be recommended for use in children of all ages.



IV. RESEARCH RECOMMENDATIONS

THERE ARE REASONABLE doubts as to whether trial results from the general population are applicable to all patients with CKD. It is beyond the scope of these guidelines to recommend all research that should be conducted in patients with dyslipidemia and CKD, or to design clinical trials. However, it is apparent that some questions are particularly well suited for study (Table 42), although these recommendations are not meant to be endorsements for specific protocols.

For children with CKD and/or a functioning kidney transplant, prospective cohort studies with long-term follow-up are recommended to determine:

- The prevalence of dyslipidemias at all stages of CKD over time
- The associations between dyslipidemias and subsequent ACVD

For children with CKD and/or a functioning kidney transplant, phase I and phase II trials, and pharmacokinetic dosing studies are recommended to establish the safety and lipid-lowering efficacy of agents (including, but not limited to):

- Bile acid sequestrants, eg, colesevelam
- Cholesterol uptake inhibitors, eg, ezetibmide
- Statins
- Fibrates
- Nicotinic acid
- Sevelamer hydrochloride
- Appropriate lipid-lowering drug combinations

For adults with CKD and/or a functioning kidney transplant, phase I and phase II trials and pharmacokinetic dosing studies are recommended to establish the safety and lipid-lowering efficacy of new agents (including, but not limited to):

- Colesevelam
- Cholesterol uptake inhibitors, eg, ezetimibe
- Appropriate lipid-lowering drug combinations

For patients with Stages 1-4 CKD, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the rate of decline in GFR in patients with any lipid profile.
- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with LDL ≥100 mg/dL (≥2.59 mmol/L).
- A statin safely reduces the rate of decline in GFR in patients with LDL ≥100 mg/dL (≥2.59 mmol/L).
- A fibrate safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L).
- A fibrate safely reduces the rate of decline in GFR in patients with triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L).

For chronic hemodialysis patients, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L).
- A fibrate safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L).
- Sevelamer hydrochloride safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (≥3.36 mmol/L).

For chronic peritoneal dialysis patients, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the incidence of

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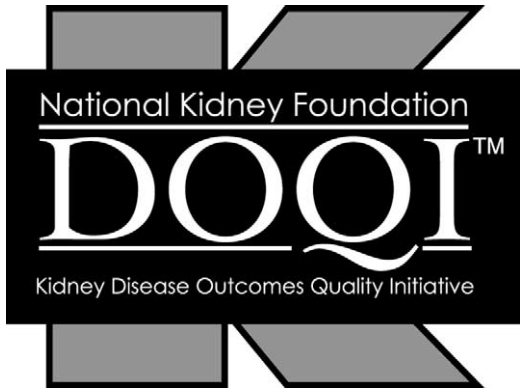
Table 42. Intervention Trials That Are Needed in Patients with Chronic Kidney Disease.

Population	Primary Intervention	Lipid Profile	Primary Endpoints
Stages 1-4 CKD	Statin	Any lipid profile, or ↑ LDL	ACVD, and/or Decline in GFR
Stages 1-4 CKD	Fibrate	↑ Triglycerides with ↑ non-HDL cholesterol	ACVD, and/or Decline in GFR
Hemodialysis	Statin, or Sevelamer hydrochloride	Any lipid profile	ACVD
Hemodialysis	Statin, or Fibrate, or Sevelamer hydrochloride	↑ Triglycerides with ↑ non-HDL cholesterol	ACVD
Peritoneal Dialysis	Statin	Any lipid profile, or ↑ LDL	ACVD
Transplant	Statin	Any lipid profile, or ↑ LDL	ACVD, and/or Decline in GFR

ACVD and all-cause mortality in patients with LDL ≥100 mg/dL (≥2.59 mmol/L).

For kidney transplant recipients, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the rate of decline in GFR in patients with any lipid profile.
- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with LDL ≥100 mg/dL (≥2.59 mmol/L).
- A statin safely reduces the rate of decline in GFR in patients with LDL ≥100 mg/dL (≥2.59 mmol/L).



V. APPENDICES

APPENDIX 1. METHODS FOR REVIEW OF ARTICLES

AIMS

THE OVERALL AIM of the project was to develop guidelines for the assessment and treatment of dyslipidemias in patients with CKD, irrespective of the underlying cause of the kidney disease.

The Work Group sought to base guidelines as much as possible on the evidence, derived from a systematic summary of the available scientific literature on dyslipidemia in patients with CKD.

Two products were developed from this process: a set of clinical practice guidelines regarding assessment and treatment of dyslipidemia, which is contained in this report; and an evidence report, which consists of the summary of the literature. Portions of the evidence report are contained in this report. The entire evidence report is on file with the National Kidney Foundation.

OVERVIEW OF THE PROCESS

The guidelines were developed using 4 basic principles set forth by K/DOQI:

- The guidelines were developed using a scientifically rigorous process, and the rationale and evidentiary basis for each guideline is clearly explained.
- A multidisciplinary Work Group, with expertise in the management of CKD, dyslipidemias, and ACVD, developed the guidelines.
- The Work Group members worked independently from organizational affiliations and had final responsibility for determining guideline content.
- The guidelines have undergone widespread critical review before they were finalized.

