



National Kidney
Foundation®

KDOQI

KDOQI CLINICAL PRACTICE GUIDELINE FOR DIABETES AND CKD: 2012 UPDATE

Abstract

The 2012 update of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Diabetes and Chronic Kidney Disease (CKD) is intended to assist the practitioner caring for patients with diabetes and CKD. Substantial high-quality new evidence has emerged since the original 2007 KDOQI guideline that could significantly change recommendations for clinical practice. As such, revisions of prior guidelines are offered that specifically address hemoglobin A_{1c} (HbA_{1c}) targets, treatments to lower low-density lipoprotein cholesterol (LDL-C) levels, and use of angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) treatment in diabetic patients with and without albuminuria. Treatment approaches are addressed in each section and the stated guideline recommendations are based on systematic reviews of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach. Limitations of the evidence are discussed and specific suggestions are provided for future research.

Keywords: Albuminuria; chronic kidney disease; Clinical Practice Guideline; diabetes; dyslipidemia; evidence-based recommendation; KDOQI.

In citing this document, the following format should be used: National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis.* 2012;60(5):850-886.

NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline is based upon a systematic literature search that included articles published through October 2010 and upon the best information available from relevant newer publications and scientific presentations through April 2012. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease Outcomes Quality Initiative (KDOQI) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is on file at the National Kidney Foundation (NKF).

Work Group Membership

Work Group Co-Chairs

Robert G. Nelson, MD, PhD
National Institutes of Health
Phoenix, AZ, USA

Katherine R. Tuttle, MD, FASN, FACP
Providence Medical Research Center
University of Washington School of Medicine
Spokane, WA, USA

Work Group

Rudolph W. Bilous, MD
The James Cook University Hospital
Middlesbrough, UK

J. Michael Gonzalez-Campoy, MD, PhD, FACE
Minnesota Center for Obesity, Metabolism and
Endocrinology, PA (MNCOME)
Eagan, MN, USA

Michael Mauer, MD
University of Minnesota Medical School
Minneapolis, MN, USA

Mark E. Molitch, MD
Northwestern University
Chicago, IL, USA

Kumar Sharma, MD, FAHA
University of California San Diego
La Jolla, CA, USA

Liason Members

Judith E. Fradkin, MD
National Institutes of Health
Bethesda, MD, USA

Andrew S. Narva, MD
National Institutes of Health
Bethesda, MD, USA

KDOQI Evidence Review Team

University of Minnesota Department of Medicine

Minneapolis VA Center for Chronic Disease Outcomes Research. Minneapolis, MN, USA:

Timothy J. Wilt, MD, MPH, Professor of Medicine and Project Director
Areef Ishani, MD, MS, Chief, Section of Nephrology, Associate Professor of Medicine
Thomas S. Rector, PhD, PharmD, Professor of Medicine
Yelena Slinin, MD, MS, Assistant Professor of Medicine
Patrick Fitzgerald, MPH, Project Manager
Maureen Carlyle, MPH, PIVOT Coordinator

KDOQI Leadership

Michael V. Rocco, MD, MSCE
KDOQI Chair

Jeffrey S. Berns, MD
Vice Chair, Guidelines and Commentary

Joseph V. Nally, Jr, MD
Vice Chair, Public Policy

Holly Kramer, MD
Vice Chair, Research

Michael J. Choi, MD
Vice Chair, Education

NKF-KDOQI Guideline Development Staff

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

Emily Howell, MA, Communications Director

Michael Cheung, MA, Guideline Development Director

Sean Slifer, BA, Guideline Development Manager

Table of Contents

Abbreviations and Acronyms	855
Reference Keys	856
Foreword	857
Executive Summary	858
Summary of Recommendations	861
Guideline 2: Management of Hyperglycemia and General Diabetes Care in CKD	862
Guideline 4: Management of Dyslipidemia in Diabetes and CKD	868
Guideline 6: Management of Albuminuria in Normotensive Patients with Diabetes	873
Research Recommendations	875
Conclusion	877
Acknowledgements	878
Biographic and Disclosure Information	879
References	883

Tables

Table 1. Grade for Strength of Recommendation in the Diabetes and CKD Guideline	859
Table 2. Grade for Quality of Evidence in the Diabetes and CKD Guideline	860
Table 3. Target and Achieved HbA _{1c} Levels in the Intensively and Conventionally Treated Groups of Three Recent Clinical Trials that Examined Different Levels of Glycemic Control in Patients with Type 2 Diabetes	863
Table 4. Dose Adjustment for Insulin Compounds and Oral Medicines for Diabetes in CKD	865
Table 5. Summary of Four Post Hoc Analyses Reports of Lipid Lowering in People with Diabetes Mellitus (DM) and CKD	869
Table 6. Fibrate Treatment in Patients with Diabetes Mellitus (DM) and CKD	870
Table 7. Dose Adjustment for Lipid Lowering Medicines in CKD	871

Figure

Figure 1. Key Questions (KQ) to Be Addressed By the Evidence Review	858
---	-----

Abbreviations and Acronyms

4D	Deutsche Diabetes Dialyse Studie
4S	Scandinavian Simvastatin Survival Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitor
AdDIT	Adolescent type 1 Diabetes cardio-renal Intervention Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ALERT	Assessment of Lescol in Renal Transplant
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Endpoints
ARB	Angiotensin receptor blocker
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events
AVOID	Aliskiren in the Evaluation of Proteinuria in Diabetes
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DAIS	Diabetes Atherosclerosis Intervention Study
DCCT	The Diabetes Control and Complications Trial
DKD	Diabetic kidney disease
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1
GRADE	Grading of Recommendation Assessment, Development, and Evaluation
HbA _{1c}	Hemoglobin A _{1c}
HDL-C	High-density lipoprotein cholesterol
HPS	Heart Protection Study
HR	Hazard ratio
JNC	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KQ	Key question
LDL-C	Low-density lipoprotein cholesterol
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease
MI	Myocardial infarction
MICROHOPE	Microalbuminuria, Cardiovascular, and Renal Outcomes in Heart Outcomes Prevention Evaluation
NHANES	National Health and Nutrition Examination Survey
NKF	National Kidney Foundation
RAS	Renin-angiotensin system
RR	Relative risk
SCr	Serum creatinine
SHARP	Study of Heart and Renal Protection
TNT	Treating to New Targets
UKPDS	UK Prospective Diabetes Study
USRDS	United States Renal Data System
VADT	Veterans Affairs Diabetes Trial
VA-HIT	Veterans Affairs High-density lipoprotein Intervention Trial
vs.	Versus
WOSCOPS	West of Scotland Coronary Prevention Study

Reference Keys

CKD NOMENCLATURE USED BY KDOQI

CKD Categories	Definition
CKD	CKD of any stage (1-5), with or without a kidney transplant, including both non-dialysis dependent CKD (CKD 1-5ND) and dialysis-dependent CKD (CKD 5D)
CKD ND	Non-dialysis-dependent CKD of any stage (1-5), with or without a kidney transplant (i.e., CKD excluding CKD 5D)
CKD T	Non-dialysis-dependent CKD of any stage (1-5) with a kidney transplant
Specific CKD Stages	
CKD 1, 2, 3, 4	Specific stages of CKD, CKD ND, or CKD T
CKD 3-4, etc.	Range of specific stages (e.g., both CKD 3 and CKD 4)
CKD 5D	Dialysis-dependent CKD 5
CKD 5HD	Hemodialysis-dependent CKD 5
CKD 5PD	Peritoneal dialysis-dependent CKD 5

Foreword

This publication of the Kidney Diseases Outcomes Quality Initiative (KDOQI) updates several areas of the 2007 KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. The need for this update was the result of increasing recognition that substantial high-quality new evidence had become available since 2007 that could significantly change recommendations for clinical practice. Using the usual rigorous analytical methods of the KDOQI process, an outstanding Work Group, under the leadership of Robert Nelson and Katherine Tuttle, working with the Minneapolis Veterans Administration Center for Chronic Disease Outcomes Research, reviewed new studies addressing management of hyperglycemia, hyperlipidemia, and albuminuria in individuals with diabetes mellitus and chronic kidney disease (CKD). Their analysis focuses on important outcomes such as all-cause mortality, CKD progression and development of end-stage renal disease (ESRD), fatal and non-fatal cardiovascular events, among others. Revisions of prior guidelines are offered that specifically address

HbA_{1c} targets, treatments to lower LDL-C levels, and use of ACE-I and ARB treatment in diabetic patients with and without albuminuria. The new guideline updates published here are each accompanied by an indication of the strength and quality of supporting evidence. Five of seven of these recommendations carry 1A or 1B grades indicative of the strength of these new recommendations and the quality of evidence supporting them. Finally, important research recommendations are proposed.

As with prior KDOQI efforts, Drs Tuttle and Nelson and members of the Work Group devoted countless hours, all voluntarily, to the development of this important document. To each of them, and to all the others involved in this effort, we offer our most sincere thanks for their dedication and commitment to helping us all provide the very best care possible to the many patients with diabetes mellitus and CKD.

Michael V. Rocco, MD, MSCE
KDOQI Chair

Jeffrey S. Berns, MD
Vice Chair, Guidelines and Commentary

Executive Summary

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem that affects millions of people from all racial and ethnic groups. Diabetes mellitus (henceforth referred to as diabetes) is the leading cause of CKD, and the rapidly increasing prevalence of diabetes worldwide virtually assures that the proportion of CKD attributable to diabetes will continue to rise. Indeed, a recent report from the National Health and Nutrition Education Survey (NHANES) found that prevalence of diabetic kidney disease (DKD) increased steadily from 1988 through 2008, and the latest United States Renal Data System (USRDS) report indicates a ~30% increase in incidence of ESRD in persons with diabetes in the USA between 1992 and 2008.^{1,2}

In 1997, as part of an effort to address the growing problem of CKD, the National Kidney Foundation (NKF) established the Kidney Disease Outcomes Quality Initiative (KDOQI) to develop clinical practice guidelines for the management of all stages of CKD.³ By 2007, with the publication of the KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease,⁴ the KDOQI reached its primary goal of producing evidence-based guidelines on the aspects of CKD most likely to improve care for patients.⁵ To ensure that practitioners and patients benefit from the latest knowledge, an essential part of

KDOQI activities is to provide regular updates of these guidelines.

Since publication of the diabetes guidelines in 2007, several large well-designed clinical trials have addressed management issues relevant to patients with diabetes and CKD. Findings from these trials suggest that the existing guideline recommendations for the management of hyperglycemia, hypertension, hyperlipidemia, and albuminuria may no longer accurately reflect current medical knowledge. To properly incorporate the new findings from these clinical trials and other recent studies into a guideline update, a systematic review of the new evidence was warranted to formally determine their applicability and methodologic quality.

This report describes updates of guidelines for the management of hyperglycemia, hyperlipidemia, and albuminuria in patients with diabetes and kidney disease as a result of this systematic review. An update of the guideline for management of blood pressure is presently underway by Kidney Disease: Improving Global Outcomes (KDIGO), an independent not-for-profit foundation governed by its own international board of directors. KDIGO was established to improve international cooperation in the development, dissemination, and implementation of clinical practice guidelines.⁶ KDOQI and KDIGO work in concert to expand the scope of guidelines relevant to the care of patients with CKD and improve the care of these patients worldwide.⁵

- KQ 1:** In patients with diabetes (type 1 or 2), with or without CKD, does intensive glycemic control (as defined by lower target glycosylated hemoglobin) improve health outcomes compared to controls?
- KQ 2:** What harms result from more intense glycemic control in individuals with diabetes (type 1 or 2)?
- KQ 3:** In patients with diabetes (type 1 or 2) and CKD, what evidence is there for specific lipid management targets (defined as goals for total cholesterol, LDL-C, HDL-C, triglycerides) that improve health outcomes?
- KQ 4:** Is there evidence for specific lipid altering agent use for patients with diabetes (type 1 or 2) and CKD?
- KQ 5:** What harms result from more intense lipid management or use of specific lipid altering agents in individuals with diabetes (type 1 or 2) and CKD?
- KQ 6:** What interventions prevent incident albuminuria and/or progression of albuminuria in patients with diabetes in whom further reduction in blood pressure is not the specific treatment objective?
- KQ 7:** Is albuminuria a valid surrogate for health outcomes in diabetes?

Figure 1. Key questions (KQ) to be addressed by the evidence review. Abbreviations: CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

METHODS

The guideline update effort was a voluntary and multidisciplinary undertaking that included input from NKF scientific staff, an evidence review team from the Minneapolis Veterans Administration Center for Chronic Disease Outcomes Research, and a Work Group of experts in relevant disciplines. The approach to the systematic literature review and the comprehensive findings prepared for this update are reported in detail elsewhere.⁷ Briefly, MEDLINE was searched to identify randomized controlled trials published between January 2003 and October 2010 that related to albuminuria, glycemic and lipid management in patients with diabetes. All titles and abstracts were assessed for their appropriateness to address key questions that were developed by the multidisciplinary team and outlined in Fig 1. Study reference lists, reviews, and meta-analyses were evaluated and references to other clinical trials were elicited from members of the Work Group. Data from each study that pertained to study quality, trial characteristics, population characteristics, efficacy, outcomes, withdrawals, and adverse events were extracted. Evidence tables were created to address the key questions. Study quality was rated as good, fair, or poor according to criteria suggested by the Cochrane Collaboration, and included information on adequate allocation concealment, method of blinding, use of the intention-to-treat principle for data analysis, reporting of dropouts, and reasons for attrition.

