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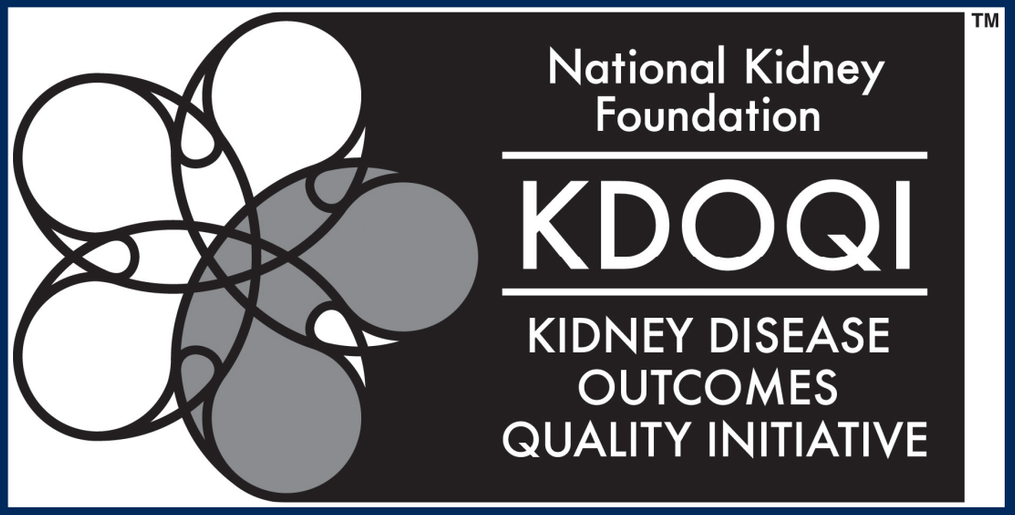

Clinical Practice Guidelines and Clinical Practice Recommendations for DIABETES AND CHRONIC KIDNEY DISEASE

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SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINES AND CLINICAL PRACTICE RECOMMENDATIONS

These Clinical Practice Guidelines (CPGs) and Clinical Practice Recommendations (CPRs) are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health care professional making use of these CPGs and CPRs is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

The National Kidney Foundation (NKF) makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

Specifically, all members of the Work Group are required to complete, sign, and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest. All affiliations are published in their entirety at the end of this publication in the Work Group members' biographical sketch and are on file at the NKF.

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Tables

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Abbreviations and Acronyms

Δ	Change
1°Pr	Primary prevention
2°Ir	Secondary intervention
4D	Deutsche Diabetes Dialyse Studie
ABCD	Appropriate Blood Pressure Control in Diabetes
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitor
ACR	Albumin-creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate
AG	Atubular glomeruli
AHA	American Heart Association
Alb	Albuminuria
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
ARR	Absolute risk reduction
ATP III	National Cholesterol Education Program Adult Treatment Panel III
AURORA	A study to evaluate the use of Rosuvastatin in subjects on regular hemodialysis: an assessment of survival and cardiovascular events
BENEDICT	Bergamo Nephrologic Diabetes Complications Trial
BMI	Body mass index
BorderlineAlb	Borderline albuminuria
BP	Blood pressure
CAD	Coronary artery disease
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CCB	Calcium channel blocker
CCr	Creatinine clearance
CI	Confidence interval
CIT	Conventional insulin injection therapy
CKD	Chronic kidney disease
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
COX-2	Cyclooxygenase-2
CPG	Clinical Practice Guideline
CPR	Clinical Practice Recommendation
Cr	Creatinine
CREATE	Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation
CR-LIPE	Carbohydrate-restricted, low iron-available, polyphenol-enriched diet
CSG	Collaborative Study Group
CT	Computed tomography
CV	Coefficient of variation
CVD	Cardiovascular disease

CYP	Cytochrome P-450
DALY	Disability-adjusted life-year
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DCCT	The Diabetes Control and Complications Trial
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
ddAVP	1-Deamino-8-D-arginine
DETES	Diabetics Exposed to Telmisartan and Enalapril Study Group
DGS	Diabetic glomerulosclerosis
DHA	Docosahexaenoic acid
DHP-CCB	Dihydropyridine calcium channel blocker
DIABHYCAR	Noninsulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril
DIAD	Detection of Ischemia in Asymptomatic Diabetics
DIGAMI	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
DKD	Diabetic kidney disease
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
ECLA	Estudios Cardiologicas Latin America Study Group
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
ESRD	End-stage renal disease
FBS	Fasting blood sugar
FDA	Food and Drug Administration
FPW	Foot process width on the mesangial surface
GBM	Glomerular basement membrane
GEMINI	Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives
GFR	Glomerular filtration rate
GIK	Glucose-insulin-potassium infusion
glom	Glomerulus
GLP-1	Glucagon-like-peptide-1
GlycoHb	Glycohemoglobin
GS	Glomerular sclerosis
HbA_{1c}	Hemoglobin A_{1c}
HD	Hemodialysis
HDL-C	High-density lipoprotein cholesterol
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HOPE	Heart Outcomes Prevention Evaluation
HPS	Heart Protection Study
HR	Hazard ratio
HTN	Hypertension
ICU	Intensive care unit
IDL	Intermediate-density lipoprotein
IDNT	Irbesartan Diabetic Nephropathy Trial
IJA	Index of junctional atrophy

IRMA-2	Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria
IU	International units
IUGR	Intrauterine growth retardation
IV	Intravenous
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
KDOQI™	Kidney Disease Outcomes Quality Initiative™
Kf	Ultrafiltration coefficient
KRT	Kidney replacement therapy
LDL-C	Low-density lipoprotein cholesterol
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease
LPD	Lower-protein diet
LVH	Left ventricular hypertrophy
M	Macroalbuminuria
m	Microalbuminuria
MacroAlb	Macroalbuminuria
MAP	Mean arterial blood pressure
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MicroAlb	Microalbuminuria
MIT	Multiple insulin injection therapy
N	Number of subjects
NCEP	National Cholesterol Education Program
nd	Not documented
NDHP-CCB	Nondihydropyridine calcium channel blocker
NHANES III	Third National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIDDM	Non–insulin-dependent diabetes mellitus
NIH	National Institutes of Health
NKF	National Kidney Foundation
Nl Cr	Normal serum creatinine
No	Number
NormoAlb	Normoalbuminuria
NPH	Neutral Protamine Hagedorn
NPV	Negative predictive value
NS	Not significant
OEI	Obesity Education Initiative Expert Panel on Identification, Evaluation, and Treatment of Overweight and Obesity in Adults
OR	Odds ratio
P	Proteinuria
PCI	Percutaneous coronary intervention
PCr	Plasma creatinine
PO	By mouth, orally
PPP	Pravastatin Pooling Project
PPV	Positive predictive value
PRESTO	Prevention of Restenosis with Tranilast and its Outcomes
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PROVE IT	Pravastatin or Atorvastatin in Evaluation and Infection Therapy
PUFA	Polyunsaturated fatty acids
PVD	Peripheral vascular disease

qd	Daily
QOL	Quality of life
RAS	Renin-angiotensin system
RCN	Radiocontrast-induced nephropathy
RCT	Randomized controlled trial
RDA	Recommended daily allowance
RDS	Respiratory distress syndrome
RENAAL	Reduction of Endpoints in Non-insulin-dependent diabetes with the Angiotensin II Antagonist Losartan
ROC	Receiver operator characteristic
RR	Relative risk
SBP	Systolic blood pressure
SCr	Serum creatinine (mg/dL)
SFA	Saturated fatty acids
SG	Globally sclerosed glomeruli
SGA	Small for gestational age
SHARP	Study of Heart and Renal Protection
SMBG	Self-monitoring of blood glucose
Sn	Sensitivity
SOLVD	Studies Of Left Ventricular Dysfunction
Sp	Specificity
Sv(PGBM/glom)	Surface density of peripheral GBM per glomerulus
SvME	Mesangial to epithelial interface
T	Total kidney cortex
TBM	Tubular basement membrane
TC	Total cholesterol
TNT	Treating to New Targets
TZD	Thiazolidinedione
UAE	Urinary albumin excretion
UKPDS	UK Prospective Diabetes Study
UPD	Usual/higher protein diet
USRDS	United States Renal Data System
VA	Veterans Affairs
VLDL	Very low-density lipoprotein
vs	Versus
Vv(AT/cortex)	Volume fraction of atrophic tubules per cortex
Vv(Int/cortex)	Volume fraction of cortical interstitium
Vv(Interstitium/tubulointerstitium)	Volume fraction of interstitium
Vv(MC/glom)	Volume fraction of mesangial cells per glomerulus
Vv(Mes/glom)	Volume fraction of mesangium per glomerulus
Vv(MM)	Volume fraction of mesangial matrix
Vv(MM/glom)	Volume fraction of mesangial matrix per glomerulus
Vv(PT/cortex)	Volume fraction of proximal tubules
WHO	World Health Organization
WOSCOP	West of Scotland Coronary Prevention Study

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Foreword

This publication of the Kidney Disease Outcomes Quality Initiative™ (KDOQI™) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (CKD) represents the first guideline that considers the unique aspects of the evaluation, diagnosis, and management of the complex patient with both diabetes mellitus and CKD.

Given the epidemic of obesity, diabetes, and cardiovascular disease and the link to CKD, it is clear that this guideline will be of immense importance to a broad audience of practioners and patients. As for all KDOQI™ guidelines, all relevant epidemiological studies and clinical trials have been reviewed to ensure a balanced presentation of the key aspects of diabetes and CKD.

The key points have been made that the combination of CKD and diabetes is a cardiovascular disease multiplier, and that these patients are at high risk of cardiovascular disease. The unique challenges of managing patients and the need to intervene early in the course of disease are discussed within the context of specific recommendations. As in all recent KDOQI™ guidelines, the difference between clinical practice guidelines (which are based on a sound evidentiary base) and clinical practice recommendations (which have a less sound evidentiary base, and on which ongoing research is needed) have been separated.

There are some topics within this guideline that address special populations (including native populations and pregnant women). These were included to ensure that 1 document could be used by practioners to address frequently asked key questions.

This guideline has been developed by using the usual rigorous methods of the KDOQI™ process and has involved multiple disciplines from both US and international sources. These perspectives have been invaluable in ensuring a robust document with broad perspective. This final version of this document has undergone revision in response to comments during the public review process, an important and integral part of the KDOQI™ guideline process. Nonetheless, as with all guideline documents, there will be a need in the future for revision in the light of new evidence and, more importantly, a concerted effort to translate the guidelines into practice.

We hope that this first guideline for the evaluation and management of patients with diabetes and kidney disease will foster additional research and facilitate implementation of key strategies for the early identification and treatment of this growing population. Implementation is an integral component of the KDOQI™ process, and it accounts for the success of its past guidelines. The Kidney Learning System component of the National Kidney Foundation is developing implementation tools that will be essential to the success of these guidelines.

In a voluntary and multidisciplinary undertaking of this magnitude, many individuals make contributions to the final product now in your hands. It is impossible to acknowledge them individually here, but to each and every one of them, we extend our sincerest appreciation. This limitation notwithstanding, a special debt of grati-

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tude is due to the members of the Work Group and their co-chairs, Katherine Tuttle and Robert Nelson. It is their commitment and dedication to the KDOQI™ process that has made this document possible.

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I. EXECUTIVE SUMMARY

EXECUTIVE SUMMARY

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy.[1,2] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative™ (NKF-KDOQI™) Clinical Practice Guidelines (CPGs) and Clinical Practice Recommendations (CPRs) on CKD estimates that CKD affects 11% of the US population,[3] and those affected are at increased risk of cardiovascular disease (CVD) and kidney failure. Kidney failure represents about 1% of the prevalent cases of CKD in the United States,[3] and the prevalence of kidney failure treated by dialysis or transplantation is projected to increase from 453,000 in 2003 to 651,000 in 2010.[3,4]

Management of CKD is costly. The Medicare CKD stage 5 population nearly doubled in the last 10 years, and the CKD population expanded, as well. Together, they account for 16.5% of Medicare expenditures, nearly double that of 10 years ago, and the total costs for kidney disease now approach 24% of Medicare expenditures.[4] A growing body of evidence suggests that some of the adverse outcomes of CKD can be prevented or delayed by preventive measures, early detection, and treatment.

NKF-KDOQI™ CPGs presently offer strategies to manage hypertension,[5] dyslipidemia,[6] bone disease,[7] anemia,[8] nutrition,[9] and CVD[10] in patients with CKD. The present Guidelines extend the scope of the NKF-KDOQI™ CPGs and CPRs by offering strategies to diagnose and manage patients with diabetes and CKD.

BACKGROUND

Epidemic of Diabetes

Nearly 21 million people in the United States, or 7% of the population, have diabetes, and about a third of those with diabetes are unaware they have the disease. About 5% to 10% of diabetes in the United States is type 1, which develops as a consequence of the body's failure to produce insulin. In some racial and ethnic groups, the proportion of cases attributable to type 1 diabetes is even less.[11] Most cases of diabetes in the United States and elsewhere are type 2, which develops because of the body's failure to produce sufficient insulin and properly use the insulin it produces. Worldwide, 171 million people have diabetes.

Diabetes prevalence is increasing most rapidly in the developed countries and in developing countries undergoing transition from traditional to modern lifestyles.[12,13] In the general US population, estimates from national surveys[14] show an 8-fold increase in the prevalence of diagnosed diabetes between 1958 and 2000. The San Antonio Heart Study[15] suggests an increasing incidence rate of type 2 diabetes is responsible, in part, for the increasing prevalence among Mexican Americans and for a borderline significant trend in non-Hispanic whites. The investigators attribute the greater prevalence of diabetes in this population more to the increasing incidence than to the decrease in cardiovascular mortality reported among people with diabetes nationally.[16] Other factors responsible for the increasing prevalence of diabetes include changes in diagnostic criteria, increased public awareness, decreasing overall mortality, growth in minority populations, a dramatic increase in the magnitude and frequency of obesity, and the widespread adoption of a sedentary lifestyle.[14] Most of the increase in diabetes prevalence is attributable to type 2 diabetes, and although much of this increase is occurring in adults, children and adolescents increasingly are affected. However, a worldwide increase in the incidence of type 1 diabetes also has been noted, particularly among children younger than 5 years.[17]

Projections of the future burden of diabetes in the US population suggest that the prevalence of diabetes will increase 165% between 2000 and 2050, with the greatest increases in the population older than 75 years and among African Americans.[18] The global burden of diabetes is expected to double between 2000 and 2030, with the greatest increases in prevalence occurring in the Middle East, sub-Saharan Africa, and India.[19] Moreover, the development of type 2 diabetes during the childbearing years also will

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increase, primarily in the developing countries (CPR 3, Fig 27).[19] Projections regarding the future burden of diabetes are based on increasing life expectancy, population growth, and progressive urbanization.[20] Of growing concern is the belief that these estimates may be too low because they do not account for the increasing frequency and magnitude of obesity and other major risk factors for diabetes.

As the population of patients with diabetes of long duration grows, reports of a dramatically increasing burden of diabetic kidney disease (DKD) are appearing from developed countries,[21] as well as from Africa,[22,23] India,[24] the Pacific Islands,[25] and Asia,[26,27] where infectious disease previously posed the greatest threat[28] (see CPR 3). Increased risk and more rapid progression of DKD[29,30] also have been reported in immigrants from developing to developed countries.[31,32]

PROBLEM OF DIABETES AND CKD

Diabetes is the leading cause of CKD in developed countries and rapidly is becoming the leading cause in developing countries as a consequence of the global increase in type 2 diabetes and obesity.[33] In the United States, microalbuminuria is found in 43%, and macroalbuminuria, in 8% of those with a history of diabetes.[3] Moreover, diabetes accounts for 45% of prevalent kidney failure, up from 18% in 1980.[4]

Substantial underdiagnosis of both diabetes and CKD leads to lost opportunities for prevention, and inadequate or inappropriate care of patients with diabetes and CKD may contribute to disease progression. Nevertheless, diabetes care has improved as the benefits of meticulous management have become widely accepted and the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins has increased in patients with diabetes.[4] Even so, fewer than 1 in 4 patients with diabetes receives at least 1 hemoglobin A_{1c} (HbA_{1c}) test, at least 1 lipid test, and at least 1 glucose testing strip each year, reflecting the need for better assessment of these high-risk patients.[4]

DKD refers to kidney disease that is specific to diabetes. Although kidney biopsy is required to diagnose diabetic glomerulopathy definitively, in most cases, careful screening of diabetic patients can identify people with DKD without the need for kidney biopsy. DKD is based in part on the finding of elevated urinary albumin excretion, which is divided arbitrarily into: (1) microalbuminuria, a modest elevation of albumin thought to be associated with stable kidney function, but a greater risk of macroalbuminuria and kidney failure; and (2) macroalbuminuria, a higher elevation of albumin associated with progressive decline in glomerular filtration rate (GFR), an increase in systemic blood pressure, and a high risk of kidney failure.

Most professional societies concerned with diabetes and kidney disease now advocate screening for microalbuminuria in patients with diabetes, and the suggested screening plan, adapted from the American Diabetes Association (ADA) guideline, is shown in Guideline 1, Fig 6.[34,35] Screening should begin 5 years after diagnosis of type 1 diabetes and at the time of diagnosis of type 2 diabetes because of the inability to establish the onset of type 2 diabetes with certainty. Because urinary albumin excretion has an intraindividual coefficient of variation (CV) of approximately 40%,[36] multiple positive test results are required for classification. Definitions of DKD by albuminuria and stage are shown in Guideline 1, Table 6.

Evidence for the usefulness of estimated GFR (eGFR) alone as a screening test for CKD in diabetes is less secure. Many patients with diabetes and CKD may have elevated or high-normal GFRs, particularly in the early years after diagnosis. Therefore, markers of kidney damage are required to detect early stages of CKD; eGFR alone can only detect CKD stage 3 or worse (Guideline 1, Table 6).

Because diabetes is a common condition, coincidence with other nondiabetic CKD is relatively frequent. Accordingly, evaluation of a person with atypical features should, in selected cases, include additional diagnostic testing, depending on the clinical presentation. Care should be used in determining the appropriate diagnostic tests because administration of radiographic contrast, with or without angiography, may pose greater risks in people with diabetes and CKD than in others.

Diabetes, CKD, and CVD

Diabetes is one of the most important risk factors for CVD. The risk imparted by diabetes

has been described as a CVD risk equivalent because the likelihood of future events may approach that of people without diabetes who have already had a myocardial infarction.[37] Such observations have led to recommendations from both the ADA and the American Heart Association (AHA) for intensive cardiovascular risk factor management in people with diabetes (Table 1).[34,38] CKD also imparts an extremely high risk of CVD. The NKF and the AHA recently issued guidelines and scientific statements recommending that people with CKD be considered in the highest risk category for CVD.[3,39] For those with both diabetes and CKD, the outlook is far worse than for either condition alone because this combination is a powerful predictor of major adverse cardiovascular events and death. The relationship between CKD severity and risk is continuous. People with diabetes and microalbuminuria have twice the CVD risk of those with normoalbuminuria,[40] and as albuminuria increases and GFR decreases, CVD risk increases progressively.[41-43] In an analysis of patients with type 2 diabetes from the UK Prospective Diabetes Study (UKPDS), rates of death and progression to macroalbuminuria were equal at the microalbuminuric stage.[41] However, at the macroalbuminuric stage, the death rate outpaced the rate of kidney disease progression (Fig 2). More people who reach CKD stage 3 will die, primarily of CVD, than progress to kidney failure, especially if they also have diabetes.[3,44]

In the Background, a focused review of relationships among diabetes, CKD, and CVD relevant to people with CKD stages 1 to 4 is presented. The review includes a discussion of intensive risk factor management for the prevention of CVD, the evaluation of coronary heart disease in patients with diabetes, and medical management and coronary revascularization in these patients. Specific recommendations for CKD stage 5 are provided in the NKF-KDOQI™ Guidelines for CVD in Dialysis Patients.[10]

People with diabetes and CKD are at high risk to both lose kidney function and experience major adverse cardiovascular events (Background, Fig 4). Treatment of risk factors reduces the likelihood of these outcomes. Fortunately, treatment strategies are largely shared for reducing kidney and cardiovascular risks. The present CPGs and CPRs for diabetes and CKD are consistent with those already established for the treatment of diabetes and CVD by the ADA and AHA.[34,38] Goals of the management approaches recommended here are intended to mitigate the devastating consequences of the spectrum of vascular complications, including kidney, heart, and others.

GOALS OF CPG AND CPR PROCESS

These CPGs seek to improve outcomes in patients with diabetes and CKD by providing strategies for the diagnosis (Guideline 1) and management (Guidelines 3 to 5 and CPRs 1 to 4) of CKD in the setting of diabetes and for the management of diabetes in the setting of CKD (Guideline 2). The general treatment of diabetes is beyond the scope of this guideline and is addressed comprehensively in the ADA guidelines.[34]

As part of an evolution in the development of CPGs, the Work Group divided its recommendations, which are based on a systematic review of the literature, into a series of Guidelines and CPRs. The Guidelines were based on a consensus within the Work Group that the strength of the evidence was sufficient to make definitive statements about appropriate clinical practice. When the strength of the evidence was not sufficient to make such statements, the Work Group offered CPRs based on the best available evidence and expert opinion. As new data become available, the strength of the evidence for many of the CPRs may become sufficient for the CPRs to become CPGs, illustrating the need for recurring reviews and updates of this document. Many of the research recommendations proposed by the Work Group were developed with the goal of strengthening the evidence for the CPRs to determine whether they should become Guidelines in the future.

The term "definitive" must be used with caution, particularly in the context of CPGs. Uncertainty is an immutable element of all scientific research, and the establishment of a Guideline should neither preclude nor render unethical further inquiry. Rather, the establishment of guidelines represents an evolving process that seeks to ensure that each patient receives the best possible care within the context of presently available medical knowledge.

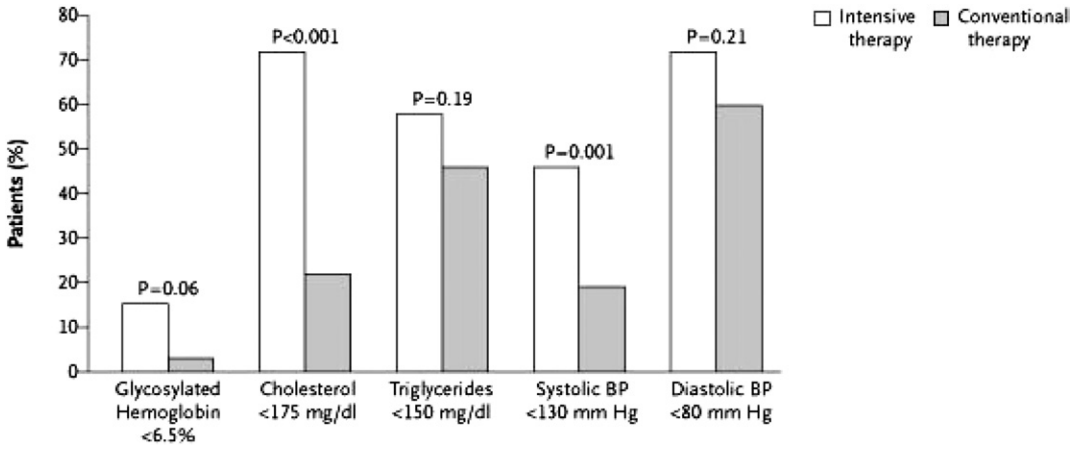

Figure 1. Percentage of patients in each group of the Steno Study who reached the intensive-treatment goals at a mean of 7.8 years.
Abbreviation: BP, blood pressure. Reprinted with permission.[45]

Scope

The target population of these CPGs is patients with CKD stages 1 to 5, including dialysis and transplant patients. However, the emphasis is on stages 1 to 4 because the evidence in stage 5 is either lacking or addressed in other NKF-KDOQI™ Guidelines. Consideration is given to the diagnosis, impact, and management of diabetes and CKD in children, adults, the elderly, pregnant women, and different racial and ethnic groups.

The intended readers are practitioners who manage patients with diabetes and CKD, including, but not limited to, primary care providers, nephrologists, cardiologists, endocrinologists/diabetologists, physician's assistants, nurse practitioners, nurses, dietitians, pharmacists, social workers, and diabetes educators. By reviewing scientific evidence from throughout the world, coordinating our efforts with guideline development processes elsewhere, and including in the Work Group experts from Latin America and Europe, as well as from North America, we believe this document has relevance beyond practitioners in North America.

The Value of Multifaceted Intervention

Although these and other guidelines present recommendations for the management of risk factors separately, in reality, multiple risk factors are managed concurrently in patients with diabetes and CKD. In the Steno Study, a multifaceted approach aimed at optimal management for a group of risk factors was evaluated in patients with type 2 diabetes and microalbuminuria.[45,46] The intervention had multiple targets, including behavioral modification and pharmacological therapies for hyperglycemia, hypertension (emphasizing renin-angiotensin system [RAS] inhibitors), dyslipidemia, CVD prevention with aspirin, and a vitamin/mineral supplement (CPR 2, Table 48). This intensive intervention was compared with usual care. A mean decrease in albuminuria (albumin decreased 20 mg/24 h) was observed in the intensive-intervention group, whereas a mean increase occurred in patients in the usual-care group (albumin increased 30 mg/24 h). Albuminuria progression and the composite outcome of CVD events or death were decreased in the group treated intensively (CPR 2, Fig 26). However, which facets of the intervention are associated with reduced risk is uncertain. Furthermore, because the intensive intervention increased the use of RAS inhibitors, the contribution of other treatments is unclear. Despite these limitations, the Work Group recognizes the importance of addressing multiple risk factors in an integrated fashion. The incremental effects of a multifaceted approach appear to add up to substantial clinical benefits, even when each of the therapeutic goals is not met (Fig 1). A long-term, targeted, intensive intervention involving multiple risk factors and using currently available therapeutic agents reduces the risk of cardiovas-

cular and microvascular events by about 50% among patients with type 2 diabetes and microalbuminuria.[45]

SUMMARY

Multiple important, but unanswerable, questions arose during the development of each Guideline and CPR. These questions led to research recommendations that should be high priorities to improve the care of patients with diabetes and CKD. The Work Group recognizes the importance of bringing new treatments into clinical research for DKD, especially for patients who have progressive kidney disease despite the current standard of care. Promising treatments, including novel agents and potential new uses of existing agents, are currently in phase 2/3 trials for DKD. These recommendations and the new treatments in clinical trials are described in the Research Recommendations section.

CPG AND CPR STATEMENTS

Guideline 1: Screening and Diagnosis of DKD

CKD in patients with diabetes may or may not represent DKD. In the absence of an established diagnosis, the evaluation of patients with diabetes and kidney disease should include investigation into the underlying cause(s).

1.1 Patients with diabetes should be screened annually for DKD. Initial screening should commence:
- **5 years after the diagnosis of type 1 diabetes; (A) or**
- **From diagnosis of type 2 diabetes. (B)**

1.1.1 Screening should include:
- **Measurements of urinary albumin-creatinine ratio (ACR) in a spot urine sample; (B)**
- **Measurement of serum creatinine and estimation of GFR. (B)**

1.2 An elevated ACR should be confirmed in the absence of urinary tract infection with 2 additional first-void specimens collected over the next 3 to 6 months. (B)
- **Microalbuminuria is defined as an ACR between 30-300 mg/g.**
- **Macroalbuminuria is defined as an ACR > 300 mg/g.**
- **2 of 3 samples should fall within the microalbuminuric or macroalbuminuric range to confirm classification.**

1.3 In most patients with diabetes, CKD should be attributable to diabetes if:
- **Macroalbuminuria is present; (B) or**
- **Microalbuminuria is present**
  - **in the presence of diabetic retinopathy, (B)**
  - **in type 1 diabetes of at least 10 years' duration. (A)**

1.4 Other cause(s) of CKD should be considered in the presence of any of the following circumstances: (B)
- **Absence of diabetic retinopathy;**
- **Low or rapidly decreasing GFR;**
- **Rapidly increasing proteinuria or nephrotic syndrome;**
- **Refractory hypertension;**
- **Presence of active urinary sediment;**
- **Signs or symptoms of other systemic disease; or**
- **>30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.**

Guideline 2: Management of Hyperglycemia and General Diabetes Care in CKD

Hyperglycemia, the defining feature of diabetes, is a fundamental cause of vascular target-organ complications, including kidney disease. Intensive treatment of hyperglycemia prevents DKD and may slow progression of established kidney disease.

2.1 Target HbA_{1c} for people with diabetes should be < 7.0%, irrespective of the presence or absence of CKD. (A)

Guideline 3: Management of Hypertension in Diabetes and CKD

Most people with diabetes and CKD have hypertension. Treatment of hypertension slows the progression of CKD.

3.1 Hypertensive people with diabetes and CKD stages 1-4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic. (A)

3.2 Target blood pressure in diabetes and CKD stages 1-4 should be < 130/80 mm Hg. (B)

Guideline 4: Management of Dyslipidemia in Diabetes and CKD

Dyslipidemia is common in people with diabetes and CKD. The risk of CVD is greatly increased in this population. People with diabetes and CKD should be treated according to current guidelines for high-risk groups.

4.1 Target low-density lipoprotein cholesterol (LDL-C) in people with diabetes and CKD stages 1-4 should be < 100 mg/dL; <70 mg/dL is a therapeutic option. (B)
4.2 People with diabetes, CKD stages 1-4, and LDL-C ≥ 100 mg/dL should be treated with a statin. (B)
4.3 Treatment with a statin should not be initiated in patients with type 2 diabetes on maintenance hemodialysis therapy who do not have a specific cardiovascular indication for treatment. (A)

Guideline 5: Nutritional Management in Diabetes and CKD

Management of diabetes and CKD should include nutritional intervention. Dietary modifications may reduce the progression of CKD.

5.1 Target dietary protein intake for people with diabetes and CKD stages 1-4 should be the recommended daily allowance (RDA) of 0.8 g/kg body weight per day. (B)

CPR 1: Management of Albuminuria in Normotensive Patients With Diabetes and Albuminuria as a Surrogate Marker

Treatments that decrease urinary albumin excretion may slow the progression of DKD and improve clinical outcomes, even in the absence of hypertension. However, most people with diabetes and albuminuria have hypertension; management of hypertension in these patients is reviewed in Guideline 3.

1.1 Normotensive people with diabetes and macroalbuminuria should be treated with an ACE inhibitor or an ARB. (C)
1.2 Treatment with an ACE inhibitor or an ARB may be considered in normotensive people with diabetes and microalbuminuria. (C)
1.3 Albuminuria reduction may be considered a treatment target in DKD. (C)

CPR 2: Multifaceted Approach to Intervention in Diabetes and CKD

Multiple risk factors are managed concurrently in patients with diabetes and CKD, and the incremental effects of treating each of these risk factors appear to add up to substantial clinical benefits.

2.1 The care of people with diabetes and CKD should incorporate a multifaceted approach to intervention that includes instruction in healthy behaviors and treatments to reduce risk factors. (C)
2.2 Target body mass index (BMI) for people with diabetes and CKD should be within the normal range (18.5-24.9 kg/m^2). (C)

CPR 3: Diabetes and CKD in Special Populations

The increasing incidence of diabetes in children, young adults, the elderly, and members of disadvantaged and transitional populations is responsible for an increasing incidence of DKD in these groups. Racial/ethnic differences in susceptibility to DKD also may play a role. In pregnant women, the presence of diabetes and CKD may adversely affect the health of both the mother and her offspring.

3.1 Screening and interventions for diabetes and CKD should focus on populations at greatest risk. (C)
3.2 Although management of diabetes and CKD in special populations should follow the same principles as management in the majority population, there are special considerations in the treatment of children, adolescents, and the elderly. (C)
3.3 Population-based interventions may be the most cost-effective means for addressing the burden of CKD in special populations. Implementation and evaluation of population-based interventions should take into account the heterogeneity of the populations at risk. (C)
3.4 Specialists in high-risk pregnancy and kidney disease should co-manage preg-

nancy in women with diabetes and CKD. (C)

3.5 Treatment of DKD with RAS inhibitors before pregnancy may improve fetal and maternal outcomes, but these medicines should be discontinued as soon as a menstrual period is missed or after a positive pregnancy test. (C)

3.6 Insulin should be used to control hyperglycemia if pharmacological therapy is necessary in pregnant women with diabetes and CKD. (C)

CPR 4: Behavioral Self-Management in Diabetes and CKD

Behavioral self-management in patients with diabetes and CKD is particularly challenging because of the intensive nature of the diabetes regimen. Education alone is not sufficient to promote and sustain healthy behavior change, particularly with such a complex regimen.

4.1 Self-management strategies should be key components of a multifaceted treatment plan with attention to multiple behaviors: (C)

- **Monitoring and treatment of glycemia,**
- **Blood pressure,**
- **Nutrition,**
- **Smoking cessation,**
- **Exercise, and**
- **Adherence to medicines.**

II. CLINICAL PRACTICE GUIDELINES

BACKGROUND

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy.[1,2] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative™ (NKF-KDOQI™) Clinical Practice Guidelines (CPGs) on CKD estimate that CKD affects 11% of the US population,[3] and those affected are at increased risk of cardiovascular disease (CVD) and kidney failure. Kidney failure represents about 1% of the prevalent cases of CKD in the United States,[3] and the prevalence of kidney failure treated by dialysis or transplantation is projected to increase from 453,000 in 2003 to 651,000 in 2010.[3,4]

Management of CKD is costly. The Medicare CKD stage 5 population nearly doubled in the last 10 years, and the CKD population expanded, as well. Together, they account for 16.5% of Medicare expenditures, nearly double that of 10 years ago, and the total costs for kidney disease now approach 24% of Medicare expenditures.[4] A growing body of evidence suggests that some of the adverse outcomes of CKD can be prevented or delayed by preventive measures, early detection, and treatment.

NKF-KDOQI™ CPGs presently offer strategies to manage hypertension,[5] dyslipidemia,[6] bone disease,[7] anemia,[8] nutrition,[9] and CVD[10] in patients with CKD. The present Guideline extends the scope of the NKF-KDOQI™ CPGs by offering strategies to diagnose and manage the treatment of patients with diabetes and CKD.

PROBLEM OF DIABETES AND CKD

Diabetes is the leading cause of CKD in developed countries and is rapidly becoming the leading cause in developing countries as a consequence of the global increase in type 2 diabetes and obesity.[33] In the United States, microalbuminuria is found in 43%, and macroalbuminuria, in 8% of those with a history of diabetes.[3] Moreover, diabetes accounts for 45% of prevalent kidney failure, up from 18% in 1980.[4]

Substantial underdiagnosis of both diabetes and CKD leads to lost opportunities for prevention, and inadequate or inappropriate care of patients with diabetes and CKD may contribute to disease progression. Nevertheless, diabetes care has improved because the benefits of meticulous management have become widely accepted and the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins has increased in patients with diabetes.[4] Even so, fewer than 1 in 4 patients with diabetes receives at least 1 hemoglobin A_{1c} (HbA_{1c}) test, at least 1 lipid test, and at least 1 glucose testing strip each year, reflecting the need for better assessment of these high-risk patients.[4]

GOALS OF CPG AND CPR PROCESS

This CPG seeks to improve outcomes in patients with diabetes and CKD by providing strategies for the diagnosis (Guideline 1) and management (Guidelines 3 to 5 and CPRs 1 to 4) of CKD in the setting of diabetes and for the management of diabetes in the setting of CKD (Guideline 2). The general treatment of diabetes is beyond the scope of this guideline, and it is comprehensively addressed in the American Diabetes Association (ADA) guidelines.[34]

As part of an evolution in the development of CPGs, the Work Group divided its recommendations, which are based on a systematic review of the literature, into a series of Guidelines and Clinical practice recommendations (CPRs). The Guidelines were based on a consensus within the Work Group that the strength of the evidence was sufficient to make definitive statements about appropriate clinical practice. When the strength of the evidence was not sufficient to make such statements, the Work Group offered CPRs based on the best available evidence and on expert opinion. As new data become available, the strength of the evidence for many of the CPRs may become sufficient for the CPRs to become CPGs, illustrating the need for recurring reviews and updates of this document. Many of the research recommendations proposed by the Work Group were developed with the goal of strengthening the evidence for the CPRs to determine whether they should become Guidelines in the future.

The term "definitive" must be used with caution, particularly in the context of CPGs. Uncertainty is an immutable element of all scientific

research, and the establishment of a Guideline should neither preclude nor render unethical further inquiry. Rather, the establishment of guidelines represents an evolving process that seeks to ensure that each patient receives the best possible care within the context of presently available medical knowledge.

Scope

The target population of this CPG is patients with CKD stages 1 to 5, including dialysis and transplant patients. However, the emphasis is on stages 1 to 4 because the evidence in stage 5 is either lacking or addressed in other NKF-KDOQI™ Guidelines. Consideration is given to the diagnosis, impact, and management of diabetes and CKD in children, adults, the elderly, pregnant women, and different racial and ethnic groups.

The intended readers are practitioners who manage patients with diabetes and CKD, including, but not limited to, primary care providers, nephrologists, cardiologists, endocrinologists/diabetologists, physician's assistants, nurse practitioners, nurses, dietitians, pharmacists, social workers, and diabetes educators. By reviewing scientific evidence from throughout the world, coordinating our efforts with guideline development processes elsewhere, and including in the Work Group experts from Latin America and Europe, as well as from North America, we believe this document has relevance beyond practitioners in North America.

DIABETES AS A PUBLIC HEALTH MANDATE

An Epidemic

Nearly 21 million people in the United States, or 7% of the population, have diabetes, and about a third of those with diabetes are unaware they have the disease. About 5% to 10% of diabetes in the United States is type 1, which develops as a consequence of the body's failure to produce insulin. In some racial and ethnic groups, the proportion of cases attributable to type 1 diabetes is even less.[11] Most cases of diabetes in the United States and elsewhere are type 2, which develops because of the body's failure to produce sufficient insulin and properly use the insulin it produces. Worldwide, 171 million people have diabetes.

Diabetes prevalence is increasing most rapidly in the developed countries and in developing countries undergoing transition from traditional to modern lifestyles.[12,13] In the general US population, estimates from national surveys[14] show an 8-fold increase in the prevalence of diagnosed diabetes between 1958 and 2000. The San Antonio Heart Study[15] suggests an increasing incidence rate of type 2 diabetes is responsible, in part, for the increasing prevalence among Mexican Americans and for a borderline significant trend in non-Hispanic whites. The investigators attribute the greater prevalence of diabetes in this population more to the increasing incidence than to the decrease in cardiovascular mortality reported among people with diabetes nationally.[16] Other factors responsible for the increasing prevalence of diabetes include changes in diagnostic criteria, increased public awareness, decreasing overall mortality, growth in minority populations, a dramatic increase in the magnitude and frequency of obesity, and the widespread adoption of a sedentary lifestyle.[14] Most of the increase in diabetes prevalence is attributable to type 2 diabetes, and although much of this increase is occurring in adults, children and adolescents are increasingly affected. However, a worldwide increase in the incidence of type 1 diabetes also has been noted, particularly among children younger than 5 years.[17]

Projections of the future burden of diabetes in the US population suggest that the prevalence of diabetes will increase 165% between 2000 and 2050, with the greatest increases in the population older than 75 years and among African Americans.[18] The global burden of diabetes is expected to double between 2000 and 2030, with the greatest increases in prevalence occurring in the Middle East, sub-Saharan Africa, and India.[19] Moreover, development of type 2 diabetes during the childbearing years also will increase, primarily in the developing countries (CPR 3, Fig 27).[19] Projections regarding the future burden of diabetes are based on increasing life expectancy, population growth, and progressive urbanization.[20] Of growing concern is the belief that these estimates may be too low because they do not account for the increasing frequency and magnitude of obesity and other major risk factors for diabetes.

As the population of patients with diabetes of long duration grows, reports of a dramatically increasing burden of diabetic kidney disease (DKD) are appearing from developed countries,[21] as well as from Africa,[22,23] India,[24] the Pacific Islands,[25] and Asia,[26,27] where infectious disease previously posed the greatest threat[28] (see CPR 3). Increased risk and more rapid progression of DKD[29,30] also have been reported in immigrants from developing to developed countries.[31,32]

Obesity and Inactivity

Obesity is one of the strongest determinants of diabetes and is a consequence of interactions between genetic susceptibility, cellular metabolism, eating behavior, culture, level of physical activity, and socioeconomic status. Because obesity is a major determinant of diabetes and other chronic diseases, an assessment of obesity should be part of the routine clinical examination of every patient. General measures of obesity (BMI, weight, and percent body fat) and measures of central fat distribution (waist circumference, waist-hip ratio, waist-thigh ratio, and waist-height ratio) predict the development of type 2 diabetes in prospective studies, regardless of age or ethnicity.[47-54] Although a strong relationship exists between the quantity of intra-abdominal fat and diabetes, BMI remains an excellent predictor of diabetes and is not improved significantly by combining it with other measures of general adiposity or body fat distribution.[55] In the kidney, obesity is associated with glomerular hyperfiltration and an increase in transcapillary hydraulic pressure,[56,57] hemodynamic changes that may accelerate the development and progression of DKD in obese people with diabetes. Hence, CPR 2 was developed to address the issue of obesity and encourage further investigation.

One of the primary determinants of obesity is physical inactivity, and a physically active lifestyle is associated with a lower incidence of type 2 diabetes in several prospective studies.[58-62] Recent clinical trials provide compelling evidence that increased physical activity, combined with dietary modification and weight loss, prevents diabetes regardless of age or ethnicity.[63-65] The Diabetes Prevention Program demonstrated that a lifestyle-modification program that included a 7% weight loss and at least 150 minutes of moderate physical activity per week was associated with a 58% reduction in the incidence of diabetes over nearly 3 years in people with impaired glucose tolerance compared with placebo.[63] Because the lifestyle changes worked equally well in all racial/ethnic groups, they should be applicable to high-risk populations worldwide. This approach to diabetes prevention provides the most cost-effective means for reducing the projected increase in the incidence of diabetes and its complications, including DKD.[66]

Ethnicity

In the United States, the burden of diabetes is borne disproportionately by ethnic and racial minorities, including African Americans, Hispanics, and Native Americans. The higher rates of diabetes in these populations relative to non-Hispanic whites are associated with a high rate of DKD, as described in CPR 3. The particularly high predisposition to diabetes is possibly on a genetic basis, when individuals are exposed to adverse conditions or rapid economic transition. Worldwide, populations of developing countries appear to be at increased risk of developing diabetes during the coming decades, perhaps for many of the same reasons.

Economic transition may be the predominant risk factor for diabetes in many developing countries. People who successfully undergo economic transition—those who migrate to cities and take industrial jobs that pay well—experience an increase in socioeconomic status and greater access to food. In India, for example, higher socioeconomic status increases the risk of diabetes.[67] The same is true among Hispanics in the United States.[68] Conversely, transition to higher socioeconomic status has the opposite effect in African Americans[69]; a finding that may be explained in part because higher socioeconomic status generally is associated with better education, greater acculturation, and the resources to make healthier food choices.[70] Therefore, although populations in rapid economic transition often are at increased risk of diabetes, proper education may mitigate or prevent the increase in the risk of diabetes often associated with this transition.

Extremes of Age

The current epidemic of obesity in children and adolescents in many parts of the world has created an epidemic of type 2 diabetes in these age groups. Although type 1 diabetes is the predominant form of diabetes in children worldwide, it is likely that type 2 diabetes will soon become the most prevalent form in many ethnic groups.[71,72] Many children with type 2 diabetes are obese at diagnosis, have a strong family history of type 2 diabetes, and are the offspring of mothers with gestational diabetes. Among Native Americans aged 15 to 19 years nationwide, the prevalence of diagnosed diabetes increased by 69% from 1990 to 1998, but remained unchanged in those younger than 15 years.[73] In Japan, a 10-fold increase in the incidence of type 2 diabetes was reported during 20 years of follow-up in children initially aged 6 to 12 years, and a 2-fold increase was reported among those initially aged 13 to 15 years, coinciding with a secular increase in the prevalence of obesity.[74,75]

The proportion of children exposed to diabetes in utero also may be increasing as more women develop diabetes during their childbearing years. In Pima Indians, a doubling of the percentage of childhood diabetes during the past 30 years is attributed to an increasing frequency of intrauterine exposure to diabetes.[76] Observations in Pima children born since 1965 indicate that offspring of mothers with diabetes have a greater prevalence of obesity throughout childhood and a much greater prevalence of type 2 diabetes.[77] Although only 3% of type 2 diabetes develops before 20 years of age,[78] those who develop diabetes in childhood and adolescence are affected disproportionately in early adulthood by the microvascular and macrovascular complications of diabetes, including DKD,[79,80] as described in CPR 3.

The World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetes[81] reported that Native Americans from Arizona and Oklahoma who had type 2 diabetes diagnosed before 30 years of age had a higher age-adjusted incidence rate of kidney failure during a mean follow-up of 9.5 years than the overall Native American population with diabetes.[82] A study of long-term microvascular and macrovascular complications in Japanese subjects with onset of type 2 diabetes before 30 years of age[83,84] found that 5% of the subjects had CKD stage 5 after 20 years' duration of diabetes, and 23% of those who also had proliferative retinopathy progressed to dialysis by a mean age of 35 years. Premature atherosclerotic vascular disease, including cerebrovascular disease and CVD, was the leading cause of death in this population and was related largely to poor glycemic control and progression to CKD stage 5. These complications have a significant economic and public health impact because they will affect those with youth-onset diabetes during their peak productive years.

Diabetes is a major cause of morbidity and mortality in the aging population. At least 20% of people older than 65 years have diabetes,[34] and the greatest increase in diabetes prevalence in the coming decades will occur in those older than 75 years.[18] The elderly are particularly prone to the cardiovascular complications of diabetes. CVD develops in the 2 years before initiation of kidney replacement therapy in more than 90% of patients aged 75 years and older with kidney failure and diabetes. Congestive heart failure is the most common cardiac condition among elderly patients with diabetes and CKD stage 5, affecting 71% of patients, followed closely by ischemic heart disease at 67%.[21]

Other comorbidities also are more prevalent in the elderly, and intensive management of these patients may pose greater risks because hypotension and hypoglycemia occur more frequently than in younger people. Although medicines for hyperglycemia, hypertension, and dyslipidemia can be used in the elderly, as in other patients with diabetes and CKD, they should be started at lower doses and carefully titrated while monitoring for responses and side effects (see CPR 3). The ADA, in collaboration with the American Geriatric Society, has published evidence-based guidelines for the management of geriatric patients with diabetes.[85]

Pregnancy

The effect of pregnancy on diabetes and CKD is examined in CPR 3. Diabetes during pregnancy is associated with an increased risk of adverse maternal and neonatal outcomes. The frequency of diabetes during pregnancy is increasing in developed countries primarily because of

increasing obesity among women of childbearing age. Early diagnosis of diabetes during pregnancy may be an important factor in improving outcomes in these mothers and their offspring. Nevertheless, much of the projected increase in diabetes prevalence during the childbearing years will occur in developing countries,[19] where resources for identifying and managing the diabetic pregnancy are limited.

Whereas the maternal complications of diabetes are well known, there is increasing evidence that the effects on the fetus are more extensive than previously thought. In addition to increased rates of macrosomia, congenital malformations, and perinatal mortality, the offspring of mothers with diabetes are prone to obesity and diabetes at a young age, leading to a vicious cycle of increasing frequencies of diabetes in successive generations.[86] In the Pima Indians, for example, the proportion of children exposed to diabetes in utero increased nearly 4-fold during the past 30 years.[76] The increased frequency of exposure to maternal diabetes was associated with a doubling of the number of cases of diabetes attributable to that exposure.[76] Moreover, the odds of having increased urinary albumin excretion was nearly 4 times as high in the offspring with diabetes who were exposed to diabetes in utero than in those exposed to a normal intrauterine environment.[87] These findings suggest that a diabetic pregnancy contributes not only to the increase in diabetes prevalence worldwide, but also to the increase in DKD among those who develop diabetes as a consequence of this exposure. Whether strict glycemic control during a diabetic pregnancy will reduce the frequency of diabetes and kidney disease in the offspring is unknown. Management of young obese women who desire to become pregnant should focus on preventing or at least delaying the onset of diabetes until after the childbearing years.

Vascular Target-Organ Complications Cause Much Morbidity and Mortality

Diabetes is associated with numerous vascular and nonvascular complications, and the vascular complications—which include CVD, peripheral vascular disease, stroke, retinopathy, neuropathy, and DKD—are responsible for most of the morbidity and mortality attributable to diabetes. The frequency of disability in people with diabetes offers an indirect means of assessing the morbidity associated with various vascular complications. Ischemic heart disease, stroke, and peripheral vascular disease increase the risk of mobility-related disability in older adults with diabetes in the United States by 2- to 3-fold relative to those without diabetes.[88,89] The Third National Health and Nutrition Examination Survey (NHANES III) found that in the United States, 25% of adults older than 60 years with diabetes cannot walk one quarter of a mile, climb 10 stairs, or do housework, and half of those in this age group have some difficulty performing these tasks.[88] Peripheral neuropathy often leads to greater limitations in performing the personal care activities of daily living, but has less impact on mobility.[89] Diabetes is the leading cause of visual deficits in developed countries among people younger than 60 years,[90,91] and visual impairment or blindness can lead to disability affecting both mobility and daily living activities.

One measure of population health and morbidity, the disability-adjusted life-year (DALY), provides an estimate of the length of life lost to premature death and the time spent in an unhealthy state. This measure is computed for the US population from data collected by the NHANES, the National Health Interview Survey, and several other nationally representative health surveys.[92] Diabetes is the 9th leading cause of DALYs among women and the 12th leading cause among men in the United States. African Americans, Hispanics, Asians, Pacific Islanders, and Native Americans have the highest DALYs related to diabetes, in keeping with their greater prevalence and earlier onset of diabetes. The impact of diabetes on DALYs and other health outcomes in these minority populations also may be affected by disparities in their health that result from their social, political, and economic disadvantage.[92]

In the United States, the death rate in people with diabetes is twice that of people without diabetes, and the major cause of the increased death rate among those with diabetes is CVD (vide infra).[93] Moreover, nearly all the excess mortality in both type 1[94] and type 2[95] diabetes is found in people with proteinuria. The WHO Multinational Study of Vascular Disease in Diabetes[96] reported that proteinuria was associated with significantly increased mortality from kid-

ney failure, CVD, and all other causes of death. Kidney and cardiovascular mortality ratios associated with proteinuria were similar for both types of diabetes, although people with type 1 diabetes were more likely to die of kidney failure than those with type 2 diabetes.[96]

DKD AND CKD

Terminology for the Kidney Disease of Diabetes

New terminology to describe kidney disease attributable to diabetes is introduced in the Diabetes and CKD guidelines. The purpose of this terminology is to clarify communication among patients, caregivers, and policy makers. For this purpose and for consistency with CKD classification, the term DKD is proposed for a presumptive diagnosis of kidney disease caused by diabetes. Although kidney biopsy is required to diagnose diabetic glomerulopathy definitively, careful screening of diabetic patients can, in most cases, identify persons most likely to have diabetic glomerulopathy without the need for kidney biopsy (see Guideline 1). The term "diabetic nephropathy" should be replaced by DKD. The term diabetic glomerulopathy should be reserved for biopsy-proven kidney disease caused by diabetes.

The goals of Guideline 1 are to facilitate identification of patients with kidney disease presumed to be caused by diabetes and distinguish them from those who should have further investigation for a different diagnosis, which may alter treatment plans. Most clinical studies of kidney disease in diabetes include patients with low glomerular filtration rate (GFR) and/or proteinuria, with a presumptive diagnosis of DKD. However, in practice, few patients have biopsy-proven DKD. Nevertheless, it would be useful to distinguish patients with CKD that is presumed to be caused by diabetes (DKD) from those with CKD from other causes on a clinical basis. DKD is based historically on the finding of proteinuria in a person with diabetes. With the development of more sensitive assays specific for albumin, DKD is now defined, in part, by increased urinary albumin excretion, which is divided arbitrarily into: (1) microalbuminuria, a modest elevation of albumin thought to be associated with stable kidney function, but a greater risk of macroalbuminuria and kidney failure; and (2) macroalbuminuria, a higher elevation of albumin associated with progressive decline in GFR, an increase in systemic blood pressure, and a high risk of kidney failure (Guideline 1, Table 6). However, these generalizations do not apply in all cases because people with normal urinary albumin excretion may have advanced DKD, whereas those with microalbuminuria may have either substantial or no pathological evidence of kidney damage. Moreover, because of the high prevalence of diabetes in the population, some individuals with diabetes may have other types of CKD. Nevertheless, in most cases, clinical measures may be used to diagnose DKD.

Screening and Diagnosis

Most professional societies concerned with diabetes and kidney disease now advocate screening for microalbuminuria in patients with diabetes, and the suggested screening plan, adapted from the ADA guideline, is shown in Guideline 1, Fig 6.[34,35] The Work Group supports these screening recommendations while recognizing the need for further studies to define the impact of microalbuminuria detection on hard clinical end points (see Guideline 1). Screening should begin after 5 years of type 1 diabetes and at the diagnosis of type 2 diabetes because of the inability to establish the onset of type 2 diabetes with certainty. Because urinary albumin excretion has an intraindividual coefficient of variation (CV) of approximately 40%,[36] multiple positive test results are required for classification. Definitions of DKD by albuminuria and stage are shown in Guideline 1, Table 6.

Evidence for the usefulness of estimated GFR (eGFR) alone as a screening test for CKD in patients with diabetes is less secure. Many patients with diabetes and CKD may have elevated or high-normal GFRs, particularly in the early years after diagnosis. Therefore, markers of kidney damage are required to detect early stages of CKD; eGFR alone can only detect CKD stage 3 or worse (Guideline 1, Table 6).

Diabetes May Coexist With Other Causes of CKD

Because diabetes is a common condition, coincidence with other nondiabetic CKD is relatively frequent. Accordingly, evaluation of a person

with atypical features should, in selected cases, include additional diagnostic testing, depending on the clinical presentation. Care should be used in determining the appropriate diagnostic tests because administration of radiographic contrast, with or without angiography, may pose greater risks in people with diabetes and CKD than in others (see Guideline 1).

Refractory hypertension and/or a significant reduction in kidney function after renin-angiotensin system (RAS) blockade should prompt consideration of renal artery stenosis because generalized vascular disease is common in diabetes. Patients with diabetes and CKD in whom refractory hypertension is suspected should be evaluated, preferably without radiocontrast, to assess whether arterial stenosis is present. Current noninvasive modalities to screen for arterial stenosis that do not include use of radiocontrast agents include magnetic resonance angiography and duplex Doppler ultrasonography. Captopril nuclear renal scans are not recommended because sensitivity of these scans is low in patients with decreased GFR or bilateral renal artery stenosis. In selected cases, imaging of the renal arteries may be undertaken with carbon dioxide or gadolinium angiography to avoid radiocontrast agents.

Hypertension associated with unilateral renal artery stenosis may be treated with medicine (preferably an ACE inhibitor or ARB) with the option of revascularization, usually by percutaneous angioplasty and stent placement. Treatment of bilateral renal artery stenosis, or unilateral renal artery stenosis in an individual with a single functioning kidney, may require revascularization to both control hypertension and prevent loss of kidney function. However, whether revascularization of unilateral or bilateral renal artery stenosis adds benefit to optimal medical management is uncertain. Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), a randomized trial sponsored by the National Institutes of Health (NIH), is addressing this key issue and should provide important direction for the management of renal artery stenosis in the future.

A number of systemic diseases that require specific therapy may occur in patients with diabetes. These diseases may present with a slow progressive decline in kidney function or a rapid decrease and may affect the kidney in various ways. Systemic diseases mostly likely to be confused with DKD are those that cause mild to moderate proteinuria and a slow progressive decrease in eGFR. Differentiation of these diseases requires clinical suspicion and appropriate diagnostic testing. It is the opinion of the Work Group that in the absence of another identifiable and treatable cause of kidney disease, patients with diabetes and CKD should be treated as if they have DKD (see Guideline 1).

DIABETES, CKD, AND CVD

Diabetes and CKD: A High-Stakes Combination for Cardiovascular Complications and Death

Diabetes is one of the most important risk factors for CVD. The risk imparted by diabetes has been viewed as a CVD equivalent because the likelihood of future events may approach that of people without diabetes who have already had a myocardial infarction.[37] Such observations have led to recommendations from both the ADA and the American Heart Association (AHA) for intensive cardiovascular risk factor management in people with diabetes (Table 1).[34,38] CKD also imparts an extremely high risk of CVD. The NKF and the AHA have recently issued guidelines and scientific statements recommending that people with CKD be considered in the highest risk category for CVD.[3,39] For those with both diabetes and CKD, the outlook is far worse than for either condition alone because the combination is one the most powerful predictors of major adverse cardiovascular events and death. The relationship between CKD severity and risk is continuous. People with diabetes and microalbuminuria have twice the CVD risk of those with normoalbuminuria,[40] and as albuminuria increases and GFR decreases, CVD risk increases progressively.[41-43] In an analysis of patients with type 2 diabetes from the UK Prospective Diabetes Study (UKPDS), rates of death and progression to macroalbuminuria were equal at the microalbuminuric stage.[41] However, at the macroalbuminuric stage, the death rate outpaced the rate of kidney disease progression (Fig 2). More people who reach CKD stage 3 will die, primarily of CVD, than progress to kidney failure, especially if they also have diabetes.[3,44]

Table 1. Goals for CVD Risk Factor Management in Patients With Diabetes[34,38]

Risk Factor	Goal of Therapy	Recommending Body
Cigarette smoking	Complete cessation	ADA
Blood pressure	<130/80 mm Hg	JNC 7 (NHLBI), ADA
LDL-C	<100 mg/dL <70 mg/dL is a therapeutic option	ATP III (NHLBI), ADA
Triglycerides, 200-499 mg/dL; HDL-C < 40 mg/dL	Non–HDL-C <130 mg/dL Increase HDL-C (no set goal)	ATP III (NHLBI), ADA
Prothrombotic state	Aspirin (75-162 mg/d)	ADA
Glucose	HbA_{1c} < 7%	ADA
Overweight and obesity (BMI ≥ 25 kg/m^2)	Lose 10% of body weight in 1 year	OEI (NHLBI)
Physical inactivity	Exercise prescription	ADA
Adverse nutrition	Limit intake of saturated fat, cholesterol, sodium; control carbohydrate and caloric intake; protein, 0.8 g/kg/d if CKD present	ADA, AHA, and NHLBI ATP III, OEI, and JNC 7

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NHLBI. National Heart, Lung, and Blood Institute; ATP III, National Cholesterol Education Program Adult Treatment Panel III; OEI, Obesity Education Initiative Expert Panel on Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.

The scope of this review of relationships among diabetes, CKD, and CVD is relevant primarily to people with CKD stages 1 to 4. Specific recommendations for CKD stage 5 are provided in the NKF-KDOQI™ Guidelines for CVD in Dialysis Patients.[10]

Intensive Risk Factor Management for Prevention of CVD

Risk factor management is the cornerstone of therapy for CVD in patients with diabetes. In the present NKF-KDOQI™ Guidelines on Diabetes and CKD, intensive management of hypertension, hyperglycemia, and dyslipidemia is emphasized. Although evidence was reviewed primarily for effects on kidney outcomes, the conclusions regarding therapeutic goals and choices of agents are strikingly similar to recommendations from the ADA and AHA for prevention and treatment of CVD (Table 1). These similarities likely reflect underlying pathological mechanisms common to both diabetic microvascular and macrovascular complications.

Recommendations for treatment of dyslipidemia in patients with diabetes and CKD are based on CVD risk reduction. The current state of evidence is insufficient to recommend treatment

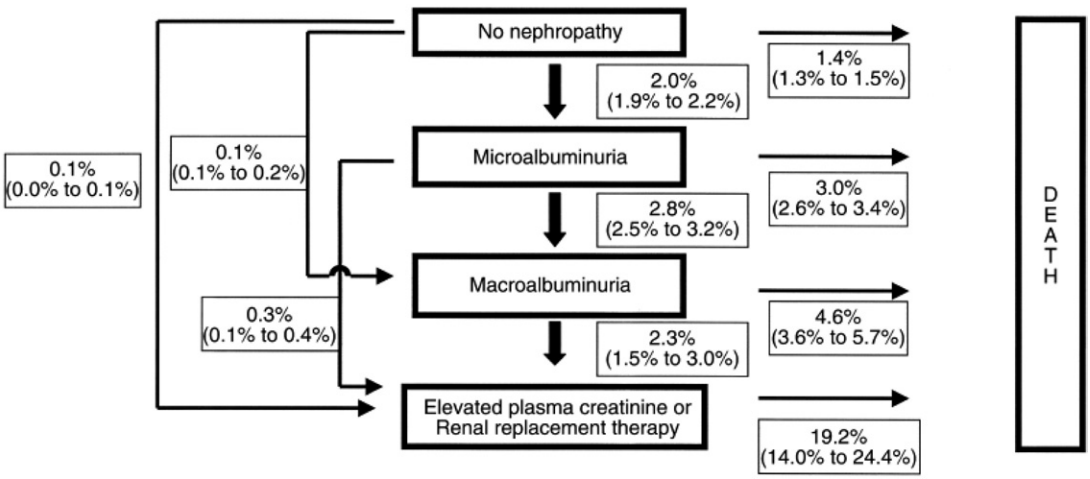

Figure 2. Annual transition rates with 95% confidence intervals through the stages of nephropathy and to death from any cause.
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Table 2. Diagnostic Testing for Coronary Heart Disease in Diabetes[34,38]

Indication	Test	Comments	Professional Society Recommendation
Typical or atypical chest discomfort Other symptoms that may suggest ischemia • Unexplained dyspnea or fatigue • Jaw, neck, arm, or shoulder discomfort • Abnormal ECG result	Exercise ECG Consider imaging modality for nondiagnostic ECG test result or with pharmacological stress test • Nuclear perfusion scan • Echocardiography Consider pharmacological stress testing for those unable to exercise • Dobutamine • Persantine Coronary angiography • Clinically significant ischemia on noninvasive testing • Diagnostic uncertainty on noninvasive testing	Obtain cardiology consultation for pharmacological stress testing, imaging, or coronary angiography No guidelines have specifically addressed the subset of patients with diabetes and CKD	ADA yes[34] AHA yes[38]
Consider screening for silent ischemia • Patient > 35 years and sedentary with plans to begin a vigorous exercise program • Carotid or lower-extremity atherosclerotic disease	Same approach as above	*Controversial* *Data on improved clinical outcomes is lacking*	ADA yes[34] AHA no[38]

Abbreviation: ECG, electrocardiogram.

of dyslipidemia for preservation of kidney function. The recommendation to treat with statins in diabetes and CKD stages 1 to 4 was based primarily on large prospective studies of patients with diabetes without markedly decreased kidney function and on a post hoc analysis from the Pravastatin Pooling Project (PPP).[97-99] In the PPP, people with diabetes and CKD had the greatest risk of CVD death, myocardial infarction, or revascularization procedures compared with those with either condition alone or neither condition.[99] They also had the largest absolute risk reduction with statin therapy (Guideline 4, Fig 19). Despite these impressive results, the evidence was considered moderate by the Work Group because it was based largely on this post hoc analysis. Prospective randomized trials are needed to confirm or refute these results and increase confidence in the data. This issue is especially germane considering results of the Deutsche Diabetes Dialyse Studie (4D), which showed no overall benefit on the primary outcome of major CVD events after initiating atorvastatin treatment in patients with type 2 diabetes receiving hemodialysis therapy (Fig 5).[100] Based on results of the 4D, initiation of statin therapy is not recommended for people with type 2 diabetes on hemodialysis therapy who do not have a specific cardiovascular indication for treatment. Ongoing studies evaluating lipid-lowering therapies for CVD risk reduction in people with diabetes and CKD are critically important to define optimal treatment strategies. Considering the very different conclusions of the PPP and 4D, the window of opportunity for statin therapy to reduce CVD risk in patients with diabetes and CKD remains to be defined.

Evaluation for Coronary Heart Disease

Cardiac ischemia is a predominant form of CVD leading to major complications and death in people with diabetes and CKD. A body of research on evaluation for coronary heart disease has lead to evidence-based CPGs from major professional societies. Coronary artery revascularization procedures are warranted in some patients. To identify appropriate candidates, further diagnostic testing should be performed based on specific clinical indications (Table 2). The recommendations from the ADA and AHA apply to people with diabetes in general.[34,38] No guidelines have been developed for the subset of patients with diabetes and CKD. In the opinion of the Work Group, these recommendations reasonably can be extrapolated to most patients who have both diabetes and CKD stages 1 to 4,

especially considering that their CVD risk is amplified over that of diabetes alone.

The specific clinical indications for noninvasive testing for coronary heart disease include typical or atypical chest discomfort or other symptoms of possible ischemia (eg, unexplained dyspnea or fatigue or jaw, neck, arm, or shoulder discomfort).[34,38] An electrocardiogram (ECG) should be included in the CVD risk assessment of all people with diabetes and repeated for any symptoms suggestive of cardiac ischemia. If an ECG result is abnormal, further diagnostic testing should be considered. Whether asymptomatic people with diabetes should undergo diagnostic testing for coronary heart disease is controversial. At present, data that such an approach improves prognosis beyond risk factor assessment and management are lacking. However, patients with diabetes and silent ischemia, especially if accompanied by cardiac autonomic neuropathy, have a poor prognosis. Therefore, the ADA recommends that screening for silent ischemia may be considered for certain high-risk characteristics: 35 years or older and sedentary with plans to begin a vigorous exercise program, and carotid or lower-extremity atherosclerotic disease.[34] The presence of traditional CVD risk factors did not predict silent ischemia in the cross-sectional Detection of Ischemia in Asymptomatic Diabetics (DIAD) study.[101] Therefore, the ADA no longer recommends screening of asymptomatic people with diabetes on the basis of risk factor clustering ($\geq$2 risk factors).[34] When the longitudinal component of DIAD is completed, data will be available on the relationship between abnormal cardiac nuclear perfusion imaging results and clinical events. In the meantime, the AHA does not endorse diagnostic testing for coronary heart disease in asymptomatic patients with diabetes because of the lack of evidence to support the benefits of testing on clinical outcomes.[38]

A noninvasive approach to diagnostic testing is preferred as the first step in evaluating coronary heart disease.[34,38] However, as discussed next, an initial invasive approach may be necessary in those with acute ischemic syndromes. According to the AHA and ADA, stress testing with exercise ECG should be the initial noninvasive strategy.[34,38] Cardiology consultation should be obtained if evaluation beyond exercise ECG testing is necessary. Those who have nondiagnostic exercise ECG test results may benefit from the addition of an imaging modality (nuclear perfusion scan or echocardiography) to the exercise procedure.[38] However, the NKF-KDOQI™ Guidelines for CVD in Dialysis Patients do not recommend exercise ECG testing because of poor exercise tolerance in general and a high prevalence of left ventricular hypertrophy in dialysis patients.[10] Many patients with advanced CKD are likely to be similarly affected. Therefore, for these patients or others who cannot exercise adequately, pharmacological stress testing (dobutamine or persantine) with imaging is indicated.[10,34,38] Coronary angiography may be performed if evidence for clinically significant ischemic heart disease is detected or for diagnostic uncertainty. As detailed in Guideline 1, people with diabetes and CKD are at high risk of acute kidney failure due to radiocontrast-induced nephropathy (RCN). Whenever possible, preventive strategies should be used to mitigate this risk (Guideline 1, Table 18). Nevertheless, considering the extremely high CVD risk in patients with diabetes and CKD, angiography should not be avoided if clinical indications for the invasive assessment and/or treatment of ischemic heart disease are present.

Medical Management of Coronary Heart Disease

RAS Inhibition. In people with diabetes and CKD, RAS inhibition is beneficial for the management of coronary heart disease and associated complications, as well as for treatment of hypertension. ACE inhibitors and ARBs reduce mortality after acute myocardial infarction,[102,103]and when used alone or in combination, these agents are equally beneficial for improving survival and reducing CVD events after myocardial infarction complicated by left ventricular dysfunction.[103] Patients with diabetes benefit at least as much as those without diabetes.[103] Similarly, in people with diabetes with chronic coronary heart disease and without left ventricular dysfunction, ACE inhibition reduces CVD death, myocardial infarction, and stroke.[104,105] Therefore, RAS inhibition is recommended for treatment of acute myocardial infarction and for chronic coronary heart disease in patients with diabetes.[34,38,102] Recent post hoc analyses indicate that ACE inhi-

bition is likely to be at least as efficacious at reducing CVD risk in people with and without diabetes and CKD, as it is for others with coronary heart disease.[106,107] As detailed in Guideline 3, data regarding effects of ACE inhibition for treatment of hypertension on DKD progression in type 2 diabetes are not as strong as in type 1 diabetes. However, given their proven cardiovascular benefits and the shared properties of ACE inhibitors and ARBs in inhibiting the RAS, either type of agent should be strongly considered for people with diabetes and CKD because they reduce the risk of both CVD events and progression of kidney disease.

β-Blockers. β-Blockers are another therapeutic class with unique benefits for CVD. Among people with and without diabetes who have had a myocardial infarction, the American College of Cardiology (ACC)/AHA guidelines recommend use of β-blockers because they reduce the risk of death, reinfarction, and recurrent ischemia.[102] β-Blockers also are recommended by the AHA for the long-term treatment of patients with diabetes and left ventricular dysfunction, but the basis of this recommendation is not as firm as for ACE inhibition.[38] Although β-blockers may mask symptoms of hypoglycemia or exacerbate glucose intolerance, these side effects usually are manageable. In addition, β-blockers vary in their effects on glycemia. For example, the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial demonstrated that in the presence of an ACE inhibitor or ARB, carvedilol stabilized glycemic control and improved insulin resistance to a greater extent than metoprolol in patients with type 2 diabetes and hypertension.[108] Therefore, considering their substantial cardiovascular benefits, the AHA recommends that β-blockers not be avoided in patients with diabetes for fear of side effects.[38] Based on their remarkably high CVD risk, the Work Group recommends that the ACC/AHA and AHA guidelines regarding use of β-blockers also be applied to the subset of patients with diabetes and CKD.