Development of the guideline and evidence report required many concurrent steps to:

- Form the Work Group and Evidence Review Team that were responsible for different aspects of the process
- Hold meetings to discuss process, methods, and results
- Develop and refine topics
- Define population of interest
- Create draft guideline statements and rationales
- Create draft summary tables
- Create data extraction forms
- Create and standardize quality assessment metrics
- Develop literature search strategies
- Perform literature searches
- Screen abstracts and retrieve full articles
- Review literature by members of the Work Group
- Extract data and perform critical appraisal of the literature
- Tabulate data from articles into summaries and create summary graphics
- Write guideline statements and rationales based on literature.

Creation of Groups

The Co-Chairs of the K/DOQI Advisory Board selected the Work Group Chair and Director of the Evidence Review Team, who then assembled groups to be responsible for the development of the guidelines and the evidence report, respectively. These groups collaborated closely throughout the project.

The Work Group consisted of "domain experts," including individuals with expertise in nephrology, nutrition, pediatrics, transplantation medicine, epidemiology, and cardiology. In addition, the Work Group included a liaison member from the Renal Physicians Association. The first task of the Work Group members was to define the overall topic and goals, including specifying the target condition, target population, and target audience. They then further developed and refined each topic, literature search strategy, and data extraction form (described below). The Work Group members were the principal reviewers of the literature, and, from these detailed reviews, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements.

The Evidence Review Team consisted of nephrologists and methodologists from Tufts-New England Medical Center with expertise in systematic review of the medical literature. They were

responsible for managing the project, including: coordinating meetings; refining goals and topics; creating the format of the evidence report; developing literature search strategies, initial review and assessment of literature; and coordinating all partners. The Evidence Review Team also managed the methodological and analytical process of the report. Throughout the project, and especially at meetings, the Evidence Review Team led discussions on systematic review, literature searches, data extraction, assessment of quality of articles, and summary reporting.

Development of Topics

Based on their expertise, members of the Work Group selected several, specific topics for review. These included the incidence or prevalence of dyslipidemia in CKD, the association of dyslipidemia with ACVD, and the treatment of dyslipidemia in patients with Stage 5 CKD (including kidney transplant recipients). For patients with Stages 1-4 CKD, topics were limited to adverse effects of dyslipidemia treatment, the effects of dyslipidemia treatment on kidney disease progression, and the effects of therapies that reduce proteinuria on dyslipidemias. The Work Group employed a selective review of evidence: a summary of reviews for established concepts (review of textbooks, reviews, guidelines and selected original articles familiar to them as domain experts); and a review of primary articles and data for new concepts.

The overall target population for guidelines on the management of dyslipidemia included all people with CKD (Stages 1-5), including all patients with kidney transplants. However, the Work Group concluded that the recently updated guidelines of the National Cholesterol Education Task Force, Adult Treatment Panel III (ATP III),[3] are applicable to patients with Stages 1-4 CKD. Therefore, the recommendations of ATP III would not need to be modified for patients with Stages 1-4 CKD, except to: (1) classify these patients in the highest risk category; (2) consider complications of lipid-lowering therapies that may result from reduced kidney function; (3) consider whether there may be indications for the treatment of dyslipidemias other than preventing ACVD; and (4) determine whether the treatment of proteinuria might also be an effective treatment for dyslipidemias. Therefore, for Stage 1-4 CKD patients, the Work Group focused its attention on the latter three issues, and otherwise recommended that the ATP III Guidelines be followed in patients with Stages 1-4 CKD. Likewise, the Work Group chose not to include children and adolescents ($<$20 years old) with Stages 1-4 CKD, who should be managed with existing guidelines, such as those of the National Cholesterol Expert Panel on Children (NCEP-C).

The Work Group concluded that in most areas the ATP III and NCEP-C were applicable to adults and children, respectively. The Work Group considered that its task was to define areas where the ATP III and NCEP-C needed modification and refinement for patients with CKD.

Refinement of Topics and Development of Materials

The Work Group and Evidence Review Team developed (a) draft guideline statements, (b) draft rationale statements that summarized the expected pertinent evidence, (c) mock summary tables containing the expected evidence, and (d) data extraction forms requesting the data elements to be retrieved from the primary articles to complete the tables. The development process included creation of initial mock-ups by the Work Group Chair and Evidence Review Team followed by iterative refinement by the Work Group members. The refinement process began prior to literature retrieval and continued through the start of reviewing individual articles. The refinement occurred by e-mail, telephone, and in-person communication regularly with local experts and with all experts during in-person meetings of the Evidence Review Team and Work Group members.

Data extraction forms were designed to capture information on various aspects of the primary articles. Forms for all topics included study setting and demographics, eligibility criteria, causes of kidney disease, numbers of subjects, study design, study funding source, population category (see below), study quality (based on criteria appropriate for each study design; see below), appropriate selection and definition of measures, results, and sections for comments and assessment of biases. Training of the Work Group members to extract data from primary articles

subsequently occurred by e-mail as well as at meetings.