In formulating the guideline statements, separate recommendation levels (1 or 2) were assigned for each specific recommendation based on the overall strength of the recommendation and separate letter grades (A, B, C, or D) were assigned based on the

overall quality of the evidence for a particular intervention and outcome (Tables 1 and 2).⁸ *Strength of guideline recommendations* was determined by the GRADE approach used by KDIGO. The overall quality and strength of evidence was assessed using methodology developed by the Agency for Healthcare Research and Quality and the Effective Health Care Program. *Quality of evidence* ratings included four categories: A) high confidence, which indicated that further research was unlikely to change the confidence in the estimate of effect; B) moderate confidence, which indicated that further research may change the confidence in the estimate of effect; C) low confidence, which indicated that further research would likely have an important impact on the confidence in the estimate of effect; and D) insufficient, which indicated that the evidence was unavailable or did not permit a conclusion.

Outcomes

The primary health outcome examined in this review was all-cause mortality. Secondary health outcomes included ESRD and cardiovascular death, non-fatal cardiovascular events, clinically significant retinopathy including vision loss, amputations, and symptomatic hypoglycemia of sufficient severity to require the assistance of another person. Intermediate outcomes examined included changes in the level of albuminuria and glomerular filtration rate, doubling of serum creatinine (SCr) concentration, and progression to CKD stage 4 or higher.⁷ The impact of treatments described in the recent clinical trials on these health and intermediate outcomes was assessed in formulating the guideline statements.

Table 1. Grade for Strength of Recommendation in the Diabetes and CKD Guideline

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

*The additional category "Not Graded" is used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Table 2. Grade for Quality of Evidence in the Diabetes and CKD Guideline

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

Nomenclature

Guideline statements have evolved since the publication of the original diabetes guideline. The moral imperative that clinicians “should” implement a particular treatment was replaced by “We recommend” if the strength of the recommendation was strong or moderately strong and “We suggest” if the strength of the recommendation was weak.⁸ This change was made to reflect the uncertainties inherent to all research findings and the need to adjust any recommendations to the needs of the individual patient.

GUIDELINE STATEMENTS

The customary practice of the NKF when the original diabetes guideline was published was to divide the statements into clinical practice guidelines and clinical practice recommendations. The

guideline statements were based on a consensus with 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 recommendations based on the best available evidence and expert opinion. The original document contained five clinical practice guidelines and four clinical practice recommendations; updates for two clinical practice guidelines and one clinical practice recommendation are reported herein. The NKF now combines these statements and refers to them all as a clinical practice guideline, while specifying the strength of each recommendation and its underlying quality of evidence. Hence, Clinical Practice Recommendation 1 in the original document is now referred to as Clinical Practice Guideline 6 in this update.

Summary of Recommendations

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 diabetic kidney disease (DKD). Intensive treatment of hyperglycemia prevents elevated albuminuria or delays its progression, but patients treated by approaches designed to achieve near normal glycemia may be at increased risk of severe hypoglycemia. Evidence that intensive treatment has an effect on loss of glomerular filtration rate (GFR) is sparse.

- 2.1: We recommend a target hemoglobin A_{1c} (HbA_{1c}) of ~7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD. (1A)
- 2.2: We recommend not treating to an HbA_{1c} target of <7.0% in patients at risk of hypoglycemia. (1B)
- 2.3: We suggest that target HbA_{1c} be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia. (2C)

Guideline 4: Management of Dyslipidemia in Diabetes and CKD

Dyslipidemia is common in people with diabetes and CKD. Cardiovascular events are a frequent cause of morbidity and mortality in this population. Lowering low-density lipoprotein cholesterol (LDL-C) with statin-based therapies reduces risk of major atherosclerotic events, but not all-cause mortality, in patients with CKD including those with diabetes.

- 4.1: We recommend using LDL-C lowering medicines, such as statins or statin/ezetimibe combination, to reduce risk of major atherosclerotic events in patients with diabetes and CKD, including those who have received a kidney transplant. (1B)
- 4.2: We recommend not initiating statin therapy in patients with diabetes who are treated by dialysis. (1B)

Guideline 6: Management of Albuminuria in Normotensive Patients with Diabetes

Treatments that produce a lasting decrease in urinary albumin excretion may slow the progression of DKD even in the absence of hypertension. However, most people with diabetes and albuminuria have hypertension. Assessment of albuminuria is addressed in Guideline 1 (2007 KDOQI Diabetes Guideline). Management of hypertension is addressed in Guideline 3 (2007 KDOQI Diabetes Guideline) and the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD.

- 6.1: We recommend not using an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) for the primary prevention of DKD in normotensive normoalbuminuric patients with diabetes. (1A)
- 6.2: We suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels ≥ 30 mg/g who are at high risk of DKD or its progression. (2C)

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 diabetic kidney disease (DKD). Intensive treatment of hyperglycemia prevents elevated albuminuria or delays its progression, but patients treated by approaches designed to achieve near normal glycemia may be at increased risk of severe hypoglycemia. Evidence that intensive treatment has an effect on loss of glomerular filtration rate (GFR) is sparse.

2.1: We recommend a target HbA_{1c} of ~7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD. (IA)

The evidence that achieving an HbA_{1c} level of ~7.0% is able to prevent the microvascular complications of diabetes was presented in detail in the original KDOQI diabetes guideline.⁴ For type 1 diabetes, evidence from the Diabetes Control and Complications Trial (DCCT),^{9,10} as well as from a meta-analysis of a number of smaller studies that preceded the DCCT,¹¹ established that this level of glycemic control decreases the risk of microalbuminuria and retinopathy compared to less stringent control. The beneficial effects of intensive therapy on these outcomes persisted during the long-term follow-up study of the DCCT subjects, called the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Despite the gradual narrowing of the difference in HbA_{1c} levels between the two DCCT groups over the first two years in the follow-up period, and levels remaining near 8% for both groups for the subsequent 12 years, the reduction in risk of microvascular complications of diabetes persisted.¹² Similar benefits of glycemic control on the development of microalbuminuria in patients with type 2 diabetes were originally observed in three studies; the Kumamoto Study,^{13,14} the United Kingdom Prospective Diabetes Study (UKPDS),^{15,16} and the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial.¹⁷ Intensive glycemic control also significantly reduced the development of macroalbuminuria in patients with type 1 diabetes, as shown in the DCCT/EDIC Study^{9,10,12} as well as the similarly designed but smaller Stockholm study,¹⁸ and in those with type 2 diabetes, as shown in the Kumamoto study^{13,14} and the VA Cooperative Study.¹⁷ The UKPDS showed a trend toward decreased development of macroalbumin-

uria, but this result did not achieve statistical significance.^{15,16}

Three new studies have added to the evidence that even more intensive glycemic control reduces the development of elevated albuminuria in patients with type 2 diabetes. In the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, more intensive control that achieved an HbA_{1c} of 6.5%, compared with standard control (HbA_{1c} 7.3%), was associated with a 21% reduction in new onset or worsening nephropathy defined by new onset macroalbuminuria, doubling of SCr, need for kidney replacement therapy, or death due to kidney disease (4.1% vs. 5.2%). Additionally, intensive glycemic control reduced development of macroalbuminuria by 30% (2.9% vs. 4.1%), and development of new onset microalbuminuria by 9% (23.7% vs. 25.7%).¹⁹ The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study similarly showed that more intensive control, achieving an HbA_{1c} of 6.4%, compared with standard control (HbA_{1c} 7.6%), resulted in a 32% reduction in the development of incident macroalbuminuria (2.7% vs. 3.9%) and a 21% reduction in the development of incident microalbuminuria (12.5% vs. 15.3%).²⁰ In the Veterans Affairs Diabetes Trial (VADT), more intensive glycemic control that achieved an HbA_{1c} of 6.9% compared with standard control (HbA_{1c} 8.4%) resulted in a 37% reduction in macroalbuminuria (7.6% vs. 12.1%) and a 32% reduction in microalbuminuria (10.0% vs. 14.7%).²¹

A few long-term observational cohort studies and secondary or post hoc analyses of interventional studies using ACE-Is or ARBs found that poorer glycemic control is associated with a greater rate of fall of GFR in patients with type 1 diabetes.²²⁻²⁶ Most of the prospective, randomized studies used as evidence for the effect of glycemic control on kidney function are limited by the small numbers of patients reaching this intermediate outcome. However, the EDIC/DCCT follow-up study recently reported that 2.0% (1.6/1000 person-years) of participants in the previously intensive treatment group and 5.5% (3.0/1000 person-years) of those in the previously conventional treatment group developed sustained estimated glomerular filtration rate (eGFR) measurements <60 mL/min/1.73 m² with a relative risk (RR) reduction of 50% (p=0.006); there were similar RR reductions for single eGFR measurements <45 mL/min/1.73 m² (50%, 1.6/1000 person-years vs. 2.5/1000 person-years,

Table 3. Target and Achieved HbA_{1c} Levels in the Intensively and Conventionally Treated Groups of Three Recent Clinical Trials that Examined Different Levels of Glycemic Control in Patients with Type 2 Diabetes

Study	Intensive Treatment		Conventional Treatment	
	Target	Achieved	Target	Achieved
ADVANCE ¹⁹	<6.5%	6.5%	Unspecified	7.3%
ACCORD ²⁹	<6.0%	6.4%	7-9%	7.5%
VADT ²¹	<6.0%	6.9%	<9%	8.4%

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial.

p=0.045) and <30 mL/min/1.73 m² (44%, 0.8/1000 person-years vs. 1.5/1000 person-years, p=0.088) and for ESRD (51%, 0.5/1000 person-years vs. 1.1/1000 person-years, p=0.098).²⁷ 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).¹⁵ None of the three more recent studies mentioned above (ADVANCE, ACCORD, VADT) showed significant benefits of more intensive glycemic control on creatinine-based estimates of GFR.¹⁹⁻²¹

Accordingly, the evidence that intensive glycemic control reduces the microvascular complications of diabetes is based almost exclusively on prevention of microalbuminuria (a predictor of actual complications), reduced progression to macroalbuminuria, and on prevention of retinopathy. Evidence for the prevention of other intermediate microvascular outcomes, including declining eGFR and doubling of SCr, is sparse. Although there is no evidence that intensive glycemic control slows progression to the clinical endpoint of ESRD, it is likely that if the earlier manifestations of kidney disease are reduced (i.e., albuminuria and earlier-stage CKD), then the eventual outcome of ESRD will also be reduced. However, such assumption presumes that benefits of intensive glycemic control are not outweighed by harms and that patients survive to reach ESRD.

2.2: We recommend not treating to an HbA_{1c} target of <7.0% in patients at risk of hypoglycemia. (1B)

The major risk of attaining HbA_{1c} levels <7.0% in people with diabetes is hypoglycemia. Risk of hypoglycemia is amplified in those with CKD, especially if kidney function is substantially reduced (CKD stages 4 and 5). At HbA_{1c} levels <7.0%, increased risk of hypoglycemia is clearly evident for patients with type 1 diabetes.^{9,18,28} Although the Kumamoto Study and UKDPS also demonstrated an increased risk of hypoglycemia in those with type 2 diabetes treated with insulin,^{14,15} the magnitude of the risk was consider-

ably less than in type 1 diabetes. The UKPDS also showed that sulfonylureas are associated with a small risk of hypoglycemia.¹⁵ The three most recent clinical trials (ADVANCE, ACCORD, and VADT) all showed substantial increases (range 1.5-3 fold) in severe and non-severe hypoglycemia among patients with type 2 diabetes who were receiving more intensive therapy. Targets for conventional and intensive glycemic therapy and the mean achieved HbA_{1c} levels in these clinical trials are shown in Table 3. Intensifying glycemic control beyond conventional management did not result in decreased risk of the primary endpoints, defined by composites of major adverse cardiovascular disease (CVD) events, in any of these studies.^{19,21,29} Moreover, there was an increase in all-cause mortality among the intensively-treated group compared to the conventionally-treated group in the ACCORD study.²⁹ The reasons for this finding are uncertain, although further analysis showed that increased mortality was not directly attributable to hypoglycemia.³⁰ Therefore, lowering HbA_{1c} to levels <7.0% is not recommended in patients with diabetes who are at risk for hypoglycemia, including those treated with insulin or sulfonylureas and/or have advanced CKD.

2.3: We suggest that target HbA_{1c} be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia. (2C)

Risks of microvascular complications are amplified with progressively increasing levels of HbA_{1c}. Good glycemic control is clearly fundamental to optimal diabetes care. However, the available evidence is insufficient to specify an upper limit for target HbA_{1c}. Nevertheless, the ADVANCE, ACCORD, and VADT studies can provide some insight into setting goals for individual patients. For example, study participants (characteristically older people with long-standing type 2 diabetes and high frequency of CVD and other co-morbidities) treated in the conventional manner were less likely to experience hypoglycemia, while risks of major clinical endpoints (all-cause mortality,

CVD mortality, non-fatal CVD events, and loss of kidney function or ESRD) were similar to those treated more intensively. The achieved HbA_{1c} values among the conventional treatment groups in these studies were 7.3-8.4%.

