Reducing Kidney Function Decline in Patients With CKD: Core Curriculum 2021

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An estimated 8% to 16% of the world's population has chronic kidney disease, defined by low glomerular filtration rate or albuminuria. Progression of chronic kidney disease is associated with adverse outcomes, including incident kidney failure with replacement therapy, accelerated cardiovascular disease, disability, and mortality. Therefore, slowing kidney function decline is paramount in the management of a patient with chronic kidney disease. Ascertaining the cause of kidney disease is an important first step and may compel specific therapies. Effective approaches that apply to the vast majority of patients with chronic kidney disease include the optimization of blood pressure and blockade of the renin-angiotensin-aldosterone system, particularly if albuminuria is present. Recent studies suggest that sodium/glucose cotransporter 2 inhibitors are highly effective treatments in patients with diabetes and/or albuminuria. For patients with type 2 diabetes, glycemic control is important in preventing the development of microvascular complications, and glucagon-like peptide 1 receptor agonists may help reduce albuminuria levels. Other strategies include correcting metabolic acidosis, maintaining ideal body weight, following diets that are low in sodium and animal protein, and avoiding potential nephrotoxins such as nonsteroidal anti-inflammatories, proton-pump inhibitors, and iodinated contrast.

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Introduction

Chronic kidney disease (CKD) affects more than 697 million individuals worldwide and is associated with increased morbidity and mortality. In 2017, 1.2 million deaths and 35.8 million disability-adjusted life-years were attributed to CKD. Among Medicare beneficiaries in the United States, annual spending for kidney failure with replacement therapy (KFRT) and earlier stages of CKD exceeded $120 billion. Different causes of kidney disease may require specific treatments such as immunosuppressive therapy. However, some strategies to delay the progression of CKD to KFRT are applicable to most patients. Early detection and treatment to slow kidney function decline are paramount to improving outcomes in patients with CKD. Hallmarks of CKD management include control of hypertension and hyperglycemia, inhibition of the renin-angiotensin-aldosterone system (RAAS), correction of metabolic acidosis, lifestyle modification, and avoidance of nephrotoxins. Two new classes of medications, sodium/glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, also improve kidney outcomes among individuals with diabetes and/or albuminuria.

Additional Readings

➢ GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2020;395:709-733.

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Blood Pressure Control

Case 1: *A 60-year-old man with CKD glomerular filtration rate category 3b (G3b) and albuminuria category 2 (A2, corresponding to an urinary albumin-creatinine ratio [UACR] of 30-300 mg/g), hypertension, and stable angina returns for a follow-up visit. His estimated glomerular filtration rate (eGFR) has declined from 57 to 44 mL/min/1.73 m^2 over the past 13 years. His blood pressure (BP) averages 135/72 mm Hg on a regimen of valsartan at 320 mg daily, amlodipine at 5 mg daily, and indapamide at 1.25 mg daily.*

Question 1: Based on the results of SPRINT, which one of the following statements is most accurate regarding a systolic BP goal of <120 versus <140 mm Hg?

a) All-cause mortality is reduced
b) CKD progresses more slowly at the lower BP goal
c) Incidence of KFRT is higher at the lower BP goal
d) Incidence of kidney transplantation is lower at the lower BP goal

Question 2: Which one of the following patients would be most appropriate for a lower BP goal to help slow the progression of CKD?

a) CKD G3aA1 with UACR of 10 mg/g
b) CKD G4A1 with critical bilateral renal artery stenosis

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

c) CKD G3bA3 with UACR of 3,000 mg/g
d) CKD G3bA3 with UACR of 1,200 mg/g and history of repeated falls

For the answers to the questions, see the following text.

The AHA/ACC recommend a goal BP <130/80 mm Hg for all patients with CKD, whereas the KDIGO guidelines recommend a target of ≤140/90 mm Hg when the UACR is <30 mg/d and ≤130/80 mm Hg when the UACR is ≥30 mg/d (Table 1). The KDIGO recommendations are based, in part, on 2 landmark randomized controlled trials. The AASK trial randomized participants without diabetes to a mean arterial pressure (MAP) goal of ≤92 versus 102-107 mm Hg. Although there was no difference in the rate of eGFR decline or a composite clinical outcome (eGFR decline, KFRT, or death) overall, participants with a baseline urinary protein-creatinine ratio of >0.22 g/g were 27% less likely to develop a doubling of serum creatinine, KFRT, or death when randomized to intensive versus standard BP control in the extended cohort phase. The MDRD Study randomized participants to a MAP goal of 92 versus 107 mm Hg. Again, there were no differences overall, but participants with proteinuria of ≥3 g/d had lesser GFR decline in the intensive BP control group. These and other trials of BP control are summarized in Table 2.

More recently, SPRINT randomized adults without diabetes but at increased risk for cardiovascular events to a systolic BP < 120 mm Hg versus < 140 mm Hg. Intensive BP control was associated with a lower risk of myocardial infarction, acute coronary syndrome, stroke, heart failure, and cardiovascular death (hazard ratio [HR], 0.75 [95% CI, 0.64-0.89]) and all-cause mortality (HR, 0.73 [95% CI, 0.60-0.90]). The results were consistent among participants with baseline CKD (n = 2,646). Intensive BP control did not prevent adverse kidney outcomes (≥50% eGFR decline or KFRT). Among participants without baseline CKD (n = 6,677), intensive BP control resulted in a 3.5-fold higher risk of ≥30% reduction in eGFR to < 60 mL/min/1.73 m^2, a finding that may reflect hemodynamic changes rather than true kidney injury.