Assessment of Dyslipidemias

Evidence supporting guideline statements regarding the assessment of dyslipidemias was sought in published studies on (1) the prevalence of dyslipidemias in CKD; (2) the association between dyslipidemias and ACVD; and (3) the association between dyslipidemias and CKD progression. To ascertain the prevalence of dyslipidemias in CKD, the Work Group and Evidence Review Team examined retrospective and prospective cohort studies. To ascertain the association between dyslipidemias and ACVD or CKD progression, the Work Group and Evidence Review Team examined retrospective and prospective cohort studies, as well as case-control studies.

Treatment of Dyslipidemias

Evidence supporting guideline statements regarding the *efficacy* of treatment of dyslipidemias was sought only in randomized controlled trials of patients with CKD. Direct and indirect evidence on the *safety* of treatment of dyslipidemias in CKD was sought in controlled and uncontrolled studies of (1) the pharmacokinetics of lipid-lowering medications in CKD; (2) possible drug interactions in CKD; and (3) possible adverse reactions to lipid-lowering therapies in CKD (including small series and case reports).

Literature Search

The Work Group and Evidence Review Team decided in advance that a systematic process would be followed to obtain information on topics that relied on primary articles. Only full journal articles of original data were included. Review articles, editorials, letters, or abstracts were not included.

Studies for the literature review were identified primarily through MEDLINE searches of English language literature conducted between December 2000 and May 2001. These searches were supplemented by relevant articles known to the domain experts and reviewers.

The MEDLINE literature searches were conducted to identify clinical studies published from 1980 through the search dates. Studies prior to 1980 were disregarded, because the Work Group concluded that treatment modalities and methods to measure dyslipidemias have changed too much to reasonably conclude that evidence from studies prior to 1980 could be applicable today.

Separate search strategies were developed for each topic. Development of the search strategies was an iterative process that included input from all members of the Work Group. The text words or MeSH headings for all topics included kidney or kidney diseases, hemodialysis, peritoneal dialysis, or kidney transplant. The searches were limited to studies on humans and published in English. The MEDLINE search strategies are included in the Evidence Report.

The topics that were selected for the searches included the incidence or prevalence of dyslipidemia, the association of dyslipidemia with ACVD, the association of dyslipidemia with CKD progression and the treatment of dyslipidemia in patients with Stage 5 CKD (including kidney transplant recipients). For patients with Stages 1-4 CKD, topics for the literature retrieval were limited to adverse effects of dyslipidemia treatment, the effects of dyslipidemia treatment on kidney disease progression, and the effects of therapies that reduce proteinuria on dyslipidemias. The team did not conduct a systematic search for all studies on dyslipidemia prevalence, association with ACVD and treatment for patients with Stages 1-4 CKD.

MEDLINE search results were screened by clinicians on the Evidence Review Team. Potential papers for retrieval were identified from printed abstracts and titles, based on study population, relevance to topic, and article type. In general, studies with fewer than 10 subjects were not included. After retrieval, each paper was screened to verify relevance and appropriateness for review, based primarily on study design and ascertainment of necessary variables. Domain experts made the final decision for inclusion or exclusion of articles. All articles included were abstracted and incorporated in the evidence tables. Overall, 10,363 abstracts were screened, 642 articles were retrieved and reviewed by the Evidence Review Team, 258 articles were reviewed by members of the Work Group, and results were extracted from 133 articles, including a number

Table 43. Example of Format for Evidence Tables for Cardiovascular Risk.

Study	N	Quality	Applicability	Adjusted[a]	Cardiovascular Disease Risk with Worsening Dyslipidemia						
					CHOL	LDL	HDL	TG	ApoA1	ApoB	Lp(a)
Cheung 2000	936	●	↑↑↑	Yes	⇔						
Kronenberg 1999	440	●	↑↑↑	Yes	⇔	⇔	⇔	⇔	⇔	↑	⇧
Zimmerman 1998	280	●	↑↑↑	Yes	⇔	⇔	↓	⇔	↓	⇔	↑

of articles not located by the MEDLINE searches, but added by Work Group members.

Format for Evidence Tables

Two types of evidence tables were prepared. Detailed tables contain data from each field of the components of the data extraction forms. These tables are contained in the Evidence Report, but are not included in the manuscript. Summary tables describe the strength of evidence according to four dimensions: study size, applicability depending on the type of study subjects, methodological quality, and results. Within each table, studies are ordered first by methodological quality (best to worst), then by applicability (most to least), and then by study size (largest to smallest). Two examples of evidence tables are shown in Tables 43 and 44.

Study Size

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that included a broad spectrum of patient populations.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population is typically defined by the inclusion and exclusion criteria. The target population was defined to include patients with chronic kidney disease, except where noted. A designation for applicability was assigned to each article, according to a 3-level scale. In making this assessment, sociodemographic characteristics were considered, as were the stated causes of chronic kidney disease, and prior treatments. If study was not considered not fully generalizable, reasons for lack of applicability were reported.

Individual tables include columns with relevant data describing the study sample and thus the applicability of the study. Examples include mean age (in years), kidney replacement therapy modality (hemodialysis, peritoneal dialysis, transplant) and type of kidney disease (eg, diabetes, hypertension).

Table 44. Example of Format for Evidence Tables for Treatment Effect.

