Chronic Kidney Disease in Type 2 Diabetes: Optimizing Glucose-Lowering Therapy

George Bakris, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After participating in the activity, the family physician should be able to:

- Appropriately screen for the presence of chronic kidney disease in patients with type 2 diabetes mellitus (T2DM).
- Identify chronic kidney disease at an early stage in patients with T2DM.
- Individualize evidence-based glucose-lowering therapy to slow the progression of kidney disease in patients with T2DM and chronic kidney disease.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes mellitus and kidney disease.

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SUPPORTER

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EPIDEMIOLOGY

Chronic kidney disease (CKD) occurs in 1 in 3 people with diabetes mellitus and 1 in 5 people with hypertension, with a prevalence of 30 million US adults (15% of the adult population).[1] Forty-five percent of new cases of end-stage kidney disease (ESKD) are due to diabetes mellitus.[2] While the incidence of ESKD has declined slightly over the past decade to 357 per million population in 2015,[2] nearly half (48%) of those with severely reduced kidney function, but not on dialysis, are not aware of having CKD.[1] Thus, it is no surprise that CKD is a common cause of all-cause mortality and cardiovascular (CV) mortality.[3] In fact, evidence suggests that CKD in people with diabetes mellitus, ie, diabetic kidney disease (DKD), may shorten a person's life span by 16 years.[4] However, the good news is that intensive treatment to achieve a glycated hemoglobin (A1c) <6.5% and fasting total cholesterol <175 mg/dL, combined with blood pressure control to levels <140/90 mmHg and

renin-angiotensin-aldosterone system blockade, can reduce the incidence of DKD in patients with T2DM and persistent microalbuminuria at baseline.[5] Over 7.8 years of treatment and 13.3 years of follow-up, the Steno-2 trial showed a significantly lower risk of developing DKD in intensively vs conventionally treated patients (relative risk, 0.44; 95% confidence interval [CI], 0.25 to 0.77; *P*=.004).[5]

CASE SCENARIO

A 63-year-old male is new to your practice several months ago. He reports that he had not seen a physician for many years. At the initial visit, he was diagnosed with type 2 diabetes mellitus (T2DM), hypertension, and low-density lipoprotein hypercholesterolemia. He has a family history of CKD.

- Blood pressure (BP): 148/98 mm Hg
- A1c: 8.8%
- Estimated glomerular filtration rate (eGFR): 59 mL/min/1.73 m^2
- Low-density lipoprotein cholesterol (LDL-C): 146 mg/dL

Treatment was initiated with metformin 1000 mg twice daily and glimepiride 1 mg once daily since his A1c of 8.8% is ≥1.5% above his glycemic target of <7%. In addition, simvastatin 40 mg daily and lisinopril/hydrochlorothiazide 40/12.5 mg daily also were started.

6-week follow up

- BP: 136/86 mmHg
- A1c: 7.4%
- Fasting plasma glucose (FPG): 145 mg/dL
- eGFR: 62 mL/min/1.73 m^2
- LDL-C: 90 mg/dL

Discussion

While the patient has had a good response to metformin and glimepiride, his A1c and FPG remain elevated (as would his postprandial glucose although not measured). As indicated in the 2019 treatment guidelines for T2DM issued by the American Diabetes Association and the American Association of Clinical Endocrinologists/American College of Endocrinology, the selection of antidiabetic medication to be added to metformin should include consideration of established atherosclerotic CV disease, heart failure, and CKD, in addition to hypoglycemia and body weight.[6,7] It is also important to screen patients for these diseases.[3,8,9]

SCREENING FOR CKD IN DIABETES

The identification of kidney disease in patients with T2DM requires assessing both glomerular function and urinary excretion of albumin since evaluation of either alone may not identify all patients with kidney disease (**FIGURE**).[6] For example, 10.1% of adults with diabetes and eGFR <60 mL/min/1.73 m^2 had an albumin-to-creatinine ratio (ACR) <30 mg/g in 2007-2010.[10]