Aspirin. Platelet inhibition with aspirin is strongly encouraged for the prevention and management of ischemic heart disease in patients with diabetes.[34,38] In the opinion of the Work Group, people with diabetes who have CKD should receive aspirin as part of a multifaceted approach to treatment, as outlined in CPR 2.

Intensive Glycemic Control in Acute and Long-Term Care Settings. Glucose-insulin-potassium infusion (GIK) and intensive glycemic control are advocated for reducing mortality risk after acute myocardial infarction or with critical illness (especially after cardiac surgery) in people with and without diabetes.[109,110] Although the ACC/AHA and the ADA recommend normalization (or nearly so) of blood glucose levels within 24 to 48 hours after myocardial infarction, more recent evidence does not substantiate this approach.[34,102] Benefits of GIK therapy were described in relatively small studies or in meta-analyses in which the reduction in mortality risk had wide confidence intervals (CIs), indicating uncertainty in the conclusions.[111] Recently, the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE) and the Estudios Cardiologicas Latin America Study Group (ECLA) formally merged into a single trial, CREATE-ECLA, that randomly assigned more than 20,000 patients with acute myocardial infarction to receive GIK therapy or not.[112] In this large trial, no benefits on death or reinfarction rates were observed after 30 days in the group as a whole or in predefined subgroups, including those with diabetes. Similarly, survival benefits of intensive insulin therapy in patients with critical illness were not substantiated in patients admitted to a medical intensive care unit irrespective of diabetes status, CVD, or kidney disease diagnosis.[113] Although a subgroup analysis of patients who remained in the intensive care unit more than 3 days suggested a survival benefit, these patients could not be identified prospectively. Furthermore, in a larger follow-up study of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, DIGAMI 2, the survival benefit of intensive glycemic control after myocardial infarction in patients with diabetes was not confirmed.[114]

Hypoglycemia is a well-recognized complication of GIK and intensive insulin therapy in the acute care setting. As discussed in Guideline 2, patients with CKD are at particularly high risk of hypoglycemia and associated morbidities with intensive regimens for glycemic control. Therefore, the position of the Work Group is that

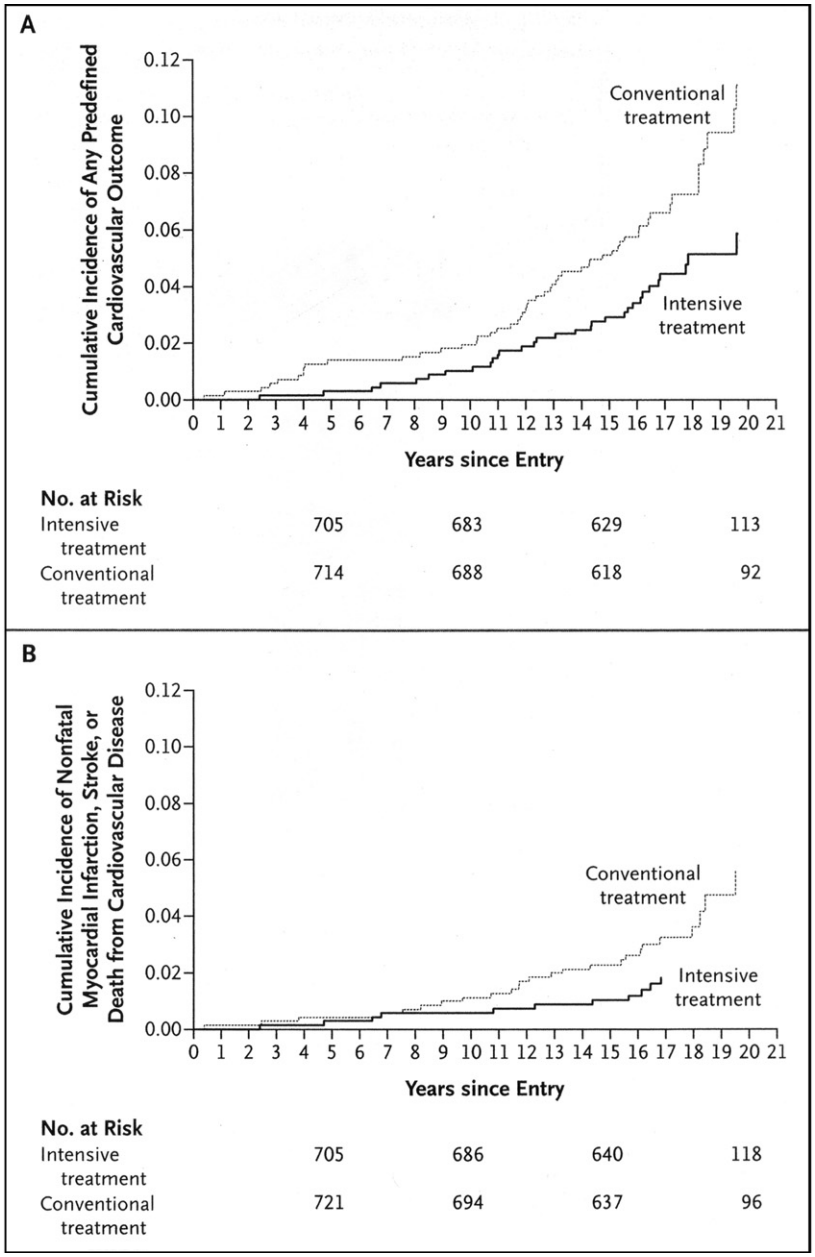

Figure 3. CVD outcomes by treatment assignment in DCCT/EDIC.
(A) Cumulative incidence of the first of any of the predefined CVD outcomes. (B) First occurrence of nonfatal myocardial infarction, stroke, or death from CVD. Compared with conventional treatment, intensive treatment reduced the risk of (A) any predefined CVD outcome by 42% (95% CI, 9% to 63%; $P = 0.02$) and (B) first occurrence of nonfatal myocardial infarction, stroke, or death from CVD by 57% (95% CI, 12% to 79%; $P = 0.02$). Reprinted with permission.[115]

current evidence does not support routine use of intensive glycemic control in acute care settings, including myocardial infarction, for patients with diabetes and CKD.

Whether long-term intensive control of glycemia reduces CVD risk has long been debated. Recent data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study indicate reduced rates of death, myocardial infarction, and stroke as many as 11 years after intensive management of type 1 diabetes has ceased (Fig 3).[115] Reduction in these major adverse CVD events was mediated in part by reduction in incidence of DKD. In the UKPDS trial, intensive glycemic control in general did not decrease the risk of myocardial infarction. However, in a subset of overweight patients who received metformin, the rate of myocardial infarction was reduced.[116] The Prospective Pioglitazone Clini-

cal Trial in Macrovascular Events (PROactive) suggested that pioglitazone may reduce all-cause mortality, myocardial infarction, and stroke in patients with type 2 diabetes.[117] In a post hoc analysis of people undergoing percutaneous coronary intervention (PCI) in the Prevention of Restenosis with Tranilast and Its Outcomes (PRESTO) trial, metformin use was associated with reduced risk of myocardial infarction and death in people with type 2 diabetes.[118] Therefore, emerging data indicate that intensive glycemic control reduces the risk of CVD events and death, but the benefits appear to be primarily in long-term, rather than acute, intensive glycemia management. In type 2 diabetes, insulin-sensitizing agents may be beneficial for reducing CVD event rates. Prospective controlled trials should be conducted to confirm these observations. Importantly, caution is advised with use of metformin in patients with CKD, as discussed in Guideline 2. Although studies regarding intensive glycemic control and CVD in people with diabetes and CKD are nonexistent, the available data provide further support for the goal of reaching an HbA_{1c} level less than 7% or as close to normal as possible without excessive episodes of hypoglycemia.

Reperfusion and Revascularization for Coronary Heart Disease

Acute Ischemic Syndromes. In virtually all aspects, management of acute myocardial infarction is similar for patients with and without diabetes.[38] Reperfusion therapies for acute ST-segment elevation myocardial infarction are founded on a strong evidence base and have become the standard of care because deaths and subsequent major adverse cardiovascular events are reduced.[102] Coronary artery reperfusion may be accomplished by using either PCI or fibrinolytic therapy. Where acute PCI is readily available with expert prompt intervention (within 90 minutes of first medical contact), this approach provides superior results compared with fibrinolysis.[102] However, when acute PCI is not available, fibrinolysis should be used as the initial treatment strategy (within 12 hours of symptom onset) if contraindications do not exist (eg, history of intracranial hemorrhage, closed head or facial trauma, or ischemic stroke within the past 3 months; uncontrolled hypertension; bleeding diathesis; or aortic dissection).[102] For acute coronary syndromes (unstable angina or non–ST-segment elevation myocardial infarction), medical management, including aspirin, heparin, glycoprotein IIb/IIIa inhibitors, β-blockers, and ACE inhibition, are indicated, usually along with coronary angiography and PCI.[119]

Evidence to guide treatment of patients with CKD is sparse. Despite their high risk of death and complications from myocardial infarction or acute coronary syndromes, those with CKD are less likely to receive reperfusion or other recommended therapies.[120-123] Suboptimal approaches to managing acute cardiac ischemic syndromes in the CKD population may result from fear of such complications as acute kidney failure or bleeding, among others. However, when recommended therapies have been given to people with CKD, risk of death was decreased in observational studies.[121-123] Data for the subset of patients with both diabetes and CKD do not exist. Clearly, this population should be included in future clinical trials of treatment for acute cardiac ischemic syndromes to define benefits and risks. In the meantime, the opinion of the Work Group is that the current standard of care for myocardial infarction and acute coronary syndromes, including PCI, fibrinolysis, antiplatelet strategies, and other recommended therapies, should be used in patients with diabetes and CKD unless specific contraindications exist.

Nonacute Ischemic Syndromes. Optimal methods of coronary artery revascularization are controversial. Advances in this field are evolving so rapidly that technologies used in trials are often considered outdated by the time the results are published. Data specifically concerning people with diabetes and CKD are lacking, but for those with either diabetes or CKD, coronary artery bypass surgery has been considered superior to percutaneous transluminal angioplasty for multiple-vessel disease.[38,124,125] The NKF-KDOQI™ Guidelines for CVD in Dialysis Patients came to a similar conclusion based on retrospective and observational data, while recommending research to include prospective controlled trials of newer stenting technologies.[97] Much of the benefit of coronary artery bypass surgery in diabetes or CKD stage 5 appears to be derived from use of the internal mammary artery.[38,97]

Studies of non–dialysis-dependent patients with CKD have been mostly observational cohort studies in which PCI did not consistently include stenting.[124,125] Since these studies were conducted, PCI approaches have progressed to almost routine use of coronary stents. In a recent subgroup analysis of a prospective clinical trial, the Arterial Revascularization Therapies Study, patients with a calculated creatinine clearance less than 60 mL/min/1.73 m^2 had similar survival free of death, myocardial infarction, or stroke whether they were randomly assigned to either coronary artery bypass surgery or PCI with multiple-vessel stenting.[126] Only repeated revascularization was less frequent with coronary artery bypass surgery.

Most recently, drug-eluting stents containing sirolimus or paclitaxel were shown to largely prevent restenosis, the most common reason for long-term failure of bare metal stents.[126-128] Although patients with diabetes have greater rates of restenosis and major adverse cardiac events after coronary artery stent placement, these complications were reduced markedly in the trials of drug-eluting stents.[127-129] Addition of abciximab to stenting procedures in patients with diabetes also has been advocated to reduce restenosis, but has not demonstrated a benefit on clinical outcomes.[130] Future studies using drug-eluting stents are likely to challenge the notion that coronary artery bypass surgery is the preferred method of revascularization in patients with diabetes.

Although controlled trials of revascularization procedures are nonexistent for people with both diabetes and CKD, the excess cardiovascular risk and deaths associated with diabetes after PCI were driven predominantly by the subset with proteinuria in a large observational cohort study.[131] This group of patients should be included in clinical trials of innovative revascularization technologies in the future. In the meantime, the opinion of the Work Group is that either coronary artery bypass grafting or stenting (single or multiple vessel) appear to be acceptable methods of revascularization in people with diabetes and CKD. Decisions about revascularization procedures should be based on individual patient characteristics, local expertise, and best judgment of the treating physicians.

RISK FACTOR MANAGEMENT IN DIABETES AND CKD

The Competing Risks Paradigm: CKD and CVD

People with diabetes and CKD are at high risk to both lose kidney function and experience major adverse cardiovascular events (Fig 4). Treatment of risk factors reduces the likelihood of these outcomes. Fortunately, treatment strategies for reducing kidney and cardiovascular risks are largely shared. The present CPGs and CPRs for diabetes and CKD are consistent with those already established for the treatment of diabetes and CVD by the ADA and AHA.[34,38] Goals of the management approaches recommended here are intended to mitigate the devastating consequences of the spectrum of vascular complications, including kidney, heart, and others.

New to the NKF-KDOQI™ Guidelines: Management of Hyperglycemia and General Diabetes Care in CKD

This is the first guideline in the NKF-KDOQI™ series to address management of hyperglycemia and general diabetes care in people with CKD. The purpose of Guideline 2 is to review the extensive literature regarding glycemic control and DKD, with an emphasis on benefits, as well as risks, of intensive treatment of blood glucose, and to provide recommendations for the care of people with diabetes complicated by kidney disease.

Hyperglycemia, the defining feature of diabetes, is a fundamental cause of vascular target-

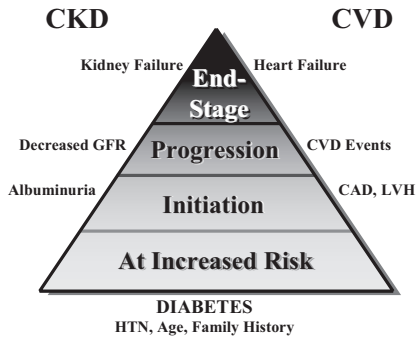

Figure 4. Diabetes amplifies the CKD and CVD paradigm.
Abbreviations: CAD, coronary artery disease; LVH, left ventricular hypertrophy; HTN, hypertension.

organ complications, including kidney disease. Intensive treatment of hyperglycemia prevents DKD and may slow progression of established kidney disease. An overall HbA_{1c} goal of less than 7.0% for people with diabetes is supported by substantial data from large prospective randomized studies of both type 1 and type 2 diabetes. Much of this support stems from benefits for some of the other major complications of diabetes, especially retinopathy. With respect to kidney outcomes, data are very strong for the development of microalbuminuria (Guideline 2, Fig 8 to Fig 11).[116,132-137] The numbers of patients progressing to more advanced outcomes, such as macroalbuminuria and low GFR, are decreased significantly with improved glycemic control, but much of this decrease is related to the smaller number developing microalbuminuria to begin with (Guideline 2, Fig 10 to Fig 12).[116,133-141] Nonetheless, even for those with more advanced disease, evidence supports reaching the recommended HbA_{1c} target.

The ADA recommends an HbA_{1c} level less than 7.0% or as close to normal as possible without excessive hypoglycemia.[34] The major risk of attaining HbA_{1c} levels less than 7.0% is the increasing development of hypoglycemia with lower glucose concentrations. For people with decreased kidney function (CKD stages 3 to 5), hypoglycemia is a major concern because of impaired clearance of insulin and some of the oral agents used to treat diabetes, as well as diminished kidney gluconeogenesis. The amount of gluconeogenesis is decreased with reduced kidney mass.[142] Reduction in gluconeogenesis may reduce the ability of a patient who is becoming hypoglycemic as the result of excessive insulin/oral agent dosage or lack of food intake to defend against hypoglycemia. Although this effect is difficult to quantify, the kidney degrades about a third of the insulin, leading to a prolonged half-life when kidney function is reduced. Patients with type 1 diabetes receiving insulin who had significant serum creatinine level elevations (mean, 2.2 mg/dL) were reported to have a 5-fold increase in the frequency of severe hypoglycemia.[143,144] Therefore, it is imperative that patients being treated intensively monitor their glucose levels closely and reduce doses of medicines (insulin and oral agents) as needed to avoid hypoglycemia (Guideline 2, Table 22 and Table 23).

A person with advanced CKD may no longer need to achieve good glycemic control to prevent deterioration in kidney function. However, intensive treatment of hyperglycemia may still prevent or slow the progression of retinopathy, neuropathy, and macrovascular disease. Survival improves with better glycemic control in patients on peritoneal dialysis[145] and hemodialysis therapy.[146] In the latter study, after adjustment for age and sex, HbA_{1c} level was a significant predictor of survival (hazard ratio [HR], 1.13 per 1.0% increment of HbA_{1c}; 95% CI, 1.03 to 1.25, $P = 0.01$).

Data for monitoring glycemic control in people with diabetes and CKD essentially are absent. Therefore, in the opinion of the Work Group, assessment of glycemic control in diabetes and CKD should follow the general standards recommended by the ADA.[34] In people receiving multiple insulin injections, self-monitoring of blood glucose (SMBG) is recommended 3 or more times daily (before meals and at bedtime). In those receiving less frequent insulin injections, oral agents, or medical nutrition therapy alone, SMBG is useful in achieving glycemic goals. Postprandial SMBG testing also may be helpful, particularly in patients with gastroparesis, to achieve postprandial glucose goals. The optimal frequency of SMBG has not been established in patients with type 2 diabetes treated by oral agents, but the ADA recommends testing sufficiently often to reach glycemic goals (Guideline 2, Table 25). In addition, HbA_{1c} level should be determined at least twice per year in stable patients who are achieving glycemic goals and more often, approximately every 3 months, in patients whose therapy has changed or who are not reaching goals.

The Work Group emphasizes prevention and treatment of all diabetic complications in people with diabetes and CKD. Assessment and management of CVD has been addressed in the preceding section. Management of retinopathy and foot care also is essential for optimal outcomes. In the absence of specific data in the diabetes and CKD population, the Work Group recommends following the standards set by the ADA.[34] An ophthalmologist or optometrist who is experienced in the diagnosis and management of diabetic retinop-

athy should perform a comprehensive dilated-eye examination annually in all people with diabetes (Guideline 2, Table 26). Patients should be educated about the importance of foot surveillance and ulcer prevention with an emphasis on self-management, as discussed in CPR 4. The feet should be examined visually at each health care visit. A comprehensive foot examination, including visual inspection, Semmes-Weinstein monofilament testing, and use of a 128-Hz tuning fork for testing of vibratory sensation, should be performed annually. Because the risk of ulcers and amputations is increased in those with diabetes and CKD, referral to foot-care specialists for annual examinations and preventive care is encouraged.

Updates to the NKF-KDOQI™ Guidelines: Management of Hypertension, Dyslipidemia, and Nutrition

Previous guidelines from the NKF-KDOQI™ series have addressed hypertension, dyslipidemia, and nutrition in CKD.[5,6,9] The purpose of Guidelines 3, 4, and 5 is to focus on care of people with both diabetes and CKD, summarize rapidly emerging literature in these fields, and translate the results into updated recommendations for clinicians.

Hypertension

The natural history of DKD is characterized by hypertension, increasing albuminuria, and decreasing GFR. In both types of diabetes, the natural history is similar, with the exception that onset of hypertension and vascular disease is earlier in the course of type 2 diabetes.[147,148] Hypertension is one of the most common comorbidities in DKD (Guideline 3, Table 29). Because the studies cited in Guideline 3, Table 29, were published before the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), hypertension generally was defined as blood pressure greater than 140/90 mm Hg.[149-153] The JNC 7 defines hypertension in those with diabetes or CKD as blood pressure greater than 130/80 mm Hg.[154] Thus, the prevalence estimates in Guideline 3, Table 29, likely represent lower range values based on current criteria for hypertension in diabetes or CKD. A large number of epidemiological studies and controlled trials have defined hypertension as a risk factor for progression of DKD, and antihypertensive treatment reduces this risk (Guideline 3, Fig 18).[5] Studies of people with type 1 or type 2 diabetes and CKD stages 1 to 4 were included in the evidence review. Based on the available evidence, the Work Group recommends a blood pressure target of less than 130/80 mm Hg with ACE inhibitors and ARBs as preferred agents, usually in combination with a diuretic, for the treatment of hypertension in diabetes and CKD (Guideline 3, Table 27). Because diabetes is highly prevalent, individuals with other types of CKD may have diabetes. The approach to antihypertensive treatment in DKD does not conflict with that recommended for CKD in general.[34,154]

The emphasis of the evidence review was on the effects of treating hypertension on kidney outcomes, although control of blood pressure also is essential for reducing CVD risk. In people with either type 1 or type 2 diabetes and microalbuminuria, prevention of DKD progression by treatment with ACE inhibitors or ARBs is supported by moderate evidence.[155-166] For the purpose of the current guidelines, this evidence was considered moderate rather than strong because of insufficient data for outcomes other than albuminuria (ie, decrease in GFR, CKD stage 5, or mortality). The Work Group seriously deliberated about whether progression of albuminuria is an acceptable surrogate outcome for progression of DKD. As detailed in CPR 1, they eventually concluded that further study of this issue is necessary to resolve the controversy. For those with hypertension and macroalbuminuria, evidence strongly supports use of ACE inhibitors in type 1 diabetes and ARBs in type 2 diabetes to prevent progression of DKD (Guideline 3, Fig 13 to Fig 15).[167-169] In the view of the Work Group, the existing evidence has been influenced heavily by the design of the studies, which used ACE inhibitors in type 1 diabetes and ARBs in type 2 diabetes. Based on biological plausibility, similar modes of action, and smaller studies, the Work Group considers these 2 classes of agents essentially interchangeable and did not distinguish between them in the guideline statement.

To achieve target blood pressure, multiple antihypertensive agents usually are required (Guideline 3, Table 32). Therefore, most people with diabetes and CKD require medicines in

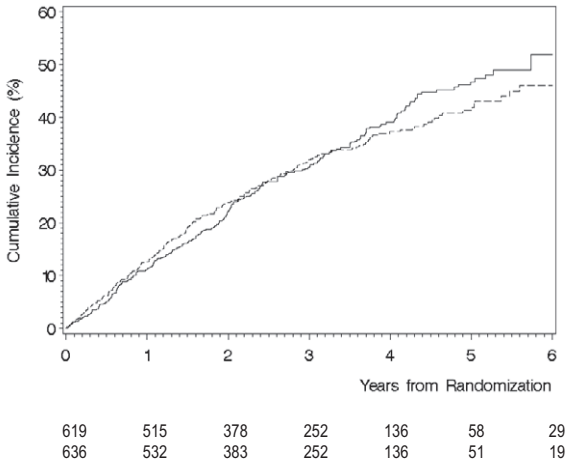

Figure 5. Cumulative incidence estimate of the combined primary end point for placebo and atorvastatin treatment groups in the 4D.
Solid line: placebo; dotted line: atorvastatin treatment. Reprinted with permission.[100]

addition to RAS inhibitors for optimal control of hypertension. Diuretics are especially useful in this population. β-Blockers and calcium channel blockers also are effective therapies. Based on a series of small studies and the Irbesartan Diabetic Nephropathy Trial (IDNT), calcium channel blockers of the dihydropyridine class may worsen proteinuria and failed to improve clinical outcomes when used as primary antihypertensive therapy in DKD.[170,171] Conversely, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) subgroup with type 2 diabetes and CKD (defined as GFR $<$ 60 mL/min/1.73 m^2), amlodipine was comparable to lisinopril or chlorthalidone for GFR decrease or onset of kidney failure when each agent was given separately.[172] However, the lack of albuminuria/proteinuria data and relatively limited sample size in this substudy preclude firm conclusions. Based on numerous studies of proteinuric kidney diseases (DKD and non-DKD),[154] it was the opinion of the Work Group that dihydropyridine calcium channel blockers should not be used in the absence of concurrent RAS inhibition for DKD characterized by microalbuminuria or macroalbuminuria. However, dihydropyridine calcium channel blockers appear to be safe in such patients if they also use an ACE inhibitor or an ARB.[173]

Dyslipidemia

Dyslipidemia is common in people with diabetes and CKD. Modifying CVD risk by using lipid-lowering agents is of great importance, as discussed (in Diabetes, CKD, and CVD). The NKF-KDOQI™ CPGs for Managing Dyslipidemia in CKD Patients were published recently,[6] and the CPGs for CVD in Dialysis Patients added new information about the management of dyslipidemia in dialysis patients.[10] Guideline 4 focuses specifically on patients with diabetes and CKD stages 1 to 5. In general, the guidelines for use of lipid-lowering agents in CKD stages 1 to 4 due to diabetes and other causes do not conflict,[174-177] although there is no direct or indirect evidence for treating patients with CKD stage 4. The Work Group recommends that people with diabetes and CKD stages 1 to 4 be treated according to current guidelines for groups at high CVD risk.[6,175] Therefore, the target low-density lipoprotein cholesterol (LDL-C) level should be less than 100 mg/dL, with less than 70 mg/dL as a therapeutic option (Guideline 4, Table 36). Lipid-lowering agents in the statin class are the preferred drug therapies. However, treatment with a statin should not be initiated in patients with type 2 diabetes on maintenance hemodialysis therapy who do not have a specific cardiovascular indication for treatment because of negative results for CVD outcomes reported recently in the 4D (Fig 5).[100] This finding represents an update from previous guidelines because 4D was the first prospective randomized trial in hemodialysis patients with diabetes.[6,10,100] Indirect evidence on the beneficial effects of pravastatin in diabetes and CKD stages 1 to 3 from recent post hoc analyses of large multicenter trials also was added.[99] Recommendations for treatment of dyslipidemia in diabetes and CKD are based on

CVD risk reduction because the current state of evidence is insufficient to support treatment for preservation of kidney function. In the opinion of the Work Group, studies to determine effects of statins or other lipid-lowering agents on progression of kidney disease are critically important to the goal of optimizing care for people with diabetes and CKD.

Nutrition

Management of diabetes and CKD should include nutritional intervention. Guideline 5 addresses dietary strategies in people with diabetes and CKD stages 1 to 4. Dietary recommendations for CKD stage 5 are provided in the KDOQI™ CPGs for Nutrition in Chronic Renal Failure.[9] Nutritional management for people with diabetes has focused traditionally on blood glucose control. However, dietary modifications may reduce the progression of CKD, as well. In particular, dietary protein intake at all stages of CKD appears to have an important impact in the population with diabetes. When dietary protein is limited, adequate caloric intake must be maintained by increasing calories from carbohydrates and/or fats. Competing needs for nutritional management of hyperglycemia, hypertension, and dyslipidemia can make determination of appropriate protein intake challenging.

A dietary protein intake of 0.8 g/kg body weight per day (about 10% of total calories), the recommended daily allowance (RDA) for this macronutrient, is a level that has been achieved in studies of nutritional intervention for diabetes and CKD. Nutrition surveys indicate that most Americans eat in excess of the RDA level.[178] In 2 meta-analyses, low-protein diets reduced risks of progression of albuminuria/proteinuria and loss of GFR, with more pronounced benefits in DKD than non-DKD (Guideline 5, Fig 21).[179,180] More recently, even a modest limitation of dietary protein (0.89 versus 1.02 g/kg body weight per day) reduced the risk of CKD stage 5 or death (relative risk [RR], 0.23; 95% CI, 0.07 to 0.72; $P = 0.04$) in people with type 1 diabetes and stage 2 CKD (inferred based on levels of albuminuria and GFR; Guideline 5, Fig 22).[181] Benefits of limiting dietary protein intake are more evident in type 1 than type 2 diabetes, but fewer studies have been done in the latter population. Based on the available evidence, the Work Group concluded that limiting dietary protein to the RDA level of 0.8 g/kg body weight per day should stabilize or reduce albuminuria, slow the decrease in GFR, and may prevent CKD stage 5.[179-186] The current recommendation for dietary protein in diabetes and CKD stages 1 to 4 represents an update to the diet recommended by the NKF-KDOQI™ CPGs for Hypertension and Antihypertensive Agents in CKD (Guideline 5, Table 43).[5]

At the other end of the spectrum, high-protein diets are a special concern in patients with diabetes because they may increase albuminuria and accelerate loss of kidney function. Based on both studies of humans and experimental models, higher protein intake appears to produce more profound glomerular hyperfiltration and kidney damage in diabetes.[153,187-196] Emerging epidemiological evidence indicates that higher protein intake (≥20% versus 10% of total daily calories) is associated with loss of kidney function in women with mildly decreased GFR (CKD stages 1 to 2 inferred) and the development of microalbuminuria in people with diabetes and hypertension.[197,198] Therefore, in the opinion of the Work Group, people with diabetes and CKD should avoid high-protein diets (≥20% of total daily calories). Some common fad diets that recommend high protein are Atkins®, Protein Power, the Zone, South Beach®, and Sugar Busters®.

In the Dietary Approaches to Stop Hypertension (DASH) and DASH-Sodium diets, a relatively high protein intake (1.4 g/kg body weight per day, or about 18% of total calories) is recommended.[199] Sources of protein in the DASH diets emphasize vegetables, low-fat or nonfat dairy products, whole grains, nuts, legumes, fish, and poultry. Red meat is eaten in only small amounts. In recent studies of people with prehypertension or untreated stage 1 hypertension, higher protein intake from either soy or predominantly vegetable sources decreased blood pressure in short-term (6 to 12 weeks) feeding studies.[200,201] Along with the DASH trials, these data suggest that predominantly nonmeat protein may have a beneficial effect on blood pressure. Small studies suggest that vegetable or soy protein sources may be kidney sparing compared with red meat sources in diabetes and CKD.[182,202] Furthermore, the risk of losing kidney function in women

with mildly decreased GFR in the Nurses Health Study was related primarily to animal meat intake.[197,198] Therefore, a DASH-type diet that emphasizes sources of protein other than red meat may be a reasonable alternative to a lower total protein intake in people with hypertension, diabetes, and CKD stages 1 to 2.

New to NKF-KDOQI™ CPRs:

How Should Albuminuria Be Managed in Normotensive Patients With Diabetes?

Increased levels of urinary albumin excretion predict increased risk of kidney and CVD outcomes in diabetes, as reviewed extensively in Guideline 1 and the preceding section, Diabetes, CKD, and CVD. Albuminuria is believed to reflect endothelial injury that extends from the glomerulus to the arterial circulation at large, thus linking this marker to both kidney disease and CVD. The concept that treatments aimed at decreasing albuminuria may improve clinical outcomes has been a subject of great interest and debate.

CPR 1 addresses the evidence for treatment of normotensive patients who have diabetes and elevated albuminuria with RAS inhibitors. Relatively few studies of these antihypertensive agents have recruited normotensive patients. In a study of type 1 diabetes with macroalbuminuria, ACE inhibitors decreased albuminuria and reduced the risk of clinical outcomes (doubling of serum creatinine level, CKD stage 5, or death) regardless of the presence or absence of hypertension.[168] A quarter of the participants in this study were normotensive. There was no significant difference in the treatment effect between normotensive and hypertensive individuals. In type 2 diabetes with macroalbuminuria, ARB treatment also reduced the risk of clinical outcomes in 2 separate studies.[167,169] However, these studies had very few participants with normal blood pressure. Treatment of microalbuminuria by ACE inhibition in normotensive people with type 1 diabetes reduces the level of albuminuria and prevent progression to macroalbuminuria in a meta-analysis.[203] A small study of normotensive patients with type 1 diabetes showed that ACE inhibition prevented new-onset microalbuminuria.[204] Several studies have evaluated ACE inhibition in normotensive people with type 2 diabetes and microalbuminuria.[104,205-207] All studies demonstrated decreased progression to macroalbuminuria and/or reduced levels of albuminuria.

In the opinion of the Work Group, change in level of albuminuria or transition between categories (normoalbuminuria, microalbuminuria, or macroalbuminuria) in normotensive people with diabetes is relatively weak evidence for change in status or prognosis of kidney disease. The rationale for this opinion is as follows. First, level of albuminuria or crossing an albumin-creatinine ratio (ACR) threshold is not a clinical end point. Second, RAS inhibitors might mask the progression of DKD marked by albuminuria. In type 1 diabetes, withdrawal of ACE inhibition caused a rapid increase in albuminuria,[208] and in type 2 diabetes, discontinuation of irbesartan in the Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria (IRMA-2) Study prompted a rapid return to pretreatment levels of albuminuria in patients receiving the lower dose of irbesartan and a partial return to pretreatment levels in those receiving the higher dose of irbesartan.[209] Third, few normotensive patients with diabetes and microalbuminuria or macroalbuminuria have been enrolled in clinical trials of treatments for kidney disease. The demonstrated benefits of RAS inhibitors for reducing and stabilizing albuminuria were noted; however, in the absence of studies with clinical end points, the Work Group found this evidence insufficient to justify a higher evidence rating.

Despite these concerns, the consensus of the Work Group was that the benefit of ACE inhibitors and ARBs for reducing albuminuria and delaying kidney disease progression are likely to be similar among most people with diabetes and microalbuminuria or macroalbuminuria regardless of their blood pressure level. Therefore, CPR 1 recommends treatment with RAS inhibition for normotensive patients with diabetes and microalbuminuria or macroalbuminuria. The Work Group encourages further research to determine effects of ACE inhibitors and ARBs on albuminuria and clinical outcomes in normotensive people with DKD.

Is Albuminuria an Acceptable Surrogate Marker for Progression of DKD?

CPR 1 addresses whether changes in albuminuria are sufficient to predict clinical outcomes in

DKD. Studies testing the hypothesis that albuminuria reduction predicts improved prognosis in DKD have been performed only as secondary analyses of studies of ARB treatment in people with type 2 diabetes and macroalbuminuria.[210-212] In these studies, level of albuminuria reduction was a marker of decreased risk of adverse outcomes. Observational analyses from the Reduction of Endpoints in Non–insulin-dependent diabetes mellitus (NIDDM) with the Angiotensin II Antagonist Losartan (RENAAL) trial found that the magnitude of albuminuria reduction predicted reduced risk for both CVD events and kidney end points (CPR 1, Fig 23 and Fig 24).[211,212] Similarly, an analysis from the IDNT found that degree of proteinuria reduction corresponded to decreased kidney end points (CPR 1, Fig 25).[210] These findings raise the hypothesis that albuminuria reduction per se has beneficial effects. However, an alternative possibility is that albuminuria reduction is a marker for patients with less severe kidney and vascular disease. A strategy of targeting treatment of albuminuria, in addition to blood pressure and other risk factors, has not been tested prospectively in patients with diabetes. Furthermore, to date, only these secondary analyses from the RENAAL trial and IDNT have directly correlated albuminuria/proteinuria reduction with clinical benefit.

In the opinion of the Work Group, there currently is insufficient evidence to assume that lowering albuminuria levels will necessarily lead to improvements in such clinical outcomes as progression to CKD stage 5, CVD events, or death. Conversely, the failure to reduce albuminuria does not preclude a beneficial clinical effect on DKD from a potential intervention. Therefore, to be considered efficacious, potential treatments for DKD must demonstrate benefits not only on albuminuria reduction, but also on such clinical end points as CKD stage 5, CVD events, or death.[213] Nevertheless, the emerging data generate a strong hypothesis that should be tested in prospective controlled studies—namely, do treatments (ACE inhibitors, ARBs, or others) that decrease albuminuria result in improved CKD and CVD outcomes in people with diabetes?

The Value of Multifaceted Intervention

Although these and other guidelines present recommendations for management of risk factors separately, in reality, multiple risk factors are managed concurrently in patients with diabetes and CKD. In addition, considering the burgeoning epidemic of obesity and its role in producing diabetes and, possibly, kidney disease, the importance of weight control should be considered in the care of patients with diabetes and CKD. CPR 2 was developed to address these issues and encourage further investigation.

In the Steno Study, a multifaceted approach aimed at optimal management for a group of risk factors was evaluated in patients with type 2 diabetes and microalbuminuria.[45,46] The intervention had multiple targets, including behavioral modification and pharmacological therapies for hyperglycemia, hypertension (emphasizing RAS inhibitors), dyslipidemia, CVD prevention with aspirin, and a vitamin/mineral supplement (CPR 2, Table 1). This intensive intervention was compared with usual care. A mean decrease in albuminuria (albumin decreased 20 mg/24 h) was observed in the intensive-intervention group, whereas a mean increase occurred in patients in the usual-care group (albumin increased 30 mg/24 h). Albuminuria progression and the composite outcome of CVD events or death were decreased in the group treated intensively (CPR 2, Fig 26). However, which facets of the intervention are associated with reduced risk is uncertain. Furthermore, because the intensive intervention increased use of RAS inhibitors, the contribution of other treatments is unclear. Despite these limitations, the Work Group recognizes the importance of addressing multiple risk factors in an integrated fashion. The incremental effects of a multifaceted approach appear to add up to substantial clinical benefits.

Obesity now is recognized as a risk factor for diabetes, hypertension, CVD, and possibly CKD. Recent estimates from NHANES report that 31% of the US population is obese (BMI $>$ 30 kg/m^2).[214] A growing body of evidence indicates that obesity is linked to CKD.[215-221] Whether this link is independent of diabetes, hypertension, or perhaps other risk factors is not yet clear. Nevertheless, obesity is associated with the development of proteinuria and loss of kidney function. Metabolic syndrome risk factors, as well as adipose-derived factors, may lead to kidney damage. Maintaining a normal weight (BMI, 18.5 to 24.9 kg/m^2) improves risk factors and may de-

crease the development or progression of CKD. The Work Group recommends that weight loss be achieved by a balanced reduction in caloric intake, rather than by diets that derive excess calories (>20%) from animal protein (Guideline 2). Regular physical exercise also is encouraged to assist in achieving and maintaining a normal weight.

Lifestyle and Behavioral Management

Strategies for behavioral change and self-management of risk factors are addressed in CPR 4. Because of the paucity of data in the diabetes and CKD population, these recommendations were extrapolated from data in other groups and thus are included in the CPR section. A proposed approach to a diabetes and CKD self-management program is provided in CPR 4, Table 56.

At the core of the diabetes epidemic and its consequent complications is a fundamental shift in lifestyle. In a relatively short time span, vigorous physical activity and limited calories have been replaced by sedentary behavior and a seemingly endless array of calorie-dense foods that are cheap and easily obtained. Thus, major challenges of the present century are the dual problems of overfeeding and obesity. Optimal management of risk factors, including hypertension, diabetes, and dyslipidemia, is emphasized in these guidelines. However, this emphasis is directed too often toward drug therapies without enough attention to key lifestyle issues. In the view of the Work Group, addressing lifestyle through behavioral change is critically important for success in reducing the devastating impact of diabetes and CKD. The Work Group considers investigation in this area of particular importance to successfully translate advances in knowledge to improvements in quality of life and health.

GUIDELINE 1: SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

CKD in patients with diabetes may or may not represent DKD. In the absence of an established diagnosis, the evaluation of patients with diabetes and kidney disease should include investigation into the underlying cause(s).

1.1 Patients with diabetes should be screened annually for DKD. Initial screening should commence:
- **5 years after the diagnosis of type 1 diabetes; (A) or**
- **From diagnosis of type 2 diabetes. (B)**

1.1.1 Screening should include:
- **Measurements of urinary ACR in a spot urine sample; (B)**
- **Measurement of serum creatinine and estimation of GFR. (B)**

1.2 An elevated ACR should be confirmed in the absence of urinary tract infection with 2 additional first-void specimens collected during the next 3 to 6 months. (B)
- **Microalbuminuria is defined as an ACR between 30-300 mg/g.**
- **Macroalbuminuria is defined as an ACR > 300 mg/g.**
- **2 of 3 samples should fall within the microalbuminuric or macroalbuminuric range to confirm classification.**

1.3 In most patients with diabetes, CKD should be attributable to diabetes if:
- **Macroalbuminuria is present; (B) or**
- **Microalbuminuria is present**
  - **in the presence of diabetic retinopathy, (B)**
  - **in type 1 diabetes of at least 10 years' duration. (A)**

1.4 Other cause(s) of CKD should be considered in the presence of any of the following circumstances: (B)
- **Absence of diabetic retinopathy;**
- **Low or rapidly decreasing GFR;**
- **Rapidly increasing proteinuria or nephrotic syndrome;**
- **Refractory hypertension;**
- **Presence of active urinary sediment;**
- **Signs or symptoms of other systemic disease; or**
- **>30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.**

BACKGROUND

DKD, traditionally termed "diabetic nephropathy," is a clinical diagnosis that historically has been based on the finding of proteinuria in a person with diabetes. This definition is independent of such markers of CKD as pathological change or a decreased GFR, and it initially was confined to those now considered to have macroalbuminuria. The development of more sensitive assays specific for albumin has since led to the detection of smaller increases, now termed microalbuminuria or "incipient nephropathy." The lower limit of microalbuminuria is set somewhat arbitrarily at an albumin excretion rate (AER) of 20 μg/min, which is equivalent to 30 mg/24 h or an ACR of 30 mg/g (Table 3).[222] These definitions have had some clinical utility in that individuals with macroalbuminuria historically had a progressive decrease in GFR associated with an increase in systemic blood pressure, whereas those with microalbuminuria were considered to

Table 3. Definitions of Abnormalities in Albumin Excretion

Category	Spot Collection (mg/g creatinine)	24-Hour Collection (mg/24 h)	Timed Collection (μg/min)
Normoalbuminuria	<30	<30	<20
Microalbuminuria	30-300	30-300	20-200
Macroalbuminuria	>300	>300	>200

Because of variability in urinary albumin excretion, at least 2 specimens, preferably first morning void, collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed 1 of these diagnostic thresholds. Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, pregnancy, marked hypertension, urinary tract infection, and hematuria may increase urinary albumin over baseline values.

have stable kidney function, yet were at high risk of subsequent development of macroalbuminuria and kidney failure.[223]

More recent information has led to a reevaluation of some of these concepts.[224-226] The finding that a substantial proportion of patients with type 1 and type 2 diabetes and microalbuminuria spontaneously regress to normoalbuminuria calls into question the inevitability of kidney disease progression (Tables 4 and 5).[224,226,227] The substantial variability in the severity of underlying pathology in type 1 diabetes[228,229] and the heterogeneous nature of pathology in type 2 diabetes[230] suggests that microalbuminuria may or may not reflect underlying DKD. Given the strongly positive relationship between the duration of diabetes and DKD, particularly in type 1 diabetes,[231] the presence of elevated albuminuria in diabetes of short duration should raise concerns about non-DKD. Furthermore, although antihypertensive therapy reduces albuminuria, there is little evidence that it affects the underlying pathology, and short-term withdrawal of antihypertensive medicines can result in increases in albuminuria to pretreatment levels.[208] Finally, the situation is complicated by the increasing use of microalbuminuria as a marker/predictor of CVD in people with and without diabetes. All these factors imply that the underlying mechanisms of albuminuria are multiple, not entirely pathology dependent, and do not fit neatly into definitions of CKD. Thus, any definition of DKD has to take all these factors into account.

Most professional societies concerned with diabetes and kidney disease now advocate screening for microalbuminuria in patients with diabetes.[34,35] These recommendations have been made although there are no conclusive data that early intervention and treatment of microalbuminuria prevents CKD stage 5 or mortality in such patients.

RATIONALE

Definitions

Definitions of DKD by albuminuria and stage are shown in Table 6. For this guideline, we included studies of people with type 1 or type 2 diabetes and CKD stages 1 to 5 regardless of whether kidney biopsies were performed. Studies of kidney transplant recipients were excluded. Because of the high prevalence of diabetes in the population, many individuals with other types of CKD also may have diabetes. Accordingly, the term DKD refers to a presumptive diagnosis of kidney disease caused by diabetes. The term diabetic glomerulopathy should be reserved for biopsy-proven kidney disease caused by diabetes.

Microalbuminuria and estimation of GFR satisfy criteria for a screening test for DKD. (Moderate)

Microalbuminuria is an independent risk factor for the development of CKD[41,232] and GFR loss[223,233] and for cardiovascular morbidity and mortality.[234,235] It is relatively common, and in studies using the cutoff points recommended in this guideline, the point prevalence of microalbuminuria varies (depending on the population) from 7% to 22% in type 1[236-238] and from 6.5% to 42% in type 2[134,239-241] diabetes. Annual incidence rates of microalbuminuria of 1% to 2% are reported consistently for both type 1 and type 2 diabetes.

Tests for microalbuminuria are widely available, relatively inexpensive, and easy to perform. Because variations in urinary concentration caused by hydration status may adversely affect the interpretation of tests of albumin concentration alone and timed collections are inconvenient and prone to inaccuracy, the Work Group recommends estimating the ACR in a spot urine sample (preferably the first morning void).[242]

The sensitivity and specificity of ACR estimates are greater than 85% compared with timed urine collections.[242] Some reported variation is dependent upon the method of albumin and creatinine measurement. Moreover, there is continuing debate around the effect of gender on the definition of normal values. Because women normally have lower urinary creatinine concentrations than men, their ACR values are higher for the same level of urinary albumin excretion. Accordingly, some investigators have recommended lower ACR cutoff values for normoalbuminuria in men than women. Whether sex-specific cutoff values improve accuracy is unknown and requires further study. Nevertheless, because urinary albumin excretion has an intraindividual CV of approximately 40%,[36] mul-

Table 4. Albuminuria as a Predictor of Albuminuria Progression in Type 1 Diabetes

Author, Year	Mean Study Duration (y)	Mean GFR	Duration of Diabetes (y)	Applicability	N	Description of Albuminuria	Results				Quality
							Improve to NormoAlb	Improve to MicroAlb	Worsen to MicroAlb	Worsen to MacroAlb	
Chaturvedi, 2001 [304]	7.3	nd	14		1,134	NormoAlb			13%	1.7%	●
Scott, 2001 [305]	4	nd	13		943	NormoAlb			12%		●
Hovind, 2004 [306]	18	SCr 0.90	Newly diagnosed		277	NormoAlb			19%	9.7%	●
					79	MicroAlb[a]	17%			34%	
Giorgino, 2004 [263] (substudy of Chaturvedi, 2001[304])	7.3	nd	16		578	MicroAlb	51%			14%	●
Perkins, 2003 [226]	6	nd	17.5		386	MicroAlb	1st period: 39%			7%	●
							2nd period: 38%			13%	
							3rd period: 40%			15%	
							6-year cumulative: 58%[b]			22%[b]	
Warram, 1996 [242]	2.5	nd	1-39		1,613	NormoAlb			1-3 y[c]: 6.4% >10y[c]: 20% >30y[c]: 52%	>30 y[c]: 27%	◎
Agardh, 1997 [307]	5	SCr 0.88	20		167	NormoAlb[d]			23/7.2%[e]	0.6%	◎
					92	BorderlineAlb[d]	44%		25%	1.1%	
					110	MicroAlb	40%	20%[e]		14%	
					64	MacroAlb	7.8%	4.7/23%[e]			
Messent, 1992 [233]	23	nd	3.8		53	NormoAlb				9%	◎
			14.1		8	MicroAlb				88%	
Osterby, 2002 [308]	8	140	11		18	MicroAlb				28%	◎
Hovind, 2001 [249]	8.7	78	22		321	MacroAlb				39/22%[f]	◎
Torffvit, 1993 [309]	5.2	nd	20		186	NormoAlb[d]			8%	1%	○
					103	High NormoAlb[d]			24%	2%	
					118	MicroAlb				14%	
					69	MacroAlb	7%	22%			
Schulz, 2000 [310]	6	nd	1-9		442	NormoAlb			4%		○

a A subset of normoalbuminuria.
b. Recalculated incidence data came from correspondence with investigators: regression and progression of microalbuminuria using classifications based on ACR: men, 20 to 200, and women, 30 to 300.
c Duration of diabetes.
d NormoAlb defined as albumin less than 12.5 mg/L. BorderlineAlb or HighNormoAlb defined as albumin of 12.5 to 30 mg/L.
e Borderline or high Normo/microalbuminuria.
f Progression/remission to nephrotic-range albuminuria.

Table 5. Albuminuria as a Predictor of Albuminuria Progression in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	Mean GFR	Duration of Diabetes (y)	Applicability	N	Description of Albuminuria	Results				Quality
							Improve to NormoAlb	Improve to MicroAlb	Worsen to MicroAlb	Worsen to MacroAlb	
Rachmani, 2000 [311]	8.9	117	1.9	🚹🚹🚹	359	NormoAlb (0-10 mg/24 h)			25%		●
					131	(10.1-20 mg/24 h)			47%		
					109	(20.1-30 mg/24 h)			85%		
Nelson, 1996[a] [312]	4	123-155	1-16.3	🚹🚹	50	MicroAlb				37% Δ 101%[b] *P* <.05	●
					34	MacroAlb				Δ 133%[b] *P* <.05	
Nelson, 1993 [313]	4.8	nd	nd	🚹	364	MacroAlb		8.5%			●
Sosenko, 2002 [314]	3.9	nd	New onset diabetes	🚹	105	NormoAlb			18%		●
UKPDS 64, 2003 [c 41]	10.4	SCr 0.93	10.4[d]	🚹🚹🚹	4,727	NormoAlb			2.0% per year	0.1% per year	○
					333	MicroAlb				2.8% per year	
					37	MacroAlb					
Chan, 1995 [315]	2.2	PCr 0.88	5.5	🚹🚹🚹	208	NormoAlb			13%	1%	○
					94	MicroAlb	31%			18%	
					72	MacroAlb	4.2%	15%			
Torffvit, 2001 [316]	9	SCr 0.9	10	🚹🚹🚹	252	NormoAlb			38%	10%	○
					103	MicroAlb				37%	
					30	MacroAlb					
Nosadini 2000 [252]	2-6	99	>10	🚹🚹	37	MicroAlb Progressors[e]	0%			22%	○
					37	MicroAlb Nonprogressors	22%			8%	
					17	MacroAlb Progressors[e]		0%			
					17	MacroAlb Nonprogressors		17%			
John, 1994 [317]	5	SCr 0.9	7-13	🚹🚹	241	NormoAlb			26%	4.1%	○
					61	MicroAlb	15%			38%	
					14	MacroAlb		7.1%			

a 69% type 2 diabetes.

b During the 4-year period, urinary ACR increased by 101% (from 84.9 to 170.9) in those with microalbuminuria ($P = 0.003$) and by 133% (from 1,123 to 2,621) in those with macroalbuminuria ($P = 0.001$).

c Longitudinal analysis of randomized controlled trial.

d New-onset diabetes at the time of trial enrollment and analyzed with a median duration of diabetes of 10.4 years.

e Progressors/nonprogressors: microalbuminuric and proteinuric patients were subdivided into progressors (below median: –0.4 %GFR among microalbuminuric and –1.8 %GFR among proteinuric patients, respectively) and nonprogressors (above median %GFR).

Table 6. Likelihood of DKD According to Staging by GFR and Level of Albuminuria

		Albuminuria		
GFR (mL/min)	CKD Stage*	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
>60	1 + 2	At risk†	Possible DKD	DKD
30-60	3	Unlikely DKD‡	Possible DKD	DKD
<30	4 + 5	Unlikely DKD‡	Unlikely DKD	DKD

*Staging may be confounded by treatment because RAS blockade could render microalbuminuric patients normoalbuminuric and macroalbuminuric patients microalbuminuric. Thus, although staging is done according to the current level of albuminuria for practical reasons, the implication of the staging undoubtedly is affected by past history. Therefore, when available, data before the initiation of therapy should be considered for classification purposes.
†Because patients with diabetes often have elevated GFR in the early years after diagnosis, GFR less than 90 mL/min may represent a significant loss of function. Kidney biopsy in these patients can show histological evidence of DKD. Patients with diabetes at increased risk of DKD include those with poor glycemic control, longer duration, hypertension, retinopathy, high-normal albuminuria, nonwhite race, and family history of hypertension, CVD, type 2 diabetes, and DKD.
‡Reduction in GFR in patients with diabetes and normoalbuminuria is well described in both type 1 and type 2 diabetes; kidney biopsy in such patients often shows evidence of diabetic glomerulopathy. However, in the absence of histological evidence, these patients should be considered to have diabetes and CKD, which may require further investigation based on the criteria described in this guideline.

tiple positive test results are required for classification.

Although microalbuminuria satisfies nearly all criteria for a screening test, it does not satisfy the criterion of providing proven clinical benefits because the impact of microalbuminuria detection on such hard clinical end points as CKD stage 5, GFR loss, or CVD morbidity/mortality has not been demonstrated unequivocally (Table 7 and Table 8). Nevertheless, the ADA and other diabetes professional societies recommend annual screening for microalbuminuria based on the treatment possibilities discussed in CPR 1. The Work Group supports these screening recommendations while recognizing the need for further studies to define the impact of microalbuminuria detection on hard clinical end points. The suggested screening plan, adapted from the ADA guideline, is shown in Fig 6.[34,35]

The evidence for the usefulness of eGFR alone as a screening test for CKD in diabetes is less secure. Many patients with diabetes and CKD may have elevated or high-normal GFRs, particularly in the early years after diagnosis. The same is true for all types of CKD. Whether values of GFR greater than 90 mL/min reflect progressive CKD may be determined best by the slope of sequential GFR estimates, rather than a single estimate. Therefore, markers of kidney damage are required to detect early stages of CKD; eGFR alone can detect only CKD stage 3 or worse. Although eGFR is recommended to classify patients with diabetes into stages of CKD (Table 6), some potential problems exist with the currently available estimating equations. The Modification of Diet in Renal Disease (MDRD) equation, presently the most widely used estimating equation for staging CKD, has been validated in only small numbers of patients with diabetes and CKD,[243] and other equations may provide better estimates of GFR in these patients.[244] An NIH-sponsored study currently is ongoing with the purpose of developing a new equation derived from multiple databases along with extensive calibration studies to ensure generalizability throughout the entire range of GFRs.

Despite their value in the vast majority of patients, currently recommended screening tests are not sufficient to identify all cases of DKD because serious diabetic glomerular lesions may occur in normoalbuminuric patients with normal GFR.[228] Normoalbuminuric patients with decreased GFR have even more severe glomerular changes.[245,246] Therefore, further evaluation, including consideration of kidney biopsy, may be required in some cases to establish the diagnosis of DKD.

Screening for kidney disease should begin 5 years after the diagnosis of type 1 diabetes and at the diagnosis of type 2 diabetes. (Moderate/Strong)

Although transient increases in albuminuria in newly diagnosed type 1 diabetes are well described, it is thought that this increase represents acute metabolic perturbations and the level of albuminuria usually reverts to normal after glycemic correction. Most longitudinal cohorts report significant increases in microalbuminuria prevalence only after 5 years' duration, although 1 cross-sectional study described a significant prevalence of around 15% in patients with 1 to 5 years of diabetes.[236] Conversely, the UKPDS found a urinary albumin concentration greater

Table 7. Albuminuria as a Predictor of DKD Progression, CVD, and Mortality in Type 1 Diabetes

Author, Year	Mean Study Duration (y)	Mean GFR	Duration of Diabetes (y)	Applicability	N	Outcome	Results (Baseline Albuminuria)			Quality
							Normo	Micro	Macro	
Messent, 1992 [233]	23	nd	NormoAlb 3.8 MicroAlb 14.1	↑↑↑	NormoAlb 53 MicroAlb 8	Cardiovascular death	17%	50%		⊕
						Non Cardiovascular death	15%	13%		
						Progression to kidney failure	7.5%	25%		
Torffvit, 1993 [309]	5.2	nd	20	↑↑↑	468	Death	1.6%	2.9%[a]	4.2%	12%	○
						Cardiovascular event or death	2%	6%	8%	42%	

a High-normoalbuminuria.

than 50 mg/L in 6.5% of newly diagnosed, mainly white patients with type 2 diabetes.[134] This group suggested an average 8-year delay in diagnosis of type 2 diabetes from the onset of beta cell failure and hyperglycemia. Moreover, 28% of these patients had hypertension at diagnosis. Accordingly, whereas screening can wait until 5 years after the onset of type 1 diabetes, the inability to establish the onset of type 2 diabetes with certainty makes screening at diagnosis mandatory.

Elevated ACR should be confirmed in the absence of urinary tract infection. (Moderate)

AER has a high day-to-day variability, probably reflecting the multiple factors that can influence the appearance of albumin in the urine.[36] These include such metabolic perturbations as ketosis and hyperglycemia and such hemodynamic factors as physical exercise, dietary protein intake, diuresis, and the presence of urinary tract infection. Because of this variability, most professional societies recommend confirmation of an elevated ACR with an additional 2 tests during the subsequent 3 to 6 months (Fig 6).[34,35] To reduce variability, these repeated estimates should be performed on first-voided urinary specimens.

In most people with diabetes, CKD should be attributable to DKD in the presence of: (1) macroalbuminuria or microalbuminuria plus retinopathy, and (2) in people with type 1 diabetes, in the presence of microalbuminuria plus duration of diabetes longer than 10 years. (Moderate/Strong)

Historically, detection of macroalbuminuria was the basis of the diagnosis of DKD (Table 6). Kidney biopsy in macroalbuminuric patients with type 1 diabetes consistently shows advanced diabetic lesions of increased mesangial volume, increased glomerular basement membrane thickness, and tubulointerstitial pathologies.[228,229,247,248] The severity of these abnormalities is related closely to the amount of albuminuria and the decrease in GFR (Table 9 and Table 10). GFR decreases relentlessly at rates greater than 10 mL/min/y in those with poorly controlled hypertension and macroalbuminuria,

Table 8. Albuminuria as a Predictor of DKD Progression, CVD, and Mortality in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	Mean GFR	Duration of Diabetes (y)	Applicability	N	Outcome	Results (Baseline Albuminuria)			Quality
							Normo	Micro	Macro	
Mortality										
Bruno, 2003 [318]	6.7	SCr 1.02	10.7		1,408	Mortality	32%	44%	58%	●
UKPDS 64, 2003 [41]	10.4	SCr 0.93	10.4		5,097	Mortality	1.4% per year	3.0% per year	4.6% per year	◎
Chan, 1995 [315]	2.2	SCr 0.88	5.5		453	Mortality	1%	2%	4%	◎
John, 1994 [317]	5	SCr 0.97	7-13		481	Mortality	5%	10%	70%	○
Cardiovascular Event										
Rachmani, 2000 [311]	8.9	117	11.8		621	Cardiovascular Event	AER (mg/24 h) 0-10: Ref; 10.1-20: OR 1.9 (NS); 20.1-30: OR 9.8 (*P* <.05)			●
Progression of CKD										
Bruno, 2003 [318]	6.7	SCr 1.02	10.7		846	CKD development	Reference	RR 1.9 NS	RR 5.5 *P* <.05	●
						CKD Stage 5 development	Reference	RR 5.2 NS	RR 25 *P* <.05	
Rachmani, 2000 [311]	8.9	117	11.8		621	GFR annual decline	AER (mg/24 h) 0-10: 1.2; 10.1-20: 1.6; 20.1-30: 2.5			●
Nelson, 1996 [312]	4	123-155	0.7-16.3		194	Change in GFR		-3% NS	-35% *P* <.05	●
						Progression to CKD			30%	
Nelson, 1993 [313]	4.8	nd	nd		364	CKD Stage 5 development			26%	●
UKPDS 64, 2003 [a 41]	10.4	SCr 0.93	10.4		5,097	Elevated PCr or KRT[b]	0.1% per year	0.3% per year	2.3% per year	◎
Chan, 1995 [315]	2.2	SCr 0.88	5.5		453	Progressive loss of kidney function[c]	-27	-43	-109	◎
Nosadini, 2000 [252]	2-6	99	10-15		108	CKD Stage 5 development		3% / 0%[d]	35% / 0%[d]	◎

a Longitudinal analysis of randomized control trial.

b PCr > 175 mol/L on 2 consecutive visits or if a PCr > 175 μmol/L was followed the next year by dialysis, kidney transplantation, or death.

c $\Delta[Cr]^{-1}\mu mol^{-1}.mo^{-1}$.

d Progressors/nonprogressors: microalbuminuric and proteinuric patients were subdivided into progressors (below median: –0.4 %GFR among microalbuminuric and –1.8 %GFR among proteinuric patients, respectively) and nonprogressors (above median %GFR).

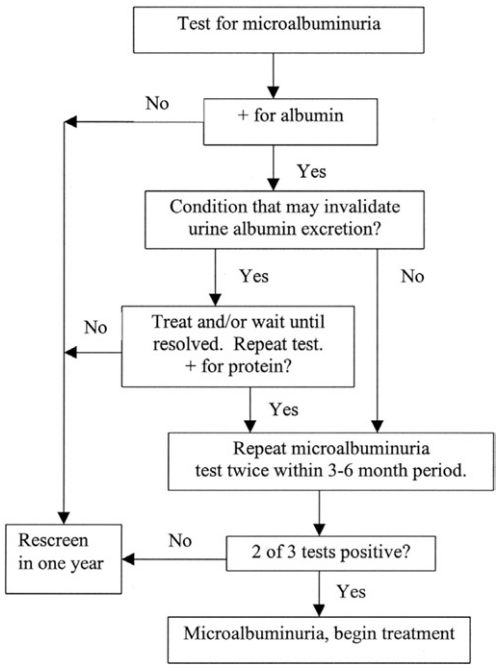

Figure 6. Screening for microalbuminuria. Reprinted with permission.[35]

but much more slowly (1 to 4 mL/min/y) in those with effective blood pressure control.[249,250]

In microalbuminuric patients with type 1 diabetes, pathological lesions tend to be less severe than in macroalbuminuric patients, but usually are significantly more advanced than those seen in normoalbuminuric individuals, particularly in the presence of hypertension.[228,229] GFR is stable at low-level microalbuminuria, but decreases at 1 to 4 mL/min/y as AER increases, and more rapidly in those with poorly controlled hypertension.[223]

The situation in type 2 diabetes is less clearcut, with only about 40% of microalbuminuric patients who undergo biopsy for research purposes showing diabetic changes typical of those seen in patients with type 1 diabetes.[230] About 30% of them have normal or near-normal biopsy results, whereas the other 30% have increased severity of tubulointerstitial, vascular, and/or glomerulosclerotic lesions unrelated to classic diabetic glomerulopathy.[230] In general, the kidney structural-functional relationships established in type 1 diabetes hold in type 2 diabetes (Table 11 and Table 12), but the correlations are less precise, especially because of a sizeable cluster of patients with type 2 diabetes and microalbuminuria or proteinuria with little or no diabetic glomerulopathy lesions.[230,251] The rate of GFR decrease in patients with type 2 diabetes, microalbuminuria, and proteinuria is greatest in those with typical diabetic glomerular lesions.[252]

The concomitant presence of retinopathy is only partly helpful in discriminating kidney pathology in patients with type 2 diabetes (Fig 7; Table 13).[147,251,253-262] In those with macroalbuminuria, the positive predictive value (PPV) of retinopathy for typical diabetic glomerulopathy ranges from 67% to 100%. However, the negative predictive value (NPV) had a broader range of 20% to 84%. These figures give sensitivities between 26% and 85% and specificities of 13% to 100%. For microalbuminuria, PPVs were lower at around 45%, but NPVs were close to 100%, giving sensitivities of 100% and specificities of 46% to 62%. Thus, the presence of retinopathy in patients with type 2 diabetes and macroalbuminuria is strongly suggestive of DKD, and its absence in microalbuminuria suggests non-DKDs. Only a small number of patients in these series were found to have non-DKD amenable to a specific therapy, and most of those individuals had other clinical features, such as nephrotic syndrome or nondiabetic systemic illness.

Duration of diabetes is related closely to the prevalence of DKD in type 1 patients. Prevalence rates of microalbuminuria and macroalbuminuria increase after 10 years, presumably reflecting cumulative glycemic exposure (see Guideline 2). Patients with type 1 diabetes, microalbuminuria, shorter diabetes duration, lower AER levels, better glycemic control, and lower blood pressure and plasma lipid concentrations are more likely to reverse to normoalbuminuria.[226,263,264] The contribution of the prepubertal years of diabetes to DKD risk may be lower than that of postpubertal years, but this remains controversial.[265-270] However, there are few good data on comparative levels of glycemic control in young children, making it difficult to control for this variable. There also may be a nonlinearity of risk of pathological damage before achievement of full growth, but this risk may be duration dependent, rather than puberty dependent.[271] Moreover, postural proteinuria may be more common during ado-

Table 9. Relationship Between Albuminuria and Kidney Morphology in Type 1 Diabetes

Author, Year	Duration of Diabetes (y)	Mean GFR	Applic-ability	N	Baseline Albuminuria	Biopsy Parameter	Albuminuria Threshold or Prevalence	Results	*P*	Quality
Drummond, 2002 [271]	8	142	🚹🚹🚹	221	7.6 μg/min	Vv(Mes/glom)	M 0% m 4%	r = +0.14	.03	●
						Vv(MM/glom)		r = +0.16	<.05	
						GBM width		NS		
						Vv(Int/cortex)		NS		
Caramori, 2002 [228]	>8	33-166	🚹🚹🚹	125	6-839 μg/min	Vv(Mes/glom)	M 19% m 17%	r = +0.75	<.001	●
						Vv(MM/glom)		r = +0.71	<.001	
						GBM width		r = +0.63	<.001	
						Sv(PGBM/glom)		r = -0.62	<.001	
Lane, 1993 [319]	17-22	73-123	🚹🚹🚹	96	15-1109 mg/d	Vv(Mes/glom)	M 35% m 18%	r = +0.57	<.001	●
						Vv(Int/cortex)		r = +0.52	<.001	
						%SG		r = +0.40	<.001	
Harris, 1991 [320]	20	91	🚹🚹🚹	43	127 mg/d	GBM width	<45 mg/d vs >250 mg/d	508 vs 739	<.0001	●
						Filtration surface/glomerulus		0.15 vs 0.10	<.0001	
Ellis, 1986 [321]	18	SCr <2.4	🚹🚹🚹	37	1-4,900 mg/d	Capillary filtration surface area/glomerulus	< vs >250 mg/d	160 vs 90	<.001	●
Brito, 1998 [247]	17	104	🚹🚹🚹	35	8 μg/min	Vv(MM/glom)	M 17% m 11%	r = +0.84[a]	<.001	●
						GBM width		r = +0.68	<.001	
						Vv(Int/cortex)		r = +0.60	<.001	
Fioretto, 1995 [322]	17	96	🚹🚹🚹	11	6-280 mg/d	Vv(Mes/glom)	M 0% m 27%	r = +0.64 Δ AER 5 y	<.05	●
						GBM width		NS Δ AER 5 y		
						Vv(Int/cortex)		NS Δ AER 5 y		
Najafian, 2003 [323]	23	76	🚹🚹🚹	8	719 μg/min	%SG	M 75% m 25%	r = +0.78	<.05	●
Bangstad, 1993 [324]	12	132	🚹🚹	17	32 μg/min	Vv(Int/cortex)	m 100%	NS		○

Abbreviations: Δ, change; GBM, glomerular basement membrane; GFR, glomerular filtration rate (mL/min); M, macroalbuminuria; m, microalbuminuria; NS, non-significant; Scr, serum creatinine (mg/dL); SG, globally sclerosed glomeruli; Sv(PGBM/glom), surface density of the peripheral glomerular basement membrane per glomerulus; Vv(Int/cortex), volume fraction of cortical interstitium; Vv(Mes/glom), volume fraction of mesangium per glomerulus; Vv(MM/glom), volume fraction of mesangial matrix per glomerulus.

a Correlation between log of albuminuria measurement and biopsy parameter.

Table 10. Relationship Between Kidney Function and Morphology in Type 1 Diabetes

Author, Year	Duration of Diabetes (y)	Mean GFR	Applic-ability	N	Baseline Albuminuria	Albuminuria Prevalence	Biopsy Parameter	Kidney Function Parameter	Results	*P*	Quality
Caramori, 2002 [228]	> 8	33-166	🚹🚹🚹	125	6-839 μg/min	M 19% m 17%	Vv(Mes/glom) Vv(MM/glom) Sv(PGBM/glom)	GFR	r = -0.48 r = -0.53 r = +0.50	<.001 <.001 <.001	●
Lane, 1993 [319]	17-22	73-123	🚹🚹🚹	96	15-1109 mg/d	M 35% m 18%	Vv(Mes/glom) Vv(Int/cortex) %SG	CCr	r = -0.41 r = -0.49 r = -0.41	<.001 <.001 <.001	●
Mauer, 1984 [248]	13.6	nd	🚹🚹🚹	45	nd	nd	GBM width	CCr	r = -0.42	NS	●
Harris, 1991 [320]	20	91	🚹🚹🚹	43	127mg/d	M 45% m 17%	%SG	CCr	r = +0.64	<.0005	●
Ellis, 1986 [321]	18	SCr <2.4	🚹🚹🚹	37	1-4900 mg/d	nd	Capillary filtration surface area/glomerulus Vv(Mes/glom)	CCr	r = +0.78 r = -0.42	<.001 <.01	●
Brito, 1998 [247]	17	104	🚹🚹🚹	35	8 μg/min	M 17% m 11%	GBM width Vv(Mes/glom) Vv(Int/cortex) TBM width	GFR	r = -0.46 r = -0.64 r = +0.01 r = -0.54	<.01 .001 NS <.001	●
Najafian, 2003 [323]	23	76	🚹🚹🚹	8	719 μg/min	M 75% m 25%	Model A[a] Model B[b]	GFR	r^2 = 0.66 r^2 = 0.94	NS <.05	●
Ellis, 1997 [325]	7.7	106	🚹🚹	59	1-195 μg/min	M 0% m 19%	Glomerular volume Total mesangial volume SvME	CCr	r = +0.34 r = +0.278 r = +0.294	.009 .04 .03	⊙
Bangstad, 1993 [324]	12	132	🚹🚹	17	32 μg/min	m 100%	GBM width Vv(MM/glom)	GFR	r = +0.12 r = +0.18	NS NS	⊙
Bjorn, 1995 [326]	M 24 m 13 NormoAlb 11	M 36 m 132 NormoAlb 129	🚹🚹	27	M 521 μg/min m 65 μg/min NormoAlb 5 μg/min	M 33% m 33%	Filtration slit width	GFR	r = +0.65	<.005	○

Abbreviations: AG, atubular glomeruli; CCr, creatinine clearance; GBM, glomerular basement membrane; GFR, glomerular filtration rate (mL/min); IJA, index of junctional atrophy; M, macroalbuminuria; m, microalbuminuria; NormoAlb, normoalbuminuria; nd, no data; NS, nonsignificant; SG, globally sclerosed glomeruli; Sv(PGBM/glom), surface density of the peripheral glomerular basement membrane per glomerulus; SvME, mesangial to epithelial interface; TBM, tubular basement membrane; Vv(AT/cortex), volume fraction of atrophic tubules per cortex; Vv(Int/cortex), volume fraction of cortical interstitium; Vv(MC/glom), volume fraction of mesangial cells per glomerulus; Vv(Mes/glom), volume fraction of mesangium per glomerulus; Vv(MM/glom), volume fraction of mesangial matrix per glomerulus; Vv(PT/cortex), volume fraction of proximal tubules.

a. Model A: predictor variables of mean glomerular volume, Vv(Mes/glom), Vv(MM/glom), Vv(MC/glom), Sv(PGBM/glom), and GBM width.

b. Model B: predictor variables of %SG, % glomeruli with tip lesion, %AG, Vv(Int/cortex), Vv(PT/cortex), Vv(AT/cortex), and mean IJA.