Study	N	Age	Quality	Applicability	Treatment	% Change			
						CHOL	LDL	HDL	TG
Soroka 1998	15	ND	○	↑	Animal-based low-protein diet vs.	-5	-6	-10	+8
					Soy-based vegetarian diet	-5	-3	-16	-4
Khajehdehi 1999	84	31.4	○	↑	Vitamin E vs.	—	-5	+15	—
					Vitamin D_3 vs.	-4	-23	+3	-10.5
					Vitamin C	-13	-16	—	-2

↑↑↑ Sample is representative of the target population, or results are definitely applicable to general chronic kidney disease population irrespective of study sample.

↑↑ Sample is representative of a relevant sub-group of the target population. For example, sample is only representative of people with a narrow range of GFR, or only a specific relevant subgroup, such as elderly individuals or patients with diabetic kidney disease. In addition, studies that report serum creatinine levels rather than estimated GFR are assigned to this category.

↑ Sample is representative of a narrow subgroup of patients only, and not well generalizable to other subgroups. For example, the study includes only patients with a rare disease. However, studies of such narrow subgroups may be extremely valuable for demonstrating "exceptions to the rule."

Results

In principle, the study design determined the type of results obtained. For studies of association of dyslipidemia and CVD the result is direction and strength of the association between level of dyslipidemia and risk of CVD. Associations are represented according to the following symbols:

⇧ Positive (not statistically significant) association (higher lipid level associated with greater risk of CVD)

⇔ No association (risk of CVD not associated with lipid level)

⇩ Negative (not statistically significant) association (higher lipid level associated with lower risk of CVD)

⬆ or ⬇ Statistically significant association ($p < 0.05$)

For randomized trials of treatment effect and for studies of prevalence of dyslipidemia, results are reported as the percent change in lipid level from baseline for each treatment examined, or for the percentage of subjects with each type of dyslipidemia (total cholesterol, LDL, HDL, triglycerides).

Quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a 3-level classification of study quality was devised:

● Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; clear description of the population and setting; clear description of an appropriate reference standard; proper measurement techniques; appropriate statistical and analytical methods; no reporting errors; and no obvious bias.

◎ Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category above. It has some deficiencies but none likely to cause major bias. Includes retrospective studies and case series.

○ Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting. Includes prospective and retrospective studies and case series.

Summarizing Reviews and Selected Original Articles

Work Group members had wide latitude in summarizing reviews and selected original articles for topics that were determined, a priori, not to require a systematic review of the literature. The use of published or derived tables and figures was encouraged to simplify the presentation.

Translation of Evidence to Guidelines

Format

This document contains 5 guidelines. The format for each guideline is outlined in Table 45. Each guideline contains 1 or more specific "guideline statements," which are presented as "bullets" that represent recommendations to the target audience. Each guideline contains background information, which is generally sufficient to interpret the guideline. A discussion of the broad concepts that frame the guidelines is provided in the preceding section of this report. The rationale for each guideline contains a series of specific "rationale statements," each supported by evidence. The guideline concludes with a discussion of limitations of the evidence review and a brief discussion of clinical applications, implementation issues, and research recommendations regarding the topic.

Strength of the Evidence

The Work Group rated the strength of each guideline using a modification of a system originally adopted by the Canadian Task Force on the

Table 45. Format for Guidelines.

Introductory Statement
Guideline Statement 1
Guideline Statement 2
Background
Rationale
Definitions (if appropriate)
Strength of Evidence
Rationale Statement 1
Supporting text
Rationale Statement 2
Supporting text
Limitations
Clinical Applications
Implementation Issues
Research Recommendations

Table 46. Dietary Modifications That May Be Appropriate for Adults with Chronic Kidney Disease. [a]

Food Choices	Choose	Decrease
Eggs (cholesterol <200 mg per day)	• Limit to 2 eggs per week, or use 2 egg whites in place of one egg, or use cholesterol-free egg substitutes regularly	• Egg yolks and whole eggs (often hidden ingredients in cookies, cakes, desserts)
Meat, poultry, and alternatives	• Lean meat products, well trimmed of fat • Poultry without skin • Fish, shellfish • Low-fat tofu; tempeh; soy protein products	• High-fat meats (sausage, bacon, organ meats such as liver, sweetbreads, brain) • Sandwich-style meats such as ham, "cold cuts", processed meats
Fish, shellfish	• Fish or shellfish, baked or broiled without additional fat	• Avoid consuming bones of fish (sardines, anchovies, fish heads, etc.) due to phosphorus content
Fats and oils (saturated fat <7% total kcal) (total fat 25%-35% total kcal)	• Unsaturated oils - safflower, sunflower, corn, soybean, cottonseed, canola, olive, peanut • Margarine - made from any of the oils above, especially soft and liquid forms • Salad dressings - made from any of the oils above	• Hydrogenated and partially hydrogenated fats • Coconut, palm kernel, palm oil, coconut and coconut milk products • Butter, lard, shortening sold in cans, bacon fat, stick margarine • Dressing made with egg yolk, cheese, sour cream, or milk
Breads and grains (dietary fiber goal of >20 g per day may be difficult with fluid restriction; focus on viscous/soluble fiber)	• Breads without toppings or cheese ingredients • Cereals: oat, wheat, corn, multigrain • Pasta, rice • Crackers - low-fat animal crackers, unsalted soda crackers and bread sticks, melba toast • Homemade breads made with recommended fats and oils	• Breads of high-fat content such as croissants, flaky dinner rolls • Granolas that contain coconut or hydrogenated fats • High-fat crackers (more than 3 g of fat per serving on label) • Commercially baked pastries and biscuits
Fruits and vegetables	• Choices within CKD diet parameters in fresh, frozen, or low-sodium canned forms	• Fried fruits or vegetables or served with butter or cream sauces; avocado
Sweets (may be restricted in diabetics or presence of high triglycerides)	• Sweets: sugar, syrup, honey, jam, preserves, candy made without fat (hard candy) • Frozen desserts: low-fat and non-fat sherbet, sorbet, fruit ice • Cookies, cakes, and pies made with egg whites or egg substitutes or recommended fats; angel food cake; fig and other fruit bar cookies • Non-dairy regular and frozen whipped toppings in moderation	• Candy made with chocolate, cream, butter, frostings • Ice cream and regular frozen desserts • Commercially baked cookies, cakes, cream and regular pies • Commercially fried pastries such as doughnuts • Whipped cream