For Question 1, (a) reduced all-cause mortality is the correct answer. A lower BP goal did not slow progression

Table 1. Summary of Guidelines for Slowing Kidney Function Decline in Patients With CKD

Guidelines	BP Control	RAAS Inhibition	Glycemic Control	Diet
KDIGO 2012	Goal BP: ≤140/90 mm Hg (if UACR < 30 mg/g) or ≤ 130/80 mm Hg (if UACR ≥ 30 mg/g)	Start ACEI or ARB if diabetes and UACR 30-300 mg/g; start ACEI or ARB if UACR ≥ 300 mg/g	Goal HbA1c ~7.0%[a]; avoid HbA1c < 7.0% if at risk of hypoglycemia; allow HbA1c > 7.0% if comorbidities, limited life expectancy, or at risk of hypoglycemia	Goal < 2 g/d of sodium; protein intake < 1.3 g/kg/d if at risk for CKD progression; protein intake 0.8 g/kg/d if GFR < 30 mL/min/1.73 m^2
AHA/ACC 2017	Goal BP: <130/80 mm Hg	Start ACEI if HTN and eGFR < 60 mL/min/1.73 m^2 or UACR ≥ 300 mg/g; use ARB if above indications and ACEI not tolerated	NA	Sodium reduction if HTN
ADA and EASD 2018 (for patients with type 2 diabetes)	NA	NA	Goal HbA1c ≤ 7.0% but should be individualized; consider SGLT2i if at risk for CKD progression; consider GLP-1RA if SGLT2i not tolerated or contraindicated	NA
ERBP 2015 (for patients with CKD G3b+)	Goal SBP: <140 mm Hg	Start ACEI if diabetes and cardiovascular indication	Goal HbA1c ≤ 8.5% if comorbidities, limited life expectancy, or at risk of hypoglycemia; goal HbA1c ≤ 7.0-8.0% otherwise	NA

None of the guidelines included recommendations relating to uric acid. Based on KDIGO CKD Work Group 2013 (*Kidney Int Suppl,* https://doi.org/10.1038/kisup.2012.77), KDIGO Diabetes Work Group 2020 (*Kidney Int,* https://doi.org/10.1016/j.kint.2020.06.019), Whelton et al 2018 (*Hypertension,* https://doi.org/10.1161/hyp.0000000000000065), Davies et al 2018 (*Diabetologia,* https://doi.org/10.1007/s00125-018-4729-5), Bilo et al 2015 (*Nephrol Dial Transplant,* https://doi.org/10.1093/ndt/gfv100).

Abbreviations: ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ERBP, European Renal Best Practice; GFR, glomerular filtration rate; GLP-1RA , glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; HTN, hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not available; SBP, systolic blood pressure; SGLT2i, sodium/glucose cotransporter 2 inhibitor; UACR, urinary albumin-creatinine ratio.

[a]The 2020 KDIGO Diabetes in CKD guideline recommends an individualized HbA1c target of <6.5% to <8.0%.

Table 2. Summary of Major Clinical Trials on Intensive Versus Standard BP Control and Kidney Function Decline

	AASK Trial and Cohort (n = 1,094)	MDRD Study (n = 840)	REIN-II (n = 335)	SPRINT (n = 9,361)
Kidney-related inclusion criteria	GFR 20-65 mL/min/1.73 m^2; UPCR ≤ 2.5 g/d	Scr 1.2 (F) or 1.4 (M) to 7.0 mg/dL or CL_{cr} < 70 mL/min/1.73 m^2; proteinuria < 10 g/d	Proteinuria 1-3 g/d and CL_{cr} < 45 mL/min/1.73 m^2 or proteinuria ≥ 3 g/d and CL_{cr} < 70 mL/min/1.73 m^2	eGFR 20-60 mL/min/1.73 m^2; proteinuria < 1 g/d
Follow-up	Range: 8.8-12.2 y	Mean: 2.2 y	Median: 1.6 y	Median: 3.3 y
% With diabetes	0	0 with "diabetes mellitus requiring insulin therapy"	0 with "type 1 diabetes mellitus"	0
Intervention	MAP ≤ 92 vs 102-107 mm Hg	MAP 92 vs 107 mm Hg	BP < 130/80 vs DBP < 90 mm Hg	SBP < 120 vs < 140 mm Hg

Subgroups	UPCR ≤0.22 g/g	UPCR >0.22 g/g	GFR 25-55 mL/min/1.73 m^2	GFR 13-24 mL/min/1.73 m^2	Proteinuria 1-3 g/d	Proteinuria ≥3 g/d	eGFR 20-59 mL/min/1.73 m^2	eGFR ≥60 mL/min/1.73 m^2
Mean baseline eGFR, mL/min/1.73 m^2	51.1	40.0	38.6[a]	18.5[a]	~32.9-35.9	~31.1-41.7	~47.8-47.9	~81.1-81.3
Baseline UPCR or UPE	Median: 0.04 g/g	Median: 0.68 g/g	Median: 0.15 g/g	Median: 0.63 g/g	Mean: ~1.7-1.8 g/d	Mean: ~4.9 g/d	NA	NA
Baseline UACR	NA	NA	NA	NA	NA	NA	Mean: ~41.1-44.1 mg/g	
Kidney function decline[c]	HR, 1.18 (0.93-1.50)	HR, 0.73 (0.58-0.93)	−1.6 (−0.8, 3.9) mL/min/3 y	−0.5 (−0.4, 1.4) mL/min/y	HR, 1.06 (0.51-2.20)	HR, 1.09 (0.55-2.19)	HR, 0.89 (0.42-1.87)	HR, 3.49 (2.44-5.10)
P interaction	0.02		0.02[b]	0.01[b]	NA		NA	

Based on information in Appel et al 2010 (*N Engl J Med,* https://doi.org/10.1056/nejmoa0910975), Klahr et al 1994 (*N Engl J Med,* https://doi.org/10.1056/nejm199403313301301), Ruggenenti et al 2005 (*Lancet,* https://doi.org/10.1016/s0140-6736(05)71082-5), SPRINT Research Group 2015 (*N Engl J Med,* https://doi.org/10.1056/nejmoa1511939).