Table 11. Relationship Between Albuminuria and Kidney Morphology in Type 2 Diabetes

Author, Year	Duration of Diabetes (y)	Mean GFR	Applic-ability	N	Baseline Albuminuria	Biopsy Parameter	Albuminuria Threshold or Prevalence	Results	*P*	Quality
Nosadini, 2000 [252]	10-15	89-107		108	33-420 µg/min	GBM width	M 31% m 69%	M 512 m 418	nd	●
						Vv(Mes/glom)		0.30 0.25	nd	
White, 2000 [327]	16	65		21	1.2 g/d	Vv(Mes/glom)	M 100%	r = +0.64	.002	●
						GBM width		r = +0.58	.006	
						Vv(Interstitium / tubulointerstitium)		r = -0.10	NS	
						Vv(MM/glom)		r = +0.65	.001	
						FPW mesangium		r = +0.60	.004	
Christiansen, 2000 [328]	4	95		35	1,362 mg/d	Vv(Mes/glom)	M 100%	r = +0.32	NS	●
Pagtalunan, 1997 [329]	3-19	>90		51	<30 to >300 mg/g	Vv(Int/cortex)	M 24% m 33% NormoAlb[a] 20% / 24%	M 28% m 25% NormoAlb[a] 22% / 23%	<.05[b]	●
						Vv(Mes/glom)		M 42% m 28% NormoAlb[a] 21% / 25%	<.05[b]	
						GBM width		M 606 m 504 NormoAlb[a] 427 / 500	<.05[b]	
Christiansen, 2001 [330]	6	97		34	1,322 mg/d	Vv(Mes/glom)	M 100%	r = +0.38[c]	<.03	○
Matsumae, 1999 [331]	9.8	66		19	2.5 g/d	Vv(Mes/glom)	M 43% m 57%	r = +0.54	<.02	○
						GBM width		r = +0.59	<.01	
						V(MM/glom)		r = +0.60	<.01	
						Vv(MM)		r = +0.66	<.005	
Meyer, 1999 [332]	13	159		16	67 mg/g	GBM width	m 100%	r = +0.11	NS	○
						Vv(Mes/glom)		r = +0.42	NS	

Abbreviations: FPW, foot process width on the mesangial surface; GBM, glomerular basement membrane; GFR, glomerular filtration rate (mL/min); M, macroalbuminuria; m, microalbuminuria; NormoAlb, normoalbuminuria; nd, no data; NS, nonsignificant; Vv(Int/cortex), volume fraction of cortical interstitium; Vv(Interstitium / tubulointerstitium), volume fraction of interstitium; Vv(Mes/glom), volume fraction of mesangium per glomerulus; Vv(MM), volume fraction of mesangial matrix; Vv(MM/glom), volume fraction of mesangial matrix per glomerulus.

a Duration of diabetes less than 6 years/longer than 6 years.

b Long-term normal albuminuria with diabetes greater than 6 years, microalbuminuria and macroalbuminuria were significant with respect to the control. Macroalbuminuria was significant with respect to normal albuminuria with diabetes less than 6 years.

c Correlation between log of albuminuria measurement and biopsy parameter.

Table 12. Relationship Between Kidney Function and Morphology in Type 2 Diabetes

Author, Year	Mean Duration of Diabetes (y)	Mean GFR	Applicability	N	Baseline Albuminuria	Albuminuria Threshold or Prevalence	Biopsy Parameter	Kidney Function Parameter	Results	*P*	Quality
Brocco, 1997 [147]	7	109		22	56 μg/min	m 100%	Category I[a]	GFR	109	<.05 vs II	●
	14	86		14	58 μg/min		Category II[b]		86	<.05 vs I and III	
	13	96		17	69 μg/min		Category III[c]		96	<.05 vs II	
White, 2000 [327]	16	65		21	1.2 g/day	M 100%	Vv(Mes/glom)	CCr	r = -0.58	.006	●
							GBM width		r = -0.23	NS	
							Vv(Interstitium / tubulointerstitium)		r = -0.58	.008	
Christiansen, 2000 [328]	4	95		35	1362 mg/day	M 100%	Vv(Mes/glom)	GFR	r = -0.43	<.01	●
Osterby, 2001 [333]	16	73		27	430 μg/min	nd	Filtration surface/nephron	GFR	r = +0.53	<.02	●
Matsumae, 1999 [331]	9.8	66		19	2.5 g/day	M 42% m 58%	Vv(Mes/glom)	CCr	r = -0.50	<.05	○
							GBM width		r = -0.71	<.001	
							Vv(MM)		r = -0.61	<.01	
							Filtration surface/nephron		r = +.70	<.001	
Lemley, 2000 [334]	<5 to >8	>90		12	10-83 mg/g	<30 vs 30-300	Δ Single nephron Kf	GFR	r = +0.75	<.005	○

Abbreviations; Δ, change; CCr, creatinine clearance; GBM, glomerular basement membrane; GFR, glomerular filtration rate (mL/min); Kf, ultrafiltration coefficient; nd, no data; NS, non-significant; Vv(Interstitium / tubulointerstitium), volume fraction of interstitium; Vv(Mes/glom), volume fraction of mesangium per glomerulus; Vv(MM), volume fraction of mesangial matrix.

a Normal or near-normal kidney structure.

b Typical diabetic nephropathology. Diabetic lesions with an approximately balances severity of glomerular, tubulointerstitial, arteriolar and global glomerulosclerotic changes.

c Atypical patterns of kidney injury. Relatively mild glomerular diabetic changes considering the disproportionately severe kidney structural changes including: 1-Tubular atrophy, tubular basement membrane thickening and reduplication and interstitial fibrosis; 2-advanced glomerular artieriolar hyalinosis; 3-increased global glomerular sclerosis.

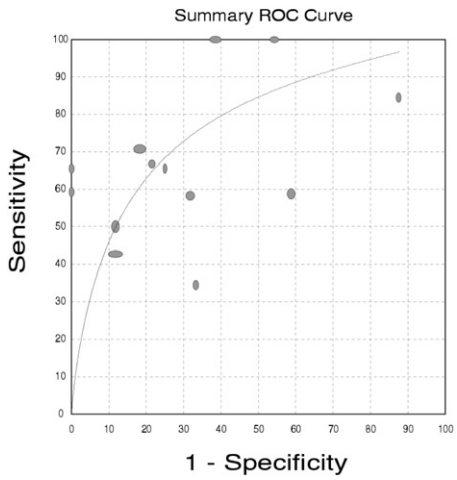

Figure 7. Receiver operator characteristic (ROC) curve of the probability that the presence of diabetic retinopathy is predictive of patients who have biopsy/histology-proven diabetic glomerulopathy.
Each ellipse represents an individual study, for which the height and width of the ellipse is representative of the inverse variance of the sensitivity and specificity, respectively.[147,251,253-262]

lescence, making the diagnosis of DKD more uncertain and the recommendation for screening by using overnight urine collections especially important in this age group. For these and other reasons, it would be incorrect in the view of the Work Group to regard the prepubertal period as risk free for the development of DKD. This topic needs additional research. Because of the clinical difficulty accurately determining the onset of type 2 diabetes, known duration is less strongly related to DKD. In Pima Indians, the duration of type 2 diabetes is known with greater accuracy and precision because of systematic screening for diabetes, and in this population, the duration of diabetes is as strongly related to DKD as in type 1 diabetes.[272]

Several small series of patients with type 1 and type 2 diabetes describe cases of typical diabetic glomerulopathy with normoalbuminuria and normal or decreased GFR. These data bring into question the reliance on increased AER alone or in combination with GFR for diagnosis of DKD. Most of these patients were women, had relatively long durations of diabetes, and usually had retinopathy and/or hypertension.[245,246,273]

Atypical clinical features should prompt evaluation for non-DKD. People with diabetes and CKD may have increased risks of testing and treatments. (Moderate)

Because diabetes is a common condition, coincidence with other nondiabetic CKD is relatively frequent. Accordingly, evaluation of a person with atypical features should include additional diagnostic testing in selected cases, depending on the clinical presentation. For example, because generalized vascular disease is common in diabetes, refractory hypertension and/or a significant decrease in kidney function after RAS blockade should prompt consideration of renal artery stenosis. Rapidly decreasing kidney function and/or increasing proteinuria (particularly if nephrotic), active urinary sediment, or evidence of other systemic disease should raise concerns about nondiabetic glomerular disease. Diagnosis of these diseases may require invasive testing or interventional procedures. Care should be used in determining the appropriate diagnostic tests because administration of radiographic contrast, with or without angiography, may pose greater risks in people with diabetes and CKD than in other people.

It is the opinion of the Work Group that in the absence of another identifiable and treatable cause of kidney disease, patients with diabetes and CKD should be treated as if they have DKD.

A kidney biopsy may be required in some patients with diabetes and CKD to determine the underlying cause of the kidney disease. (Moderate)

The risk of complications associated with percutaneous native kidney biopsy in patients with DKD is no greater than the risk faced by patients with most other causes of CKD.[274,275] The majority of complications are from bleeding and include microscopic hematuria, decrease in hemoglobin level, gross hematuria, perinephric hematomas, and arteriovenous fistulae.[276,277] Women are more likely to bleed than men, and other commonly identified risk factors for bleeding include younger age, decreased GFR, elevated systolic and diastolic blood pressure, and prolonged bleeding and partial thromboplastin times.[274,276,278,279] The number of needle passes during kidney biopsy also increases the risk of bleeding, particularly if the number exceeds 4[276]

Table 13. Predictive Value of Diabetic Retinopathy for Diagnosis of DKD in Biopsy Studies

Author, Year	Study Design	Duration of Diabetes (y)	Applic-ability	Baseline Proteinuria	DGS	Glomerulo-sclerosis[a]	Retinopathy (N)	No Retinopathy (N)	Sensitivity (Sn) Specificity (Sp)	Quality
Type 1 Diabetes										
Klein, 2005 [335]	RCT	12	🧍🧍🧍	6-8 µm/min	100%	DM	163	89	Sn: 65%	●
						Non-DM	nd	nd	—	
							—	—		
Amoah, 1988 [253]	Retrospective cross-sectional	>5	🧍🧍🧍	nd	88%	DM	36	7	Sn: 84%	○
						Non-DM	4	2	Sp: 33%	
							PPV: 90%	NPV: 22%		
Richards, 1992 [260]	Retrospective cross-sectional	6-9	🧍	5 g/L	86%	DM	18	1	Sn: 95%	○
						Non-DM	0	3	Sp: 100%	
							PPV: 100%	NPV: 75%		
Type 2 Diabetes										
Brocco, 1997 [147]	Prospective cross-sectional	7-14	🧍🧍🧍	20-200 µg/min 100%	26%	DM	14	0	Sn: 100%	●
						Non-DM	15	24	Sp: 62%	
							PPV: 48%	NPV: 100%		
Wong, 2002 [262]	Prospective cross-sectional	4-8	🧍🧍	≥1 g/d 100%	35%	DM	17	7	Sn: 71%	●
						Non-DM	8	36	Sp: 82%	
							PPV: 68%	NPV: 84%		
Mak, 1997 [258]	Prospective cross-sectional	~7	🧍🧍	>1 g/d 100%	67%	DM	20	14	Sn: 59%	⊙
						Non-DM	10	7	Sp: 41%	
							PPV: 67%	NPV: 33%		
Christiansen, 2000 [254]	Prospective longitudinal (study entry)	5-10	🧍🧍🧍	>300 mg/d 100%	77%	DM	17	9	Sn: 65%	⊙
						Non-DM	0	8	Sp: 100%	
							PPV: 100%	NPV: 53%		
Christiansen, 2000 [254]	Prospective longitudinal (study end-8 years)	13-18	🧍🧍🧍	>300 mg/d 100%	77%[b]	DM	22	4	Sn: 85%	⊙
						Non-DM	7	1	Sp: 13%	
							PPV: 76%	NPV: 20%		
Parving, 1992 [251]	Prospective cross-sectional	8-10	🧍🧍🧍	>300 mg/d 100%	77%	DM	16	11	Sn: 59%	⊙
						Non-DM	0	8	Sp: 100%	
							PPV: 100%	NPV: 42%		
Amoah,1988 [253]	Retrospective cross-sectional	>5 (64%)	🧍🧍🧍	nd	71%	DM	21	21	Sn: 50%	○
						Non-DM	2	15	Sp: 88%	
							PPV: 91%	NPV: 42%		
Olsen, 1996 [259]	Retrospective cross-sectional	2- 20	🧍🧍	nd	88%	DM	19	10	Sn: 66%	○
						Non-DM	1	3	Sp: 75%	
							PPV: 95%	NPV: 23%		
Schwartz, 1998 [336]	RCT, subgroup	14-17	🧍🧍	>500 mg/d 100%	100%	DM	23	8	Sn: 26%	○
						Non-DM	nd	nd	—	
							—	—		

(Continued)

Table 13 (Cont'd). Predictive Value of Diabetic Retinopathy for Diagnosis of DKD in Biopsy Studies

Author, Year	Study Design	Duration of Diabetes (y)	Applicability	Baseline Proteinuria	DGS	Glomerulosclerosis[a]	Retinopathy (N)	No Retinopathy (N)	Sensitivity (Sn) Specificity (Sp)	Quality
Kanauchi, 1998 [337]	Cross-sectional	nd	↑	nd	100%	DM	99	122	Sn: 45%	○
						Non-DM	nd	nd	—	
							—	—		
John, 1994 [256]	Prospective cross-sectional	nd	↑	nd	19%	DM	6	8	Sn: 43%	○
						Non-DM	7	53	Sp: 88%	
							PPV: 46%	NPV: 87%		
Serra, 2002 [261]	Prospective cross-sectional	>10 80%	↑	>500 mg/d	74%	DM	9	17	Sn: 35%	○
						Non-DM	3	6	Sp: 67%	
							PPV: 75%	NPV: 26%		
Kleinknecht, 1992 [257]	Retrospective cross-sectional	10-15	↑	>3 g/d	60%	DM	14	7	Sn: 67%	○
						Non-DM	3	11	Sp: 79%	
							PPV: 82%	NPV: 61%		
Richards, 1992 [260]	Retrospective cross-sectional	6-9	↑	3 g/L	52%	DM	14	10	Sn: 58%	○
						Non-DM	7	15	Sp: 68%	
							PPV: 67%	NPV: 60%		

Abbreviation: DM, diabetes mellitus.
a Biopsy characteristics of mixed and nondiabetic glomerulosclerosis were categorized as Non-DM glomerulosclerosis.
b Proportion of diabetic glomerulosclerosis categorized at baseline.

or 5 passes.[274] Use of real-time imaging appears to improve the success and safety of the procedure.[276,280] To reduce the risk of bleeding complications,[274,276,277,279,281-287] anticoagulant medicines should be stopped in advance of the biopsy, blood pressure should be controlled, and 1-deamino-8-D-arginine (ddAVP) may be given immediately before the procedure if bleeding time is prolonged (Table 14).

Caution should be used when administering radiographic contrast agents to patients with diabetes and CKD because their risk of RCN is higher than in those without these diseases. (Moderate/Strong)

RCN is identified by both a change in kidney function (eg, GFR or serum creatinine level) and the time course over which kidney function changes. A standard definition of RCN does not exist, but definitions used in previous studies have included increases in serum creatinine concentration ranging from 0.5 mg/dL to a doubling of the concentration and decreases in GFR ranging from 25% to dialysis requirement.[288-290] In general, most studies assess kidney function within 48 to 72 hours after contrast administration. Serum creatinine concentration usually increases within 48 hours of radiographic contrast administration and peaks within 7 days.

The lack of a standardized definition of RCN makes comparisons between studies difficult. Nevertheless, the risk of RCN is higher in people with diabetes and CKD than in either condition alone. In general, the incidence of RCN is less than 3% in patients with neither diabetes nor CKD, 5% to 10% in those with diabetes, 10% to 20% in those with CKD (greater at later stages), and 20% to 50% in those with both diabetes and CKD (Table 15).[291,292]

Patients who develop RCN have greater mortality, both short and long term, than those who do not.[293,294] Accordingly, efforts to prevent or minimize RCN should be implemented in those with diabetes and CKD. However, the evidence for prevention of RCN in these patients is relatively limited (Table 16 and Table 17). Many studies do not report incidence of RCN by the presence of diabetes and CKD, and those that do often are derived from subgroup analyses so the number of patients is small. Despite these limita-

Table 14. Strategies to Prevent Bleeding After Kidney Biopsy

• Assess personal and family history for bleeding diathesis[276,277]
• Stop anticoagulants before the scheduled procedure[276,284] ○ Stop aspirin at least 1 wk before procedure[276,281,284] ○ Stop nonsteroidal anti-inflammatory agents several days before (to ensure 4-5 half-lives have elapsed) ○ Stop warfarin and consider switch to heparin in advance of procedure[283] ○ Stop heparin before procedure
• Check complete blood count and coagulation parameters before biopsy[276] ○ Complete blood count[276] ○ Platelet count[276] ○ Prothrombin time, partial thromboplastin time[276] ○ Bleeding time[276]—controversial[279,285,286]
• Check kidney function ○ Use equation to estimate GFR
• Consider administration of ddAVP for abnormal bleeding time and/or low GFR[276,279,282,286] ○ 0.3 μg/kg given in 50 mL of saline over 15-30 min immediately before procedure[287]
• Control blood pressure on day of procedure[274] ○ May give oral agents before procedure to decrease blood pressure[274]

tions, several strategies have been developed that may reduce RCN risk in people with diabetes and CKD, as well as in other populations. First, concomitant nephrotoxins (eg, nonsteroidal anti-inflammatory agents, aminoglycosides, and amphotericin) should be discontinued, if possible, before administering the radiographic contrast agent.[295] Second, intravenous fluids should be administered, but caution should be used in determining the amount of fluid to avoid fluid overload. Most studies evaluated 0.45% sodium chloride at a dose of 1 mL/kg/h over 6 to 12 hours, but they did not include patients with advanced CKD.[296] A recent study suggested that 0.9% sodium chloride may be better than 0.45% sodium chloride for preventing RCN.[298] Third, a greater volume of contrast is associated with an increased risk of RCN. In the general population, administration of more than 100 mL of hyperosmolar radiographic contrast increases the risk of RCN, but in those with diabetes and an eGFR less than 30 mL/min/1.73 m^2, as little as 30 mL of radiographic contrast agent can lead to acute kidney failure.[298] Hence, the use of radiographic contrast material should be kept to the minimum amount necessary for the evaluation required.[297] Fourth, the type of contrast material affects the risk of RCN. Nonionic radiographic contrast material may confer a lower risk of RCN than ionic contrast material.[287] Moreover, a randomized controlled trial reported that iso-osmolar radiographic contrast (eg, iodixanol) is associated with significantly lower incidences of RCN than a low-osmolar contrast agent in patients with diabetes and CKD.[288] Fifth, because lactic acidosis may occur with RCN in patients with diabetes receiving metformin, this medicine should be withheld for 48 hours before infusion of contrast medium and after exposure, until the estimate or measure of GFR is greater than 40 mL/min/1.73 m^2.[299] Use of metformin is not

Table 15. Observed Incidence of Acute Kidney Failure After PCI That Included Administration of Radiocontrast, Stratified by Baseline Serum Creatinine and Diabetes Status[292]

Serum Creatinine (mg/dL)	Risk, All Patients (%)	Risk, Patients With Diabetes (%)	Risk, Patients Without Diabetes (%)	Patients With *v* Without Diabetes, OR (95% CI) and *P*
0-1.1	2.4 (n = 3,965)	3.7 (n = 809)	2.0 (n = 3,156)	1.86 (1.20-2.89) 0.005
1.2-1.9	2.5 (n = 3,318)	4.5 (n = 710)	1.9 (n = 2,608)	2.42 (1.54-3.79) <0.001
2.0-2.9	22.4 (n = 179)	22.4 (n = 67)	22.3 (n = 112)	1.00 (0.48-2.08) NS
≥3.0	30.6 (n = 124)	33.9 (n = 62)	27.4 (n = 62)	1.36 (0.63-2.92) NS

Abbreviations: OR, odds ratio; NS, not significant.

Table 16. Effect of Interventions to Decrease the Risk of RCN in People With Diabetes and CKD Undergoing Angiographic Procedures

Author, Year	N		Mean GFR	Applic-ability	Radiocontrast Type	Intervention Type	Comparator	Outcome RCN (Definition)	Baseline Value	Net Effect	*P*	Quality
	Diabetes	CKD										
Stone, 2003[a] [338]	153	68	29		Low osmolar	Fenoldopam	Placebo	Δ SCr ≥25%	—	RR 1.11	NS	●
Kurnik, 1998[b] [339]	123	123	≤65		High osmolar	Anaritide	Placebo	Δ SCr	2.1	+0.4	.003[c]	●
										+0.5	.003[c]	
										+0.6	.003[c]	
Wang, 2000[b] [340]	100	158	SCr 2.8		Low osmolar	SB 209670	Placebo	Δ SCr ≥0.5 / 25%	—	67% vs 39%	.009	●
								Δ SCr 48 hr	2.9	+0.4	.01	
Mueller, 2002 [298]	217	276	84		nd	0.9% NaCl	0.45% NaCl	Δ SCr ≥0.5	—	0% vs 5.5%	.01	◎
								Δ SCr	1.0	-0.08	.04	
Solomon, 1994 [341]	41	78	SCr 2.1		High osmolar/low Osmolar/low osmolar	Mannitol Furoseminde	NaCl	Δ SCr ≥0.5	—	38% vs 14%	NS	◎
								Δ SCr ≥0.5	—	43% vs 14%	NS	
Tumlin, 2002 [342]	24	45	17-19		Iso-osmolar/low osmolar	Fenoldopam	0.5% NaCl	Δ SCr ≥0.5 or 25%	—	38% vs 64%	NS	◎
Weisberg, 1994 [343]	22	50	33		High osmolar	Dopamine + ANP + mannitol[d]	0.45% NaCl	Δ SCr >25%	—	RR 5.78	<.05	◎
Kini, 2001 [344]	116	nd	SCr 2.1		Nonionic low osmolar	Fenoldopam	Historical control	Δ SCr >25%	—	3.5% vs 26.2%	NS	○
Louis, 1996 [345]	51	nd	SCr 2.3		nd	1L 0.45% NaCl + mannitol	None	Kidney failure	—	12%	nd	○
Kapoor, 2002 [346]	70	70	86		High osmolar	Oral theophylline	None	Δ GFR	86	6.5 vs –18.6	NS vs .008	○
								Δ SCr	1.2	–0.17	NS vs .03	
Kapoor, 1996 [347]	40	5	SCr 1.5		Urograffin	Dopamine	None	Δ SCr	1.5	–0.5	NS vs .01	○
								Δ SCr >25%	—	0% vs 50%	nd	
Sterner, 2000 [348]	17	17	11 (HD) 20 (No HD)		Iohexol/iodixanol/ioxaglat	Hemodialysis	None	CCr	11(20)	0 vs +3	nd	○
Maydoon, 2001 [349]	nd	46	SCr 2.4		Low osmolar, nonionic (Fenoldopam group) High osmolar, ionic (no treatment group)	Fenoldopam	Dopamine+ ANP + Mannitol + NaCl[e]	Δ SCr >25%	—	14% vs 7%	nd	◯

a ***N***-Acetylcysteine was administered before the procedure.
b Any elective radiographic procedure.
c ***P*** value within group.
d Analyzed as 1 treatment group.
e Results from a published series "with similarly at risk patients" Weisberg 1994.

Table 17. Type of Radiocontrast Agent and Risk of RCN in Diabetes and/or CKD

Author, Year	N			Mean GFR	Applic-ability	Radiocontrast Dose Rate		Outcome (RCN)	Baseline Value	Net Effect	*P*	Quality
	Total	Diabetes	CKD									
RCTs: Low-osmolar vs high-osmolar radiocontrast												
Rudnick, 1995 [290]	359	0	0	SCr 1.01	🚹🚺	140 mL	139 mL	Δ SCr ≥1[a]	—	0%	nd	●
	315	315	0	SCr 0.98					—	+0.1%	nd	
	296	0	296	SCr 1.77					—	-3.3%	nd	
	213	213	213	SCr 2.03					—	-15%	nd	
Talierco, 1991 [350]	325	47 Type 1:26		SCr 1.84	🚹	134 mL	144 mL	Δ SCr	nd	+0.1	NS	⊙
Barret, 1992[b] [289]	249	25	25	SCr 1.35-2.25	🚹🚺	100 mL	120 mL	25% Δ SCr	—	12% v 0%	nd	○
		11	11	SCr > 2.25						14% v 75%	nd	
Nonrandomized, controlled study: Low-osmolar vs high-osmolar radiocontrast												
Lautin, 1991 [351]	303	152	73	SCr 1.35 24% >1.5 mg/dL	🚹🚺	78 mL	81 mL	Δ SCr > 0.3 and >20% on d 1-3 and 5-7	1.35	-30%	NS	○
								Δ SCr > 0.3 and >20% on d 1-3		-27%	NS	
								Δ SCr > 0.3 and >20% on d 1-2		-21%	NS	
								Δ SCr ≥2.0 on d 1 or 2		-16%	NS	
								Δ SCr ≥1.0 on d 1		-13%	NS	
RCT: Iso-osmolar vs low-osmolar radiocontrast												
Aspelin, 2003 [288]	135	135	135	50 47	🚹🚺🚺	163 mL	162 mL	peak Δ SCr in 3 d	1.49 (1.6)	-0.42	.001	●
								peak Δ SCr in 7 d		-0.17	.003	
								Δ SCr >0.5 in 3 d	—	OR: 0.09	NS	
Nonrandomized, controlled studies: Low-osmolar radiocontrast vs no control												
Manske, 1990 [297]	70	70	70	14	🚹🚺	31 mL	—	Δ SCr	5.9	+0.4	<.001	○
Lundquist, 1998 [352]	100	17	17	54	🚹	50 mL	—	25% Δ SCr	109	+4.1	NS	○
								25% Δ CCr	52	+2.1	NS	

a $P < 0.002$ for total group low-osmolar vs high-osmolar.
b Cardiac catheterization, intravenous pyelography, or computed tomographic scan with contrast.

Table 18. Preventive Strategies for RCN

Stop drugs that increase risk of RCN or lactic acidosis 48 h before procedures when possible[295,299] • Nonsteroidal anti-inflammatory agents • Aminoglycosides • Amphotericin B • Metformin*
Administer intravenous fluid at 1 mL/kg/h for 6-12 h before the radiographic contrast procedure • Use 0.9% normal saline or sodium bicarbonate, 154 mEq/L[295,296,298] • Watch for volume overload in those with CKD stage 4 or congestive heart failure
N-Acetylcysteine, 600 mg, orally twice daily the day before and day of radiographic contrast procedure [299,302]
Minimize radiographic contrast volume[297] • <30 mL if possible
Consider iso-osmolar or nonionic radiographic contrast material[288,290]
Consider hemofiltration in people with serum creatinine level > 2 mg/dL[301]

*Withhold metformin until the measure or estimate of GFR is greater than 40 mL/min/1.73 m^2 to reduce risk of lactic acidosis.[299]

recommended in patients with diabetes and CKD (see Guideline 2).

Although there is much interest in finding medicines to prevent RCN, few are known to be beneficial and none has been studied in a large population of patients with diabetes and CKD. Table 18 summarizes the clinical trials that report results in patients with diabetes and CKD. Studies examining the effectiveness of *N*-acetylcysteine, sodium bicarbonate, and hemofiltration have not specifically reported results for patients with diabetes and CKD. Nevertheless, in the opinion of the Work Group, it is reasonable to consider these approaches for people with diabetes and CKD, considering their high risk of RCN (Table 18).[295,300-302]

The European Society of Urogenital Radiology[299] and the American College of Radiology (www.acr.org/s_acr/sec.asp?CID=2131&DID=16687; last accessed January 31, 2006) offer guidelines for use of contrast media. These guidelines and results of a number of clinical trials are described in a recent review of methods for preventing RCN. The American guidelines mention the use of *N*-acetylcysteine and other potential prophylactic drug therapies without specifically recommending these approaches.

LIMITATIONS

No data are available to confirm that detection of microalbuminuria and initiation of treatment at this early stage of DKD leads to a decrease in hard end points (GFR decrease, CKD stage 5, and mortality). Furthermore, the predictive value of microalbuminuria for DKD is not as high as originally considered. Whether the lower predictive value is due to changes in disease natural history, improved therapies, or overestimation by the original studies is uncertain.[224] However, as many as 30% to 50% of microalbuminuric patients may revert to normoalbuminuria,[224,226,263,264] and whether this regression is spontaneous or not cannot be determined if the patient is on ACE inhibitor or ARB treatment. Nevertheless, some data suggest benefit of intensive glycemic and blood pressure control in patients with microalbuminuria. A detailed discussion of treatment of albuminuria (microalbuminuria and macroalbuminuria) and evaluation of outcomes can be found in CPR 1.

The current recommendations for microalbuminuria screening by the ADA[34,35] do not specifically recommend use of a first morning urine sample or overnight collections. However, postural microalbuminuria or proteinuria may be a confounding factor, particularly in young type 1 patients. Despite these limitations, it is clear that patients who are persistently normoalbuminuric tend to be at low risk of DKD, whereas microalbuminuric patients have a 3- to 4-fold increased risk. For classification purposes, the Work Group recommends that health care providers consider as macroalbuminuric all patients who have been diagnosed as such before ACE-inhibitor and/or ARB treatment.

Another limitation of this guideline relates to the classic definition of DKD according to AER, which has been used in the vast majority of treatment trials (see CPR 1). AER does not map easily to the KDOQI™ stages of CKD (Table 6) because staging is based on eGFR. Thus, while GFR may be elevated or within the normal range

in people with elevated urinary albumin excretion, loss of GFR within CKD stage 1 may already represent DKD. The formulae estimating GFR from serum creatinine values are problematic in their application to patients with diabetes.[244] Nonetheless, measures of albuminuria in combination with estimates of GFR will serve as useful guides in assessing and managing patients with diabetes and CKD. The Work Group developed a novel grid (Table 6) to combine staging by albuminuria classification and GFR, although at this time, evidence to define DKD probabilities within each box of this table is lacking.

IMPLEMENTATION ISSUES

The diagnosis and staging of DKD in an individual patient should include an evaluation of other related factors. Apart from albuminuria and GFR, patients should be evaluated for the presence of hypertension, poor glycemic control, dyslipidemia, and smoking. A family history of DKD or hypertension and/or CVD and stroke in parents without diabetes also is relevant. Moreover, in patients developing DKD, hypertension and dyslipidemia may be risk predictors, concomitants, or consequences. Because DKD typically does not occur in isolation, patients with DKD should have regular surveillance for other microvascular and macrovascular complications. These issues are covered in more detail elsewhere in these guidelines under the sections relating to background, blood pressure control, glycemic control, lipid management, lifestyle issues, and multifactorial intervention.

Ideally, ACR should be measured in first-void urine samples, but sometimes this may be impractical. Alternatively, if a random urine specimen is abnormal, the second test could be done in a first-voided morning sample obtained within the subsequent 3 to 6 months. Screening for microalbuminuria in patients with type 2 diabetes, if leading to multifactorial interventions, can result in reduced risks of cardiovascular events, progression of albuminuria, and development or progression of retinopathy and neuropathy.[303] Similar studies in patients with type 1 diabetes are lacking. Several cost-benefit analyses of screening for microalbuminuria have been published using various models. These models refer mostly to type 1 diabetes and have not been confirmed prospectively in clinical trials. International standards for measurement of creatinine and albumin should be adopted, and quality control between laboratories should be established. There should also be standardized reporting of ACRs with internationally agreed-upon categorical definitions.

GUIDELINE 2: MANAGEMENT OF HYPERGLYCEMIA AND GENERAL DIABETES CARE IN CHRONIC KIDNEY DISEASE

Hyperglycemia, the defining feature of diabetes, is a fundamental cause of vascular target-organ complications, including kidney disease. Intensive treatment of hyperglycemia prevents DKD and may slow the progression of established kidney disease.

2.1 Target HbA_{1c} for people with diabetes should be < 7.0%, irrespective of the presence or absence of CKD. (A)

BACKGROUND

Diabetes mellitus is the most common cause of kidney failure in the United States[4] and is among the most common causes in the rest of the world. A large number of epidemiological studies and controlled trials have defined risk factors for progression of DKD and response to treatment.[3] The purpose of this guideline is to review this literature with respect to glycemic control and translate the results into practical strategies for clinicians who treat people with diabetes and CKD, either due to DKD or other causes.

RATIONALE

Most of the evidence for this guideline comes from studies of intensive glycemic control in people with type 1 and 2 diabetes and CKD stages 1 and 2 (Table 19 and Table 20). End points include the initial development of microalbuminuria (urinary albumin excretion between 30 and 300 mg/24 h or 30 and 300 mg/g creatinine), progression to macroalbuminuria (>300 mg/24 h or >300 mg/g creatinine), and change in kidney function. Very few studies addressed the benefits and risks of intensive glycemic control in later stages of CKD, let alone in patients who are undergoing dialysis or have received kidney transplants.

Lowering HbA_{1c} levels to approximately 7.0% reduces the development of microalbuminuria. (Strong)

Type 1 Diabetes (Table 19)

A number of observational studies have shown that poorer glycemic control predicts the development of microalbuminuria.[353-359] Several small prospective intervention studies from the early 1980s also showed that improved glycemic control reduced the development and progression of elevated albuminuria; however, in most cases, the small sizes of the cohorts precluded statistically significant changes.[360-366] A meta-analysis of these studies concluded that intensive therapy significantly reduced the risk of nephropathy progression (odds ratio [OR], 0.34; 95% CI, 0.20 to 0.58; $P < 0.001$).[367] The DCCT was a multicenter randomized clinical trial of 1,441 subjects with type 1 diabetes that compared the effects of intensive glucose control with conventional treatment on the development and progression of the long-term complications of type 1 diabetes.[132] At baseline, mean HbA_{1c} levels were similar in both treatment groups. By 3 months after randomization, mean HbA_{1c} level was approximately 2% lower in the intensive-treatment group than the conventional-treatment group, and this difference was maintained throughout the study (7.2% versus 9.1%; $P < 0.001$).[132] After a mean of 6.5 years, intensive therapy reduced the occurrence of microalbuminuria by 34% (95% CI, 2% to 56%) in the primary-prevention group (no retinopathy and urinary AER < 28 μg/min at baseline) and by 43% (95% CI, 21% to 58%) in the secondary-intervention group, who had early complications at baseline (background retinopathy with or without microalbuminuria, but normal GFR; Fig 8).[132,368] To assess whether their reduced risk of DKD persisted long term, 1,349 of these subjects were evaluated as part of the EDIC study at the year 7 to 8 post-DCCT visit.[133] Data were analyzed according to the original intensive- versus conventional-treatment groups, and the primary-prevention and secondary-intervention cohorts were combined. The previous difference in HbA_{1c} levels for the intensive versus conventional group (7.2% and 9.1%, respectively) in the DCCT gradually narrowed during the first 2 years in the follow-up period and then remained near 8% for both groups for the subsequent 6 years. Eighty-seven new cases of microalbuminuria (15.8%) occurred in the conventional-treatment group, and 39 (6.8%), in the intensive-treatment group, for an RR reduction of 59% (95% CI, 39% to 73%, $P < 0.0001$; Fig 9).

Table 19. Effect of Glycemic Control on Kidney Function and Albuminuria in Type 1 Diabetes[a]

Author, Year	Study Duration (y)	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)	Comparator	Outcome	Baseline Value[b]	Net Effect		P	Quality
Insulin Therapy													
Kidney Function													
DCCT, 1995 [368]	9[c]	726 1°Pr	125	MacroAlb/MicroAlb 6%	🚹🚹🚹	Intensive insulin	Standard care	Final GFR	123 (126)	125 (126)		.08	●
		715 2°Ir	127						130 (125)	121 (122)		NS	
Reichard, 1993 [138]	7.5	93	125	MacroAlb 5% MicroAlb 23%	🚹🚹🚹	Intensive insulin	Standard insulin	Δ GFR	122 (126)	+3		.04	●
Dailey, 2000 [398]	1.5	49	57	2.0 g/d	🚹🚹	Pulsatile IV insulin	Intensive insulin[d]	Δ CCr	57	+5.5		.03	○
Albuminuria													
DCCT/EDIC, 2003 [133]	14.5	1349	126	MacroAlb 2% MicroAlb 10%	🚹🚹🚹	Intensive insulin	Standard care	Development of MacroAlb	—	OR 0.16		<.001	●
								Development of MicroAlb	—	OR 0.41		<.001	
DCCT, 1995 [368]	9	726 1°Pr	125	MacroAlb/MicroAlb 6%	🚹🚹🚹	Intensive insulin	Standard care	AER >208 µg/min	—	1°Pr	RR 0.56	NS	●
									—	2°Ir	RR 0.44	<.01	
								AER >70 µg/min	—	1°Pr	RR 0.61	NS	
									—	2°Ir	RR 0.44	<.01	
								Sustained AER >70 µg/min	—	1°Pr	RR 0.46	NS	
									—	2°Ir	RR 0.33	<.01	
								AER >28 µg/min	—	1°Pr	RR 0.66	NS	
									—	2°Ir	RR 0.57	<.01	
		715 2°Ir	127					Sustained AER >28 µg/min	—	1°Pr	RR 0.44	NS	
									—	2°Ir	RR 0.39	<.01	
								Δ AER (%/year)	—	1°Pr	-0.79	NS	
									—	2°Ir	-6.72	<.001	
Reichard, 1993 [138]	7.5	93	125	MacroAlb 5% MicroAlb 23%	🚹🚹🚹	Intensive insulin	Standard insulin	Δ UAE (µg/min)	56(63)	-67		.04	●
Intensive Glycemic Control													
Reichard, 1996 [399]	10	91	125	MacroAlb 5%	🚹🚹🚹	Intensive glycemic control	Standard control	GFR	123 (127)	+5		NS	●
								UAE progression	nd	-17%[e]		.01	

Abbreviations: 1°Pr, primary prevention; 2°Ir, secondary intervention.

a For DCCT/EDIC Study, only data from 1995 and 2003 publications included.

b Baseline value of outcomes in the treatment (comparator) arm.

c Mean duration of follow-up, 6.5 years for GFR outcome.

d DCCT style intensive treatment.

e Values are % of patients.

Table 20. Effect of Glycemic Control on Kidney Function and Albuminuria in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value[b]	Net Effect	*P*	Quality
Insulin Therapy												
Kidney Function												
Levin, 2000 [135]	2	88	89	MacroAlb/MicroAlb 0%	🧍	Intensive insulin (multiple/d)	Standard insulin (1-2x/d)	Δ CCr	89	+3%	NS	○
		53		MicroAlb 100%						-5%	NS	
Albuminuria												
Ohkubo, 1995 [136]	6	51 1°Pr	SCr <1.5	MicroAlb <50%	🧍🧍	Intensive insulin (4x/d)	Conventional insulin (1-2x/d)	New onset nephropathy	—	8% vs 28%	.03	○
		51 2°Ir								12% vs 32%	.04	
		102 All						Progression of albuminuria		RR 0.3	NS	
Shichiri, 2000 [137]	8	99	SCr <1.5	MicroAlb <50%	🧍🧍	Intensive insulin (4x/d)	Conventional insulin (1-2x/d)	Progression of albuminuria	—	RR 0.26	nd	○
Levin, 2000 [135]	2	140	89	MacroAlb/MicroAlb 38%	🧍	Intensive insulin (multiple/d)	Standard insulin (1-2x/d)	Δ ACR (mg/dL)	0.04	-0.095	.043	○
		88		MacroAlb/MicroAlb 0%				Δ ACR (mg/dL)	0.04	-0.045	NS	
		53		MicroAlb 100%				ACR >0.30	—	12% vs 36%	.04	
Insulin Therapy and Oral Hypoglycemic Agents												
UKPDS 33, 1998 [134]	10	3867	PCr 0.9	*P* 2%	🧍🧍	Insulin Chlorpropamide 500 mg Glibenclamide 20 mg Glipizide 40 mg	Conventional treatment (diet)	CKD Stage 5	—	RR 0.73	NS	●
								PCr doubling	—	RR 0.26	<.05	
								Proteinuria	—	RR 0.66	.04	
								MicroAlb	—	RR 0.67	<.05	

Abbreviations: 1°Pr, primary prevention; 2°Ir, secondary intervention.

a Maximum dose.

b Baseline value of outcomes in the treatment (comparator) arm.

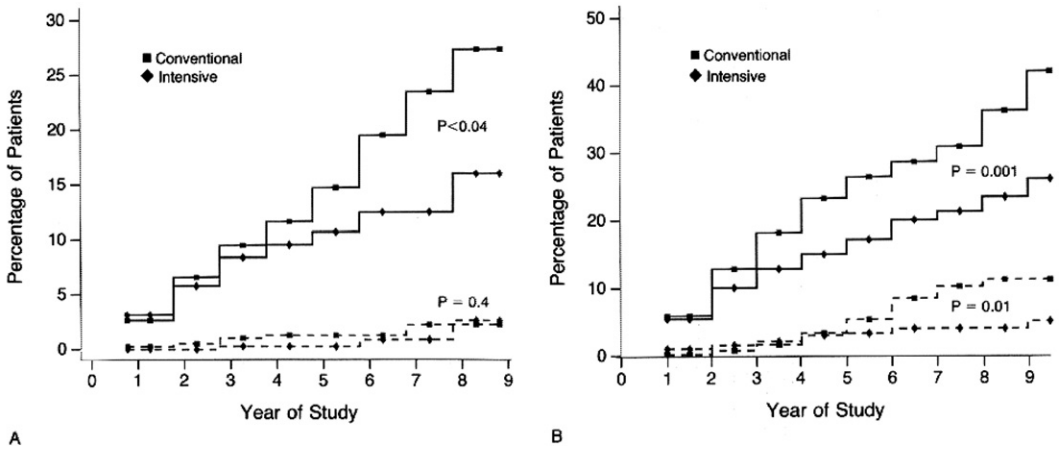

Figure 8. Cumulative incidence of urinary albumin excretion of 300 mg/24 h or greater (dashed line) and 40 mg/24 h or greater (solid line) in patients with type 1 diabetes mellitus receiving intensive or conventional therapy.
(A) In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk of microalbuminuria by 34% ($P <$ 0.04). (B) In the secondary-intervention cohort, patients with urinary albumin excretion of 40 mg/24 h or greater at baseline were excluded from the analysis of the development of microalbuminuria. Intensive therapy reduced the adjusted mean risk of albuminuria by 56% ($P = 0.01$) and the risk of microalbuminuria by 43% ($P = 0.001$) compared with conventional therapy. Reprinted with permission.[132]

Type 2 Diabetes (Table 20)

Observational studies have shown a similar association of poor glycemic control with the development of elevated albuminuria in type 2 diabetes.[369-373] Three major intervention studies also have been carried out. In a study design similar to the DCCT, the Kumamoto study separated 110 Japanese subjects with type 2 diabetes into primary-prevention and secondary-intervention cohorts and then randomly assigned them to intensive (HbA_{1c}, 7.1%) or conventional (HbA_{1c}, 9.4%) glycemic control with insulin.[136] During the 6-year study period, a significant reduction of both new-onset and progressive DKD was found

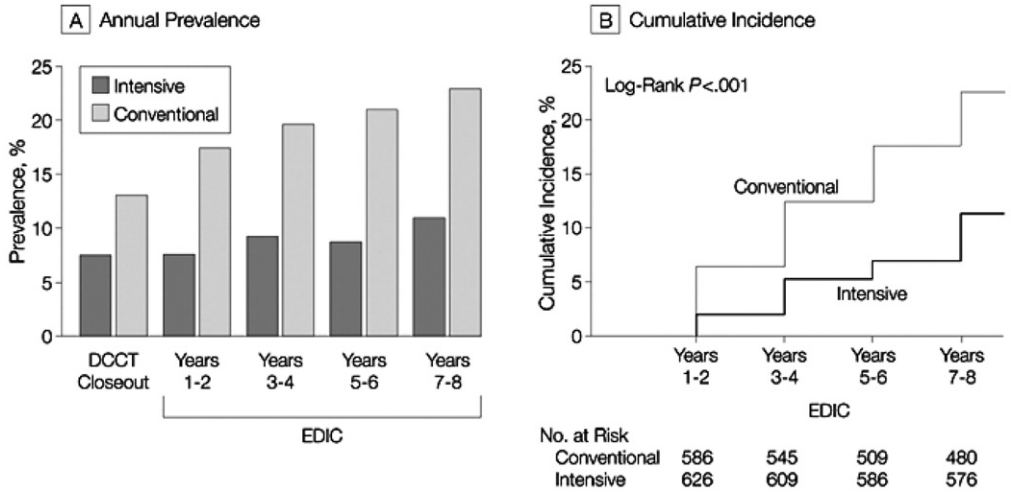

Figure 9. Prevalence and cumulative incidence of microalbuminuria.
Microalbuminuria defined as AER of 28 μg/min or greater, equivalent to 40 mg/24 h. (A) Prevalence at the end of the DCCT and during the EDIC Study. Differences between the 2 treatment groups are significant at each time after DCCT closeout ($P < 0.001$). (B) Cumulative incidence of new cases in the EDIC Study for participants in the intensive- and conventional-treatment groups with normal albuminuria at the beginning and end of the DCCT. The difference in cumulative incidences is significant by the log-rank test ($P < 0.001$). Reprinted with permission.[133]

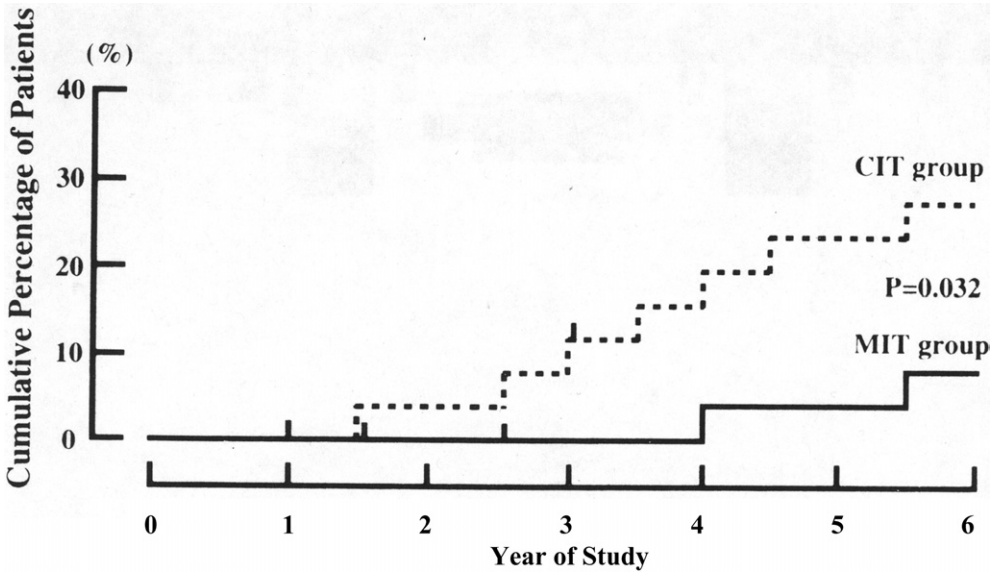

Figure 10. Cumulative incidence of DKD after 6 years of follow-up in patients with type 2 diabetes treated by intensive (solid line) and conventional (dashed line) insulin injection therapy in the primary-prevention cohort of the Kumamoto study. Dropout patients are indicated by short vertical lines on the solid and dashed lines. Abbreviations: MIT, multiple insulin injection therapy group; CIT, conventional insulin injection therapy group. Reprinted with permission.[136]

in subjects who received intensive glycemic control. In the prevention cohort, 7.7% of subjects in the intensive-treatment group developed elevated albuminuria versus 28.0% in the conventional-treatment group ($P = 0.03$; Fig 10). After 8 years, the proportions developing microalbuminuria were 11.5% and 43.5%, respectively (Fig 11).[137] The UKPDS randomly assigned newly diagnosed patients with type 2 diabetes to intensive management using a sulfonylurea or insulin or to conventional management with diet alone. Average HbA_{1c} level for the intensive group was 7.0% compared with 7.9% for the conventional group during the study.[134] After 9 years of intensive therapy, RR reduction for the development of microalbuminuria was 24% (95% CI, 9% to 38%; $P = 0.0006$).[134] No difference in risk reduction was seen whether intensive therapy was achieved with sulfonylurea or insulin.[116] In the Veterans Affairs (VA) Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial, 95 men with a mean duration of diabetes of 7.8 years and no microalbuminuria were randomly assigned to intensive diabetes control (mean HbA_{1c}, 7.1% at 2 years) or conventional control (mean HbA_{1c},

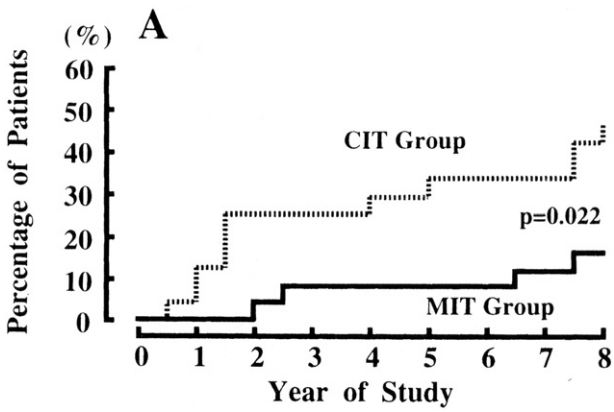

Figure 11. Cumulative incidence of DKD after 8 years of follow-up in patients with type 2 diabetes treated by intensive (solid line) and conventional (dashed line) insulin injection therapy in the primary-prevention cohort of the Kumamoto study.
Dropout patients are indicated by short vertical lines on the solid and dashed lines. Abbreviations: MIT, multiple insulin injection therapy group; CIT, conventional insulin injection therapy group. Reprinted with permission.[137]

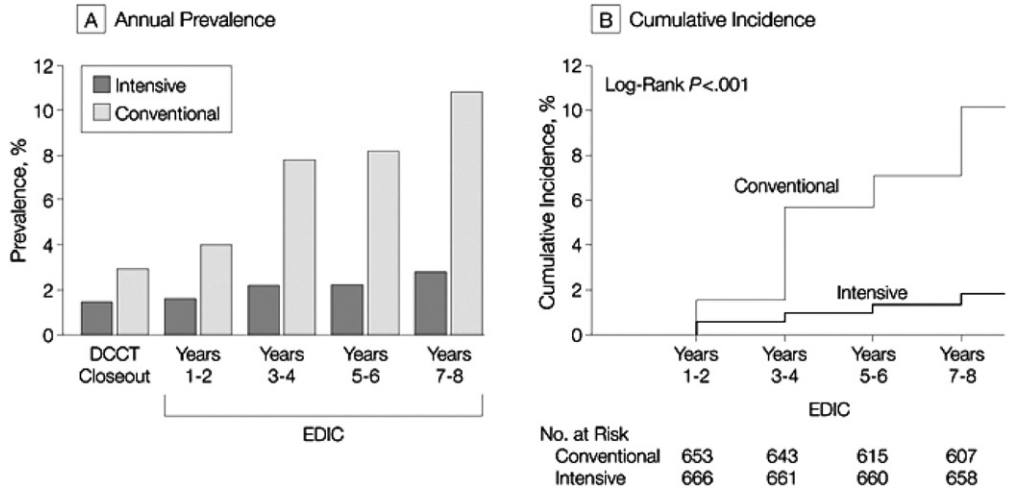

Figure 12. Prevalence and incidence of albuminuria.
Albuminuria was defined as AER of 208 μg/min or greater, equivalent to 300 mg/24 h. (A) Prevalence of clinical albuminuria at the end of the DCCT and during the EDIC Study. Differences between treatment groups are significant at each time point after DCCT close-out ($P < 0.01$). (B) Cumulative incidence of new cases in the EDIC Study for participants in the intensive- and conventional-treatment groups with either normoalbuminuria or microalbuminuria at the end of the DCCT. The difference in cumulative incidences is significant ($P < 0.001$). Reprinted with permission.[133]

9.2% at 2 years). In this study, 17% of the intensively treated group developed microalbuminuria, whereas 35% of the conventionally treated group developed microalbuminuria after 2 years ($P = 0.05$).[135]

Lowering HbA_{1c} levels to approximately 7.0% reduces the development of macroalbuminuria. (Moderate)

Type 1 Diabetes (Table 19)

In the DCCT, new cases of macroalbuminuria occurred in 5.6% of the conventional-treatment group and 0.8% of the intensive-treatment group, for an RR reduction of 84% (95% CI, 58% to 94%; $P = 0.0002$; Fig 8).[132,368] For those who progressed from microalbuminuria to macroalbuminuria, intensive therapy also reduced the RR significantly (83%; 95% CI, 21% to 96%; $P = 0.0236$).[132,368] In the EDIC follow-up study, 8 years after the end of the DCCT, previous intensive therapy within the DCCT was associated with only 9 cases (1.4%) of macroalbuminuria versus 59 cases (9.4%) in the previous conventional-therapy group, an RR of 84% (95% CI, 67% to 92%; Fig 12).[133] In the similarly designed Stockholm study of 102 patients with type 1 diabetes, intensive insulin therapy resulting in a mean HbA_{1c} of 7.1% was associated with macroalbuminuria in only 1 of 48 patients (2.1%), whereas conventional therapy, resulting in a mean HbA_{1c} of 8.5%, was associated with macroalbuminuria in 9 of 54 patients (16.6%; $P = 0.01$).[138]

Type 2 Diabetes (Table 20)

In type 2 diabetes, data from the Kumamoto study showed that 11.5% of the intensive-treatment group progressed to macroalbuminuria versus 32.0% of the conventional-treatment group ($P = 0.04$).[136] In the long-term follow-up of participants in the Kumamoto study, 2 years after completion of the original randomized trial, the difference in HbA_{1c} was maintained, as was the significant reduction in the development of macroalbuminuria (16% in the previous intensive group and 40% in the previous conventional group; $P = 0.04$).[137] In the UKPDS, the RR reduction for the development of macroalbuminuria with insulin or sulfonylureas was 33% at 9 years (4.4% versus 6.5%, intensive versus conventional), but this finding was not statistically significant.[134] In the VA study, 12% of those in the intensive-treatment group who entered with microalbuminuria progressed to macroalbuminuria, whereas 36% of those in the conventional-

Table 21. Effect of TZDs on Albuminuria, Glycemia, and Blood Pressure in Type 2 Diabetes

Author, Year	Mean Study Duration	N	Mean GFR	Albuminuria	Applicability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value[b]	Net Effect	*P*	Quality
Albuminuria												
Bakris, 2003 [379]	1 y	120 30[c]	nd	MicroAlb 25%		Rosiglitazone 8 mg	Glyburide 10.5 mg	Δ ACR	—	-14% -22%	NS NS	⊙
Nakamura, 2001 [381]	6 mo	28	CCr 105	MicroAlb 100%		Pioglitazone 30 mg	Placebo	Δ UAE (μg/min)	96.7 (79.4)	-58	<.01	⊙
Nakamura, 2001 [382]	1 y	16 16	CCr 105 CCr 101	MacroAlb 100% MicroAlb 100%		Troglitazone 400 mg	Glibenclamide 5 mg	Δ UAE (μg/min)	126 (122) 684 (692)	-8 -90	NS <.01	⊙
Imano, 1998 [380]	12 wk	30	nd	MicroAlb 100%		Troglitazone 400 mg	Metformin 500 mg	Δ ACR (mg/g)	70 (72)	-56	nd[d]	○
Glycemia												
Nakamura, 2001 [381]	6 mo	28	CCr 105	MicroAlb 100%		Pioglitazone 30 mg	Placebo	Δ HbA_{1c} (%)	8.4 (8.0)	-2.3	nd[d]	⊙
Nakamura, 2001 [382]	1 y	16 16	CCr 105 CCr 101	MacroAlb 100% MicroAlb 100%		Troglitazone 400 mg	Glibenclamide 5 mg	Δ HbA_{1c} (%)	8.2 (8.4) 8.8 (8.7)	-0.2 +0.1	nd[e]	⊙
Imano, 1998 [380]	12 wk	30	nd	MicroAlb 100%		Troglitazone 400 mg	Metformin 500 mg	Δ HbA_{1c} (%)	8.9 (8.8)	-0.3	nd[e]	○
Blood Pressure												
Nakamura, 2001 [381]	6 mo	28	CCr 105	MicroAlb 100%		Pioglitazone 30 mg	Placebo	Δ SBP (mm Hg)	126 (128)	+2	nd	⊙
Nakamura, 2001 [382]	1 y	16 16	CCr 105 CCr 101	MacroAlb 100% MicroAlb 100%		Troglitazone 400 mg	Glibenclamide 5 mg	Δ SBP (mm Hg)	136 (132) 138 (136)	-8 -4	nd	⊙
Imano, 1998 [380]	12 wk	30	nd	MicroAlb 100%		Troglitazone 400 mg	Metformin 500 mg	Δ BP (mm Hg)	148 (147)/80 (71)	-2/+5	nd	○

a Maximum dose.
b Baseline value of outcomes in the treatment (comparator) arm.
c Subgroup of patients with baseline microalbuminuria (data obtained from graph).
d *P* significant in the treatment arm for before versus after treatment.
e *P* significant in the treatment and comparator arm for before versus after treatment.

treatment group progressed in this fashion ($P = 0.04$).[135]

For all these studies in both type 1 and type 2 diabetes, the overall numbers of individuals with microalbuminuria who developed macroalbuminuria were small, but less with intensive therapy. Accordingly, differences in progression rates from microalbuminuria to macroalbuminuria with intensive therapy compared with conventional treatment generally were not statistically significant, although the trends were to reduce progression.

Lowering HbA_{1c} levels to approximately 7.0% reduces the rate of decrease in GFR. (Weak)

A few long-term observational studies have shown that poorer glycemic control is associated with a greater rate of decrease in GFR in patients with type 1 diabetes.[374-376] In studies of other interventions, such as ACE inhibitors or ARBs, HbA_{1c} levels often were included as covariates. In the Collaborative Study Group (CSG) analysis of the early captopril trial of patients with type 1 diabetes and CKD stages 2 to 3 (inferred from GFR and proteinuria levels), a higher HbA_{1c} level was associated with an increased risk of doubling of serum creatinine concentration.[377] A correlation ($r = 0.69$; $P = 0.01$) between HbA_{1c} level and rate of decrease in GFR also was found in a similar analysis of a much smaller group of patients followed up at the Steno Diabetes Center who were being treated with ACE inhibitors.[378]

Most prospective randomized studies used as evidence for the effect of glycemic control on kidney function are limited by the small number of patients reaching an outcome of a decrease in GFR. In a study of only 6 patients with type 1 diabetes in whom the rate of decrease in GFR was compared before and after institution of intensive insulin therapy, the change from 1.35 $\pm$ 0.31 to 0.69 $\pm$ 0.13 mL/min/mo was not statistically significant, probably because of the small number of subjects.[141] Another study found that more intensive glycemic treatment with just a modest decrease in HbA_{1c} of 1.2% resulted in preservation of GFR during 2 years compared with a usual-treatment group.[140] None of 48 patients in the intensive-treatment group and 6 of 54 in the conventional-treatment group in the Stockholm study decreased their GFR ($P = 0.02$).[138] In the EDIC/DCCT follow-up study, 0.7% of the previously intensive-treatment group and 2.8% of the previously conventional-treatment group developed serum creatinine concentrations of 2.0 mg/dL or greater ($P = 0.004$), and 1% versus 4%, respectively, developed measured creatinine clearance values less than 70 mL/min/1.73 m^2 ($P < 0.001$).[133] For patients with type 2 diabetes, intensive treatment in the UKPDS was associated with a 67% risk reduction for a doubling of plasma creatinine levels at 9 years (0.71% of the intensive group and 1.76% of the conventional group; $P = 0.027$).[134] In a small randomized study from Italy, 34 patients with type 2 diabetes who underwent intensive treatment with insulin and achieved an HbA_{1c} level of 7.0% stabilized their rate of decrease in GFR, whereas those randomly assigned to metformin achieved an HbA_{1c} of 8.0% and had a greater decrease in GFR during a 4-year period.[139]

Thiazolidinediones may have unique properties that reduce albuminuria. (Weak)

Several relatively small short-term studies have evaluated whether thiazolidinediones (TZDs) decrease albuminuria more than standard therapy with other oral agents (metformin or sulfonylureas) or dietary treatment for hyperglycemia in patients with type 2 diabetes and microalbuminuria (Table 21).[379-382] Albuminuria was decreased or trends in this direction were observed with TZD treatment in all these studies. Whether this putative benefit was caused by better control of risk factors or the TZDs per se is not clear from the available evidence because TZD treatment was associated with larger decreases in glycemia or correlated with decreases in blood pressure.[379,381,382]

COMPARISON WITH OTHER GUIDELINES

This guideline is consistent with the ADA guidelines,[34] which recommend that adults with diabetes achieve an HbA_{1c} level less than 7.0% or as close to normal as possible without excessive episodes of hypoglycemia, with the goal of reducing all complications of diabetes. Although the ADA does not have a separate guideline for patients with DKD, it recognizes that certain populations may require special considerations and that less intensive glycemic goals may be indicated in patients with severe or frequent

hypoglycemia. The American Association of Clinical Endocrinologists, the International Diabetes Federation Global Guidelines, and the European NIDDM Working Group proposed that the HbA_{1c} goal be less than 6.5% (www.rbh.nthames.nhs.uk/PRESTIGE/niddm/niddm.htm; last accessed 7/27/2006).[383] Again, this level is recommended with the goal of reducing all complications of diabetes. None of these organizations has a separate guideline specific to DKD.

LIMITATIONS

An overall glycemic goal for people with diabetes of less than 7.0% is very strongly supported by substantial data from large prospective randomized studies of both type 1 and type 2 diabetes. Much of this support stems from benefits for some of the other major complications of diabetes, especially retinopathy. With respect to kidney outcomes, data are very strong for the development of microalbuminuria. The numbers of patients progressing to more advanced outcomes, such as macroalbuminuria and decreases in GFR, are decreased significantly with improved glycemic control, but much of this decrease is related to the smaller number developing microalbuminuria to begin with. Nonetheless, even for those with more advanced disease, evidence supports reaching the recommended HbA_{1c} target.

IMPLEMENTATION ISSUES

Drug Therapies

The major risk for patients attaining HbA_{1c} levels less than 7.0% is the increasing development of hypoglycemia with lower glucose concentrations. This is particularly true for those with type 1 diabetes being treated with insulin.[132,138,384] Although the risk is increased in those with type 2 diabetes being treated with insulin,[134,137] the magnitude of the risk is considerably less. The UKPDS also showed that sulfonylureas are associated with a small risk of hypoglycemia.[134]

Special Considerations in CKD Stages 3 to 5

Patients with decreased kidney function (CKD stages 3 to 5) have increased risks for hypoglycemia for 2 reasons: (1) decreased clearance of insulin and some of the oral agents used to treat diabetes, and (2) impaired kidney gluconeogenesis. With reduced kidney mass, the amount of gluconeogenesis carried out by the kidney is decreased.[142] This reduction in gluconeogenesis may reduce the ability of a patient who is becoming hypoglycemic as the result of excessive insulin/oral agent dosage or lack of food intake to defend against hypoglycemia. However, this effect is difficult to quantify. About one third of insulin degradation is carried out by the kidney, and impaired kidney function is associated with a prolonged half-life of insulin. Thus, patients with type 1 diabetes receiving insulin who had significant creatinine elevations (mean, 2.2 mg/dL) had a 5-fold increase in the frequency of severe hypoglycemia.[143,144] Therefore, it is imperative that patients being treated intensively monitor their glucose levels closely and reduce doses of medicines (insulin and oral agents) as needed to avoid hypoglycemia.

With progressive decreases in kidney function, decreased clearances of the sulfonylureas or their active metabolites also have been found,[385-387] necessitating a decrease in drug dosing to avoid hypoglycemia. Table 22 provides recommendations for dosing of drugs used to treat hyperglycemia in patients with CKD stages 3 to 5. First-generation sulfonylureas (eg, chlorpropamide, tolazamide, and tolbutamide) generally should be avoided in patients with CKD because these agents rely on the kidney to eliminate both the parent drug and active metabolites, resulting in increased half-lives and risk of hypoglycemia. Of the second-generation sulfonylureas (eg, glipizide, gliclazide, glyburide, and glimepiride), glipizide and gliclazide are preferred agents because they do not have active metabolites and do not increase the risk of hypoglycemia in patients with CKD. In the meglitinide class, nateglinide has increased active metabolites with decreased kidney function,[388,389] but increased active metabolites do not occur with repaglinide, another meglitinide.[390] Metformin should not be given to patients with serum creatinine concentrations of 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women because it is cleared by the kidney and may build up with even modest impairment of kidney function, putting patients at risk of lactic acidosis.[391] However, hypoglycemia is not a problem with met-

Table 22. Dosing Adjustments by CKD Stage for Drugs Used to Treat Hyperglycemia

Class	Drug	Dosing Recommendation CKD Stages 3, 4, or Kidney Transplant	Dosing Recommendation Dialysis
First-generation sulfonylureas	Acetohexamide	Avoid	Avoid
	Chlorpropamide	Reduce dose by 50% when GFR <70 and ≥50 mL/min/1.73 m^2 Avoid when GFR <50 mL/min/1.73 m^2	Avoid
	Tolazamide	Avoid	Avoid
	Tolbutamide	Avoid	Avoid
Second-generation sulfonylureas	Glipizide	Preferred sulfonylurea No dose adjustment necessary	Preferred sulfonylurea No dose adjustment necessary
	Gliclazide	Preferred sulfonylurea No dose adjustment necessary Not available in US	Preferred sulfonylurea No dose adjustment necessary Not available in US
	Glyburide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Alpha-glucosidase inhibitors	Acarbose	Not recommended in patients with SCr >2 mg/dL	Avoid
	Miglitol	Not recommended in patients with SCr >2 mg/dL	Avoid
Biguanides	Metformin	Contraindicated with kidney dysfunction defined as SCr ≥1.5 mg/dL in men or ≥1.4 mg/dL in women	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	Initiate at low dose, 60 mg before each meal	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary	No dose adjustment necessary
Incretin mimetic	Exenatide	No dose adjustment necessary	No dose adjustment necessary
Amylin analog	Pramlintide	No dose adjustment necessary for GFR 20-50 mL/min/1.73 m^2	No data available
DPP-4 inhibitor	Sitagliptin	Reduce dose by 50% (50mg/day) when GFR < 50 and ≥ 30 mL/min/1.73 m^2 and by 75% (25 mg/day) when GFR < 30 mL/min/1.73 m^2	Reduce dose by 75% (25 mg/day)

formin. Rosiglitazone is cleared by the liver and does not have to be reduced with impaired kidney function.[392] Therefore, rosiglitazone does not increase the risk of hypoglycemia in patients with CKD, but it has the potential, along with pioglitazone, to worsen fluid retention.

Table 23 lists the available insulin preparations that may be used in diabetes and CKD. Doses are not specified by level of kidney function, but should be adjusted based on frequent monitoring to balance goals of glycemic control with avoiding hypoglycemia. Other considerations that are not specific to the level of kidney function include avoiding or minimizing the occurrence of interactions with drugs used to lower blood glucose. Table 24 lists clinically relevant

Table 23. Insulin Preparations Categorized by Duration of Effect

Duration of Effect	Insulin Preparation
Rapid-acting	Regular insulin Lispro insulin solution Insulin aspartate solution Insulin glulisine
Intermediate-acting	Isophane insulin suspension (NPH)
Long-acting	Insulin glargine Insulin detemir

Table 24. Clinically Relevant Interactions With Drugs Used to Treat Hyperglycemia

Class	Drug	Interaction	Managing the Interaction
Meglitinides	Repaglinide	Gemfibrozil increases repaglinide concentrations and half-life Inhibitors of CYP3A4 system	Combining repaglinide and gemfibrozil is not recommended. If clinically necessary, reduce the dose of repaglinide and monitor blood glucose carefully to avoid hypoglycemia
	Nateglinide	Nateglinide inhibits CYP2C9	Initiate doses of 2C9 substrates (eg, amiodarone, fluoxetine, phenytoin, and warfarin) at lower doses and monitor carefully
Thiazolidinediones	Pioglitazone	Pioglitazone may interact with CYP3A4 inducers or inhibitors	If combined use of pioglitazone with a CYP3A4 inducer is necessary, consider reducing dose of pioglitazone and careful blood glucose monitoring to avoid hypoglycemia
	Rosiglitazone	Gemfibrozil increases rosiglitazone area under the curve and half-life by inhibiting CYP2C8	If combination treatment with gemfibrozil and rosiglitazone is necessary, decrease rosiglitazone dose by 50%-70% and monitor blood glucose carefully to avoid hypoglycemia

Abbreviation: CYP, cytochrome P-450.

drug interactions. Other potential drug interactions also may exist.