[a]Diet decisions should be made in consultation with a CKD dietitian to adapt food choices to the patient's individual medical and nutritional condition. Careful selection of foods within each category will be necessary to stay within phosphorus, potassium, and sodium restrictions. [3;30;284;286-288]

Periodic Health Examination.[445] Accordingly, recommendations were graded A, B, or C (Table 7) when:

(A) It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves net health outcomes.
(B) It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderate evidence that the practice improves net health outcomes.
(C) It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence, poor evidence, or on the opinions of the Work Group and reviewers, that the practice might improve net health outcomes.

Health outcomes are conditions or health-related events that can be perceived by individuals to have an important effect on their lives. Improving net health outcomes implies that benefits outweigh risks, and that the action is cost-effective. The strength of evidence was assessed taking into account (1) methodological quality of the studies; (2) whether or not the study was carried out in the target population, ie, patients with CKD, or in other populations; and (3) whether the studies examined health outcomes

Table 47. Nutritional Characteristics of Some Protein-Source Food Items.[a]

Protein Source	Calories (kcal)	Total Fat (g)	Saturated Fat (g)	Cholesterol (mg)
Beef eye of round, roasted	140	4	2	60
Beef top round steak, broiled	150	4	1	70
Pork tenderloin, roasted whole	140	4	1	65
Chicken breast, baked	120	2	1	70
Chicken drumstick, baked	130	4	1	80
Turkey breast, baked	120	1	0	55
Turkey wing, baked	140	3	1	60
Ground beef (10%), broiled, well-done	210	11	4	85
Ground beef (17%), broiled, well-done	230	13	5	85
Ground turkey	195	12	5	60
Orange roughy, broiled	70	1	0	20
Blue crab, steamed	90	1	0	80
Sole, broiled	100	1	0	60
Halibut, broiled	120	2	0	30

[a]Three-ounce servings, trimmed after cooking, skin removed.[447]

Table 48. Margarines Containing Plant Sterol/Stanol Esters.[a]

Nutrition Facts	Benecol®	Benecol Light®	Take Control®	Take Control Light®
Kilocalories (Kcal)	80	45	80	45
Kilocalories from fat	80	45	50	40
Total fat (g)	9	5	8	5
Saturated fat (g)	1	0.5	1	0.5
Polyunsaturated fat (g)	3	2	2	2
Monounsaturated fat (g)	4	2.5	4.5	2
Cholesterol (mg)	0	0	<5	5
Sodium (mg)	110	110	85	85
Carbohydrate (g)	0	0	0	0
Protein (g)	0	0	0	0
Potassium (mg)	3.5	3.5	*	*
Phosphorus (mg)	<1	<1	*	*
Plant sterol content	1.7 g stanol esters	1.7 g stanol esters	1,650 mg soybean extract	1,650 mg soybean extract
Comments	Cook, bake or fry		Can be used in cooking; contains 60% soybean and canola oils	Contains 35% soybean and canola oils

[a]One serving (1 tablespoon) of margarines.[447] Benecol® and Benecol Light® are registered trademarks of Neil Consumer Health-Care, (Fort Washington, PA), a division of Johnson & Johnson (www.benecol.com). Take Control® and Take Control Light® are registered trademarks of Unilever Bestfoods, Engelwood Cliffs, NJ (www.takecontrol.com).
*Insignificant amount.

