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.

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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).

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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.

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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, nonfatal 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

	Implications		
Grade*	**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 filtratin 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. (*1A*)

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 macroalbuminuria, 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 Diamicron 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 m^2 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 m^2 (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

	Intensive Treatment		Conventional Treatment	
Study	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 Diamicron Modified Release Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial.

p=0.045) and <30 mL/min/1.73 m^2 (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 considerably 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 CKD[33] 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 some[34-38] 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.
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***These levels are controversial (see text).

GFR :::30 mL/min/1.73 m^2.[49] Although hypoglycemia has not been demonstrated to increase substantially 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 m^2. Similarly, nateglinide should be used with caution when the GFR is <30 mL/min/1.73 m^2, 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 m^2 without further change when the GFR declines to 30 mL/min/1.73 m^2;[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 m^2 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 m^2, 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 m^2 and stopped when <30 mL/min/1.73 m^2; 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 m^2 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 m^2.[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 m^2 and by 64% with a GFR of <30 mL/min/1.73 m^2.[62] Therefore, exenatide is not recommended for use with a GFR <30 mL/min/1.73 m^2. 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 m^2 .[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 al[68] 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 al[69] 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 to15 mL/min/1.73 m^2, 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. (*1B*)**

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 analyses[73-76] 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) trial[77] randomized 9438 participants :::40 years old with CKD (mean eGFR of 27 mL/min/1.73 m^2) to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo, and followed them for 5 years. 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], nonhemorrhagic 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) trial[78] 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. (*1B*)**

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	Atorvastin, 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 1-mol/L (1.24 mg/dL) for women, and >130 1-mol/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; p=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 p=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 AURORA[81] 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 trial[82] found that fatal and nonfatal cardiac events were significantly reduced if the pretreatment 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 trial[77] indicated that risk for the primary outcome of major atherosclerotic events other than death was reduced by simvastatin/ezitimibe 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 cardiorenal 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

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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 m^2) 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 addressed 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 trial[77] 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 nonserious 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 3[4] 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 MICROHOPE[96] 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 1[99] 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 Group[102] 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 conclusive 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 m^2 with albuminuria :::20 mg/g and <200 mg/g; 3) eGFR 30-60 mL/min/1.73 m^2 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-ezitimibe 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-ezitimibe 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.

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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.

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EVIDENCE REVIEW TEAM

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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-

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