Assessment of Glycemic Control and Complications Other Than Kidney Disease

An additional factor that may hinder good glycemic control in patients with progressive kidney disease is some degree of inaccuracy of the HbA_{1c} measurement in reflecting ambient glucose concentrations. Factors that may contribute to falsely decreased values include a reduced red blood cell lifespan, hemolysis, and iron deficiency, whereas falsely increased values may occur due to carbamylation of the hemoglobin and acidosis. However, the relationship between HbA_{1c} and glucose concentrations was not different between patients with normal kidney function and those with kidney failure (mean creatinine, 6.6 mg/dL), but some hemodialysis patients had lower than expected HbA_{1c} concentrations relative to the ambient glucose concentrations.[393] Opposite findings for dialysis patients were reported.[394] In a comparison of different affinity high-performance liquid chromatography methods, the Variant II (Bio-Rad Laboratories) method showed a positive bias (0.59% at 6% HbA_{1c} and 0.88% at 9% HbA_{1c}), but other methods (Primus CLC330, Diamat, Unimate) did not show clinically significant biases (www.missouri.edu/~diabetes/ngsp/index.html; last accessed October 8, 2006).[391] Neither peritoneal dialysis nor hemodialysis acutely change HbA_{1c} levels.[392] Fructosamine generally correlated more poorly with glucose than did HbA_{1c} in patients with CKD stages 4 and 5.[395,396]

The patient on long-term dialysis therapy no longer needs to achieve good glycemic control to prevent deterioration of kidney function. However, good control may still prevent or slow the progression of retinopathy, neuropathy, and possibly macrovascular disease. Survival improves with better glycemic control in patients on peritoneal dialysis[145] and hemodialysis therapy.[146] In the latter study, after adjustment for age and sex, HbA_{1c} was a significant predictor of survival (hazard ratio [HR], 1.133 per 1.0% increment of HbA_{1c}; 95% CI, 1.028 to 1.249; $P = 0.012$).[146]

In the opinion of the Work Group, assessment of glycemic control in diabetes and CKD should follow the standards set by the ADA (Table

Table 25. ADA Standards for Assessment of Glycemic Control[34]

Measurement	Frequency	Goal
HbA_{1c}	Twice per year in stable patients who are achieving goals Every 3 mo after change in treatment or if goal not achieved	<7.0%
Preprandial capillary glucose	Treated with multiple insulin injections: ≥3 times daily Treated with fewer insulin injections, oral agents, or medical nutrition therapy alone: daily, sufficiently often to achieve goals	90-130 mg/dL (5.0-7.2 mmol/L)
Peak postprandial capillary glucose (1-2 h after beginning a meal)	As needed May be particularly helpful in patients with gastroparesis and those using rapid insulin injections before meals to adjust the dose-meal calculation	<180 mg/dL (<10.0 mmol/L)

Table 26. ADA Standards for Assessment of Retinopathy and Foot Care[379]

Complication	Evaluation	Setting	Frequency
Retinopathy	Comprehensive dilated eye examination or nonmydriatic digital stereoscopic retinal imaging	Ophthalmologist or optometrist who is knowledgeable and experienced in diabetic retinopathy or nonmydriatic digital stereoscopic retinal imaging	Annually
Foot ulcers*	Visual inspection	Self-management	Daily
	Visual inspection	Health care encounters	Each visit
	Semmes-Weinstein monofilament testing, 128-Hz tuning fork	Health care encounters	Annually
	Pedal pulses†	Health care encounters	Annually
	Comprehensive examination and preventive care	Refer high-risk patients to foot and/or vascular specialists[b]	Annually, more often as needed

*High-risk patients include those with CKD, CVD, peripheral vascular disease, neuropathy with loss of protective sensation, reduced ankle-brachial index, or altered biomechanics, callus, bony deformity, nail pathology, retinopathy, diabetes duration longer than 10 years, and poor glycemic control.
†Consider obtaining an ankle-brachial index at initial screening for peripheral arterial disease because many patients with peripheral arterial disease are asymptomatic.

25).[34] In people receiving multiple insulin injections, SMBG is recommended 3 or more times daily (before meals and at bedtime). In those receiving less frequent insulin injections, oral agents, or medical nutrition therapy alone, SMBG is useful in achieving glycemic goals. Postprandial SMBG testing also may be helpful, particularly in patients with gastroparesis, to achieve postprandial glucose goals and in patients using rapid insulin injections before meals to adjust the dose-meal calculation. The optimal frequency of SMBG has not been established in patients with type 2 diabetes treated by oral agents, but the ADA recommends testing sufficiently often to reach glycemic goals. In addition, HbA_{1c} levels should be determined at least twice per year in stable patients who are achieving glycemic goals and more often, approximately every 3 months, in patients whose therapy has changed or who are not reaching goals.

Other microvascular and macrovascular complications of diabetes are common in those with CKD. Assessment and management of CVD is addressed in the Background section of these guidelines. Screening and treatment of retinopathy and foot care also are essential to the care of patients with diabetes and kidney disease. In the absence of specific data in the diabetes and CKD population, the Work Group recommends following the standards set by the ADA (Table 26).[34] An ophthalmologist or optometrist who is knowledgeable and experienced in the diagnosis and management of diabetic retinopathy should perform a comprehensive dilated eye examination annually in all people with diabetes. Recently, nonmydriatic digital stereoscopic retinal imaging has proved to be a sensitive and specific method to screen and diagnose retinopathy, and it is being used in many facilities. In a recent study, sensitivity was 98% and specificity was 100%.[397] Patients should be educated about the importance of foot surveillance and ulcer prevention, with an emphasis on self-management as discussed in CPR 4. The feet should be examined visually at each health care visit. A comprehensive foot and vascular examination including visual inspection, Semmes-Weinstein monofilament testing, use of a 128-Hz tuning fork for testing of vibratory sensation, and evaluation of pedal pulses should be performed annually. Because the risk of ulcers and amputations is high in those with diabetes and CKD, referral to foot-care specialists for annual examinations and preventive care is encouraged.

GUIDELINE 3: MANAGEMENT OF HYPERTENSION IN DIABETES AND CHRONIC KIDNEY DISEASE

Most people with diabetes and CKD have hypertension. Treatment of hypertension slows the progression of CKD.

3.1 Hypertensive people with diabetes and CKD stages 1-4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic. (A)

3.2 Target blood pressure in diabetes and CKD stages 1-4 should be < 130/80 mm Hg. (B)

BACKGROUND

The natural history of DKD is characterized by hypertension, along with increasing albuminuria and decreasing GFR. In both type 1 and type 2 diabetes, the natural history is similar, with the exception that onset of hypertension and vascular disease is earlier in the course of kidney disease in type 2 diabetes.[147,148] A large number of epidemiological studies and controlled trials have defined hypertension as a risk factor for progression of DKD, and antihypertensive treatment reduces this risk.[3]

The purpose of this guideline is to provide a focused update of the diabetes and CKD section of the NKF-KDOQI™ CPGs on Hypertension and Antihypertensive Agents in CKD.[5] The rapidly emerging literature in this field was reviewed to update the guidelines. A major difference in the present guideline is that the recommendation for ACE-inhibitor or ARB treatment in normotensive people with diabetes and microalbuminuria or macroalbuminuria was placed in CPR 1. This change was made because very few normotensive patients were included in existing studies and data are limited primarily to surrogate outcomes (albuminuria/proteinuria). Studies in which albuminuria reduction by RAS inhibition was a specified outcome also were reviewed. Because these studies were limited to secondary analyses of clinical trials of ARBs in patients with type 2 diabetes and DKD, this discussion also was placed in CPR 1.

RATIONALE

For this guideline, studies of people with type 1 or type 2 diabetes and CKD stages 1 to 4 were included. Studies of kidney transplant recipients were excluded. Because of the high prevalence of diabetes, many individuals with other types of CKD also may have diabetes. In general, the guidelines for use of antihypertensive agents in kidney disease due to diabetes and other causes do not conflict.[34,154]

ACE inhibitors and ARBs were compared with other classes of antihypertensive agents. In these studies, diuretics frequently were used as additional antihypertensive agents to achieve blood pressure control. Few studies directly compared ACE inhibitors and ARBs with each other in DKD, and with the exception of 1 study,[400] all focused on changes in blood pressure, rather than markers of kidney disease or clinical outcomes. In addition, data comparing other classes of antihypertensive agents are provided. The main recommendations for this guideline and for doses of ACE inhibitors and ARBs are shown in Table 27 and Table 28, respectively.

Most patients with DKD have hypertension. (Strong)

Hypertension is one of the most common comorbidities in DKD (Table 29).[149-153] Because the studies cited in Table 29 were published before the JNC 7 report, hypertension generally was defined as blood pressure greater than 140/90 mm Hg. The JNC 7 defines hypertension in those with diabetes or CKD as blood

Table 27. Hypertension and Antihypertensive Agents in DKD

Clinical Assessment	Target Blood Pressure		Preferred Agents for CKD		Other Agents to Reduce CVD Risk and Reach Target Blood Pressure	
Blood pressure ≥130/80 mm Hg	<130/80 mm Hg	B	ACE inhibitor or ARB	A	Diuretic preferred, then β-blocker or calcium channel blocker	A

Note: Letters in shaded areas denote strength of recommendations.

Table 28. Doses of ACE Inhibitors and ARBs for Adults

Drug Name (Trade Name)	Starting Dose	Goal Dose*
ACE Inhibitors		
Benazepril (Lotensin)	10 mg daily	20-40 mg/d in 1-2 divided doses
Captopril (Capoten)	6.25-25 mg 3 times per day	25-150 mg 2 or 3 times per day
Enalapril (Vasotec)	5 mg daily	10-40 mg daily in 1-2 divided doses
Fosinopril (Monopril)	10 mg daily	20-80 mg daily
Lisinopril (Prinivil, Zestril)	10 mg daily	20-40 mg daily
Moexipril (Univasc)	7.5 mg daily	7.5-30 mg daily in 1-2 divided doses
Perindopril (Aceon)	4 mg daily	4-16 mg daily in 1-2 divided doses
Quinapril (Accupril)	10-20 mg daily	20-80 mg daily in 1-2 divided doses
Ramipril (Altace)	1.25 mg daily (CCr <40 mL/min/1.73 m^2) 2.5 mg daily	1.25-20 mg daily in 1-2 divided doses
Trandolopril (Mavik)	1 mg daily	2-4 mg daily
ARBs		
Candesartan (Atacand)	16 mg as monotherapy	2-32 mg daily in 1-2 divided doses
Eprosartan (Teveten)	600 mg daily (monotherapy)	400-800 mg daily in 1-2 divided doses
Irbesartan (Avapro)	150 mg daily	150-300 mg daily
Losartan (Cozaar)	25-50 mg daily	25-100 mg daily in 1-2 divided doses
Omesartan (Benicar)	20 mg daily (monotherapy)	20-40 mg daily
Telmisartan (Micardis)	40 mg daily	40-80 mg daily
Valsartan (Diovan)	80 or 160 mg daily	80-320 mg daily

*Goal doses should be at the higher end of the dose range when possible.

pressure greater than 130/80 mm Hg. Thus, these prevalence estimates likely represent lower range values based on current criteria for hypertension in diabetes or CKD. The onset of hypertension in type 1 diabetes generally signifies the onset of DKD. Conversely, hypertension in type 2 diabetes may occur in the absence of DKD.

Higher levels of blood pressure are associated with more rapid progression of DKD. (Strong)

A number of prospective studies show a strong relationship between a higher level of blood pressure and an increased risk of kidney failure and worsening kidney function in DKD.[401-403] Some studies suggest that higher systolic blood pressure is more important than higher diastolic blood pressure or high pulse pressure for kidney disease progression.[173,403]

ACE inhibitors and ARBs are effective in slowing progression of kidney disease characterized by microalbuminuria in hypertensive patients with type 1 or type 2 diabetes. (Moderate)

ACE inhibitors and ARBs decrease urine albumin excretion, slow the increase in albumin excretion, and delay the progression from microalbuminuria to macroalbuminuria in kidney disease due to type 1 or type 2 diabetes (Table 30).[155-166] Although most patients in these studies were hypertensive, some patients were not (by conventional criteria) because of their early stage of kidney disease. Consequently, patients in the ACE-inhibitor or ARB group had lower mean blood pressure during follow-up than patients in the control group. A "head-to-head" comparison of an ACE inhibitor versus ARB in a small study of predominantly microalbuminuric

Table 29. Prevalence of Hypertension in DKD

Clinical Features	Prevalence (%)
Type 1 diabetes, microalbuminuria	30-50
Type 1 diabetes, macroalbuminuria	65-88
Type 2 diabetes, microalbuminuria	40-83
Type 2 diabetes, macroalbuminuria	78-96

The prevalence in type 2 diabetes varies among ethnic populations and thus has a wider range.[149-153]

Table 30. Effect of Antihypertensive Agents on CKD and Hypertension in Type 1 and Type 2 Diabetes

Author, Year	N	Applicability	Baseline [a]			Comparators BP Outcomes		Clinical Outcomes				Methodological Quality
			Mean GFR	Proteinuria (mg/24 h) [b] denotes albuminuria	Mean BP (mm Hg)	Comparator 1 Final Mean BP (mm Hg)	Comparator 2 Final Mean BP (mm Hg)	Kidney Disease Progression	Proteinuria	CVD and Mortality	LVH	
Chronic Kidney Disease & Type 1 Diabetes												
ACE-I vs Placebo												
Lewis, 1993 [168]	409	🚹🚹🚹	84	2500	137/85	Captopril 96 (MAP)	Placebo 100 (MAP)	+[c]				●
ACE-I vs Dihydropyridine CCB												
Tarnow, 1999 [429]	52	🚹🚹	88	1338[b]	152/95	Lisinopril 142/82	Nisoldipine 153/84				NS	○
ACE-I vs Dihydropyridine CCB vs β-Blocker												
Sawicki, 1997 [430]	33	🚹🚹	80	1600[b]	146/90	Ramipril 138/86	Felodipine 137/82	NS	NS[b]			○
						Ramipril 138/86	Metoprolol 144/86	NS	NS[b]			
						Felodipine 137/82	Metoprolol 144/86	NS	NS[b]			
Chronic Kidney Disease & Type 2 Diabetes												
ACE-I vs Placebo												
Trevisan, 1995 [165]	152	🚹🚹🚹	SCr 1.0	89	147/90	Ramipril 142/87	Placebo 149/87		+[c]			●
Ruggenenti, 2004 [419]	1204	🚹🚹	SCr 0.9	7.2	151/87	Trandolapril 139/81	Placebo 142/83		+[bc]			◎
ACE-I + Non-Dihydropyridine CCB vs Placebo												
Ruggenenti, 2004 [419]	1204	🚹🚹	SCr 0.9	7.6	151/87	Trandolapril + Verapamil 139/80	Placebo 142/83		+[bc]			◎
ACE-I vs Diuretic												
						Lisinopril	Chlorthalidone					
Rahman, 2005 [172]	3674	🚹🚹	103[d] (≥90)	nd	146/85[d]	136/75[e]	134/75[e]	NS				●
	5944		75[d] (60-89)		146/84[d]			NS				
	1888		50[d] (<60)		147/83[d]			NS				
	5433[d]		50[d] (30-59)					NS[d]		NS[d]		
ACE-I vs β-Blocker												
Bakris, 1996 [406]	34	🚹🚹🚹	67	2700	155/97	Lisinopril 134/84	Atenolol 138/84	+				●
Schnack, 1996 [164]	105	🚹🚹🚹	82	127 mg/g Cr[b]	170/100	Ramipril 150/85	Atenolol 150/80		+[c]			◎

Author, Year	N	Applicability	Baseline [a]			Comparators BP Outcomes		Clinical Outcomes				Methodological Quality
			Mean GFR	Proteinuria (mg/24 h) [b] denotes albuminuria	Mean BP (mm Hg)	Comparator 1 Final Mean BP (mm Hg)	Comparator 2 Final Mean BP (mm Hg)	Kidney Disease Progression	Proteinuria	CVD and Mortality	LVH	
Chronic Kidney Disease & Type 2 Diabetes (continued)												
ACE-I vs Dihydropyridine CCB												
Schrier, 2002 [424]	480		82	30-300	137/84	Enalapril nd	Nisoldipine nd	NS				●
Estacio, 2000 [409]	470		83	30-300	156/98	Enalapril 132/78	Nisoldipine 138/86	NS				●
Agardh, 1996 [155]	335		102	94[b]	163/99	Lisinopril 147/88	Nifedipine 150/88		+[c]			●
De Cesaris, 1996 [158]	46		148	151	155/100	Benazepril 143/86	Nicardipine 144/84		+[c]			●
Chan, 1992 [156]	102		66	65[b]	120 (MAP)	Enalapril 99 (MAP)	Nifedipine 97 (MAP)		+[c]			●
Chan, 2000 [157]	102		74	73[b]	172/92	Enalapril nd	Nifedipine nd		+[c]			●
Velussi, 1996 [431]	18		110	76	183/95	Cilazapril 135/74	Amlodipine 135/74	NS				○
ACE-I vs Non-Dihydropyridine CCB												
Bakris, 1996 [406]	36		67	2700	155/97	Lisinopril 134/84	Verapamil 138/86	NS				●
ARB vs Placebo												
Brenner, 2001 [167]	1513		SCr 1.9	1237 mg/g Cr[b]	152/82	Losartan 140/74	Placebo 142/74	+[c]				●
Lewis, 2001 [169]	1148		SCr 1.7	2900[b]	160/87	Irbesartan 140/77	Placebo 144/80	+[c]				●
Parving, 2001 [161]	396		110	84[b]	153/90	Irbesartan 150 mg 143/83	Placebo 141/83		+			●
	395		108	77[b]	153/90	Irbesartan 300 mg 141/83	Placebo 141/83		+			
ARB vs ACE-I												
Barnett, 2004 [400]	216		93	67[b]	152/86	Telmisartan 143/78	Enalapril 146/83	NS	NS			○
ARB vs Dihydropyridine CCB												
Lewis, 2001 [169]	1146		SCr 1.7	2900[b]	160/87	Irbesartan 140/77	Amlodipine 141/77	+[c]				●

(Continued)

Table 30 (Cont'd). Effect of Antihypertensive Agents on CKD and Hypertension in Type 1 and Type 2 Diabetes

Author, Year	N	Applicability	Baseline [a]			Comparators BP Outcomes		Clinical Outcomes				Methodological Quality
			Mean GFR	Proteinuria (mg/24 h) [b] denotes albuminuria	Mean BP (mm Hg)	Comparator 1 Final Mean BP (mm Hg)	Comparator 2 Final Mean BP (mm Hg)	Kidney Disease Progression	Proteinuria	CVD and Mortality	LVH	
Chronic Kidney Disease & Type 2 Diabetes (continued)												
ARB vs ARB+ACE-I												
Mogensen, 2000[422]	197	🚹🚹🚹	104	64	163/96	Candesartan +14/+10 (change)	Lisinopril + Candesartan +25/+16 (change)		**NS**			●
CCB vs Diuretic												
						Amlodipine	Chlorthalidone					
Rahman 2005 [172]	3674	🚹🚹	103[d] (≥90)	nd	146/85[d]	135/75[e]	134/75[e]	**NS**				●
	5944		75[d] (60-89)		146/84[d]			**NS**				
	1888		50[d] (<60)		147/83[d]			**NS**				
	5433[d]		50[d] (30-59)					**NS**[d]		**NS**[d]		
CCB vs Placebo												
Lewis, 2001 [169]	1136	🚹🚹🚹	SCr 1.7	2900[b]	158/87	Amlodipine 141/77	Placebo 144/88	**NS**				●
Ruggenenti, 2004 [419]	1204	🚹🚹	SCr 0.9	8.4	150/87	Verapamil 141/82	Placebo 142/83		**NS**			○

Note: Clinical Outcomes: Coding of comparison of study arm 1 versus study arm 2: "+" better, "-" worse (with reference to benefit for patient). "NS" comparison was not statistically significant. Kidney Disease Progression: This includes: doubling of SCr, increase in SCr, loss of GFR or CCr, CKD Stage 5 (dialysis or transplantation). GFR is given in mL/min/1.73 m^2 or mL/min, creatinine clearance (CCr) is given in mL/min/1.73 m^2 or mL/min. Serum creatinine (SCr) is given in mg/dL that is reported only if GFR or CCr are not given. To convert serum creatinine from mg/dL to µmol/L, multiply by 88.4. Results from controlled trials which primarily studied kidney disease progression outcomes, but included all-cause mortality in their primary composite outcomes, were subsumed under kidney disease progression outcomes. Proteinuria includes: increase in proteinuria; increase from microalbuminuria to macroalbuminuria. Proteinuria or albuminuria (denoted by [b]) is given in mg/24 h. CVD and mortality includes: CVD death (myocardial infarction and stroke), nonfatal myocardial infarction, unstable angina or acute coronary syndrome, heart failure, cerebrovascular event, critical leg ischemia or peripheral vascular disease or amputation, any revascularization such as coronary, cerebrovascular, or peripheral revascularization. LVH includes increase in left ventricular hypertrophy or increase in left ventricular mass or volume.

Abbreviations: NS,= No significant difference between the 2 interventions.

+ = Comparator 1 showed significant benefit compared to comparator 2.

a Baseline data from comparator 1 group are reported.

b Albuminuria.

c Effect preserved after adjustment for arterial blood pressure during follow-up.

d The total number of subjects with GFR of 30-59 mL/min/1.73 m^2 in the 3 treatment arms (lisinopril, chlorthalidone and amlodipine), including diabetic and nondiabetic patient data from abstracts.

e Blood pressure values include participants with and without diabetes.

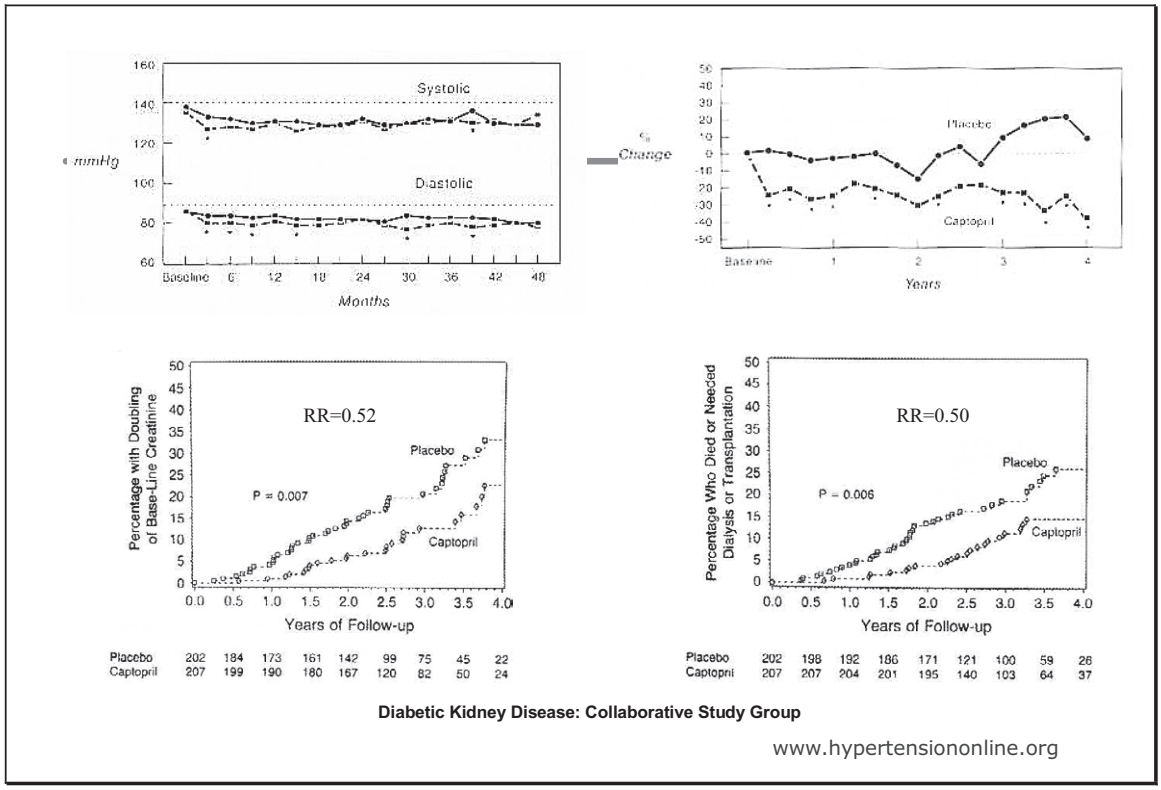

Figure 13. Results from the CSG captopril trial.
Changes in (A) blood pressure and (B) proteinuria. Squares, captopril group; circles, placebo group. Cumulative event rates for (C) doubling of baseline serum creatinine and (D) for death, dialysis, or transplantation. Modified with permission.[168]

hypertensive patients with type 2 diabetes and a GFR greater than 70 mL/min/1.73 m^2 demonstrated equivalent efficacy of the 2 agents in slowing loss of kidney function, given similar levels of blood pressure reduction.[400] Follow-up in most studies of microalbuminuric patients generally was in the range of 2 to 4 years, so GFR often was stable.

Because no trials of ACE inhibitors or ARBs in patients with diabetes and microalbuminuria have demonstrated a reduction in such clinical outcomes as CKD stage 5, doubling of serum creatinine level, or death, the Work Group concluded that evidence for treatment of microalbuminuric patients with these medicines is moderate. This represents a change in level of evidence grading from "strong" in the NKF-KDOQI™ CPGs on Hypertension and Antihypertensive Agents in CKD.[5] At the time of the present review, the Work Group believed that the change in evidence grading would encourage studies of long-term outcomes and other types of agents. However, in the absence of participation in such a clinical trial, the Work Group recommends this treatment despite moderate evidence.

ACE inhibitors are more effective than other antihypertensive classes in slowing progression of kidney disease characterized by macroalbuminuria in hypertensive patients with type 1 diabetes. (Strong)

The CSG trial of captopril in diabetic nephropathy demonstrated that ACE inhibitors are effective in reducing albuminuria and slowing the decrease in GFR and onset of kidney failure in patients with type 1 diabetes and macroalbuminuria (Table 30).[168,171,404,405] In the placebo group, blood pressure was controlled with other antihypertensive agents as necessary. Figure 13 shows results from the CSG trial.[168] In that study, the

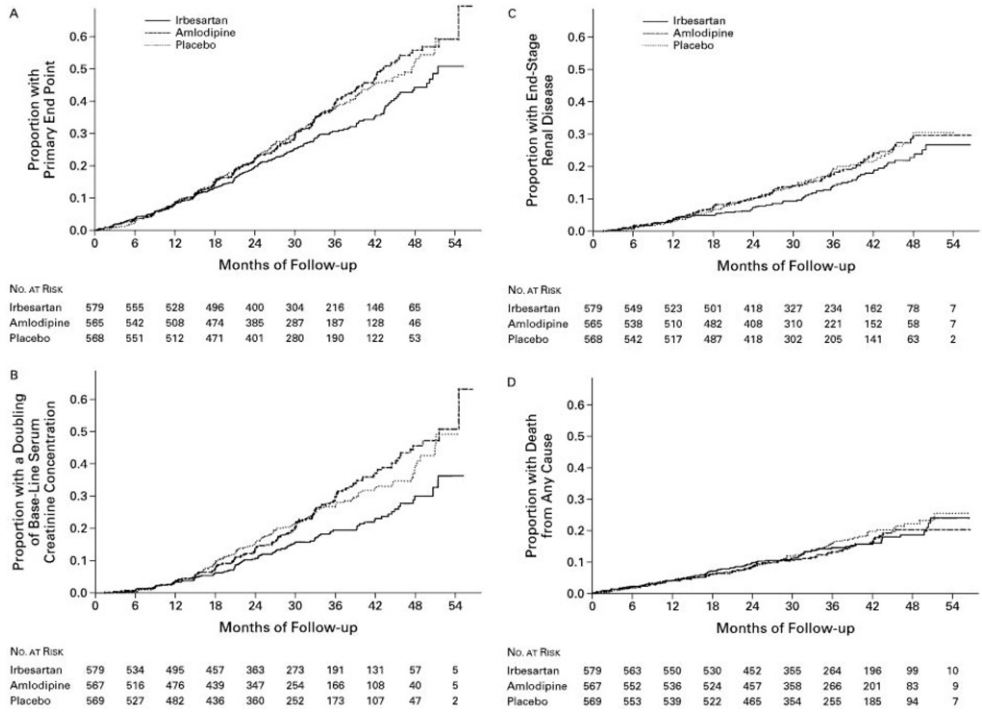

Figure 14. Results from the IDNT.
Kaplan-Meier curves of the percentage of patients with (A) the primary composite end point and its individual components, (B) a doubling of the serum creatinine concentration, (C) CKD stage 5, and (D) death from any cause. Reprinted with permission.[169]

beneficial effect of ACE inhibitors was greater in patients with decreased GFR at baseline, possibly because the end point, a doubling of baseline serum creatinine level, is achieved more quickly in patients with reduced GFR. The effects of ACE inhibitors may be caused in part by the antihypertensive effect and in part by additional mechanisms because kidney benefits appeared to be greater than expected for blood-pressure lowering.

ARBs are more effective than other antihypertensive classes in slowing progression of kidney disease characterized by macroalbuminuria in hypertensive patients with type 2 diabetes. (Strong)

A number of high-quality randomized controlled trials demonstrate that ARBs are more effective than other antihypertensive drug classes in slowing the decline in GFR and onset of kidney failure in patients with type 2 diabetes and macroalbuminuria. Figure 14 and Figure 15 show the results from IDNT and the RENAAL, 2 large studies of patients with macroalbuminuria and decreased GFR at the time of enrollment.[167,169] In these studies, the effects of ARBs may be caused in part by the antihypertensive effect and in part by additional mechanisms because kidney benefits appeared to be greater than expected for blood-pressure lowering.

ACE inhibitors may be more effective than other antihypertensive classes in slowing the progression of kidney disease characterized by macroalbuminuria in hypertensive patients with type 2 diabetes. (Weak)

Data on the efficacy of ACE inhibitors in kidney disease caused by type 2 diabetes are uncertain. Some studies show greater reduction in albuminuria and slower decrease in GFR compared with other hypertensive agents (Table 30).[405-408] However, small sample size, use of surrogate outcomes, and inconsistent results pre-

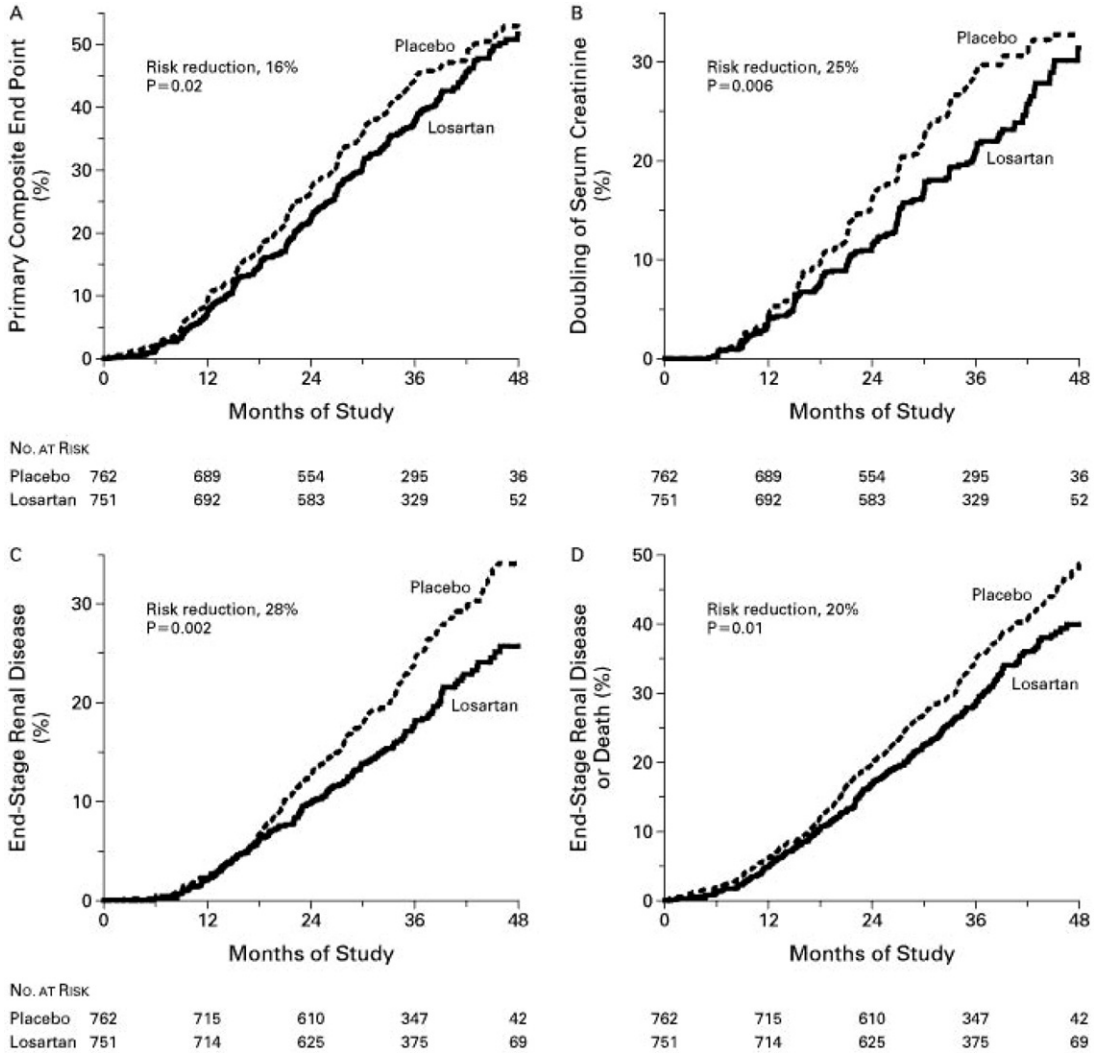

Figure 15. Reduction of end points in type 2 diabetes with losartan in RENAAL.
Kaplan-Meier curves of the percentage of patients with (A) the primary composite end point and its individual components, (B) a doubling of the serum creatinine concentration, (C) CKD stage 5, and (D) the combined end point of CKD stage 5 or death. Reprinted with permission.[167]

clude clear conclusions. A recent analysis of the subgroup of patients with type 2 diabetes and estimated GFR less than 60 mL/min/1.73 m^2 enrolled in ALLHAT showed no beneficial effects of an ACE inhibitor (lisinopril) compared with a diuretic (chlorthalidone) or a calcium channel blocker (amlodipine) on decrease in GFR or onset of kidney failure during a 4-year interval when each agent was used separately.[172] Of note, measures of albuminuria or proteinuria were not available in that study. Therefore, the Work Group concluded that the ALLHAT results do not rule out a beneficial effect of ACE inhibitors on DKD characterized by macroalbuminuria in type 2 diabetes.

Based on the shared properties of ACE inhibitors and ARBs in inhibiting the RAS and a recent small study,[400] ACE inhibitors may be as effective as ARBs in slowing progression of kidney disease caused by type 2 diabetes. In the opinion of the Work Group, either ARBs or ACE inhibitors can be used to treat DKD in hypertensive people with type 2 diabetes and macroalbuminuria.

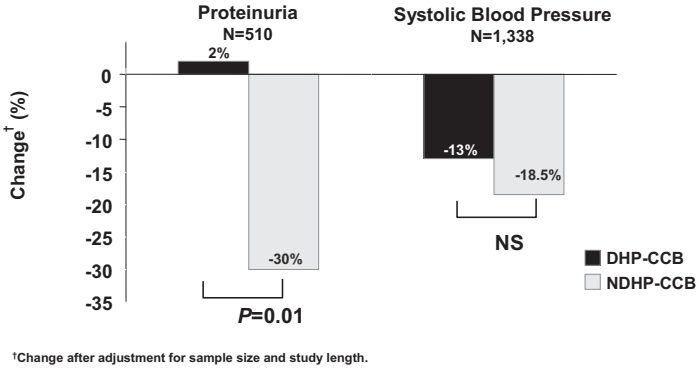

Figure 16. Systematic review of studies of DKD and non-DKD.
The graph shows the change in blood pressure and proteinuria from baseline in trials that prospectively randomized various calcium antagonists and looked at either doubling of creatinine, CKD stage 5 and death, or rate of decrease in GFR. All studies used in this analysis also had a minimum of 1 year follow-up. Change in albuminuria was assessed in the context of outcomes of kidney disease. Abbreviations: DHP-CCB, dihydropyridine calcium channel blocker group; NDHP-CCB, nondihydropyridine calcium channel blocker group. Reprinted with permission.[413]

ARBs may be more effective than other antihypertensive agents in slowing progression of kidney disease characterized by macroalbuminuria in hypertensive patients with type 1 diabetes. (Weak)

There are insufficient data on the efficacy of ARBs in kidney disease caused by type 1 diabetes. The Work Group found no long-term clinical trials on the use of ARBs in patients with DKD caused by type 1 diabetes. However, based on the shared properties of both drug classes in inhibiting the RAS, ARBs may be as effective as ACE inhibitors in slowing progression of kidney disease caused by type 1 diabetes. In the opinion of the Work Group, ARBs can be used as an alternative class of agents to treat DKD in hypertensive people with type 1 diabetes and macroalbuminuria if ACE inhibitors cannot be used.

Diuretics may potentiate the beneficial effects of ACE inhibitors and ARBs in hypertensive patients with DKD. (Moderate)

Between 60% and 90% of patients in studies of hypertension treatment in DKD used either thiazide-type or loop diuretics in addition to ACE inhibitors or ARBs.[167-169,409] Conversely, diuretic use in the ACE-inhibitor group of ALLHAT was restricted by protocol; only 18% of this group received a thiazide diuretic.[172] Other studies have shown that the combination of thiazide diuretics with agents that block the RAS is more effective than either type of treatment alone for lowering blood pressure.[410-412] Because most hypertensive patients with DKD require more than 1 antihypertensive agent to reach the target blood pressure of less than 130/80 mm Hg, it is the opinion of the Work Group that most of these patients should be treated with a diuretic in combination with an ACE inhibitor or an ARB to reach the target blood pressure.

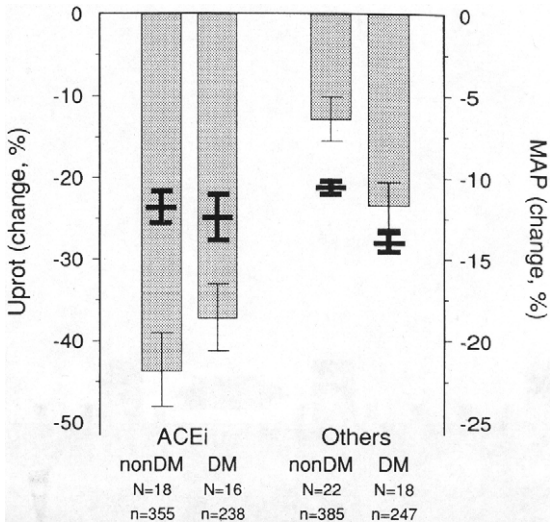

Figure 17. Meta-analysis of studies of DKD and non-DKD.
Effects of blood pressure-lowering agents in DKD and non-DKD. Shown are the weighted mean results with 95% CIs for proteinuria (bars) and blood pressure (bold print) that were obtained in studies that compared the effects of an ACE inhibitor(ACEi) with that of another blood pressure–lowering agent. (Left) Results obtained with ACE inhibitors are shown subdivided to the type of kidney disease (nondiabetic [nonDM] and diabetic nephropathy [DM]). (Right) Results obtained with the comparator drugs. Abbreviation: Uprot, urinary protein; MAP, mean arterial pressure. Reprinted with permission.[414]

ACE inhibitors, ARBs, and nondihydropyridine calcium channel blockers have a greater antiproteinuric effect than other antihypertensive classes in hypertensive patients with DKD. (Strong)

Two meta-analyses have demonstrated a greater effect of ACE inhibitors compared with other classes of antihypertensive agents on reducing proteinuria in DKD (Fig 16 and Fig 17).[413,414] Other studies show a larger effect of ARBs than other classes.[415-417] Some studies also suggest that β-blockers may be effective, but this has not been observed consistently.[418] A systematic review demonstrates that nondihydropyridine calcium channel blockers have substantially greater antiproteinuric effects than dihydropyridine calcium channel blockers, an effect that translated into greater slowing of kidney disease progression and reduced cardiovascular event rates in those with proteinuria greater than 300 mg/d.[413] In contrast to the benefits of nondihydropyridine calcium channel blockers for reducing proteinuria, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) recently reported that nondihydropyridine calcium channel blockers used alone did not decrease the incidence rate of microalbuminuria relative to placebo in hypertensive patients with type 2 diabetes with normal urinary albumin excretion at baseline. Additionally, they did not enhance the effect of ACE inhibitors to prevent microalbuminuria when used in combination.[419]

The combination of an ACE inhibitor and an ARB can reduce proteinuria more than either agent alone.[420-422] Whether the benefit of combination therapy is additive or synergistic (greater than the sum of all agents) is difficult to determine because of uncertainties about the maximum antiproteinuric effect of single agents. Moreover, because such combination therapy further lowers blood pressure, whether this is a general blood pressure effect or a specific response to more complete RAS inhibition is unclear. Despite these uncertainties, in the opinion of the Work Group, it is reasonable to use a combination of an ACE inhibitor and an ARB in hypertensive patients with DKD. Combination therapy should be considered for those with controlled blood pressure, but who have persistent high-level macroalbuminuria or ACR greater than 500 mg/g.

Dihydropyridine calcium channel blockers, when used to treat hypertension in the absence of ACE inhibitors or ARBs, are less effective than other agents in slowing progression of DKD. (Strong)

Numerous studies have shown that dihydropyridine calcium channel blockers are less efficacious than ACE inhibitors, ARBs, and nondihydropyridine calcium channel blockers in reducing albuminuria in DKD.[170] IDNT showed that the dihydropyridine amlodipine was less effective in slowing kidney disease progression than the ARB irbesartan.[169] IDNT also compared amlodipine with a placebo group treated with other agents, primarily diuretics and β-blockers.[169] GFR decline and onset of kidney failure were similar in these 2 groups. Conversely, ALLHAT showed no detrimental effect of amlodipine compared with lisinopril or chlorthalidone on GFR decline or onset of kidney failure in type 2 diabetes when each agent was given separately.[172] However, the lack of albuminuria/proteinuria data in ALLHAT and the relatively limited sample size of the diabetic CKD subgroup (defined by eGFR < 60 mL/min/1.73 m^2) preclude firm conclusions. Based on numerous studies of proteinuric kidney disease, including DKD and non-DKD,[5] it was the opinion of the Work Group that dihydropyridine calcium channel blockers should not be used in DKD in the absence of concurrent RAS inhibition. However, dihydropyridine calcium channel blockers probably can be used safely in patients taking an ACE inhibitor or an ARB.[173]

A systolic blood pressure goal even lower than 130 mm Hg may be more effective in slowing the progression of DKD. (Weak)

A meta-analysis of 8 trials in DKD and 4 trials in non-DKD suggests that a lower blood pressure goal may slow progression of kidney disease (Fig 18).[423] This analysis is limited by the inability to control other factors related to rate of progression. Some studies have addressed a lower blood pressure goal independent of antihypertensive drug class (Table 31). These studies suggest that lower blood pressure levels are associated with lower levels of proteinuria. One study demonstrated a greater reduction in proteinuria in ramipril-treated patients who achieved a lower blood pressure goal (mean arterial blood pres-

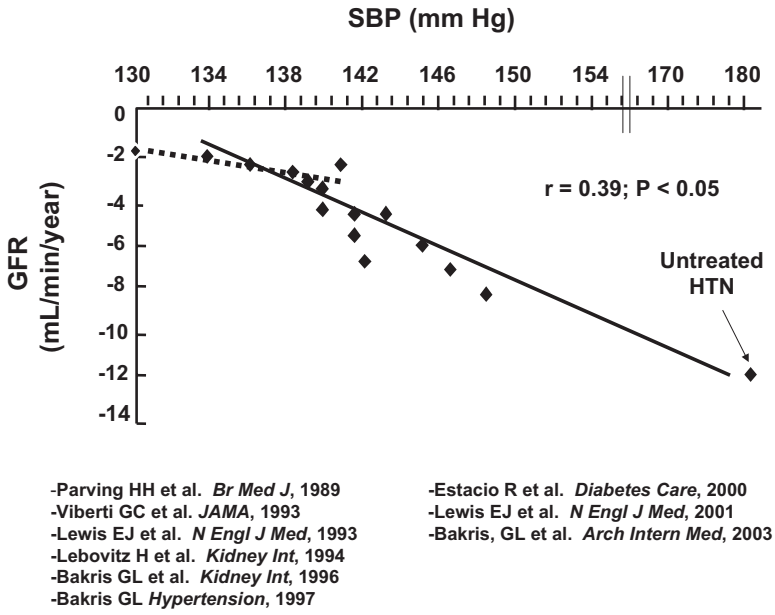

Figure 18. Blood pressure level and rate of GFR decline in controlled trials of DKD.
Diamonds represent the mean achieved systolic blood pressure (SBP) and mean rate of calculated or directly measured GFR decline in the studies of DKD. Results not adjusted for other factors associated with rate of decline in GFR. The dotted line represents a flattening of possible benefit of blood pressure lowering at blood pressure levels less than 140 mm Hg. Abbreviation: HTN, hypertension.

sure [MAP] $<$ 92 mm Hg, equivalent to blood pressure $<$ 125/75 mm Hg) compared with a usual blood pressure goal (MAP $<$ 107 mm Hg, equivalent to blood pressure $<$ 140/90 mm Hg).[171] The Appropriate Blood Pressure Control in Diabetes (ABCD) trial showed a trend toward greater slowing of GFR decrease at the lower achieved systolic blood pressure of 128 mm Hg.[409,424] Studies in non-DKD suggest a lower blood pressure goal is more effective in slowing kidney disease progression in patients with proteinuria.[5] Because DKD typically is accompanied by proteinuria, it was the opinion of the Work Group that a lower blood pressure goal may be beneficial for DKD, as well. There is insufficient evidence to define this lower blood pressure goal or the threshold level of proteinuria above which the lower blood pressure goal is indicated. As in non-DKD,[5] it was the opinion of the Work Group that a systolic blood pressure goal even lower than 130 mm Hg should be considered for patients with persistent high-level macroalbuminuria (ACR $>$ 500 mg/g). Lowering of systolic blood pressure levels to less than 110 mm Hg should be avoided.[5]

Multiple antihypertensive agents are usually required to reach target blood pressure (Strong).

Table 32 shows the target and achieved systolic blood pressure and the number of antihypertensive agents used in randomized trials of antihypertensive agents to slow the progression of DKD.[167-169,424] Multiple agents usually were required.

COMPARISONS WITH OTHER GUIDELINES

This guideline generally is consistent with other recent guidelines, including the NKF-KDOQI™ CPGs on Hypertension and Antihypertensive Agents in CKD,[5] the ADA Standards of Medical Care in Diabetes,[34] and JNC 7.[154] All these guidelines support the use of diuretics with either ACE inhibitors or ARBs as initial therapy to achieve the systolic blood pressure goal of less than 130 mm Hg in patients with diabetes. Moreover, the JNC 7 defines hypertension in individuals with diabetes or CKD as blood pressure greater than 130/80 mm Hg. The guidelines of the European Society of Hypertension also recommend use of an ACE inhibitor or an ARB for those with diabetes and CKD.[425]

LIMITATIONS

No claims of superiority between ACE inhibitors and ARBs can be made in type 1 diabetes because no randomized trials have compared these agents head-to-head in slowing the progression of kidney disease in this type of diabetes. However, a head-to-head comparison in type 2 diabetes suggested clinical equivalency of these agents.[400]

Table 31. Effect of Different Blood Pressure Targets on CKD in Type 1 and Type 2 Diabetes

Author, Year	N	Applicability	Baseline [a]			Comparators Target BP and Mean BP at End of Study (mm Hg)		Clinical Outcomes				Methodological Quality
			Mean GFR	Proteinuria (mg/24 h)	Mean BP (mm Hg)	Comparator 1	Comparator 2	Kidney Disease Progression	Proteinuria	CVD and Mortality	LVH	
Type 1 Diabetes												
Lewis, 1999 [171]	129		62	1	95 (MAP)	MAP <92 nd	MAP 100-107 nd	**NS**				●
Type 2 Diabetes												
UKPDS 38, 1998 [432]	1148		SCr <2	3% M 14% m [b]	159/94	<150/85	<180/105	**NS**	**+** [c]	**NS**		●
Schrier, 2002 [424]	480		82	30-300	135/84	DBP <75 128/75	DBP 80-89 137/81	**NS**				●
Estacio, 2000 [409]	470		83	30-300	156/98	DBP <75 132/78	DBP 80-89 138/86	**NS**				●

Abbreviation: NS,= No significant difference between the 2 interventions.

+ = Comparator 1 showed significant benefit compared to comparator 2.

a Baseline data from comparator 1 group are reported.

b 3.5% with baseline urine albumin ≥300 mg/L, 12% with baseline urine albumin ≥ 50 and <300 mg/L.

c Progression to urine albumin ≥50 mg/L statistically significant at 6 years, progression to urine albumin ≥300 mg/L was not.

Table 32. Summary of Number of Antihypertensive Agents Required to Reach Target Blood Pressure

Study, Year	Target Blood Pressure (mm Hg)	Achieved Blood Pressure (mm Hg)	Mean Number of Agents
IDNT, 2001 [169]	Systolic <135	Systolic 138	2.6
RENAAL, 2001 [167]	Systolic <140	Systolic 141	2.7
ABCD, 2000 [409]	Diastolic <75 or 80-89*	132/78 and 138/86*	2.4
CSG Captopril Trial, 1993 [168]	Systolic <140, Diastolic <90	Mean arterial pressure 96±8 and 100±8†	1-3†

* Denotes intensive blood pressure control group and moderate blood pressure control group, respectively.
† Denotes captopril and placebo groups, respectively; number of agents inferred from report; there were approximately 25% normotensive participants.

Combinations of ACE inhibitors with ARBs are effective in slowing progression of non-DKD, an observation related to further reduction in proteinuria rather than blood-pressure lowering.[426,427] No trials with clinical outcomes have evaluated such a combination for treatment of DKD. Other combinations, such as aldosterone blockade with ACE inhibition, may reduce albuminuria independent of blood pressure changes in DKD. All studies to date that have evaluated combinations of RAS inhibitors have been performed in hypertensive patients with diabetes with advanced CKD and macroalbuminuria. Whether such combinations would be useful or tolerated in early-stage DKD, including normotensive patients, is unknown.

A recent meta-analysis concluded that RAS inhibition with either ACE inhibitors or ARBs is no more effective at preventing GFR loss or such clinical outcomes as doubling of serum creatinine level or CKD stage 5 than other antihypertensive agents in hypertensive patients with diabetes.[428] However, studies selected for the active comparator portion of the meta-analysis included heterogeneous groups that did not consistently have hypertension (present in 86%) or macroalbuminuria (mean albumin, 520 mg/g; range, 7 to 3,000 mg/g). The Work Group concurs that blood pressure control is a predominant mechanism for kidney protection, but that the meta-analysis does not negate evidence for benefits of RAS inhibition in patients with diabetes, hypertension, and macroalbuminuria. The Work Group acknowledges the issues raised by this meta-analysis and supports further study, particularly with active comparisons of RAS inhibition with other interventions for blood pressure control.

IMPLEMENTATION ISSUES

Multiple interventions are needed to slow the progression of kidney disease and reduce the risk of CVD in DKD. Generally, the approach requires 3 or more antihypertensive agents, intensive insulin therapy in type 1 diabetes, 2 or more drugs for glucose control in type 2 diabetes, at least 1 lipid-lowering agent, and emphasis on lifestyle modification, including diet, exercise, and smoking cessation. One obstacle to achieving adherence is the number of medicines and the complexity of these regimens. Therefore, the selection of antihypertensive agents must include considerations of cost, side effects, and convenience.

Selection of antihypertensive agents also should include consideration of their effects on diabetes management. The GEMINI trial demonstrated that, in the presence of an ACE inhibitor or ARB, carvedilol stabilized glycemic control and improved insulin resistance to a greater extent than metoprolol in patients with type 2 diabetes and hypertension.[108] Moreover, new-onset microalbuminuria was 48% lower when carvedilol was added to RAS inhibition compared with metoprolol.

Because blood pressure control is a key objective in management of DKD, antihypertensive agents, including ACE inhibitors and ARBs, should be titrated to achieve moderate to maximal doses approved for the treatment of hypertension. In addition, reducing dietary sodium ($<$2.3 g/d) is critical to optimize the effectiveness of medication used to control blood pressure (see Guideline 5).

Assessment of Blood Pressure

The Work Group recommends that blood pressure be measured at each health care en-

Table 33. Recommended Intervals for Follow-Up Evaluation of Blood Pressure, GFR, and Potassium

	After Initiation or Changes in Antihypertensive Therapy	
Clinical Condition	**<4 wk**	**4-12 wk**
Systolic blood pressure (mm Hg)	≥140 or <120	120-139
GFR (mL/min/1.73 m^2)	<60	≥60
Serum potassium (mEq/L)		
If on ACE inhibitor or ARB	>4.5	≤4.5
If on a diuretic	≤4.5	>4.5
	After Blood Pressure Is at Goal and Drug Doses Are Stable	
	1-6 mo	**6-12 mo**
GFR (mL/min/1.73 m^2)	<60	≥60
GFR decline (mL/min/1.73 m^2/y)	≥4	<4
Risk factors for faster CKD progression or acute eGFR decline, comorbidities*	Yes	No

Note: Adapted from NKF-KDOQI™ CPGs on Hypertension and Antihypertensive Agents in CKD.[5]

*Administration of nephrotoxins (eg, nonsteroidal anti-inflammatory drugs including cyclooxygenase-2 (COX-2) inhibitors, aminoglycosides, amphotericin B, intravenous iodinated radiographic contrast media, cyclosporine, or tacrolimus), volume depletion, obesity, sleep apnea, smoking, excessive alcohol intake, and clinical CVD (brain, heart, abdomen, legs).

counter in people with diabetes and CKD. This recommendation is consistent with guidelines from the NKF-KDOQI™ CPGs on Hypertension and Antihypertensive Agents in CKD,[5] the ADA Clinical Practice Recommendations,[34] and JNC 7.[154] Blood pressure greater than 130/80 mm Hg should be confirmed on a separate day. Because of the frequent occurrence of autonomic neuropathy in diabetes and CKD, orthostatic blood pressure should be measured. The Work Group concurred that the schedule for follow-up evaluation of blood pressure, as outlined in the NKF-KDOQI™ CPGs on Hypertension and Antihypertensive Agents in CKD, is appropriate for those who have diabetes as well as CKD (Table 33).[5]

GUIDELINE 4: MANAGEMENT OF DYSLIPIDEMIA IN DIABETES AND CHRONIC KIDNEY DISEASE

Dyslipidemia is common in people with diabetes and CKD. The risk of CVD is greatly increased in this population. People with diabetes and CKD should be treated according to current guidelines for high-risk groups.

4.1 Target LDL-C in people with diabetes and CKD stages 1-4 should be < 100 mg/dL; <70 mg/dL is a therapeutic option. (B)

4.2 People with diabetes, CKD stages 1-4, and LDL-C ≥ 100 mg/dL should be treated with a statin. (B)

4.3 Treatment with a statin should not be initiated in patients with type 2 diabetes on maintenance hemodialysis who do not have a specific cardiovascular indication for treatment. (A)

BACKGROUND

Diabetes is associated with a high risk of morbidity and premature mortality.[433,434] Most adverse diabetes outcomes are due to macrovascular or microvascular complications.[134] Macrovascular complications are common and severe; up to 80% of patients with type 2 diabetes will develop or die of CVD. Based on this severity of risk, prevention and management of CVD must be considered in the care of patients with diabetes and CKD. Therefore, these patients are strong candidates for treatment of dyslipidemia. Modifying CVD risk by using lipid-lowering agents is of tremendous importance and is a cost-effective strategy in people with type 2 diabetes.[435,436]

The NKF-KDOQI™ CPGs for Managing Dyslipidemia in CKD were established recently and CPGs for CVD in Dialysis Patients added new information on the inverse association between cholesterol level and mortality.[6,10] The purpose of this guideline is to focus on patients with diabetes and CKD and to update the previous guidelines. Results from the first prospective randomized trial in hemodialysis patients with diabetes and indirect evidence from a recent post hoc analysis of 3 large multicenter trials on the beneficial effects of lipid-lowering therapy in diabetes and CKD were added to this guideline.

RATIONALE

For this guideline, we included studies of patients with type 1 or type 2 diabetes and CKD stages 1 to 5. Because of the high prevalence of diabetes in the population, many individuals with other types of CKD also may have diabetes. In general, the guidelines for use of lipid-lowering agents in CKD stages 1 to 4 due to diabetes and other causes agree with each other,[174-177] although there is no direct or indirect evidence for treating patients with CKD stage 4. Because CKD per se markedly increases the risk of CVD, CKD may be considered a risk equivalent for CVD when assessing the need for lipid lowering.

Most patients with diabetes and CKD have dyslipidemia. (Strong)

Patients with diabetes and CKD typically have low levels of high-density lipoprotein cholesterol (HDL-C), high triglyceride levels, and average levels of LDL-C; LDL particles in people with diabetes tend to be smaller, denser, and possibly more atherogenic.[437-440]

Elevated LDL-C can effectively be treated with statins in diabetes and CKD. (Strong)

In general, cholesterol lowering with statin therapy is efficacious in patients with diabetes, including those without manifest coronary heart disease and those with relatively low LDL-C levels.[97,98]

Most patients with diabetes and CKD are at very high risk to develop macrovascular complications. (Strong)

The Adult Treatment Panel III (ATP III) guidelines of the National Cholesterol Education Program (NCEP)[175] identified diabetes as a high-risk condition. This designation was based on evidence that most patients with diabetes have a greatly increased 10-year risk (>20%) of developing CVD. The onset of CVD in patients with diabetes carries a poor prognosis, both at the time of an acute CVD event and in the postevent period. In the Heart Protection Study (HPS),

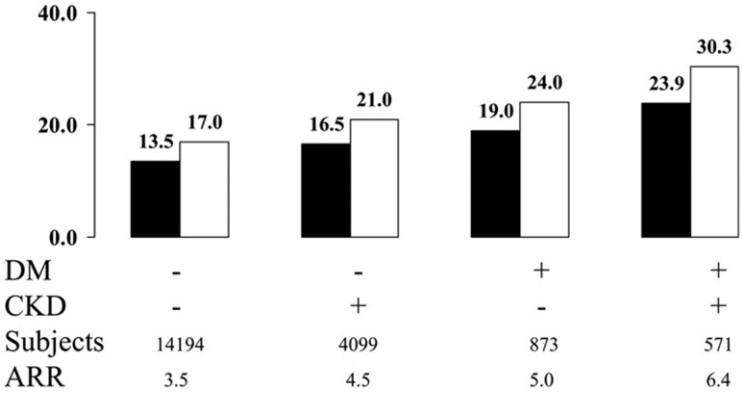

Figure 19. Effect of pravastatin on the absolute risk reduction (ARR) of fatal coronary disease, nonfatal myocardial infarction, or coronary revascularization by CKD and diabetes (DM) status. Reprinted with permission.[99]

patients who had both diabetes and CVD were at very high risk of future CVD events.[97] When type 2 diabetes is complicated by CKD, the cardiovascular risk increases dramatically; in particular, in patients with microalbuminuria or macroalbuminuria, it is approximately 2 to 4 times as high as in normoalbuminuric patients.[40] The presence of CKD can be considered an additional cardiovascular risk factor per se.

LDL-C–lowering therapy decreases the risk of CVD in diabetes and CKD stages 1 to 3. (Moderate)

Primary and secondary prevention trials, including those in people with diabetes, have documented substantial cardiovascular benefit from administration of statins.[441,442] The recent primary prevention Collaborative Atorvastatin Diabetes Study (CARDS) reported an impressive decrease in cardiovascular deaths in people with type 2 diabetes in the absence of markedly decreased kidney function.[98] In terms of absolute risk reduction, patients in the HPS with diabetes and CVD received the greatest benefit from statin therapy.[97]

A post hoc analysis of data from the PPP (a subject-level database combining results from 3 randomized trials of pravastatin, 40 mg daily, versus placebo) included 19,737 subjects, of whom 4,099 (20.8%) had CKD, but not diabetes, at baseline; 873 (4.4%) had diabetes, but not CKD; and 571 (2.9%) had both conditions.[99] CKD was defined as eGFR less than 60 mL/min/1.73 m^2 or GFR of 60 to 89.9 mL/min/1.73 m^2 with trace or more proteinuria. The primary composite outcome was time to myocardial infarction, coronary death, or percutaneous/surgical coronary revascularization. The incidence of the primary outcome was lowest in individuals with neither CKD nor diabetes (15.2%), intermediate in subjects with only CKD (18.6%) or only diabetes (21.3%), and highest in subjects with both characteristics (27.0%). Pravastatin significantly reduced the risk of the primary outcome by 25% in subjects with CKD and concomitant diabetes and by 24% in subjects with neither characteristic. The absolute reduction in risk of the primary outcome due to pravastatin use was highest in subjects with both CKD and diabetes (6.4%) and lowest in subjects with neither characteristic (3.5%; Fig 19). This study provides indirect evidence that pravastatin treatment effectively decreases the risk of CVD in diabetes with CKD stages 1 to 3. The study does not provide evidence for a protective effect of pravastatin in more advanced stages of CKD because patients with more severe impairment of kidney function were excluded from the trials. More advanced stages of CKD also were excluded from the West of Scotland Coronary Prevention Study (WOSCOP),[443] a primary prevention trial, and from the Cholesterol and Recurrent Events (CARE) Study[444] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study,[445] 2 secondary intervention studies.

In the opinion of the Work Group, people with diabetes and CKD (other than stage 5) should receive LDL-C–lowering therapy. The high risk associated with diabetes and CKD supports initiation of statin therapy when LDL-C is greater than 100 mg/dL, with an option to achieve an LDL-C goal of less than 70 mg/dL.

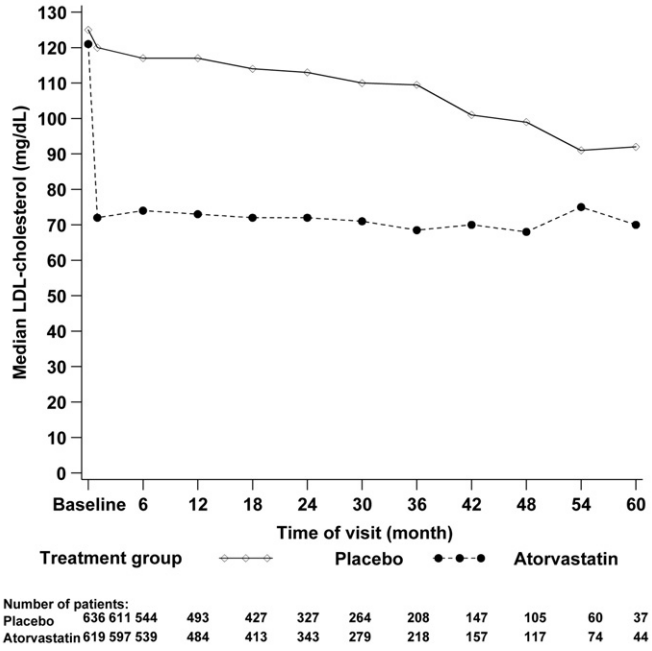

Figure 20. Median change in LDL-C concentrations from baseline until the end of the 4D. To convert values for LDL-C to mmol/L, multiply by 0.02586. Reprinted with permission.[100]

Atorvastatin treatment in patients with type 2 diabetes on maintenance hemodialysis treatment does not improve cardiovascular outcomes. (Strong)

The 4D, a multicenter, randomized, double-blind, and prospective study, randomly assigned 1,255 patients with type 2 diabetes on maintenance hemodialysis to receive 20 mg of atorvastatin per day or matching placebo.[446] After 4 weeks of treatment, atorvastatin reduced the median LDL-C level by 42%, and placebo, by 1.3%. At least 1-mmol/L difference in LDL-C level was maintained throughout the treatment period (Fig 20). During a median follow-up of 4 years, 469 patients (37%) reached the primary end point (a composite of cardiac death, nonfatal myocardial infarction, and fatal and nonfatal stroke): 226 assigned to atorvastatin and 243 assigned to placebo (RR, 0.92; 95% CI, 0.77 to 1.10; $P = 0.37$; Figure 20). Atorvastatin had no effect on the single components of the primary end point with the exception of fatal stroke, in which RR was 2.03 (95% CI, 1.05 to 3.93; $P = 0.04$). Secondary end points, such as all combined cardiac events (RR, 0.82; 95% CI, 0.68 to 0.99; $P = 0.03$), were reduced, but not all combined cerebrovascular events (RR, 1.12; 95% CI, 0.81 to 1.55; $P = 0.49$) or total mortality (RR, 0.93; 95% CI, 0.79 to 1.08; $P = 0.33$).[100]

Despite the high rate of cardiovascular events and the pronounced LDL-C lowering by atorvastatin, a significant reduction in the incidence of the composite primary end point was not achieved (patients with an LDL-C $>$ 190 mg/dL were not included in 4D). In contrast to 4D, CARDS reported that people with type 2 diabetes who received atorvastatin had an RR for stroke of 0.52 (95% CI, 0.31 to 0.89) compared with placebo.[98] The rate of fatal and nonfatal stroke decreased from 2.8% to 1.5% (39 versus 21 patients), whereas in the 4D, it increased from 7.0% to 9.7% (44 versus 59 patients). This unexplained finding of an increase in fatal stroke requires further study. The 4D is the first large-scale cardiovascular outcome trial that does not show overall benefit from administration of a potent dose of a statin and does not confirm the generally accepted assumption that for every 30-mg/dL change in LDL-C level, the RR of coronary heart disease is changed in proportion by about 30%. The result is in accordance with observational data in patients on hemodialysis therapy that do not link dyslipidemia with reduced survival; opposite trends have been noted.[447] 4D results are in contrast to an observational retrospective analysis of hemodialysis patients in the US Renal Data System (USRDS) Morbidity and Mortality Study, Wave 2,[448] which

indicated that the risk of cardiovascular death decreases by 36% in statin users compared with nonusers. This finding illustrates the difficulty associated with basing treatment decisions on uncontrolled observational studies.[448,449] Perhaps the pathogenesis of cardiovascular events in patients with diabetes on hemodialysis therapy may be different, at least in part, from that in patients without CKD stage 5. Additional information on the inverse association between cholesterol concentration and mortality is presented in the NKF-KDOQI™ CPGs for CVD in Dialysis Patients.[10]

Dyslipidemia may increase albuminuria and accelerate progression of DKD. Whether treatment with statins slows progression of DKD is uncertain. (Weak)

A number of observational studies have reported that dyslipidemia is associated with decreased kidney function in the general population and in patients with CKD, with or without diabetes, as extensively reviewed in the NKF-KDOQI™ CPGs for Managing Dyslipidemia in CKD.[6] An analysis of the lipid profile of the DCCT/EDIC cohort of patients with type 1 diabetes demonstrated a specific profile in DKD that is characterized by high triglyceride levels, predominantly in the very-low-density-lipoprotein (VLDL) subclasses. In men, high intermediate-density lipoprotein (IDL), high LDL particle concentration, and a shift from larger toward smaller LDL-C, apolipoprotein B, and small (noncardioprotective) HDL-C particles were associated with CKD.[439] In the RENAAL Study, the RR of reaching the primary composite end point (doubling of serum creatinine level, CKD stage 5, or death) among patients in the upper quartile of the distribution for total cholesterol and LDL-C was significantly higher than for those in the lower quartile.[450]

Small short-term randomized studies report mixed results of the effect of statins on progression of DKD (Table 34). In patients with type 1 diabetes and microalbuminuria, simvastatin had no beneficial effect on either albuminuria or GFR.[451] However, some randomized trials in type 2 diabetes reported beneficial effects of statins on albuminuria and GFR relative to pretreatment levels,[452-454] but not relative to placebo or an alternative class of treatment for dyslipidemia.[455-457]

Whether dyslipidemia causes reduced kidney function, results from reduced kidney function, or whether other conditions, such as proteinuria, cause both reduced kidney function and dyslipidemia cannot be determined from the available data. Large, double-blind, randomized, placebo-controlled, clinical trials that examine the effect of dyslipidemia treatment on progression of DKD have not been done. This is the only approach that can adequately test the hypothesis that treatment of dyslipidemia provides benefit for kidney outcomes. At present, primary and secondary prevention of CVD is the principal reason to evaluate and treat dyslipidemia in patients with diabetes and CKD.

For patients with type 2 diabetes who are taking statins, routine monitoring of liver function tests or muscle enzymes is not recommended except in specific circumstances. (Strong)

The current literature suggests that statins are safe. Although discontinuation and nonadherence rates are approximately 15% or more in many clinical trials, rates of discontinuation typically do not differ from those of placebo. Rates of elevated liver or muscle enzyme levels did not differ between the statin and placebo groups in the 4D or in recent large-scale studies in people with and without diabetes from the general population. Ongoing large-scale trials in diabetic and nondiabetic CKD and dialysis patients (A study to evaluate the use of Rosuvastatin in subjects on regular hemodialysis: an assessment of survival and cardiovascular events [AURORA]; and Study of Heart and Renal Protection [SHARP]) have already accumulated substantial patient treatment years and have not reported serious adverse events related to liver or muscle function. On the basis of the safety data pertaining to these drugs, routine monitoring of muscle enzymes and liver function tests probably is not warranted unless patients have symptoms,[458,459] have baseline abnormalities of liver function test results or myopathy, or are taking other drugs that interact with statins to increase the risk of adverse events.