Table 49. Contents of Some Commercially Available Cereals High in Fiber.[447]

Product[a]	Serving Size	Fiber (g)	Potassium (mg)	Phosphorus (mg)
All Bran®	1/2 cup	10	310	300
Post Bran Flakes®	2/3 cup	6	180	150
Cheerios®	1 cup	3	90	100
Quaker Crunchy Bran®	3/4 cup	5	56	36
Fiber One®	1/2 cup	13	230	150
Common Sense Oat Bran®	1/2 cup	4	120	150
General Mills Raisin Bran®	3/4 cup	3	220	150
Kellogg's Raisin Bran®	1 cup	8.2	350	200
Post Raisin Bran®	1 cup	8	380	250
General Mills Wheaties®	1 cup	3	110	100
Quaker Old Fashioned Oatmeal®	1/2 cup dry	3.7	143	183
Ralston Oatmeal®	3/4 cup cooked	4.6	116	110

[a]Registered trademarks: All Bran®, Common Sense Oat Bran®, and Kellogg's Raisin Bran®, Kellogg USA Inc, Battle Creek, MI; Post Bran Flakes® and Post Raisin Bran®, Kraft Foods Inc., Northfield, IL; Cheerios®, Fiber One®, General Mills Raisin Bran®, and Wheaties®, General Mills, Minneapolis, MN; Quaker Crunchy Bran® and Quaker Old Fashioned Oatmeal®, Quaker Oats Company, Chicago, IL; Ralston Oatmeal®, Ralston Foods, a division of Ralcorp, St. Louis, MO

directly, or examined surrogate measures for those outcomes, eg, improving dyslipidemia rather than reducing CVD (Table 8).

Limitations of Approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and searches were limited to English language publications. Manual searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the literature search were included in the review, as were essential studies identified during the review process.

APPENDIX 2. THERAPEUTIC LIFESTYLE CHANGE: DIET FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

Comprehensive nutrition counseling should be offered to all patients with CKD, given the high incidence of malnutrition and other nutritional abnormalities. Detailed guidelines of the

Table 50. Contents of Some Fruits High in Fiber.[447]

Fruit	Serving Size	Fiber (g)	Potassium (mg)	Phosphorus (mg)
Apple, raw, skin	Medium	3.7	159	10
Blackberries, raw	1/2 cup	3.8	141	15
Orange, navel, raw	1 fruit	3.1	233	25
Peaches, canned, water pack	1 cup	3.2	242	24
Pear, canned, water pack	1 cup	4.0	129	17
Raspberries, raw	1/2 cup	4.2	94	8

Table 51. Contents of Some Vegetables High in Fiber.[447]

Vegetable	Serving Size	Fiber (g)	Potassium (mg)	Phosphorus (mg)
Broccoli, boiled[a]	1/2 cup	2.3	228	4.6
Brussels sprouts, boiled	1/2 cup	2	247	44
Carrots, sliced, boiled	1/2 cup	2.6	177	23
Corn, boiled	1/2 cup	2.3	204	84
Mixed vegetables, frozen	1/2 cup	4	154	46
Green peas, frozen, boiled	1/2 cup	4.4	134	72
Spinach, boiled[a]	1/2 cup	2.2	419	150

[a]May be soaked to remove additional potassium. Soak for several hours, drain this water, replace with new water, and cook the vegetable as usual.

K/DOQI Nutrition Work Group for adults and children recommend a regular assessment of nutritional status and intervention by a renal dietitian.[446] However, dietary management of patients with dyslipidemias is not specifically addressed in the K/DOQI nutrition guidelines. Therefore, the Work Group made the following recommendations (Table 46).

During the initial assessment and subsequent follow-up of patients with CKD, it is important to assess malnutrition and protein energy deficits. If the patient is well nourished, dietary modifications for dyslipidemias can be undertaken safely. In some patients with CKD, standard CKD diet recommendations may have already appropriately reduced many foods with high unsaturated fats such as milk products.

It is important to consider patients with low total cholesterol. A low total cholesterol level, especially in association with chronic protein-energy deficits and/or the presence of comorbid conditions, may signal malnutrition. Patients with cholesterol <150 mg/dL (<3.88 mmol/L) should be assessed for possible nutritional deficiencies. For patients with malnutrition or protein-energy deficits, improving nutrition should be the primary goal. Dietary recommendations may include high-protein foods, with a liberal intake of foods high in saturated fat. However, in the majority of cases, acceptable protein sources low in saturated fat should be encouraged (Table 47). Low-fat dairy products, nuts, seeds, and beans may provide protein, but potassium and phosphorus contents should still be limited. Overall, healthy food preparation should be encouraged, such as using peanut, canola, or olive oil in cooking, since these are high in monounsaturated fats.

Plant Sterols

Plant sterols block the absorption of cholesterol from the small intestine by entering into micelles, which are needed for cholesterol to dissolve. Consequently, endogenous and dietary cholesterol becomes insoluble, and is therefore excreted in the stool. Plant sterols themselves are not absorbed or excreted well. Studies in the general population have shown that the intake of 2-3 g of plant sterols per day lowers LDL by 6% to 15%, with minimal change to HDL or triglycerides.[3] Reductions in LDL have been seen in hypercholesterolemic children[448,449] and adults.[450-452] The use of esters needs to take into account daily total fat consumption, and adjustments in caloric intake may also be needed. There is no contraindication to the use of plant sterols in patients with CKD; however, they should be used as a fat substitute and not for other therapeutic reasons. Unfortunately, some commercial products are expensive (Table 48).

