Kidney Case Conference: How I Treat

GLP-1 Receptor Agonists in Diabetic Kidney Disease

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Introduction

Ms. AM is a 42-year-old American Indian woman who is referred to nephrology clinic for progressive CKD. She developed type 2 diabetes at age 19. The patient also has hypertension, hyperlipidemia, and obesity. She had two pregnancies complicated by preeclampsia and underwent menopause at the age of 39. She has no history of cardiovascular events, but a chest computed tomography performed 5 years ago showed incidental coronary artery calcification.

Five years ago, her eGFR was 54 ml/min per 1.73 m², and the urine albumin-creatinine ratio (UACR) was 360 mg/g. Her eGFR has since declined to 24 ml/min per 1.73 m² with UACR of 1200 mg/g. Serum potassium is 4.8 mEq/L, and hemoglobin A1c is 8.2%. Lipid levels include total cholesterol of 177 mg/dl, HDL cholesterol of 32 mg/dl, triglycerides of 255 mg/dl, and LDL cholesterol of 94 mg/dl. BP is 142/94 mm Hg with body mass index at 38 kg/m². Medications include lisinopril 40 mg/d, amlodipine 5 mg/d, atorvastatin 20 mg/d, metformin 500 mg/d, and insulin glargine 15–20 units nightly.

How should her hyperglycemia and CKD risk be managed?

Discussion

Patients with type 2 diabetes and CKD are at high risk for cardiovascular disease and kidney failure. Kidney Disease Improving Global Outcomes recently published a clinical practice guideline for management of diabetes and CKD (1,2).

Multirisk factor modification reduces cardiovascular events by >50% in type 2 diabetes (1,3). This patient has a high lifetime risk of cardiovascular disease >50% (3). She has women-specific risk-enhancing factors of preeclampsia and early menopause and risk related to American Indian race. Additionally, she has diabetes-related risk factors with long duration of type 2 diabetes >10 years, macroalbuminuria, and low eGFR (3). Finally, detection of coronary artery calcification indicates the presence of subclinical coronary atherosclerosis. Together, these factors increase her 10-year cardiovascular risk, for which high-intensity statin is recommended (3). We recommend increasing atorvastatin to 40–80 mg/d. Of note, high-intensity doses of rosuvastatin in patients with eGFR<30 ml/min per

1.73 m² should not be used. Additionally, this patient needs better BP control with a target <130/80 mm Hg or possibly lower (3). Amlodipine could be increased to 10 mg/d if she does not have edema. She may also consider aspirin 81 mg/d for cardiovascular prevention if she is not at elevated risk for bleeding (3). Counseling on diet and increasing physical activity should be undertaken as part of a team-based approach (1,3).

To preserve kidney function, patients with type 2 diabetes and albuminuria are recommended to be treated by an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker with titration to the highest tolerated dose according to the product label (1,2). We encourage continued use of lisinopril 40 mg daily as long as her potassium level remains ≤5.5 mEq/L. The patient has experienced rapid eGFR decline (>5 ml/min per 1.73 m² per year) to stage 4 CKD, and thus, her metformin should be discontinued (1). In patients with type 2 diabetes and CKD with eGFR≥30 ml/min per 1.73 m², a sodium-glucose cotransporter-2 inhibitor (SGLT2i) is recommended to be started as first line, as SGLT2i have proven benefits in risk reduction for cardiovascular events (particularly heart failure) and CKD progression (1). However, because her eGFR is lower, an SGLT2i is not recommended to be initiated.

The next preferred glucose-lowering agent for patients with type 2 diabetes and CKD is a long-acting glucagon-like peptide 1 receptor agonist (GLP1RA) because of benefits in reducing atherosclerotic cardiovascular events in cardiovascular outcome trials. It also reduces albuminuria and may slow eGFR decline (1). Glucagon-like peptide 1 (GLP1) is an incretin hormone secreted from the intestine after ingestion of nutrients that stimulates release of insulin from the pancreas (4). GLP1 also slows gastric emptying and decreases appetite stimulation. GLP1 receptor agonists stimulate this pathway to lower blood glucose and body weight. Importantly, GLP1RAs reduce risk of major adverse cardiovascular events (MACEs) in patients with type 2 diabetes, as has been demonstrated for liraglutide, semaglutide, albiglutide, and dulaglutide (5–8). In the LEADER trial, the risk reduction for the MACE outcome conferred by liraglutide was even greater among individuals with eGFR<60 ml/min per 1.73 m² compared with those with eGFR≥60 ml/min per 1.73 m² (hazard ratio

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[HR], 0.69; 95% confidence interval [95% CI], 0.57 to 0.85 versus HR, 0.94; 95% CI, 0.83 to 1.07; P interaction=0.01) (5). Although most GLP1RA cardiovascular outcome trials enrolled patients with established cardiovascular disease, REWIND (evaluating dulaglutide) enrolled 68% participants without cardiovascular disease, making it largely a primary prevention trial (8). Notably, the MACE reduction was similar among those with and without previous cardiovascular disease.

Although there has not been a completed kidney outcome trial for GLP1RA, the cardiovascular outcome trials of GLP1RA have included patients with eGFR as low as 15 ml/min per 1.73 m² with secondary outcomes for kidney disease. The GLP1RAs with demonstrated favorable CKD outcomes include lixisenatide, exenatide (once weekly), liraglutide, semaglutide, albiglutide, and dulaglutide. In a meta-analysis of seven cardiovascular outcome trials, GLP1RA reduced risk for a composite kidney outcome (macroalbuminuria, eGFR decline, progression to kidney failure, or death from kidney disease) by 17% (HR, 0.83; 95% CI, 0.78 to 0.89) compared with placebo, which was largely driven by albuminuria reduction (9).

