Stemming the Progression of Diabetic Kidney Disease: The Role of the Primary Care Clinician

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Identify the risks of kidney disease and their consequences in patients with T2DM.
- Initiate evidence-based therapy to slow the progression of kidney disease in patients with T2DM and CKD.
- Become familiar with the mineralocorticoid receptor antagonist and endothelin receptor antagonist under late-phase investigation.

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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Dr. Bakris discloses that he is a principal investigator for Bayer's FIDELIO diabetic nephropathy outcome trial, a steering committee member for the Novo Nordisk FLOW trial, and on the CALM-2 steering committee for Vascular Dynamic.

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METHOD OF PARTICIPATION

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DEFINITION

Chronic kidney disease (CKD) is defined as ≥1 abnormalities of kidney structure or function that have been present for >3 months and have health implications.[1] Markers of kidney damage include albuminuria (urine albumin excretion rate ≥30 mg/24 hours or urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), urine sediment abnormalities, electrolyte and other abnormalities caused by tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation. Decreased kidney function is indicated by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

EPIDEMIOLOGY

CKD is a common disease that affects 37 million U.S. adults, more than 1 in 7, with the highest prevalence among those age 20 to 54.[2] Nearly one-half (48%) of individuals with severely reduced kidney function, but not on dialysis, are not aware of having CKD.[2] CKD is especially common among persons with diabetes or hypertension, their combination representing approximately 3 out of 4 new cases of CKD.[3] Other risk factors for CKD include heart disease, obesity, family history of CKD, certain ethnicities (ie, African Americans, Hispanic Americans, Asians, Pacific Islanders, and Native Americans), older age, low birth weight, smoking, and acute kidney injury, as well as exposure to heavy metals and excessive alcohol use, recreational drugs, or analgesic medications.[2,4]

There is a bi-directional relationship between CKD and cardiovascular disease because CKD is an independent risk factor for coronary heart disease, heart failure, and stroke. CKD also increases the risk of pulmonary failure, anemia, immune failure, metabolic bone disease, anorexia, and edema.[2] Cognition also is affected as CKD progresses, independent of age-related changes, affecting both lower-order and higher-order cognitive abilities.[5]

The natural history of CKD in persons with diabetic kidney disease (DKD) progresses from glomerular hyperfiltration to rising albuminuria, declining eGFR, and finally end-stage kidney disease.[6-8] It is important to recognize that albuminuria can precede a decline in the eGFR by more than a decade.[6,9] Analysis of data from the ACCORD trial showed that among persons with type 2 diabetes mellitus (T2DM), those with non-albuminuric CKD showed a slower rate of decline in eGFR than those with albuminuric non-CKD or albuminuric CKD.[10] Further data supporting the importance of recognizing and managing albuminuria is the finding that higher UACR is associated with a greater risk of cardiovascular death, independent of eGFR.[1]

CARDIOVASCULAR OUTCOME TRIALS

The contribution of hyperglycemia to kidney disease and the microvascular benefits of reducing blood glucose are the basis of the goal for achieving glycemic control in persons with T2DM. There was, however, little evidence demonstrating cardiovascular benefit with glucose-lowering medication. In fact, a 2007 systematic review and meta-analysis showed a significantly increased risk of myocardial infarction and suggested a higher risk of cardiovascular death in patients with T2DM treated with rosiglitazone.[11] Although the finding related to cardiovascular death subsequently was proven inaccurate,[12,13] the FDA issued guidance in 2008 requiring pharmaceutical manufacturers to evaluate the cardiovascular risk of new glucose-lowering medications for T2DM in a cardiovascular outcome trial (CVOT).[14]

Since 2008, more than 20 CVOTs have demonstrated that the cardiovascular safety of each of the dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and sodium glucose cotransporter-2 inhibitors (SGLT-2i) investigated is non-inferior to placebo as part of standard therapy. Moreover, linagliptin,[15] saxagliptin,[16] dulaglutide,[17] liraglutide,[18] semaglutide (injectable),[19] canagliflozin,[20] dapagliflozin,[21,22] and empagliflozin[23] have been shown to significantly reduce the occurrence of one or more kidney endpoints compared with placebo. Endpoints included change in UACR, serum creatinine, and/or eGFR, as well as time to dialysis and renal death. Among these medications shown to reduce kidney endpoints, only linagliptin and canagliflozin have been investigated in a clinical trial specifically powered to assess kidney outcomes in high-risk patients with T2DM.

The CARMELINA trial included adults with T2DM, a history of vascular disease, UACR >200 mg/g, and reduced eGFR and micro- or macroalbuminuria; patients with end-stage kidney disease (ESKD) were excluded.[15] Participants were randomized to linagliptin, 5 mg/d, or placebo in addition to standard care. After a median follow up of 2.2 years, the renal-specific composite outcome (time to first occurrence of adjudicated death because of renal failure, ESKD, or sustained ≥40% decrease in eGFR) did not differ between the linagliptin and placebo groups (9.4% and 8.8%, respectively; $P = .62$).