To screen for DKD, a spot urine sample for albumin is acceptable rather than timed or 24-hour collections (**TABLE 1**),[6] but is subject to false-negative and false-positive results. Two of three spot urine specimens collected within a 3- to 6-month period should be abnormal before considering the patient to have albuminuria.[6] The eGFR should be calculated from the serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or some other validated formula.[6]

CASE SCENARIO (CONT'D)

The patient's eGFR of 62 mL/min/1.73 m^2 indicates he has evidence of kidney disease.[3] However, subsequent measurement of his urinary ACR reveals a level of 200 mg/g. This coupled with his family history of kidney disease places him at moderate risk.[3]

Assessing the ACR is an important prognostic factor for disease progression. A recent meta-analysis involving 675,904 people (80% with diabetes mellitus) and 7462 with ESKD showed that change in ACR was consistently associated with subsequent risk of ESKD across different eGFRs, presence or absence of diabetes, and sex.[11] The risk for ESKD progression among those who had a sustained reduction >30% in albuminuria over 2 years was reduced by 22%. The association was somewhat stronger among patients with a higher baseline ACR than among those with a lower baseline ACR.

Screening should also seek to identify other causes of CKD since diabetes mellitus is only one of several independent risk factors for CKD. In addition to age >60 years, risk factors include uncontrolled hypertension, obesity, heart failure, tobacco use, family history, and prior history of acute kidney injury.[12]

TREATMENT

Early identification of patients with or at risk for CKD allows for early intervention with the goal of preventing progression of kidney dysfunction. Comprehensive treatment of DKD requires a combination of nonpharmacologic and pharmacologic therapy to address hyperglycemia and other risk factors for DKD. In appropriate patients, treatment includes smoking cessation and weight loss through dietary modification and increased physical activity. To alter disease progression, an angiotensin converting enzyme inhib-

FIGURE Prognosis of CKD by stage[3]

				Albuminuria-to-creatinine ratio		
				A1	A2	A3
				NL-Mildly ↑	Moderately ↑	Severely ↑
				<30 mg/g	30-300 mg/g	>300 mg/g
eGFR (mL/min/1.73 m²)	G1	Normal/High	≥90	Low risk	Moderate risk	High risk
	G2	Mildly ↓	60-89	Low risk	Moderate risk	High risk
	G3a	Mildly-Moderately ↓	45-59	Moderate risk	High risk	Very high risk
	G3b	Moderately-Severely ↓	30-44	High risk	Very high risk	Very high risk
	G4	Severely ↓	15-29	Very high risk	Very high risk	Very high risk
	G5	Kidney failure	<15	Very high risk	Very high risk	Very high risk

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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itor or angiotensin receptor blocker at maximum doses is recommended in all patients with DKD and ACR ≥30 mg/g, with the strongest evidence of benefit found in those with albuminuria >300 mg/day.[6,13-15]

The benefits of intensive therapy vs standard therapy for glycemic control on kidney function have been well established. The United Kingdom Prospective Diabetes Study (UKPDS) showed significantly greater reduction in microalbuminuria, proteinuria, and doubling of the serum creatinine at 9 years with intensive therapy (to achieve fasting plasma glucose <108 mg/dL) vs standard therapy (primarily diet).[16] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial showed significantly greater reduction in new/worsening nephropathy, development of macroalbuminuria, and development of microalbuminuria at a median of 5 years with intensive therapy (to achieve A1c <6.5%) compared with standard therapy (to achieve A1c defined on the basis of local guidelines).[17] Similarly, the Veterans Affairs Diabetes Trial (VADT) showed significantly greater reduction in worsening of albuminuria and progression from normo- to microalbuminuria/macroalbuminuria at a median of 5.6 years with intensive therapy (to achieve A1c <6.0%) compared with standard therapy (to achieve A1c defined on the basis of local guidelines).[18]

Cardiovascular safety of antidiabetic medications

CASE SCENARIO (CONT'D)

The patient has an A1c of 7.4% and FPG 145 mg/dL despite optimized metformin and glimepiride therapy. Based on his eGFR and ACR, he is at moderate risk of progression to ESKD. How would you modify his antidiabetic therapy?