Table 34. Effect of Lipid-Lowering Treatments on Kidney Function and Albuminuria in Type 1 and Type 2 Diabetes

Author, Year	Mean Study Duration	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value[b]	Net Effect	*P*	Quality
Type 1 Diabetes												
Hommel, 1992 [450]	3 mo	21	68	MacroAlb 100%	🚹🚹	Simvastatin 12.5 mg	Placebo	Δ GFR	72 (64)	-3	NS	⊙
								Δ Albuminuria (mg/d)	698 (755)	-22	NS	
Zhang, 1995 [461]	3 mo	20	nd	MicroAlb 100%	🚹🚹	Pravastatin 20 mg	Placebo	UAE (μg/min)	65 (65)	-5	NS	⊙
Type 2 Diabetes												
Nagai, 2000 [453]	4 y	71	SCr 0.9	ACR 105	🚹🚹	Pravastatin 10 mg	Bezafibrate 400 mg	Δ ACR (mg/g)	102 (108)	+3.3	NS	⊙
Nakamura, 2001 [451]	6 mo	60	SCr 0.85	MicroAlb 100%	🚹🚹	Cerivastatin 0.15 mg	Placebo	UAE (μg/min)	98 (94)	-64	nd[c]	⊙
Lam, 1995 [452]	2 y	34	84	MacroAlb 100%	🚹🚹	Lovastatin 20-60 mg	Placebo	Δ GFR	83 (84)	+9	NS[d]	⊙
								24 h urine protein (g)	0.8 (1.1)	-0.4	NS	
Tonolo, 2000 [454]	10 mo	26	68	MicroAlb 100%	🚹🚹	Simvastatin 20 mg	Cholestyramine 18 g	Δ AER (mg/d)	154 (154)	-38	nd[c]	⊙
Nielsen, 1993 [456]	4 mo	18	97	MicroAlb 100%	🚹🚹	Simvastatin 10-20 mg	Placebo	Δ GFR	97 (97)	-4	NS	⊙
								UAE (μg/min)	18 (33)	-0.4[e]	NS	
Smulders, 1997 [457]	1 y	15	SCr 0.9	MicroAlb 100%	🚹	Gemfibrozil 1,200 mg	Placebo	Δ ACR (%)	8.9 (14.2)	-29%	NS	○

a Maximum dose.
b Baseline value of outcomes in the treatment (comparator) arm.
c *P* value significant in the treatment arm for before vs after treatment.
d In placebo arm, there was a significant decrease in GFR over 24 months compared to baseline (-10 mL/min, $P < 0.025$).
e Net difference of geometric means at baseline and 18 weeks.

Table 35. Dosing Adjustments of Medicines to Treat Lipid Disorders in CKD

Class	Drug	Recommended Adult Dosing Range	Dose in CKD
Bile acid sequestrants	Cholestyamine	2-4 packets or full scoops daily (divided into 2 doses)	No dosage adjustment needed
	Colestipol	5-30 g/d in once or divided doses	No dosage adjustment needed
	Colesevelam	3 tablets taken twice daily with meals or 6 tablets once daily with meals	No dosage adjustment needed
Statins	Atorvastatin	10-80 mg daily	No dosage adjustment needed
	Fluvastatin	20-80 mg daily	Dose adjustments not needed for mild to moderate kidney disease Use caution in patients with severe kidney disease Fluvastatin not studied at doses > 40 mg in these patients
	Lovastatin	Immediate release: 10-80 mg daily in a single dose or divided doses Extended release: 10 -60 mg daily in a single dose	In patients with CCr < 30 mL/min, doses > 20 mg daily should be used cautiously
	Pravastatin	10-40 mg daily	No dosage adjustment needed
	Rosuvastatin	5-40 mg daily	No dose modification necessary for patients with mild to moderate kidney disease CCr < 30 mL/min/1.73 m^2, not on hemodialysis, initiate dosing at 5 mg daily and do not exceed 10 mg daily
	Simvastatin	5-80 mg daily	Initiate therapy at 5 mg daily in patients with severe kidney disease
Fibric acid derivatives	Gemfibrozil	1,200 mg daily in 2 divided doses before meals	Decrease dose or consider alternative therapy in patients with SCr > 2 mg/dL
	Fenofibrate	54-160 mg daily	Initiate therapy at 54 mg daily and assess the effects on kidney function and lipid concentrations Minimize doses in patients with CCr < 50 mL/min as rate of drug clearance is greatly reduced.
Other	Niacin	Extended release: 500-2,000 mg daily Immediate release: 1-2 g given 2-3 times daily	No dosing adjustments needed
	Ezetimibe	10 mg daily	No dosing adjustments needed

Abbreviations: CCr, creatinine clearance; SCr, serum creatinine.

COMPARISON WITH OTHER GUIDELINES

The 2004 NCEP Report on ATP III Guidelines

A recent NCEP report discussed the implications of the ATP III guidelines.[175] Results from the HPS and the Pravastatin or Atorvastatin in Evaluation and Infection Therapy (PROVE IT) Study suggested that additional benefit may be obtained by reducing LDL-C levels to less than 100 mg/dL. While awaiting the results of the Treating to New Targets (TNT) Study to prove the efficacy of lowering LDL-C to very low levels, the NCEP report stated that "until these trials are completed, prudence requires that setting an LDL-C goal of <70 mg/dL for high-risk patients must be left as a therapeutic option on

Table 36. NKF-KDOQI™ CPGs for Managing Dyslipidemia in CKD Stages 1 to 4[6]

Measurement	Frequency	Goal
Complete lipid profile Total cholesterol, HDL-C, triglycerides, LDL-C, non–HDL-C*	Annually or 2-3 mo after change in treatment or clinical status†	LDL-C < 100 mg/dL; <70 mg/dL is a therapeutic option Statins are preferred therapy

*Non–HDL-C = total cholesterol – HDL-C.
†Change in albuminuria/proteinuria or GFR.

the basis of clinical trial evidence, whereas a goal of <100 mg/dL can be retained as a strong recommendation." Since that NCEP report, TNT has been completed and showed that intensive lipid-lowering therapy reaching a mean target LDL-C level of 77 mg/dL with 80 mg of atorvastatin per day in patients with stable coronary heart disease provides significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day.[460] Factors that favor a decision to reduce LDL-C levels to less than 70 mg/dL are those that place patients in the category of very high risk.[175]

Based on these data, it is the opinion of the Work Group that people with type 2 diabetes and CKD stages 1 to 4 may receive additional benefit from intensified treatment with a statin to reduce LDL-C levels to less than 70 mg/dL. Data from the 4D suggest that initiating lipid lowering with a statin in hemodialysis patients with type 2 diabetes may come too late to translate into substantial improvement in cardiovascular outcomes, possibly because of additional or alternative pathological mechanisms.

LIMITATIONS

These guideline recommendations should be validated in people with diabetes and CKD stage 4. All available studies systematically excluded people with severe impairment of kidney function. In addition, there are no prospective randomized controlled trials available in diabetes and CKD stages 1 to 3. Recommendations made for patients in the latter stages of CKD have been made based on post hoc analysis with limited numbers of patients. Results from ongoing prospective randomized trials, such as the SHARP, are eagerly awaited. The guideline recommendation for the therapeutic option of an LDL-C goal less than 70 mg/dL was based on the very high CVD risk in people with diabetes and CKD. However, the clinical trial evidence for this goal is based on studies of patients with coronary heart disease. Studies of the target population (diabetes and CKD stages 1 to 4) are needed to verify this recommendation. Data from AURORA are needed to prove whether a recommendation to withhold statin treatment in patients with type 2 diabetes on hemodialysis is justified.

IMPLEMENTATION ISSUES

Dosing adjustments of statins and fibric acid derivatives may be required in patients with diabetes and advanced CKD (Table 35). Ezitimibe may be considered as an adjunct to achieve LDL-C goals, particularly if statin doses are limited due to concern about side effects.

In the opinion of the Work Group, some caveats should be considered for implementing recommendations made in this guideline. First, the 4D results may not apply to patients who are already on drug therapy for LDL-C. Therefore, statin treatment may continue into CKD stage 5 if initiated at an earlier CKD stage. Second, the 4D results do not preclude statin treatment for hemodialysis patients with type 2 diabetes and LDL-C >190 mg/dL or specific cardiovascular indications. According to ATP-III these indications include coronary heart disease and coronary heart disease risk equivalents (eg, non-coronary atherosclerotic disease or multiple risk factors that confer a 10-year Framingham risk >20%).

Assessment of Lipids

A complete lipid profile, including total cholesterol, HDL-C, and triglycerides, should be directly measured in people with diabetes and CKD. LDL-C is calculated from these values by using the Friedewald formula, as recommended by the ATP III Guidelines.[175] Because dyslipidemia associated with diabetes and CKD may occur without an elevated LDL-C level due to increased lipoprotein remnants, non–HDL-C (total cholesterol – HDL-C) also is a useful measure.[175] The NKF-KDOQI™ CPGs for Managing Dyslipidemia in CKD recommend assessment of the lipid profile at least annually in people with CKD stages 1 to 4.[6] Repeated measurements should be made 2 to 3 months after starting or adjusting lipid-lowering treatment or with substantial changes in albuminuria/proteinuria or GFR (Table 36).

GUIDELINE 5: NUTRITIONAL MANAGEMENT IN DIABETES AND CHRONIC KIDNEY DISEASE

Management of diabetes and CKD should include nutritional intervention. Dietary modifications may reduce progression of CKD.

5.1 Target dietary protein intake for people with diabetes and CKD stages 1-4 should be the RDA of 0.8 g/kg body weight per day. (B)

BACKGROUND

Nutritional management for people with diabetes has traditionally focused on blood glucose control. However, dietary protein intake at all stages of CKD appears to have an important impact in this population. If dietary protein is limited, adequate caloric intake must be maintained by increasing calories from carbohydrates and/or fats. Competing needs for nutritional management of hyperglycemia, hypertension, and dyslipidemia can make determination of appropriate protein intake challenging. Furthermore, the diet for diabetes and CKD should consider the qualitative, as well as the quantitative, aspects of proteins, carbohydrates, and fats. To address dietary recommendations for people with diabetes and CKD stages 1 to 4, studies evaluating interventions that reduced or altered sources of dietary protein and other nutrients were reviewed (Table 37 to Table 41). Dietary recommendations for CKD stage 5 are provided in the KDOQI™ CPGs for Nutrition in Chronic Renal Failure.[9]

RATIONALE

A dietary protein intake of 0.8 g/kg body weight per day, the RDA for this macronutrient, is a level that has been achieved in studies of diabetes and CKD. Reduction in albuminuria and stabilization of kidney function have been reported with dietary protein intake at the RDA level. Nutrition surveys indicate that most people eat in excess of the RDA for dietary protein. (Moderate)

Key studies that evaluated reduction or alteration of dietary protein are summarized in Table 42. Based on 2 meta-analyses, low-protein diets reduced risks of loss of kidney function (GFR or creatinine-based measurements) and/or increased albuminuria (measured as urinary excretion of either albumin or total protein), with more pronounced benefits in DKD than in non-DKD (Fig 21).[179,180] More recently, even a modest limitation of dietary protein (0.89 versus 1.02 g/kg body weight per day) substantially reduced the risk of CKD stage 5 or death (RR, 0.23; 95% CI, 0.07 to 0.72; $P = 0.04$) in people with type 1 diabetes and CKD stage 2 (inferred based on levels of albuminuria and GFR; Fig 22). These patients (85% to 89% during the course of the study) also received ACE inhibitors and had similar control of blood pressure and other risk factors irrespective of diet group assignment, indicating that reducing dietary protein provided benefits beyond established medical therapies.[181] Benefits of limiting dietary protein intake are more evident in type 1 than type 2 diabetes, but fewer studies have been done in the latter population. Based on the available evidence (Table 37 and Table 38), the Work Group concluded that limiting dietary protein will slow the decrease in kidney function and progression of albuminuria, and it may prevent CKD stage 5.

At the other end of the spectrum, high-protein diets are a particular concern in patients with diabetes because they increase albuminuria and may accelerate loss of kidney function. Glomerular hyperfiltration and increased intraglomerular pressure are well-recognized mechanisms of kidney damage induced by excess dietary protein. Based on both human studies and experimental models, higher protein intake appears to have more pronounced effects on kidney hemodynamics and kidney damage in diabetes.[187-196,463] Emerging epidemiological evidence indicates that higher protein intake (≥20% versus 10% of total daily calories) is associated with loss of kidney function in women with mild kidney insufficiency (defined as estimated GFR < 80 and > 55 mL/min/1.73 m^2) and development of microalbuminuria in people with diabetes and hypertension.[197,198] Therefore, in the opinion of the Work Group, people with diabetes and CKD should avoid high-protein diets

Table 37. Effect of Low-Protein Diets on Mortality, Kidney Function, Albuminuria, and Risk Factors in Type 1 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applic-ability	LPD Prescribed (Achieved) (g/kg/d)	UPD (g/kg/d)	Outcome	Baseline Value LPD (UPD)	Net Effect	*P*	Quality
Mortality + CKD Stage 5												
Hansen, 2002 [181]	4	82	68	MacroAlb 100%	🚹🚹🚹	0.6 (0.9)	1.02	Mortality + CKD Stage 5	—	RR 0.23	.01	●
Kidney Function												
Hansen, 2002 [181]	4	82	68	MacroAlb 100%	🚹🚹🚹	0.6 (0.9)	1.02	Slope GFR (mL/min/y)	-7.6 (-6.6)[a]	-3.8 vs -3.9	NS	●
Zeller, 1991 [478]	~2.9	35	48	MacroAlb 100%	🚹🚹	0.6 (nd)	≥1	Slope GFR (mL/min/y)	—	-3.1 vs -12.1	.02	⊙
Dullaart, 1993 [183]	2	30	127	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (0.8)	1.09	Δ GFR	131 (122)	-8	NS	⊙
Hansen, 1999 [189]	1 mo	29	93	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (0.9)	1.1	Δ GFR	94 (92)	-6.1	NS	⊙
Raal, 1994 [186]	6 mo	22	58	P 100%	🚹🚹	0.8 (0.9)	2.00	Δ GFR	50 (66)	+11	nd	⊙
Brouhard, 1990 [479]	1	15	81	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (nd)	1.0	Δ GFR	89 (72)	+7	<.05	⊙
Meloni, 2002 [184]	1	32	45	P 2.9 g/d	🚹🚹	0.6 (0.7)[b]	1.39[b]	Δ GFR	46 (44)[b]	+0.1	nd	○
Albuminuria												
Hansen, 2002 [181]	4	82	68	MacroAlb 100%	🚹🚹🚹	0.6 (0.9)	1.02	Δ Albuminuria (mg/d)	690 (721)	-41	NS	●
Zeller, 1991 [478]	~2.9	35	48	MacroAlb 100%	🚹🚹	0.6 (0.7)	1.08	Δ Proteinuria (mg/d)	3,144 (4266)[c]	-1220	nd	⊙
Dullaart, 1993 [183]	2	30	127	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (0.8)	1.09	Δ UAE (µg/min)	36 (31)	-11	NS	⊙
Hansen, 1999 [189]	1 mo	29	93	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (0.8)	1.1	Δ Albuminuria (mg/d)	397 (438)	-29%	<.05	⊙
								Δ Fractional albumin excretion (%)	nd	-28	NS	
Raal, 1994 [186]	6 mo	22	58	P 100%	🚹🚹	0.8 (0.9)	2.00	Δ Fractional albumin clearance (x 10^{-3})	0.94 (0.60)	-0.92	nd	⊙
								Δ Urinary Protein (g/d)	2.15 (1.90)	-1.36	nd[d]	
Brouhard, 1990 [479]	1	15	81	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (nd)	1.0	Δ UAE (µg/min)	521 (171)	-1362	<.05	⊙
Blood Pressure (mm Hg)												
Hansen, 2002 [181]	4	82	68	MacroAlb 100%	🚹🚹🚹	0.6 (0.9)	1.02	Δ BP	140/85 (138/85)	0/+1	NS	●
Hansen, 1999 [189]	1 mo	29	93	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (0.8)	1.1	Δ BP (MAP)	95 (100)	-2	NS	⊙
Raal, 1994 [186]	6 mo	22	58	P 100%	🚹🚹	0.8 (0.9)	2.00	Δ BP	141/88 (143/90)	+3/+7	nd	⊙
Brouhard, 1990 [479]	1	15	81	MacroAlb/MicroAlb 100%	🚹🚹	0.6 (nd)	1.0	Δ BP	127/83 (135/83)	+11/+3	NS	⊙

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applicability	LPD Prescribed (Achieved) (g/kg/d)	UPD (g/kg/d)	Outcome	Baseline Value LPD (UPD)	Net Effect	*P*	Quality
Hemoglobin A_{1c} (%)												
Hansen, 2002 [181]	4	82	68	MacroAlb 100%	↑↑↑	0.6 (0.9)	1.02	Δ HbA_{1c}	9.8 (9.6)	-0.3	NS	●
Dullaart, 1993 [183]	2	30	127	MacroAlb/MicroAlb 100%	↑↑	0.6 (0.8)	1.09	Δ HbA_{1c}	7.8 (7.8)	0	NS	○
Hansen, 1999 [180]	1 mo	29	93	MacroAlb/MicroAlb 100%	↑↑	0.6 (0.8)	1.1	Δ HbA_{1c}	8.4 (8.6)	-0.3	NS	○
Brouhard, 1990 [479]	1	15	81	MacroAlb/MicroAlb 100%	↑↑	0.6 (nd)	1.0	Δ HbA_{1c}	6.8 (7.8)	+0.2	NS	○
Lipids (mg/dL)												
Dullaart, 1993 [183]	2	30	127	MacroAlb/MicroAlb 100%	↑↑	0.6 (0.8)	1.09	Δ Total Cholesterol	224 (239)	+5	NS	○
								Δ LDL	151 (159)	+1	NS	
Raal, 1994 [186]	6 mo	22	58	P 100%	↑↑	0.8 (0.9)	2.00	Δ Total Cholesterol	279 (237)	-37	nd	○
								Δ LDL	152 (148)	-25	nd	

a "Before the study."
b Data reported for combined cohort of patients with type 1 (N = 32) and type 2 (N = 37) diabetes.
c Statistically significant difference between baseline values.
d *P* value significant in the low-protein arm for before versus after treatment.

(≥20% of total daily calories). Some common fad diets that recommend high protein are Atkins®, Protein Power, the Zone, South Beach®, and Sugar Busters®.

Diets for people with diabetes have traditionally been 15% to 20% protein.[464] The NHANES 1999 to 2000 indicated that the majority of Americans consume 15% of total daily calories or approximately 1.04 g/kg body weight per day as protein, substantially more than the 0.8 g/kg body weight per day RDA.[178] In the DASH and DASH-Sodium diets, a higher protein intake (1.4 g/kg body weight per day) is recommended.[199] However, sources of protein in the DASH diets emphasize vegetables, low-fat or nonfat dairy products, whole grains, nuts, legumes, fish, and poultry. Red meat is eaten in only small amounts. In recent studies of people with prehypertension or untreated stage 1 hypertension, higher protein intake from either soy or predominantly vegetable sources reduced blood pressure in short-term (6 to 12 weeks) feeding studies.[200,201] Along with the DASH trials, these data suggest that predominantly nonmeat protein may have a beneficial effect on blood pressure. However, whether the blood pressure effect is due to the protein content or other dietary components, such as potassium or isoflavones, is unknown.[465] Several small studies indicate that vegetable or soy protein sources also may be kidney sparing compared with red-meat sources in diabetes and CKD, and in the Nurses Health Study, the risk of losing kidney function in women with mild kidney insufficiency was related primarily to animal meat intake.[182,185,197,202,466] Higher dairy or vegetable protein intake did not increase this risk. Therefore, a DASH-type diet that emphasizes sources of protein other than red meat may be a reasonable alternative to a lower total protein intake in people with hypertension, diabetes, and CKD stages 1 to 2. Nevertheless, people who achieve the RDA for protein, 0.8 g/kg body weight per day, and maintain an adequate caloric intake remain well nourished. Regardless of the level of protein intake, 50% to 75% of the protein should be of high biological value, derived predominantly from lean poultry, fish, and soy- and vegetable-based proteins.

Table 38. Effect of Low-Protein Diets on Kidney Function, Albuminuria, and Risk Factors in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albumin-uria	Applic-ability	Prescribed (Achieved) LPD (g/kg/d)	UPD (g/kg/d)	Outcome	Baseline Value LPD (UPD)	Net Effect	*P*	Quality
Kidney Function												
Pijls, 1999 [462]	6 mo	121	83	MicroAlb 32%	⚥	0.8 (1.12)	1.15	Δ CCr	81 (85)	-1	NS	⊙
	1									-1.5	NS	
Meloni, 2002 [184]	1	37	44	P 2.2 g/day	⚥	0.6 (0.68)[a]	1.39[a]	Δ GFR	46 (44)[a]	+0.1	nd	○
Gross, 2002 [466]	4 wk	13	SCr 1.0	MicroAlb 100%	♂	0.5-0.8 (0.66)	Usual:1.43	GFR	nd	Final 94 vs 107	<.05	○
							Chicken: 1.35			Final 94 vs 103	<.05 (Usual vs Chicken: <.05)	
		15	SCr 0.9	MacroAlb/MicroAlb 0%			Usual:1.43		nd	Final 94 vs 113	<.05	
							Chicken: 1.35			Final 94 vs 101	NS (Usual vs Chicken: NS)	
Albuminuria												
Pijls, 1999 [462]	6 wk	121	83	MicroAlb 32%	⚥	0.8 (1.12)	1.15	Δ Albuminuria (mg/d)	21.4 (21.3)	- 14% vs +11	.01	⊙
								Δ Fractional Albumin Clearance (x 10^{-6})	4.05 (3.94)	-22%	.03	
	1							Δ Albuminuria (mg/d)	21.4 (21.3)	-8% v +4%	NS	
								Δ Fractional Albumin Clearance (x 10^{-6})	4.05 (3.94)	-10%	NS	
Meloni, 2002 [184]	1	69	44	P 2.5 g/day	⚥	0.6 (0.68)	1.39	Δ Proteinuria (g/d)	2.4 (2.6)	-0.9	<.01	○
Gross, 2002 [466]	4 wk	13	SCr 1.0	MicroAlb 100%	♂	0.5-0.8 (0.66)	Usual:1.43	AER (mg/min)	nd	Final 52 vs 64	NS	○
							Chicken: 1.35			Final 52 vs 34	<.05 (Usual vs Chicken: <.05)	
		15	SCr 0.9	MacroAlb/MicroAlb 0%			Usual:1.43		nd	Final 3.9 vs 2.9	NS	
							Chicken: 1.35			Final 3.9 vs 3.8	NS (Usual vs Chicken: NS)	
Blood Pressure (mm Hg)												
Pijls, 1999 [462]	6 mo	121	83	MicroAlb 32%	⚥	0.8 (1.12)	1.15	Δ BP	138/79 (138/79)	-5/-5	.07/.009	⊙
	1									-4/-3	NS	
Meloni, 2002 [184]	1	69	44	P 2.5 g/d	⚥	0.6 (0.68)	1.39	Δ BP	139/86 (140/84)	-1/-3	NS	○

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albumin-uria	Applic-ability	Prescribed (Achieved) LPD (g/kg/d)	UPD (g/kg/d)	Outcome	Baseline Value LPD (UPD)	Net Effect	*P*	Quality
Hemoglobin A_{1c} (%)												
Pijls, 1999 [462]	1	121	83	MicroAlb 32%		0.8 (1.12)	1.15	Δ HbA_{1c}	7.6 (7.7)	+0.1	.08	⊙
Meloni, 2002 [184]	1	69	44	P 2.5 g/d		0.6 (0.68)	1.39	HbA_{1c}	7.2 (6.7)	-1.2 vs -0.5	NS	○
Lipids (mg/dL)												
Meloni, 2002 [184]	1	69	44	P 2.5 g/d		0.6 (0.68)	1.39	Δ Total Cholesterol	233 (245)	+29	NS	○
Gross, 2002 [466]	4 wk	13	SCr 1.0	MicroAlb 100%		0.5-0.8 (0.66)	Usual:1.43	Total Cholesterol	nd	Final 174 vs 201	<.05	○
							Chicken: 1.35			Final 174 vs 176	NS (Usual vs Chicken: <.05)	
		15	SCr 0.9	MacroAlb/MicroAlb 0%			Usual:1.43		nd	Final 174 vs 176	NS	
							Chicken: 1.35			Final 174 vs 179	NS (Usual vs Chicken: NS)	
		13	SCr 1.0	MicroAlb 100%			Usual:1.43	LDL	nd	Final 104 vs 126	NS	
							Chicken: 1.35			Final 104 vs 108	NS (Usual vs Chicken: NS)	
		15	SCr 0.9	MacroAlb/MicroAlb 0%			Usual:1.43		nd	Final 98 vs 100	NS	
							Chicken: 1.35			Final 98 vs 106	NS (Usual vs Chicken: NS)	
Albumin/Prealbumin												
Meloni, 2002 [184]	1	69	44	P 2.5 g/d		0.6 (0.68)	1.39	Δ Albumin (g/L)	4.7 (4.1)	-1.2	<.01	○
								Δ Prealbumin (mg/dL)	41 (39)	-19.5	<.01	

a Data reported for combined cohort of patients with type 1 (N = 32) and type 2 (N = 37) diabetes.
b 46% type 1 diabetes.

Table 39. Effect of Miscellaneous Diets on Kidney Function, Albuminuria, and Risk Factors in Type 1 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applicability	Treatment (qd)	Comparator	Outcome	Baseline Value[a]	Net Effect	*P*	Quality
Kidney Function												
Muhlhauser, 1996 [480]	4 wk	16	88	MacroAlb 100%		NaCl 6 g supplement	Placebo	Δ GFR	89 (87)	-2	NS	⊙
Dullaart, 1992 [469]	2	36	114	MacroAlb/MicroAlb 100%		High Linoleic Acid (PUFA:SFA = 1.0)	Control diet	Δ GFR	106 (120)	+7	NS	○
Albuminuria												
Muhlhauser, 1996 [480]	4 wk	16	88	MacroAlb 100%		NaCl 6 g supplement	Placebo	Δ Proteinuria (g/day)	0.71 (1.00)	+0.64	NS	⊙
Dullaart, 1992 [469]	2	36 nd[b]	114	MacroAlb/MicroAlb 100%		High Linoleic Acid (PUFA:SFA = 1.0)	Control diet	Δ AER (μg/min) ↑AER (μg/min)	17 (26) >20 (>20)	+39% RR 1.33	<.05 NS	○
Blood Pressure (mm Hg)												
Muhlhauser, 1996 [480]	4 wk	16	88	MacroAlb 100%		NaCl 6 g supplement	Placebo	Δ BP	134/86 (130/86)	+4.9/+5.3	NS	⊙
Dullaart, 1992 [469]	2	36	114	MacroAlb/MicroAlb 100%		High Linoleic Acid (PUFA:SFA = 1.0)	Control diet	Δ MAP	~93 (~94)	0	NS	○
Hemoglobin A_{1c} (%)												
Dullaart, 1992 [469]	2	36	114	MacroAlb/MicroAlb 100%		High Linoleic Acid (PUFA:SFA = 1.0)	Control diet	Δ HbA_{1c}	~7.4 (~7.4)	0	NS	○
Lipids (mg/dL)												
Dullaart, 1992 [469]	2	36	114	MacroAlb/MicroAlb 100%		High Linoleic Acid (PUFA:SFA = 1.0)	Control diet	Δ TC Δ LDL	~225 (~240) ~150 (~165)	-20 -5	NS NS	○

a Baseline value of outcomes in the treatment (comparator) arm.
b Subgroup analyzed with baseline AER > 20 μg/min and number of subjects is not documented.

Table 40. Effect of Miscellaneous Diets on Mortality, Kidney Function, Albuminuria, and Risk Factors in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)	Comparator	Outcome	Baseline Value [a]	Net Effect	*P*	Quality
Mortality												
Facchini, 2003 [481]	3.9	170	63	P 2.4 g/d		CR-LIPE	Low protein 0.8 g/kg	Mortality	—	HR 0.69	<.02	○
Kidney Function												
Facchini, 2003 [481]	3.9	170	63	P 2.4 g/d		CR-LIPE	Low protein 0.8 g/kg	CKD Stage 5	—	HR 0.76	<.05	○
								Double SCr (Cumulative %)	—	21% vs 39%	<.01	
Wheeler, 2002 [482]	6 wk	17	100	MicroAlb 100%		Plant protein diet 107 g	Animal protein diet[b] 107 g total	Δ GFR	100 (116)	+6	NS	○
Bakris, 1996 [483]	4 wk	15	66	MacroAlb 100%		Na 50 mEq Clonidine	Na 250 mEq Clonidine	Δ CCr	66[c]	-1	nd	○
						Na 50 mEq Nifedipine	Na 250 mEq Nifedipine			-3	nd	
						Na 50 mEq Diltiazem	Na 250 mEq Diltiazem			-3	nd	
Albuminuria												
Wheeler, 2002 [482]	6 wk	17	100	MicroAlb 100%		Plant protein diet 107 g	Animal protein diet[b] 107 g total	Δ AER (µg/min)	68 (53)	-28	NS	○
Bakris, 1996 [483]	4 wk	15	66	MacroAlb 100%		Na 50 mEq Clonidine	Na 250 mEq Clonidine	Δ UAE (mg/d)	3396[c]	+301	nd	○
						Na 50 mEq Nifedipine	Na 250 mEq Nifedipine			-255	nd	
						Na 50 mEq Diltiazem	Na 250 mEq Diltiazem			-1154	nd	
Blood Pressure (mm Hg)												
Facchini, 2003 [481]	3.9	170	63	P 2.4 g/d		CR-LIPE	Low protein 0.8 g/kg	Δ BP (MAP)	107 (108)	-6	NS	○
Wheeler, 2002 [482]	6 wk	17	100	MicroAlb 100%		Plant protein diet 107 g	Animal protein diet[b] 107 g total	Δ BP	145/83 (145/82)	+1/+1	NS	○
Bakris, 1996 [483]	4 wk	15	66	MacroAlb 100%		Na 50 mEq Clonidine	Na 250 mEq Clonidine	Δ BP	173/101[c]	-2/-2	nd[d]	○
						Na 50 mEq Nifedipine	Na 250 mEq Nifedipine			-4/-1	nd[d]	
						Na 50 mEq Diltiazem	Na 250 mEq Diltiazem			-3/-1	nd[d]	
Hemoglobin A_{1c} (%)												
Facchini, 2003 [481]	3.9	170	63	P 2.4 g/d		CR-LIPE	Low protein 0.8 g/kg	Δ HbA_{1c} (%)	7.6 (7.6)	-0.7	NS	○
Wheeler, 2002 [482]	6 wk	17	100	MicroAlb 100%		Plant protein diet 107 g	Animal protein diet[b] 107 g total	Δ HbA_{1c} (%)	8.1 (7.9)	-0.1	NS	○

(Continued)

Table 40 (Cont'd). Effect of Miscellaneous Diets on Mortality, Kidney Function, Albuminuria, and Risk Factors in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applicability	Treatment (qd)	Comparator	Outcome	Baseline Value [a]	Net Effect	*P*	Quality
Lipids (mg/dL)												
Facchini, 2003 [481]	3.9	170	63	P 2.4 g/d	↑↑	CR-LIPE	Low protein 0.8 g/kg	Δ TC (mg/dL)	212 (220)	+20	NS	○
								Δ LDL (mg/dL)	139 (139)	+8	NS	
Wheeler, 2002 [482]	6 wk	17	100	MicroAlb 100%	↑↑	Plant protein diet 107 g	Animal protein diet[b] 107 g total	Δ TC (mg/dL)	183 (183)	0	NS	○
Azadbakht, 2003 [182]	7 wk	14	SCr 1-2.5	MacroAlb 100%	↑	Low protein - Soy (0.8 g/kd; 35%/30%/35%[c])	Low protein - Usual (0.8 g/kg; 0%/30%/70%[c])	Δ TC (mg/dL)	201(197)	-16	<.01	○
								Δ LDL (mg/dL)	145 (144)	-8	<.04	

a Baseline value of outcomes in the treatment (comparator) arm.
b 60% animal, 40 % plant protein.
c Overall baseline for all subjects on low Na diet and no antihypertensive treatment in crossover study.
d *P* value significant in both arms for before vs after treatment.
e Soy protein % / other vegetable protein % / animal protein %.

If dietary protein intake is limited, an increase in carbohydrates and/or fats is required for adequate caloric intake. Increasing intake of omega-3 and monounsaturated fats may confer benefits on CKD. (Weak/Opinion)

Evidence of biological activity of dietary fats and carbohydrates indicates that an exclusive focus on protein is too limiting with regard to broad effects on health in people with diabetes and CKD. When protein intake is limited, caloric distribution of the other macronutrients must be addressed. According to the National Academy of Sciences, Institute of Medicine, nonprotein calories (90% of total) should be distributed as 30% or less from dietary fats and up to 60% obtained from complex carbohydrates.[467] The ADA recommends that carbohydrates be derived primarily from whole grains, fruits and vegetables, and nonfat or low-fat dairy products.[174] Although glycemic effects are determined strongly by total amount of carbohydrate, low-glycemic index foods (a measure of type of carbohydrate) may decrease postprandial hyperglycemia and improve overall blood glucose control.[174] Dietary fiber is encouraged and may produce metabolic benefits on glycemia and lipids.[174]

The optimal distribution of calories between fatty acid classes remains to be determined. Recommendations for fatty acids usually combine polyunsaturated fatty acids together without differentiating between categories. Few studies have examined the effects of fatty acid intake or supplements on markers of kidney disease and risk factors in patients with diabetes (Table 41).[468-472] Moreover, these studies were short term and performed in small numbers of people, precluding firm conclusions. Nevertheless, the available evidence suggests that increased intake of omega-3 and monounsaturated fatty acids may be considered because of potentially favorable effects on progression of CKD (Table 41). Fatty acid intake can be modified easily by substituting canola oil, a blend that includes both omega-3 and monounsaturated fats, for vegetable oils. Several brands of salad dressings and butter replacement products made from canola oil are available in most grocery stores. To reduce intake of saturated fat, consumption of red

Table 41. Effect of Fatty Acid Supplements on Kidney Function, Albuminuria, and Risk Factors in Type 1 and Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)	Comparator	Outcome	Baseline Value[a]	Net Effect	*P*	Quality
Type 1 Diabetes												
Kidney Function												
Rossing, 1996 [472]	1	29	112	MacroAlb/MicroAlb 100%		Fish oil EPA 2.0 g, DHA 2.6 g	Olive oil	Slope GFR	—	10.6 vs 4.5	NS	⊙
								Δ GFR	116 (108)	-6	NS	
Albuminuria												
Rossing, 1996 [472]	1	29	112	MacroAlb/MicroAlb 100%		Fish oil EPA 2.0 g, DHA 2.6 g	Olive oil	Δ Albuminuria (mg/d)	780 (650)	+7%	NS	⊙
								Δ Fractional Albumin Clearance (x 10^{-6})	127 (134)	+11	NS	
Hamazaki, 1990 [470]	6 mo	9	SCr 1.0	MicroAlb 100%		EPA 1.8 g	No intervention	Δ UAE (mg/g)	68 (71)	-56	nd[b]	⊙
Blood Pressure (mm Hg)												
Rossing, 1996 [472]	1	29	112	MacroAlb/MicroAlb 100%		Fish oil EPA 2.0 g, DHA 2.6 g	Olive oil	Δ BP	141/82 (140/78)	-3/-1	NS	⊙
Hamazaki, 1990 [470]	6 mo	9	SCr 1.0	MicroAlb 100%		EPA 1.8 g	No intervention	Δ BP	128/75 (112/70)	-14/-9	nd	⊙
Hemoglobin A_{1c} (%)												
Rossing, 1996 [472]	1	29	112	MacroAlb/MicroAlb 100%		Fish oil EPA 2.0 g, DHA 2.6 g	Olive oil	Δ HbA_{1c} (%)	8.8 (9.2)	-0.3	NS	⊙
Hamazaki, 1990 [470]	6 mo	9	SCr 1.0	MicroAlb 100%		EPA 1.8 g	No intervention	Δ HbA_{1c} (%)	7.1 (6.3)	+0.8	nd	⊙
Lipids (mg/dL)												
Rossing, 1996 [472]	1	29	112	MacroAlb/MicroAlb 100%		Fish oil EPA 2.0 g, DHA 2.6 g	Olive oil	Δ TC (mg/dL)	195 (196)	+13	NS	⊙
								Δ LDL (mg/dL)	113 (125)	+17	NS	
Hamazaki, 1990 [470]	6 mo	9	SCr 1.0	MicroAlb 100%		EPA 1.8 g	No intervention	Δ TC (mg/dL)	185 (217)	+8	nd	⊙
Type 2 Diabetes												
All Outcomes												
Hamazaki, 1990 [470]	6 mo	17	SCr 0.9	MicroAlb 100%		EPA 1.8 g	No intervention	Δ UAE (mg/g)	65 (46)	-20	nd[b]	⊙
								Δ BP	142/77 (130/75)	+1/+4	nd	
								Δ HbA_{1c} (%)	5.8 (6.8)	+0.1	nd	
								Δ TC (mg/dL)	185 (197)	-6	nd	

a Baseline value of outcomes in the treatment (comparator) arm

b *P* value significant in the treatment arm for before vs after treatment.

Table 42. Key Studies Evaluating Effects of Dietary Protein Restriction or Other Alterations on Kidney Outcomes in Patients With Diabetes and CKD

Author, Sample Size, Study Duration	Study Diets (protein, g/kg body weight per day)	Kidney Outcome Measured; Significant Compared With Higher Protein Diet? Yes/No
Pedrin,[180] n = 108, 9-33 mo	0.5-0.85 No description of other components of diet	Urinary excretion of albumin or total protein: yes Decline in GFR or creatinine-based measurements: yes
Hansen,[181] n = 82, 48 mo	0.89 *vs* 1.02 No description of other components of diet	Decline in GFR: yes RR of CKD stage 5 or death: yes 10% *vs* 27% RR, 0.23 (0.07-0.720; *P* = 0.04)
Azadbakht,[182] n = 14, 18 wk	0.8 g: 70% animal, 30% vegetable After 4-wk washout: 0.8 g; 35% soy protein, 30% vegetable Both diets provided 2 g sodium, 2 g potassium, and 1,500 mg phosphorus	Proteinuria: yes GFR: no
Meloni,[184] n = 69, 12 mo	0.6 g *vs* free diet: 1.38 g No description of other components of diet	CCr: no GFR: no Proteinuria: yes
Dullart,[183] n = 31, 2 y	0.6 g/kg Usual diet: 1.09 g Detailed diet analysis was provided	Albuminuria: yes Renal hemodynamics: yes, year 1 only
Pijls, [462] n = 131, 28 mo	0.8 g with isocaloric replacement of protein kcal by unsaturated fat and carbohydrates in combination with water-soluble nondigestible carbohydrate Usual diet: restriction of saturated fatty acids as focus of diet: 1.19 g/kg Subjects met with the dietitian every 3 mo	GFR: no Albuminuria: no
Raal,[186] n = 22, 6 mo	0.8 g/kg >1.6 g/kg	Albuminuria: yes GFR: yes Proteinuria: yes
Pecis, [185] n = 15, 9 wk	0.5 g/kg: 7% protein, 33% fat, 60% carbohydrate Normoprotein isocaloric test diet in which white meat, chicken, and fish substituted for the red meat of the usual diet: 1.2 g/kg Usual diet: 1.4 g/kg Some additional nutrient analysis provided of diets	GFR: yes for both low-protein diet and test diet *vs* usual diet
Jibani, [202] n = 8, 24 wk	Predominantly vegetarian diet: 30% total protein as animal with remainder from vegetable protein	Fractional albumin clearance: yes

Abbreviation: CCr, creatinine clearance.

meats should be reduced, and low-fat or nonfat dairy products should be used.

People with diabetes and CKD should receive intervention from a specialty-trained registered dietitian that includes individualized management of multiple nutritional aspects. (Moderate)

The diet for diabetes and CKD is more complicated than that for either condition alone. The management of diabetes and CKD involves multiple nutrients (macronutrients and micronutrients), including protein, carbohydrate, fat, sodium, potassium, and phosphate, among many others. Nutritional intervention should be individualized and completed in an interactive manner. Patients should identify achievable goals and lifestyle behaviors they want to modify. Several studies have documented that frequent patient contact with a registered dietitian accomplishes dietary goals and/or improves clinical

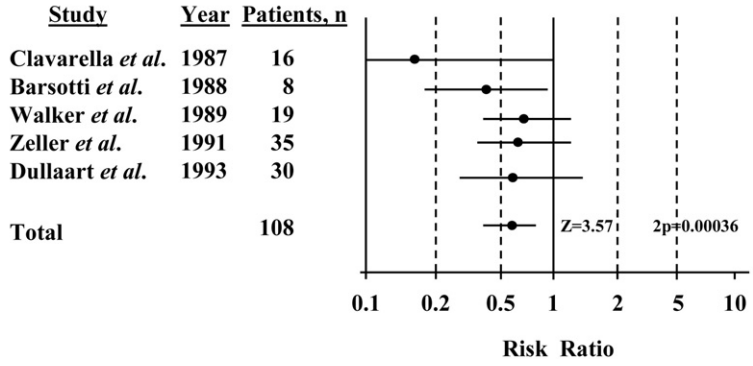

Figure 21. Meta-analysis demonstrating reduced risk of progression of DKD (loss of kidney function or increased albuminuria) by treatment with low-protein diets.
Reprinted with permission.[180]

outcomes.[45,473-475] This finding includes studies of patients with microalbuminuria and diabetes,[45] dialysis patients who have diabetes,[474] and patients with decreased GFR.[475] Because this observation applies across a wide spectrum of patients, those with diabetes and CKD at all stages are likely to benefit from interaction with a registered dietitian.

COMPARISONS WITH OTHER GUIDELINES

The NKF-KDOQI™ Guidelines on Hypertension and Antihypertensive Agents in CKD recommended a version of the DASH diet with modifications for CKD stages 3 to 4.[5,199] These modifications decreased dietary protein from 1.4 g/kg body weight per day to 0.6 to 0.8 g/kg body weight per day, as well as restricted phosphorus (0.8 to 1.0 g/d) and potassium (2 to 4 g/d).[5] Based on concerns about potential detrimental effects of high-protein diets on the kidney and evidence for kidney and survival benefits at approximately the RDA level in diabetes and CKD stages 1 to 2, the Work Group concluded that a protein intake that meets, but does not exceed, the RDA would be prudent at earlier stages of CKD (Table 43). The ADA endorses a dietary protein intake of 0.8 g/kg body weight per day for people with DKD.[34] An additional restriction to 0.6 g/kg body weight per day is suggested should glomerular filtration rate begin to decrease. The dietary protein recommendation should be based on idealized body weight because obesity, which is highly prevalent in the diabetes and CKD population, otherwise would lead to overestimating the dietary protein recommendation.

Dietary sodium reduction to 2.3 g/d (100 mmol/d) is recommended based on the DASH and DASH-Sodium diets.[199] Because most people with diabetes and CKD have hypertension characterized by enhanced sodium retention, this limitation should apply. Recommendations for phosphorus and potassium are the same for CKD with and without diabetes. Phosphorus binders may be needed in patients with advanced CKD because of the emphasis on whole grains and dairy products.

The Institute of Medicine established guidelines for intake of omega-3 fatty acids, which recognize significant variances in physiological

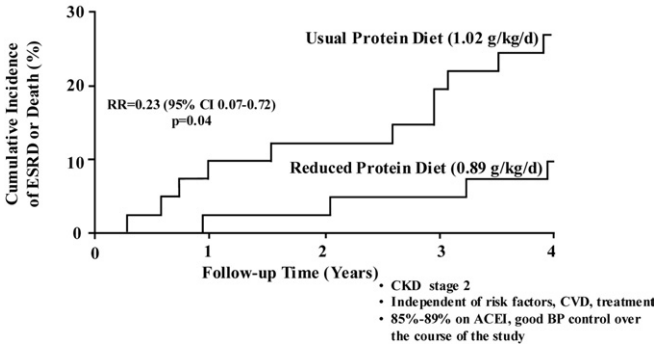

Figure 22. Effect of reduced dietary protein intake on CKD stage 5 and death in type 1 diabetes and CKD Stage 2 (inferred) at baseline.
Reprinted with permission.[181]

Table 43. A Balanced Approach to Nutrition in CKD With or Without Diabetes: Macronutrient Composition and Mineral Content

	Stage of CKD		
Nutrient	**1-2**	**1-4**	**3-4**
Sodium (g/d)		<2.3	
Total fat* (% of calories)		<30	
Saturated fat (% of calories)		<10	
Cholesterol (mg/d)		<200	
Carbohydrate (% of calories)		50-60	
Protein (g/kg/d, % of calories)			
No diabetes	1.4 (~18)		0.6-0.8 (~8-10)
Diabetes	0.8 (~10)		0.6-0.8 (~8-10)
Phosphorus (g/d)	1.7		0.8-1.0
Potassium (g/d)	>4		2.4

Note: Adapted from the DASH diet and NKF-KDOQI™ CPGs for Hypertension and Antihypertensive Agents in CKD, modified for diabetes and stages of CKD.[5,199]

*Adjust so total calories from protein, fat, and carbohydrate are 100%. Emphasize such whole-food sources as fresh vegetables, whole grains, nuts, legumes, low-fat or nonfat dairy products, canola oil, olive oil, cold-water fish, and poultry.

potency between different omega-3 fatty acids. Adequate intake of alpha-linolenic acid was established as 1.6 g/d for men and 1.1 g/d for women, with substitution of up to 10% of these amounts by the more physiologically potent eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[467] The AHA and the KDOQI™ CPGs for CVD in Dialysis Patients recommend including 1 serving of cold-water fish in the diet 3 times per week.[10,476] It is possible that 3 servings of cold-water fish, such as salmon, mackerel, herring, and albacore tuna, would provide EPA and DHA in excess of the 10% of adequate intake amounts for men and women. The Work Group is not aware of studies indicating disadvantages from this amount of EPA or DHA. However, some concerns exist related to the potential for unacceptable levels of mercury or other contaminants. Nevertheless, in the opinion of the Work Group, these recommendations may be considered for the diabetes and CKD population.

LIMITATIONS

Studies of dietary protein interventions in diabetes and CKD are relatively few, short term, completed in small numbers of participants, and have limited documentation of DKD. In addition, both the qualitative (eg, beef, chicken, or soy sources) and quantitative definition of a low-protein diet differ tremendously among studies. Substantial differences in amounts and types of fat and carbohydrate also have not been acknowledged adequately. This type of variability is a potential explanation for the inconsistent results observed between studies evaluating the effect of protein intake on kidney outcomes.

IMPLEMENTATION ISSUES

As detailed in CPR 4, adherence to nutritional regimens is particularly challenging. Therefore, methods to improve adherence are crucial to achieve nutritional goals. In addition, diets recommended by health care professionals often are viewed as unpalatable and unattractive. Culinary approaches to enhance appeal of nutrient-appropriate foods should be encouraged, along with methods to make food preparation easy and inexpensive. An example of a meal plan that meets the nutritional goals of this guideline is provided in Appendix 1. A professional chef designed the menu and accompanying recipes in collaboration with registered dietitians experienced with diabetes and CKD. In the view of the Work Group, these types of creative approaches facilitate interest and feasibility for lifestyle modification in diabetes and CKD.

Schedule for Nutritional Assessment and Intervention

The Renal Dietitians Dietetic Practice Group of the American Dietetic Association recommends nutritional assessment and intervention at the diagnosis of CKD and quarterly thereafter.[477] Considering that diabetes further complicates CKD care, frequency of assessment may be

adjusted based on the needs of individual patients. A registered dietitian who is knowledgeable of both conditions should perform nutritional assessments and interventions. Obtaining accurate dietary histories often is challenging because of the subjective nature of reporting and difficulty with recall. For some key nutrients in the regimen recommended for diabetes and CKD, such as sodium and protein (estimated by urinary urea nitrogen excretion), 24-hour urine studies are useful to assess intake and guide counseling. Close monitoring of patients who follow a dietary protein restriction is important to ensure adequate, but not excessive, protein intake.

III. CLINICAL PRACTICE RECOMMENDATIONS

CLINICAL PRACTICE RECOMMENDATION 1: MANAGEMENT OF ALBUMINURIA IN NORMOTENSIVE PATIENTS WITH DIABETES AND ALBUMINURIA AS A SURROGATE MARKER

Treatments that lower urinary albumin excretion may slow progression of diabetic kidney disease (DKD) and improve clinical outcomes, even in the absence of hypertension. However, most people with diabetes and albuminuria have hypertension; management of hypertension in these patients is reviewed in Guideline 3.

1.1 Normotensive people with diabetes and macroalbuminuria should be treated with an ACE inhibitor or an ARB. (C)

1.2 Treatment with an ACE inhibitor or an ARB may be considered in normotensive people with diabetes and microalbuminuria. (C)

1.3 Albuminuria reduction may be considered a treatment target in DKD. (C)

BACKGROUND

This CPR addresses the evidence for treatment of normotensive patients who have diabetes and elevated albuminuria with ACE inhibitors and ARBs. RAS inhibition effectively reduces albuminuria progression and improves clinical outcomes in hypertensive patients with DKD, but relatively few studies, particularly of antihypertensive agents, have specifically recruited normotensive people with diabetes and elevated albuminuria. Although there is a greater body of evidence that evaluates ACE inhibitors in type 1 diabetes and ARBs in type 2 diabetes (Table 44 to Table 46), the Work Group views their relative benefits as interchangeable for early and late stages of DKD. Accordingly, the Work Group assumes, as in Guideline 3, that a class effect exists across these agents, although several individual agents of each class have not been tested with clinical end points in kidney disease. This assumption is based on consistency among studies with agents of either class and it reflects the opinion of the Work Group. Nevertheless, the effectiveness of individual agents may differ.

The role of albuminuria change as a surrogate end point for clinical outcomes in the setting of DKD also is discussed. Albuminuria usually is present in DKD. Many studies in people with diabetes and microalbuminuria or macroalbuminuria have targeted stabilization or reduction in albuminuria levels as surrogate end points for progression of kidney disease. Studies evaluating interventions aimed at reducing albuminuria primarily used ACE inhibitors and ARBs.

Relationships between glomerular structural lesions and the presence or absence of microalbuminuria in diabetes are not straightforward. In addition, intrapatient variability in albuminuria measurements is large, and there is controversy about the standardization of the measurement itself. For all these reasons, the Work Group concluded that the evidence for using albuminuria as a surrogate marker for clinical outcomes was not sufficiently strong to merit a guideline statement. In turn, this conclusion influenced the Work Group's interpretation of the strength of the evidence for use of ACE inhibitors or ARBs in diabetic patients who are normotensive and have either macroalbuminuria or microalbuminuria. Therefore, the evidence ratings in CPR 1 were downgraded from those given for corresponding statements in the KDOQI™ Guidelines on Hypertension and Antihypertensive Agents in CKD.

RATIONALE

Definitions

The definition of microalbuminuria is albumin-creatinine ratio (ACR) of 30 to 300 mg/g, and of macroalbuminuria, ACR greater than 300 mg/g (Guideline 1). The definition of hypertension is blood pressure of 130/80 mm Hg or greater (Guideline 3).

Normotensive people with diabetes and macroalbuminuria should receive an ACE inhibitor or an ARB. (Moderate/Weak)

In type 1 diabetes with macroalbuminuria, ACE inhibitors decrease albuminuria and reduce the risk of clinical outcomes regardless of the presence or absence of hypertension. A randomized controlled trial in people with type 1 diabetes and macroalbuminuria found that ACE inhibitors reduced the risk of the combined outcome of doubling of serum creatinine level, CKD stage 5, and death.[168] A quarter of the participants were

Table 44. Effect of ACE Inhibitors on Mortality, CVD, Kidney Function, Albuminuria, and Miscellaneous Outcomes in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value [b]	Net Effect	*P*	Quality
Mortality												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%		Ramipril 1.25 mg	Placebo	All cause mortality	—	HR 1.04	NS	●
UKPDS 39, 1998 [486]	9	758	nd	MacroAlb 2% MicroAlb 18%		Captopril 100 mg	Atenolol 100 mg	All cause mortality	—	RR 1.14	NS	○
								Diabetes-related death	—	RR 1.27	NS	
Composite Clinical Outcome												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%		Ramipril 1.25 mg	Placebo	CVD death, CVD event, CKD Stage 5	—	HR 1.03	NS	●
HOPE, 2000 [104]	4.5	3,577	SCr 1.1	MicroAlb 32%		Ramipril 10 mg	Placebo	MI, Stroke or CVD death	—	RR 0.75	.0004	○
Cardiovascular Disease												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%		Ramipril 1.25 mg	Placebo	MI	—	HR 0.79	NS	●
UKPDS 39, 1998 [486]	9	758	nd	MacroAlb 2% MicroAlb 18%		Captopril 100 mg	Atenolol 100 mg	Stroke	—	RR 1.12	NS	○
								PVD	—	RR 1.48	NS	
Kidney Function												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%		Ramipril 1.25 mg	Placebo	CKD Stage 5	—	HR 0.93	NS	●
								SCr doubling	—	HR 0.81	NS	
Ahmad, 1997 [487]	5	103	124	MicroAlb 100%		Enalapril 10 mg	Placebo	Δ GFR	124	None	NS	○
Albuminuria												
Marre, 2004 [485] DIABHYCAR	4	1,868	SCr 1.0	MacroAlb 26% MicroAlb 74%		Ramipril 1.25 mg	Placebo	Regression of albuminuria	—	RR 0.86	.07	●
Capes, 2000[c] [488] SOLVD	2	970	nd	MacroAlb/MicroAlb 0%		Enalapril 20 mg	Placebo	New proteinuria	—	RR 0.39	.01	●
HOPE, 2000 [104]	4.5	3,577	SCr 1.1	MicroAlb 32%		Ramipril 10 mg	Placebo	Macroalbuminuria	—	RR 0.76	.03	○
								Microalbuminuria	—	RR 0.91	NS	
Ahmad, 1997 [487]	5	103	124	MicroAlb 100%		Enalapril 10 mg	Placebo	Macroalbuminuria	—	ARR 0.84[d]	<.001	○
								Δ AER (μg/min)	55 (53)	-67	<.05	
Miscellaneous Outcomes												
UKPDS 39, 1998 [486]	9	758	nd	MacroAlb 2% MicroAlb 18%		Captopril 100 mg	Atenolol 100 mg	Microvascular disease	—	RR 1.29	NS	○

a Maximum daily dose.
b Baseline value of outcomes in the treatment (comparator) arm.
c Types 1 and 2 diabetes.
d Absolute risk reduction over 5-year period.

Table 45. Effect of ARBs on Mortality, Kidney Function, and Albuminuria in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albumin-uria	Applic-ability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value[b]	Net Effect	*P*	Quality
Lewis, 2001 [169]	2.6	1,715	SCr 1.7	MacroAlb 100%	🧍🧍🧍	Irbesartan 300 mg	Placebo	SCr doubling, CKD Stage 5, or death	—	RR 0.80	.02	●
								CKD Stage 5	—	RR 0.77	NS	
								SCr doubling	—	RR 0.6	.003	
								Δ CCr/year	nd	+1.0	nd	
								Δ Proteinuria (g/d)	2.9 (2.9)	-0.8	nd	
Brenner, 2001 [167] RENAAL	3.4	1,513	SCr 1.9	MacroAlb 100%	🧍🧍🧍	Losartan 100 mg	Placebo	SCr doubling, ESRD, or death	—	HR 0.84	.02	●
								ESRD	—	HR 0.72	.002	
								SCr doubling	—	HR 0.75	.006	
								Δ GFR/year	nd	+0.8	.01	
								Δ ACR (mg/g)	1237 (1261)	-35%	<.001	
Parving, 2001 [161]	2	590	109	MicroAlb 100%	🧍🧍🧍	Irbesartan 300 mg	Placebo	Δ CCr	108 (109)	-4.8	NS	●
								New onset nephropathy	—	HR 0.3	<.001	
								Δ UAE (µg/min))	53.4 (54.8)	-36%[c]	<.001	
						Irbesartan 150 mg		Δ CCr	110 (109)	-2.4	NS	
								New onset nephropathy	—	HR 0.61	.08	
								Δ UAE (µg/min)	58.3 (54.8)	-22%[c]	<.001	

a Maximum daily dose.
b Baseline value of outcomes in the treatment (comparator) arm.
c Reduction in the level of urinary albumin excretion throughout the study.

Table 46. Effect of ARBs versus ACE Inhibitors on Kidney Function and Albuminuria in Type 2 Diabetes

Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applicability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value[b]	Net Effect	*P*	Quality
Barnett, 2004 [400] DETES	5	216	93	MacroAlb 18% MicroAlb 82%	↑↑↑	Telmisartan 80 mg	Enalapril 20 mg	Δ GFR	93	-3	NS	O
								Δ UAE (μg/min)	46.2	+4%	NS	

a Maximum daily dose.
b Baseline value of outcomes in the treatment arm.

normotensive. There was no significant difference in the treatment effect between the normotensive and hypertensive individuals.

In type 2 diabetes with macroalbuminuria, ARB treatment reduces the risk of clinical outcomes. A 300-mg daily dose of irbesartan reduced proteinuria levels (significance not reported) and the risk of doubling of serum creatinine level compared with 10 mg daily of amlodipine or placebo in mostly hypertensive people with type 2 diabetes and nephropathy.[169] In another study, losartan significantly reduced the ACR and the risks of CKD stage 5 and doubling of serum creatinine level compared with placebo.[167] These 2 studies had very few participants with normal blood pressure.

Overall, patients with diabetes, macroalbuminuria, and normal blood pressure rarely were included in the available studies. Therefore, evidence for ACE-inhibitor or ARB treatment in these patients was considered moderate to weak. Nevertheless, based on this limited evidence, the Work Group recommends treatment with an ACE inhibitor or an ARB in this group of patients.

In normotensive people with diabetes and microalbuminuria, use of an ACE inhibitor or an ARB may be considered. (Weak)

Few studies have evaluated ACE inhibitors or ARBs for the treatment or prevention of microalbuminuria in normotensive people with type 1 diabetes. A meta-analysis of clinical trials in people with type 1 diabetes found that ACE inhibitors reduced both the level of albuminuria and progression from microalbuminuria to macroalbuminuria in normotensive subjects.[203] In addition, a recent study (N = 73) found that only 8% of participants treated with 10 mg of enalapril daily compared with 31% of participants receiving a placebo developed microalbuminuria.[204]

Because most people with type 2 diabetes and albuminuria have hypertension, few studies have evaluated normotensive people with type 2 diabetes and microalbuminuria. One small study (N = 94) found that enalapril treatment reduced progression to macroalbuminuria by 30% ($P < 0.001$), with only 12% of patients in the treatment group progressing versus 42% in the placebo group.[206] Similarly, another study (N = 62)

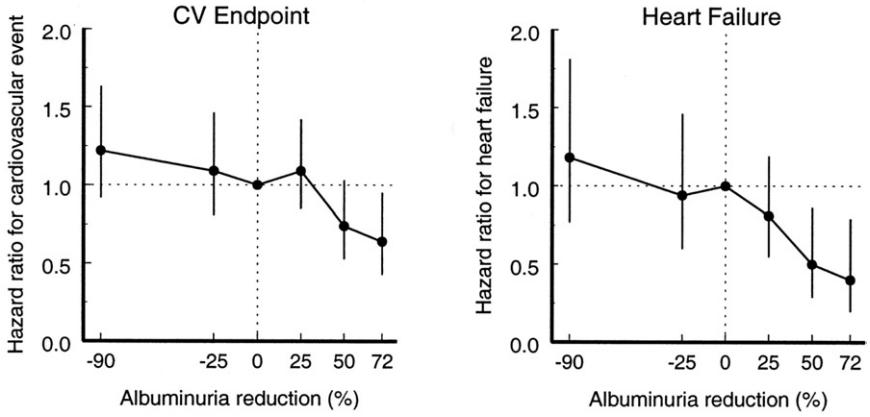

Figure 23. Hazard ratios for CVD and heart failure end points as a function of percent change in 6-month albuminuria in the RENAAL trial.
Relation is corrected for a series of risk markers. Abbreviation: CV, cardiovascular. Reprinted with permission.[211]

found that enalapril significantly reduced albuminuria after 4 years of treatment, whereas participants randomly assigned to placebo experienced an increase in albuminuria.[207] Another small study (N = 19) in normotensive people with either microalbuminuria or macroalbuminuria found that albuminuria increased over 2 years in the placebo group, but decreased significantly with perindopril treatment ($P < 0.05$).[205] Similarly, ACE inhibitors may decrease albuminuria and reduce the risk of kidney and CVD outcomes. The Heart Outcomes Prevention Evaluation (HOPE) trial found that ramipril reduced the risk of the combined end point of myocardial infarction, stroke, or death due to CVD in people with type 2 diabetes. It also reduced progression to macroalbuminuria in subjects with microalbuminuria at baseline, but did not lower the risk of new cases of microalbuminuria.[104]

In the opinion of the Work Group, a change in albuminuria or transition between categories (normoalbuminuria, microalbuminuria, or macroalbuminuria) in normotensive people with diabetes is relatively weak evidence for change in status or prognosis of kidney disease. The rationale for this opinion is as follows. First, level of albuminuria or crossing an ACR threshold is not a clinical end point. Second, RAS inhibitors might mask the progression of DKD marked by albuminuria. In type 1 diabetes, withdrawal of ACE inhibition caused a rapid increase in albuminuria,[208] and in type 2 diabetes, discontinuation of irbesartan in the IRMA-2 study prompted a rapid return to pretreatment levels of albuminuria in patients receiving the lower dose of irbesartan and a partial return to pretreatment levels in those receiving the higher dose of irbesartan.[209] Third, few normotensive patients with diabetes and microalbuminuria have been enrolled in clinical trials of treatments for kidney disease. The demonstrated benefits of RAS inhibition for reducing and stabilizing albuminuria were noted, yet in the absence of studies with clinical end points, the Work Group found this evidence insufficient to justify a higher rating.

Albuminuria change may be an acceptable surrogate marker for clinical outcomes in DKD. (Weak/Opinion)

Studies testing the hypothesis that albuminuria reduction predicts improved prognosis in DKD have been performed only as secondary analyses of studies of ARB treatment in people with type 2 diabetes and macroalbuminuria.[210-212] In these studies, level of albuminuria reduction was a marker of decreased risk of adverse outcomes. Observational analyses from the RENAAL trial found that the magnitude of albuminuria reduction predicted reduced risk of both CVD events and kidney end points (Fig 23 and Fig 24).[211,212] Similarly, an analysis from the IDNT found that degree of proteinuria reduction corresponded to decreased kidney end points (Fig 25).[210] These findings raise the hypothesis that albuminuria reduction per se has beneficial effects. However, an alternative possibility is that albuminuria reduction is a marker for patients with less severe kidney and vascular disease. A strategy of targeting treatment of albuminuria, in addition to blood pressure and other risk factors, has not been tested prospectively in patients with diabetes. Furthermore, to date, only

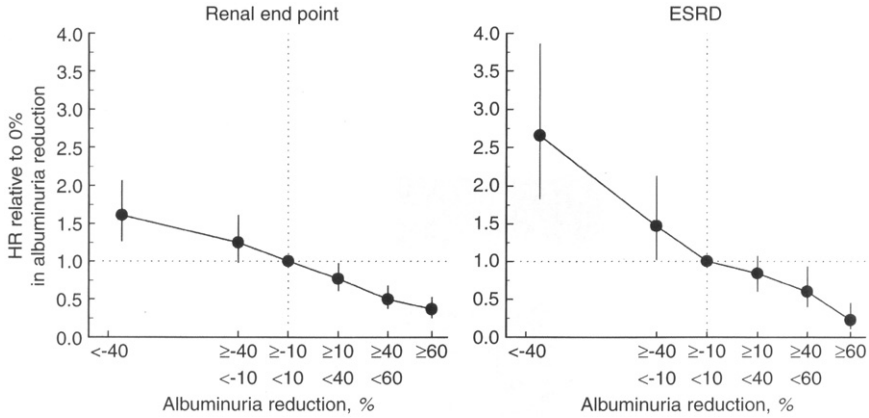

Figure 24. Hazard ratios for kidney end points (doubling of serum creatinine, CKD stage 5, or death) and CKD stage 5 as a function of percent change in 6-month albuminuria in the RENAAL trial. Relation is corrected for a series of risk markers. Abbreviation: ESRD, end-stage renal disease. Reprinted with permission.[212]

these secondary analyses from the RENAAL trial and IDNT have directly correlated albuminuria/proteinuria reduction with clinical benefit.

New interventions to prevent or slow the progression of DKD are urgently needed. Interventions that reduce albuminuria or delay its increase may be promising as potential therapies for DKD. However, in the opinion of the Work Group, there currently is insufficient evidence to assume that lowering albuminuria levels will necessarily lead to improvements in clinical outcomes, such as progression to CKD stage 5, CVD events, or death. Conversely, the failure to reduce albuminuria does not preclude a beneficial clinical effect on DKD from a potential intervention. Therefore, to be considered efficacious, potential treatments for DKD must demonstrate benefits not only on albuminuria reduction, but also on such clinical end points as CKD stage 5, CVD events, or death.[213]

LIMITATIONS

Most studies that assessed the efficacy of ACE inhibitors or ARBs in people with diabetes and albuminuria were conducted in people with hypertension or in a mix of subjects with and without hypertension. Therefore, there are not abundant data to direct therapy for normotensive people with diabetes who have microalbuminuria or macroalbuminuria. However, the consensus of the Work Group was that the benefits of ACE inhibitors and ARBs for reducing albuminuria and delaying kidney disease progression are likely to be similar among most people with diabetes and albuminuria, regardless of their blood pressure level.

In addition, in people with type 2 diabetes, microalbuminuria may represent early kidney injury or may be a manifestation of endothelial dysfunction and generalized vascular injury. The relative contribution of these 2 causes may vary

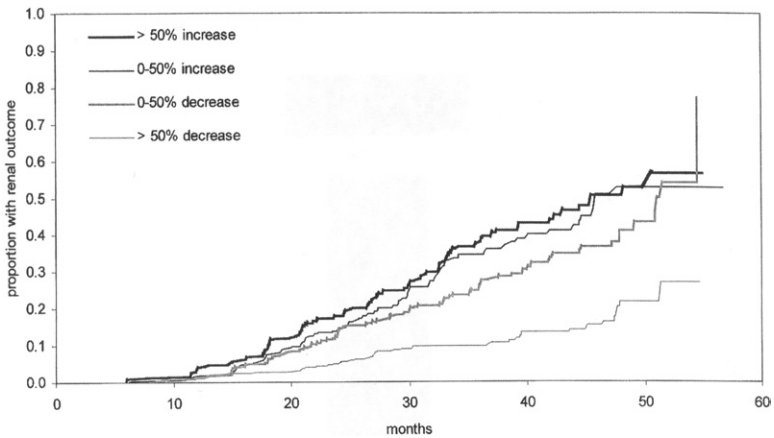

Figure 25. Kaplan-Meier analysis of kidney end points (doubling of serum creatinine [SCr], SCr level > 6 mg/dL, or CKD stage 5) by level of proteinuria change in the first 12 months of the IDNT.
Reprinted with permission.[210]

in each patient. Given the uncertainty regarding the presence of kidney disease in subjects with microalbuminuria and the lack of clinical end points in trials of patients with diabetes and microalbuminuria, the Work Group's recommendations for use of ACE inhibitors and ARBs in normotensive people with diabetes and microalbuminuria are less strong than in those with macroalbuminuria.

IMPLEMENTATION ISSUES

In normotensive people with diabetes and albuminuria, the target dose of ACE inhibitors or ARBs is unknown. In the absence of side effects or adverse events (eg, hyperkalemia), the Work Group recommends titration up to the maximum approved dose.

Placing people with microalbuminuria and diabetes on therapy with an ACE inhibitor or ARB may lead to less attention to glycemic control. The National Health and Nutrition Examination Survey (NHANES) 1999 to 2000 demonstrated that glycemic control has worsened in patients with diabetes and microalbuminuria, which may be caused by health care providers believing that RAS inhibition will reduce albuminuria and thus protect patients from clinical end points.[484] The Work Group emphasizes the importance of glycemic control to prevent and treat albuminuria, as well as to reduce the overall risks of diabetes.

CLINICAL PRACTICE RECOMMENDATION 2: MULTIFACETED APPROACH TO INTERVENTION IN DIABETES AND CHRONIC KIDNEY DISEASE

Multiple risk factors are managed concurrently in patients with diabetes and CKD, and the incremental effects of treating each of these risk factors appear to add up to substantial clinical benefits.

2.1 The care of people with diabetes and CKD should incorporate a multifaceted approach to intervention that includes instruction in healthy behaviors and treatments to reduce risk factors. (C)

2.2 Target BMI for people with diabetes and CKD should be within the normal range (18.5-24.9 kg/m^2). (C)

BACKGROUND

This CPR provides a summary of current evidence for a multifaceted approach to intervention in the management of diabetes and CKD. Studies evaluating multifaceted interventions and various other approaches to reducing albuminuria or improving clinical outcomes were reviewed (Table 47).