In the CREDENCE trial, participants were treated with renin-angiotensin-aldosterone inhibitor therapy at baseline and had a mean eGFR of 56 mL/min/1.73 m^2 and UACR of 927 mg/g.[24] This trial showed that canagliflozin significantly reduced a renal-specific composite outcome (ESKD, doubling of serum creatinine, or renal death) over the median follow up of 2.62 years in patients with an eGFR as low as 30 mL/min/1.73 m^2. In addition, the risk of ESKD was 32% lower in the canagliflozin group compared with placebo (hazard ratio: 0.68; 95% confidence interval 0.54 to 0.86; $P < .001$).

Recently, the DAPA-CKD trial was stopped early after a routine assessment of efficacy and safety showed earlier than anticipated benefits with dapagliflozin for the primary endpoint of a composite of renal function or death in patients with CKD regardless of the presence of T2DM.[25,26]

The 1 DPP-4i, 3 GLP-1RA, and 3 SGLT-2i medications with a demonstrated kidney benefit—with preference given to the SGLT-2is—are recommended by the American Diabetes Association for patients with T2DM and established CKD who do not achieve adequate glycemic control with lifestyle management combined with metformin.[27] Although this rec-

ommendation is for secondary prevention, that is, in patients with established CKD, evolving evidence suggests there might be a role for these medications for primary prevention, meaning patients who do not have established CKD.[28,29]

The kidney benefits of selected glucose-lowering medications and their rapidly evolving role in treating patients with T2DM and CKD is a reminder of the importance of identifying patients with DKD and early use of comprehensive evidence-based treatment that includes SGLT-2is as recommended.

CASE SCENARIO

Louise, age 69, was diagnosed with T2DM 4 years ago. Her glycated hemoglobin (A1c) was 8.8% at diagnosis. Her A1c has remained above her target of <7%, rising to 7.8% over the past 9 months. Louise complains of puffiness in her hands and feet.

Vital signs: within normal limits

Labs: eGFR 56 mL/min/1.73 m^2 (60 mL/min/1.73 m^2 17 months ago); UACR 35 mg/g

Current medications: metformin, DPP-4i, atorvastatin, ramipril, and low-dose aspirin

How would you modify her therapy?

RISK FACTOR MANAGEMENT

Goals of therapy

Evaluation of the management plan requires reviewing the treatment goals. In the case of patients with DKD, the overarching goal is to reduce the risks of kidney disease progression and cardiovascular disease.[30] To achieve this, comprehensive treatment is needed to address/include the following[9,30]:

- Glycemic control
- Blood pressure control
- Renin-angiotensin-aldosterone system (RAAS) blockade
- Lipid management
- Lifestyle/physical activity
- Smoking cessation
- Nutrition
- Aspirin (low-dose)

Glycemic control

The American Diabetes Association recommends an A1c <8% for patients with advanced microvascular or macrovascular complications, extensive comorbidities, limited life expectancy, or history of severe hypoglycemia.[31] By comparison, the National Kidney Foundation (NKF) recommends a target A1c of <6.5% to <8% in patients with T2DM and non-dialysis dependent CKD to prevent or delay progression of microvascular complications.[30,32] The NKF recommendation advises that safe achievement of lower A1c targets, such as A1c <6.5% or <7%, could be facilitated by blood glucose self-monitoring or combined continuous glucose monitoring and glucose-lowering medications that are not associated with hypoglycemia.[30] Moreover, the NKF recommends treatment consisting of lifestyle management in combination with metformin and SGLT-2i therapy, with additional drug therapy as needed for glycemic control. The use of both metformin and SGLT-2i therapy is contingent on an eGFR ≥30 mL/min/1.73 m^2.[30] A GLP-1RA shown to offer a cardiovascular benefit may be used as an alternative to metformin or SGLT-2i.

Blood pressure control

Blood pressure is also a key target and should be ≤140/90 mm Hg in patients with DKD and urine albumin excretion <30 mg/24 hours or those with a 10-year atherosclerotic cardiovascular disease (ASCVD) risk <15%.[32,33] [The American College of Cardiology ASCVD Risk Estimator Plus may be found here: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/.] Target blood pressure is ≤130/80 mm Hg in patients with DKD and urine albumin excretion ≥30 mg/24 hours or 10-year ASCVD risk >15%.[32,33] RAAS blockade with an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) is recommended in patients with albuminuric CKD and hypertension.