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; BP, blood pressure; CL_{cr}, creatinine clearance; DBP, diastolic blood pressure; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; F, female; HR, hazard ratio; KFRT, kidney failure with replacement therapy; M, male; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; NA, not available; REIN, Ramipril Efficacy in Nephropathy; SBP, systolic blood pressure; Scr, serum creatinine; SPRINT, Systolic Blood Pressure Intervention Trial; UACR, urinary albumin-creatinine ratio; UPCR, urinary protein-creatinine ratio; UPE, urine protein excretion.

[a]Denotes GFR.

[b]For interaction with baseline proteinuria (<1 g/d vs 1 to <3 g/d vs ≥3 g/d).

[c]Defined in each study as follows: AASK (HR for doubling of serum creatinine, KFRT, or death); MDRD Study (mean difference in rate of GFR decline); REIN-II (HR for KFRT); SPRINT, baseline eGFR 20-59 mL/min/1.73 m^2 (HR for first occurrence of ≥50% reduction in eGFR, maintenance dialysis, or kidney transplantation); SPRINT, eGFR ≥ 60 mL/min/1.73 m^2 (HR for ≥30% reduction in eGFR to a level of <60 mL/min/1.73 m^2). Values in parentheses are 95% CI.

of CKD, and SPRINT was not powered to assess KFRT and kidney transplantation events. For Question 2, (c) the patient with CKD G3bA3 and a UACR of 3,000 mg/g would most likely benefit from a lower BP goal based on subgroup analysis from clinical trials. Patients with A1 albuminuria, critical bilateral renal artery stenosis, or repeated falls are less likely to benefit from a lower BP goal or may be at higher risk of treatment-related complications.

Additional Readings

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RAAS Inhibition

Case 2: *A 46-year-old woman with type 2 diabetes returns for her second appointment. Her history is notable for retinopathy and CKD G3aA3 attributed to diabetic kidney disease. She denies having orthostatic symptoms or chest discomfort. Her automated office BP is 118/75 mm Hg on atenolol and chlorthalidone. Laboratory testing reveals stable eGFR (at 55 mL/min/1.73 m^2) with a UACR of 1,200 mg/g.*

Question 3: Which one of the following would be the most appropriate antihypertensive therapy to help slow CKD progression?

a) No change in therapy because her BP is controlled to goal
b) Change atenolol to an angiotensin receptor blocker (ARB)
c) Change chlorthalidone to an ARB
d) Add an ARB to the current 2-drug regimen

Case 3: *A 56-year-old woman with CKD G3aA3 due to biopsy-proven diabetic kidney disease has an average out-of-office BP of 144/83 mm Hg on a regimen of lisinopril at 20 mg daily, chlorthalidone at 50 mg daily, and amlodipine at 10 mg daily. Her UACR is 800 mg/g.*

Question 4: Which one of the following interventions would be most appropriate to reduce the risk of CKD progression?

a) Add an ARB to the current regimen
b) Change lisinopril to a mineralocorticoid receptor antagonist (MRA)
c) Increase the lisinopril dosage
d) Change chlorthalidone to indapamide

For the answers to the questions, see the following text.

The cornerstone of albuminuria management is RAAS inhibition. The KDIGO guidelines recommend that all adults with CKD, hypertension, and a UACR of >300 mg/g be treated with an angiotensin-converting enzyme inhibitor (ACEI) or ARB. Among those with diabetes and UACR > 30 mg/g, ACEI or ARB use should be considered. RAAS inhibition in patients with CKD and hypertension is also supported by all major hypertension guidelines (Table 1). Multiple trials have demonstrated that ACEI or ARB therapy delays CKD progression among individuals with albuminuria (Table 3). The REIN trial, which randomized patients with CKD to ramipril versus placebo, showed that mean GFR decline was significantly slower in the ramipril group among participants with proteinuria ≥ 3 g/d. In the RENAAL study, patients with type 2 diabetes and CKD randomized to losartan treatment had a 16% lower risk of developing a doubling of serum creatinine, KFRT, or death compared with the placebo group. Similarly, IDNT reported that irbesartan treatment was associated with a lower risk of a doubling of serum creatinine, serum creatinine ≥ 6.0 mg/dL, KFRT, or death compared with amlodipine or placebo treatments among patients with hypertension and CKD attributed to type 2 diabetes. Finally, in AASK, use of ramipril was independently associated with 22% and 38% lower risks of the clinical composite outcome (GFR decline ≥50% or ≥25 mL/min/1.73 m^2 from baseline, KFRT, or death) compared with metoprolol and amlodipine, respectively.

The current literature does not support the use of dual blockade with an ACEI and ARB in diabetic kidney disease. VA NEPHRON-D, which randomized veterans with type 2 diabetes and CKD G2-G3bA3 to losartan plus lisinopril or losartan alone, was terminated early due to safety concerns, with the combination therapy group having a markedly higher risk of hyperkalemia (HR, 2.8 [95% CI, 1.8-4.3]) and acute kidney injury (HR, 1.7 [95% CI, 1.3-2.2]) compared with the monotherapy group. Additionally, there was no significant difference in risk of kidney function decline between the 2 treatment groups, though the follow-up period was short (Table 3).