RATIONALE

The care of people with diabetes and CKD should incorporate a multifaceted approach to intervention. (Moderate/Weak)

The Steno Study was a randomized trial that investigated a multifaceted treatment approach (intensive intervention) versus usual care in people with type 2 diabetes and microalbuminuria. The intensive intervention had multiple targets, including behavioral modification and pharmacological therapies for hyperglycemia, hypertension (emphasizing RAS inhibitors), dyslipidemia, CVD prevention with aspirin, and vitamin/mineral supplementation (Table 48). Compared with usual care, patients receiving the intensive intervention had significantly larger mean decreases in systolic blood pressure (11 mm Hg), diastolic blood pressure (4 mm Hg), fasting plasma glucose (34 mg/dL), glycosylated hemoglobin (0.7%), triglycerides (50 mg/dL), total cholesterol (47 mg/dL), and LDL-C (34 mg/dL). These changes corresponded to a mean reduction of albuminuria (albumin reduced 20 mg/24 h) for the intensive intervention, whereas there was a mean increase in patients receiving usual care (albumin increased 30 mg/24 h). The intensive intervention reduced albuminuria progression, retinopathy, neuropathy, and a composite outcome of CVD events or death (Fig 26).[45,46] Other interventions using some of the individual components, such as aspirin or vitamins C or E, did not reduce albuminuria in smaller short-term studies.[489,490] Furthermore, vitamin E did not prevent the development or progression of albuminuria or reduce CVD or mortality in a large long-term study of people with type 2 diabetes.[491]

As key components of multifaceted intervention, clinicians should encourage people with diabetes and CKD to adopt healthy lifestyles that include improved nutrition, exercise, and smoking cessation. Although not clearly associated with better kidney outcomes (such as doubling of serum creatinine or CKD stage 5), control of hyperglycemia, blood pressure, and lipids improve other relevant health outcomes in people with diabetes irrespective of the presence of CKD. For example, although glycemic control has not been proven beneficial for kidney outcomes, it reduces risks for retinopathy and neuropathy.[134,136,367,492] Additionally, treatment of elevated LDL-C improves cardiovascular outcomes in people with diabetes (except for those with LDL-C concentrations between 120 and 190 mg/dL who initiate statin therapy while on hemodialysis therapy, Guideline 5).[100,177]

A critical component of the comprehensive care of people with diabetes and CKD is management of diabetes according to current standards (Guideline 2). Targets for glycemic control should be achieved with a combination of lifestyle approaches, behavioral self-management, and medicines (Guidelines 2 and 5, CPR 4). Particular attention should be given to appropriate screening for common comorbidities and referral to specialists, such as those for eye and foot care. Considering the greatly increased CVD risk in people with diabetes and CKD, risk factors should be managed with a goal of minimizing CVD

Table 47. Effect of Miscellaneous Treatments on Mortality, Kidney Function, and Albuminuria in Type 2 Diabetes

Author, Year	Mean Study Duration	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value[b]	Net Effect	*P*	Quality
Lonn, 2002[c] [491]	4.5 y	3654	SCr 1.1	MicroAlb 32%	🧍🧍	Vitamin E 400 IU	Placebo	Mortality	—	RR 0.93	NS	●
								MI, Stroke, CVD death	—	RR 1.03	NS	
								New onset microalbuminuria	—	RR 0.91	NS	
								New onset nephropathy / macroalbuminuria	—	RR 1.12	NS	
Gaede, 1999 [46]	3.8 y	149	117	MicroAlb 100%	🧍🧍	Metoprolol 100 mg Vitamin C 1250 mg Vitamin E 100 mg Aspirin 150 mg	Standard Care	Diabetic nephropathy	—	OR 0.27	.01	●
Gaede, 2003 [45]	8 y	130	nd	MicroAlb 100%	🧍🧍🧍	Intensive multiple risk intervention[d]	Conventional therapy[d]	Δ GFR	nd	+2	NS	●
								Diabetic nephropathy	—	HR 0.39	.003	
Gaede, 2003 [489]	4 wk	31	102	MacroAlb 16% MicroAlb 84%	🧍🧍	Aspirin 150 mg	Placebo	Δ AER (mg/d)	201 (205)	+2.0%	NS	⊙
Gaede, 2001 [490]	4 wk	29	SCr 1.0	MacroAlb 31% MicroAlb 69%	🧍🧍	Vit C 1250 mg Vit E 680 IU	Placebo	Δ AER (mg/d)	112 (112)	+19%	.04	⊙
Hoshino, 2002 [494]	18 mo	16	88	MicroAlb 100%	🧍	Ibudilast 30 mg	No treatment	Δ CCr (mL/min)	87 (88)	+8	NS	⊙
								UAE (mg/g)	72 (62)	-47	<.05	
Manning, 2003 [493]	6 mo	46	nd	MicroAlb 26%	🧍🧍	Premarin 0.625 mg Provera 2.5 mg	Placebo	Δ ACR (mg/g)	25 (5)	0	NS	○
Shindo, 1993 [495]	2 wk	23	63	MacroAlb/MicroAlb 100%	🧍	Iloprost 10 mcg	No treatment	Δ CCr (mL/min)	68 (58)	-0.54	NS	○
								Δ AER (mg/d)	255 (231)	-129	nd[e]	

a Maximum daily dose.
b Baseline value of outcomes in the treatment (comparator) arm.
c 2% Type 1 diabetes.
d Intensive versus Conventional: Hypoglycemic agent/insulin 88% vs 72%; ACE Inhibitor/ARB 84% vs 44%; Statin 57% vs 14%; Aspirin 58% vs 35%; Vitamin/mineral supplement 42% vs 0%.
e *P* value significant in the treatment arm for before versus after treatment.

Table 48. Summary of Steno Trial Multifaceted Intervention for Diabetes and CKD[45,46]

Treatment Goals
Systolic blood pressure < 130 mm Hg
Diastolic blood pressure < 80 mm Hg
Glycosylated hemoglobin < 6.5%
Total cholesterol < 175 mg/dL
Triglycerides < 150 mg/dL
ACE inhibitor or ARB irrespective of blood pressure
Aspirin irrespective of prevalent vascular disease
Smoking cessation
Vitamin/mineral supplement

events, as well as reducing progression of kidney disease (Background, Guidelines 2 to 4). Treatments, such as aspirin and β-blockers, which are known to reduce CVD risk in other high-risk populations, should be strongly considered in those with diabetes and CKD.

A normal BMI (18.5 to 24.9 kg/m^2) may reduce the risk of loss of kidney function and CVD. (Opinion)

Estimates from the NHANES indicate that 31% of the US population is obese (BMI $>$ 30 kg/m^2),[214] and obesity is a risk factor for diabetes, hypertension, and CVD. There is a growing

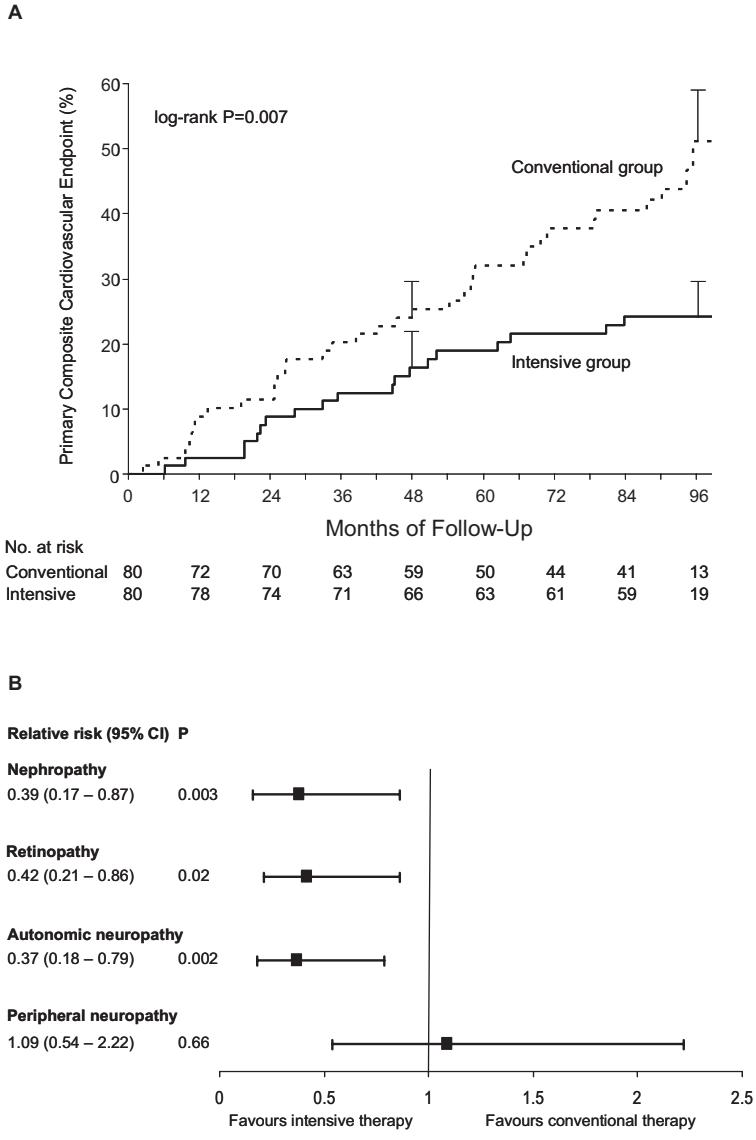

Figure 26. Reduction of end points with intensive multifactorial therapy in the Steno 2 Study.
Kaplan-Meier estimates of (A) the composite end point of death from cardiovascular causes, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease in the conventional-therapy group and intensive-therapy group and (B) relative risk (RR) of the development or progression of nephropathy, retinopathy, and autonomic and peripheral neuropathy during the average follow-up of 7.8 years in the intensive-therapy group compared with the conventional-therapy group. *P* in A was calculated with use of the log-rank test. The bars in A show standard errors. Abbreviation: CI, confidence interval. Reproduced with permission.[45]

Table 49. Proposed Mechanisms for Associations Between Obesity and CKD[100,177,214,215,219,221,492]

Physical compression of the kidneys by visceral obesity
RAS activation
Hyperinsulinemia
Sympathetic activation
Overnutrition
Glomerular hyperfiltration
Proteinuria-associated kidney damage
Blood pressure elevation

body of evidence that obesity also is a risk factor for CKD.[215-221] Whether that risk is independent of diabetes, hypertension, or other risk factors is not yet clear. Nevertheless, obesity is associated with the development of proteinuria and loss of kidney function. The development of metabolic risk factors, as well as adipocyte-derived factors, in response to obesity may lead to kidney damage, albuminuria, and loss of glomerular filtration rate (GFR). Mechanisms that may play a role in the relationship between obesity and CKD are summarized in Table 49. Maintaining a normal BMI (18.5 to 24.9 kg/m^2) reduces various risk factors for CKD and CVD, which may decrease the development or progression of these diseases. Weight loss should be achieved by a balanced reduction in calorie intake, rather than by diets that derive the majority of calories from animal protein (Guideline 5). Weight management should include a plan for regular physical exercise.

LIMITATIONS

Multifaceted intervention includes components that may not be directly beneficial for kidney-related outcomes. Because RAS inhibitors are a major component of the intensive intervention, importance of the other components is uncertain. The design of the multifaceted intervention makes it difficult to determine which facets are associated with reduced risk. Whether people already treated with RAS inhibitors would benefit from intensive intervention was not addressed.

Generalizability of this intervention to other clinical settings is unknown. Importantly, studies of multifaceted intervention have been performed only in patients with type 2 diabetes with microalbuminuria. Although multifaceted intervention seems likely to benefit people with type 1 diabetes and CKD, or later stages of CKD in type 2 diabetes, this opinion is based solely on extrapolation. Prospective studies are required to determine benefits and risks of multifaceted intervention across stages of CKD in both types 1 and 2 diabetes.

Studies of various treatments with the potential to influence CKD (albuminuria) in the setting of diabetes were reviewed. However, these treatments were either ineffective (hormone therapy with estrogen/progestin in postmenopausal women)[493] or the studies were inconclusive (prostaglandin analogues).[494,495] Whether additional types of treatment will provide incremental benefit to the previously described multifaceted intervention is unknown.

The health benefits of maintaining a normal BMI are not defined in people with diabetes and CKD. Optimal targets for BMI and weight loss should be determined.

IMPLEMENTATION ISSUES

The Steno intensive intervention study is a model for a multidisciplinary team approach to care of people with diabetes and microalbuminuria. This specialty clinic–based approach is used successfully for other medical conditions (eg, heart failure and human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS] care), but it requires a critical mass of patients and the presence of specially trained health care personnel.

Other types of interventions that have been used for guideline implementation include computer reminders, provider feedback, and provider incentives. Because of the multifaceted components to the care of both diabetes and CKD, the clinical team approach may be the most effective in settings where feasible. These teams typically are established by large health care organizations.

Prevention and treatment of obesity are major public health concerns. Effective, safe, and sustained weight loss interventions are elusive, and the impact on relevant clinical outcomes is unclear. A longitudinal clinical team approach may be an effective strategy for treatment of obesity in the setting of diabetes and CKD.

CLINICAL PRACTICE RECOMMENDATION 3: DIABETES AND CHRONIC KIDNEY DISEASE IN SPECIAL POPULATIONS

The increasing incidence of diabetes in children, young adults, the elderly, and members of disadvantaged and transitional populations is responsible for an increasing incidence of DKD in these groups. Racial/ethnic differences in susceptibility to DKD also may play a role. In pregnant women, the presence of diabetes and CKD may adversely affect the health of both the mother and her offspring.

3.1 Screening and interventions for diabetes and CKD should focus on populations at greatest risk. (C)

3.2 Although management of diabetes and CKD in special populations should follow the same principles as management in the majority population, there are special considerations in the treatment of children, adolescents, and the elderly. (C)

3.3 Population-based interventions may be the most cost-effective means for addressing the burden of CKD in special populations. Implementation and evaluation of population-based interventions should take into account the heterogeneity of the populations at risk. (C)

3.4 Specialists in high-risk pregnancy and kidney disease should co-manage pregnancy in women with diabetes and CKD. (C)

3.5 Treatment of DKD with RAS inhibitors before pregnancy may improve fetal and maternal outcomes, but these medicines should be discontinued as soon as a menstrual period is missed or after a positive pregnancy test. (C)

3.6 Insulin should be used to control hyperglycemia if pharmacological therapy is necessary in pregnant women with diabetes and CKD. (C)

BACKGROUND

This CPR addresses 4 distinct, but overlapping, groups with diabetes and CKD: children and adolescents, pregnant women, the elderly, and members of disadvantaged and transitional populations. The latter group is made up predominantly, but not exclusively, of people from less-developed countries undergoing economic and social change and by racial and ethnic minorities in developed countries.

In the United States, the burden of diabetes and CKD is borne disproportionately by ethnic and racial minorities. Worldwide, populations of developing countries appear to be at greatest risk of developing diabetes and CKD during the next several decades. Early intervention in these high-risk populations provides the best opportunity for reducing the morbidity and mortality associated with diabetes and CKD. Children[79] and elderly people[496] who are members of these populations appear to be at particularly high risk of morbidity associated with DKD. Moreover, the number of young women with diabetes who become pregnant and already have kidney disease is increasing, yet little is known about the effect of diabetes and CKD on these women or on their offspring.

This CPR describes the burden of diabetes and CKD in special populations and suggests strategies for improving care in these highly susceptible groups. Maternal and fetal outcomes among pregnant women with type 1 diabetes and CKD also are described. However, few studies have evaluated the benefit of treating pregnant women who have diabetes and CKD with interventions aimed at decreasing the risk of maternal and fetal adverse outcomes, and none of these studies included women with type 2 diabetes or with CKD stage 5 treated by either kidney transplantation or dialysis.

RATIONALE

The worldwide epidemic of diabetes disproportionately affects the developing world. (Strong)

The global burden of diabetes is expected to double between 2000 and 2030, with the greatest increases in prevalence occurring in the Middle East, sub-Saharan Africa, and India.[19] Much of this increase will be driven by urbanization and the increase in the population older than 65 years. Countries with the highest numbers of estimated cases of diabetes in 2000 and projections for 2030 are shown in Table 50. Development of diabetes during the childbearing years also will increase, primarily in the developing

Table 50. Countries With the Highest Numbers of Estimated Cases of Diabetes for 2000 and 2030

	2000		2030	
Ranking	Country	People with diabetes (millions)	Country	People with diabetes (millions)
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	U.S.	17.7	U.S.	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9
6	Pakistan	5.2	Brazil	11.3
7	Russian Federation	4.6	Bangladesh	11.1
8	Brazil	4.6	Japan	8.9
9	Italy	4.3	Philippines	7.8
10	Bangladesh	3.2	Egypt	6.7

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countries (Fig 27).[19] Projections of the future burden of diabetes in the US population suggest that the prevalence of diabetes will increase 165% between 2000 and 2050, from 11 to 29 million, with the greatest increases in the population older than 75 years and among African Americans.[18]

As the population of patients with diabetes with significant duration of disease grows, reports of a dramatically increasing burden of diabetic CKD are appearing from Africa,[22,23] India,[24] Pacific Islands,[25] and Asia,[26,27] where infectious disease previously posed the greatest threat.[28] Increased risk and more rapid progression of DKD[29,30] also have been reported in immigrants to Europe from South Asia.[31,32]

Minorities bear a disproportionate burden of diabetic CKD in the United States. (Strong)

Disparities in the incidence of diabetic CKD stage 5 among racial/ethnic groups in the United States have existed for many years, but the magnitude of these disparities has increased in recent years (Fig 28). Between 1999 and 2002, a total of 35% of the new cases of CKD stage 5 due to diabetes in the United States were members of racial minorities, with incidence rates 4 times as high among African Americans and Native Americans than among whites.[4] Excess burden of CKD also is well documented among Pacific Islanders[497,498] and Hispanics.[499] Several studies suggest a greater risk and more rapid development of DKD in racial minorities, and these studies attribute the increased susceptibility to both genetic factors[496,500-503] and socioeconomic barriers, including decreased access to care.[504]

Special populations may demonstrate different patterns of comorbid conditions and a different course of CKD than the majority population. (Moderate)

The natural history of diabetic complications may be falsely perceived as benign when diabetes first emerges as a major problem in a population because few people will have diabetes of sufficient duration to develop the usual complications.[505] Nevertheless, once diabetes has established itself, differences in the rate of development and frequency of diabetic complications, including CKD, have emerged among racial/ethnic groups.[82,506,507] These differences may be attributable to such factors as age at onset of diabetes,[82] diet, exercise patterns, living conditions, access to medical care, education, infections, environmental toxins, and inherited susceptibility.

The frequency of nondiabetic CKD differs among special populations with diabetes. (Moderate)

Higher rates of non-DKD in people with diabetes have been documented in Zuni Indians[508] and Aborigines,[509] emphasizing the importance of a careful diagnostic evaluation in patients with diabetes from high-risk groups. In populations with decreased access to care, when care is often received only late in the course of disease, the cause of kidney disease may be attributed, by

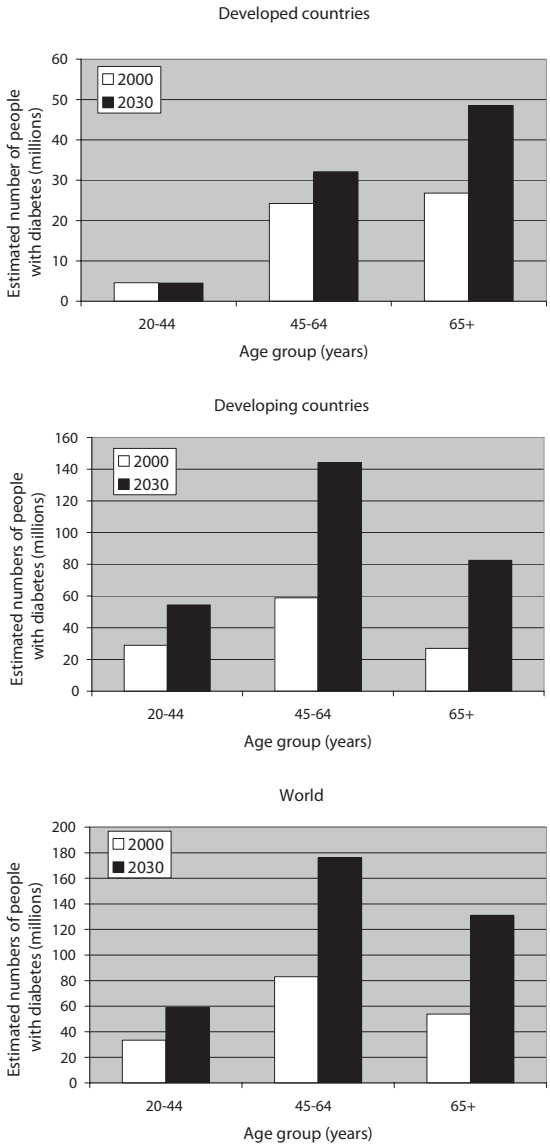

Figure 27. Estimated number of adults with diabetes by age group and year for the developed and developing countries and for the world.
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default, to the most common cause in that group (eg, hypertension in African Americans[510] and type 2 diabetes in Native Americans) without adequate investigation.

Diabetes and CKD are increasing among children and adolescents. (Strong/Moderate)

The worldwide increase in childhood obesity has increased the prevalence of type 2 diabetes among children and adolescents.[511] Whereas all populations in the United States have shown dramatic increases in the overall prevalence of obesity (>10% in 2- to 5-year-olds and >15% in 6- to 19-year-olds), the greatest increases have occurred in ethnic and racial minorities.[512] At the same time, there has been a worldwide increase in the incidence of type 1 diabetes, particularly among children younger than 5 years old.[17] Given that duration of diabetes, rather than age of onset, is the more predominant risk factor for DKD, increasing rates of both type 1 and type 2 diabetes in children and adolescents undoubtedly will lead to an increase in DKD in these age groups, a finding that is already being reported in some populations.[79,80,82]

In many racial/ethnic groups, type 2 diabetes has already become—or is rapidly becoming—the predominant cause of childhood diabetes.[72,513,514] While optimal treatment of childhood type 2 diabetes is essential to reduce the burden of DKD, public health interventions that promote proper diet and increase exercise may offer the best opportunity to reduce disease burden through primary prevention of obesity and diabetes.[71]

Children and adolescents with diabetes and CKD have special treatment considerations. (Weak/Opinion)

CKD stage 3 or greater due to DKD is rare in children and adolescents. Also, children and adolescents are more likely to revert from microalbuminuria to normoalbuminuria than adults (see Guideline 1). Nonetheless, those children and adolescents with diabetes and CKD pose a number of unique concerns. Accordingly, specialists in diabetes and kidney disease with experience in these age groups should be involved in their care. Data regarding treatment of hyperglycemia, hypertension, and dyslipidemia in children with diabetes and adolescents with CKD are almost nonexistent. However, therapeutic lifestyle changes (diet, exercise, and weight loss, when appropriate) are prudent for each of these risk factors. In the opinion of the Work Group, treatment goals for glycemia in type 1 diabetes and CKD should follow the American Diabetes Association (ADA) Standards of Care for children and adolescents (Table 51).[174] Given the greater risk of hypoglycemia in those with decreased

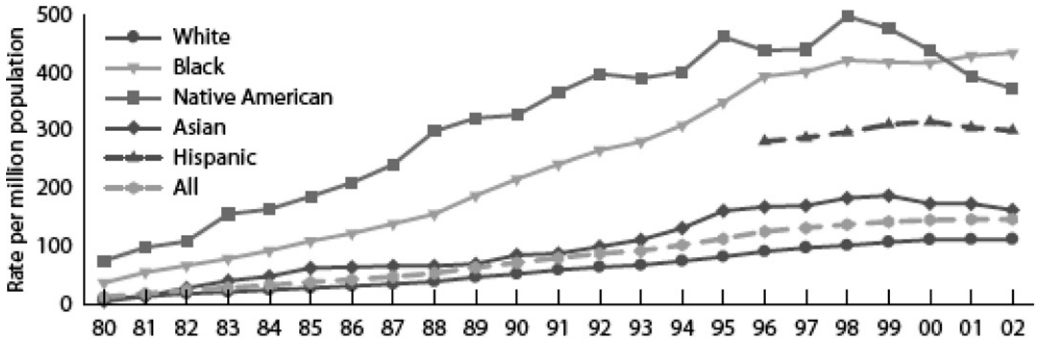

Figure 28. Adjusted incident rates of CKD stage 5 due to diabetes by race/ethnicity.
Incident CKD stage 5 patients adjusted for age and gender. For Hispanic patients, we present data beginning in 1996, the first full year after the April 1995 introduction of the revised Medical Evidence form, which contains more specific questions on race and ethnicity. The data reported here have been supplied by the US Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.[4]

kidney function, treatment goals must be carefully individualized. In patients with type 2 diabetes, therapeutic lifestyle changes should be the initial interventions for hyperglycemia.[513] If lifestyle changes do not succeed in achieving a goal of near-normal glycemia ($HbA_{1c} < 7\%$), drug therapy should be initiated.[513] Although the ADA recommends oral agents as first-line therapy for children or adolescents with type 2 diabetes, only metformin is approved by the Food and Drug Administration (FDA) for this use—and only in children older than 10 years. However, metformin should be avoided in children and adolescents with diabetes and CKD. Cautions regarding the use of other oral agents in children and adolescents with diabetes and CKD are the same as those described for adults (Guideline 2, Table 22), with the exception that TZDs should not be used because of concerns about liver toxicity due to the experience with troglitazone.

According to the NKF-KDOQI™ CPGs on Hypertension and Antihypertensive Agents in CKD, the target blood pressure in children and adolescents with CKD is less than the 90th percentile for age, sex, and height or less than 130/80 mm Hg, whichever is lower.[5] The ADA recommends a similar goal in children and adolescents with diabetes.[174] Therefore, in the opinion of the Work Group, a target blood pressure less than the 90th percentile for age, sex, and height or less than 130/80 mm Hg, whichever is lower, should be applied to children and adolescents with both

Table 51. Plasma Blood Glucose and HbA_{1c} Goals for Type 1 Diabetes by Age Group

	Plasma Blood Glucose Goal Range (mg/dL)			
Values by age (y)	Before Meals	Bedtime/Overnight	HbA_{1c} (%)	Rationale
Toddlers and preschoolers (<6)	100-180	110-200	≤8.5 (but ≥ 7.5)	• High risk and vulnerability to hypoglycemia
School age (6-12)	90-180	100-180	<8	• Risk of hypoglycemia and relatively low risk of complications before puberty
Adolescents and young adults (13-19)	90-130	90-150	<7.5*	• Risk of hypoglycemia • Developmental and psychological issues
Key concepts in setting glycemic goals: Goals should be individualized and lower goals may be reasonable based on benefit-risk assessment Blood glucose goals should be higher than those listed in children with frequent hypoglycemia or hypoglycemia unawareness Postprandial blood glucose values should be measured when there is a disparity between preprandial blood glucose values and HbA_{1c} levels				

*A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia
Reprinted with permission.[174]

CKD and diabetes. Although not approved for use by the FDA, both the NKF and the ADA suggest that ACE inhibitors are the drugs of choice for treatment of blood pressure in children and adolescents with diabetes and/or CKD.[5,174] ARBs are reasonable alternatives if ACE inhibitors are not tolerated.[5] Adolescent girls must be counseled fully and repeatedly about pregnancy prevention while on ACE inhibitors or ARBs and about immediate discontinuation of these agents should pregnancy be suspected.

Drug therapy should be considered for either severe hypertriglyceridemia (triglycerides > 500 mg/dL) or marked elevations in LDL-C (>160 mg/dL) that are unresponsive to control of hyperglycemia or therapeutic lifestyle changes as outlined in the NKF-KDOQI™ CPGs on Managing Dyslipidemias in CKD.[6] Fibric acid derivatives are the preferred agents for hypertriglyceridemia, but they are not FDA approved for use in children or adolescents. Statins are preferred for elevated LDL-C levels, and atorvastatin has received FDA approval for use in children and adolescents with familial hypercholesterolemia. The ADA suggests an LDL-C target of less than 100 mg/dL in children and adolescents with diabetes.[174] Adolescent girls must be counseled fully and repeatedly about pregnancy prevention while on statin therapy and about immediate discontinuation of these agents should pregnancy be suspected.

Children and adolescents should be referred to a registered dietitian experienced in managing diabetes and CKD in this age group. For those who are obese, weight loss strategies should include both increased physical activity and a well-balanced diet. As per Guideline 5, high-protein diets (>20% of calories) should be avoided in children and adolescents with diabetes and CKD. However, low-protein diets (<10% of calories) also should be avoided because of concerns about providing adequate nutrition for growth and development and because proof of efficacy is lacking in this age group.

Elderly people with diabetes and CKD have special treatment considerations. (Weak/Opinion)

Elderly people with diabetes and CKD often have a number of comorbidities, particularly CVD, as well as cognitive and functional impairments. Therefore, the benefits of intensive risk factor management should be considered judiciously in light of these increased risks. Because hypoglycemia and hypotension are particular concerns, less intensive goals should be considered based on individual circumstances. Drug therapies for hyperglycemia, hypertension, and dyslipidemia can be used as in other patients with diabetes and CKD. However, drugs should be started at low doses and carefully titrated to monitor for responses and side effects.

The greater frequency of comorbid conditions in the elderly with diabetes is responsible for a greater prevalence of elevated albuminuria unrelated to DKD. Accordingly, the appearance of elevated albuminuria is less likely to be a sign of progressive kidney disease, even in those with diabetes of long duration.[515] GFR may be a more specific marker of DKD in the elderly compared with albuminuria.[516] Development of diabetic complications, including CKD, is associated strongly with mortality in elderly people,[517] and poor outcomes are associated with nonadherence to the medical regimen.[518] The high cost for caring for elderly people with CKD may be reduced through the aggressive management of CVD.[519]

The presence of microalbuminuria in pregnant women with type 1 diabetes increases risks of adverse maternal and child outcomes, including preeclampsia and preterm delivery. Macroalbuminuria further increases these risks and also may increase risk of perinatal mortality. (Strong/Moderate)

Case-control and cohort studies involving more than 1,300 pregnant women with type 1 diabetes were reviewed to identify adverse maternal and child outcomes in pregnancies complicated by both diabetes and CKD (Table 52) and the predictors of these adverse outcomes (Table 53). All entries in the summary tables refer to these studies in type 1 diabetes. Microalbuminuria increases risks of preeclampsia and preterm delivery up to 8 times.[520,521] Macroalbuminuria further increases these risks to more than 30 times[522-524] (Table 52). Macroalbuminuria also

Table 52. Adverse Maternal and Child Outcomes in Pregnancies Complicated by Diabetes and CKD

Author, Year	Population	N	Applicability	Maternal Outcomes (%[a])				Child Outcomes (%[a])					Quality
				Mortality	Pre-eclampsia	Cesarean Section	Other	Mortality	Malformation	Preterm Birth	ICU Stay/RDS	SGA	
Hiilesmaa, 2000 [521]	White Class F	67			57								●
	White Class NF	616			24								
	No DM	854			8								
Miodovnik, 1996 [557]	White Class F	46			**65**	76	CKD Stage 5: 26	9	11	**22**	**20**		○
	White Class NF	136			**9**	69	CKD Stage 5: 0	1	6	**10**	**8**		
Ekbom, 2001 [520]	DM/Macroalb	11			**64**			0	9	**45**		**45**	○
	DM/Macroalb	26			**42**			4	4	**23**		**4**	
	DM/Macroalb	203			**6**			1.5	2.5	**6**		**2**	
Kimmerle, 1995 [524]	DM/Nephropathy CCr <80 mL/min	10				**100**		0	20	**60**	**50**	**30** [b]	○
	DM/Nephropathy CCr >80 mL/min	26				**80**		0	0	**19**	**15**	**19** [b]	
	DM/No nephropathy	110				**64**		0	1	**3**	**1**	**2**	
Rossing, 2002 [558]	DM/Alb/Nl Cr Pregnant [c]	26					Δ CCr -3.2 [d] Alb 786 [e] CKD Stage 5: 23						○
	DM/Alb/Nl Cr Not pregnant [c]	67					Δ CCr -3.2 [d] Alb 882 [e] CKD Stage 5: 24						
Sibai, 2000 [526]	DM/Proteinuria	86						3.5		**29**	**70**	**14**	○
	DM/No proteinuria	376						2.1		**13**	**46**	**3**	
Nielsen, 1997 [528]	White Class F	23							17 [i]				○
	White Class NF	138							9 [i]				
Vaarasmaki, 2000 [527]	White Class F+R	32								34		25	○
	DM Type 1	296						**3.0**	**5.4**	**19**	**49**	**5.8**	
	No DM or CKD	44,678						**0.7**	**0.7**	**5**	**7**	**2.3**	
Vaarasmaki, 2002 [559]	White Class F+R	20			47								○
	White Class B	nd			6								
Purdy, 1996 [532]	DM/Nephropathy/ Elevated SCr/ Pregnant	11					Δ 1/SCr -2.99 [f] (partum) **Δ 1/SCr -8.13 [f] (post-partum)**						○
	DM/Nephropathy/ Elevated SCr/ Not pregnant	111					**Δ 1/SCr -1.03 [f]**						

(Continued)

Table 52 (Cont'd). Adverse Maternal and Child Outcomes in Pregnancies Complicated by Diabetes and CKD

Author, Year	Population	N	Applicability	Maternal Outcomes (%[a])				Child Outcomes (%[a])					Quality
				Mortality	Pre-eclampsia	Cesarean Section	Other	Mortality	Malformation	Preterm Birth	ICU Stay/RDS	SGA	
Biesenbach, 2000 [522]	DM/Nephropathy	10	↑		**60**	60			10	**60**	30	**50**	○
	DM/No nephropathy	30			6	60			0	0	0	0	
Mackie, 1996 [531]	DM/Nephropathy SCr = 1.4-2.8 mg/dL	11	↑						45 [g]	Median 31 + 2 wk	100 [h]		○
	DM/Nephropathy SCr <1.4 mg/dL	13							8 [g]	Median 36 + 4 wk	38 [h]		

Note: White's classification: Class B, insulin-requiring DM onset after 20 years of age with duration less than 10 years; Class F, insulin-requiring diabetes with diabetic nephropathy; Class NF, insulin-requiring diabetes without diabetic nephropathy; Class R, insulin-requiring DM with proliferative retinopathy.

Abbreviations: DM, diabetes mellitus.

a Bold values are significantly different from each other.

b No statistical difference between 2 groups with nephropathy.

c 16-year follow-up.

d mL/min/y.

e mg/24 h, unclear time frame.

f dL/mg/mo.

g Spontaneous abortions or therapeutic abortions for multiple congenital malformations or death at 9 months postpartum with multiple congenital malformations (1 baby of mother with impaired kidney function).

h Of live births.

i Spontaneous abortions and malformations.

appears to increase the risk of preterm birth, small-for-gestational-age infants, and perinatal mortality independent of preeclampsia.[525-527] Furthermore, higher HbA_{1c} in the first trimester of pregnancy increases the risk of major malformations (Table 53).[528] Therefore, women with diabetes and CKD who are pregnant should be monitored and treated as high-risk patients. In the opinion of the Work Group, pregnant women with diabetes and CKD should be co-managed by specialists in high-risk pregnancies and kidney disease.

Albuminuria in pregnant women with type 1 diabetes does not increase the risk of worsening of DKD unless kidney function also is impaired. (Strong/Moderate)

Only a few studies have explored the progression of DKD in pregnant women. Clinically significant worsening of kidney disease is apparent only in women who already have increased baseline levels of serum creatinine and albuminuria. These patients have a greater GFR decline during pregnancy and a higher risk of progression to CKD stage 5 after delivery.[520,524,529-532]

The effect of CKD on the outcome of pregnancy in women with type 2 diabetes is unknown. (Opinion)

Due to the increasing prevalence of type 2 diabetes in younger women, some may become pregnant after the development of kidney disease. In the absence of data regarding pregnancy in women with type 2 diabetes and CKD, it is the opinion of the Work Group that they should be managed according to the same principles as women with type 1 diabetes and CKD because their risks are likely to be at least as great as in women with type 1 diabetes.

Medical management of CKD should be adjusted during pregnancy in women with diabetes. (Weak/Opinion)

Recommendations regarding the medical management of hypertension, hyperglycemia, dyslipidemia, and nutrition in pregnant women with diabetes and CKD are outlined in Table 54.

Table 53. Predictors of Adverse Maternal and Child Outcomes in Pregnancies Complicated by Diabetes and CKD

Author, Year	Number of Pregnant Women			Applicability	Predictor	Outcome	Univariate	Multivariate	Quality
	High-Risk Category		Diabetes						
Miodovnik, 1996 [557]	White Class F	46			HbA_{1c}	CKD Stage 5	Trend		⊙
Kimmerle, 1995 [524]	Diabetes / Nephropathy	36			CCr, 1st trimester	Gestational age at delivery	*P* = .006		⊙
					DBP, 3rd trimester		*P* = .01		
					SBP		NS		
					Glycemic control		NS		
					Proteinuria		NS		
Sibai, 2000 [526]	Diabetes / Proteinuria	86	462		Proteinuria	Preterm birth		2.6 (1.5-4.6)	⊙
						SGA		5.4 (2.7-18)	
						Neonatal ICU		2.6 (1.5-4.4)	
						Perinatal death		1.8 (0.5-6.8)	
Nielsen, 1997 [528]	White Class F	23	54 [a]		White class F	Spontaneous abortion + malformation		2.2 (0.4-11)[a]	⊙
Gordon, 1996 [523]	White Class F	45			Proteinuria (g/day)	Gestational age at delivery	r = -0.33 *P* = .025		○
					SCr (mg/dL)		r = -0.39 *P* = .009		
					HbA_{1c}		NS		
					Proteinuria (g/24 hr)	Birth weight	r = -0.37 *P* = .01		
					SCr (mg/dL)		r = -0.35 *P* = .02		
					HbA_{1c}		NS		
Vaarasmaki, 2000 [527]	White Class F + R	32	296		White class F+R	Adverse fetal outcome	2.8 (1.6-4.8)		○
Bar, 1999 [536]	Diabetes / Nephropathy	24			HTN, pre-existing	Complication (pre-eclampsia, preterm delivery, IUGR)	*P* = .0004		○
					CCr		NS		
					Proteinuria		NS		
Purdy, 1996 [532]	Diabetes / Nephropathy / Elevated SCr	11			HbA_{1c}	Permanent worsened kidney function	NS		○
Reece, 1990 [560]	White Class F + R	10			SCr, preconception	SCr, postdelivery	NS		○

Note: White's classification: Class F, insulin-requiring diabetes with diabetic nephropathy; Class R, insulin-requiring diabetes with proliferative retinopathy.
a Reference group is White class B.

Table 54. Management of Pregnant Women With Diabetes and CKD[174,533-535]

Risk Factor	Treatment	Goal	Cautions
Hypertension	*Preferred:* Methyldopa Labetolol *Add-on drugs:* Hydralazine Long-acting calcium channel blockers	Treat if blood pressure >140-160/90-105 mm Hg Target blood pressure undetermined. Consider target of <130/80 mm Hg because of CKD. Avoid hypotension	Stop ACE inhibitors and ARBs after first missed menstrual period or positive pregnancy test Atenolol may cause fetal growth retardation in first trimester Avoid diuretics unless given for hypertension preconception and no evidence of preeclampsia. If diuretic is continued during pregnancy, dose should be reduced
Hyperglycemia	Insulin	HbA_{1c} as close to normal as possible (<1% above upper limit of normal)	Excessive hypoglycemia
Hyperlipidemia	None		Stop statins and other lipid-lowering drugs after first missed menstrual period or positive pregnancy test
Nutrition	Liberalize dietary protein to 1.0-1.2 g/kg/d (preconception weight)		

ACE inhibitors and ARBs should be stopped at the first indication of possible pregnancy in women with diabetes and CKD. Methyldopa and labetolol are preferred antihypertensive agents during pregnancy. (Weak/Opinion)

Uncontrolled studies of women with diabetes, macroalbuminuria, and normal GFR who were treated with captopril, 37.5 to 75 mg/d, for at least 6 months before pregnancy and discontinued immediately after a missed menstrual period or a positive pregnancy test showed no deterioration of kidney function 2 years after delivery.[536,537] ACE inhibitors and ARBs have adverse effects on the fetus during the second and third trimester, including acute kidney failure in neonates, lung toxicity, and skull hypoplasia.[538] Emerging evidence suggests that risk of fetal abnormalities (congenital malformations of the cardiovascular system, central nervous system, and kidney) during ACE-inhibitor treatment extends to the first trimester.[539] Therefore, RAS inhibitors should be discontinued immediately after a missed menstrual period or a positive pregnancy test in women with diabetes and CKD.[5] Women and adolescent girls with childbearing potential who are treated with RAS inhibitors should be counseled about these risks.

Treatment of hypertension should follow the guidelines adopted by the American College of Obstetrics and Gynecology.[533] Because antihypertensive therapy does not reduce the risk of preeclampsia and may cause potential harm to the fetus, hypertension should be treated cautiously. Based on extensive experience, methyldopa has long been considered the drug of choice by many experts. Labetolol now also is considered a preferred agent because combined α- and β-blockade may better preserve uterine perfusion. β-Blockers are considered reasonable add-on or alternative therapies. However, some data suggest that atenolol early in pregnancy may cause fetal growth retardation. Long-acting calcium channel blockers or hydralazine also are considered reasonable

add-on therapy. Diuretics usually are avoided in pregnancy, particularly when there are concerns about preeclampsia. However, if a pregnant woman with chronic hypertension has been treated with a diuretic before conception, it is not necessary to discontinue the therapy as long as there are no signs of preeclampsia. Nevertheless, most experts recommend reducing the diuretic dose and carefully monitoring the patient.[534,535]

Insulin is the preferred pharmacological therapy for hyperglycemia in pregnant women with diabetes and CKD. (Opinion)

Oral antidiabetic medicines have successfully controlled hyperglycemia in women with type 2 diabetes during pregnancy, but these studies did not include patients with CKD.[540,541] In the opinion of the Work Group, insulin remains the pharmacological treatment of choice for hyperglycemia during pregnancy in women with diabetes and CKD, and goals for glycemic control should be the same as those for women without CKD.[542-544]

Dyslipidemia should not be treated during pregnancy in women with diabetes and CKD. (Opinion)

Pharmacological treatment of lipid abnormalities during pregnancy is not currently recommended due to potential risks to the fetus.[545] Nevertheless, maternal hypercholesterolemia is associated with the development of fetal atherosclerosis,[546] so this recommendation may change as results of additional studies of statins and other agents during pregnancy become available. However, until such studies are available, it is the opinion of the Work Group that statins and other lipid-lowering therapies should be discontinued after a missed menstrual period or a positive pregnancy test result in women with diabetes and CKD. Women and adolescent girls with childbearing potential who are treated with lipid-lowering therapies should be counseled about these risks.

Dietary protein intake should not be restricted during pregnancy in women with diabetes and CKD. (Opinion)

Limitation of dietary protein in women with diabetes and CKD should be liberalized during pregnancy to ensure adequate nutrition for the fetus. In the opinion of the Work Group, these patients should be counseled to increase their intake of protein to 1 to 1.2 g/kg (prepregnancy weight) per day.

Pregnant women with diabetes and CKD stage 5 treated by kidney transplantation or dialysis should be managed according to the recommendations for earlier stages of CKD. (Opinion)

Pregnant women with diabetes and CKD stage 5 (kidney transplantation or dialysis) have not been included in treatment studies. Therefore, in the opinion of the Work Group, strategies for the management of hyperglycemia, hypertension, and dyslipidemia may be extrapolated from the recommendations for women with earlier stages of CKD. The scope of the evidence review did not include specific management of CKD stage 5 in pregnancy.

IMPLEMENTATION ISSUES

Population-based interventions in special populations, including systematic community screening and surveillance, have been successful in reducing the burden of DKD, particularly when they are applied early in the course of the disease.[547,548] Such approaches, including the NKF Kidney Early Evaluation Program, are effective in identifying asymptomatic people with CKD from high-risk populations.[549] Interventions targeted at high-risk special populations and implemented in the primary care and community settings have reduced the rate of diabetic complications, including CKD stage 5.[550-552] Successful community-based model programs have been implemented in Australian Aboriginal communities[553] and rural India.[554]

Poor access to care and late referral for nephrological intervention are associated with poor outcomes in United States racial minorities.[555] Improving outcomes for special populations will require not only changes in standards of clinical care, but also efforts to improve access to care for these high-risk groups. Understanding the cultural and socioeconomic milieu of the target populations is essential for successful interventions.[556]

Addressing the increased burden of diabetes and CKD in developing countries where health resources are severely limited will require creativity and collaboration with public health professionals. Unfortunately, the increase in diabetes and other chronic diseases is occurring in many countries that are still experiencing a high prevalence of infectious disease, including an increase in the burden of HIV/AIDS. Limited resources may be strained by these competing health problems.

CLINICAL PRACTICE RECOMMENDATION 4: BEHAVIORAL SELF-MANAGEMENT IN DIABETES AND CHRONIC KIDNEY DISEASE

Behavioral self-management in diabetes and CKD is particularly challenging because of the intensive nature of the diabetes regimen. Education alone is not sufficient to promote and sustain healthy behavior change, particularly with such a complex regimen.

4.1 Self-management strategies should be key components of a multifaceted treatment plan with attention to multiple behaviors: (C)
- **Monitoring and treatment of glycemia,**
- **Blood pressure,**
- **Nutrition,**
- **Smoking cessation,**
- **Exercise, and**
- **Adherence to medicines.**

BACKGROUND

The success of strategies to promote glycemic control and minimize progression of CKD depends upon patient self-management, or the ability and willingness of the patient to change and subsequently maintain appropriate behaviors regarding diet, physical activity, medicines, self-monitoring, and medical follow-up visits. Adherence to complex regimens often is poor. Interventions to enhance adherence require intensive education and behavioral counseling. Maintenance of adherence requires ongoing support from a variety of health care professionals.

RATIONALE

Due to complexity of the behavioral self-management regimen for diabetes and CKD and high frequency of nonadherence, alternative approaches to traditional education should be considered. (Moderate/Weak)

Self-management requires intensive education and behavioral adjustments in many areas, as well as taking a variety of medicines.[561] Given the risks associated with diabetes and CKD, people with these conditions should engage in a rigorous self-monitoring regimen that typically includes blood glucose and blood pressure; examining skin integrity; obtaining regular foot, eye, medical, and dental examinations; and reporting complications to their health care providers. Glucose self-monitoring is particularly important for balancing physical activity and diet against medicines to control glycemia and prevent or impede the progression of complications.[116,134,562-564] This regimen requires tremendous effort on the part of the patient. Efforts to adopt new behaviors may fail due to inadequate knowledge; lack of motivation; poor problem-solving skills; limited emotional, financial, and/or social resources; or a disease-management regimen that exceeds cognitive capacity. To our knowledge, no studies have specifically examined adherence of people with diabetes and CKD to self-management regimens. However, the challenges of modifying behavior to achieve adherence and successful self-management for those with diabetes are well established (Table 55).

A recent meta-analysis examining factors that influence adherence to disease management regimens found that patients have the least difficulty with circumscribed regimens (eg, medicines) and the most difficulty with regimens requiring extensive behavior change (eg, dietary change). Perhaps because of the extensive behavior change required of those with diabetes, patients with diabetes had among the lowest rates of adherence across a range of 17 disease states, second only to those with sleep disorders.[565] A survey of 2,056 adults with diabetes from across the United States found the most frequently reported adherence problem was diet, followed by exercise and blood glucose monitoring.[566]

Dietary habits that develop over a lifetime can be particularly difficult to change. Individual perceptions of dietary restrictions, particularly feelings of deprivation, are difficult for patients and health care professionals to address. In addition to personal eating preferences, many foods have social, cultural, and/or religious meaning to patients, making feelings of loss even more significant. In addition, the dietary regimen for diabetes and CKD is complex. Ideal self-management requires vigilance

Table 55. Systematic Reviews of Behavioral Studies in People With Diabetes

Author, Year	Dates	No. of Studies (N)	Study Eligibility Criteria	Interventions	Outcomes	Conclusions
Efficacy of Self-Management Education						
Norris, 2002 [593]	1980-1999	31 (4,263)	RCT Type 2 diabetes, adults GlycoHb outcome English language	Educational	GlycoHb	GlycoHb decreased by: 0.76% during or immediately after intervention (significant) 0.26% at 1-3 mo after intervention (non-significant) 0.27% at ≥4 mo after intervention (significant) Greatest effect in studies with the most interventionist contact time Intervention effects diminish after intervention is withdrawn
Steed, 2003 [594]	1980-2001	36 (4,661)	Clinical trial Type 1 or 2 diabetes, adults English language	Educational Self-management Psychological	QOL or psychological well-being Self-management	Interventions to reduce depression may enhance self-management Psychological interventions reduce depression more than educational or self-management Interventions resulting in improved psychological well-being or QOL had both short- and long-term effects
Norris, 2001 [576]	1980-1999	72 (9,682)	RCT Type 2 diabetes, adults English language	Knowledge/information Lifestyle behaviors (diet/exercise) Skill development (glucose monitoring, foot care) Coping skills	GlycoHb QOL Knowledge Dietary change Physical activity Psychological measures	14 of 54 studies reporting GlycoHb found improvements Knowledge not consistently associated with improvements in glycemic control Studies with a shorter follow-up (≤6 mo) demonstrated greater effectiveness Collaborative interventions showed more favorable results than didactic approaches, especially if repetitive and ongoing Lifestyle interventions generally failed to show improvements
Adherence						
DiMatteo, 2004 [565]	1948-1998	569 total, 23 diabetes (1,536)	Cross-sectional studies (Types 1 and 2 diabetes, adults and children) Adherence to recommendations outcome Excluded intervention studies English language	Recommendations for routine clinical care	Adherence to recommendation	Average nonadherence rate in studies of diabetes is 32% Across a range of 17 disease conditions, patients with diabetes had the second lowest rates of adherence Among all 17 disease conditions, patients most adherent to circumscribed regimens (eg, medication: 79%), – least to those requiring pervasive behavior change (eg, diet: 59%) Among all 17 disease conditions, education positively correlated with adherence in chronic disease

Author, Year	Dates	No. of Studies (N)	Study Eligibility Criteria	Interventions	Outcomes	Conclusions
Cramer 2004 [570]	1966-2003	20 (328,095 retrospective; 254 prospective)	All study designs Type 2 diabetes, implied Drug dosing regimen specified Method for calculating adherence rates described	Factors influencing adherence to diabetes medications	Adherence to medications	Prospective, observational studies of oral agents show: Adherence rates ranged from 61%-85% Adherence rates decreased as number of doses per day increased Self-reported adherence higher than that measured with electronic monitoring (92% *v* 75%) Studies of insulin adherence show: Patients newly starting insulin adhered 80% at 24 mo Adherence to insulin less than to oral agents (73% *v* 86%, retrospective data) Retrospective analyses of adherence to oral agents show: Adherence rates ranged from 36%-93% Depressed patients had lower adherence rates (85% *v* 93%) Once-daily regimens had higher adherence than twice daily (61% *v* 52%) Monotherapy had higher adherence than polytherapy (49% *v* 36%)
Efficacy of Self-Care Interventions						
Sarkisian, 2003 [589]	1985-2000	12 (1,956)	Clinical trials nd on diabetes type >55 y old or African American or Latino English language	Self-care interventions (involving changing knowledge, beliefs, or behavior)	HbA_{1c} QOL Symptoms	4 of 8 RCTs and 3 of 4 pre-post designs found statistically significant reductions in HbA_{1c} Studies that included patients with higher HbA_{1c} more often found statistically significant differences in glycemic control
Norris, 2002 [595]	1966-2000	30 (3,773)	Intervention studies Types 1 and 2 diabetes, adults and children Conducted in market economies Met minimum quality standards English language	Interventions delivered outside of traditional clinical settings	GlycoHb Psychosocial Behavioral	Self-management education is effective in improving glycemic control when delivered in community gathering places for adults with type 2 diabetes, and for home-based interventions in children and adolescents with type 1 diabetes Insufficient evidence regarding other settings
Education and Behavioral Interventions						
Gary, 2003 [596]	1966-1999	18 (2720)	RCT Type 2 diabetes Glycemic control or weight loss outcome English language	Behavioral or counseling component	GlycoHb FBS Adherence	Interventions resulted in a net HbA_{1c} change of -0.43% (significant). FBS was not significantly different. The interventionist with the greatest effect size was physician, followed by nurse and dietitian No difference in group versus individual modes of intervention delivery Effect size greatest on adherence to medications, followed by exercise, diet, and glucose self-monitoring
Ellis, 2004 [577]	1990-2000	28 (2,439)	RCT Types 1 and 2 diabetes, adults Outpatient settings HbA_{1c} outcome (at 12 weeks minimum) English language	Educational	HbA_{1c}	Interventions resulted in a net HbA_{1c} change of -0.32% (significant) Meta-regression found the following intervention characteristics to be significantly associated with effect (each associated with lower HbA_{1c}): Face-to face delivery Cognitive reframing Including exercise content in the intervention No dose response (but limited variability in this factor across studies)

(Continued)

Table 55 (Cont'd). Systematic Reviews of Behavioral Studies in People With Diabetes

Author, Year	Dates	No. of Studies (N)	Study Eligibility Criteria	Interventions	Outcomes	Conclusions
Computer-Assisted Intervention						
Balas, 2004 [597]	1976-2001	44 (5,766)	RCT Types 1 and 2 diabetes, adults and children	Computer assisted interventions: Prompting (providers) Decision support for insulin dose (providers) Diabetes education (patients)	Glycemic control Processes of care	Computer-assisted insulin dose adjustment with home glucose records changed GlycoHb by -0.14% (significant) and blood glucose by -5.9 mg/dL (significant) Computerized reminders significantly improved process of care

Abbreviations: RCT, randomized controlled trial; QOL, quality of life; FBS, fasting blood dugar; GlycoHb, glycohemoglobin.

regarding the content of meals and balancing nutritional intake with medicines and physical activity to achieve good glycemic control. Patients should be aware of day-to-day patterns in their blood glucose levels to make informed choices. However, a study found that patients typically purchase enough capillary blood sampling supplies to self-monitor their blood glucose for only 70% of possible days in the first 4 years after diagnosis and for only 50% of days thereafter.[567] Moreover, at least 20% of patients with either type 1 or type 2 diabetes do not monitor their blood glucose at all.[568,569] Although glucose meters generally are inexpensive and easy to use, glucose testing strips are quite expensive, and some insurance companies provide little or no coverage for these supplies.

A recently completed systematic review of 20 studies conducted between 1966 and 2003 measured adherence to diabetes medicines (Table 55).[570] The study found that, among patients using oral agents, adherence rates ranged from 36% to 93% and were even lower for insulin. Adherence also was found to be related inversely to the number of diabetes medicines prescribed. Thus, the addition of medicines for other common comorbid conditions (eg, hypertension and dyslipidemia) is likely to further reduce adherence. Rates of adherence to an exercise program ranged from 19% to 30% in people with diabetes,[571,572] indicating that compliance issues impact on multiple aspects of disease management. Another study found that only 7% of patients adhered to all aspects of their diabetes regimen.[573]

The management plan should include careful coordination of care, addressing both diabetes and CKD. (Moderate/Weak)

Although intensive glycemic control reduces diabetes complications,[116,134,562,564] once patients develop CKD, there may be a tendency to place less emphasis on glucose management. While no studies document inattention to glycemic control in early-stage CKD, a recent review of dialysis patient records found diabetes management to be suboptimal.[574] Individuals with diabetes and CKD require the attention of a health care team that can address social, educational, emotional, and medical consequences of both condi-

Table 56. Components and Principles of a Diabetes and CKD Self-Management Education Program

Describe the disease processes for diabetes and CKD, as well as treatment options. Provide explanations in lay terminology and evaluate the patient's understanding of educational efforts. Assess and address the patient's beliefs about the nature, cause, and treatment of their illness. Explain consequences of nonadherence.
Promote social support by involving significant others in educational activities.
Incorporate appropriate nutritional management. Attention should be paid to cultural food preferences in dietary counseling.
Describe use of medicines for therapeutic effectiveness. Discuss side effects of medicines and emphasize the importance of discussing side effects with the primary-care provider. Explain that the health care professional and patient can work together to find the right treatment regimen.
Discuss the importance of monitoring glucose and blood pressure. Relate the nature of the disease (ie, hypertension is asymptomatic and hyperglycemia often is asymptomatic, yet both require continual treatment).
Preventing, detecting, and treating acute complications.
Preventing (through risk-reduction behavior), detecting, and treating long-term complications. Risk-reduction behaviors include smoking cessation, exercise, weight loss, diet, and medication management, as appropriate.
Goal setting and problem solving. Setting stepped easily achievable goals enables patients to experience success and a sense of self-efficacy. Encourage patients to discuss barriers to adherence (eg, transportation, economic issues, social support) and refer as appropriate.
Integrating psychosocial adjustment to daily life. Assess for depression and refer as appropriate.
Promoting preconception care, management during pregnancy, and gestational diabetes management (if applicable).

tions. The ADA has developed Standards for Diabetes Self-Management Education.[575] These standards summarize evidence that self-management education is most effective when delivered by a multidisciplinary team. This team should include a combination of expertise in medical treatment, nutrition, teaching skills, and behavioral psychology. Each patient should have an individualized assessment, educational plan, and periodic reassessment pertaining to educational needs. Table 56 lists the components and principles of a diabetes and CKD self-management program, combining educational elements from the ADA Standards,[575] Guideline 5 of the NKF-KDOQI™ CPGs for Hypertension and Antihypertensive Agents in CKD,[5] and predictors of nonadherence.

Behavioral adherence should be assessed in all patients, particularly in those who do not respond to therapy. (Weak/Opinion)

Intensive glycemic control may increase the number of hypoglycemic episodes, with the need to increase food intake to cover peak times of insulin action. Although DCCT and UKPDS demonstrated that patients receiving intensive treatment had better glycemic control, they also were more likely to experience weight gain than those receiving usual care. Intensive treatment also may mask poor adherence to the treatment regimen, especially adherence to diet and physical activity. Over time, inattention to behavioral aspects of the regimen may mitigate the potential benefits of intensive treatment.

Self-management approaches based in behavioral medicine may be effective in enhancing adherence to the management regimen for diabetes and CKD. (Weak/Opinion)

No studies were found of interventions to enhance adherence of individuals to management regimens for diabetes and CKD. However, 2 meta-analyses have been published that provide valuable information about the most effective approaches for encouraging adherence to the diabetes regimen (Table 55). The first summarized the results of 72 studies conducted between 1980 and 1999. Interventions that were collaborative in nature (rather than didactic/lecture format) resulted in better glycemic control, particularly if the intervention contacts were repetitive and ongoing. Knowledge was not consistently related to glycemic control, and factors other than knowledge are needed to achieve long-term behavioral change.[576] The second conducted a meta-regression analysis on 28 studies between 1990 and 2000 to characterize the components of behavioral interventions most likely to result in improved glycemic control. Face-to-face delivery (compared with telecommunication and written materials), cognitive reframing (involving goal setting and problem solving as opposed to didactic education), and interven-

Table 57. Self-Management Principles

Self-Management Principles	Implementation Examples
Verbal persuasion; changing health beliefs, values, and perceptions of risk and severity of disease; convincing patient of the benefits of behavior change	Provide comprehensive education regarding the disease, management regimen, consequences of adherence, consequences of nonadherence
Tailoring messages to patient's readiness to change; addressing patient's intentions to engage in required behavior change; addressing preexisting beliefs and preferences about the disease and its management regimen	Determine the motivational level of the patient to incorporate self-management behaviors into their daily lives (eg, readiness to begin a regimen of exercise) and tailor educational efforts accordingly. Address normative and/or cultural beliefs about the disease and its management that could influence adherence
Self-monitoring; self-regulation; establishing "feedback loops"	Assist patients in developing self-awareness of their behaviors, as well as their physical health (eg, use of diet or physical activity logs, weekly weights, self-monitoring blood pressure)
Stimulus control; enhancing patient's ability to gain and maintain control over factors that influence their behavior	Assist patients in identifying factors/stimuli that predispose them to unhealthy patterns of behavior or nonadherence to the regimen. Assist patients in changing their response to the stimulus (eg, when tempted to have a soft drink, choose sugar free), or avoid the stimulus altogether (eg, when shopping for groceries avoid the soft-drink and snack aisles)
Goal setting	Assist patients in identifying overall health goals (eg, I want to lower my HbA_{1c}). Then assist them in identifying easily achievable intermediate or "stepped" goals, which lead to the overall health goal (eg, this week, instead of drinking 3 regular soft drinks each day, I will limit myself to 2). Help the patient monitor their progress in meeting goals (eg, for 5 of 7 days this week I was able to limit myself to only 2 cans of soft drinks). Set new goals as appropriate (eg, next week I will reduce my intake of soft drinks to 1 each day). When goals are not reached, assess reasons for failure and then reformulate goals
Problem solving, prevention of relapse	Use scenarios or patient examples of situations that threaten adherence, followed by discussion on how such situations can be addressed. Relapse prevention is a problem-solving approach in which "high-risk" situations for nonadherence are addressed and dealt with in advance
Social support	Involve family and friends in helping patient make behavioral changes (eg, involve the person responsible for food preparation in the home to attend dietary education with the patient, start a walking program with a friend)
Building self-confidence or self-efficacy; reinforcing positive beliefs about the probability of successful self-management	Persuade the patient that they are able to achieve behavioral goals. Past experience does not have to dictate future success or failure. By establishing easily achievable "stepped" goals, the patient experiences success in reaching their goals. Attribute successes in meeting goals to the patient's efforts
Addressing barriers	Barriers to adherence are identified from the patient's perspective. Assist the patient in addressing patient-identified barriers (eg, pharmaceutical assistance with smoking cessation, use of pill minders in those who cannot remember to take medications, addressing economic barriers to glucose self-monitoring, healthy eating, or adherence to the medication regimen)
Positive reinforcement	Provide positive feedback for improvement in adherence and/or health status, encourage participant to reward self for improvements

Adapted from Guideline 5 of the NKF-KDOQI™ CPGs for Hypertension and Antihypertensive Agents in CKD.[5]

tions that included an exercise component were key to improving glycemic control.[577] The principles noted in Table 57 enhance adherence to medical management in other patient populations and, in the opinion of the Work Group, should be applicable to patients with diabetes and CKD.

Complex regimens require multiple lifestyle changes. However, targeting multiple behaviors may have a negative impact on treatment.[578] For example, in a study of hypertension treatments, participants who were instructed to follow a low-sodium diet and lose weight were less adherent than those who were instructed to follow either 1 of these regimens alone.[579] Thus, targeting a single behavior or sequencing the introduction of various components of the diabetes and CKD management regimen may be required for successful self-management.

Assessments and educational efforts should take into consideration modifiable barriers to self-management, should be culturally appropriate, and should consider the unique learning needs of the patient. (Weak/Opinion)

Modifiable predictors of nonadherence to medical therapies in patients with hypertension include side effects of medicines, complexity of the regimen, cost and financial difficulties, depression, socioeconomic status, transportation issues, and social support.[5] Modifiable predictors of nonadherence to the diabetes regimen include depression,[580] self-efficacy (the patient's confidence in their ability to successfully manage their disease),[581-584] and health literacy.[585] In a study of exercise behavior of individuals with type 2 diabetes, nonexercisers were found to have more negative attitudes. They perceived physical discomfort, feared hypoglycemia, and had perceptions that they were too overweight. They also reported a lack of family support for engaging in exercise.[586]

Cultural factors also play a role in adherence. Ethnic minorities are overrepresented among people with diabetes.[587] They also have a higher burden of diabetes and CKD than whites.[499,588] A recent review of studies targeting ethnic minorities with diabetes found that adherence was improved by tailoring the intervention to age or culture, use of group counseling or support, and involvement of significant others (Table 55).[589]

Cognitive deficits are common in individuals with diabetes.[590,591] This problem appears to be associated with poor glycemic control, although obesity, hypertension, and depression also may contribute.[592] Problems with cognitive function have obvious implications for adherence in that individuals with these deficits may have difficulty with memory, organizing information, and solving self-management problems.

Behavior change requires repeated contacts and sustained support from the health care team. (Weak/Opinion)

A meta-analysis summarized the numerous clinical trials that have been done to enhance the adherence of people with diabetes to self-management regimens (Table 55).[593] These studies generally define adherence as an educational or behavioral issue. Those that conceptualized adherence as an educational issue tested interventions that involved the development of materials or unique teaching approaches to help people with diabetes learn about the disease and its management. Those that conceptualized adherence as a behavioral issue employed techniques based in behavioral medicine or psychology to foster behavior change (eg, motivational interviewing, verbal persuasion, goal setting, positive reinforcement, social support, and coping, among others). Regardless of how adherence was conceptualized, these studies found that interventions to enhance adherence tend to improve glycemic control. The greatest improvements were made in interventions involving frequent contact with the patients. Unfortunately, improvements generally were lost within 1 to 3 months after stopping the intervention.[583] No literature was found regarding the frequency and duration of contacts required to make and sustain behavior change in patients with diabetes and CKD. However, given that CKD only complicates the self-management regimen, the Work Group concluded that interventions to support and sustain behavior change should be comparable to or exceed those required for good self-management of diabetes.

LIMITATIONS

Research that pertains to self-management in those with diabetes and CKD is virtually nonexistent. Accordingly, evidence regarding adherence to blood pressure management regimens and to self-management of diabetes were extrapolated to people with diabetes and CKD.

IMPLEMENTATION ISSUES

Simplification of the management regimen (including medicines, diet, physical activity, and self-monitoring requirements) may be helpful for encouraging adherence. Focusing on one aspect of the regimen and/or sequential introduction of requirements may be helpful.

Incorporation of behavioral strategies to enhance self-management optimally requires a multidisciplinary team effort (physician, diabetes educator, nutritionist, nurse, pharmacist, and/or social worker). Self-management, as described, requires frequent and repeated contacts with health care professionals for education, goal setting, evaluation of progress, and teaching self-

monitoring and problem-solving skills. Establishing and maintaining self-management behaviors likely will require multiple ongoing contacts with members of the health care team.

Education of the patient regarding medicines should include, at a minimum, the reason the medicine is being prescribed, instruction regarding side effects, importance of adherence, consequences of nonadherence, and signs or symptoms that should trigger a return call or visit to a health care provider. If appropriate, the patient should be instructed that other medicines are available if side effects become unmanageable. All information should be relayed to the patient in lay terms.

Referral to a social worker, diabetes educator, dietitian, nurse, case manager, or pharmacist for appropriate counseling should be considered when encountering such barriers to regimen adherence as cost; cultural factors and cultural beliefs; misperceptions or misunderstandings regarding diabetes and CKD, its treatment, and the consequences of nonadherence; or apparent inability to take medicines on a regular basis (ie, forgetfulness, or difficulty managing a complex medication regimen).

Aging of the population will require regular reassessment of the patient's ability to independently handle the management regimen.

Development of culturally sensitive educational materials and services is necessary to ensure adherence to medical recommendations and requires time and resources that may be beyond the control of the individual clinician.

The approach to the patient should be individualized, taking into consideration his or her culture, economic situation, knowledge and beliefs regarding the disease and treatment, response to medication (in particular, side effects), ability (emotional, functional, cognitive, visual) to adhere to the prescribed regimen, and changes in status over time.

IV. RESEARCH RECOMMENDATIONS

Guideline 1. Screening and Diagnosis of Diabetic Kidney Disease

What is the best screening test for DKD? Microalbuminuria is the best available test for screening of DKD, but it is imprecise. For this reason, additional research on the use of new biomarkers or better use of already available markers may lead to the important advances in this field. Markers may include:

- Urinary immunonreactive intact albumin and shed podocytes;
- Genetic risk indicators;
- Blood and/or urine changes in growth factors, cytokines, inflammatory markers, or markers of oxidative stress;
- Innovative kidney imaging or tissue studies.

Appropriately weighted risk algorithms should be derived using predictive variables:

- AER within the normoalbuminuric or microalbuminuric range;
- Retinopathy status;
- Clinical and ambulatory blood pressure measurements;
- Glycemic control;
- Diabetes duration;
- Lipid levels;
- Age;
- Sex;
- Race;
- Family history.

Improved measures of glomerular filtration rate (GFR) should be developed and may include:

- More reliable creatinine measurement methods;
- Modifications of existing formulas;
- Application of new GFR markers, such as cystatin C;
- Development of simplified direct GFR measurements.

How should albuminuria be measured? Additional studies on urinary albumin measurements, including predictive values of gender-specific ACR cutoffs, urine collection methods, and processing of urine samples, are warranted.

What is the rate of progression of DKD in people with reduced GFR, but normal urinary albumin excretion? How does this compare with the rate in those with elevated urinary albumin excretion?

Does regression of albuminuria modify the long-term progression of DKD?

What is the effect of promising agents to prevent RCN in patients with various stages of CKD and both types of diabetes?

What is the best common definition of RCN?

Guideline 2. Management of Hyperglycemia and General Diabetes Care in CKD

Does intensive treatment of glycemia reduce progression of CKD, or prevent CKD stage 5 and CVD events, in people with diabetes and CKD (secondary prevention)? Do effects differ by albuminuria status (normoalbuminuria, microalbuminuria, macroalbuminuria) or level of GFR?

Do the TZDs have kidney or CVD benefits beyond glycemic control in people with diabetes and CKD?

Are risks of fluid retention with TZDs greater in people with CKD?

What is/are the best methods for assessing glycemic control in CKD?

What are the best methods for administering insulin in patients on dialysis?

What are the best ways of countering the hyperglycemic effects of glucocorticoids, cyclosporine, and tacrolimus in the transplant patient?

Are there kidney or CVD benefits beyond glycemic control of GLP-1 analogues (incretin mimetic or amylin analog) or DPP-4 inhibitors in people with DKD?

What are the risks in using GLP-1 analogues (incretin mimetic or amylin analog) or DPP-4 inhibitors in people with diabetes and CKD?

Guideline 3. Management of Hypertension in Diabetes and CKD

What are optimal doses of ACE inhibitors and ARBs for kidney disease protection in people with diabetes and hypertension?

What is the role of ARBs or other classes of antihypertensive agents, either alone or in combination with ACE inhibitors, on slowing kidney disease progression and preventing CVD in hypertensive people with DKD?

What is the optimal level of blood pressure to slow DKD progression? The question regarding the optimal level of blood pressure reduction for cardiovascular risk reduction may be answered in 2008 by the ACCORD trial. However, this may not answer the question about kidney protection.