Years of intensive glycemic control (HbA_{1c} ~ 7%) are required before a reduction in the incidence of complications, such as kidney failure or blindness, becomes evident.^{9,10,15,16} Therefore, when instituting intensive therapy for hyperglycemia in patients with limited life expectancy, the potential benefits must be balanced against risks. With intensified insulin treatment, there is an increased risk of hypoglycemia and weight gain. In individuals 70-79 years of age who are taking insulin, the probability of falls begins to increase with HbA_{1c} <7%.³¹ Moreover, in patients with type 2 diabetes, one study showed that the presence of co-morbidities abrogates benefits of lower HbA_{1c} levels on CVD events.³² Therefore, a target HbA_{1c} of >7.0% is suggested for patients with diabetes who are at risk of hypoglycemia and have clinically-significant co-morbidities or limited life expectancy.

LIMITATIONS

Recommendations regarding glycemic control in patients with diabetes and CKD are based primarily on reductions in the appearance and progression of albuminuria, yet the relationship between elevated albuminuria and clinical endpoints is often discordant. Less is known about appropriate glycemic control in patients with diabetes and more advanced CKD, because no prospective, randomized clinical trials evaluating the level of glycemic control on health outcomes have been carried out in patients with CKD stages 3-5. Extended follow-up of patients with type 1 diabetes in DCCT/EDIC showed a beneficial effect of prior intensive therapy on later CKD endpoints, but the numbers of patients were small. A recent observational, claims-based study in people with type 1 or type 2 diabetes and CKD³³ reported a U-shaped relationship between HbA_{1c} level and risk of death, with deaths increasing significantly for HbA_{1c} levels below 6.5% and above 8% over nearly 4 years of follow-up. Risks of doubling of SCr, ESRD, CVD events, and hospitalization increased in a graded manner with higher levels of HbA_{1c}.

HbA_{1c} levels of ~7-9% are associated with better outcomes for survival, hospitalization, and CVD in patients on hemodialysis in some³⁴⁻³⁸ but not all observational studies;^{39,40} however, this relationship has not been tested in prospective, randomized studies. Nevertheless, patients with diabetes who are treated by dialysis or kidney transplant may continue to benefit from good glycemic control because of reductions in eye and neurologic outcomes. Complicating

glycemic management in patients with diabetes and advanced CKD, however, are the many new medicines now available for glycemic control; some which are potentially useful and others which are harmful or must be used with care due to reduced clearance of the drug or its metabolites by the kidneys.

IMPLEMENTATION ISSUES

Management of hyperglycemia involves a multifactorial approach that includes medicines, proper nutrition and meal planning, and physical activity. Each of these approaches may need to be modified in the setting of CKD. Nutritional management in diabetes and CKD is addressed in Guideline 5 and physical activity is addressed in Clinical Practice Recommendation 4 of the previously published guideline.⁴

Special Considerations in Advanced CKD

The risk of hypoglycemia is increased in patients with substantial decreases in eGFR (CKD stages 4 and 5) for two reasons: (1) decreased clearance of insulin and of some of the oral agents used to treat diabetes and (2) impaired renal gluconeogenesis with reduced kidney mass.⁴¹ The contribution of reduced renal function to the risk of hypoglycemia is difficult to quantify. About one-third of insulin degradation is carried out by the kidneys and impairment of kidney function is associated with a prolonged half-life of insulin. Patients with type 1 diabetes receiving insulin who have significant creatinine elevations (mean 2.2 mg/dL) have a 5-fold increase in the frequency of severe hypoglycemia.^{42,43} Therefore, it is imperative that patients being treated intensively monitor their glucose levels closely and reduce their doses of medicine as needed to avoid hypoglycemia.

Progressive falls in kidney function result in decreased clearances of the sulfonylureas or their active metabolites,⁴⁴⁻⁴⁶ necessitating a decrease in drug dosing to avoid hypoglycemia. Table 4 provides recommendations for drug dosing of medicines used to treat hyperglycemia in patients with CKD. First generation sulfonylureas (e.g., chlorpropamide, tolazamide, and tolbutamide) should be avoided altogether in patients with CKD. These agents rely on the kidneys to eliminate both the parent drug and its active metabolites, resulting in increased half-lives and the risk of hypoglycemia. Of the second-generation sulfonylureas (e.g., glipizide, glyburide, and glimepiride), glipizide is the preferred agent as it does not have active metabolites and does not increase the risk of hypoglycemia in patients with CKD. An increase in the levels of the active metabolite of nateglinide occurs with decreased kidney function,^{47,48} but this increase does not occur with the similar drug, repaglinide.⁴⁹ On the other hand, repaglinide can accumulate when the

Table 4. Dose Adjustment for Insulin Compounds and Oral Medicines for Diabetes in CKD

Medication Class and Agents	CKD stages 3, 4, and 5 ND
Insulin	
Glargine	No advised dose adjustment*
Detemir	No advised dose adjustment*
Neutral Protamine Hagedorn (NPH)	No advised dose adjustment*
Regular	No advised dose adjustment*
Aspart	No advised dose adjustment*
Lispro	No advised dose adjustment*
Glulisine	No advised dose adjustment*
First-generation sulfonylureas	
Acetohexamide**	Avoid use
Chlorpropamide	GFR 50-80 mL/min/1.73 m ² : reduce dose 50%, GFR <50 mL/min/1.73 m ² : avoid use
Tolazamide	Avoid use
Tolbutamide	Avoid use
Second-generation sulfonylureas	
Glipizide	No dose adjustment
Glimepiride	Start conservatively at 1 mg daily
Glyburide	Avoid use
Gliclazide**	No dose adjustment
Meglitinides	
Repaglinide	If GFR <30 mL/min/1.73 m ² start conservatively at 0.5 mg with meals
Nateglinide	If GFR <30 mL/min/1.73 m ² start conservatively at 60 mg with meals
Biguanides	
Metformin***	United States FDA label states, "do not use if SCr ≥1.5 mg/dL in men, ≥1.4 mg/dL in women" British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR <30 mL/min/1.73 m ²
Thiazolidinediones	
Pioglitazone	No dose adjustment
Rosiglitazone	No dose adjustment
Alpha-glucosidase inhibitors	
Acarbose	Avoid if GFR <30 mL/min/1.73 m ²
Miglitol	Avoid if GFR <25 mL/min/1.73 m ²
DPP-4 inhibitor	
Sitagliptin	GFR >50 mL/min/1.73 m ² : 100 mg daily GFR 30-50 mL/min/1.73 m ² : 50 mg daily GFR <30 mL/min/1.73 m ² : 25 mg daily
Saxagliptin	GFR >50 mL/min/1.73 m ² : 5 mg daily GFR ≤50 mL/min/1.73 m ² : 2.5 mg daily
Linagliptin	No dose adjustment
Vildagliptin**	GFR ≥50 mL/min/1.73 m ² : 50 mg twice daily GFR <50 mL/min/1.73 m ² : 50 mg daily
Incretin mimetic	
Exenatide	Not recommended in GFR <30 mL/min/1.73 m ²
Liraglutide	Not recommended in GFR <60 mL/min/1.73 m ²
Amylin analog	
Pramlintide	No dose adjustment and not recommended for patients with CKD stage 4 or greater
Dopamine receptor agonist	
Bromocriptine mesylate*	Not studied in patients with reduced GFR

*Adjust dose based on patient response.

**Not currently licensed for use in the U.S.

***These levels are controversial (see text).

GFR ≤30 mL/min/1.73 m².⁴⁹ Although hypoglycemia has not been demonstrated to increase substan-

tially with progressive falls in GFR,^{49,50} it would seem prudent to start treatment with a 0.5 mg dose

of repaglinide with each meal and titrate upwards cautiously when the GFR is <30 mL/min/1.73 m². Similarly, nateglinide should be used with caution when the GFR is <30 mL/min/1.73 m², starting with 60 mg at meals and cautiously titrating upwards.

Metformin does not cause hypoglycemia. Lactic acidosis, however, is a rare and serious side effect of metformin use, which can occur when toxic levels of metformin accumulate. Metformin is cleared by the kidneys, thus its use in CKD is restricted. A United States Food and Drug Administration (FDA) mandated black-box warning exists regarding the risk of lactic acidosis with metformin use. The label indicates that metformin should not be used in men with a SCr of ≥ 1.5 mg/dL or in women with a SCr of ≥ 1.4 mg/dL. It is also reasonable to consider a GFR cutoff for metformin use as well, since SCr can translate into different eGFR levels depending on weight, race or age. The clearance of metformin decreases by about 75% when the GFR is <60 mL/min/1.73 m² without further change when the GFR declines to 30 mL/min/1.73 m²;⁵¹ however, serum concentrations of metformin at both of these lower GFR levels are only about two-fold higher than in normal kidney function and these levels are still only about 3% of those found in patients with true metformin-associated lactic acidosis.^{51,52} In studies of patients continuing to receive metformin with GFR levels in the 30-60 mL/min/1.73 m² range, lactic acidosis is still exceedingly rare even in the presence of comorbid conditions like congestive heart failure, chronic obstructive pulmonary disease, and liver disease.^{53,54} Given its marked clinical benefit, restriction of metformin use based on the creatinine cutoffs provided by the FDA, or a GFR cutoff of <60 mL/min/1.73 m², has been called into question.^{55,56} At present the exact GFR cutoff for metformin use to avoid lactic acidosis is controversial. A recent review proposed that metformin use be reevaluated when GFR is <45 mL/min/1.73 m² and stopped when <30 mL/min/1.73 m²; this advice was adopted by the British National Formulary and the Japanese Society of Nephrology.^{57,58,58a}

The thiazolidinediones, pioglitazone and rosiglitazone, do not lead to hypoglycemia, are metabolized by the liver, and thus can be used in CKD. However, fluid retention is a major limiting side effect and they should not be used in advanced heart failure and CKD. They have been linked with increased fracture rates and bone loss;⁵⁹ thus the appropriate use in patients with underlying bone disease (such as renal osteodystrophy) needs to be considered. The FDA has restricted use of rosiglitazone based on information linking the medicine with increased cardiovascular events.⁶⁰ Currently, rosiglitazone has to be dispensed

by the manufacturer and may no longer be prescribed, except by physicians registered to do so.

Acarbose, a disaccharidase inhibitor, is only minimally absorbed, but with reduced kidney function, serum levels of the drug and its metabolites increase significantly. Although no adverse effects have been reported, its use in patients with a GFR <26 mL/min/1.73 m² is not recommended.⁶¹ Miglitol has greater systemic absorption and undergoes kidney excretion, and it should not be used in patients with GFR <25 mL/min/1.73 m².⁶¹

The dipeptidyl peptidase (DPP-4) inhibitors, sitagliptin, saxagliptin, linagliptin, and vildagliptin decrease the breakdown of the incretin hormones, such as glucagon-like peptide 1 (GLP-1), and improve both fasting and post-prandial glucose levels. All can be used in CKD patients but sitagliptin, saxagliptin, and vildagliptin need downward dose adjustments as detailed in Table 4.

Exenatide and liraglutide are injectable incretin mimetics that facilitate insulin secretion, decrease glucagon secretion, delay gastric emptying and cause early satiety. Although their use is associated with pancreatitis in some patients, the overall frequency of pancreatitis with their use is not greater than in patients with diabetes using other agents. Exenatide is excreted by the kidneys, and its clearance is reduced by 36% with a GFR of 45 mL/min/1.73 m² and by 64% with a GFR of <30 mL/min/1.73 m².⁶² Therefore, exenatide is not recommended for use with a GFR <30 mL/min/1.73 m². Furthermore, exenatide has been associated with acute kidney injury or acceleration of CKD progression in case reports.^{63,64} Liraglutide is fully degraded elsewhere in the body, and the kidneys are not a major organ of elimination.⁶⁵ In single dosing, there is no effect on the area under the curve in subjects with stages 4 and 5 CKD.⁶⁵ However, there are few data on long term use and the manufacturer recommends avoiding this medicine when GFR is <60 mL/min/1.73 m².⁵⁷

Pramlintide is an injectable amylin analog available as a complement to insulin therapy and normally it is given with each meal. Although pramlintide is metabolized and eliminated predominantly by the kidneys, it has a wide therapeutic index and dosage adjustments are not usually required in the presence of mild-to-moderate decreases in GFR. However, use of pramlintide is not recommended for patients with CKD stage 4 or greater.

Bromocriptine mesylate is a dopamine agonist that is predominantly metabolized in the liver and only 2-6% appears in the urine. No studies evaluating the safety of this medicine in patients with reduced GFR have been performed; therefore it should be used with caution in patients with CKD.