Other comorbidities

Other comorbidities, such as obesity,[34] dyslipidemia,[35] smoking,[36] etc., should be treated as recommended by existing guidelines.[9]

RAAS inhibitor therapy

The ACE-I and ARB medication classes have been shown to effectively reduce albuminuria, and even reverse moderately increased albuminuria, thereby avoiding or delaying the progression of CKD to ESKD in patients with DKD.[30] There appears to be no difference between ACE-I and ARB in renal outcomes or side effects.[37] Because the albuminuria-lowering effect, as well as side effects, are dose-related, it is important to optimize ACE-I or ARB therapy by starting at a low dosage and increasing to the highest tolerated recommended dosage.

Blocking aldosterone with a steroid-based mineralocorticoid receptor antagonist (MRA), such as spironolactone or eplerenone, might be beneficial in patients with resistant hypertension who have eGFR >45 mL/min/1.73 m^2 and no history of hyperkalemia.[30] Additive benefits are observed with the addition of a steroid-based MRA to an ACE-I or ARB.[38-40] The use of steroid-based MRA therapy is limited by adverse events, such as hyperkalemia in patients with stage ≥3 CKD.[41,42]

Management of RAAS inhibitor complications with approved therapies, eg, patiromer or sodium zirconium cyclosilicate for chronic hyperkalemia, is recommended by KDIGO rather than decreasing the dose of RAAS inhibitor therapy.[30]

The kidney and medications

In patients with CKD, it is important to be mindful of how medications are cleared so as to appropriately dose those that are primary cleared by the kidneys. These include metformin, many of the DPP-4is, GLP-1RAs, and SGLT-2is, as well as ACE-Is and ARBs, and several statins. The nephrotoxic potential of medications also must be considered because inappropriate use could cause acute kidney injury. Examples include ACE-Is and ARBs, diuretics, and nonsteroidal anti-inflammatory drugs. The most up-to-date source for information about use in kidney disease remains the FDA-approved product label.

CASE SCENARIO (CONTINUED)

To address the patient's worsening glycemic control, the addition of a SGLT-2 inhibitor is appropriate. Consideration should also be given to intensifying RAAS inhibitor therapy by increasing the dose of ramipril, if possible, with close monitoring of the serum potassium.

CONSIDERATIONS FOR NEPHROLOGIST REFERRAL

Many patients with kidney disease can be managed successfully in the primary care setting, depending on the provider's comfort. However, patients for whom nephrology referral might be considered include[43]:

- uncertain etiology of kidney disease
- eGFR <30 mL/min/1.73 m^2
- rapidly progressing kidney disease
- difficult management issues, such as anemia, metabolic bone disease, secondary hyperparathyroidism, resistant hypertension, and electrolyte disturbances.

When seeking a nephrology referral, it might be helpful to begin the referral request with: "Per KDIGO guidelines, I am referring this patient because of uncontrolled hypertension, stage 4 CKD, serum creatinine increased 25% in 6 months, (or similar reason)."

MEDICATIONS IN LATE-STAGE INVESTIGATION FOR CKD

Beyond the medications previously discussed, numerous agents are undergoing clinical investigation for CKD and are not yet approved for use in the United States. Three of these are the non-steroidal MRAs esaxerenone and finerenone and the endothelin-1 (ET-1) receptor antagonist atrasentan. Esaxerenone has not entered phase 3 clinical trials in the United States and will not be discussed further.[44]

Finerenone

The importance of aldosterone in causing cardiovascular and kidney injury beyond the effects of renin and angiotensin II increasingly is being recognized.[45] Patients with DKD show increased activity of the mineralocorticoid receptor, which might be driven by increased levels of circulating aldosterone, altered cortisol activity, or increased local expression of the mineralocorticoid receptor itself.[46] Whereas the steroid-based MRAs bind to the ligand domain of the mineralocorticoid receptor, finerenone induces a conformational change within the mineralocorticoid receptor. This change is thought to result in less potassium retention compared with steroid-based MRAs.[37]

ARTS-DN Trial

The safety and efficacy of finerenone were investigated in the Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) in patients with diabetes and high or very high albuminuria; most received concomitant treatment with an ACE-I or ARB.[47] Patients (N = 823) were randomized to 1 of 7 finerenone dosage levels or placebo for 90 days. Dosage levels of finerenone were 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg/d. At baseline, 37% of patients had very high albuminuria (UACR ≥300 mg/g) and 40% had an eGFR ≤60 mL/min/1.73 m^2. Finerenone demonstrated a dose-dependent reduction in UACR compared with placebo at 90 days, with significant reductions achieved at daily dosages ≥7.5 mg (7.5 mg, 0.79, $P = .004$; 10 mg, 0.76, $P = .001$; 15 mg, 0.67, $P < .001$; 20 mg, 0.62, $P < .001$).