Do ACE inhibitors or ARBs prevent progression of kidney disease in patients with diabetes and CKD, defined by low GFR without albuminuria?

Guideline 4. Management of Dyslipidemia in Diabetes and CKD

What is the effect of lipid lowering with statins on CVD in patients with diabetes and CKD stages 1 to 4?

What is the impact of inflammation (ie, high C-reactive protein) on the response to lipid lowering with statins in diabetes and CKD stage 5? This question may be answered by subgroup analysis and biomarker determinations of the 4D participants.

What is the effect of statin treatment on progression of DKD? Do effects differ by albuminuria status (normoalbuminuria, microalbuminuria, macroalbuminuria) or level of GFR?

Guideline 5. Nutritional Management in Diabetes and CKD

Randomized clinical trials in diabetes and CKD examining the role of nutrition on clinical outcomes are needed. Diet interventions are extremely challenging, but are required to identify new therapeutic options.

Studies examining specific nutrients on kidney disease would be beneficial. What is the effect of 0.8 g of protein/kg body weight per day on GFR and urinary albumin excretion with the diet defined as follows:

- 30% fat: 5% saturated, 5% omega-6, 10% omega-3, 10% omega-9.
- 60% carbohydrate calories; predominantly (40% to 45%) whole grains, fruits, and vegetables.

The above question modified for amino acid composition by altering the protein source:

- soy protein;
- lean poultry and fish;
- vegetable protein only;
- 50% protein as fish rich in omega-3 fatty acids.

What is the best strategy for nutrition interventions? Evaluate types and frequency of nutrition education sessions provided by a registered dietitian in conjunction with medical management.

What is the effect of nutritional intervention on progression of DKD using the diagnostic criteria defined in the NKF-KDOQI™ guidelines? Do effects differ by albuminuria status (normoalbuminuria, microalbuminuria, macroalbuminuria) or level of GFR?

CPR 1. Management of Albuminuria in Normotensive Patients With Diabetes and Albuminuria as a Surrogate Marker in DKD

What is the effect of RAS inhibition (ACE inhibitors and ARBs) on albuminuria and clinical outcomes in normotensive people with DKD?

What is the relationship between magnitude of albuminuria change and risks of CKD and CVD in people with DKD?

What is the optimal "target value" for urine albumin excretion in DKD during treatment with ACE inhibitors and ARBs?

Do different types of treatment that reduce albuminuria improve clinical outcomes in DKD?

CPR 2. Multifaceted Intervention for People With Diabetes and CKD

Which facets of the intensive multifaceted intervention are associated with reduced risks of CKD and CVD?

Do people with diabetes and CKD already treated with RAS inhibitors benefit from intensive multifaceted intervention?

Does intensive multifaceted intervention provide CKD and CVD benefits at earlier or later stages of CKD in diabetes?

Can intensive multifaceted intervention for diabetes and CKD be accomplished in other clinical settings?

In overweight and obese people (BMI > 24.9 kg/m^2) with diabetes and CKD, what is the effect of weight loss using a balanced calorie-restricted diet on glycemic control, GFR, urinary albumin excretion, and CVD risk factors?

What are the benefits and risks of using rimonabant for weight loss in people with diabetes and CKD?

CPR 3. Diabetes and CKD in Special Populations

What are the most effective means of translating clinical knowledge into public health interventions for DKD? While evaluation of direct clinical and public health efforts will be essential, development of systems models can be useful planning tools for predicting the most cost-effective way to use the limited resources that will be available in the countries most affected by DKD in the future.

What are the prenatal and early childhood factors that lead to later development of diabetes and CKD?

What are the causes of different risks of DKD progression and mortality after onset of kidney replacement therapy in various ethnic groups? Native Americans on dialysis therapy have better survival compared with Caucasians in the United States, while Canadian First Nations members have similar survival as Canadian Caucasians. This difference in relative survival suggests that nongenetic factors may play a significant role in survival.

Are inexpensive combination antihypertensive agents safe and effective for DKD in populations of developing countries? Such an approach could have great clinical impact, particularly where limited resources are available for purchasing drugs. The effectiveness of low-cost interventions using less expensive generic drugs to control risk factors for DKD has been demonstrated in rural India.

Are programmatic efforts to improve the care of patients with CKD worldwide effective, such as the NKF Kidney Disease—Improving Global Outcomes and the International Society of Nephrology Commission for the Global Advancement of Nephrology? These programs should be regularly assessed.

What are effects of interventions that may decrease the risk of preeclampsia and preterm delivery in women with diabetes and CKD? This is an especially challenging population that should be included in clinical trials.

What factors influence maternal and fetal outcomes in women with type 2 diabetes and CKD?

CPR 4. Behavioral Self-Management in Diabetes and CKD

To what extent do low-dose combinations of medicines for treatment of diabetes and CKD reduce adverse effects and improve adherence?

Do optimal interventions combine behavioral approaches with pharmacological therapies to improve management of risk factors for diabetes and CKD? Particular attention should be paid to identifying which behavioral strategies are most effective in producing the desired change.

What are effective strategies for maintaining long-term adherence to self-care requirements for management of diabetes and CKD?

New Treatments for DKD

The Work Group recognizes the importance of bringing new treatments into clinical research for DKD, especially for patients who have progressive kidney disease despite the current standard of care. Promising treatments, including novel agents and potential new uses of existing agents, are currently in phase 2/3 trials for DKD (listed below).

- Novel therapies:
  - Protein kinase C-β inhibition—ruboxistaurin;
  - Glycosaminoglycans—sulodexide;
  - Inhibition of advanced glycation end product formation—pyridoxamine;
  - Antifibrotic treatment—pirfenidone, anti-connective tissue growth factor antibody;
  - Endothelin antagonism—avosentan, SP301;
  - Direct renin inhibition—aliskiren.
- New uses of existing agents:
  - Aldosterone blockade—spironolactone, epleronone;
  - Anti-inflammatory—pentoxifylline;
  - Peroxisome proliferator activators (TZDs)—rosiglitazone, pioglitazone.

APPENDIX 1: NUTRITIONAL MANAGEMENT OF DIABETES AND CHRONIC KIDNEY DISEASE

Sample meal plan

MENU

Breakfast

Peanut Butter Oatmeal
Fresh Sliced Pears
Very Berry Smoothie

Lunch

Baked Salmon on a Toasted Hamburger Bun
Roasted Asparagus Spears With a Spicy Tofu Hollandaise[a]
Sliced Pineapple With Strawberry Lemon Thyme[b] Sorbet[c]

Snack

Cucumbers With Horseradish and Dill Dip
Mixed Nuts

Dinner

Grilled Vegetables on Bulgur Pilaf[d]
Sliced Avocado
Rum-Baked Apples

a. Hollandaise is traditionally a butter, egg yolk, and lemon juice emulsified sauce.
b. Lemon thyme is a fresh herb that has a lemon wood like flavor.
c. Sorbet is frozen fruit juices or fruit puree with no milk product.
d. Bulgur is a wheat berry with the bran removed, steam-cooked, dried, and ground.

RECIPES

Peanut Butter Oatmeal

1⅓ cups uncooked oatmeal
4 tablespoons peanut butter
¼ cup honey

Cook oatmeal in water following the directions on the package, omit the salt. Divide cooked oatmeal into 4 bowls and dollop 1 tablespoon of peanut butter and 1 tablespoon of honey in each bowl.

Analysis

4 servings per recipe, serving size ⅔ cup, calories 258, total fat 10 g, saturated fat 1.7 g, monounsaturated fat 4.5 g, polyunsaturated fat 0.53 g, omega-3 fat 0 g, cholesterol 0 mg, calcium 1.3 mg, sodium 76 mg, phosphorus 123 mg, potassium 210 mg, total carbohydrates 39 g, dietary fiber 3.7 g, sugar 19 g, protein 7 g.

Very Berry Tofu Smoothie

1 lb fresh strawberries, cleaned and hulled
2 cups blueberries
9 oz tofu, silken, extra firm
½ teaspoon ground ginger
2 pinches of red pepper flakes
¼ teaspoon rum extract
1 tablespoon honey

Table 58. Nutrient Composition of This Full-Day Meal Plan

Nutrient	Amount	% of Calories	Goal (Stage 1-2)	Goal (Stage 3-4)
Calories	1,765			
Sodium (g/d)	0.8		<2.4	
Total fat (g/d)	62	32	<30% of calories	
Saturated fat (g/d)	9	4.5	<10% of calories	
Cholesterol (mg/d)	49		200 mg	
Carbohydrate (g/d)	269	61	50-60	
Protein (g/kg/d, % of calories)	56 g/d (0.8 g/kg/d for 70 kg person)	13	0.8 (~10%)	0.6-0.8 (~8%-10%)
Phosphorus (g/d)	1.0		1.7	0.8-1.0
Potassium (g/d)	3.0		>4	2.4

This meal plan also provides 1.9 g linolenic acid, 0.3 g eicosapentaenoic acid (EPA), and 1 g decosahexaenoic acid (DHA). Dietary fiber is 40 g.
Since nutritional recommendations vary by chronic kidney disease (CKD) stage, meal plans should be individualized. For example, the potassium content of this meal plan may be too high for some people with CKD stages 3 and 4. Nutrient content is provided for each recipe. Adjustments to the meal plan may be made to meet individual goals.

1 teaspoon lemon juice
½ cup ice

Blend all together and serve.

Analysis

4 servings per recipe, serving size 1 cup, calories 125, total fat 1.8 g, saturated fat 0.2 g, monounsaturated fat 0.3 g, polyunsaturated fat 0.8 g, omega-3 fat 0.1 g, cholesterol 0 mg, calcium 44 mg, sodium 42 mg, phosphorus 100 mg, potassium 339 mg, total carbohydrates 22 g, dietary fiber 6 g, sugar 15.5 g, protein 6 g.

Baked Salmon With Roasted Asparagus on Cracked Wheat Bun

16 oz. fresh salmon fillet
1 tablespoon lemon juice
1 tablespoon Butter Buds®
12 oz. fresh asparagus spears (woody stems removed), washed
1 tablespoon olive oil
4 cracked wheat or whole grain hamburger buns, toasted

Preheat oven to 400°F. Place asparagus spears on a cookie sheet and spray with olive oil. Roast in the oven for 10 minutes or until tender and slightly brown. Remove from the oven and allow to cool.

Spray baking dish with olive oil. Place salmon filets in baking dish and drizzle lemon juice over the top of each filet. Bake 15 to 20 minutes until the salmon is flakey to the touch. Serve salmon on a toasted hamburger bun, sprinkle with Butter Buds, roasted asparagus and Habanero Hollandaise Sauce.

Habanero Hollandaise Sauce

6 oz tofu—silken, extra firm, drained and crumbled
¼ cup vegetable stock
¼ cup fresh lemon juice
½ teaspoon sugar
¼ teaspoon turmeric
½ teaspoon diced habanero chili (out of the jar), more if you like it spicier

Combine all ingredients in a food processor and process until smooth. Refrigerate overnight before serving.

Analysis

4 servings per recipe, serving size approximately 3 oz, calories 475, total fat 20 g, saturated fat 3 g, monounsaturated fat 10 g, polyunsaturated fat 5.5 g, omega-3 fat 2.6 g, cholesterol 62 mg, calcium 230 mg, sodium 495 mg, phosphorus 364 mg, potassium 810 mg, total carbohydrates 43 g, dietary fiber 5 g, sugar 8 g, protein 32 g

Fresh Pineapple With Strawberry Lemon Thyme Sorbet

30 oz. fresh sliced pineapple

Strawberry Lemon Thyme Sorbet

2 cups fresh ripe strawberries, hulled, washed, and dried
1 cup lemon thyme simple syup
2 tablespoons orange juice
2 tablespoons lemon juice

In a food processor add strawberries, ½ cup lemon thyme simple syrup and process until smooth. Add the other ½ cup of simple syrup, orange and lemon juice. Mix and pour into ice-cube trays. Freeze. When frozen, remove cubes into the food processor and mix thoroughly. Pour back into the same ice-cube trays, cover, and freeze until needed.

Arrange fresh pineapple on a chilled plate. Soften sorbet, spoon 2 tablespoons over the pineapple and allow to melt before serving.

Lemon Thyme Simple Syrup

1 cup water
1 cup sugar
6 to 8 sprigs of fresh lemon thyme

Mix water and sugar in a sauce pan, bring water and sugar to a boil, and turn down the heat to a slow simmer so that the bubbles just break the surface, and cook for 10 minutes. Remove from the heat and steep lemon thyme sprigs in the syrup as it cools to room temperature. Strain the sprigs and keep refrigerated up to 4 weeks.

Analysis

10 servings per recipe, serving size approximately 2 heaping tablespoons over 3 oz. of sliced pineapple, calories 127, total fat 0 g, saturated fat 0 g, monounsaturated fat 0g, polyunsaturated fat 0 g, omega-3 fat 0 g, cholesterol 0 mg, calcium

20 mg, sodium 1.7 mg, phosphorus 15 mg, potassium 156 mg, total carbohydrates 33 g, dietary fiber 1.9 g, sugar 29 g, protein 1 g

Cucumbers With Horseradish Dill Dip

1 ½ teaspoons shallots, minced
1 ½ teaspoons dried dill
2 tablespoons fresh dill
8 oz tofu, extra firm, drained and crumbled
2 teaspoons horseradish, creamy style
Pinch of dry mustard
⅛ teaspoon turmeric
⅛ teaspoon cayenne pepper
¼ cup rice milk
1 teaspoon Dijon mustard
2 teaspoons lemon juice
2 teaspoons Miran sweet rice wine
⅛ teaspoon onion powder
2 tablespoons white cider vinegar
2 English cucumbers
Fresh dill sprigs for garnish (2 tablespoons)

Mix all ingredients except the cucumbers in a food processor. Refrigerate overnight. Slice cucumbers, serve with dip spooned over the top, and garnish with fresh dill sprigs.

Analysis

6 servings per recipe, serving size approximately 2 oz, calories 52, total fat 1 g, saturated fat 0.15 g, monounsaturated fat 0.2 g, polyunsaturated fat 0.5 g, omega-3 fat 0 g, cholesterol 0 mg, calcium 37 mg, sodium 71 mg, phosphorus 68 mg, potassium 241 mg, total carbohydrates 8 g, dietary fiber 0.7 g, sugar 4 g, protein 4 g

Bulgur Pilaf

2 tablespoons olive oil
½ onion, diced
2 medium carrots, diced
1 teaspoon dried basil
½ teaspoon dried oregano
½ teaspoon dried thyme
1 clove garlic, minced
½ cup brown rice
¾ cup bulgur wheat
¼ cup milled flax seeds[a]
4 cups vegetable stock

a. Milled flax seed are ground seeds from the flax plant that have a nutty flavor; milled seeds are a source of omega-3 oils.

In a medium sauce pan heat olive oil over medium heat, add onions, carrots, and cook until onions become translucent. Add basil, oregano, thyme, and garlic; cook for another minute. Stir in rice and keep stirring until rice starts to turn brown. Add vegetable stock, bring to a boil, cover, and turn down to simmer and cook for 15 minutes. After cooking for 15 minutes stir in bulgur and flax seed and simmer for another 30 minutes or until the stock is absorbed. Fluff pilaf with fork. Let stand 10 minutes before serving.

Analysis

6 servings per recipe, serving size approximately ⅔ cup, calories 180, total fat 7 g, saturated fat 0.8 g, monounsaturated fat 3.7 g, polyunsaturated fat 1.7 g, omega-3 fat 0.8 g, cholesterol 0 mg, calcium 42 mg, sodium 24 mg, phosphorus 124 mg, potassium 266 mg, total carbohydrates 28 g, dietary fiber 8 g, sugar 1.5 g, protein 5 g

Grilled Vegetables

3 medium zucchinis, sliced
2 heads of anise (fennel), sliced
8 button mushrooms, quartered
4 Roma tomatoes cut into eighths
1 red onion, cut in half and then sliced
2 tablespoon fresh basil leaves, shredded
1 teaspoon fresh thyme
1 teaspoon fresh oregano

Dressing:

1 clove garlic, minced
2 ½ teaspoons Dijon mustard
3 tablespoons lemon juice
4 tablespoons olive oil
½ teaspoon fresh black pepper

Make the dressing by adding all of the ingredients together in a mixing bowl and whisking.

In a large mixing bowl add all the vegetables together. Pour ¼ cup of dressing over the vegetables and stir until all the vegetables have been lightly coated. Then cook vegetable mixture either on a grill or in your oven.

Outdoor Grilling

While your grill is heating to 400°F, oil a grill basket to cook the vegetables in and place the basket on the preheating grill. When the basket is

hot add your vegetable mixture to your basket and cook until the vegetables turn golden brown. Remember to stir them every 5 to 7 minutes to allow the browning to occur evenly with all the vegetables.

Oven Broiling

Turn your oven to broil. Spread vegetables out into a single layer on a cookie sheet and broil until vegetables begin to turn golden brown. Turn vegetables over and keep broiling until vegetables are tender.

When the vegetables are brown, pour grilled vegetables into a serving bowl and add the remaining dressing and fresh herbs.

Analysis

4 servings per recipe, serving size approximately ½ cup, calories 198, total fat 15 g, saturated fat 2 g, monounsaturated fat 10 g, polyunsaturated fat 2 g, omega-3 fat 0.19 g, cholesterol 0 mg, calcium 54 mg, sodium 96 mg, phosphorus 138 mg, potassium 887 mg, total carbohydrates 16 g, dietary fiber 4 g, sugar 8 g, protein 4.5 g

Rum-Baked Apples

4 Granny Smith apples, peeled, cored, and sliced
2 teaspoons lemon juice
1 teaspoon ground cinnamon
½ cup brown sugar
⅛ teaspoon ground nutmeg
¼ teaspoon ground cloves
1 tablespoon all-purpose flour
6 tablespoons rolled oats
2 teaspoons honey
1 teaspoon canola oil

Sauce:

2 cups rice milk
3 tablespoons cornstarch
¼ cup cold water
½ teaspoon rum extract

Coat sliced apples with lemon juice. Mix dry ingredients together, cinnamon, sugar, nutmeg, cloves, flour, and oats. Mix dry ingredients with apples and place in a nonstick baking dish. Drizzle honey over the top and spray the top with canola oil. Bake in a preheated 350°F oven for 40 to 50 minutes until the apples are tender.

Sauce

Heat rice milk to a simmer, mix cornstarch in cold water together until the lumps are dissolved. Whisk the cornstarch mixture into the simmering rice milk and keep whisking until mixture thickens. Remove from heat and add rum extract. Serve warm over the baked apple mixture.

Analysis

4 servings per recipe, serving size approximately ⅔ cup, calories 283, total fat 3 g, saturated fat 0.2 g, monounsaturated fat 1.5 g, polyunsaturated fat 0.7 g, omega-3 fat 0.11 g, cholesterol 0 mg, calcium 42.7 mg, sodium 55 mg, phosphorus 86 mg, potassium 277 mg, total carbohydrates 65 g, dietary fiber 4.3 g, sugar 40.3 g, protein 2 g

APPENDIX 2: METHODS FOR EVALUATING EVIDENCE

AIM

The overall aim of the project was to develop CPGs and CPRs for management of the coexisting conditions of diabetes and CKD.

The Work Group developed the guidelines and recommendations using an evidence-based approach. Evidence regarding the guideline topics was derived primarily from a systematic summary of the available scientific literature. When sufficient evidence was lacking, recommendations were developed that reflect expert opinion. When appropriate, available guidelines or systematic reviews were used to support the current guidelines and recommendations.

OVERVIEW OF PROCESS

Development of the guidelines and recommendations required many concurrent steps to:

- Form the Work Groups and Evidence Review Team that were to be responsible for different aspects of the process;
- Confer to discuss process, methods, and results;
- Develop and refine topics;
- Define exact populations of interest;
- Create draft guideline statements and rationales;
- Create data extraction forms;
- Create and standardize quality assessment and applicability metrics;
- Develop and perform literature search strategies;
- Screen abstracts and retrieve full articles;
- Review articles;
- Extract data and perform critical appraisal of the literature;
- Tabulate data from articles into summary tables;
- Assess the overall strengths of the bodies of evidence; and
- Write guideline statements and rationales based on literature and Work Group consensus.

An Evidence Review Team, composed of experts in systematic review and guideline development, guided the Work Group in all methods and aspects of guideline development. The Work Group and the Evidence Review Team met in four 2-day meetings over 18 months.

Creation of Groups

The Chair and Co-Chair of the KDOQI™ Advisory Board selected the Co-Chairs of the Work Group and the Director of the Evidence Review Team, who then assembled groups to be responsible for the development of the guidelines. The Work Group and the Evidence Review Team collaborated closely throughout the project.

The Work Groups consisted of domain experts, including individuals with expertise in adult and pediatric nephrology, adult and pediatric diabetology and endocrinology, cardiology, pharmacology, social work, nursing, and nutrition. The first task of the Work Group members was to define the overall topics and goals of the guidelines. They then further developed and refined each topic, literature search strategies, and data extraction forms (described below). The Work Group members were the principal reviewers of the literature; from their reviews and detailed data extractions, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements. Completed data extractions were shared among Work Group members.

The Evidence Review Team consisted of nephrologists, physician-methodologists, and research assistants from Tufts-New England Medical Center with expertise in systematic review of the medical literature. They supported the Work Groups in refining the topics and clinical questions so that literature searches could be undertaken. They also instructed the Work Group members in all steps of systematic review and critical literature appraisal. The Evidence Review Team coordinated the methodological and analytical process of the report, defined and standardized the methodology of performing literature searches, of data extraction and of summarizing the evidence in summary tables. They performed literature searches, organized abstract and article screening, created forms to extract relevant data from articles, organized Work Group member data extraction, and tabulated results.

Throughout the project the Evidence Review Team led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, and grading of the quality of the body of evidence and the strength of guideline recommendations.

Refinement of Guideline Topics and Development of Materials

The goals of the Work Group spanned a diverse group of topics, which would have been too large for a comprehensive review of the literature. Based on their expertise, members of the Work Group focused on specific questions deemed clinically relevant and amenable to systematic review. Other sources of data included previously published guidelines and systematic reviews.

The Work Groups and Evidence Review Team developed: (1) draft guideline statements, (2) draft rationale statements that summarized the expected pertinent evidence, and (3) data extraction forms requesting the data elements to be retrieved from the primary articles. The topic refinement process began before literature retrieval and continued through the process of reviewing individual articles.

Literature Search

The Work Group members developed specific questions with regards to predictors and interventions related to specific outcomes. Search strategies were developed according to specific study topics, study design, and years of publication. Studies for the literature review were identified through MEDLINE searches of English language literature of human studies from January 1990 to December 2003. Selective updates were performed through May 2005. Broad MeSH (medical subject heading) terms and text words were used so that searches were both general in scope for high sensitivity in identification of pertinent literature and specific to preliminary topics selected by the Work Groups. The searches were also supplemented by articles identified by Work Group members through August 2005.

The principal kidney-related search terms used included: kidney, renal, kidney disease, albuminuria, proteinuria, hematuria, and hyperfiltration. Principal diabetes-related terms included: diabetes mellitus, hyperglycemia, retinopathy, and pregnancy in diabetes.

Only full journal articles of original data were included. Editorials, letters, abstracts, and unpublished reports were not included. Selected review articles, however, were included for background material. A separate search for systematic reviews of health education in diabetes was conducted for the behavioral management recommendation.

MEDLINE search results were screened by members of the Evidence Review Team for relevance using predefined eligibility criteria, described below. Retrieved articles were screened by the Evidence Review Team. Potentially relevant studies were sent to Work Group members for rescreening and data extraction. Domain experts made the final decision for inclusion or exclusion of all articles.

Generation of Data Extraction Forms

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, severity of kidney disease, type of diabetes, numbers of subjects, study design, study funding source, comorbid conditions, descriptions of relevant risk factors or interventions, description of outcomes, statistical methods, results, study quality based on criteria appropriate for each study design (see below), study applicability (see below), and sections for comments and assessment of biases. Training of the Work Group members to extract data from primary articles occurred at face-to-face meetings, supplemented by e-mails and teleconferences.

Generation of Evidence Tables

The Evidence Review Team condensed the information from the data extraction forms into evidence tables, which summarized individual studies. These tables were created for the Work Group members to assist them with review of the evidence and are not included in the guidelines. All Work Group members (within each topic) received copies of all extracted articles and all evidence tables. During the development of the

Table 59. Topics for Which Systematic Reviews of Primary Studies Were Performed

Topic	Study Eligibility	Articles Reviewed*	Articles Included†
Association of albuminuria with CKD and CVD outcomes	Prospective; longitudinal; N ≥ 250; albuminuria outcomes ≥ 6 mo, other outcomes ≥ 12 mo	24	21
Imaging/biopsy in DM	Any study	42	22
Association of albuminuria with retinopathy	Any study	16	14
Radiographic contrast and safety in DM and CKD	Any study	21	20
GFR equation and cystatin C in DM	Any study	12	--
Kidney function and DM (pediatric)	Longitudinal	23	--
Hyperfiltration and DM	Any study	8	--
Glycohemoglobin in CKD	Any study	5	--
Glycemic control risks in DM and CKD	RCT; albuminuria outcomes ≥6 mo, other outcomes ≥12 mo	4	--
DM treatment pharmacokinetics and adverse events	Prospective	9	--
Treatment of albuminuria in DM (including CVD- and DM-related treatments)	RCT; ≥6 mo; albuminuria a primary outcome For antihypertensive studies, N ≥100, ACE-I or ARB, and since KDOQI™ blood pressure guideline search (2001)	41	34
Dietary treatments and nutrition in DM	For dietary treatments: RCT; lipid outcomes ≥1 mo (and since KDOQI™ lipids guidelines, 2002), albuminuria outcomes ≥6 mo, other outcomes ≥12 mo. For other nutrition studies: prospective study.	27	18
Pregnancy in DM and CKD	Any study	18	15

Abbreviations: (--), summary tables specific to these topics were not created; CVD, cardiovascular disease; DM, diabetes mellitus; RCT, randomized controlled trial; GFR, glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
*By Work Group members, after screening by Evidence Review Team.
†Included in Summary Tables. Does not include additional studies that were data extracted and/or reviewed in depth and used as background or ancillary material.

evidence tables, the Evidence Review Team checked the data extraction for accuracy and rescreened the accepted articles to verify that each of them met the initial screening criteria determined by the Work Group.

Format for Summary Tables

Summary tables describe the studies according to 4 dimensions: study size and follow-up duration, applicability or generalizability, results, and methodological quality. Within each table, the studies are first grouped by outcome type.

Data entered into summary tables by the Evidence Review Team were derived from the data extraction forms, evidence tables, and/or the articles. All summary tables were reviewed by the Work Group members.

Within each outcome section of 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). Results are presented by using the appropriate metric or summary symbols, as defined in the table footnotes.

Systematic Review Topics, Study Eligibility Criteria, and Literature Yield

The topics listed in Table 59 were systematically reviewed. Predefined eligibility criteria are included. These were based on the study designs of the available literature (eg, whether there were an "adequate" number of randomized trials) and the volume of the literature (eg, whether there were "so many" studies that restriction based on such factors as study size or duration were deemed appropriate).

For the primary literature topics, the literature searches yielded 11,378 citations. Of these, 765 articles were retrieved in full. An additional 57 studies were added by Work Group members. From all 822 articles, 250 were extracted and included. Of these, 142 studies are included in Summary Tables. A supplemental search for systematic reviews of diabetes

and health education yielded 901 citations, of which 10 systematic reviews were summarized.

Grading of Individual Studies

Study Size and Duration

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of effects 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. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

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. The study population typically is defined primarily by the inclusion and exclusion criteria. The target population varied somewhat from topic to topic, but generally was defined to include patients with both CKD and diabetes (ideally DKD, CKD caused directly by diabetes mellitus). More specific criteria were sometimes appropriate, for example, subjects with retinopathy or pregnant women. A designation for applicability was assigned to each article, according to a 3-level scale. In making this assessment, sociodemographic characteristics were considered, as well as comorbid conditions and prior treatments. Applicability is graded in reference to the population of interest for each topic.

Sample is representative of the target population, or results are definitely applicable to the target population irrespective of study sample.

Sample is representative of a relevant subgroup of the target population. For example, sample is only representative of people with macroalbuminuria, or all elderly individuals.

Sample is representative of a narrow subgroup of patients only, and not well generalizable to other subgroups. For example, the study includes only a small number of patients or older patients with new-onset diabetes. Studies of such narrow subgroups may be extremely valuable for demonstrating exceptions to the rule.

Results

In general, the result is summarized by both the direction and strength of the association. Depending on the study type, the results may refer either to dichotomous outcomes, such as the presence of retinopathy or a laboratory test above or below a threshold value, or to the association of continuous variables with outcomes, such as serum laboratory tests. We accounted for the magnitude of the association and both the clinical and statistical significance of the associations. Criteria for indicating the presence of an association varied among predictors depending on their clinical significance. Both univariate and multivariate associations are presented, when appropriate. The following metrics were used: prevalence, relative effects (relative risk [RR], odds ratio [OR], hazard ratio [HR], or net change—change from baseline in the intervention group minus the change in the control group), correlation (r or r^2), and test accuracy (sensitivity, specificity, and positive and negative predictive value). The choice of metric often was limited by the reported data. For some studies, only the statistical significance was reported.

Methodological 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. Not retrospective studies or case series.
- ◉ 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.
- ○ 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.

Summarizing Reviews and Selected Original Articles

Work Group members had wide latitude in summarizing reviews and selected original articles for topics that were determined not to require a systemic review of the literature. However, a thorough review and summary of systematic reviews of diabetes and health education was performed.

Format of Guidelines and Clinical Practice Recommendations

The format for each CPG and CPR chapter is outlined in Table 60. Each CPG or CPR contains one or more specific "statements," which are presented as "bullets" that represent recommendations to the target audience. Each CPG or CPR contains background information, which is generally sufficient for interpretation. A discussion of the broad concepts that frame the CPGs and CPRs is provided in the preceding section of this report. The rationale for each CPG contains a series of specific "rationale statements," each supported by evidence. The CPG or CPR concludes with a discussion of limitations of the evidence and a brief discussion of clinical applications, and implementation issues regarding the topic. Research recommendations for topics related to all CPGs and CPRs are compiled in a separate chapter.

Table 60. Format for Guidelines

Introductory Statement
Guideline or CPR Statement 1
Guideline or CPR Statement 2
BACKGROUND
RATIONALE
Definitions (if appropriate)
Rationale statement 1
Supporting text and tables
Rationale statement 2
Supporting text and tables
LIMITATIONS
IMPLEMENTATION ISSUES

Rating the Strength of Guidelines and Rationale Statements

Grading the Strength of Evidence

The overall strength of each guideline or clinical practice recommendation statement was rated by assigning either "A", "B", or "C (CPR)" as described in Table 61.

The strength of evidence was graded using a rating system that primarily takes into account: (1) methodological quality of the studies; (2) whether the study was carried out in the target population, ie, patients with CKD and diabetes, or in other populations; and (3) whether the studies examined health outcomes directly or examined surrogate measures for those outcomes, eg, reducing death or improving albuminuria (Table 62). These 3 separate study characteristics were combined to provide a preliminary strength of evidence provided by pertinent studies. In addition, aspects of the GRADE recommendations for grading the quality of evidence and the strength of recommendations were incorporated to determine a final strength of evidence.[598]

Thus, specific criteria for assessing the quality of the body of evidence (including an initial categorization of evidence quality based on study designs of the available studies) were discussed with the Work Group. For questions of interventions, quality was High, if randomized controlled trials; Low, if observational studies; Very Low, if other types of evidence. The quality rating was then decreased if there were serious limitations to individual study quality, if there were important inconsistent results across studies, if the

Table 61. Rating the Strength of Guideline and CPR Statements

Grade	Recommendation
A	It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.
B	It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.
C (CPR)	It is recommended that clinicians consider following the CPR for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers that the practice might improve 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 health outcomes implies that benefits outweigh any adverse effects.

applicability of the studies to the population of interest was limited, if the data were imprecise or sparse, or if there was thought to be a high likelihood of bias. The quality rating for observational studies was increased if there was strong evidence of an association (ie, significant RR or OR of about >2 [or <0.5] based on consistent evidence from 2 or more observational studies, with no plausible confounders), if there was evidence of a dose-response gradient, or if plausible confounders would have reduced the effect. Four final quality categories were used: High, Moderate, Low, and Very Low.

The Work Group and Evidence Review Team also discussed how the strength of the evidence would be determined based on the quality of evidence across all outcomes of interest, taking into account the relative importance of each of the outcomes (eg, death and CKD progression having greater weight than albuminuria or glucose levels) and a balance between net benefits and additional considerations, such as costs (resource utilization), feasibility, availability, likely differences in patient values, likely differences among populations and regions.

Each major item of evidence discussed in the Rationale sections for each CPG and CPR was given a strength rating. Upon consideration of the strength of evidence for the various sections of the body of evidence for a given set of recommendation statements, a determination was made whether the set of statements rise to the level of a CPG or whether the body of evidence is sufficiently weak to warrant only a CPR. Sets of statements that were graded as being Strong or Moderately Strong were designated as Guidelines. In the absence of strong or moderately strong quality evidence or when additional considerations did not support strong or moderately strong evidence-based recommendations, the

Table 62. Rating the Quality of Evidence

		Methodological Quality		
Outcome	**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]	Moderately strong[b]	Weak[h]
Health outcome(s)	**Other than the target population**	Moderately strong[c]	Moderately strong[d]	Weak[h]
Surrogate measure for health outcome(s)	**Target population**	Moderately strong[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 health outcomes.
Moderately strong- [b]Evidence is sufficient to determine effects on 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.

Work Group could elect to issue expert opinion-based recommendations termed CPRs. These recommendations are based on the consensus of the Work Group that the practice might improve health outcomes. As such, the Work Group recommends that clinicians consider following the recommendation for eligible patients. These recommendations are based on either weak evidence or on the opinions of the Work Group.

In addition, the Work Group adopted a convention for using existing expert guidelines issued for populations other than the target population. Grades for the strength of evidence assigned by the professional societies that issued the guidelines were adopted. When the guideline or the evidence was not graded, this Work Group assumed that the guideline would be based on at least moderately strong evidence. The extrapolation of these guideline recommendations from the general populations to the target population was considered to support grade B recommendations.

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. Hand 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. No meta-analyses were performed.

WORK GROUP BIOGRAPHIES

Pablo Aschner, MD, MSc, is Associate Professor and Head of the Endocrinology Unit at the Javeriana University School of Medicine and Scientific Sub-director at the Colombian Diabetes Association Clinical Research Center in Bogotá, Colombia. He specializes in Internal Medicine and Endocrinology and has a Master's degree in Clinical Epidemiology. He has served as a member of the World Health Organization Expert Advisory Panel on chronic degenerative diseases. He is also a past President of the Latin American Diabetes Association and the Latin American Diabetes Epidemiology Group. He also serves as a member of the International Diabetes Federation task force on Epidemiology. Dr Aschner has received compensation for lectures and/or consultations from AstraZeneca, Bayer, GlaxoSmithKline, Merck Sharp Dohme, and Sanofi-Aventis.

George L. Bakris, MD, is Professor of Medicine and Director of the Hypertension Unit at University of Chicago-Pritzker School of Medicine. He previously served as Director, Renal Research at Ochsner Clinic and Director of the Nephrology Fellowship Program at University of Texas, San Antonio. Dr Bakris currently serves as a National Kidney Foundation (NKF) representative for the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood pressure (JNC 6 and JNC 7) and is a board-certified specialist in hypertension. He has received numerous National Institutes of Health (NIH) grants for clinical trials, including the African-American Study of Kidney Disease (AASK), Genetics of Hypertension (SCOR), and the K30 Clinical Trials Center awards. Dr Bakris has received compensation for lectures or consultations, research funds or grants from Abbott, AstraZeneca, ATLAS Foundation, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Kos Pharmaceuticals, Merck, Novartis, Sanofi-Aventis, and Walgreens.

Rudolf W. Bilous, MD, is Professor of Clinical Medicine and Honorary Consultant Physician at the University of Newcastle, UK. He received his fellowship from the Royal College of Physicians in London. From 1985 to 1987, he served as the Juvenile Diabetes Foundation International (JDFI) Post-Doctorate Fellow at the University of Minnesota and the NIH Fellow at Guy's Hospital in London from 1980 to 1982. He is currently serving as the Specialty Advisory Committee Chair for Endo/Diabetes of the Joint Committee for Higher Medical Training, as well as the Chairman of Professional Advisory Council Executive of Diabetes—UK (formerly the British Diabetic Association). Dr Bilous is also the Vice President of the European Diabetic Nephropathy Study Group, and his research interest has focused on diabetic nephropathy and clinical diabetes, including hypertension. Dr Bilous has received research grants from, or participated in clinical trials funded by AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Lilly Industries, Novo-Nordisk, Roche Pharmaceuticals, Sanofi, and Takeda Pharmaceuticals.

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Jeffrey A. Cutler, MD, MPH, is Senior Scientific Advisor, Division of Epidemiology and Clinical Applications at the National Heart, Lung, and Blood Institute (NHLBI). He is involved with many NHLBI studies, including serving as a member of the Steering Committee for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial and the Executive Committee for the Trials of Hypertension Prevention. Dr Cutler has received several awards from the US Public Health Service, including 2 Commendation Medals, an Outstanding Service Medal, and a Meritorious Services Medal. His areas of research and special interest include the prevention and treatment of hypertension, other cardiovascular disease (CVD) prevention, clini-

cal trials methods, and nutrition. Dr Cutler is affiliated with the American Heart Association (AHA), American Public Health Association, Society of Epidemiologic Research, Council on Epidemiology and Prevention—World Heart Federation, and American College of Preventive Medicine.

D. Jordi Goldstein-Fuchs, DSc, RD, currently is working as a clinical and research renal nutrition specialist in Sparks, Nevada. She is completing her 10th year as Editor of the *Journal of Renal Nutrition*. Dr Goldstein first became interested in kidney disease while studying for her Master's degree at the MGH Institute of Health Professions. Her research thesis was in the area of urea kinetic modeling, and the resulting publication was awarded the Mary P. Huddleson Award by the American Dietetic Association. After working as a renal dietitian for several years, Dr Goldstein returned to graduate school and received her Doctor of Science degree in Nutrition Science from Boston University. Her doctoral work was in the area of essential fatty acids and experimental kidney disease. She is the author of multiple scientific publications and book chapters. Dr Goldstein is a recipient of the 2003 Service Award from the NKF Council on Renal Nutrition. She is also a member of several nutrition and kidney societies, including the International Society of Renal Nutrition & Metabolism, the Council on Renal Nutrition of the NKF, and the American Dietetic Association. Dr Goldstein is a reviewer for several nutrition and nephrology journals, and she has received a research grant from Davita Inc.

Thomas H. Hostetter, MD, is a faculty member at Albert Einstein College of Medicine. He was a senior scientific adviser and director of the National Kidney Disease Education Program at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). He was also Professor of Medicine at the University of Minnesota, where he was Director of the Renal Division in the Department of Internal Medicine for 15 years. He received his bachelor's degree in chemistry from Yale University. After graduating from Baylor College of Medicine, Dr Hostetter served his internship at Baylor and his residency at the Peter Bent Brigham Hospital. Following his nephrology fellowship at Brigham, he became a faculty member at Harvard Medical School. Dr Hostetter's major research interest is in the mechanisms of progressive kidney disease. He has served on several editorial boards, General Medicine B study section of the NIH, the Nephrology board of the American Board of Internal Medicine, the councils of the American and International Societies of Nephrology, and was president of the American Society of Nephrology from 1999 to 2000.

S. Michael Mauer, MD, is Professor of Pediatrics and Co-Director of Pediatric Nephrology at the University of Minnesota School of Medicine. He has more than 30 years of research interest in diabetic nephropathy, including diabetic nephropathy animal models, and human structural-functional relationships, pathophysiology, natural history, effects of pancreas transplantation, and clinical trials of glycemic control and renin-angiotensin system blockade. He is also working on diabetic nephropathy biomarkers and predictors. Dr Mauer has received research funds from Merck.

Mark E. Molitch, MD, is Professor of Medicine in the Division of Endocrinology, Metabolism, and Molecular Medicine at Northwestern University Feinberg School of Medicine. He received his fellowship at UCLA-Harbor General Hospital and is certified in Internal Medicine, as well as Endocrinology and Metabolism. Dr Molitch's areas of special interest are pathogenesis and treatment of diabetic nephropathy and pituitary tumors. In 1997, he received the Outstanding Physician Educator Award from the American Diabetes Association (ADA). Dr Molitch has received research funds, grants, or contracts from Abbott, Amgen, Bristol Myers Squibb, Eli Lilly & Co, Genentech, Ipsen, Joslin Research Foundation, Juvenile Diabetes Research Foundation, Novartis, Novo-Nordisk, Pfizer, Sanofi-Aventis, and Takeda Pharmaceuticals.

Andrew Narva, MD, is Director of National Kidney Disease Education Program at the National Institute of Diabetes and Digestive and Kidney Diseases. He has previously worked as a physician in Indian Health Service (IHS) since 1981 and served for 6 years as a general internist at the Keams Canyon (Arizona) and Albuquerque Service Units. Since completion of a nephrology fellowship in 1989, he has provided care to patients with kidney disease throughout New Mexico as the Albuquerque Area Nephrologist

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Robert G. Nelson, MD, PhD *(Work Group Co-Chair)*, is a Staff Clinician at the NIDDK in Phoenix, Arizona. He received his medical degree and residency training in Internal Medicine and Public Health and General Preventive Medicine at Loma Linda University in California. He received an MPH at Harvard School of Public Health and a PhD in epidemiology from the University of California, Los Angeles. His research interests include complications of type 2 diabetes, and his primary research focus is diabetic nephropathy. He served previously as a Work Group member on the KDOQI™ Clinical Practice Guidelines for Chronic Kidney Disease (CKD): Evaluation, Classification, and Stratification. Dr Nelson has received study drugs from Merck for an ongoing clinical trial.

Marc A. Pfeffer, MD, PhD, is a Professor of Medicine, Harvard Medical School; Senior Physician Cardiovascular Division, Brigham and Women's Hospital; Fellow of the American College of Cardiology; and a member of 3 councils of the AHA (High Blood Pressure Research, Basic Science, and Clinical Cardiology). He serves on national and regional committees and prominent editorial boards. Dr Pfeffer's major interests are the pathophysiology of progressive cardiac dysfunction following myocardial infarction or systemic hypertension, and clinical management strategies for myocardial infarction and left ventricular dysfunction. He has served as the principal investigator of major clinical trials of angiotensin-converting enzyme inhibition postinfarction (SAVE and HEART) and as director of clinical centers for the Cholesterol and Recurrent Events (CARE) trial. Dr Pfeffer served as Co-Chair of the NIH/NHLBI-sponsored PEACE study, as well as co-chair of CHARM and principal investigator of VALIANT. Dr Pfeffer currently serves as the principal investigator of TREAT and Co-Chair of the ARISE trial. He has received research funds, grants, contracts or compensation for lectures, conferences or consultations from Amgen, AstraZeneca, AtheroGenics, Novartis and Sanofi-Aventis.

Michelle M. Richardson, PharmD, BCPS, is Clinical Associate Professor at Northeastern University's School of Pharmacy and Assistant Professor at Tufts University School of Medicine. She also serves on the Special and Scientific Staff of the William B. Schwartz, Division of Nephrology at Tufts-New England Medical Center. She received pharmacy residency training at the Warren G. Magnuson Clinical Center at the NIH, completed an Outcomes Research fellowship from Tufts-New England Medical Center, and is board certified in pharmacotherapy. Her special interests include pharmacotherapy in patients with kidney disease, health status, and patient satisfaction. Dr Richardson has received research funds, grants, or contracts from Amgen, Dialysis Clinic, and Ortho Biotech.

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REFERENCES

1. Dirks JH, de Zeeuw D, Agarwal SK, et al: Prevention of chronic kidney and vascular disease: Toward global health equity—The Bellagio 2004 Declaration. Kidney Int Suppl 98:S1-S6, 2005

2. Lysaght MJ: Maintenance dialysis population dynamics: Current trends and long-term implications. J Am Soc Nephrol 13:S37-S40, 2002 (suppl 1)

3. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification, and stratification. Am J Kidney Dis 39:S1-266, 2002 (suppl 1)

4. US Renal Data System: USRDS 2004 Annual Data Report. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2004

5. National Kidney Foundation: K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Am J Kidney Dis 43:S1-S290, 2004 (suppl 1)

6. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Management of Dyslipidemias in Patients With Kidney Disease. Am J Kidney Dis 41:S1-S91, 2003 (suppl 3)

7. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 42:S1-S201, 2003 (suppl 3)

8. National Kidney Foundation: KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 47:S1-S145, 2006 (suppl 3)

9. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. Am J Kidney Dis 35:S1-S140, 2000 (suppl 2)

10. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. Am J Kidney Dis 45:S1-S153, 2005 (suppl 3)

11. Knowler WC, Bennett PH, Bottazzo GF, Doniach D: Islet cell antibodies and diabetes mellitus in Pima Indians. Diabetologia 17:161-164, 1979

12. West KM: Diabetes in American Indians, in Levine R, Luft R (eds): Advances in Metabolic Disorders, vol 9. New York, NY, Academic, 1978, pp 29-47

13. Zimmet P: Globalization, coca-colonization and the chronic disease epidemic: Can the doomsday scenario be averted? J Intern Med 247:301-310, 2000

14. Engelgau MM, Geiss LS, Saaddine JB, et al: The evolving diabetes burden in the United States. Ann Intern Med 140:945-950, 2004

15. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP: Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: Results from the San Antonio Heart Study. Arch Intern Med 159:1450-1456, 1999

16. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. JAMA 281:1291-1297, 1999

17. Gale EA: The rise of childhood type 1 diabetes in the 20th century. Diabetes 51:3353-3361, 2002

18. Boyle JP, Honeycutt AA, Narayan KM, et al: Projection of diabetes burden through 2050: Impact of changing demography and disease prevalence in the U.S. Diabetes Care 24:1936-1940, 2001

19. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047-1053, 2004

20. Colagiuri S, Borch-Johnsen K, Glumer C, Vistisen D: There really is an epidemic of type 2 diabetes. Diabetologia 48:1459-1463, 2005

21. US Renal Data System: USRDS 2005 Annual Data Report. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2005

22. Motala AA, Pirie FJ, Gouws E, Amod A, Omar MA: Microvascular complications in South African patients with long-duration diabetes mellitus. S Afr Med J 91:987-992, 2001

23. Wanjohi FW, Otieno FC, Ogola EN, Amayo EO: Nephropathy in patients with recently diagnosed type 2 diabetes mellitus in black Africans. East Afr Med J 79:399-404, 2002

24. Ramachandran A, Snehalatha C, Latha E, Vijay V, Viswanathan M: Rising prevalence of NIDDM in an urban population in India. Diabetologia 40:232-237, 1997

25. Simmons D, Schaumkel J, Cecil A, Scott DJ, Kenealy T: High impact of nephropathy on five-year mortality rates among patients with type 2 diabetes mellitus from a multi-ethnic population in New Zealand. Diabet Med 16:926-931, 1999

26. Park JY, Kim HK, Chung YE, Kim SW, Hong SK, Lee KU: Incidence and determinants of microalbuminuria in Koreans with type 2 diabetes. Diabetes Care 21:530-534, 1998

27. Wu AY, Kong NC, de Leon FA, et al: An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: The MicroAlbuminuria Prevalence (MAP) Study. Diabetologia 48:17-26, 2005

28. Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC, Gautier JF: Diabetes in Africans. Part 1: Epidemiology and clinical specificities. Diabetes Metab 27:628-634, 2001

29. Earle KK, Porter KA, Ostberg J, Yudkin JS: Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant 16:286-290, 2001

30. Koppiker N, Feehally J, Raymond N, Abrams KR, Burden AC: Rate of decline in renal function in Indo-Asians and whites with diabetic nephropathy. Diabet Med 15:60-65, 1998

31. Chandie Shaw PK, van Es LA, Paul LC, Rosendaal FR, Souverijn JH, Vandenbroucke JP: Renal disease in relatives of Indo-Asian type 2 diabetic patients with end-stage diabetic nephropathy. Diabetologia 46:618-624, 2003

32. Chandie Shaw PK, Vandenbroucke JP, Tjandra YI, et al: Increased end-stage diabetic nephropathy in Indo-Asian immigrants living in The Netherlands. Diabetologia 45:337-341, 2002

33. Zimmet P, Alberti KG, Shaw J: Global and societal implications of the diabetes epidemic. Nature 414:782-787, 2001

34. Standards of medical care in diabetes—2006. Diabetes Care 29:S4-S85, 2006 (suppl 1)

35. Molitch ME, DeFronzo RA, Franz MJ, et al: Nephropathy in diabetes. Diabetes Care 27:S79-S83, 2004 (suppl 1)

36. Feldt-Rasmussen B: Microalbuminuria and clinical nephropathy in type 1 (insulin-dependent) diabetes mellitus: Pathophysiological mechanisms and intervention studies. Dan Med Bull 36:405-415, 1989

37. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229-234, 1998

38. Grundy SM, Howard B, Smith S Jr, Eckel R, Redberg R, Bonow RO: Prevention Conference VI: Diabetes and Cardiovascular Disease: Executive summary: Conference proceeding for healthcare professionals from a special writing group of the American Heart Association. Circulation 105:2231-2239, 2002

39. Sarnak MJ, Levey AS, Schoolwerth AC, et al: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 108:2154-2169, 2003

40. Dinneen SF, Gerstein HC: The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med 157:1413-1418, 1997

41. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR: Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 63:225-232, 2003

42. Miettinen H, Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non-insulin-dependent diabetic subjects. Stroke 27:2033-2039, 1996

43. Valmadrid CT, Klein R, Moss SE, Klein BE: The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med 160:1093-1100, 2000

44. Foley RN, Murray AM, Li S, et al: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol 16:489-495, 2005

45. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348:383-393, 2003

46. Gaede P, Vedel P, Parving HH, Pedersen O: Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: The Steno type 2 randomised study. Lancet 353:617-622, 1999

47. Carey VJ, Walters EE, Colditz GA, et al: Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol 145:614-619, 1997

48. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 17:961-969, 1994

49. Kaye SA, Folsom AR, Sprafka JM, Prineas RJ, Wallace RB: Increased incidence of diabetes mellitus in relation to abdominal adiposity in older women. J Clin Epidemiol 44:329-334, 1991

50. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjostrom L: Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: Results from a prospective population study in Gothenburg, Sweden. Int J Obes 13:413-423, 1989

51. Ohlson LO, Larsson B, Svardsudd K, et al: The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 Years of follow-up of the participants in the study of men born in 1913. Diabetes 34:1055-1058, 1985

52. Sargeant LA, Bennett FI, Forrester TE, Cooper RS, Wilks RJ: Predicting incident diabetes in Jamaica: The role of anthropometry. Obes Res 10:792-798, 2002

53. Warne DK, Charles MA, Hanson RL, et al: Comparison of body size measurements as predictors of NIDDM in Pima Indians. Diabetes Care 18:435-439, 1995

54. Wei M, Gaskill SP, Haffner SM, Stern MP: Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans—A 7-year prospective study. Obes Res 5:16-23, 1997

55. Tulloch-Reid MK, Williams DE, Looker HC, Hanson RL, Knowler WC: Do measures of body fat distribution provide information on the risk of type 2 diabetes in addition to measures of general obesity? Comparison of anthropometric predictors of type 2 diabetes in Pima Indians. Diabetes Care 26:2556-2561, 2003

56. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U: Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol 278:F817-F822, 2000

57. Ribstein J, du Cailar G, Mimran A: Combined renal effects of overweight and hypertension. Hypertension 26:610-615, 1995

58. Folsom AR, Kushi LH, Hong CP: Physical activity and incident diabetes mellitus in postmenopausal women. Am J Public Health 90:134-138, 2000

59. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 325:147-152, 1991

60. Kriska AM, Saremi A, Hanson RL, et al: Physical activity, obesity, and the incidence of type 2 diabetes in a high-risk population. Am J Epidemiol 158:669-675, 2003

61. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: A prospective study of exercise and incidence of diabetes among US male physicians. JAMA 268:63-67, 1992

62. Manson JE, Rimm EB, Stampfer MJ, et al: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 338:774-778, 1991

63. Knowler WC, Barrett-Connor E, Fowler SE, et al: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393-403, 2002

64. Pan XR, Li GW, Hu YH, et al: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 20:537-544, 1997

65. Tuomilehto J, Lindstrom J, Eriksson JG, et al: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344:1343-1350, 2001

66. Molitch ME, Fujimoto W, Hamman RF, Knowler WC: The diabetes prevention program and its global implications. J Am Soc Nephrol 14:S103-S107, 2003 (suppl 2)

67. Ramachandran A, Snehalatha C, Vinitha R, et al: Prevalence of overweight in urban Indian adolescent school children. Diabetes Res Clin Pract 57:185-190, 2002

68. Pazmino PA, Pazmino AK: Diabetic renal failure in Texas: Influence of ethnicity and household income. Tex Med 99:57-65, 2003

69. Brancati FL, Whelton PK, Kuller LH, Klag MJ: Diabetes mellitus, race, and socioeconomic status. A population-based study. Ann Epidemiol 6:67-73, 1996

70. Hazuda HP, Haffner SM, Stern MP, Eifler CW: Effects of acculturation and socioeconomic status on obesity and diabetes in Mexican Americans. The San Antonio Heart Study. Am J Epidemiol 128:1289-1301, 1988

71. Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M: Type 2 diabetes in the young: The evolving epidemic: The International Diabetes Federation Consensus Workshop. Diabetes Care 27:1798-1811, 2004

72. Singh R, Shaw J, Zimmet P: Epidemiology of childhood type 2 diabetes in the developing world. Pediatr Diabetes 5:154-168, 2004

73. Acton KJ, Burrows NR, Moore K, Querec L, Geiss LS, Engelgau MM: Trends in diabetes prevalence among American Indian and Alaska native children, adolescents, and young adults. Am J Public Health 92:1485-1490, 2002

74. Kitagawa T, Owada M, Urakami T, Yamauchi K: Increased incidence of non-insulin dependent diabetes mellitus among Japanese schoolchildren correlates with an increased intake of animal protein and fat. Clin Pediatr (Phila) 37:111-115, 1998

75. Urakami T, Kubota S, Nitadori Y, Harada K, Owada M, Kitagawa T: Annual incidence and clinical characteristics of type 2 diabetes in children as detected by urine glucose screening in the Tokyo metropolitan area. Diabetes Care 28:1876-1881, 2005

76. Dabelea D, Hanson RL, Bennett PH, Roumain J, Knowler WC, Pettitt DJ: Increasing prevalence of type II diabetes in American Indian children. Diabetologia 41:904-910, 1998

77. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 308:242-245, 1983

78. Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al: Type 2 diabetes among North American children and adolescents: An epidemiologic review and a public health perspective. J Pediatr 136:664-672, 2000

79. Krakoff J, Lindsay RS, Looker HC, Nelson RG, Hanson RL, Knowler WC: Incidence of retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. Diabetes Care 26:76-81, 2003

80. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG: Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 296:421-426, 2006

81. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M: Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: General description and morbidity. Diabetologia 44:S3-S13, 2001 (suppl 2)

82. Lee ET, Lu M, Bennett PH, Keen H: Vascular disease in younger-onset diabetes: Comparison of European, Asian and American Indian cohorts of the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 44:S78-S81, 2001 (suppl 2)

83. Uchigata Y: Long-term outcome of type 2 diabetes in adolescence, in Silink M, Kida K, Rosenbloom AL (eds): Type 2 Diabetes in Childhood and Adolescence: A Global Perspective. New York, NY, Dunitz, 2003, pp 187-210

84. Yokoyama H, Okudaira M, Otani T, et al: Existence of early-onset NIDDM Japanese demonstrating severe diabetic complications. Diabetes Care 20:844-847, 1997

85. Brown AF, Mangione CM, Saliba D, Sarkisian CA: Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 51:S265-S280, 2003 (suppl)

86. Pettitt DJ, Knowler WC: Diabetes and obesity in the Pima Indians: A crossgenerational vicious cycle. J Obes Weight Regul 7:61-65, 1988

87. Nelson RG, Morgenstern H, Bennett PH: Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. Diabetes 47:1489-1493, 1998

88. Gregg EW, Beckles GL, Williamson DF, et al: Diabetes and physical disability among older U.S. adults. Diabetes Care 23:1272-1277, 2000

89. Volpato S, Blaum C, Resnick H, Ferrucci L, Fried LP, Guralnik JM: Comorbidities and impairments explaining the association between diabetes and lower extremity disability: The Women's Health and Aging Study. Diabetes Care 25:678-683, 2002

90. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 102:520-526, 1984

91. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 102:527-532, 1984

92. McKenna MT, Michaud CM, Murray CJ, Marks JS: Assessing the burden of disease in the United States using disability-adjusted life years. Am J Prev Med 28:415-423, 2005

93. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB: Mortality among diabetics in a national sample. Am J Epidemiol 128:389-401, 1988

94. Borch-Johnsen K, Andersen PK, Deckert T: The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 28:590-596, 1985

95. Nelson RG, Pettitt DJ, Carraher MJ, Baird HR, Knowler WC: Effect of proteinuria on mortality in NIDDM. Diabetes 37:1499-1504, 1988

96. Stephenson JM, Kenny S, Stevens LK, Fuller JH, Lee E: Proteinuria and mortality in diabetes: The WHO Multinational Study of Vascular Disease in Diabetes. Diabet Med 12:149-155, 1995

97. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet 360:7-22, 2002

98. Colhoun HM, Betteridge DJ, Durrington PN, et al: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 364:685-696, 2004

99. Tonelli M, Keech A, Shepherd J, et al: Effect of pravastatin in people with diabetes and chronic kidney disease. J Am Soc Nephrol 16:3748-3754, 2005

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

101. Wackers FJ, Young LH, Inzucchi SE, et al: Detection of silent myocardial ischemia in asymptomatic diabetic subjects: The DIAD study. Diabetes Care 27:1954-1961, 2004

102. Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 110:282-292, 2004

103. Pfeffer MA, McMurray JJ, Velazquez EJ, et al: Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 349:1893-1906, 2003

104. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Lancet 355:253-259, 2000

105. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 342:145-153, 2000

106. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. Ann Intern Med 134:629-636, 2001

107. Tokmakova MP, Skali H, Kenchaiah S, et al: Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: The Survival And Ventricular Enlargement (SAVE) Study. Circulation 110:3667-3673, 2004

108. Bakris GL, Fonseca V, Katholi RE, et al: Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A randomized controlled trial. JAMA 292:2227-2236, 2004

109. Malmberg K, Ryden L, Efendic S, et al: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): Effects on mortality at 1 year. J Am Coll Cardiol 26:57-65, 1995

110. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359-1367, 2001

111. Yusuf S, Mehta SR, Diaz R, et al: Challenges in the conduct of large simple trials of important generic questions in resource-poor settings: The CREATE and ECLA trial program evaluating GIK (glucose, insulin and potassium) and low-molecular-weight heparin in acute myocardial infarction. Am Heart J 148:1068-1078, 2004

112. Mehta SR, Yusuf S, Diaz R, et al: Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: The CREATE-ECLA randomized controlled trial. JAMA 293:437-446, 2005

113. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. N Engl J Med 354:449-461, 2006

114. Malmberg K, Ryden L, Wedel H, et al: Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): Effects on mortality and morbidity. Eur Heart J 26:650-661, 2005

115. Nathan DM, Cleary PA, Backlund JY, et al: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353:2643-2653, 2005

116. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854-865, 1998

117. Dormandy JA, Charbonnel B, Eckland DJ, et al: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): A randomised controlled trial. Lancet 366:1279-1289, 2005

118. Kao J, Tobis J, McClelland RL, et al: Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. Am J Cardiol 93:1347-1350, A1345, 2004

119. Gibler WB, Cannon CP, Blomkalns AL, et al: Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department: A scientific statement from the American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care), Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration With the Society of Chest Pain Centers. Circulation 111:2699-2710, 2005

120. Freeman RV, Mehta RH, Al Badr W, Cooper JV, Kline-Rogers E, Eagle KA: Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. J Am Coll Cardiol 41:718-724, 2003

121. Reddan DN, Szczech L, Bhapkar MV, et al: Renal function, concomitant medication use and outcomes following acute coronary syndromes. Nephrol Dial Transplant 20:2105-2112, 2005

122. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB: Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med 137:555-562, 2002

123. Wright RS, Reeder GS, Herzog CA, et al: Acute myocardial infarction and renal dysfunction: A high-risk combination. Ann Intern Med 137:563-570, 2002

124. Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA: Survival after coronary revascularization among patients with kidney disease. Circulation 110:1890-1895, 2004

125. Reddan DN, Szczech LA, Tuttle RH, et al: Chronic kidney disease, mortality, and treatment strategies among patients with clinically significant coronary artery disease. J Am Soc Nephrol 14:2373-2380, 2003

126. Ix JH, Mercado N, Shlipak MG, et al: Association of chronic kidney disease with clinical outcomes after coronary revascularization: The Arterial Revascularization Therapies Study (ARTS). Am Heart J 149:512-519, 2005

127. Moussa I, Leon MB, Baim DS, et al: Impact of sirolimus-eluting stents on outcome in diabetic patients: A SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 109:2273-2278, 2004

128. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, et al: Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: The diabetes and sirolimus-eluting stent (DIABETES) trial. Circulation 112:2175-2183, 2005

129. Hermiller JB, Raizner A, Cannon L, et al: Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: The TAXUS-IV trial. J Am Coll Cardiol 45:1172-1179, 2005

130. Mehilli J, Kastrati A, Schuhlen H, et al: Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. Circulation 110: 3627-3635, 2004

131. Marso SP, Ellis SG, Tuzcu M, et al: The importance of proteinuria as a determinant of mortality following percutaneous coronary revascularization in diabetics. J Am Coll Cardiol 33:1269-1277, 1999

132. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977-986, 1993

133. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: The Epidemiology of Diabetes Interventions and Complications (EDIC) Study. JAMA 290:2159-2167, 2003

134. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837-853, 1998

135. Levin SR, Coburn JW, Abraira C, et al: Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. Diabetes Care 23:1478-1485, 2000

136. Ohkubo Y, Kishikawa H, Araki E, et al: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. Diabetes Res Clin Pract 28:103-117, 1995

137. Shichiri M, Kishikawa H, Ohkubo Y, Wake N: Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 23:B21-B29, 2000 (suppl 2)

138. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 329:304-309, 1993

139. Brocco E, Velussi M, Cernigoi AM, et al: Evidence of a threshold value of glycated hemoglobin to improve the course of renal function in type 2 diabetes with typical diabetic glomerulopathy. J Nephrol 14:461-471, 2001

140. Holman RR, Dornan TL, Mayon-White V, et al: Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. Lancet 1:204-208, 1983

141. Viberti GC, Bilous RW, Mackintosh D, Bending JJ, Keen H: Long term correction of hyperglycaemia and progression of renal failure in insulin dependent diabetes. Br Med J 286:598-602, 1983

142. Gerich JE, Meyer C, Woerle HJ, Stumvoll M: Renal gluconeogenesis: Its importance in human glucose homeostasis. Diabetes Care 24:382-391, 2001

143. Hasslacher C, Wittmann W: [Severe hypoglycemia in diabetics with impaired renal function]. Dtsch Med Wochenschr 128:253-256, 2003

144. Muhlhauser I, Toth G, Sawicki PT, Berger M: Severe hypoglycemia in type I diabetic patients with impaired kidney function. Diabetes Care 14:344-346, 1991

145. Yu CC, Wu MS, Wu CH, et al: Predialysis glycemic control is an independent predictor of clinical outcome in type II diabetics on continuous ambulatory peritoneal dialysis. Perit Dial Int 17:262-268, 1997

146. Morioka T, Emoto M, Tabata T, et al: Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care 24:909-913, 2001

147. Brocco E, Fioretto P, Mauer M, et al: Renal structure and function in non-insulin dependent diabetic patients with microalbuminuria. Kidney Int Suppl 63:S40-S44, 1997

148. Dalla Vestra M, Saller A, Bortoloso E, Mauer M, Fioretto P: Structural involvement in type 1 and type 2 diabetic nephropathy. Diabetes Metab 26:S8-S14, 2000 (suppl 4)

149. de Courten MP, Pettitt DJ, Knowler WC: Hypertension in Pima Indians: Prevalence and predictors. Public Health Rep 111:S40-S43, 1996 (suppl 2)

150. Go RC, Desmond R, Roseman JM, Bell DS, Vanichanan C, Acton RT: Prevalence and risk factors of microalbuminuria in a cohort of African-American women with gestational diabetes. Diabetes Care 24:1764-1769, 2001

151. Parving HH, Hommel E, Mathiesen E, et al: Prevalence of microalbuminuria, arterial hypertension, retinopa-

thy and neuropathy in patients with insulin dependent diabetes. Br Med J 296:156-160, 1988

152. Tobe SW, McFarlane PA, Naimark DM: Microalbuminuria in diabetes mellitus. CMAJ 167:499-503, 2002

153. Wachtell K, Palmieri V, Olsen MH, et al: Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE Study. Losartan Intervention for Endpoint Reduction. Am Heart J 143:319-326, 2002

154. Chobanian AV, Bakris GL, Black HR, et al: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42:1206-1252, 2003

155. Agardh CD, Garcia-Puig J, Charbonnel B, Angelkort B, Barnett AH: Greater reduction of urinary albumin excretion in hypertensive type II diabetic patients with incipient nephropathy by lisinopril than by nifedipine. J Hum Hypertens 10:185-192, 1996

156. Chan JC, Cockram CS, Nicholls MG, Cheung CK, Swaminathan R: Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: One year analysis. BMJ 305:981-985, 1992

157. Chan JC, Ko GT, Leung DH, et al: Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. Kidney Int 57:590-600, 2000

158. De Cesaris R, Ranieri G, Andriani A, et al: Effects of benazepril and nicardipine on microalbuminuria in normotensive and hypertensive patients with diabetes. Clin Pharmacol Ther 60:472-478, 1996

159. Laffel LM, McGill JB, Gans DJ: The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. Am J Med 99:497-504, 1995

160. Mathiesen ER, Hommel E, Giese J, Parving HH: Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. BMJ 303:81-87, 1991

161. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345:870-878, 2001

162. Ravid M, Lang R, Rachmani R, Lishner M: Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med 156:286-289, 1996

163. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M: Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 118:577-581, 1993

164. Schnack C, Hoffmann W, Hopmeier P, Schernthaner G: Renal and metabolic effects of 1-year treatment with ramipril or atenolol in NIDDM patients with microalbuminuria. Diabetologia 39:1611-1616, 1996

165. Trevisan R, Tiengo A: Effect of low-dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin-dependent diabetic patients. North-East Italy Microalbuminuria Study Group. Am J Hypertens 8:876-883, 1995

166. Viberti G, Mogensen CE, Groop LC, Pauls JF: Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. JAMA 271:275-279, 1994

167. Brenner BM, Cooper ME, de Zeeuw D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861-869, 2001

168. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 329:1456-1462, 1993

169. Lewis EJ, Hunsicker LG, Clarke WR, et al: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851-860, 2001

170. Koshy S, Bakris GL: Therapeutic approaches to achieve desired blood pressure goals: Focus on calcium channel blockers. Cardiovasc Drugs Ther 14:295-301, 2000

171. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ: Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. Am J Kidney Dis 34:809-817, 1999

172. Rahman M, Pressel S, Davis BR, et al: Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: A report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 165:936-946, 2005

173. Bakris GL, Weir MR, Shanifar S, et al: Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAAL Study. Arch Intern Med 163:1555-1565, 2003

174. Standards of medical care in diabetes. Diabetes Care 28:S4-S36, 2005 (suppl 1)

175. Grundy SM, Cleeman JI, Merz CN, et al: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 110:227-239, 2004

176. Snow V, Aronson MD, Hornbake ER, Mottur-Pilson C, Weiss KB: Lipid control in the management of type 2 diabetes mellitus: A clinical practice guideline from the American College of Physicians. Ann Intern Med 140:644-649, 2004

177. Vijan S, Hayward RA: Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: Background paper for the American College of Physicians. Ann Intern Med 140:650-658, 2004

178. Wright JD, Wang C-Y, Kennedy-Stephenson J, Ervin RB: Dietary intake of ten key nutrients for public health, United States: 1999-2000. Hyattsville, MD, Centers for Disease Control and Prevention, National Center for Health Statistics, 2003, pp 1-4

179. Kasiske BL, Lakatua JD, Ma JZ, Louis TA: A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. Am J Kidney Dis 31:954-961, 1998

180. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: A meta-analysis. Ann Intern Med 124:627-632, 1996

181. Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH: Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int 62:220-228, 2002

182. Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A: Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. Eur J Clin Nutr 57:1292-1294, 2003

183. Dullaart RP, Beusekamp BJ, Meijer S, van Doormaal JJ, Sluiter WJ: Long-term effects of protein-restricted diet on albuminuria and renal function in IDDM patients without clinical nephropathy and hypertension. Diabetes Care 16:483-492, 1993

184. Meloni C, Morosetti M, Suraci C, et al: Severe dietary protein restriction in overt diabetic nephropathy: Benefits or risks? J Ren Nutr 12:96-101, 2002

185. Pecis M, de Azevedo MJ, Gross JL: Chicken and fish diet reduces glomerular hyperfiltration in IDDM patients. Diabetes Care 17:665-672, 1994

186. Raal FJ, Kalk WJ, Lawson M, et al: Effect of moderate dietary protein restriction on the progression of overt diabetic nephropathy: A 6-mo prospective study. Am J Clin Nutr 60:579-585, 1994

187. Brenner BM, Meyer TW, Hostetter TH: Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 307:652-659, 1982

188. Gin H, Aparicio M, Potaux L, et al: Low-protein, low-phosphorus diet and tissue insulin sensitivity in insulin-dependent diabetic patients with chronic renal failure. Nephron 57:411-415, 1991