Fiber

Viscous fiber should be increased by 5-25 g per day to help reduce total cholesterol and LDL.[3] High-fiber diets require additional fluid intake, which may be difficult for the anuric dialysis patient who is often limited to 1 L of fluid per day. Many high-fiber foods are also

Table 52. Contents of Some Breads High in Fiber.[447]

Bread	Serving Size	Fiber (g)	Potassium (mg)	Phosphorus (mg)
Pumpernickel	1 slice	2.1	67	57
American rye	1 slice	1.9	53	40
Whole wheat	1 slice	1.9	71	64

restricted in the renal diet due to their high phosphorus and/or potassium content. These foods may have to be included more often, and the phosphate binder or potassium content of the dialysate may need to be adjusted, to maintain normal serum phosphorus and potassium. Since each company varies the ingredients in their brands, it is essential to read nutrition labels, and to use those lowest in potassium and phosphorus. For example, a 1-cup portion of Kellogg's Raisin Bran® (Kelloggs, Battle Creek, MI) has less potassium and phosphorus than Post's Raisin Bran® (Kraft Foods, Inc., Northfield, IL). Common foods containing natural fiber are described in Tables 49, 50, 51, and 52.

Patients who are unable to consume adequate fiber through their diet can add natural fiber in the form of a tasteless powder to their meals (Table 53). Psyllium is a viscous fiber recommended by the ATP III.[3] The most common commercial product is Metamucil® (Proctor and Gamble, Cincinnati, OH). It should be mixed with 8 oz of fluid per dose, which may be difficult due to strict fluid restrictions in the dialysis patient. Magnesium may also be an excipient in some psyllium products, and those should be avoided. Sugar-free products are available for use in diabetics. Psyllium is also made generically, and it is imperative to review the product insert before use to ensure that it contains low amounts of potassium, sodium, and magnesium. Unifiber® (Niche Pharmaceuticals, Inc., Roanoke, TX) contains powdered cellulose, corn syrup solids and xanthan gum, and can easily be blended into applesauce, Cream of Wheat, or 3-4 fluid ounces of apple juice or water to provide 3 g of natural fiber. These products do not interfere with the absorption of medications or vitamins. Constipation is a chronic problem for dialysis patients who are restricted in the actual amount of fiber and fluid they can consume. Osmotic agents such as Polyethylene Glycol 3350, NF Powder, eg, Miralax® 17 g orally (Braintree Laboratories, Braintree, MA) or other products, may be needed to relieve constipation.

Table 53. The Electrolyte Content of Some Commonly Used Fiber Supplements.

Product	Fiber (g)	Kilocalories	Sodium (mg)	Potassium (mg)	Phosphorus (mg)
Metamucil®	3 g per dose	—	—	30 mg per dose	—
Metamucil Wafers®	3 g per 2 wafers	—	—	60 mg per dose	—
Unifiber®	1 Tbsp (3 g)	4	0	0	0
Hyfiber®	1 Tbsp (3 g)	14	15	12	—

Metamucil® and Metamucil Wafers® are registered trademarks of Procter and Gamble, Cincinnati, OH; Unifiber® is a registered trademark of Niche Pharmaceuticals, Inc., Roanoke, TX; Hyfiber® is a registered trademark of National Nutrition Lancaster, PA

BIOGRAPHICAL SKETCHES OF WORK GROUP MEMBERS

Bertram Kasiske, MD, FACP, (*Work Group Chair*), is Director of Nephrology at Hennepin County Medical Center and Professor of Medicine at the University of Minnesota, and is Director of Transplant Nephrology at Fairview University Medical Center. He also serves as Deputy Director of the United States Renal Data System (USRDS) Coordinating Center. Dr Kasiske is the Editor-in-Chief of the *American Journal of Kidney Diseases*. In addition, he serves on the Board of Directors of the United Network for Organ Sharing (UNOS). His areas of research and special interest include cardiovascular disease, hyperlipidemia, and chronic renal allograft nephropathy. Dr Kasiske has a research grant from Merck; has lectured for Roche, Novartis, Wyeth, and Fujisawa; and has been a consultant to Wyeth and Novartis.

Fernando G. Cosio, MD, (*Work Group Vice-Chair*) is currently Senior Associate Consultant at the Mayo Clinic and Professor of Medicine at the Mayo Clinic Medical School in Rochester, MN. Until August 2002 Dr Cosio was Professor of Medicine and Pathology in the Departments of Internal Medicine and Pathology, Division of Nephrology, at The Ohio State University. He is a member of the National Kidney Foundation, the American Society of Transplant Physicians, the American Diabetes Association, the American Association of Immunologists, the International Society of Nephrology, and The American Society of Nephrology. Dr Cosio has served on the Scientific Program Committee of the National Kidney Foundation's Clinical Nephrology Meetings. He also served on the Clinical Resource Policy Group and the Promotion and Tenure Committee, which he also chaired, at the Ohio State University, and is a past chairman of Clinical Research Center Advisory Committee in that institution. Dr Cosio is a reviewer for the *American Journal of Kidney Diseases*, the *Journal of the American Society of Nephrology*, the *Journal of Immunology*, *Kidney International*, and the *American Journal of Transplantation*, and was a reviewer of national grants for the National Institutes of Health (NIH), the American Diabetes Association, and the National Institute of Digestive and Kidney Disease, Subcommittee D, which he also chaired. In addition to the NIH, he has received grants from the Juvenile Diabetes Foundation and the National Kidney Foundation of Ohio.