Decreased sodium intake may enhance the renoprotective effects of RAAS inhibitors. A meta-analysis of 11 studies (23 cohorts with 516 participants) reported that dietary sodium restriction (average decrease of 92 mmol/d) was associated with a 32% lower urine albumin excretion. The reduction in urine albumin excretion was greater in the cohorts with concomitant RAAS blockade therapy than in those without (pooled mean differences of −41.9% and −17.2%, respectively; $P = 0.01$ for interaction), suggesting a synergistic effect of low sodium intake with RAAS inhibition. In a post hoc analysis of 500 participants in the REIN and REIN II trials receiving ramipril therapy, a diet with > 14 g/d of salt was associated with 3.3-fold and 2.4-fold greater risks of KFRT compared with diets of <7 g/d and 7 to 14 g/d of salt, respectively. Importantly, the proteinuria-reducing effects of ramipril were greatest in the low-sodium diet group. In another post hoc analysis of the RENAAL study and IDNT (n = 1,177), ARB therapy was associated with a 43% lower risk of a renal event, defined as a doubling of serum creatinine or KFRT, compared with non-RAAS inhibitor therapy among participants in the lowest tertile of the 24-hour urinary sodium-creatinine ratio with no significant difference in risk between the 2 treatment groups for higher tertiles of sodium intake ($P < 0.001$ for interaction; Fig 1). Given these findings, patients on RAAS inhibitors for treatment of albuminuria should be encouraged to follow a low-sodium diet.

For patients intolerant of ACEI/ARB therapy, an MRA can be considered. A recent meta-analysis of 31 randomized controlled trials evaluated the efficacy and safety of MRAs (spironolactone, eplerenone, canrenone, or finerenone) compared with active control or placebo in reducing albuminuria. In the 18 trials (n = 2,036) that examined UACR as an outcome, proportional change in UACR from baseline to end of treatment was 22% lower in MRA treatment compared with active control and placebo. The effect persisted when comparing MRAs to placebo (n = 1,436 in 11 trials) in patients on ACEI/ARB therapy. When comparing MRAs to renin-angiotensin blockers, there was no significant difference in change in albuminuria (n = 201 in 2 trials), but the risk of incident hyperkalemia was 70% higher (n = 855 in 5 trials). Although reduction in albuminuria is not a universally accepted surrogate end point for KFRT, the FIDELIO-DKD trial of patients with type 2 diabetes and CKD (>98% on concomitant ACEI or ARB therapy) reported that

Table 3. Summary of Major Clinical Trials on ACEI and ARB Therapy on Kidney Function Decline

	REIN, Stratum 2 (n = 166)	RENAAL (n = 1,513)	AASK Trial (n = 1,094)	IDNT (n = 1,715)	VA NEPHRON-D (n = 1,448)
Kidney-related inclusion criteria	CL_{cr} 20-70 mL/min/1.73 m^2; proteinuria ≥ 3 g/d	Scr 1.3-3.0 mg/dL; UACR ≥ 300 mg/g	GFR 20-65 mL/min/1.73 m^2; UPCR ≤ 2.5 g/d	Scr 1.0 (F) or 1.2 (M) to 3.0 mg/dL; proteinuria ≥ 900 mg/d	eGFR 30-<90 mL/min/1.73 m^2; UACR ≥ 300 mg/g
Follow-up	Mean: ~1.3 y	Mean: 3.4 y	Range: 3.0-6.4 y	Mean: 2.6 y	Median: 2.2 y
% With diabetes	0[a]	100%	0	100%	100%
% With HTN	87%	93%[b]	100%	100%	NA
Intervention	Ramipril vs placebo	Losartan vs placebo	Ramipril vs metoprolol vs amlodipine	Irbesartan vs placebo vs amlodipine	Losartan + lisinopril vs losartan + placebo
Mean baseline eGFR, GFR, or Scr	GFR 37.4-40.2 mL/min/1.73 m^2	Scr ~1.9 mg/dL[c]	GFR 45.6 mL/min/1.73 m^2	Scr ~1.7 mg/dL[c]	eGFR ~53.6-53.7 mL/min/1.73 m^2
Baseline UPCR or UPE	Mean: 5.1-5.6 g/d	NA	Median: 0.08 g/g	Median: ~2.9 g/d	Median: ~1.6-2.1 g/g
Baseline UACR or UAE	NA	Median: ~1,237-1,261 mg/g	NA	Median: ~1.9 g/d	Median: 847 mg/g
Kidney function decline[d]	0.53 vs 0.88 mL/min/mo; $P = 0.03$[e]	HR, 0.84 (0.72-0.98)	Risk reduction for ramipril: 22% (1%-38%) vs metoprolol, 38% (14%-56%) vs amlodipine	RR for irbesartan: 0.81 (0.67-0.99) vs placebo, 0.76 (0.63-0.92) vs amlodipine	HR, 0.88 (0.70-1.12)

Based on information in GISEN Group 1997 (*Lancet,* https://doi.org/10.1016/S0140-6736(96)11445-8), Brenner et al 2001 (*N Engl J Med,* https://doi.org/10.1056/nejmoa011161), Wright et al 2002 (*JAMA,* https://doi.org/10.1001/jama.288.19.2421), Lewis et al 2001 (*N Engl J Med,* https://doi.org/10.1056/nejmoa011303), Fried et al 2013 (*N Engl J Med,* https://doi.org/10.1056/nejmoa1303154).

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CL_{cr}, creatinine clearance; eGFR, estimated glomerular filtration rate; F, female; GFR, glomerular filtration rate; HTN, hypertension; HR, hazard ratio; IDNT, Irbesartan Diabetic Nephropathy Trial; KFRT, kidney failure with replacement therapy; M, male; NA, not available; RENAAL, Reduction in End Points in Non–Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan; RR, relative risk; Scr, serum creatinine; REIN, Ramipril Efficacy in Nephropathy; UACR, urinary albumin-creatinine ratio; UAE, urine albumin excretion; UPCR, urinary protein-creatinine ratio; UPE, urine protein excretion; VA NEPHRON-D, Veterans Affairs Nephropathy in Diabetes Study.