TABLE 1 Screening recommendations for CKD in diabetes[6]

	Adults	Children/adolescents
Who?	T1DM: Duration ≥5 years T2DM: All Comorbid hypertension: All	At puberty or age >10 years, whichever is earlier, once the child has had diabetes ≥5 years
How?	Urinary albumin (eg, spot urinary albumin-to-creatinine ratio) *and* Estimated glomerular filtration rate	Urinary albumin (morning preferred) with spot urinary albumin-to-creatinine ratio
When?	At least once a year	At least once a year

Abbreviations: CKD, chronic kidney disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The choice of pharmacologic therapy for intensifying antidiabetic therapy has become more challenging in recent years due to the availability of several new classes of medications. At the same time, these options provide greater opportunity for treatment individualization.

More than a decade ago, evidence emerged suggesting an elevated risk of myocardial infarction with rosiglitazone.[19] These concerns led the US Food and Drug Administration (FDA) in 2008 to require industry sponsors of new medications for T2DM to demonstrate in a clinical trial that a new medication is not associated with an unacceptable increase in CV risk relative to a control group at higher risk of a CV event.[20]

More than 15 CV outcome trials have been completed in accordance with the FDA requirements. All completed

TABLE 2 Renal outcomes from cardiovascular outcome trials

Renal outcomes	Rate/100 patient-years		Hazard ratio (95% CI)	*P*	Rate/100 patient-years		Hazard ratio (95% CI)	*P*
	Active	Placebo			Active	Placebo		
SGLT-2 inhibitors	**Canagliflozin[24]**				**Dapagliflozin[25]**			
Doubling of SCr, ESKD, or renal death	0.15	0.28	0.53					
Doubling of SCr, ESKD, or renal or CV death	1.32	1.58	0.82					
Doubling of SCr and eGFR ≤45 mL/min/1.73 m^2								
Doubling of SCr and eGFR ≤45 mL/min/1.73 m^2, initiation of renal-replacement therapy, or renal death								
Initiation of renal-replacement therapy								
≥40% reduction in eGFR, renal-replacement therapy, or renal death	0.55	0.90	0.60 (0.47-0.77)					
≥40% reduction in eGFR, renal death, ESKD, or renal or CV death	1.69	2.16	0.77		1.08	1.41	0.76 (0.67-0.87)	
≥40% decrease in eGFR to <60 mL/min/1.73 m^2, ESKD, or renal death					3.7	7.0	0.53 (0.43-0.66)	
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)					
Progression to macroalbuminuria								
Incident or worsening nephropathy								
GLP-1 receptor agonists	**Liraglutide[21,22]**				**Semaglutide[23]**			
New onset of persistent macroalbuminuria or a doubling of SCr and eGFR ≤45 mL/min/1.73 m^2, need for continuous renal-replacement therapy, or death from renal diseases	1.5	1.9	0.78 (0.67-0.92)	0.003				
New onset of persistent macroalbuminuria	0.9	1.21	0.74 (0.60-0.91)	0.004				
New or worsening persistent macroalbuminuria, persistent doubling of SCr and eGFR <45 mL/min/1.73 m^2, or need for continuous renal-replacement therapy					1.86	3.06	0.64 (0.46-0.88)	0.005

Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1, glucagon-like peptide-1; SCr, serum creatinine; SGLT-2, sodium glucose cotransporter-2.