Assessment of Glycemic Control

Inaccuracy of the HbA_{1c} measurement in reflecting ambient glucose concentrations must be considered in the assessment of glycemic control in patients with progressive kidney disease. Factors that may contribute to falsely decreased values include a reduced red blood cell lifespan, transfusions, and hemolysis. On the other hand, falsely increased values may occur due to carbamylation of the hemoglobin and acidosis. However, Morgan et al found that the relationship between HbA_{1c} and glucose levels was not different between patients with normal kidney function and those with kidney failure (creatinine mean of 6.6 mg/dL), but some hemodialysis patients had lower than expected HbA_{1c} levels relative to the ambient glucose concentrations.⁶⁶ Opposite findings for dialysis patients were reported by Joy et al;⁶⁷ an HbA_{1c} increase of 1% correlated with a change in mean glucose of 20 mg/dL in hemodialysis patients and 30 mg/dL in those with normal kidney function. Studies published since the release of the previous KDOQI diabetes guidelines contributed further to our understanding of the relationship between HbA_{1c} and glucose in advanced CKD. Inaba et al⁶⁸ found lower correlation of plasma glucose levels with HbA_{1c} levels in patients with diabetes on hemodialysis ($r = 0.520$) compared to those with normal kidney function ($r = 0.630$), and they also had shallower regression slopes. Riveline et al⁶⁹ also found a shallower regression slope for hemodialysis patients compared to those without DKD. At lower levels of glucose (<160 mg/dL and HbA_{1c} <7.5%), hemodialysis patients tended to have higher glucose levels for a given

HbA_{1c}, whereas at higher levels the correlations were similar. When patients with CKD stages 3 and 4 were evaluated, glucose levels were also found to be slightly higher than expected for given HbA_{1c} levels.⁷⁰ Iron supplementation or erythropoietin administration lead to a modest fall of 0.5-0.7% in HbA_{1c} along with the rise in total hemoglobin in patients with advanced CKD. These effects are likely due to the formation of new red cells and to alterations in hemoglobin glycation rates.^{68,71} Importantly, all of these studies show a very wide variability in the glucose-HbA_{1c} relationship.⁶⁶⁻⁷¹ The modest changes with decreasing eGFR from 75 to 15 mL/min/1.73 m², and even with hemodialysis, do not appear to be of clinical significance compared to the wide inter-individual variability. Neither peritoneal nor hemodialysis acutely change HbA_{1c} levels.⁷² Fructosamine or glycated albumin correlate either more poorly^{66,67,69} or better^{68,70} with blood glucose than HbA_{1c} in patients with stages 4 and 5 CKD. Nevertheless, a recent prospective study found that glycated albumin, which reflects glycemic control over a 2-week period, is a better predictor of mortality and hospitalizations than HbA_{1c} in dialysis patients with diabetes.³⁵ In summary, HbA_{1c} remains the best clinical marker of long-term glycemic control, particularly if combined with self-monitoring of blood glucose, in patients with diabetes and CKD. Other markers such as glycated albumin that reflect glycemic control over a shorter period may be of greater value for predicting clinical outcomes in patients with advanced CKD.

Guideline 4: Management of Dyslipidemia in Diabetes and CKD

Dyslipidemia is common in people with diabetes and CKD. Cardiovascular events are a frequent cause of morbidity and mortality in this population. Lowering low-density lipoprotein cholesterol (LDL-C) with statin-based therapies reduces risk of major atherosclerotic events, but not all-cause mortality, in patients with CKD including those with diabetes.

4.1: We recommend using LDL-C lowering medicines, such as statins or statin/ezetimibe combination, to reduce risk of major atherosclerotic events in patients with diabetes and CKD, including those who have received a kidney transplant. (IB)

The evidence that lowering the LDL-C concentration reduces the risk of major atherosclerotic events in patients with diabetes and CKD (other than stage 5) was presented in detail in the original KDOQI diabetes guideline.⁴ Recommendations were based largely on four post hoc analyses⁷³⁻⁷⁶ that reported results of lipid lowering therapy for a subpopulation of patients with CKD and diabetes compared with placebo (Table 5).

A new clinical trial has added to the evidence that lowering LDL-C reduces cardiovascular events in a wide range of patients with diabetes and CKD. The Study of Heart and Renal Protection (SHARP) trial⁷⁷ randomized 9438 participants ≥ 40 years old with CKD (mean eGFR of 27 mL/min/1.73 m²) to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo, and followed them for 5 years. Thirty-three percent of the patients (n=3023) were receiving maintenance dialysis at randomization and 23% (n=2094) of the participants had diabetes, with equal proportions in the simvastatin plus ezetimibe and placebo groups. Statin plus ezetimibe therapy was associated with a significant 17% relative reduction in the risk of the primary outcome of major atherosclerotic events (coronary death, myocardial infarction [MI], non-hemorrhagic stroke, or any revascularization) compared with placebo (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.74-0.94). This finding was attributable in large part to significant reductions in non-hemorrhagic stroke and arterial revascularization procedures. There was no reduction in the risk of all-cause mortality, and among the patients with CKD not treated by dialysis at randomization (n=6247), treatment with simvastatin plus ezetimibe did not reduce the frequency of doubling of the baseline SCr concentration or progression to ESRD. Although the

study was not powered to reliably estimate the effect of treatment on primary outcomes among clinical subgroups, the proportional effect on major atherosclerotic events did not appear to differ between those with or without diabetes.

The Assessment of Lescol in Renal Transplant (ALERT) trial⁷⁸ examined the effect of statin therapy on cardiovascular risk reduction in 2102 patients with functioning kidney transplants who were followed for 5-6 years. Fluvastatin therapy (40-80 mg/day), compared with placebo, was associated with a significant 35% relative reduction in the risk of cardiac death or definite nonfatal MI (HR, 0.65; 95% CI, 0.48-0.88). The study included a pre-specified analysis for a subset of 396 patients with diabetes, of whom 197 were randomized to fluvastatin and 199 to placebo. In this subset, the benefit was similar in magnitude as in the overall cohort, but was not statistically significant (HR, 0.71; 95% CI, 0.41-1.21), suggesting limitations of under-powering due to small sample size. Given these limitations and the lack of a significant interaction between diabetes and treatment assignment for the primary outcome, the Work Group based its recommendation for statin treatment in kidney transplant patients on the overall results from the ALERT study.

Accordingly, the evidence that treatment with statin or statin/ezetimibe combination improves health outcomes is based primarily on prevention of CVD events. There is no evidence from these trials that such treatment improves kidney disease outcomes, including doubling of SCr or progression to ESRD, or all-cause mortality.

4.2: We recommend not initiating statin therapy in patients with diabetes who are treated by dialysis. (IB)

Results of the Die Deutsche Diabetes Dialyse Studie (4D)⁷⁹ motivated the recommendation regarding statin treatment in patients with type 2 diabetes on maintenance hemodialysis in the original KDOQI diabetes guideline.⁴ Concerns that the results of 4D were attributable to the futility of a single intervention in such high-risk patients inspired A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis (AURORA)⁸⁰, a clinical trial that randomized 2776 patients on hemodialysis to rosuvastatin 10 mg a day and placebo. Only 26% of the patients in AURORA had diabetes. As found in 4D, AURORA reported no significant effect of statin therapy on the primary cardiovascular outcome that included cardiac death or non-fatal MI and fatal or non-fatal

Table 5. Summary of Four Post Hoc Analyses Reports of Lipid Lowering in People with Diabetes Mellitus (DM) and CKD

Study	# treated/# with DM and CKD	Randomized statin	CVD outcome vs. placebo	Definition of kidney impairment	Kidney outcome vs. placebo
OSCOPS, CARE, LIPID – Tonelli ⁷⁶	290/571	Pravastatin, 40 mg/day	All cause mortality 18.0% on pravastatin vs. 19.2%. (Absolute reduction decreased from 6.4 to 3.5% comparing people with DM and CKD to those with neither). HR for CABG or PTCA 0.69, (95% CI 0.47-1.01). HR for stroke, 1.12 (95% CI 0.63-1.97).	GFR <60 mL/min/1.73 m ² or GFR 60-89 mL/min/1.73 m ² concomitant with trace or greater proteinuria on dipstick urinalysis	Not reported
4S – Chonchol ⁷³	105/200	Simvastatin, 20 mg/day	All cause mortality 13.5% on simvastatin vs. 27.9%	GFR <75 mL/min/1.73 m ²	Not reported
CARDS – Colhoun ⁷⁴	482/970	Atorvastatin, 10 mg/day	All cause mortality 5.6% on atorvastatin vs. 6.2%. Stroke 1.2% on atorvastatin vs. 3.1% on placebo. Coronary revascularization 1.0% on atorvastatin vs. 2.5% on placebo.	GFR <60 mL/min/1.73 m ²	20.5% regression from micro- to normoalbuminuria vs. 19.4%.
HPS – Collins ⁷⁵	142/310	Simvastatin, 40 mg/day	All cause mortality not reported.	Creatinine >110 μmol/L (1.24 mg/dL) for women, and >130 μmol/L (1.47 mg/dL) for men	Significantly smaller fall in the GFR during follow-up (5.9 [0.1] vs. 6.7 [0.1] mL/min, difference –0.8 [0.2] mL/min; <i>p</i> =0.0003). This difference appeared to be slightly larger among those who had diabetes than among those who did not (–1.4 [0.4] mL/min vs. –0.5 [0.2] mL/min; heterogeneity <i>p</i> =0.08).

Abbreviations: 4S, Scandinavian Simvastatin Survival Study; CABG, coronary artery bypass graft surgery; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events; CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; HPS, Heart Protection Study; HR, hazard ratio; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; PTCA, percutaneous coronary angiography WOSCOPS, West of Scotland Coronary Prevention Study.

Table 6. Fibrate Treatment in Patients with Diabetes Mellitus (DM) and CKD

Study	# treated/# with DM and CKD	Randomized fibrate	CVD Outcome	Regression from micro- to normoalbuminuria
VA-HIT – Tonelli ⁸⁶	136/297	Gemfibrozil, 600 mg BID	Composite outcome 26.5% (36/136) in the gemfibrozil treated group vs. 41.0% (66/161) in the placebo	Not reported
FIELD – Keech ^{85,87}	4895/9795	Fenofibrate, 200 mg/day (mean dose)	Not reported	47.0% (462/983) in the fenofibrate group vs. 39.3% (400/1017) in the placebo group
DAIS – Ansquer ⁸⁴	155/314	Fenofibrate, 200 mg/day	Not reported	37.7% (20/53) in the fenofibrate group vs. 34.1% (15/44) in the placebo group

Abbreviations: BID, twice a day; DAIS, Diabetes Atherosclerosis Intervention Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; VA-HIT, Veterans Affairs High-density lipoprotein Intervention Trial.

stroke, either in the overall study population or in the subgroup of patients with diabetes. A subsequent post hoc analysis of the participants with diabetes in AURORA⁸¹ found that treatment with rosuvastatin significantly reduced the risk of a redefined end point of cardiac death or non-fatal MI by 32%, but significantly increased the risk of hemorrhagic stroke by more than 5-fold. Although the number of hemorrhagic strokes among participants with diabetes in AURORA was small and the overall stroke rate did not differ by treatment group, the finding is concerning, since the original report from the 4D trial found that treatment with atorvastatin was associated with 2-fold increase in fatal stroke.⁷⁹ A recent post hoc analysis of the 4D trial⁸² found that fatal and nonfatal cardiac events were significantly reduced if the pre-treatment LDL-C was >145 mg/dL. Although these post hoc analyses provide a different look at the data from the previous studies, they must be viewed as hypothesis-generating, and therefore do not alter the main message of the guideline update, which is based on the primary pre-specified outcomes from these clinical trials.

The SHARP trial⁷⁷ indicated that risk for the primary outcome of major atherosclerotic events other than death was reduced by simvastatin/ezetimibe combination among a wide range of patients with CKD. Yet, the “subgroup” of over 3000 patients on dialysis did not show a statistically significant reduction in risk of the primary outcome. The SHARP investigators advocate that this group is still likely to benefit because of lack of statistical heterogeneity. However, even as a subgroup, this is still the largest trial of LDL cholesterol-lowering conducted to-date in patients on dialysis. Taking into account the 4D and AURORA trials along with the SHARP data, overall evidence to support a favorable effect of initiating LDL-cholesterol lowering treatment on atherosclerotic events in dialysis patients is lacking. Moreover, since most of

the clinical CVD events experienced by hemodialysis patients with diabetes are deaths, for which statins provide little or no benefit as illustrated in the SHARP trial,⁷⁷ the Work Group concluded that the available evidence continues to support the recommendation that statin therapy not be initiated in dialysis patients with diabetes. Whether previously treated patients should be continued on statin therapy once they commence dialysis, or not, has not been studied, and as such, data are insufficient to provide guidance for this group.

LIMITATIONS

With the exception of SHARP, data to support recommendations for LDL cholesterol-lowering come from post hoc subgroup analyses of clinical trials that included CKD patients with and without diabetes. Nevertheless, a growing body of evidence demonstrates a clear benefit of statin therapy on clinical CVD events among patients with diabetes. This benefit holds true across a wide range of CKD stages, perhaps with the exception of those on dialysis. Of note, the Adolescent type 1 diabetes mellitus cardio-renal Intervention Trial (AddIT)⁸³ is under way, and will provide data on the effectiveness of atorvastatin and quinapril to prevent cardiovascular and kidney complications in adolescents with type 1 diabetes.