[a]None with "insulin-dependent diabetes mellitus."

[b]Percentage receiving anti-HTN drugs at baseline.

[c]Neither eGFR nor GFR is not available.

[d]Defined in each study as follows: REIN (GFR decline per month); RENAAL (HR for Scr doubling, KFRT, or death); IDNT (RR for Scr doubling, Scr ≥ 6.0 mg/dL, KFRT, or death); AASK (GFR decline ≥ 50% or ≥ 25 mL/min/1.73 m^2 from baseline, KFRT, or death); VA NEPHRON-D (HR for first occurrence of absolute decline in eGFR ≥ 30 mL/min/1.73 m^2 if eGFR at randomization ≥ 60 mL/min/1.73 m^2, relative decline in eGFR ≥ 50% if eGFR at randomization < 60 mL/min/1.73 m^2; eGFR < 15 ml/min/1.73 m^2; KFRT; or death).

[e]Analysis among 117 participants with at least 3 GFR measurements.

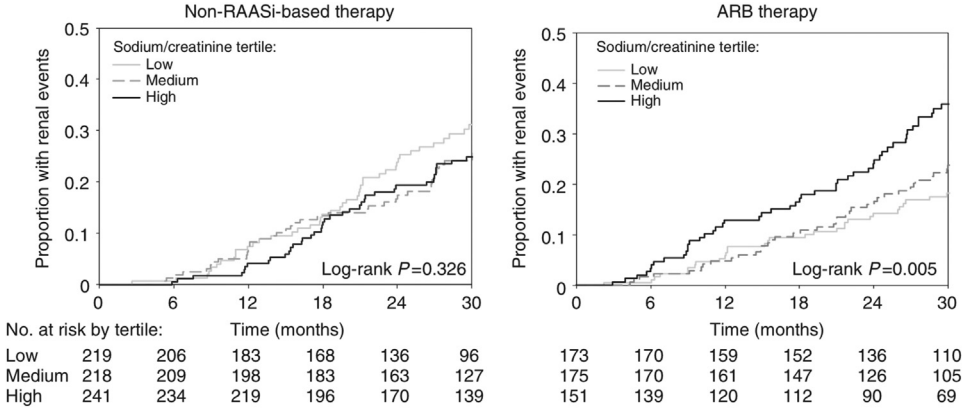

Figure 1. Kaplan-Meier curves for renal events by tertiles of 24-hour urinary sodium-creatinine ratio (<121 mmol/g; 121 to <153 mmol/g; ≥153 mmol/g) among RENAAL and IDNT trial participants on non–RAASi-based therapy and ARB therapy. Renal event defined as a doubling of serum creatinine from baseline or KFRT (RENAAL and IDNT) or serum creatinine ≥ 6.0 mg/dL (IDNT only). Abbreviations: ARB, angiotensin receptor blocker; IDNT, Irbesartan Diabetic Nephropathy Trial; KFRT, kidney failure with replacement therapy; non-RAASi, non–renin-angiotensin-aldosterone system inhibitor; RENAAL, Reduction in End Points in Non–Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan. Adapted from Heerspink et al 2012 (*Kidney Int,* https://doi.org/10.1038/ki.2012.74) with permission of the copyright holder. Original graphic © 2012 International Society of Nephrology.

finerenone conferred an 18% lower risk of composite kidney outcome (sustained decline in eGFR by ≥40% or to <15 mL/min/1.73 m^2, KFRT, or death from kidney causes) compared with placebo. Thus, MRAs reduce albuminuria and may also slow CKD progression. These benefits, however, must be balanced against the potential risk of hyperkalemia.

In Question 3, (b) changing atenolol to an ARB is the correct answer. ACEIs and ARBs have been shown to slow the progression of CKD in patients with diabetes while β-blockers have not. In the management of hypertension, β-blockers are an add-on therapy after the use of first-line agents such as ACEIor ARBs and thiazide diuretics. Adding an ARB to the current regimen is less desirable, as this may result in hypotension in a patient with BP already controlled to goal.

In Question 4, (c) increasing the lisinopril dose is the best answer. Combination ACEI and ARB therapy is associated with an increased risk of adverse outcomes. Although an MRA may reduce albuminuria when combined with an ACEI or ARB, no randomized controlled trials have been performed to support changing an ACEI to an MRA with the intent of slowing progression to KFRT. Exchanging chlorthalidone for indapamide is not anticipated to slow this progression.

Additional Readings

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Glycemic Control

Case 4: *A 48-year-old man with type 2 diabetes is seen for a routine follow-up visit. He has stable CKD (G3aA2 for 3 years) in addition to retinopathy, hypertension, and hyperlipidemia. He is currently taking losartan at 50 mg daily, metoprolol at 75 mg twice daily, metformin at 500 mg twice daily, and atorvastatin at 20 mg daily. His BP is 127/68 mm Hg with a heart rate of 64 bpm. The remainder of the physical examination is unremarkable. Laboratory evaluation demonstrates his eGFR is 52 mL/min/1.73 m^2, UACR 35 mg/g, and hemoglobin A1c (HbA1c) 7.9%.*

Question 5: Which one of the following interventions would be most likely to slow the progression of his CKD?

a) Increase losartan to reduce BP to < 120/80 mm Hg
b) Change metoprolol to a dihydropyridine calcium channel blocker
c) Increase metformin to target HbA1c < 7%
d) No changes, as the management of hypertension and glycemic control are at goal

For the answer to the question, see the following text.