In the ARTS-DN trial, there was no difference in the overall incidence of adverse events and serious adverse events between the finerenone groups and the placebo group. Treatment was discontinued because of an adverse event in 4.3% and 3.2% of finerenone- and placebo-treated patients, respectively. An increase in serum potassium to ≥5.6 mEq/L, leading to treatment discontinuation, occurred in 1.7% and 0% of finerenone- and placebo-treated patients, respectively. The occurrences of a decrease ≥40% in the eGFR at any time post-baseline through 120 days generally were similar in the placebo and finerenone groups.

FIDELIO-DKD and FIGARO-DKD Trials

Finerenone is being evaluated in 2 randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical tri-

als: Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD)[48] and Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD)[49] trial. Both trials examine adults with T2DM and albuminuria concomitantly treated with an ACE-I or ARB. Patients are randomized to finerenone, 10 or 20 mg/d, or placebo with dosages titrated based on serum potassium level and change in eGFR. The primary endpoints are a composite of time to first occurrence of kidney failure, sustained decrease of eGFR ≥40% for ≥4 weeks, or renal death (FIDELIO-DKD) or time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure hospitalization (FIGARO-DKD). FIDELIO-DKD was completed in April 2020, with preliminary analysis indicating that a significant benefit in the primary endpoint was achieved with finerenone vs placebo; full results have not been published yet. FIGARO-DKD is expected to be completed in July 2021.

Atrasentan

Atrasentan is an endothelin-1 (ET-1) receptor antagonist. ET-1 exerts potent vasoconstrictive effects on the efferent renal vasculature resulting in reduced renal blood flow and glomerular hyperfiltration.[50,51] In addition, ET-1 is thought to promote kidney injury by activating pro-inflammatory and profibrotic pathways.[52,53] Increased production of ET-1 results from hyperglycemia, insulin resistance, obesity, dyslipidemia, RAAS activation, endothelial dysfunction, and increased oxidative stress.[52] A limitation of blocking endothelin receptors is sodium and water retention.[37]

The safety and efficacy of atrasentan were demonstrated in the RADAR trial, which examined patients with T2DM, albuminuria, and decreased kidney function.[54] After 12 weeks of treatment, atrasentan, 0.75 and 1.25 mg/d, significantly reduced albuminuria vs placebo by 35% and 38%, respectively, with no significant change in eGFR.

SONAR Trial

Based on the results of the RADAR trial, the phase 3 Study of Diabetic Nephropathy with Atrasentan (SONAR) trial was conducted in adults with T2DM, UACR of 300 to 5000 mg/g, eGFR of 25 to 75 mL/min/1.73 m^2, and brain natriuretic peptide ≤200 pg/mL.[55] Patients underwent a run-in phase (N=5630) to optimize ACE-I/ARB and/or diuretic therapy followed by a 6-week enrichment phase (N=5117) to identify those treated with atrasentan, 0.75 mg/d, who had a ≥30% reduction in UACR without substantial fluid retention (responders). Responders (N=2648) and non-responders (N=1020) were separately randomized to atrasentan, 0.75 mg/d, or placebo.

The trial was terminated early after a median follow up of 2.2 years because of a lower-than-planned event rate. Significantly fewer patients in the atrasentan "responder" group experienced the primary endpoint (composite of time to first occurrence of doubling of serum creatinine, onset of ESKD, or kidney death) compared with placebo (6% vs 7.9%; $P = .0047$).[56] Similarly, among "responders" and "non-responders" combined, significantly fewer patients treated with atrasentan experienced the primary endpoint (8.3% vs 10.5%; $P = .0023$). Significant reductions in individual kidney endpoints were observed as well. Significantly more patients treated with atrasentan experienced hypervolemia/fluid retention (36.6% vs 32.3%) or anemia (18.5% vs 10.3%), as well as a serious adverse event (36.3% vs 32.6%). There was no difference between the 2 groups on serious heart failure events (1.7% vs 1.1%). Overall, the results of SONAR showed that patients with T2DM and CKD who initially experience a substantial reduction of UACR without significant sodium and fluid retention achieve a reduction of kidney events.

SUMMARY

Among patients with T2DM, CKD is common, resulting in an increased risk of cardiovascular, lung, bone, and other events. The UACR and eGFR are independent predictors of cardiovascular events. Achieving target glycemic and blood pressure goals is important for reducing the risk and progression of CKD. RAAS inhibitor therapy is well-established for reducing adverse kidney events. Based upon evolving evidence, SGLT-2 inhibitors are recommended to reduce kidney events in patients with T2DM and established CKD. To overcome limitations with currently available MRAs, the non-steroidal MRA finerenone is in late-stage development and has demonstrated significant reductions in key kidney endpoints. Atrasentan, an ET-1 receptor antagonist, provides a new approach to treating CKD and has demonstrated significant reductions in kidney endpoints.

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