Other lipid altering medicines may also be of value in the management of patients with diabetes and CKD, but the Work Group concluded that the available evidence for these medicines was not yet sufficient to make specific management recommendations. Randomized treatment trials that examined the effect of fibrates relative to placebo in patients with diabetes and CKD are summarized in Table 6.⁸⁴⁻⁸⁶ The Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT)⁸⁶ found evidence that gemfibrozil reduces risk of major cardiovascular events (fatal coronary heart disease, nonfatal MI, and stroke) by 42% com-

Table 7. Dose Adjustment for Lipid Lowering Medicines in CKD

Medication Class and Agents	No CKD or stages 1-2	CKD stage 3	CKD stages 4-5	Kidney transplant
Statins (mg/day)				
Atorvastatin	10-80	10-80	10-80	10-20
Fluvastatin	20-80	20-80	10-80	10-80
Lovastatin	10-80	10-80	10-40	10-40
Pravastatin	10-40	10-40	10-20	10-20
Rosuvastatin	5-40	5-20	5-10	5
Simvastatin	5-40	5-40	5-20	5-20
Bile acid sequestrants (g/day)				
Cholestipol	5-30	5-30	5-30	5-30
Cholestyramine	4-16	4-16	4-16	4-16
Colesevelam	2.6-3.8	2.6-3.8	2.6-3.8	2.6-3.8
Fibric acid derivatives (mg/day)				
Bezafibrate*	400-600	200	Avoid	Avoid
Clofibrate	1000-2000	500	500	Avoid
Ciprofibrate*	200	Unknown	Avoid	Unknown
Fenofibrate	96	48	Avoid	Avoid
Gemfibrozil	1200	1200	600	600
Other (mg/day)				
Ezetimibe	10	10	10	Unknown
Niacin	2000	2000	1000	Unknown

*Not currently licensed for use in the U.S.

pared with placebo (RR, 0.58; 95% CI, 0.38-0.89) in a post hoc analysis of 297 individuals with low eGFR (GFR <75 mL/min/1.73 m²) and diabetes. The Diabetes Atherosclerosis Intervention Study (DAIS)⁸⁴ and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study^{85,87} reported that fenofibrate treatment significantly lowered the risk of developing new onset microalbuminuria compared with placebo (RR, 0.87 in patients with type 2 diabetes; 95% CI, 0.77-0.97). Fenofibrate also promoted regression from microalbuminuria to normoalbuminuria (RR, 1.15; 95% CI, 1.04-1.28, n=2260, 2 trials), but did not change the risk of progression from microalbuminuria to macroalbuminuria (RR, 1.07; 95% CI, 0.43-2.63, 1 trial, n=97). There is moderate evidence that fenofibrate decreases risk of progression from normoalbuminuria to microalbuminuria and leads to regression of microalbuminuria to normoalbuminuria compared with placebo in patients with type 2 diabetes. None of the trials of fibrate therapy in diabetes published since the original guideline reported CVD or kidney disease outcomes for the subgroup of patients with CKD.

IMPLEMENTATION ISSUES

Management of dyslipidemia involves a multifactorial approach that includes medicines, proper nutrition, and physical activity. Each of these approaches may need to be modified in the setting of CKD. Nutritional management in diabetes and CKD is addressed in Guideline 5 and physical activity is ad-

ressed in Clinical Practice Recommendation 4 of the previously published guideline.⁴

Higher doses of statins may be beneficial in some patients with diabetes and mild-to-moderate CKD (stages 1-3). The Treating to New Targets trial (TNT)⁸⁸ reported a benefit for secondary prevention of major cardiovascular events from treatment with atorvastatin, 80 mg/day compared with atorvastatin, 10 mg/day, in 546 patients with diabetes and CKD and pre-existing coronary artery disease over 5 years of follow-up. The risk of stroke was 4.8% (13/273) for the higher dose, compared with 7.3% (20/271) for the lower dose. There was no reduction in all-cause mortality.

Higher doses of lipid lowering medicines, however, are associated with increased risk of myopathy,⁸⁹ particularly among patients with reduced kidney function.⁹⁰ Therefore, doses of some lipid-lowering medicines should be modified in moderate-to-advanced CKD (stages 3-5). Additionally, reliance less on higher dosing of statins and more on combination therapy to reduce LDL-C is an attractive strategy. The SHARP trial⁷⁷ addressed this issue by using lower dose simvastatin (20 mg/day) and adding the cholesterol-absorption inhibitor ezetimibe (10 mg/day) to achieve an average LDL-C reduction of about 1 mmol/L. Table 7 provides guidance for drug dosing of lipid-lowering medicines in patients with CKD. Updated recommendations on management of dyslipidemia in CKD (including diabetes) are expected from KDIGO in 2013.

Of note, the U.S. FDA issued a Safety Announcement in June 2011 that recommends limited use of the highest approved dose of simvastatin (80 mg) because of increased risk of myopathy. Simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle injury. Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. In addition to these new limitations, the FDA is requiring changes to the simvastatin label to add new contraindications (concurrent cyclosporine or gemfibrozil use) and dose limitations for use with other medicines such as calcium channel

blockers or amiodarone. The lovastatin label has also been updated extensively with new contraindications and dose limitations when it is taken with certain medicines that can increase the risk of myopathy; and human immunodeficiency virus and hepatitis C virus protease inhibitors are now contraindicated with simvastatin and lovastatin because of increased risk of myopathy. The FDA has also added information to statin labels about the potential for generally non-serious and reversible cognitive side effects and reports of increased HbA_{1c} levels. Further information can be obtained at the FDA website (fda.gov/Drugs/DrugSafety).

Guideline 6: Management of Albuminuria in Normotensive Patients with Diabetes

Treatments that produce a lasting decrease in urinary albumin excretion may slow the progression of DKD even in the absence of hypertension. However, most people with diabetes and albuminuria have hypertension. Assessment of albuminuria is addressed in Guideline 1.⁴ Management of hypertension is addressed in Guideline 3⁴ and the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD.

6.1: We recommend not using an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) for the primary prevention of DKD in normotensive normoalbuminuric patients with diabetes. (1A)

There is currently strong evidence that use of agents that block the renin-angiotensin system (RAS) does not prevent the development of microalbuminuria or slow the rate of biopsy-assessed diabetic renal lesions in normoalbuminuric normotensive patients with type 1 diabetes, at least over a study duration of 4-5 years.⁹¹⁻⁹³

Studies in normoalbuminuric normotensive patients with type 2 diabetes are fewer but also show no benefit.^{91,94} For normoalbuminuric patients with type 2 diabetes and hypertension, or pre-existing CVD, use of ACE-Is with or without diuretics reduces the absolute risk of developing microalbuminuria by 2-4% over 4-5 years.⁹⁵⁻⁹⁷ However, these studies used a variety of definitions of microalbuminuria, were often based on single urine samples taken at 1-2 year intervals, and were not tested for a durable effect vs. a transient hemodynamic effect of RAS blockade. More stringent definitions of microalbuminuria using multiple timed collections at more frequent intervals revealed incidence rates of 3-4% per annum,^{91,97} less than half the incidence reported by studies using less stringent definitions of microalbuminuria such as MICROHOPE⁹⁶ and ADVANCE.⁹⁵ Thus, the evidence does not support a clinical benefit of intervention to prevent the intermediate outcome of persistent microalbuminuria or the changes in kidney structure associated with DKD.

6.2: We suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels ≥ 30 mg/g who are at high risk of DKD or its progression. (2C)

There are no long-term studies that show a benefit of treatment with RAS blocking agents on CKD

progression or health outcomes in normotensive patients with diabetes and increased levels of albuminuria. Some of these patients, perhaps especially those with additional risk factors for DKD, may benefit from such treatment, although there is no strong evidence to support this belief. Those more likely to develop or progress to more serious DKD include patients with increasing levels of albuminuria in the microalbuminuria range, macroalbuminuria, declining glomerular filtration rate, increasing blood pressure, presence of retinopathy, elevated lipids and/or uric acid concentrations, or a family history of hypertension, macrovascular disease, or DKD. Patients with microalbuminuria and none of these additional risk factors may be at relatively low risk of DKD or its progression and could be followed without treatment with RAS blocking agents to see whether some of these additional risk factors subsequently develop. The presence of macroalbuminuria without retinopathy, especially if present within 10 years of diabetes onset, suggests a need for investigations to rule out nondiabetic kidney diseases.

In hypertensive patients with type 1 and type 2 diabetes, RAS blocking agents prevent development of macroalbuminuria, but even after two or more years of treatment, albuminuria increases soon after the withdrawal of these drugs.⁹⁸ This observation calls into question the durability of the treatment effect on underlying disease processes.

For patients with macroalbuminuria and moderately reduced eGFR, there is strong evidence showing that angiotensin-converting enzyme (ACE) inhibition in type 1⁹⁹ and ARBs in type 2^{100,101} diabetes confer benefit in terms of loss of GFR (both rates of decline in eGFR and doubling of baseline SCr) and ESRD, but few of these patients are normotensive. Furthermore, there are no long-term studies that examine the renoprotective efficacy of ACE-Is in type 2 or ARBs in type 1 diabetes.

Fundamental to the interpretation of all of these studies is the definition of hypertension, which is currently under review by KDIGO and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). Early studies in "normotensive" patients with type 1 diabetes used definitions of the upper limit of normal for blood pressure that would now be considered hypertension. The meta-analysis published by the ACE Inhibitors in Diabetic Nephropathy Trialist Group¹⁰² included studies in patients with type 1 diabetes whose upper limit of baseline blood pressures at inclusion ranged from 145-160 mm Hg systolic and

90-120 mm Hg diastolic. These investigators also did not report correction for systolic pressure, only for diastolic. Moreover, preferred statistical approaches to controlling for the effects of blood pressure are debatable, and as such, are not established methodologies.

LIMITATIONS

Past recommendations regarding management of albuminuria in patients with diabetes assumed that the appearance of microalbuminuria signaled an inevitable progression to macroalbuminuria. There is increasing evidence, however, of spontaneous remission of microalbuminuria in up to 40% of patients with type 1 diabetes,^{103,104} while about 30-40% remain microalbuminuric and do not progress to macroalbuminuria over 5-10 years of follow-up.¹⁰⁵ Whether this observation reflects a better understanding of the natural course of albuminuria in diabetes or is, in part, a response to treatment is uncertain, but the adoption of a blanket policy for the use of RAS blocking drugs in these patients has made it difficult to explore other potential therapies and hindered studies of the natural history of early diabetic nephropathy.

The use of albuminuria as a surrogate marker of benefit of intervention in DKD was the subject of an FDA/NKF symposium in 2008.¹⁰⁶ Major questions were raised about how to define abnormal albuminuria; at what level should intervention take place; how many tests over what period of time would be required before intervention should commence; what would be regarded as an adequate response to intervention and how would this be defined; and how would long term benefit be measured? The conference produced a consensus report that concluded that the evidence was not strong enough to use changes in albuminuria as an adequate surrogate endpoint of long term kidney benefit in people with diabetes or other kidney disease.

A major confounding problem with interpreting studies of intervention in the course of DKD is changing natural history. In the 1970s, the median time to ESRD from the development of overt (dipstick positive) proteinuria in type 1 diabetes was <7 years;¹⁰⁷ it is now >14 years.¹⁰⁵ The incidence of ESRD in type 1 diabetes from Finland is now only 7.8% at 30 years duration.¹⁰⁸ Recent data from the DCCT/EDIC cohort shows a 10 year incidence of 3% for ESRD in 325 patients with incident microalbuminuria during the course of the study.¹⁰⁵ Thus, intervention studies with benefit in terms of health outcomes related to kidney disease as their primary end point could require many years of observation, and be costly in terms of resource. For these reasons, such studies are unlikely to be performed. In clinical practice, changes in eGFR and albuminuria are suggested to be used together to monitor kidney status, even in the absence of conclu-

sive evidence that they predict precisely long-term reduction in risk of actual health outcomes such as ESRD.

IMPLEMENTATION ISSUES

Dosages for ACE-Is or ARBs

In normotensive persons with diabetes and albuminuria the target dose of ACE-Is or ARBs is unknown. In the absence of side effects or adverse events (e.g., hyperkalemia or acute kidney injury) the Work Group suggests titration up to the maximum approved dose for the treatment of hypertension.

Cautions About Usage of ACE-Is and ARBs

The use of a combination of ACE-Is and ARBs as a dual blockade of the RAS cannot be recommended at present. At least 1 clinical trial has shown an increase in adverse events, particularly impaired kidney function and hyperkalemia, compared to either agent alone, despite a reduction in albuminuria using combination therapy.^{109,110}

The use of ACE-Is and ARBs in early pregnancy is reportedly associated with harm to the fetus (neonatal acute kidney injury; lung toxicity; skull hypoplasia; congenital malformations of the cardiovascular system, central nervous system, and kidney),¹¹¹ although more recent studies have not confirmed these risks.^{112,113} The FDA is currently reviewing its advice on the use of these agents in the first trimester.