The 2020 KDIGO guidelines on diabetes in CKD recommend that HbA1c goals be individualized based on CKD severity, comorbidities, and hypoglycemia risk, among other factors (Table 4). Dosing adjustments or discontinuation of glucose-lowering agents are often necessary as CKD progresses. In particular, insulins, sulfonylureas, and meglitinides are more likely to cause hypoglycemia in a patient with reduced kidney function.

Most major randomized controlled trials have suggested that intensive glycemic control reduces albuminuria and possibly also kidney function decline in patients with diabetes (Table 5). In the ADVANCE-ON and DCCT/EDIC studies, intensive glycemic control was associated with a 46% lower risk of KFRT or death from kidney disease and 50% lower risk of incident eGFR < 60 mL/min/1.73 m^2, respectively. A large meta-analysis of the ADVANCE, ACCORD, UKPDS, and VADT trials showed that more intensive glycemic control was associated with a 20% lower risk of developing a primary kidney event (ie, incident eGFR < 30 mL/min/1.73 m^2, UACR > 300 mg/g, KFRT, or death from kidney disease), mostly due to a reduction in risk of albuminuria. Participants with more intensive control were also more likely to have regression of UACR from >300 to 30-300 mg/g (HR, 1.23 [95% CI, 1.03-1.48]), regression of UACR from 30-300 to <30 mg/g

Table 4. Factors to Consider When Determining Hemoglobin A1c Targets in Patients With Diabetes and CKD

Factors	Goal hemoglobin A1c	
	<6.5%	<8.0%
CKD severity	Lower (eg, G1)	Higher (eg, G5)
Macrovascular complications	None or mild	Severe
Comorbidities	None or few	Many
Life expectancy	Long	Short
Hypoglycemia awareness	Good	Diminished
Resources for hypoglycemia management	Available	Limited
Likelihood of treatments causing hypoglycemia	Low	High

Based on information in KDIGO Diabetes Work Group 2020 (*Kidney Int*, https://doi.org/10.1016/j.kint.2020.06.019).
Abbreviations: CKD, chronic kidney disease; G, glomerular filtration rate category.

(HR, 1.15 [95% CI, 1.03-1.28]), and maintenance of UACR < 30 mg/g (HR, 1.16 [95% CI, 1.08-1.25]).

For Question 5, (c) targeting a HbA1c of 7% or less is the best option among those listed to help slow CKD progression. In patients with CKD G4-G5 or significant competing comorbidities where risk of hypoglycemia is higher and benefits of intense control less well established, the HbA1c target should be individualized. The patient's BP is currently controlled to goal, and further reduction or substitution of a dihydropyridine calcium blocker for a β-blocker has not been shown to slow CKD progression.

Additional Readings

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SGLT2 Inhibitors

Case 4, cont'd: *The patient returns for a follow-up visit. His CKD has steadily worsened over the past 12 months. Laboratory studies reveal:*

Parameter	Present	6 mo prior	12 mo prior
Sodium, mEq/L	132	134	131
Potassium, mEq/L	5.3	5.2	5.4
Glucose, mg/dL	315	280	210
eGFR, mL/min/1.73 m²	46	51	52
UACR, mg/g	1,000	400	35
HbA1c	9.4%	—	7.9%

Question 6: Which one of the following interventions would be the next best step?

a) Start treatment with a SGLT2 inhibitor to reduce albuminuria
b) Start treatment with a SGLT2 inhibitor to achieve an HbA1c <7%
c) Do not start treatment with a SGLT2 inhibitor because of a risk for worsening hyperkalemia
d) Do not start treatment with a SGLT2 inhibitor because of a risk for worsening hyponatremia

Case 5: *A 70-year-old woman with moderate obesity (body mass index [BMI] of 32 kg/m²) and uncontrolled diabetes mellitus (HbA1c 8.2%) returns to discuss the management of her CKD G3aA2. Her history includes coronary artery disease and recurrent furunculosis requiring antibiotics several times per year.*

Question 7: In counseling her on the potential benefits and risks of therapy with an SGLT2 inhibitor, for which one of the following adverse effects is she at greatest risk?

a) Genitourinary fungal infections
b) Lower extremity amputation
c) Severe hypoglycemia
d) Acute kidney injury

For the answers to the questions, see the following text.

In recent years, SGLT2 inhibitors have emerged as new, exciting therapies for delaying CKD progression, particularly among patients with type 2 diabetes and/or albuminuria. Current ADA and EASD guidelines recommend

Table 5. Summary of Major Clinical Trials on Intensive Versus Standard Glycemic Control on Kidney Outcomes