The AWARD-7 trial evaluated a GLP1RA among patients with moderate to severe CKD (stages 3 and 4), comparing dulaglutide with insulin glargine as basal therapy for hyperglycemia (10). Dulaglutide produced similar glycemic control to insulin but with lesser eGFR decline. Notably, dulaglutide was safe in moderate to severe CKD and reduced hemoglobin A1c to a goal of 7%–7.5% with a 50% reduction in hypoglycemia rates. Dulaglutide has received approval for glycemic control in type 2 diabetes with eGFR as low as 15 ml/min per 1.73 m². Little data exist for patients with kidney failure, and dulaglutide should be used with caution in this group. There is currently a dedicated kidney outcome trial for GLP1RA (NCT03819153); the FLOW trial will evaluate whether semaglutide slows CKD progression in patients with type 2 diabetes on a background of angiotensin receptor blocker or angiotensin-converting enzyme inhibitor therapy.

Back to the Patient

Metformin should be stopped, and initiation of a GLP1RA is recommended (Figure 1). GLP1RA agents can cause gastrointestinal side effects, mainly nausea, which generally improve over time. Although GLP1RA agents do not cause hypoglycemia when used alone, there is risk of hypoglycemia when a GLP1RA is combined with insulin or insulin secretagogues. As shown in AWARD-7, we can stop the patient's insulin glargine and use GLP1RA as her basal glucose-lowering agent. To minimize gastrointestinal side effects, we suggest starting dulaglutide 0.75 mg once per week for 1 month and then titrating up to a maintenance dose of 1.5 mg once weekly. Other GLP1RAs may also be used according to formulary availability (4).

Daily self-monitoring of blood glucose is important because she may need short-acting premeal insulin according to personalized goals. A continuous glucose monitor would be ideal, but these devices may not be covered by insurance, and socioeconomic factors may limit access. We recommend using hemoglobin A1c to monitor long-term
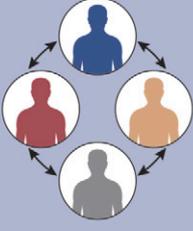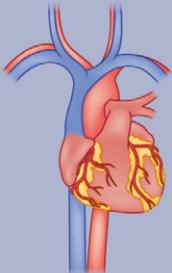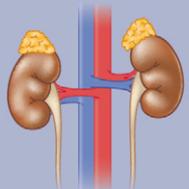

Multidisciplinary collaboration	Lifestyle management	Cardiovascular disease prevention	Kidney protection	Glucose management
• Primary care • Endocrinolgy • Nephrology • Cardiology • Nutrition/dietitian • Exercise physiologist	• Diet management • Increase physical activity • Weight loss if indicated • Smoking cessation	• High-intensity statin • BP control <130/80 mm Hg or lower • Consider aspirin • GLP1-RA for cardiovascular disease prevention	• ACE inhibitor or ARB • GLP1-RA for kidney protection	• Stop (or do not start) metformin • Do not initiate SGLT2i • Initiate GLP1-RA at lowest dose, titrate slowly up as tolerates • Consider GLP1-RA as basal regimen. May be able to stop insulin glargine • Humalog insulin prn before meals if blood sugar >150 mg/dL

Figure 1. | **Strategies for glucose and risk factor management in patients with type 2 diabetes and stage 4 CKD (eGFR 15–24 ml/min per 1.73 m²).** ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme; GLP1-RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

glycemic control. Hemoglobin A1c goals should be individualized to targets ranging from <6.5% to <8.0% depending on age and comorbidities (1). Ideally, we could set a target hemoglobin A1c <7.0% because there is lower risk of hypoglycemia with GLP1RA. We will recheck her hemoglobin A1c, eGFR, and UACR in 3 months to reassess her glycemia and CKD status.

Patients with diabetes and CKD benefit from team-based, multidisciplinary care (2). A patient-centered approach that involves shared decision making, active patient engagement, and communication between health care providers is critical for improved outcomes.

Disclosures

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group: KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Available at https://www.kidney-international.org/article/S0085-2538(20)30718-3/fulltext.
2. Navaneethan SD, Zoungas S, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, Liew A, Michos ED, Olowu WA, Sadusky T, Tandon N, Tuttle KR, Wanner C, Wilkens KG, Lytvyn L, Craig JC, Tunnicliffe DJ, Howell M, Tonelli M, Cheung M, Earley A, Rossing P, de Boer IH, Khunti K: Diabetes management in chronic kidney disease: Synopsis of the 2020 KDIGO clinical practice guideline. *Ann Intern Med* 174: 385–394, 2021
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr., Virani SS, Williams KA Sr., Yeboah J, Ziaeian B: 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *J Am Coll Cardiol* 74: 1428–1429, 2019 10.1016/j.jacc.2019.07.010]. *J Am Coll Cardiol* 74: 1376–1414, 2019
4. Alicic RZ, Cox EJ, Neumiller JJ, Tuttle KR: Incretin drugs in diabetic kidney disease: Biological mechanisms and clinical evidence. *Nat Rev Nephrol* 17: 227–244, 2021
5. Mann JFE, Fonseca V, Mosenzon O, Raz I, Goldman B, Idorn T, von Scholten BJ, Poulter NR: Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. *Circulation* 138: 2908–2918, 2018
6. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators: Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 375: 1834–1844, 2016
7. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr., Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, Thorpe KM, McMurray JJV, Del Prato S; Harmony Outcomes committees and investigators: Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): A double-blind, randomised placebo-controlled trial. *Lancet* 392: 1519–1529, 2018
8. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T; REWIND Investigators: Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. *Lancet* 394: 121–130, 2019
9. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC, McMurray JJV: Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 7: 776–785, 2019
10. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, Botros FT: Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): A multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 6: 605–617, 2018