Newer Agents that Target the RAS

One 6-month phase 2 study of Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) reported a further reduction of albuminuria with the addition of the direct renin inhibitor aliskiren to losartan in patients with type 2 diabetes and microalbuminuria.¹¹⁴ A phase 3 study, Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE), was subsequently initiated in 3 groups of patients with type 2 diabetes: 1) albuminuria ≥ 200 mg/g; 2) eGFR 30-60 mL/min/1.73 m² with albuminuria ≥ 20 mg/g and <200 mg/g; 3) eGFR 30-60 mL/min/1.73 m² with CVD. However, ALTITUDE was stopped early due to therapeutic futility and increased risk of stroke and adverse events including hyperkalemia, hypotension, and ESRD or death due to kidney disease. Given these findings, dual blockade of the RAS with direct renin inhibition and either ACE-I or ARB cannot be recommended. Indeed, the manufacturer (Novartis) recommends that aliskiren be stopped in diabetic patients treated with ACE-I or ARB, and in April 2012 the U.S. FDA announced a new contraindication against the use of aliskiren with ACE-Is or ARBs in patients with diabetes because of the risk of kidney impairment, hypotension, and hyperkalemia.

Research Recommendations

These guideline updates, and the clinical trials on which they were based, illustrate the importance of continuing to conduct research that challenges or expands established clinical practice. As stated in the original guideline, uncertainty is an immutable element of all scientific research, and the establishment of a guideline should neither preclude nor render unethical further inquiry.⁴ Even as knowledge regarding approaches to managing diabetes to prevent or treat DKD and related complications has advanced substantially since the publication of the original KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease, many essential questions remain to be answered. The original guideline publication provided a list of research suggestions that meaningfully informed the investigative agenda, one of many indications of the importance of these efforts. The present research recommendations arose directly from the guideline update process. The Work Group provided research suggestions they considered key to advancing knowledge concerning clinical care. These suggestions are arranged by topic area in order to link back to the specific guidelines. Some of the recommendations are not for new research studies *per se*, but are proposals for how research studies might be designed to enhance their value, validity, or generalizability.

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

1. Determine effects of glycemic control on early and late GFR loss and health outcomes of CKD. Evaluate different levels of glycemic control to optimize safety as well as clinical outcomes of survival, hospitalization, and CVD events in advanced CKD and/or ESRD.
2. Perform validation studies of HbA_{1c}, glycated albumin, and potentially other markers of long-term glycemic control in patients with diabetes and various stages of CKD.
3. Assess metformin safety in patients with CKD stages 4 and 5.

Guideline 4: Management of Dyslipidemia in Diabetes and CKD

1. Perform clinical trials of statins for primary and secondary prevention of CVD in patients with diabetes and CKD stages 1-4 and meta-analyses of completed studies in CKD stage 5.
2. Conduct studies of other lipid-lowering agents for primary and secondary prevention of CVD,

or patient level meta-analyses of completed studies, in patients with diabetes and CKD stages 1-4.

3. Establish LDL-C levels for treatment and initiation of therapy as well as targets for primary and secondary prevention in patients with diabetes by CKD stage.
4. Evaluate lipid-lowering therapy for CVD in patients with diabetes who are treated by hemodialysis or peritoneal dialysis, or who have received a kidney transplant.
5. Examine results of previous studies, e.g., SHARP, by CKD stage.
6. Examine data from completed clinical trials to assess effects of lipid lowering agents on outcomes such as albuminuria, eGFR, and ESRD in participants with diabetes.
7. Examine lipid-lowering therapy for CVD in adolescent patients with diabetes.

Guideline 6: Management of Albuminuria in Normotensive Patients with Diabetes

1. Durability of RAS inhibition for the delay in microalbuminuria onset should be tested by a treatment washout phase of at least two months duration.
2. Post hoc adjustment for blood pressure differences may be fraught with faulty assumptions. Therefore, equivalent blood pressure levels are an important design element to be considered in future clinical trials that test specificity of a drug's mechanism of action independent of blood pressure effects.
3. Since the "endpoint" of preventing incident albuminuria derives validity from predicting increased risk of GFR loss, treatments to reduce albuminuria should not be offset by greater GFR decline. Measurement of GFR (e.g., eGFR or other more precise methods) should be performed as a companion to albuminuria. In clinical trials to demonstrate prevention of elevated albuminuria, the demonstration of normoalbuminuria at baseline should follow washout of at least of two months duration from previous RAS blockade, with careful blood pressure control by alternative antihypertensive agents. This approach is necessary to avoid randomization of participants in whom albuminuria is already present, but masked by RAS treatment, an effect which may be posited in several studies where there was rapid progres-

- sion to microalbuminuria in the first few months after randomization to placebo.
4. Given the limitations of albuminuria as an outcome measure and the recent consensus panel's recommendation against acceptance of albuminuria as a surrogate outcome,¹⁰⁶ studies are needed to evaluate durability of effects on urinary albumin excretion. The categorization of albuminuria outcomes should be based on a minimum of two of three consecutive urine samples being in the same category.¹¹⁵
 5. Consider an indication for regulatory approval based on demonstration of a lasting reduction in urinary albumin excretion, but conditional upon firm commitment to continue long-term studies to determine effects on GFR loss and clinically relevant outcomes.
 6. Evaluate the relative roles of ACE-Is, ARBs, renin blockers, and mineralocorticoid receptor blockers on progression of DKD in patients with albuminuria.
 7. Kidney biopsy outcomes based on carefully measured structural variables that correlate strongly with GFR loss may reduce the duration of primary prevention or early intervention DKD clinical trials.⁹³ Consider enzyme replacement for Fabry's Disease as an example.¹¹⁶
 8. Clinical trials represent important opportunities to advance knowledge beyond addressing the primary hypotheses themselves. Protocols should include plans for acquiring and banking blood, urine, DNA, and other samples for eventual biomarker discovery and validation. Consider the DCCT as an example.¹¹⁷

Conclusion

Earlier and more aggressive therapeutic intervention is believed to be responsible, at least in part, for the general decline in the incidence of ESRD attributable to diabetes among several racial and ethnic groups in recent years.² Encouraged by these observations and by the results of previous trials using less aggressive endpoints, several large, well-designed clinical trials were conducted among patients with diabetes to determine whether even earlier or more intensive therapy might further reduce the frequency of CKD and important health outcomes of CKD, including ESRD. Results from these trials suggest that “more is not always better,” as such interventions often did not improve clinical outcomes, and in some settings were actually harmful. After examining the new evidence, the Work Group moved each guideline to a more conservative position than was taken in the original guideline published in 2007.

Clinical Practice Guideline 2 was modified to recommend that a target HbA_{1c} of ~7% is mainly useful to prevent or delay microvascular complications including DKD in both type 1 and type 2 diabetes. A recent series of three large clinical trials found nominal to no benefit of more intensive glycemic control (target HbA_{1c} levels <7%) on macrovascular complications or clinical kidney disease endpoints (loss of function or requirements for dialysis or transplantation) in older people with established type 2 diabetes. Moreover, the risk of severe hypoglycemia was high.¹⁹⁻²¹ Therefore, a target HbA_{1c} <7% is not recommended for patients with diabetes at risk of hypoglycemia, a group that includes many in the CKD population. Finally, patients with diabetes and advanced CKD often have multiple co-morbidities or limited life expectancy that would nullify the potential benefits of intensive glycemic control. In such patients, an extension of target HbA_{1c} to >7% is suggested.

Clinical Practice Guideline 4 was updated to reflect the results of recent clinical trials of lipid-lowering therapies that included patients with diabetes and CKD. In particular, the SHARP trial added new data

to support treatment with a statin-ezetimibe combination in patients with CKD.⁷⁷ This treatment reduced risks of major atherosclerotic events, but not deaths or health outcomes related to kidney disease. Additionally, SHARP and AURORA expanded the knowledge base about initiating statins or statin-ezetimibe in patients with diabetes treated by hemodialysis.^{77,80} Taken together, these data do not provide convincing evidence for benefits on overall clinical CVD events in this specific group. Guideline 4 no longer includes recommendations for an LDL-C concentration at which statin therapy should be initiated or a therapeutic target concentration to be achieved because the studies were not conducted in this manner and evidence is lacking to guide therapy by LDL-C concentration.

Clinical Practice Recommendation 1, now referred to as Clinical Practice Guideline 6, was revised to recommend that ACE-Is and ARBs not be used in patients with diabetes and CKD who have normal blood pressure and normoalbuminuria. Clinical trials of patients with either type 1 or 2 diabetes found these treatments did not reduce the development of elevated urinary albumin excretion or the structural evidence of DKD.^{91,93} The use of ACE-Is or ARBs is still suggested in normotensive patients with diabetes and elevated albuminuria who are at high risk of DKD or its progression, but this suggestion is based on low-level evidence.

This update to the KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease reflects our understanding of the present state of knowledge. Many questions about optimal management of DKD remain unanswered and numerous new ones have arisen. The research recommendations described above are intended to guide forthcoming research agendas and, hopefully, lead to results that further advance knowledge and inform future updates. Ultimately, the goal of this quest is to deliver optimal care that improves and prolongs the lives of people with diabetes and CKD.

Acknowledgements

Guideline recommendations included in this Update were published originally in the American Journal of Kidney Diseases in 2007 and were reproduced with permission from the NKF.

We thank Drs Michael Rocco and Jeffrey Berns for their careful review of this manuscript; and Kerry Willis, Emily Howell, and Michael Cheung from the National Kidney Foundation for help coordinating the work of the group and preparing the manuscript.

The Work Group is indebted to the evidence review team from the Minneapolis Veterans Administration Center for Chronic Disease Outcomes Research, who worked tirelessly to assemble the evidence and creatively to synthesize the information. The Work Group appreciates the careful review of the draft guideline and suggestions for improvement by external reviewers. Each comment was carefully considered and, whenever possible, suggestions for change were incorporated into the final report. As a result, this Update of the KDOQI Clinical Practice Guideline for Diabetes and Chronic Kidney Disease is the product of the Work Group, the Evidence Review Team, the NKF, and all those who contributed their effort to improve the updated guideline.

The following individuals provided feedback on the draft guideline during public review. Participation in the review does not necessarily constitute endorsement of the content of the report by the individuals or the organization or institution they represent.

Muhammed Al Rohani; Mona Al-Rukhaimi; Mustafa Arici; Brent Arnold; Juan F Agurto Ayala; Ninos

Ayez; Li Baohua; Karen Basinger; Tran Thanh Binh; Anabelle Blas; Karen Burchell; Eduardo Guimarães Camargo; Vicente Girard Campolo; Anup Chaudhari; Xianggeng Chi; Danielle Cooney; Andrew Crannage; Paul Crawford; William C Cushman; Mary Date; Chaicharn Deerochanawong; Pam Earll; Magdy El Sharkawy; Alicia Elbert; Thomas G Ferguson; Olivia Georgescu; Mirela Liana Gliga; Elaine Go; Teresia Goldberg; Suzanne Gore; Linda B Haas; Georg Hasche; Parin Hedayati; Koen Hens; Chih-Jung Ho; Adriana M Hung; Deepa Jayaram; Chandra Mauli Jha; Sharon Karp; Johannes Kessel; J S Kumar; Craig B Langman; Brian J Lee; Edgar V Lerma; Benjamin Littenberg; Zhi-Hong Liu; Tarek S H Mahmoud; Kay Marioni; Mahendra Maru; Aletha Matsis; Amanda Medland; Klemens B Meyer; Sergio Mezzano; Gabriel Mircescu; Linda W Moore; Giuseppe Mule; John Ndungo Nderitu; Allen R Nissenson; Shashidhar Shree Niwas; Oscar Noboa; Nazanin Noori; Karim Nooruddin; David K Ofsa; John Okogbaa; Vuddhidej Ophascharoensuk; Bassam Abu Oun; Päivi Maria Paldánus; Meda E Pavkov; Jessie Pavlinac; Frederik Persson; Kevin A Peterson; Cibele Rodrigues; Bento Fortunato Cardoso dos Santos; Sharon R Schatz; Michael Schwenk; Mitesh B Sheth; Sandra Pinho Silveiro; David R Smith; María José Soler Romeo; Laura Strickland; Tony Tanrongshao; Rowan G Walker; David C Wheeler; Sara Wolfson; Mai-Szu Wu; Jing Xu; Yukio Yuzawa; Zhao Zhenwu; Yun-Ping Zhou; Carmine Zoccali; Kim Zuber.

Biographic and Disclosure Information

Rudolf W. Bilous, MD, is Professor of Clinical Medicine at Newcastle University and Honorary Consultant Physician at the James Cook University Hospital, Middlesbrough, UK. He studied medicine at Guy's Hospital and completed his clinical training at various hospitals in London. He was an NIH Fellow at the Unit for Metabolic Medicine at Guy's from 1980-1982 working for Professor Harry Keen and with Drs John Pickup and Giancarlo Viberti examining the effects of metabolic control on microvascular complications. From 1985-1987 he was Juvenile Diabetes Research Foundation (JDRF) Fellow at the University of Minnesota working for Drs Mike Steffes and Michael Mauer. He was awarded his MD from the University of London in 1987 and elected Fellow of the Royal College of Physicians of London in 1991. He served as secretary and Chair of the Specialty Advisory Committee for Endocrinology and Diabetes and Chairman of the Professional section of Diabetes UK. He is currently Chairman of the workgroup reviewing the National Institute for Health and Clinical Excellence (NICE) guideline for Diabetes in Pregnancy and President of the European Diabetic Nephropathy Study Group of the European Association for the Study of Diabetes. Dr Bilous reported the following disclosures: Travel bursaries: Boehringer Ingelheim; Speaker honoraria: Animas Corp, Boehringer Ingelheim, Novo Nordisk and Roche. He is the recipient of research funding from Diabetes UK.