	ADVANCE (n = 11,140)	ACCORD (n = 10,251)	UKPDS (n = 3,867)	VADT (n = 1,791)	DCCT (n = 1,441)	EDIC (n = 1,349)
Kidney-related inclusion criteria	Not specified	Scr ≤ 132.6 μmol/L	Scr ≤ 175 μmol/L	Scr ≤ 1.6 mg/dL	Scr < 1.2 mg/dL or CL_{cr} > 100 mL/min/1.73 m^2; UAE < 40 mg/d	Scr < 1.2 mg/dL or CL_{cr} > 100 mL/min/1.73 m^2; UAE < 40 mg/d
Follow-up	Median: 5 y	Mean: ~3.5 y	Median: ~10 y	Median: 5.6 y	Mean: 6.5 y	Mean: ~8 y
Diabetes type	Type 2	Type 2	Type 2	Type 2	Type 1	Type 1
Diabetes duration	Median: 7 y	Median: ~10 y	"Newly diagnosed"	Mean: ~11.5 y	Mean: ~2.6[a] and ~8.6-8.9[b] y	Mean: ~12 y
Intervention	HbA1c ≤6.5% vs standard[a]	HbA1c <6.0% vs 7.0%-7.9%	Median HbA1c ~7.0% vs ~7.9%	Median HbA1c ~6.9% vs 8.4%	HbA1c <6.05% vs standard	None (obs follow-up of DCCT)
Mean baseline HbA1c	~7.5%	~8.1%	7.08%	~9.4%	~8.8%[b] and ~8.9%-9.0%[c]	~7.4%[d] and 9.1%[e]
Baseline eGFR, CL_{cr}, or Scr	Mean eGFR ~78.0-78.3 mL/min/1.73 m^2	Median eGFR ~90 mL/min/1.73 m^2	NA	Mean Scr ~1.0 mg/dL	Mean CL_{cr} ~127-128[b] and ~128-130[c] mL/min	Mean CL_{cr} ~122 mL/min
Baseline UACR or UAE[f]	Median UACR ~14.9-15.0 μg/mg	Median UACR ~1.54 mg/mmol	NA	NA	Mean UAE ~12[b] and ~19-21[c] mg/d	Median UAE 8.6[d] and 10.1[e] mg/d
Kidney outcome[g]	UACR ≥ 30 μg/mg: HR, 0.91 (0.85-0.98); UACR > 300 μg/mg: HR, 0.70 (0.57-0.85); KFRT: HR, 0.35 (0.15-0.83)	UACR ≥ 30 mg/g: HR, 0.79 (0.69-0.90); UACR ≥ 300 mg/g: HR, 0.69 (0.55-0.85); KFRT or SCr >291.72 μmol/L: HR, 0.95 (0.73-1.24)	UACR ≥ 30 mg/g: RR, 0.70 (0.46-1.07); "Proteinuria": RR, 0.58 (0.23-1.43); Pcr doubling: RR, 1.25 (0.16-9.55)	Any ↑ in albuminuria: 9.1% vs 13.8% (P = 0.01); from normal to UACR ≥ 30 mg/g: 10.0% vs 14.7% (P = 0.03); Scr doubling: 8.8% vs 8.8% (P = 0.99)	Risk reduction: 39% (21%-52%) for UAE ≥ 40 mg/d; 54% (19%-74%) for UAE ≥300 mg/d	Risk reduction: 59% (39%-73%) for UAE ≥ 40 mg/d; 84% (67%-92%) for UAE > 300 mg/d
					Risk reduction: 50% (18%, 69%)[h] for sustained eGFR < 60 mL/min/1.73 m^2	

Based on information in Perkovic et al 2013 (*Kidney Int,* https://doi.org/10.1038/ki.2012.401), Ismail-Beigi 2010 (*Lancet,* https://doi.org/10.1016/s0140-6736(10)60576-4), UKPDS Group 1998 (*Lancet,* https://doi.org/10.1016/S0140-6736(98)07019-6), Duckworth et al 2009 (*N Engl J Med,* https://doi.org/10.1056/nejmoa0808431), DCCT group 1993 (*N Engl J Med,* https://doi.org/10.1056/nejm199309303291401), EDIC group 2003 (*JAMA,* https://doi.org/10.1001/jama.290.16.2159), DCCT/EDIC group 2011 (*N Engl J Med,* https://doi.org/10.1056/nejmoa1111732).

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CL_{cr}, creatinine clearance; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio; obs, observational; RR, relative risk; Scr, serum creatinine; UAE, urine albumin excretion; UKPDS, UK Prospective Diabetes Study; UACR, urinary albumin-creatinine ratio; UPCR, urinary protein-creatinine ratio; VADT, Veterans Affairs Diabetes Trial.

[a]Based on local guidelines.
[b]Primary prevention cohort of the DCCT.
[c]Secondary intervention cohort of the DCCT.
[d]Intensive group of original DCCT.
[e]Conventional group of original DCCT.
[f]Baseline UPCR information not available.
[g]For UKPDS, from 0-15 years of follow-up with outcome assessed every 3 years.
[h]Over median follow-up of 22 years (includes DCCT and EDIC years 1-16).

that SGLT2 inhibitors be considered in all patients with type 2 diabetes at risk of CKD progression, regardless of cardiovascular disease history (Table 1).

Initial reports of the potential kidney protective effects of SGLT2 inhibitors came from cardiovascular outcome trials. These studies, however, primarily included individuals with mild or no CKD and were limited by small numbers of kidney events. In 2019, the results of the landmark CREDENCE trial were published. This trial, the first to examine the association of a SGLT2 inhibitor with a primary kidney outcome, reported that among patients with type 2 diabetes and CKD G2-G3bA3, randomization to canagliflozin was associated with a 30% lower risk (95% CI, 18%-41%) of developing a composite outcome (KFRT, sustained eGFR < 15 ml/min/1.73 m^2, doubling of serum creatinine from baseline, death from kidney disease, or death from cardiovascular disease) compared with placebo. Similar conclusions were obtained when considering individual components of the composite outcome. Importantly, all participants were on an ACEI or ARB, thus suggesting that the benefits of canagliflozin extended beyond standard pharmacologic therapy (ie, RAAS inhibition).

Neuen et al performed a meta-analysis of four randomized, controlled trials that investigated the effect of SGLT2 inhibitors on major kidney outcomes among patients with type 2 diabetes and eGFR ≥ 30 mL/min/1.73 m^2: CREDENCE, CANVAS Program, EMPA-REG OUTCOME, and DECLARE-TIMI 58. The majority of patients in the latter 3 trials did not have baseline CKD

(Table 6). Among 38,723 participants, use of SGLT2 inhibitors was associated with a 33% lower risk of a composite outcome of dialysis, transplantation, or death from kidney disease compared with placebo. Importantly, the benefits of SGLT2 inhibitors were statistically significant in all subgroups of baseline eGFR (30 to <45, 45 to <60, 60 to <90, and ≥90 mL/min/1.73 m^2). The eGFR decline was also slower in the SGLT2 inhibitor group versus placebo in CREDENCE (absolute difference, 2.74 [95% CI, 2.37-3.11] mL/min/1.73 m^2 per year), CANVAS Program (absolute difference, 1.18 [95% CI, 1.02-1.35] mL/min/1.73 m^2 per year), and EMPA-REG OUTCOME (absolute difference, 1.68 [95% CI, 1.02-1.35] mL/min/1.73 m^2 per year).