trials have shown the dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium glucose cotransporter-2 inhibitors (SGLT-2is) investigated to not increase the primary composite endpoint of CV death, nonfatal myocardial infarction, and nonfatal stroke (MACE) more than 30% compared to placebo as part of standard antidiabetic care. Moreover, some GLP-1RAs (albiglutide, dulaglutide, liraglutide, semaglutide) and SGLT-2is (canagliflozin, dapagliflozin, empagliflozin) were shown to significantly reduce the primary MACE endpoint. Furthermore, significant improvement has been observed with the GLP-1RAs liraglutide[21,22] and semaglutide[23] and the SGLT-2is

	Rate/100 patient-years		Hazard ratio (95% CI	*P*
	Active	Placebo		
	Empagliflozin[26]			
	0.63	1.15	0.54	<.001
	0.55	0.97	0.56 (0.39-0.79)	<.001
	0.63	1.15	0.54 (0.40-0.75)	<.001
	0.10	0.21	0.45 (0.21-0.97)	.04
	4.18	6.49	0.62 (0.54-0.72)	<.001
	4.78	7.60	0.61 (0.53-0.70)	<.001

canagliflozin,[24] dapagliflozin,[25] and empagliflozin[26] in some kidney endpoints (**TABLE 2**). The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial[27] (discussed below), which investigated canagliflozin, is the only renal outcome trial that also had CV outcomes as prespecified secondary endpoints.

It must be kept in mind that since these CV outcome trials were not head-to-head trials, comparison of results among the antidiabetic medications is not possible. However, a meta-analysis by Zelniker et al showed renal and CV benefits by all agents with different baseline levels of risk.[28] In addition, primary and secondary endpoints, as well as inclusion and exclusion criteria, were often different. Some trials were for primary and secondary prevention (liraglutide, semaglutide; canagliflozin, dapagliflozin), while empagliflozin was investigated only for secondary prevention. In addition, these CV outcome trials included only a small percentage of patients with pre-existing DKD.

In contrast, the CREDENCE trial included only patients with T2DM and established CKD.[29] Among the inclusion criteria were: age ≥30 years, A1c 6.5% to 12%, eGFR 30 to <90 mL/min/1.73 m^2, and ACR >300 to 500 mg/g. Patients were required to be stabilized on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Glucose-lowering and use of all other therapies were at the discretion of the treating physician according to local guidelines. Treatment with canagliflozin or placebo was continued until the trial was stopped by the data safety monitoring board for overwhelming efficacy to reduce CV events and slow CKD progression in the absence of a clear safety signal.

CREDENCE was stopped early at a median follow up of 2.62 years (N=4401) after a planned interim analysis showed the requisite number of primary outcome events had been reached.[27] From a baseline of 8.3%, the mean A1c reduction at 42 months following randomization was 0.43% with canagliflozin and 0.32% for placebo. The primary composite outcome, ie, ESKD, doubling of the serum creatinine, or renal or CV death, was significantly lower in the canagliflozin group than the placebo group (4.32 vs 6.12 per 100 patient-years, respectively; hazard ratio 0.70, 95% CI 0.59-0.82, *P*=.00001) (**TABLE 3**).[27] The number needed to treat (NNT) was 22 for the primary MACE outcome and 16 for dialysis. In addition, a significant reduction in several individual kidney endpoints were observed. Rates of adverse events and serious adverse events were similar in the canagliflozin and placebo groups, as were the rates of lower-limb amputation and fracture. The results of CREDENCE indicate that canagliflozin may be an effective treatment option for CV, as well as kidney, protection in patients with T2DM and CKD. These benefits were observed in patients with DKD, 99% of whom were on background ACE-I/ARB therapy, the only approved renoprotective medications in patients with T2DM, and in patients with eGFR well below 45 mL/min/1.73 m^2, the lower limit recommended for canagliflozin.