J. Michael Gonzalez-Campoy, MD, PhD, FACE, is medical director and CEO of the Minnesota Center for Obesity, Metabolism, and Endocrinology (MNCOME). He is a recognized national expert on diabetes and obesity, and a proponent of adiposopathy as a treatment target. He received his MD, PhD degree (PhD in physiology and biophysics – hormonal regulation of renal function) from Mayo Medical School and Mayo Graduate School in Rochester, MN, and completed his residency in internal medicine at the Mayo Graduate School of Medicine. Dr Gonzalez-Campoy obtained a fellowship in diabetes, metabolism and endocrinology at the University of Minnesota Medical School. Dr Gonzalez-Campoy is member of the Board of Trustees of the American College of Endocrinology, past member of the American Association of Clinical Endocrinologists (AACE) board of directors, and the AACE liaison to the National Diabetes Education Program (NDEP). Dr Gonzalez-Campoy reported the following disclosures: Ownership: Minnesota Center for Obesity, Metabolism and Endocrinology, PA. Payments accepted from patients and third party payers (HMOs, PPOs, government, relatives); Speaker honoraria: American Association of Clinical

Endocrinologists, Amylin, Boehringer Ingelheim, Consensus Medical Communications, Council of State Bioscience Associations (CSBA), Eastern European Medical Society, Forest, Hennepin County Medical Center, International Society of Clinical Densitometrists, OurCreatus, Santarus, and Tethys; Research Grants: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Ipsen, Leptos, MNCOME Foundation, Novo Nordisk, Sanofi-Aventis; Consultant: Allergan, Amylin, Boehringer Ingelheim, Centers for Disease Control, Consensus Medical Communications, EndocrineWeb, Kitch Attorneys and Counselors, Leptos, Medtronic, Merck, National Diabetes Education Program, National Institutes of Health, National Minority Quality Forum, Pfizer, Roche, Shindler-Neff (law firm), Tethys, ValenTx, and WebMD/Medscape.

Judith E. Fradkin, MD, is the Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases (DEMD) for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health (NIH). Previously, Dr Fradkin directed the Institute's research programs in diabetes, cystic fibrosis, endocrinology, and metabolic diseases. Dr Fradkin came to NIDDK as a clinical associate in 1979 after an endocrinology fellowship at Yale University. She studied at the University of California at San Francisco in 1975 and completed an internship and residency at Harvard's Beth Israel Hospital in Boston. Dr Fradkin is currently responsible for planning and implementation of multiple major clinical trials initiated by NIDDK, while coordinating diabetes research as chair of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) and coordinating the trans-DHHS planning and implementation of a special appropriation for type 1 diabetes research. Dr Fradkin works in collaboration with the Centers for Disease Control and Prevention to develop and implement activities of the National Diabetes Education Program. As a practicing endocrinologist, she continues to treat patients at the National Naval Medical Center in Bethesda, MD, where she has worked as a staff endocrinologist since the early 1980s. Dr Fradkin reported no relevant financial relationships.

Michael Mauer, MD, is Professor of Pediatrics and Medicine and Director of Pediatric Solid Organ Transplantation at the University of Minnesota School of Medicine. He has more than 35 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 and studies of Fabry renal disease. Dr Mauer reported the following disclosures: Grant/Research Support: Genzyme, JDRF, NIH; Consultant: Abbott, Boehringer Ingelheim, Cebix, Noxxon, Genzyme, and Sanofi-Aventis.

Mark E. Molitch, MD, is the Martha Leland Sherwin Professor of Endocrinology 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. He has participated in the analysis of kidney function in several long-term diabetes studies, including the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study, the Diabetes Prevention Program (DPP), and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study. Dr Molitch reported the following disclosures: Grant/Research Support: Abbott, Eli Lilly, NIH, Novartis, Sanofi-Aventis, and Reata.

Andrew S. Narva, MD, has served as Director of the National Kidney Disease Education Program at the National Institute of Diabetes and Digestive and Kidney Diseases since 2006. From 1981 to 2006 he worked as a physician for the Indian Health Service (IHS) providing direct care to American Indian patients with kidney disease throughout New Mexico as the Albuquerque Area Nephrologist and providing technical consultation and support to all IHS areas and to tribes as the Chief Clinical Consultant for Nephrology for IHS. He has served as a member of the Medical Review Board of End-Stage Renal Disease Network 15, the NKF Kidney Early Evaluation Program, and on the Steering Committee for the National Quality Forum Renal Endorsement Maintenance Project. Dr Narva serves on the Expert Panel on JNC 8 and the Working Group on CKD, International Federation of Clinical Chemistry and Laboratory Medicine. Dr Narva reported no relevant financial relationships.

Robert G. Nelson, MD, PhD (Work Group Co-Chair), is a Senior Investigator at the National Institute of Diabetes and Digestive and Kidney Diseases in Phoenix, Arizona. His research interests for the past 26 years include the 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 a clinical trial.

Kumar Sharma, MD, FAHA, is Professor of Medicine and Director of the Center for Renal Translational Medicine at the University of California, San Diego. Dr Sharma has maintained a strong clinical practice with a focus on patients with type 1 and type 2 diabetes and kidney disease. He has conducted NIH-funded and industry supported investigator-initiated clinical trials. He has a major interest in the development of clinical biomarkers of kidney disease progression. His research efforts have focused on the pathogenesis of diabetic kidney disease (diabetes nephropathy, DN). His laboratory helped define the central role of the cytokine Transforming Growth Factor- β (TGF- β) in DN by using cell culture and animal models and translated these findings to the human condition. These studies contributed to the development of the highly innovative anti-fibrotic approaches (e.g., pirfenidone) that are currently being tested in clinical research trials under Dr Sharma's guidance. Recently, Dr Sharma has focused his attention on the contribution of the kidney to systemic complications in diabetes and obesity. His group was the first to describe the role of adiponectin on podocyte function and has also focused on the role of energy metabolism (via AMP-activated protein kinase) on development of kidney disease. His group has also used novel genomic, proteomic, and metabolomic methods for clinical applications and for kidney disease. The goal of his research efforts is to develop new diagnostic and therapeutic approaches for personalized medicine in diabetes complications and kidney disease. Dr Sharma reported the following disclosures: Grant/Research Support: Abbott, American Diabetes Association, JDRF, NIDDK, and Veterans Administration; Consultant: Johnson & Johnson, Pfizer.

Katherine R. Tuttle, MD, FASN, FACP (Work Group Co-Chair), is the Executive Director for Research at Providence Sacred Heart Medical Center, Spokane, Washington. Her research interests are in the areas of diabetic kidney disease, hypertension, renal vascular disease, and nutrition. She is Associate Editor of the *Clinical Journal of the American Society of Nephrology*. Dr Tuttle was chair of the Healthcare Professional Workgroup for the National Diabetes Education Program (NIH and CDC) from 2007-2011. She has been chair of the Institutional Review Board – Spokane since 1999. Dr Tuttle has received the Outstanding Clinical Faculty award and is a Clinical Professor of Medicine at the University of Washington School of Medicine with a dual appointment as Professor of Basic Medical Sciences at Washington State University. In 2009, she received the YWCA woman of Achievement Award in

Science. Dr Tuttle has received research funds, grants, or contracts from Eli Lilly and Johnson & Johnson.

KDOQI LEADERSHIP

Michael V. Rocco, MD, MSCE (KDOQI Chair), is Professor of Medicine and Nephrology at Wake Forest University School of Medicine in Winston-Salem, North Carolina. He received his MD degree at Vanderbilt University in Nashville, Tennessee and also served his Internal Medicine residency at Vanderbilt. He completed a nephrology fellowship at the University of Pennsylvania in Philadelphia, Pennsylvania and received a master's degree in epidemiology at Wake Forest University. He was the Principal Investigator (PI) at the Wake Forest clinical site for the NIH-sponsored HEMO Study, Dialysis Access Consortium fistula study, and the Acute Renal Failure Trial Network (ATN Study). He is the principal investigator for the NIH Frequent Hemodialysis Network (FHN) clinical trial in daily nocturnal hemodialysis and is the clinical center PI at Wake Forest for both the FHN daily study and the NIH SPRINT study. He currently serves as the Chair for the National Kidney Foundation's KDOQI. Dr Rocco reported the following disclosures: Consultant: Amgen, DaVita, and Mitsubishi-Tanabe.

Jeffrey S. Berns, MD (Vice Chair, Guidelines and Commentary), is Professor of Medicine at the Perelman School of Medicine, University of Pennsylvania and the Penn Presbyterian Medical Center of Philadelphia, University of Pennsylvania School of Medicine. Dr Berns is also the Associate Dean for Graduate Medical Education, Nephrology Fellowship Program Director and Associate Chief of Renal, Electrolyte and Hypertension Division at the University of Pennsylvania Health System. He obtained his medical degree from Case Western Reserve University and completed his nephrology fellowship at Yale University School of Medicine. His professional activities include his service as a long-standing Work Group member of the KDOQI Anemia guideline from 1995-2007 and currently he is the KDOQI Vice Chair for Guidelines and Commentary and Updates and also a member of the National Quality Forum ESRD Steering Committee. Dr Berns has authored over 130 publications and is on the editorial board of *Clinical Nephrology*, *CJASN*, and *Seminars in Dialysis*. In recognition for his contributions, he received the Leonard Berwick Memorial Teaching Award in 2008 and the Penn Medicine Patient Advocacy Award in 2010. Dr Berns reported the following disclosures: Advisor/Consultant: Affymax, Amgen, and Takeda.

EVIDENCE REVIEW TEAM

Timothy J. Wilt, MD, MPH, is a Professor of Medicine at the University of Minnesota and Core Investi-

gator in the Center for Chronic Disease Outcomes Research at the Veterans Affairs Medical Center in Minneapolis, MN. He has a research agenda which involves conducting clinical trials, systematic reviews and meta-analysis to evaluate the effects of health care interventions on outcomes in adults with chronic diseases. Dr Wilt primarily focuses on the epidemiology, prevention and treatment of prostate disease. Dr Wilt reported no relevant financial relationships.

Areef Ishani, MD, MS, is the Chief of Nephrology at the Minneapolis VA Health Care System and an Associate Professor of Medicine at the University of Minnesota. His primary research interests are in chronic kidney disease, acute kidney injury and end-stage renal disease. Dr Ishani reported no relevant financial relationships.

Thomas S. Rector, PhD, PharmD, is a Professor of Medicine at the University of Minnesota and Core Investigator in the Center for Chronic Disease Outcomes Research at the Veterans Affairs Medical Center in Minneapolis, MN. He has collaborated on several systematic reviews commissioned by the Agency for Healthcare Research and Quality and the VA Evidence Synthesis Program. His primary research interests are heart failure, clinical epidemiology of pharmaceutical outcomes, patient-reported outcome measures and research methods. Dr Rector reported no relevant financial relationships.

Yelena Slinin, MD, MS, is a staff Nephrologist at the Minneapolis VA Medical Center and an Assistant Professor of Medicine at the University of Minnesota. Dr Slinin completed her term as a Clinical Scholar at the Minneapolis Center for Epidemiologic and Clinical Research. Her primary research interests are optimal medical care delivery and outcomes of patient with kidney disease, evidence-based medicine, and critical literature appraisal. Dr Slinin reported no relevant financial relationships.

Patrick Fitzgerald, MPH, is a Project Manager at the Center for Chronic Disease Outcomes Research (CCDOR) in Minneapolis, Minnesota. Mr. Fitzgerald received his Master's in Public Health Administration and Policy Management from the University of Minnesota where the primary focus of his graduate work was health care policy and payment system reform. He has worked as a project coordinator at the Veterans Affairs Medical Center performing drug efficacy and comparative effectiveness trials. His current position involves conducting systematic reviews of literature for public and private entities looking to develop best practice recommendations for evidence-based medi-

cine. Mr Fitzgerald reported no relevant financial relationships.

Maureen Carlyle, MPH, is a medical editor and project coordinator, at the Minneapolis VA Center for Chronic Disease Outcomes Research and is

affiliated with the Minnesota Evidence-based Practice Center at the University of Minnesota. Her primary research interests are evidence-based medicine, systematic review methodology and chronic diseases research. Ms Carlyle reported no relevant financial relationships.