189. Hansen HP, Christensen PK, Tauber-Lassen E, Klausen A, Jensen BR, Parving HH: Low-protein diet and kidney function in insulin-dependent diabetic patients with diabetic nephropathy. Kidney Int 55:621-628, 1999

190. Hostetter TH, Meyer TW, Rennke HG, Brenner BM: Chronic effects of dietary protein in the rat with intact and reduced renal mass. Kidney Int 30:509-517, 1986

191. Meek RL, Cooney SK, Flynn SD, et al: Amino acids induce indicators of response to injury in glomerular mesangial cells. Am J Physiol Renal Physiol 285:F79-F86, 2003

192. Tuttle KR, Bruton JL: Effect of insulin therapy on renal hemodynamic response to amino acids and renal hypertrophy in non-insulin-dependent diabetes. Kidney Int 42:167-173, 1992

193. Tuttle KR, Bruton JL, Perusek MC, Lancaster JL, Kopp DT, DeFronzo RA: Effect of strict glycemic control on renal hemodynamic response to amino acids and renal enlargement in insulin-dependent diabetes mellitus. N Engl J Med 324:1626-1632, 1991

194. Tuttle KR, Johnson EC, Cooney SK, et al: Amino acids injure mesangial cells by advanced glycation end products, oxidative stress, and protein kinase C. Kidney Int 67:953-968, 2005

195. Tuttle KR, Puhlman ME, Cooney SK, Short RA: Effects of amino acids and glucagon on renal hemodynamics in type 1 diabetes. Am J Physiol Renal Physiol 282:F103-F112, 2002

196. Zatz R, Meyer TW, Rennke HG, Brenner BM: Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. Proc Natl Acad Sci U S A 82:5963-5967, 1985

197. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC: The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med 138:460-467, 2003

198. Wrone EM, Carnethon MR, Palaniappan L, Fortmann SP: Association of dietary protein intake and microalbuminuria in healthy adults: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 41:580-587, 2003

199. Sacks FM, Svetkey LP, Vollmer WM, et al: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 344:3-10, 2001

200. Appel LJ, Sacks FM, Carey VJ, et al: Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: Results of the OmniHeart randomized trial. JAMA 294:2455-2464, 2005

201. He J, Gu D, Wu X, et al: Effect of soybean protein on blood pressure: A randomized, controlled trial. Ann Intern Med 143:1-9, 2005

202. Jibani MM, Bloodworth LL, Foden E, Griffiths KD, Galpin OP: Predominantly vegetarian diet in patients with incipient and early clinical diabetic nephropathy: Effects on albumin excretion rate and nutritional status. Diabet Med 8:949-953, 1991

203. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 134:370-379, 2001

204. Ahmad J, Shafique S, Abidi SM, Parwez I: Effect of 5-year enalapril therapy on progression of microalbuminuria and glomerular structural changes in type 1 diabetic subjects. Diabetes Res Clin Pract 60:131-138, 2003

205. Cordonnier DJ, Pinel N, Barro C, et al: Expansion of cortical interstitium is limited by converting enzyme inhibition in type 2 diabetic patients with glomerulosclerosis. The Diabiopsies Group. J Am Soc Nephrol 10:1253-1263, 1999

206. Ravid M, Savin H, Jutrin I, Bental T, Lang R, Lishner M: Long-term effect of ACE inhibition on development of nephropathy in diabetes mellitus type II. Kidney Int Suppl 45:S161-S164, 1994

207. Sano T, Hotta N, Kawamura T, et al: Effects of long-term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: Results of a 4-year, prospective, randomized study. Diabet Med 13:120-124, 1996

208. Mathiesen ER, Hommel E, Hansen HP, Smidt UM, Parving HH: Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. BMJ 319:24-25, 1999

209. Andersen S, Brochner-Mortensen J, Parving HH: Kidney function during and after withdrawal of long-term irbesartan treatment in patients with type 2 diabetes and microalbuminuria. Diabetes Care 26:3296-3302, 2003

210. Atkins RC, Briganti EM, Lewis JB, et al: Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 45:281-287, 2005

211. de Zeeuw D, Remuzzi G, Parving HH, et al: Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation 110:921-927, 2004

212. de Zeeuw D, Remuzzi G, Parving HH, et al: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. Kidney Int 65:2309-2320, 2004

213. Calvo G, de Andres-Trelles F: Albuminuria as a surrogate marker for drug development: A European Regulatory perspective. Kidney Int Suppl 92:S126-S127, 2004

214. Flegal KM, Carroll MD, Ogden CL, Johnson CL: Prevalence and trends in obesity among US adults, 1999-2000. JAMA 288:1723-1727, 2002

215. Kidney Early Evaluation Program. Am J Kidney Dis 45:S1-S135, 2005 (suppl 2)

216. Hall JE, Henegar JR, Dwyer TM, et al: Is obesity a major cause of chronic kidney disease? Adv Ren Replace Ther 11:41-54, 2004

217. Hall JE, Jones DW, Kuo JJ, da Silva A, Tallam LS, Liu J: Impact of the obesity epidemic on hypertension and renal disease. Curr Hypertens Rep 5:386-392, 2003

218. Iseki K: Factors influencing the development of end-stage renal disease. Clin Exp Nephrol 9:5-14, 2005

219. Saxena A, Chopra R: Renal risks of an emerging "epidemic" of obesity: The role of adipocyte-derived factors. Dial Transplant 33:11-21, 2004

220. Soto FC, Higa-Sansone G, Copley JB, et al: Renal failure, glomerulonephritis and morbid obesity: Improvement after rapid weight loss following laparoscopic gastric bypass. Obes Surg 15:137-140, 2005

221. Wiggins KJ, Johnson DW: The influence of obesity on the development and survival outcomes of chronic kidney disease. Adv Chronic Kidney Dis 12:49-55, 2005

222. Mogensen CE, Chachati A, Christensen CK, et al: Microalbuminuria: An early marker of renal involvement in diabetes. Uremia Invest 9:85-95, 1985

223. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T: The natural course of microalbuminuria in insulin-dependent diabetes: A 10-year prospective study. Diabet Med 12:482-487, 1995

224. Caramori ML, Fioretto P, Mauer M: The need for early predictors of diabetic nephropathy risk: Is albumin excretion rate sufficient? Diabetes 49:1399-1408, 2000

225. Forsblom CM, Groop PH, Ekstrand A, Groop LC: Predictive value of microalbuminuria in patients with insulin-dependent diabetes of long duration. BMJ 305:1051-1053, 1992

226. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS: Regression of microalbuminuria in type 1 diabetes. N Engl J Med 348:2285-2293, 2003

227. Araki S, Haneda M, Sugimoto T, et al: Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. Diabetes 54:2983-2987, 2005

228. Caramori ML, Kim Y, Huang C, et al: Cellular basis of diabetic nephropathy: 1. Study design and renal structural-functional relationships in patients with long-standing type 1 diabetes. Diabetes 51:506-513, 2002

229. Fioretto P, Steffes MW, Mauer M: Glomerular structure in nonproteinuric IDDM patients with various levels of albuminuria. Diabetes 43:1358-1364, 1994

230. Fioretto P, Mauer M, Carraro A, et al: Renal structural changes in non-insulin-dependent diabetes mellitus. Am J Hypertens 10:184S-188S, 1997 (suppl 1)

231. Krolewski M, Eggers PW, Warram JH: Magnitude of end-stage renal disease in IDDM: A 35 year follow-up study. Kidney Int 50:2041-2046, 1996

232. Microalbuminuria Collaborative Study Group: Risk factors for development of microalbuminuria in insulin dependent diabetic patients: A cohort study. United Kingdom. BMJ 306:1235-1239, 1993

233. Messent JW, Elliott TG, Hill RD, Jarrett RJ, Keen H, Viberti GC: Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: A twenty-three year follow-up study. Kidney Int 41:836-839, 1992

234. MacLeod JM, Lutale J, Marshall SM: Albumin excretion and vascular deaths in NIDDM. Diabetologia 38:610-616, 1995

235. Yudkin JS, Forrest RD, Jackson CA: Microalbuminuria as predictor of vascular disease in non-diabetic subjects. Islington Diabetes Survey. Lancet 2:530-533, 1988

236. Microvascular and acute complications in IDDM patients: The EURODIAB IDDM Complications Study. Diabetologia 37:278-285, 1994

237. Lloyd CE, Stephenson J, Fuller JH, Orchard TJ: A comparison of renal disease across two continents; The epidemiology of diabetes complications study and the EURODIAB IDDM Complications Study. Diabetes Care 19:219-225, 1996

238. Marshall SM, Alberti KG: Comparison of the prevalence and associated features of abnormal albumin excretion in insulin-dependent and non-insulin-dependent diabetes. Q J Med 70:61-71, 1989

239. Collins VR, Dowse GK, Finch CF, Zimmet PZ, Linnane AW: Prevalence and risk factors for micro- and macroalbuminuria in diabetic subjects and entire population of Nauru. Diabetes 38:1602-1610, 1989

240. Nelson RG, Kunzelman CL, Pettitt DJ, Saad MF, Bennett PH, Knowler WC: Albuminuria in type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in Pima Indians. Diabetologia 32:870-876, 1989

241. Simmons D, Shaw LM, Scott DJ, Kenealy T, Scragg RK: Diabetic nephropathy and microalbuminuria in the community. The South Auckland Diabetes Survey. Diabetes Care 17:1404-1410, 1994

242. Warram JH, Gearin G, Laffel L, Krolewski AS: Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. J Am Soc Nephrol 7:930-937, 1996

243. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM: Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of

GFR in health and in chronic kidney disease. J Am Soc Nephrol 16:459-466, 2005

244. Ibrahim H, Mondress M, Tello A, Fan Y, Koopmeiners J, Thomas W: An alternative formula to the Cockcroft-Gault and the Modification of Diet in Renal Diseases formulas in predicting GFR in individuals with type 1 diabetes. J Am Soc Nephrol 16:1051-1060, 2005

245. Caramori ML, Fioretto P, Mauer M: Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: An indicator of more advanced glomerular lesions. Diabetes 52:1036-1040, 2003

246. Lane PH, Steffes MW, Mauer SM: Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. Diabetes 41:581-586, 1992

247. Brito PL, Fioretto P, Drummond K, et al: Proximal tubular basement membrane width in insulin-dependent diabetes mellitus. Kidney Int 53:754-761, 1998

248. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC: Structural-functional relationships in diabetic nephropathy. J Clin Invest 74:1143-1155, 1984

249. Hovind P, Rossing P, Tarnow L, Toft H, Parving J, Parving HH: Remission of nephrotic-range albuminuria in type 1 diabetic patients. Diabetes Care 24:1972-1977, 2001

250. Viberti GC, Bilous RW, Mackintosh D, Keen H: Monitoring glomerular function in diabetic nephropathy. A prospective study. Am J Med 74:256-264, 1983

251. Parving HH, Gall MA, Skott P, et al: Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. Kidney Int 41:758-762, 1992

252. Nosadini R, Velussi M, Brocco E, et al: Course of renal function in type 2 diabetic patients with abnormalities of albumin excretion rate. Diabetes 49:476-484, 2000

253. Amoah E, Glickman JL, Malchoff CD, Sturgill BC, Kaiser DL, Bolton WK: Clinical identification of nondiabetic renal disease in diabetic patients with type I and type II disease presenting with renal dysfunction. Am J Nephrol 8:204-211, 1988

254. Christensen PK, Gall MA, Parving HH: Course of glomerular filtration rate in albuminuric type 2 diabetic patients with or without diabetic glomerulopathy. Diabetes Care 23:B14-B20, 2000 (suppl 2)

255. Fioretto P, Mauer M, Brocco E, et al: Patterns of renal injury in NIDDM patients with microalbuminuria. Diabetologia 39:1569-1576, 1996

256. John GT, Date A, Korula A, Jeyaseelan L, Shastry JC, Jacob CK: Nondiabetic renal disease in noninsulin-dependent diabetics in a south Indian hospital. Nephron 67:441-443, 1994

257. Kleinknecht D, Bennis D, Altman JJ: Increased prevalence of non-diabetic renal pathology in type II diabetes mellitus. Nephrol Dial Transplant 7:1258-1259, 1992

258. Mak SK, Gwi E, Chan KW, et al: Clinical predictors of non-diabetic renal disease in patients with non-insulin dependent diabetes mellitus. Nephrol Dial Transplant 12: 2588-2591, 1997

259. Olsen S, Mogensen CE: How often is NIDDM complicated with non-diabetic renal disease? An analysis of renal biopsies and the literature. Diabetologia 39:1638-1645, 1996

260. Richards NT, Greaves I, Lee SJ, Howie AJ, Adu D, Michael J: Increased prevalence of renal biopsy findings other than diabetic glomerulopathy in type II diabetes mellitus. Nephrol Dial Transplant 7:397-399, 1992

261. Serra A, Romero R, Bayes B, Lopez D, Bonet J: Is there a need for changes in renal biopsy criteria in proteinuria in type 2 diabetes? Diabetes Res Clin Pract 58:149-153, 2002

262. Wong TY, Choi PC, Szeto CC, et al: Renal outcome in type 2 diabetic patients with or without coexisting nondiabetic nephropathies. Diabetes Care 25:900-905, 2002

263. Giorgino F, Laviola L, Cavallo Perin P, Solnica B, Fuller J, Chaturvedi N: Factors associated with progression to macroalbuminuria in microalbuminuric type 1 diabetic patients: The EURODIAB Prospective Complications Study. Diabetologia 47:1020-1028, 2004

264. Hovind P, Tarnow L, Parving HH: Remission and regression of diabetic nephropathy. Curr Hypertens Rep 6:377-382, 2004

265. Bognetti E, Calori G, Meschi F, Macellaro P, Bonfanti R, Chiumello G: Prevalence and correlations of early microvascular complications in young type I diabetic patients: Role of puberty. J Pediatr Endocrinol Metab 10:587-592, 1997

266. Holl RW, Grabert M, Thon A, Heinze E: Urinary excretion of albumin in adolescents with type 1 diabetes: Persistent versus intermittent microalbuminuria and relationship to duration of diabetes, sex, and metabolic control. Diabetes Care 22:1555-1560, 1999

267. Holl RW, Pavlovic M, Heinze E, Thon A: Circadian blood pressure during the early course of type 1 diabetes. Analysis of 1,011 ambulatory blood pressure recordings in 354 adolescents and young adults. Diabetes Care 22:1151-1157, 1999

268. Kostraba JN, Dorman JS, Orchard TJ, et al: Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. Diabetes Care 12:686-693, 1989

269. Olsen BS, Sjolie AK, Hougaard P, et al: The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes. J Diabetes Complications 18:160-164, 2004

270. Pavlovic M, Holl RW, Haeberle U, et al: Angiotensin I converting enzyme and angiotensinogen gene polymorphisms related to 24-h blood pressure in paediatric type I diabetes mellitus. Eur J Pediatr 158:18-23, 1999

271. Drummond K, Mauer M: The early natural history of nephropathy in type 1 diabetes: II. Early renal structural changes in type 1 diabetes. Diabetes 51:1580-1587, 2002

272. Nelson RG, Newman JM, Knowler WC, et al: Incidence of end-stage renal disease in type 2 (non-insulin-dependent) diabetes mellitus in Pima Indians. Diabetologia 31:730-736, 1988

273. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G: Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care 27:195-200, 2004

274. Eiro M, Katoh T, Watanabe T: Risk factors for bleeding complications in percutaneous renal biopsy. Clin Exp Nephrol 9:40-45, 2005

275. Whittier WL, Korbet SM: Timing of complications in percutaneous renal biopsy. J Am Soc Nephrol 15:142-147, 2004

276. Korbet SM: Percutaneous renal biopsy. Semin Nephrol 22:254-267, 2002

277. Whittier WL, Korbet SM: Renal biopsy: update. Curr Opin Nephrol Hypertens 13:661-665, 2004

278. Manno C, Strippoli GF, Arnesano L, et al: Predictors of bleeding complications in percutaneous ultrasound-guided renal biopsy. Kidney Int 66:1570-1577, 2004

279. Mattix H, Singh AK: Is the bleeding time predictive of bleeding prior to a percutaneous renal biopsy? Curr Opin Nephrol Hypertens 8:715-718, 1999

280. Mendelssohn DC, Cole EH: Outcomes of percutaneous kidney biopsy, including those of solitary native kidneys. Am J Kidney Dis 26:580-585, 1995

281. Cahill RA, McGreal GT, Crowe BH, et al: Duration of increased bleeding tendency after cessation of aspirin therapy. J Am Coll Surg 200:564-573; quiz, A559-A561, 2005

282. Donovan KL, Thomas DM, Wheeler DC, Macdougall IC, Williams JD: Experience with a new method for percutaneous renal biopsy. Nephrol Dial Transplant 6:731-733, 1991

283. Kearon C, Hirsh J: Management of anticoagulation before and after elective surgery. N Engl J Med 336:1506-1511, 1997

284. Nass K, O'Neill WC: Bedside renal biopsy: Ultrasound guidance by the nephrologist. Am J Kidney Dis 34:955-959, 1999

285. Peterson P, Hayes TE, Arkin CF, et al: The preoperative bleeding time test lacks clinical benefit: College of American Pathologists' and American Society of Clinical Pathologists' position article. Arch Surg 133:134-139, 1998

286. Stiles KP, Hill C, LeBrun CJ, Reinmuth B, Yuan CM, Abbott KC: The impact of bleeding times on major complication rates after percutaneous real-time ultrasound-guided renal biopsies. J Nephrol 14:275-279, 2001

287. Zeigler ZR, Megaludis A, Fraley DS: Desmopressin (d-DAVP) effects on platelet rheology and von Willebrand factor activities in uremia. Am J Hematol 39:90-95, 1992

288. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ: Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 348:491-499, 2003

289. Barrett BJ, Parfrey PS, Vavasour HM, et al: Contrast nephropathy in patients with impaired renal function: High versus low osmolar media. Kidney Int 41:1274-1279, 1992

290. Rudnick MR, Goldfarb S, Wexler L, et al: Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial. The Iohexol Cooperative Study. Kidney Int 47:254-261, 1995

291. Parfrey PS, Griffiths SM, Barrett BJ, et al: Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med 320:143-149, 1989

292. Rihal CS, Textor SC, Grill DE, et al: Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 105:2259-2264, 2002

293. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW: Acute renal failure after coronary intervention: Incidence, risk factors, and relationship to mortality. Am J Med 103:368-375, 1997

294. Nolin TD, Himmelfarb J, Matzke GR: Drug-induced kidney disease, in DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM (eds): Pharmacotherapy: A Physiological Approach. New York, NY, McGraw-Hill, 2005, pp 871-890

295. Merten GJ, Burgess WP, Gray LV, et al: Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. JAMA 291:2328-2334, 2004

296. Sadeghi HM, Stone GW, Grines CL, et al: Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. Circulation 108:2769-2775, 2003

297. Manske CL, Sprafka JM, Strony JT, Wang Y: Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 89:615-620, 1990

298. Mueller C, Buerkle G, Buettner HJ, et al: Prevention of contrast media-associated nephropathy: Randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 162:329-336, 2002

299. Thomsen HS: Guidelines for contrast media from the European Society of Urogenital Radiology. AJR Am J Roentgenol 181:1463-1471, 2003

300. Marenzi G, Marana I, Lauri G, et al: The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 349:1333-1340, 2003

301. Pannu N, Manns B, Lee H, Tonelli M: Systematic review of the impact of *N*-acetylcysteine on contrast nephropathy. Kidney Int 65:1366-1374, 2004

302. Alonso A, Lau J, Jaber BL, Weintraub A, Sarnak MJ: Prevention of radiocontrast nephropathy with *N*-acetylcysteine in patients with chronic kidney disease: A meta-analysis of randomized, controlled trials. Am J Kidney Dis 43:1-9, 2004

303. Barrett BJ, Parfrey PS: Clinical practice. Preventing nephropathy induced by contrast medium. N Engl J Med 354:379-386, 2006

304. Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers RE, Fuller JH: Microalbuminuria in type 1 diabetes: Rates, risk factors and glycemic threshold. Kidney Int 60:219-227, 2001

305. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS: A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. Diabetes 50:2842-2849, 2001

306. Hovind P, Tarnow L, Rossing P, et al: Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: Inception cohort study. BMJ 328:1105, 2004

307. Agardh CD, Agardh E, Torffvit O: The association between retinopathy, nephropathy, cardiovascular disease and long-term metabolic control in type 1 diabetes mellitus: A 5 year follow-up study of 442 adult patients in routine care. Diabetes Res Clin Pract 35:113-121, 1997

308. Osterby R, Hartmann A, Bangstad HJ: Structural changes in renal arterioles in type I diabetic patients. Diabetologia 45:542-549, 2002

309. Torffvit O, Agardh CD: The predictive value of albuminuria for cardiovascular and renal disease. A 5-year

follow-up study of 476 patients with type I diabetes mellitus. J Diabetes Complications 7:49-56, 1993

310. Schultz CJ, Neil HA, Dalton RN, Dunger DB: Oxforn Regional Prospective Study G: Risk of nephropathy can be detected before the onset of microalbuminuria during the early years after diagnosis of type 1 diabetes. Diabetes Care 23:1811-1815, 2000

311. Rachmani R, Levi Z, Lidar M, Slavachevski I, HalfOnn E, Ravid M: Considerations about the threshold value of microalbuminuria in patients with diabetes mellitus: Lessons from an 8-year follow-up study of 599 patients. Diabetes Res Clin Pract 49:187-194, 2000

312. Nelson RG, Bennett PH, Beck GJ, et al: Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. Diabetic Renal Disease Study Group. N Engl J Med 335:1636-1642, 1996

313. Nelson RG, Knowler WC, McCance DR, et al: Determinants of end-stage renal disease in Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus and proteinuria. Diabetologia 36:1087-1093, 1993

314. Sosenko JM, Hu D, Welty T, Howard BV, Lee E, Robbins DC: Albuminuria in recent-onset type 2 diabetes: The Strong Heart Study. Diabetes Care 25:1078-1084, 2002

315. Chan JC, Cheung CK, Cheung MY, Swaminathan R, Critchley JA, Cockram CS: Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM. Diabetes Care 18:1013-1016, 1995

316. Torffvit O, Agardh CD: The impact of metabolic and blood pressure control on incidence and progression of nephropathy. A 10-year study of 385 type 2 diabetic patients. J Diabetes Complications 15:307-313, 2001

317. John L, Rao PS, Kanagasabapathy AS: Rate of progression of albuminuria in type II diabetes. Five-year prospective study from south India. Diabetes Care 17:888-890, 1994

318. Bruno G, Biggeri A, Merletti F, et al: Low incidence of end-stage renal disease and chronic renal failure in type 2 diabetes: A 10-year prospective study. Diabetes Care 26:2353-2358, 2003

319. Lane PH, Steffes MW, Fioretto P, Mauer SM: Renal interstitial expansion in insulin-dependent diabetes mellitus. Kidney Int 43:661-667, 1993

320. Harris RD, Steffes MW, Bilous RW, Sutherland DE, Mauer SM: Global glomerular sclerosis and glomerular arteriolar hyalinosis in insulin dependent diabetes. Kidney Int 40:107-114, 1991

321. Ellis EN, Steffes MW, Goetz FC, Sutherland DE, Mauer SM: Glomerular filtration surface in type I diabetes mellitus. Kidney Int 29:889-894, 1986

322. Fioretto P, Steffes MW, Sutherland DE, Mauer M: Sequential renal biopsies in insulin-dependent diabetic patients: Structural factors associated with clinical progression. Kidney Int 48:1929-1935, 1995

323. Najafian B, Kim Y, Crosson JT, Mauer M: Atubular glomeruli and glomerulotubular junction abnormalities in diabetic nephropathy. J Am Soc Nephrol 14:908-917, 2003

324. Bangstad HJ, Osterby R, DahlJorgensen K, et al: Early glomerulopathy is present in young, type 1 (insulin-dependent) diabetic patients with microalbuminuria. Diabetologia 36:523-529, 1993

325. Ellis EN, Warady BA, Wood EG, et al: Renal structural-functional relationships in early diabetes mellitus. Pediatr Nephrol 11:584-591, 1997

326. Bjorn SF, Bangstad HJ, Hanssen KF, et al: Glomerular epithelial foot processes and filtration slits in IDDM patients. Diabetologia 38:1197-1204, 1995

327. White KE, Bilous RW: Type 2 diabetic patients with nephropathy show structural-functional relationships that are similar to type 1 disease. J Am Soc Nephrol 11:1667-1673, 2000

328. Christensen PK, Larsen S, Horn T, Olsen S, Parving HH: Causes of albuminuria in patients with type 2 diabetes without diabetic retinopathy. Kidney Int 58:1719-1731, 2000

329. Pagtalunan ME, Miller PL, JumpingEagle S, et al: Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest 99:342-348, 1997

330. Christensen PK, Larsen S, Horn T, Olsen S, Parving HH: Renal function and structure in albuminuric type 2 diabetic patients without retinopathy. Nephrol Dial Transplant 16:2337-2347, 2001

331. Matsumae T, Jimi S, Uesugi N, Takebayashi S, Naito S: Clinical and morphometrical interrelationships in patients with overt nephropathy induced by non-insulin-dependent diabetes mellitus. A light- and electron-microscopy study. Nephron 81:41-48, 1999

332. Meyer TW, Bennett PH, Nelson RG: Podocyte number predicts long-term urinary albumin excretion in Pima Indians with type II diabetes and microalbuminuria. Diabetologia 42:1341-1344, 1999

333. Osterby R, Tapia J, Nyberg G, et al: Renal structures in type 2 diabetic patients with elevated albumin excretion rate. APMIS 109:751-761, 2001

334. Lemley KV, Abdullah I, Myers BD, et al: Evolution of incipient nephropathy in type 2 diabetes mellitus. Kidney Int 58:1228-1237, 2000

335. Klein R, Zinman B, Gardiner R, et al: ReninAngiotensin SS: The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: The Renin-Angiotensin System Study. Diabetes 54:527-533, 2005

336. Schwartz MM, Lewis EJ, LeonardMartin T, Lewis JB, Batlle D: Renal pathology patterns in type II diabetes mellitus: Relationship with retinopathy. The Collaborative Study Group. Nephrol Dial Transplant 13:2547-2552, 1998

337. Kanauchi M, Kawano T, Uyama H, Shiiki H, Dohi K: Discordance between retinopathy and nephropathy in type 2 diabetes. Nephron 80:171-174, 1998

338. Stone GW, McCullough PA, Tumlin JA, et al: Fenoldopam mesylate for the prevention of contrast-induced nephropathy: A randomized controlled trial. JAMA 290:2284-2291, 2003

339. Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS: Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 31:674-680, 1998

340. Wang A, Holcslaw T, Bashore TM, et al: Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. Kidney Int 57:1675-1680, 2000

341. Solomon R, Werner C, Mann D, D'Elia J, Silva P: Effects of saline, mannitol, and furosemide to prevent acute

decreases in renal function induced by radiocontrast agents. N Engl J Med 331:1416-1420, 1994

342. Tumlin JA, Wang A, Murray PT, Mathur VS: Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: A pilot trial in the prevention of contrast nephropathy. Am Heart J 143:894-903, 2002

343. Weisberg LS, Kurnik PB, Kurnik BR: Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 45:259-265, 1994

344. Kini AA, Sharma SK: Managing the high-risk patient: Experience with fenoldopam, a selective dopamine receptor agonist, in prevention of radiocontrast nephropathy during percutaneous coronary intervention. Rev Cardiovasc Med 2:S25, 2001 (suppl 1)

345. Louis BM, Hoch BS, Hernandez C, et al: Protection from the nephrotoxicity of contrast dye. Ren Fail 18:639-646, 1996

346. Kapoor A, Kumar S, Gulati S, Gambhir S, Sethi RS, Sinha N: The role of theophylline in contrast-induced nephropathy: A case-control study. Nephrol Dial Transplant 17:1936-1941, 2002

347. Kapoor A, Sinha N, Sharma RK, et al: Use of dopamine in prevention of contrast induced acute renal failure—A randomised study. Int J Cardiol 53:233-236, 1996

348. Sterner G, Frennby B, Kurkus J, Nyman U: Does post-angiographic hemodialysis reduce the risk of contrast-medium nephropathy? Scand J Urol Nephrol 34:323-326, 2000

349. Madyoon H: Clinical experience with the use of fenoldopam for prevention of radiocontrast nephropathy in high-risk patients. Rev Cardiovasc Med 2:S26-30, 2001 (suppl 1)

350. Taliercio CP, Vlietstra RE, Ilstrup DM, et al: A randomized comparison of the nephrotoxicity of iopamidol and diatrizoate in high risk patients undergoing cardiac angiography. J Am Coll Cardiol 17:384-390, 1991

351. Lautin EM, Freeman NJ, Schoenfeld AH, et al: Radiocontrast-associated renal dysfunction: A comparison of lower-osmolality and conventional high-osmolality contrast media. AJR Am J Roentgenol 157:59-65, 1991

352. Lundqvist S, Holmberg G, Jakobsson G, et al: Assessment of possible nephrotoxicity from iohexol in patients with normal and impaired renal function. Acta Radiol 39:362-367, 1998

353. Bojestig M, Arnqvist HJ, Karlberg BE, Ludvigsson J: Glycemic control and prognosis in type I diabetic patients with microalbuminuria. Diabetes Care 19:313-317, 1996

354. Chantelau E, Wichmann P: Pathological proteinuria in patients with insulin-dependent diabetes mellitus: Relation to intensive insulin therapy. Exp Clin Endocrinol 99:164-168, 1992

355. Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D: Glucose control and the renal and retinal complications of insulin-dependent diabetes. JAMA 261:1155-1160, 1989

356. Coonrod BA, Ellis D, Becker DJ, et al: Predictors of microalbuminuria in individuals with IDDM. Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care 16:1376-1383, 1993

357. Klein R, Klein BE, Moss SE: The incidence of gross proteinuria in people with insulin-dependent diabetes mellitus. Arch Intern Med 151:1344-1348, 1991

358. Krolewski AS, Laffel LM, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med 332:1251-1255, 1995

359. McCance DR, Hadden DR, Atkinson AB, Johnston H, Kennedy L: The relationship between long-term glycaemic control and diabetic nephropathy. Q J Med 82:53-61, 1992

360. The Kroc Collaborative Study Group: Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. N Engl J Med 311:365-372, 1984

361. Beck-Nielsen H, Olesen T, Mogensen CE, et al: Effect of near normoglycemia for 5 years on progression of early diabetic retinopathy and renal involvement. Diabetes Res 15:185-190, 1990

362. Dahl-Jorgensen K, Bjoro T, Kierulf P, Sandvik L, Bangstad HJ, Hanssen KF: Long-term glycemic control and kidney function in insulin-dependent diabetes mellitus. Kidney Int 41:920-923, 1992

363. Dahl-Jorgensen K, Hanssen KF, Kierulf P, Bjoro T, Sandvik L, Aagenaes O: Reduction of urinary albumin excretion after 4 years of continuous subcutaneous insulin infusion in insulin-dependent diabetes mellitus. The Oslo Study. Acta Endocrinol (Copenh) 117:19-25, 1988

364. Feldt-Rasmussen B, Mathiesen ER, Deckert T: Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. Lancet 2:1300-1304, 1986

365. Feldt-Rasmussen B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T: Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: An update of the Steno studies. Diabetologia 34:164-170, 1991

366. Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T: Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. Diabetes 34:S74-S79, 1985 (suppl 3)

367. Wang PH, Lau J, Chalmers TC: Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. Lancet 341:1306-1309, 1993

368. The Diabetes Control and Complications (DCCT) Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int 47:1703-1720, 1995

369. Gilbert RE, Tsalamandris C, Bach LA, et al: Long-term glycemic control and the rate of progression of early diabetic kidney disease. Kidney Int 44:855-859, 1993

370. Kawazu S, Tomono S, Shimizu M, et al: The relationship between early diabetic nephropathy and control of plasma glucose in non-insulin-dependent diabetes mellitus. The effect of glycemic control on the development and progression of diabetic nephropathy in an 8-year follow-up study. J Diabetes Complications 8:13-17, 1994

371. Klein R, Klein BE, Moss SE, Cruickshanks KJ: Ten-year incidence of gross proteinuria in people with diabetes. Diabetes 44:916-923, 1995

372. Nelson RG, Knowler WC, Pettitt DJ, Hanson RL, Bennett PH: Incidence and determinants of elevated urinary albumin excretion in Pima Indians with NIDDM. Diabetes Care 18:182-187, 1995

373. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. Diabetes Care 21:116-120, 1998

374. Klein R, Klein BE, Moss SE, Cruickshanks KJ, Brazy PC: The 10-year incidence of renal insufficiency in people with type 1 diabetes. Diabetes Care 22:743-751, 1999

375. Mulec H, Blohme G, Grande B, Bjorck S: The effect of metabolic control on rate of decline in renal function in insulin-dependent diabetes mellitus with overt diabetic nephropathy. Nephrol Dial Transplant 13:651-655, 1998

376. Nyberg G, Blohme G, Norden G: Impact of metabolic control in progression of clinical diabetic nephropathy. Diabetologia 30:82-86, 1987

377. Breyer JA, Bain RP, Evans JK, et al: Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. The Collaborative Study Group. Kidney Int 50:1651-1658, 1996

378. Parving HH, Rossing P, Hommel E, Smidt UM: Angiotensin-converting enzyme inhibition in diabetic nephropathy: Ten years' experience. Am J Kidney Dis 26:99-107, 1995

379. Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI: Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens 17:7-12, 2003

380. Imano E, Kanda T, Nakatani Y, et al: Effect of troglitazone on microalbuminuria in patients with incipient diabetic nephropathy. Diabetes Care 21:2135-2139, 1998

381. Nakamura T, Ushiyama C, Osada S, Hara M, Shimada N, Koide H: Pioglitazone reduces urinary podocyte excretion in type 2 diabetes patients with microalbuminuria. Metabolism 50:1193-1196, 2001

382. Nakamura T, Ushiyama C, Suzuki S, et al: Effect of troglitazone on urinary albumin excretion and serum type IV collagen concentrations in type 2 diabetic patients with microalbuminuria or macroalbuminuria. Diabet Med 18:308-313, 2001

383. The American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: The AACE system of intensive diabetes self-management—2002 Update. Endocr Pract 8:S40-S82, 2002 (suppl 1)

384. The Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 46:271-286, 1997

385. Asplund K, Wiholm BE, Lundman B: Severe hypoglycaemia during treatment with glipizide. Diabet Med 8:726-731, 1991

386. Jonsson A, Rydberg T, Sterner G, Melander A: Pharmacokinetics of glibenclamide and its metabolites in diabetic patients with impaired renal function. Eur J Clin Pharmacol 53:429-435, 1998

387. Rosenkranz B, Profozic V, Metelko Z, Mrzljak V, Lange C, Malerczyk V: Pharmacokinetics and safety of glimepiride at clinically effective doses in diabetic patients with renal impairment. Diabetologia 39:1617-1624, 1996

388. Inoue T, Shibahara N, Miyagawa K, et al: Pharmacokinetics of nateglinide and its metabolites in subjects with type 2 diabetes mellitus and renal failure. Clin Nephrol 60:90-95, 2003

389. Nagai T, Imamura M, Iizuka K, Mori M: Hypoglycemia due to nateglinide administration in diabetic patient with chronic renal failure. Diabetes Res Clin Pract 59:191-194, 2003

390. Schumacher S, Abbasi I, Weise D, et al: Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. Eur J Clin Pharmacol 57:147-152, 2001

391. Davidson MB, Peters AL: An overview of metformin in the treatment of type 2 diabetes mellitus. Am J Med 102:99-110, 1997

392. Thompson-Culkin K, Zussman B, Miller AK, Freed MI: Pharmacokinetics of rosiglitazone in patients with end-stage renal disease. J Int Med Res 30:391-399, 2002

393. Morgan L, Marenah CB, Jeffcoate WJ, Morgan AG: Glycated proteins as indices of glycaemic control in diabetic patients with chronic renal failure. Diabet Med 13:514-519, 1996

394. Joy MS, Cefalu WT, Hogan SL, Nachman PH: Long-term glycemic control measurements in diabetic patients receiving hemodialysis. Am J Kidney Dis 39:297-307, 2002

395. Little RR, Tennill AL, Rohlfing C, et al: Can glycohemoglobin be used to assess glycemic control in patients with chronic renal failure? Clin Chem 48:784-786, 2002

396. Saloranta C, Groop L, Ylinen K, Teramo K, Tolppanen EM, Tallgren LG: The usefulness of micro- and macrochromatographic determinations of glycohemoglobin in diabetic patients with nephropathy. Clin Nephrol 25:186-192, 1986

397. Ahmed J, Ward TP, Bursell SE, Aiello LM, Cavallerano JD, Vigersky RA: The sensitivity and specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. Diabetes Care 29:2205-2209, 2006

398. Dailey GE, Boden GH, Creech RH, et al: Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism 49:1491-1495, 2000

399. Reichard P, Pihl M, Rosenqvist U, Sule J: Complications in IDDM are caused by elevated blood glucose level: The Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. Diabetologia 39:1483-1488, 1996

400. Barnett AH, Bain SC, Bouter P, et al: Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 351:1952-1961, 2004

401. Bakris GL, Williams M, Dworkin L, et al: Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 36:646-661, 2000

402. Klag MJ, Whelton PK, Randall BL, et al: Blood pressure and end-stage renal disease in men. N Engl J Med 334:13-18, 1996

403. Perry HM Jr, Miller JP, Fornoff JR, et al: Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension 25:587-594, 1995

404. Bakris GL, Slataper R, Vicknair N, Sadler R: ACE inhibitor mediated reductions in renal size and microalbuminuria in normotensive, diabetic subjects. J Diabetes Complications 8:2-6, 1994

405. Parving HH, Hovind P: Microalbuminuria in type 1 and type 2 diabetes mellitus: Evidence with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers for treating early and preventing clinical nephropathy. Curr Hypertens Rep 4:387-393, 2002

406. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S: Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int 50:1641-1650, 1996

407. Bakris GL, Smith AC, Richardson DJ, et al: Impact of an ACE inhibitor and calcium antagonist on microalbuminuria and lipid subfractions in type 2 diabetes: A randomised, multi-centre pilot study. J Hum Hypertens 16:185-191, 2002

408. Bakris GL, Weir M: ACE inhibitors and protection against kidney disease progression in patients with type 2 diabetes: What's the evidence. J Clin Hypertens (Greenwich) 4:420-423, 2002

409. Estacio RO, Jeffers BW, Gifford N, Schrier RW: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 23:B54-B64, 2000 (suppl 2)

410. Bakris GL: The role of combination antihypertensive therapy and the progression of renal disease hypertension: Looking toward the next millennium. Am J Hypertens 11:158S-162S, 1998 (suppl)

411. Melian EB, Jarvis B: Candesartan cilexetil plus hydrochlorothiazide combination: A review of its use in hypertension. Drugs 62:787-816, 2002

412. Weir MR, Smith DH, Neutel JM, Bedigian MP: Valsartan alone or with a diuretic or ACE inhibitor as treatment for African American hypertensives: Relation to salt intake. Am J Hypertens 14:665-671, 2001

413. Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A: Differential effects of calcium antagonist subclasses on markers of nephropathy progression. Kidney Int 65:1991-2002, 2004

414. Gansevoort RT, Sluiter WJ, Hemmelder MH, de Zeeuw D, de Jong PE: Antiproteinuric effect of blood-pressure-lowering agents: A meta-analysis of comparative trials. Nephrol Dial Transplant 10:1963-1974, 1995

415. Chan JC, Critchley JA, Tomlinson B, Chan TY, Cockram CS: Antihypertensive and anti-albuminuric effects of losartan potassium and felodipine in Chinese elderly hypertensive patients with or without non-insulin-dependent diabetes mellitus. Am J Nephrol 17:72-80, 1997

416. Sica DA, Bakris GL: Type 2 diabetes: RENAAL and IDNT—The emergence of new treatment options. J Clin Hypertens (Greenwich) 4:52-57, 2002

417. Viberti G, Wheeldon NM: Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: A blood pressure-independent effect. Circulation 106:672-678, 2002

418. Bakris GL, Mangrum A, Copley JB, Vicknair N, Sadler R: Effect of calcium channel or beta-blockade on the progression of diabetic nephropathy in African Americans. Hypertension 29:744-750, 1997

419. Ruggenenti P, Fassi A, Ilieva AP, et al: Preventing microalbuminuria in type 2 diabetes. N Engl J Med 351:1941-1951, 2004

420. Jacobsen P, Andersen S, Jensen BR, Parving HH: Additive effect of ACE inhibition and angiotensin II receptor blockade in type I diabetic patients with diabetic nephropathy. J Am Soc Nephrol 14:992-999, 2003

421. Jacobsen P, Andersen S, Rossing K, Jensen BR, Parving HH: Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. Kidney Int 63:1874-1880, 2003

422. Mogensen CE, Neldam S, Tikkanen I, et al: Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The Candesartan And Lisinopril Microalbuminuria (CALM) Study. BMJ 321:1440-1444, 2000

423. Hart PD, Bakris GL: Managing hypertension in the diabetic patient, in Egan BM, Basile JN, Lackland DT (eds): Hot Topics in Hypertension. Philadelphia, PA, Hanley & Belfus, 2004, pp 249-252

424. Schrier RW, Estacio RO, Esler A, Mehler P: Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 61:1086-1097, 2002

425. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 21:1011-1053, 2003

426. Nakao N, Seno H, Kasuga H, Toriyama T, Kawahara H, Fukagawa M: Effects of combination treatment with losartan and trandolapril on office and ambulatory blood pressures in non-diabetic renal disease: A COOPERATE-ABP substudy. Am J Nephrol 24:543-548, 2004

427. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. Lancet 361:117-124, 2003

428. Casas JP, Chua W, Loukogeorgakis S, et al: Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. Lancet 366:2026-2033, 2005

429. Tarnow L, Sato A, Ali S, Rossing P, Nielsen FS, Parving HH: Effects of nisoldipine and lisinopril on left ventricular mass and function in diabetic nephropathy. Diabetes Care 22:491-494, 1999

430. Sawicki PT: Stabilization of glomerular filtration rate over 2 years in patients with diabetic nephropathy under intensified therapy regimens. Diabetes Treatment and Teaching Programmes Working Group. Nephrol Dial Transplant 12:1890-1899, 1997

431. Velussi M, Brocco E, Frigato F, et al: Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. Diabetes 45:216-222, 1996

432. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317:703-713, 1998

433. National Diabetes Data Group: Diabetes in America (ed 2). Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995

434. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 20:614-620, 1997

435. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 287:2542-2551, 2002

436. Vijan S, Hayward RA: Treatment of hypertension in type 2 diabetes mellitus: Blood pressure goals, choice of agents, and setting priorities in diabetes care. Ann Intern Med 138:593-602, 2003

437. Barrett-Connor E, Grundy SM, Holdbrook MJ: Plasma lipids and diabetes mellitus in an adult community. Am J Epidemiol 115:657-663, 1982

438. Feingold KR, Grunfeld C, Pang M, Doerrler W, Krauss RM: LDL subclass phenotypes and triglyceride metabolism in non-insulin-dependent diabetes. Arterioscler Thromb 12:1496-1502, 1992

439. Jenkins AJ, Lyons TJ, Zheng D, et al: Lipoproteins in the DCCT/EDIC cohort: Associations with diabetic nephropathy. Kidney Int 64:817-828, 2003

440. Quaschning T, Schomig M, Keller M, et al: Non-insulin-dependent diabetes mellitus and hypertriglyceridemia impair lipoprotein metabolism in chronic hemodialysis patients. J Am Soc Nephrol 10:332-341, 1999

441. Armitage J, Bowman L: Cardiovascular outcomes among participants with diabetes in the recent large statin trials. Curr Opin Lipidol 15:439-446, 2004

442. Cheung BM, Lauder IJ, Lau CP, Kumana CR: Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. Br J Clin Pharmacol 57:640-651, 2004

443. Shepherd J, Cobbe SM, Ford I, et al: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 333:1301-1307, 1995

444. Sacks FM, Pfeffer MA, Moye LA, et al: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335:1001-1009, 1996

445. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 339:1349-1357, 1998

446. Wanner C, Krane V, Marz W, et al: Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D Study): Demographic and baseline characteristics. Kidney Blood Press Res 27:259-266, 2004

447. Iseki K, Yamazato M, Tozawa M, Takishita S: Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. Kidney Int 61:1887-1893, 2002

448. Seliger SL, Weiss NS, Gillen DL, et al: HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. Kidney Int 61:297-304, 2002

449. Mason NA, Bailie GR, Satayathum S, et al: HMG-coenzyme a reductase inhibitor use is associated with mortality reduction in hemodialysis patients. Am J Kidney Dis 45:119-126, 2005

450. Hommel E, Andersen P, Gall MA, et al: Plasma lipoproteins and renal function during simvastatin treatment in diabetic nephropathy. Diabetologia 35:447-451, 1992

451. Nakamura T, Ushiyama C, Hirokawa K, Osada S, Shimada N, Koide H: Effect of cerivastatin on urinary albumin excretion and plasma endothelin-1 concentrations in type 2 diabetes patients with microalbuminuria and dyslipidemia. Am J Nephrol 21:449-454, 2001

452. Lam KS, Cheng IK, Janus ED, Pang RW: Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. Diabetologia 38:604-609, 1995

453. Nagai T, Tomizawa T, Nakajima K, Mori M: Effect of bezafibrate or pravastatin on serum lipid levels and albuminuria in NIDDM patients. J Atheroscler Thromb 7:91-96, 2000

454. Tonolo G, Melis MG, Formato M, et al: Additive effects of simvastatin beyond its effects on LDL cholesterol in hypertensive type 2 diabetic patients. Eur J Clin Invest 30:980-987, 2000

455. Appel GB, Radhakrishnan J, Avram MM, et al: Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care 26:1402-1407, 2003

456. Nielsen S, Schmitz O, Moller N, et al: Renal function and insulin sensitivity during simvastatin treatment in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. Diabetologia 36:1079-1086, 1993

457. Smulders YM, van Eeden AE, Stehouwer CD, Weijers RN, Slaats EH, Silberbusch J: Can reduction in hypertriglyceridaemia slow progression of microalbuminuria in patients with non-insulin-dependent diabetes mellitus? Eur J Clin Invest 27:997-1002, 1997

458. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C: ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 40:567-572, 2002

459. Phillips PS, Haas RH, Bannykh S, et al: Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 137:581-585, 2002

460. LaRosa JC, Grundy SM, Waters DD, et al: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352:1425-1435, 2005

461. Zhang A, Vertommen J, Van Gaal L, De Leeuw I: Effects of pravastatin on lipid levels, in vitro oxidizability of non-HDL lipoproteins and microalbuminuria in IDDM patients. Diabetes Res Clin Pract 29:189-194, 1995

462. Pijls LT, de Vries H, Donker AJ, van Eijk JT: The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: A randomized trial. Nephrol Dial Transplant 14:1445-1453, 1999

463. Vora JP, Thomas D, Peters JR, Coles GA, Williams JD: Preservation of renal haemodynamic response to an oral protein load in non-insulin-dependent diabetes mellitus. Diabet Med 10:715-719, 1993

464. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care 25:202-212, 2002

465. Cutler JA, Obarzanek E: Nutrition and blood pressure: Is protein one link? Toward a strategy of hypertension prevention. Ann Intern Med 143:74-75, 2005

466. Gross JL, Zelmanovitz T, Moulin CC, et al: Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: A randomized crossover trial. Diabetes Care 25:645-651, 2002

467. Food and Nutrition Board, Institute of Medicine of the National Academies: Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (macronutrients). Washington, DC, National Academies Press, 2005

468. Bouhanick B, Suraniti S, Berrut G, et al: Relationship between fat intake and glomerular filtration rate in normotensive insulin-dependent diabetic patients. Diabete Metab 21:168-172, 1995

469. Dullaart RP, Beusekamp BJ, Meijer S, Hoogenberg K, van Doormaal JJ, Sluiter WJ: Long-term effects of linoleic-acid-enriched diet on albuminuria and lipid levels in type 1 (insulin-dependent) diabetic patients with elevated urinary albumin excretion. Diabetologia 35:165-172, 1992

470. Hamazaki T, Takazakura E, Osawa K, Urakaze M, Yano S: Reduction in microalbuminuria in diabetics by eicosapentaenoic acid ethyl ester. Lipids 25:541-545, 1990

471. Mollsten AV, Dahlquist GG, Stattin EL, Rudberg S: Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. Diabetes Care 24:805-810, 2001

472. Rossing P, Hansen BV, Nielsen FS, Myrup B, Holmer G, Parving HH: Fish oil in diabetic nephropathy. Diabetes Care 19:1214-1219, 1996

473. Goeddeke-Merickel CM: The goals of comprehensive and integrated disease state management for diabetic kidney-disease patients. Adv Chronic Kidney Dis 12:236-242, 2005

474. McMurray SD, Johnson G, Davis S, McDougall K: Diabetes education and care management significantly improve patient outcomes in the dialysis unit. Am J Kidney Dis 40:566-575, 2002

475. Milas NC, Nowalk MP, Akpele L, et al: Factors associated with adherence to the dietary protein intervention in the Modification of Diet in Renal Disease Study. J Am Diet Assoc 95:1295-1300, 1995

476. Kris-Etherton PM, Harris WS, Appel LJ: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 106:2747-2757, 2002

477. Wiggins KL (ed): Nutrition care of adult pre-ESRD patients, in Guidelines for Nutrition Care of Renal Patients (ed 3). Chicago, IL, American Dietetic Asssociation, 2002, pp 6-13

478. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR: Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 324:78-84, 1991

479. Brouhard BH, LaGrone L: Effect of dietary protein restriction on functional renal reserve in diabetic nephropathy. Am J Med 89:427-431, 1990

480. Muhlhauser I, Prange K, Sawicki PT, et al: Effects of dietary sodium on blood pressure in IDDM patients with nephropathy. Diabetologia 39:212-219, 1996

481. Facchini FS, Saylor KL: A low-iron-available, polyphenol-enriched, carbohydrate-restricted diet to slow progression of diabetic nephropathy. Diabetes 52:1204-1209, 2003

482. Wheeler ML, Fineberg SE, Fineberg NS, Gibson RG, Hackward LL: Animal versus plant protein meals in individuals with type 2 diabetes and microalbuminuria: Effects on renal, glycemic, and lipid parameters. Diabetes Care 25:1277-1282, 2002

483. Bakris GL, Smith A: Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. Ann Intern Med 125:201-204, 1996

484. Saydah SH, Fradkin J, Cowie CC: Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 291:335-342, 2004

485. Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Menard J, for the DIABHYCAR-Study-Investigators: Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: Randomised, double blind, placebo controlled trial (the DIABHYCAR study). BMJ 328:495, 2004

486. UK Prospective Diabetes Study Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 317:713-720, 1998

487. Ahmad J, Siddiqui MA, Ahmad H: Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. Diabetes Care 20:1576-1581, 1997

488. Capes SE, Gerstein HC, Negassa A, Yusuf S: Enalapril prevents clinical proteinuria in diabetic patients with low ejection fraction. Diabetes Care 23:377-380, 2000

489. Gaede P, Hansen HP, Parving HH, Pedersen O: Impact of low-dose acetylsalicylic acid on kidney function in type 2 diabetic patients with elevated urinary albumin excretion rate. Nephrol Dial Transplant 18:539-542, 2003

490. Gaede P, Poulsen HE, Parving HH, Pedersen O: Double-blind, randomised study of the effect of combined treatment with vitamin C and E on albuminuria in type 2 diabetic patients. Diabet Med 18:756-760, 2001

491. Lonn E, Yusuf S, Hoogwerf B, et al: Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: Results of the HOPE study and MICRO-HOPE substudy. Diabetes Care 25:1919-1927, 2002

492. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 287:2563-2569, 2002

493. Manning PJ, Sutherland WH, Allum AR, de Jong SA, Jones SD: HRT does not improve urinary albumin excretion in postmenopausal diabetic women. Diabetes Res Clin Pract 60:33-39, 2003

494. Hoshino T, Ikeda T: Inhibitory effect of ibudilast on urinary albumin excretion in type 2 diabetes mellitus with microalbuminuria. Nephron 90:154-157, 2002

495. Shindo H, Tawata M, Yokomori N, Hosaka Y, Ohtaka M, Onaya T: Iloprost decreases urinary albumin excretion rate in patients with diabetic nephropathy. Diabetes Res Clin Pract 21:115-122, 1993

496. Young BA, Pugh JA, Maynard C, Reiber G: Diabetes and renal disease in veterans. Diabetes Care 27:B45-B49, 2004 (suppl 2)

497. Mau MK, West M, Sugihara J, Kamaka M, Mikami J, Cheng SF: Renal disease disparities in Asian and Pacific-based populations in Hawai'i. J Natl Med Assoc 95:955-963, 2003

498. Thompson CF, Simmons D, Collins JF, Cecil A: Predisposition to nephropathy in Polynesians is associated with family history of renal disease, not diabetes mellitus. Diabet Med 18:40-46, 2001

499. Pugh JA, Stern MP, Haffner SM, Eifler CW, Zapata M: Excess incidence of treatment of end-stage renal disease in Mexican Americans. Am J Epidemiol 127:135-144, 1988

500. Bowden DW, Colicigno CJ, Langefeld CD, et al: A genome scan for diabetic nephropathy in African Americans. Kidney Int 66:1517-1526, 2004

501. Gitter J, Langefeld CD, Rich SS, Pedley CF, Bowden DW, Freedman BI: Prevalence of nephropathy in black patients with type 2 diabetes mellitus. Am J Nephrol 22:35-41, 2002

502. Imperatore G, Knowler WC, Nelson RG, Hanson RL: Genetics of diabetic nephropathy in the Pima Indians. Curr Diab Rep 1:275-281, 2001

503. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV: Ethnic disparities in diabetic complications in an insured population. JAMA 287:2519-2527, 2002

504. Krop JS, Coresh J, Chambless LE, et al: A community-based study of explanatory factors for the excess risk for early renal function decline in blacks vs whites with diabetes: The Atherosclerosis Risk in Communities Study. Arch Intern Med 159:1777-1783, 1999

505. Rate RG, Knowler WC, Morse HG, et al: Diabetes mellitus in Hopi and Navajo Indians. Prevalence of microvascular complications. Diabetes 32:894-899, 1983

506. Lemley KV: A basis for accelerated progression of diabetic nephropathy in Pima Indians. Kidney Int Suppl 83:S38-S42, 2003

507. Sievers ML, Bennett PH, Roumain J, Nelson RG: Effect of hypertension on mortality in Pima Indians. Circulation 100:33-40, 1999

508. Tentori F, Stidley CA, Scavini M, et al: Prevalence of hematuria among Zuni Indians with and without diabetes: The Zuni Kidney Project. Am J Kidney Dis 41:1195-1204, 2003

509. Hoy WE, Mathews JD, McCredie DA, et al: The multidimensional nature of renal disease: Rates and associations of albuminuria in an Australian Aboriginal community. Kidney Int 54:1296-1304, 1998

510. Zarif L, Covic A, Iyengar S, Sehgal AR, Sedor JR, Schelling JR: Inaccuracy of clinical phenotyping parameters for hypertensive nephrosclerosis. Nephrol Dial Transplant 15:1801-1807, 2000

511. Sinha R, Fisch G, Teague B, et al: Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 346:802-810, 2002

512. Ogden CL, Flegal KM, Carroll MD, Johnson CL: Prevalence and trends in overweight among US children and adolescents, 1999-2000. JAMA 288:1728-1732, 2002

513. American Diabetes Association: Type 2 diabetes in children and adolescents. Diabetes Care 23:381-389, 2000

514. Botero D, Wolfsdorf JI: Diabetes mellitus in children and adolescents. Arch Med Res 36:281-290, 2005

515. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM: Albuminuria and renal insufficiency prevalence guides population screening: Results from the NHANES III. Kidney Int 61:2165-2175, 2002

516. Wasen E, Isoaho R, Mattila K, Vahlberg T, Kivela SL, Irjala K: Renal impairment associated with diabetes in the elderly. Diabetes Care 27:2648-2653, 2004

517. Otiniano ME, Markides KS, Ottenbacher K, Ray LA, Du XL: Self-reported diabetic complications and 7-year mortality in Mexican American elders. Findings from a community-based study of five Southwestern states. J Diabetes Complications 17:243-248, 2003

518. Kuo YF, Raji MA, Markides KS, Ray LA, Espino DV, Goodwin JS: Inconsistent use of diabetes medications, diabetes complications, and mortality in older Mexican Americans over a 7-year period: Data from the Hispanic established population for the epidemiologic study of the elderly. Diabetes Care 26:3054-3060, 2003

519. Mix TC, St Peter WL, Ebben J, et al: Hospitalization during advancing chronic kidney disease. Am J Kidney Dis 42:972-981, 2003

520. Ekbom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Molvig J, Mathiesen ER: Pregnancy outcome in type 1 diabetic women with microalbuminuria. Diabetes Care 24:1739-1744, 2001

521. Hiilesmaa V, Suhonen L, Teramo K: Glycaemic control is associated with pre-eclampsia but not with pregnancy-induced hypertension in women with type I diabetes mellitus. Diabetologia 43:1534-1539, 2000

522. Biesenbach G, Grafinger P, Zazgornik J, Helmut, Stoger: Perinatal complications and three-year follow up of infants of diabetic mothers with diabetic nephropathy stage IV. Ren Fail 22:573-580, 2000

523. Gordon M, Landon MB, Samuels P, Hissrich S, Gabbe SG: Perinatal outcome and long-term follow-up associated with modern management of diabetic nephropathy. Obstet Gynecol 87:401-409, 1996

524. Kimmerle R, Zass RP, Cupisti S, et al: Pregnancies in women with diabetic nephropathy: Long-term outcome for mother and child. Diabetologia 38:227-235, 1995

525. Dunne FP, Chowdhury TA, Hartland A, et al: Pregnancy outcome in women with insulin-dependent diabetes mellitus complicated by nephropathy. QJM 92:451-454, 1999

526. Sibai BM, Caritis S, Hauth J, et al: Risks of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol 182:364-369, 2000

527. Vaarasmaki MS, Hartikainen A, Anttila M, Pramila S, Koivisto M: Factors predicting peri- and neonatal outcome in diabetic pregnancy. Early Hum Dev 59:61-70, 2000

528. Nielsen GL, Sorensen HT, Nielsen PH, Sabroe S, Olsen J: Glycosylated hemoglobin as predictor of adverse fetal outcome in type 1 diabetic pregnancies. Acta Diabetol 34:217-222, 1997

529. The Diabetes Control and Complications Trial Research Group: Effect of pregnancy on microvascular complications in the diabetes control and complications trial. Diabetes Care 23:1084-1091, 2000

530. Hemachandra A, Ellis D, Lloyd CE, Orchard TJ: The influence of pregnancy on IDDM complications. Diabetes Care 18:950-954, 1995

531. Mackie AD, Doddridge MC, Gamsu HR, Brudenell JM, Nicolaides KH, Drury PL: Outcome of pregnancy in patients with insulin-dependent diabetes mellitus and nephropathy with moderate renal impairment. Diabet Med 13:90-96, 1996

532. Purdy LP, Hantsch CE, Molitch ME, et al: Effect of pregnancy on renal function in patients with moderate-to-severe diabetic renal insufficiency. Diabetes Care 19:1067-1074, 1996

533. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 183:S1-S22, 2000 (suppl)

534. Podymow T, August P, Umans JG: Antihypertensive therapy in pregnancy. Semin Nephrol 24:616-625, 2004

535. August P, Lindheimer M: Chronic hypertension and pregnancy, in Lindheimer MD, Roberts JM, Cunningham FG (eds): Chelsey's Hypertensive Disorders in Pregnancy (ed 2). Stamford, CT, Appleton & Lange, 1999, pp 650-653

536. Bar J, Chen R, Schoenfeld A, et al: Pregnancy outcome in patients with insulin dependent diabetes mellitus and diabetic nephropathy treated with ACE inhibitors before pregnancy. J Pediatr Endocrinol Metab 12:659-665, 1999

537. Hod M, van Dijk DJ, Karp M, et al: Diabetic nephropathy and pregnancy: The effect of ACE inhibitors prior to pregnancy on fetomaternal outcome. Nephrol Dial Transplant 10:2328-2333, 1995

538. Shotan A, Widerhorn J, Hurst A, Elkayam U: Risks of angiotensin-converting enzyme inhibition during pregnancy: Experimental and clinical evidence, potential mechanisms, and recommendations for use. Am J Med 96:451-456, 1994

539. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al: Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 354:2443-2451, 2006

540. Jacobson GF, Ramos GA, Ching JY, Kirby RS, Ferrara A, Field DR: Comparison of glyburide and insulin for the management of gestational diabetes in a large managed care organization. Am J Obstet Gynecol 193:118-124, 2005

541. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O: A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 343:1134-1138, 2000

542. Preconception care of women with diabetes. Diabetes Care 26:S91-S93, 2003 (suppl 1)

543. Gestational diabetes mellitus. Diabetes Care 26: S103-S105, 2003 (suppl 1)

544. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Number 60, March 2005. Pregestational diabetes mellitus. Obstet Gynecol 105:675-685, 2005

545. Miller VT: Dyslipoproteinemia in women. Special considerations. Endocrinol Metab Clin North Am 19:381-398, 1990

546. Napoli C, D'Armiento FP, Mancini FP, et al: Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. J Clin Invest 100:2680-2690, 1997

547. Levitt NS, Bradshaw D, Zwarenstein MF, Bawa AA, Maphumolo S: Audit of public sector primary diabetes care in Cape Town, South Africa: High prevalence of complications, uncontrolled hyperglycaemia, and hypertension. Diabet Med 14:1073-1077, 1997

548. Wesson DE: Can risk factor modification prevent nephropathy in type 2 diabetes mellitus? Am J Kidney Dis 36:1054-1056, 2000

549. KEEP: Kidney Early Evaluation Program. Annual atlas of the National Kidney Foundation's early evaluation program data. Am J Kidney Dis 42:S1-S61, 2003 (suppl 4)

550. Acton KJ, Shields R, Rith-Najarian S, et al: Applying the diabetes quality improvement project indicators in the Indian Health Service primary care setting. Diabetes Care 24:22-26, 2001

551. Burrows NR, Narva AS, Geiss LS, Engelgau MM, Acton KJ: End-stage renal disease due to diabetes among southwestern American Indians, 1990-2001. Diabetes Care 28:1041-1044, 2005

552. Geiss L, Engelgau M, Pogach L, et al: A national progress report on diabetes: Successes and challenges. Diabetes Technol Ther 7:198-203, 2005

553. Hoy WE, Wang Z, Baker PR, Kelly AM: Reduction in natural death and renal failure from a systematic screening and treatment program in an Australian Aboriginal community. Kidney Int Suppl 83:S66-S73, 2003

554. Mani MK: Prevention of chronic renal failure at the community level. Kidney Int Suppl 83:S86-S89, 2003

555. Ifudu O, Dawood M, Homel P, Friedman EA: Excess morbidity in patients starting uremia therapy without prior care by a nephrologist. Am J Kidney Dis 28:841-845, 1996

556. Dean HJ: Dancing with many different ghosts: Treatment of youth with type 2 diabetes. Diabetes Care 25:237-238, 2002

557. Miodovnik M, Rosenn BM, Khoury JC, Grigsby JL, Siddiqi TA: Does pregnancy increase the risk for development and progression of diabetic nephropathy? Am J Obstet Gynecol 174:1180-1189, 1996

558. Rossing K, Jacobsen P, Hommel E, et al: Pregnancy and progression of diabetic nephropathy. Diabetologia 45:36-41, 2002

559. Vaarasmaki M, Anttila M, Pirttiaho H, Hartikainen AL: Are recurrent pregnancies a risk in type 1 diabetes? Acta Obstet Gynecol Scand 81:1110-1115, 2002

560. Reece EA, Winn HN, Hayslett JP, Coulehan J, Wan M, Hobbins JC: Does pregnancy alter the rate of progression of diabetic nephropathy? Am J Perinatol 7:193-197, 1990

561. Geiss LS, Rolka DB, Engelgau MM: Elevated blood pressure among U.S. adults with diabetes, 1988-1994. Am J Prev Med 22:42-48, 2002

562. United Kingdom Prospective Diabetes Study (UKPDS): 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 310:83-88, 1995

563. The Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 342:381-389, 2000

564. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR: Sulfonylurea inadequacy: Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care 25:330-336, 2002

565. DiMatteo MR: Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. Med Care 42:200-209, 2004

566. Glasgow RE, Hampson SE, Strycker LA, Ruggiero L: Personal-model beliefs and social-environmental barriers related to diabetes self-management. Diabetes Care 20:556-561, 1997

567. Litwak LE, Mileo Vaglio R, Alvarez A, Gutman RA: [Self monitoring of capillary blood glucose. Evaluation of long-term results (3 to 7 years)]. Medicina (B Aires) 59:71-78, 1999

568. Beckles GL, Engelgau MM, Narayan KM, Herman WH, Aubert RE, Williamson DF: Population-based assessment of the level of care among adults with diabetes in the U.S. Diabetes Care 21:1432-1438, 1998

569. Evans JM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD: Frequency of blood glucose monitoring in relation to glycaemic control: Observational study with diabetes database. BMJ 319:83-86, 1999

570. Cramer JA: A systematic review of adherence with medications for diabetes. Diabetes Care 27:1218-1224, 2004

571. Kamiya A, Ohsawa I, Fujii T, et al: A clinical survey on the compliance of exercise therapy for diabetic outpatients. Diabetes Res Clin Pract 27:141-145, 1995

572. Kravitz RL, Hays RD, Sherbourne CD, et al: Recall of recommendations and adherence to advice among patients with chronic medical conditions. Arch Intern Med 153:1869-1878, 1993

573. Cerkoney KA, Hart LK: The relationship between the health belief model and compliance of persons with diabetes mellitus. Diabetes Care 3:594-598, 1980

574. Flauto RP, Leon JB, Sehgal AR: The provision and outcomes of diabetic care of hemodialysis patients. Am J Kidney Dis 41:125-131, 2003

575. Mensing C, Boucher J, Cypress M, et al: National standards for diabetes self-management education. Diabetes Care 27:S143-S150, 2004 (suppl 1)

576. Norris SL, Engelgau MM, Narayan KM: Effectiveness of self-management training in type 2 diabetes: A systematic review of randomized controlled trials. Diabetes Care 24:561-587, 2001

577. Ellis SE, Speroff T, Dittus RS, Brown A, Pichert JW, Elasy TA: Diabetes patient education: A meta-analysis and meta-regression. Patient Educ Couns 52:97-105, 2004

578. Wing RR, Goldstein MG, Acton KJ, et al: Behavioral science research in diabetes: Lifestyle changes related to obesity, eating behavior, and physical activity. Diabetes Care 24:117-123, 2001

579. Hypertension Prevention Trial Research Group: The Hypertension Prevention Trial: Three-year effects of dietary changes on blood pressure. Arch Intern Med 150:153-162, 1990

580. Ciechanowski PS, Katon WJ, Russo JE: Depression and diabetes: Impact of depressive symptoms on adherence, function, and costs. Arch Intern Med 160:3278-3285, 2000

581. Hurley AC, Shea CA: Self-efficacy: strategy for enhancing diabetes self-care. Diabetes Educ 18:146-150, 1992

582. Johnston-Brooks CH, Lewis MA, Garg S: Self-efficacy impacts self-care and HbA_{1c} in young adults with type I diabetes. Psychosom Med 64:43-51, 2002

583. McCaul KD, Glasgow RE, Schafer LC: Diabetes regimen behaviors. Predicting adherence. Med Care 25:868-881, 1987

584. Senecal C, Nouwen A, White D: Motivation and dietary self-care in adults with diabetes: Are self-efficacy and autonomous self-regulation complementary or competing constructs? Health Psychol 19:452-457, 2000

585. Schillinger D, Grumbach K, Piette J, et al: Association of health literacy with diabetes outcomes. JAMA 288:475-482, 2002

586. Swift CS, Armstrong JE, Beerman KA, Campbell RK, Pond-Smith D: Attitudes and beliefs about exercise among persons with non-insulin-dependent diabetes. Diabetes Educ 21:533-540, 1995

587. Smedley BD, Stith AY, Nelson AR: Unequal Treatment Confronting Racial and Ethnic Disparities in Healthcare. Washington, DC, Institute of Medicine, National Academy Press, 2002

588. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. N Engl J Med 321:1074-1079, 1989

589. Sarkisian CA, Brown AF, Norris KC, Wintz RL, Mangione CM: A systematic review of diabetes self-care interventions for older, African American, or Latino adults. Diabetes Educ 29:467-479, 2003

590. Bruce DG, Casey GP, Grange V, et al: Cognitive impairment, physical disability and depressive symptoms in older diabetic patients: The Fremantle Cognition in Diabetes Study. Diabetes Res Clin Pract 61:59-67, 2003

591. Logroscino G, Kang JH, Grodstein F: Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years. BMJ 328:548, 2004

592. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB: Lower cognitive function in the presence of obesity and hypertension: The Framingham heart study. Int J Obes Relat Metab Disord 27:260-268, 2003

593. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM: Self-management education for adults with type 2 diabetes: A meta-analysis of the effect on glycemic control. Diabetes Care 25:1159-1171, 2002

594. Steed L, Cooke D, Newman S: A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. Patient Educ Couns 51:5-15, 2003

595. Norris SL, Nichols PJ, Caspersen CJ, et al: Increasing diabetes self-management education in community set-

tings. A systematic review. Am J Prev Med 22:S39-S66, 2002 (suppl 4)

596. Gary TL, Genkinger JM, Guallar E, Peyrot M, Brancati FL: Meta-analysis of randomized educational and behavioral interventions in type 2 diabetes. Diabetes Educator 29:488-501, 2003

597. Balas EA, Krishna S, Kretschmer RA, Cheek TR, Lobach DF, Boren SA: Computerized knowledge management in diabetes care. Med Care 42:610-621, 2004

598. Atkins D, Best D, Briss PA, et al: Grading quality of evidence and strength of recommendations. BMJ 328:1490, 2004