TABLE 3 Renal outcomes in patients with type 2 diabetes mellitus and established chronic kidney disease–the CREDENCE trial[27]

Canagliflozin	Hazard ratio[a] (95% CI)	*P*
Doubling of SCr, ESKD, or renal or CV death	0.70 (0.59-0.82)	.00001
Doubling of SCr, ESKD, or renal death	0.66 (0.53-0.81)	<.001
Doubling of SCr	0.60 (0.48-0.76)	<.001
ESKD	0.68 (0.54-0.86)	.002
CV death or HF hospitalization	0.69 (0.57-0.83)	<.001
CV death, MI, or stroke	0.80 (0.67-0.95)	.01
CV death	0.78 (0.61-1.00)	.05
HF hospitalization	0.61 (0.47-0.80)	<.001

Abbreviations: CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure; MI, myocardial infarction; SCr, serum creatinine.
[a]Favoring canagliflozin

IMPLICATIONS FOR PATIENT CARE

CKD is common in patients with T2DM and causes substantial morbidity and early death. The effectiveness of intensive antidiabetic therapy, as well as controlling other risk factors, in reducing the progression of kidney disease emphasizes the importance of early identification and intervention. Annual screening using both eGFR and ACR in patients with T2DM is, therefore, critical.

Recent data demonstrate reduced CV and renal events with several medications used for T2DM, including the GLP-1RAs liraglutide and semaglutide and the SGLT-2is canagliflozin, dapagliflozin, and empagliflozin. Only canagliflozin has been prospectively investigated in a clinical trial limited to patients with T2DM and advanced CKD, showing significant reduction in several composite and individual kidney endpoints with a very safe profile. Use of medications shown to reduce kidney events is recommended in the 2019 ADA and AACE/ACE guidelines. However, patient affordability may be a limiting factor. It is, therefore, important for healthcare providers to advocate for health care system changes that improve affordability of optimal treatment for patients. ●

REFERENCES

1. U.S. Centers for Disease Control and Prevention. National chronic kidney disease fact sheet, 2017. Published 2017. https://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf. Accessed March 25, 2019.
2. United States Renal Data System. 2017 USRDS Annual Data Report/Volume 2- ESRD in the United States. Published 2017. https://www.usrds.org/2017/download/2017_Volume_2_ESRD_in_the_US.pdf. Accessed July 1, 2019.
3. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011).* 2013;3(1):19-62.
4. Wen CP, Chang CH, Tsai MK, et al. Diabetes with early kidney involvement may shorten life expectancy by 16 years. *Kidney Int.* 2017;92(2):388-396.
5. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med.* 2008;358(6):580-591.
6. American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S1-S193.
7. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Executive Summary. *Endocr Pract.* 2019;25(1):69-100.
8. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation.* 2019:Cir0000000000000678.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-e239.
10. Kramer H, Boucher RE, Leehey D, et al. Increasing mortality in adults with diabetes and low estimated glomerular filtration rate in the absence of albuminuria. *Diabetes Care.* 2018;41(4):775-781.
11. Coresh J, Heerspink HJL, Sang Y, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol.* 2019;7(2):115-127.
12. Gatwood J, Chisholm-Burns M, Davis R, et al. Evidence of chronic kidney disease in veterans with incident diabetes mellitus. *PLoS One.* 2018;13(2):e0192712.
13. Chapter 3: Management of progression and complications of CKD. *Kidney Int Suppl (2011).* 2013;3(1):73-90.
14. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018;71(19):e127-e248.
15. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311(5):507-520.
16. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359(15):1577-1589.
17. 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.* 2008;358(24):2560-2572.
18. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360(2):129-139.
19. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356(24):2457-2471.
20. US Food and Drug Administration. Guidance for Industry. Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Published 2008. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guiddances/ucm071627.pdf. Accessed February 6, 2018.
21. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4):311-322.
22. Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(9):839-848.
23. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
24. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.
25. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357.
26. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375(4):323-334.
27. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380(24):2295-2306.
28. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose co-transporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus: A systematic review and meta-analysis of cardiovascular outcomes trials. *Circulation.* 2019;139(17):2022-2031.
29. Jardine MJ, Mahaffey KW, Neal B, et al. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. *Am J Nephrol.* 2017;46(6):462-472.