References

1. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA*. Jun 22 2011;305(24):2532-2539.
2. US Renal Data System. USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. *Am J Kidney Dis*. 2012;59(1)(suppl 1):e1-e420.
3. Eknoyan G, Levin NW. Impact of the new K/DOQI guidelines. *Blood Purif*. 2002;20(1):103-108.
4. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis*. Feb 2007;49(2 Suppl 2):S1-S180.
5. Rocco MV, Berns JS. KDOQI in the era of global guidelines. *Am J Kidney Dis*. Nov 2009;54(5):781-787.
6. Eknoyan G, Lameire N, Barsoum R, et al. The burden of kidney disease: improving global outcomes. *Kidney Int*. Oct 2004;66(4):1310-1314.
7. Slinin Y, Ishani A, Rector T, et al. Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and chronic kidney disease: A systematic review for a clinical practice guideline for the National Kidney Foundation. *Am J Kidney Dis*. 2012; 60(5):747-769.
8. Uhlig K, Macleod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. Dec 2006;70(12):2058-2065.
9. The DCCT 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*. Sep 30 1993;329(14):977-986.
10. The DCCT Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int*. Jun 1995;47(6):1703-1720.
11. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet*. May 22 1993;341(8856):1306-1309.
12. Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). *Arch Intern Med*. Jul 27 2009;169(14):1307-1316.
13. 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*. May 1995;28(2):103-117.
14. 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*. Apr 2000;23 Suppl 2:B21-29.
15. 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*. Sep 12 1998;352(9131):837-853.
16. 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*. Sep 12 1998;352(9131):854-865.
17. Levin SR, Coburn JW, Abairra 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*. Oct 2000;23(10):1478-1485.
18. 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*. Jul 29 1993;329(5):304-309.
19. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. Jun 12 2008;358(24):2560-2572.
20. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet*. Aug 7 2010;376(9739):419-430.
21. Duckworth W, Abairra C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. Jan 8 2009;360(2):129-139.
22. 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*. Nov 1996;50(5):1651-1658.
23. 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*. May 1999;22(5):743-751.
24. 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*. Mar 1998;13(3):651-655.
25. Nyberg G, Blohme G, Norden G. Impact of metabolic control in progression of clinical diabetic nephropathy. *Diabetologia*. Feb 1987;30(2):82-86.
26. Parving HH, Rossing P, Hommel E, Smidt UM. Angiotensin-converting enzyme inhibition in diabetic nephropathy: ten years' experience. *Am J Kidney Dis*. Jul 1995;26(1):99-107.
27. de Boer IH, Sun W, Cleary PA, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*. Dec 22 2011;365(25):2366-2376.
28. The DCCT Research Group. TDR. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes*. Feb 1997;46(2):271-286.
29. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. Jun 12 2008;358(24):2545-2559.
30. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909.
31. Schwartz AV, Vittinghoff E, Sellmeyer DE, et al. Diabetes-related complications, glycemic control, and falls in older adults. *Diabetes Care*. Mar 2008;31(3):391-396.
32. Greenfield S, Billimek J, Pellegrini F, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study. *Ann Intern Med*. Dec 15 2009;151(12):854-860.
33. Shurraw S, Hemmelgarn B, Lin M, et al. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. *Arch Intern Med*. Nov 28 2011;171(21):1920-1927.

34. Drechsler C, Krane V, Ritz E, Marz W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. *Circulation*. Dec 15 2009;120(24):2421-2428.
35. Freedman BI, Andries L, Shihabi ZK, et al. Glycated albumin and risk of death and hospitalizations in diabetic dialysis patients. *Clin J Am Soc Nephrol*. Jul 2011;6(7):1635-1643.
36. Hayashino Y, Fukuhara S, Akiba T, et al. Diabetes, glycaemic control and mortality risk in patients on haemodialysis: the Japan Dialysis Outcomes and Practice Pattern Study. *Diabetologia*. Jun 2007;50(6):1170-1177.
37. Kalantar-Zadeh K, Kopple JD, Regidor DL, et al. A1C and survival in maintenance hemodialysis patients. *Diabetes Care*. May 2007;30(5):1049-1055.
38. Oomichi T, Emoto M, Tabata T, et al. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. *Diabetes Care*. Jul 2006;29(7):1496-1500.
39. Shurraw S, Majumdar SR, Thadhani R, Wiebe N, Tonelli M. Glycemic control and the risk of death in 1,484 patients receiving maintenance hemodialysis. *Am J Kidney Dis*. May 2010;55(5):875-884.
40. Williams ME, Lacson E, Jr., Wang W, Lazarus JM, Hakim R. Glycemic control and extended hemodialysis survival in patients with diabetes mellitus: comparative results of traditional and time-dependent Cox model analyses. *Clin J Am Soc Nephrol*. Sep 2010;5(9):1595-1601.
41. Gerich JE, Meyer C, Woerle HJ, Stumvoll M. Renal gluconeogenesis: its importance in human glucose homeostasis. *Diabetes Care*. Feb 2001;24(2):382-391.
42. Hasslacher C, Wittmann W. [Severe hypoglycemia in diabetics with impaired renal function]. *Dtsch Med Wochenschr*. Feb 7 2003;128(6):253-256.
43. Muhlhauser I, Toth G, Sawicki PT, Berger M. Severe hypoglycemia in type I diabetic patients with impaired kidney function. *Diabetes Care*. Apr 1991;14(4):344-346.
44. Asplund K, Wiholm BE, Lundman B. Severe hypoglycemia during treatment with glipizide. *Diabet Med*. Oct 1991;8(8):726-731.
45. 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*. Feb 1998;53(6):429-435.
46. 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*. Dec 1996;39(12):1617-1624.
47. 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*. Aug 2003;60(2):90-95.
48. Nagai T, Imamura M, Iizuka K, Mori M. Hypoglycemia due to nateglinide administration in diabetic patient with chronic renal failure. *Diabetes Res Clin Pract*. Mar 2003;59(3):191-194.
49. 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*. May 2001;57(2):147-152.
50. Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function. *Diabetes Care*. Mar 2003;26(3):886-891.
51. Sambol NC, Chiang J, Lin ET, et al. Kidney function and age are both predictors of pharmacokinetics of metformin. *J Clin Pharmacol*. Nov 1995;35(11):1094-1102.
52. Frid A, Sterner GN, Londahl M, et al. Novel assay of metformin levels in patients with type 2 diabetes and varying levels of renal function: clinical recommendations. *Diabetes Care*. Jun 2010;33(6):1291-1293.
53. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur J Intern Med*. Oct 2002;13(7):428-433.
54. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010(4):CD002967.
55. Nye HJ, Herrington WG. Metformin: the safest hypoglycaemic agent in chronic kidney disease? *Nephron Clin Pract*. 2011;118(4):c380-383.
56. Pilmore HL. Review: metformin: potential benefits and use in chronic kidney disease. *Nephrology (Carlton)*. Jun 2010;15(4):412-418.
57. British National Formulary: www.bnf.org. Accessed November 15th, 2011.
58. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care*. Jun 2011;34(6):1431-1437.
- 58a. Japanese Society of Nephrology Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012 (In Japanese). Tokyo Igakusya (Tokyo, Japan), 2012.
59. Grey A. Skeletal consequences of thiazolidinedione therapy. *Osteoporos Int*. Feb 2008;19(2):129-137.
60. FDA Postmarket Drug Safety Information for Patients and Providers, FDA significantly restricts access to the diabetes drug Avandia. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm>. September 23, 2010.
61. Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. *Semin Dial*. Sep-Oct 2004;17(5):365-370.
62. Linnebjerg H, Kothare PA, Park S, et al. Effect of renal impairment on the pharmacokinetics of exenatide. *Br J Clin Pharmacol*. Sep 2007;64(3):317-327.
63. Johansen OE, Whitfield R. Exenatide may aggravate moderate diabetic renal impairment: a case report. *Br J Clin Pharmacol*. Oct 2008;66(4):568-569.
64. Weise WJ, Sivanandy MS, Block CA, Comi RJ. Exenatide-associated ischemic renal failure. *Diabetes Care*. Feb 2009;32(2):e22-23.
65. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. *Br J Clin Pharmacol*. Dec 2009;68(6):898-905.
66. Morgan L, Marenah CB, Jeffcoate WJ, Morgan AG. Glycated proteins as indices of glycaemic control in diabetic patients with chronic renal failure. *Diabet Med*. Jun 1996;13(6):514-519.
67. Joy MS, Cefalu WT, Hogan SL, Nachman PH. Long-term glycemic control measurements in diabetic patients receiving hemodialysis. *Am J Kidney Dis*. Feb 2002;39(2):297-307.
68. Inaba M, Okuno S, Kumeda Y, et al. Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. *J Am Soc Nephrol*. Mar 2007;18(3):896-903.
69. Riveline JP, Teynie J, Belmouaz S, et al. Glycaemic control in type 2 diabetic patients on chronic haemodialysis: use of a continuous glucose monitoring system. *Nephrol Dial Transplant*. Sep 2009;24(9):2866-2871.
70. Freedman BI, Shihabi ZK, Andries L, et al. Relationship between assays of glycemia in diabetic subjects with advanced chronic kidney disease. *Am J Nephrol*. 2010;31(5):375-379.
71. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. *Diabetes Care*. Nov 2010;33(11):2310-2313.

72. 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*. Apr 1986;25(4):186-192.
73. Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. *Am J Kidney Dis*. Mar 2007;49(3):373-382.
74. Colhoun HM, Betteridge DJ, Durrington PN, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis*. Nov 2009;54(5):810-819.
75. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. Jun 14 2003;361(9374):2005-2016.
76. Tonelli M, Keech A, Shepherd J, et al. Effect of pravastatin in people with diabetes and chronic kidney disease. *J Am Soc Nephrol*. Dec 2005;16(12):3748-3754.
77. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. Jun 25 2011;377(9784):2181-2192.
78. Jardine AG, Holdaas H, Fellstrom B, et al. Fluvastatin prevents cardiac death and myocardial infarction in renal transplant recipients: post-hoc subgroup analyses of the ALERT Study. *Am J Transplant*. Jun 2004;4(6):988-995.
79. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. Jul 21 2005;353(3):238-248.
80. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. Apr 2 2009;360(14):1395-1407.
81. Holdaas H, Holme I, Schmieder RE, et al. Rosuvastatin in diabetic hemodialysis patients. *J Am Soc Nephrol*. Jul 2011;22(7):1335-1341.
82. Marz W, Genser B, Drechsler C, et al. Atorvastatin and low-density lipoprotein cholesterol in type 2 diabetes mellitus patients on hemodialysis. *Clin J Am Soc Nephrol*. Jun 2011;6(6):1316-1325.
83. Adolescent type 1 Diabetes cardio-renal Interventional Trial Research Group. Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AdDIT). *BMC Pediatr*. 2009;9:79.
84. Ansquer JC, Foucher C, Rattier S, Taskinen MR, Steiner G. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis*. Mar 2005;45(3):485-493.
85. Davis TM, Ting R, Best JD, et al. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia*. Feb 2011;54(2):280-290.
86. Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int*. Sep 2004;66(3):1123-1130.
87. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. Nov 26 2005;366(9500):1849-1861.
88. Shepherd J, Kastelein JP, Bittner VA, et al. Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. *Mayo Clin Proc*. Aug 2008;83(8):870-879.
89. Armitage J, Bowman L, Wallendszus K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. Nov 13 2010;376(9753):1658-1669.
90. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. *N Engl J Med*. Aug 21 2008;359(8):789-799.
91. Bilous R, Chaturvedi N, Sjolie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. *Ann Intern Med*. Jul 7 2009;151(1):11-20.
92. The EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet*. Jun 21 1997;349(9068):1787-1792.
93. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*. Jul 2 2009;361(1):40-51.
94. Haller H, Ito S, Izzo JL, Jr., et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med*. Mar 10 2011;364(10):907-917.
95. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. Sep 8 2007;370(9590):829-840.
96. 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*. Jan 22 2000;355(9200):253-259.
97. Ruggenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med*. Nov 4 2004;351(19):1941-1951.
98. 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*. Dec 2003;26(12):3296-3302.
99. 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*. Nov 11 1993;329(20):1456-1462.
100. 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*. Sep 20 2001;345(12):861-869.
101. 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*. Sep 20 2001;345(12):851-860.
102. ACE Inhibitors in Diabetic Nephropathy Trialist Group. 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*. Mar 6 2001;134(5):370-379.
103. 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*. May 8 2004;328(7448):1105-1109.
104. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med*. Jun 5 2003;348(23):2285-2293.
105. de Boer IH, Rue TC, Cleary PA, et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Arch Intern Med*. Mar 14 2011;171(5):412-420.

106. Levey AS, Cattran D, Friedman A, et al. Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis.* Aug 2009;54(2):205-226.
107. Watkins PJ, Parsons V, Bewick M. The prognosis and management of diabetic nephropathy. *Clin Nephrol.* Jun 1977;7(6):243-249.
108. Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. *JAMA.* Oct 12 2005;294(14):1782-1787.
109. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med.* Jan 1 2008;148(1):30-48.
110. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet.* Aug 16 2008;372(9638):547-553.
111. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med.* Jun 8 2006;354(23):2443-2451.
112. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. *BMJ.* 2011;343:d5931.
113. Porta M, Hainer JW, Jansson SO, et al. Exposure to candesartan during the first trimester of pregnancy in type 1 diabetes: experience from the placebo-controlled DIabetic RETinopathy Candesartan Trials. *Diabetologia.* Jun 2011;54(6):1298-1303.
114. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med.* Jun 5 2008;358(23):2433-2446.
115. Caramori ML, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? *Diabetes.* Sep 2000;49(9):1399-1408.
116. Desnick RJ. Enzyme replacement therapy for Fabry disease: lessons from two alpha-galactosidase A orphan products and one FDA approval. *Expert Opin Biol Ther.* Jul 2004;4(7):1167-1176.
117. Lin J, Glynn RJ, Rifai N, et al. Inflammation and progressive nephropathy in type 1 diabetes in the diabetes control and complications trial. *Diabetes Care.* Dec 2008;31(12):2338-2343.