Judith Beto, PhD, RD, FADA, is a Research Associate at Loyola University Medical Center and a Professor of Nutrition Sciences at Dominican University in River Forest, IL. In addition, she is a Volunteer Nutritional Counselor at the Cook County Department of Public Health Primary Referral Clinic and a member of the Curriculum Committee of the Advisory Council at the Cooking and Hospitality Institute of Chicago. A Fellow of the American Dietetic Association, she serves on the organization's Research Practice Group and Renal Dietitians Practice Group, which she also chaired. Dr Beto is on the National Kidney Foundation's Council on Renal Nutrition, where she serves on the Research Grant Committee, and has been a past National Program Chairman and Executive Committee member. She has also served on the NKF's Scientific Advisory Board and is a member and past president of the Illinois Council on Renal Nutrition of the National Kidney Foundation of Illinois. In addition to being selected as a nominee for the United States Department of Agricultural Food and Agricultural Sciences Excellence in College and University Teaching Awards Program, she has received many honors, including the Excellence Award for Outstanding Achievement as a Dietetics Educator from the American Dietetic Association Region V. Dr Beto is a past editor of *the Journal of Renal Nutrition*, past associate editor of *Perspectives in Applied Nutrition*, and has authored numerous journal articles, books and book chapters. She has received grants from the National Kidney Foundation's Council on Renal Nutrition, the American Dietetic Association Foundation, and Dominican University, and is on the Scientific Advisory Board of R&D Laboratory, Marina del Ray, CA.

Kline Bolton, MD, FACP, is Professor of Medicine at University of Virginia in Charlottesville, where he is Chief of the Division of Nephrology and Director of the Nephrology Clinical Research Center, Kidney Center and Renal

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Operations. He has received special honors from organizations ranging from the American Society for Clinical Investigation to the International Society of Nephrology. He has published many articles in journals ranging from *American Journal of Kidney Diseases* and *Kidney International* to *Immunologic Renal Diseases*, and contributed to numerous text books, including the *Textbook of the Autoimmune Diseases* and the *Textbook of Nephrology*. He is Chairman of the Renal Physicians Association Work Group on *Appropriate Preparation of Patients for Renal Replacement Therapy.* Dr Bolton serves on the Advisory Boards for Amgen and Ortho-Biotech. His research interests are in refining the epitope(s) involved in causing Goodpasture's syndrome, treating glomerulonephritis, and disease management of CKD and ESRD.

Blanche M. Chavers, MD, is Professor of Pediatrics at the University of Minnesota. She is a member of the American Society of Nephrology, The American Society of Pediatric Nephrology, the American Society of Transplantation, The International Society of Nephrology, and the International Society of Pediatric Nephrology. Dr Chavers is on the Public Policy Committee of the American Society of Pediatric Nephrology. She is also a past member of the Scientific Advisory Committee of the North American Pediatric Renal Transplant Cooperative Study and is Deputy Director of the Cardiovascular Special Studies Center, US Renal Data System, NIH, and served on the Board of Directors of the Minnesota International Health Volunteers. Dr Chavers has been on the editorial boards of *Colleagues* and *Pediatric Nephrology*, and is Co-editor of the *American Journal of Kidney Diseases*. She has been published numerous times in a variety of journals and books. Dr Chavers has been a recipient of the Mary Jane Kugel Award from the Juvenile Diabetes Foundation, the International Diabetes Center Award of Honor, the NIH Clinical Investigation Award, and the Viking Children's Fund Fellowship Award. Her areas of research and special interest include diabetic neuropathy, pediatric kidney transplantation, and cardiovascular disease in children with kidney disease. Dr Chavers has received grants from the Department of Health and Human Services for the National Health and Nutrition Survey IV (NHANES), the US Renal Data System, and Roche Global Development.

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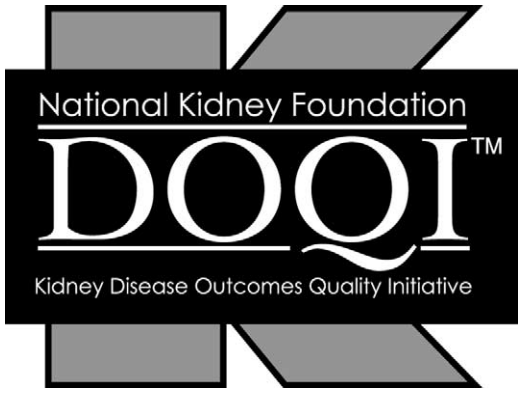

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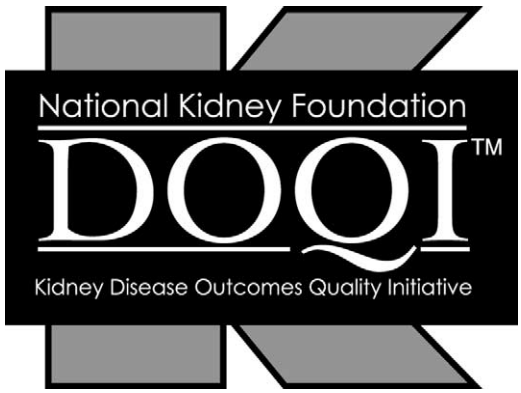
Participation in the review does not necessarily constitute endorsement of the content of the report by the individuals or the organization or institution they represent.



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