More recently, the DAPA-CKD trial demonstrated that the renoprotective effects of SGLT2 inhibitors likely extend beyond patients with type 2 diabetes. This trial, which enrolled individuals with CKD (32.5% without type 2 diabetes), was stopped early because of clear efficacy of dapagliflozin over placebo for the primary outcome

Table 6. Summary of Trials on SGLT2 Inhibitors With Kidney Outcomes in Patients With and Without Type 2 Diabetes

Trial	CREDENCE (n = 4,401)	CANVAS Program (n = 10,142)	EMPA-REG OUTCOME (n = 7,020)	DECLARE-TIMI 58 (n = 17,160)	DAPA-CKD (n = 4,304)
Study or Participant Characteristics					
Inclusion criteria	eGFR 30-<90 mL/min/1.73 m^2; UACR > 300-5,000 mg/g	eGFR ≥ 30 mL/min/1.73 m^2	eGFR ≥ 30 mL/min/1.73 m^2	CL_{cr} ≥ 60 mL/min	eGFR 25-75 mL/min/1.73 m^2; UACR 200-5,000 mg/g
SGLT2i	Canagliflozin	Canagliflozin	Empagliflozin	Dapagliflozin	Dapagliflozin
Median follow-up, y	2.6	2.4	3.1	4.2	2.4
Baseline ACEI or ARB use	4,395 (99.9%)	8,116 (80%)	5,666 (81%)	13,950 (81%)	1354 (31%)[a]; 2,870 (67%)[b]
eGFR, mL/min/1.73 m^2					
≥90	0 (0)	2,476 (24%)	1,538 (22%)	8,162 (48%)	0 (0)
60-<90	1,809 (41%)	5,625 (55%)	3,661 (52%)	7,732 (45%)	454 (11%)
45-<60	1,279 (29%)	1,485 (15%)	1,249 (18%)	1,265 (7%)	1,328 (31%)
30-<45	1,313 (30%)	554 (5%)	570 (8%)	NA	1,898 (44%)
<30	0 (0)	0 (0)	0 (0)	0 (0)	624 (14%)
Missing	0 (0)	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)	0 (0)
UACR, mg/g					
<30	0 (0)	7,007 (69%)	4,171 (59%)	11,644 (68%)	NA[c]
30-300	0 (0)	2,266 (22%)	2,013 (29%)	4,030 (24%)	NA
>300[c]	4,401 (100%)	760 (7%)	769 (11%)	1,169 (7%)	NA
Missing	0 (0)	109 (1%)	67 (1%)	317 (2%)	NA
RR or HR Ratio Comparing SGLT2i With Placebo					
Dialysis, Tx, or death from kidney disease	0.72 (0.54-0.97)	0.56 (0.23-1.32)	0.90 (0.30-2.67)	0.42 (0.20-0.87)	NA
Dialysis, Tx, or sustained eGFR < 15 mL/min/1.73 m^2[,d]	0.68 (0.54-0.86)	0.77 (0.30-1.97)	0.60 (0.18-1.98)	0.31 (0.13-0.79)	0.64 (0.50-0.82)
Substantial loss of kidney function[e]; dialysis, Tx, or sustained eGFR < 15 mL/min/1.73 m^2[,d]; or death from kidney disease	0.66 (0.53-0.81)	0.53 (0.33-0.84)	0.54 (0.40-0.75)	0.53 (0.43-0.66)	0.56 (0.45-0.68)

All participants in CREDENCE, CANVAS Program, EMPA-REG OUTCOME, and DECLARE-TIMI 58 were with type 2 diabetes. In DAPA-CKD, 67.5% of participants were with type 2 diabetes. Based on information in Neun et al 2019 (*Lancet Diabetes Endocrinol,* https://doi.org/10.1016/s2213-8587(19)30256-6), and Heerspink et al 2020 (*N Engl J Med,* https://doi.org/10.1056/nejmoa2024816).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CANVAS, Canagliflozin Cardiovascular Assessment Study; CL_{cr}, creatinine clearance; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; KFRT, kidney failure with replacement therapy; NA, not available; RR, relative risk; SGLT2i, sodium/glucose cotransporter 2 inhibitor; Tx, transplantation; UACR, urinary albumin-creatinine ratio.

[a]On ACEI.

[b]On ARB.

[c]n = 2,079 (48%) with UACR of >1,000 mg.

[e]Defined as a doubling of serum creatinine with the exception of DECLARE-TIMI 58 (sustained 40% decline in eGFR) and DAPA-CKD (sustained 50% decline in eGFR).

[d]Except for the EMPA-REG OUTCOME trial, which did not include sustained eGFR < 15 mL/min/1.73 m^2.

(sustained eGFR decline ≥ 50% from baseline, KFRT, sustained eGFR < 15 mL/min/1.73 m^2, or death from kidney or cardiovascular cause), with an HR of 0.61 (95% CI, 0.51-0.72). The benefits of dapagliflozin were consistent in participants with and without type 2 diabetes. Safety profiles were similar between the 2 treatment arms with the exception of volume depletion (more common with dapagliflozin) and major hypoglycemia (more common with placebo).

Several mechanisms have been proposed for how SGLT2 inhibitors improve kidney outcomes. Blockade of SGLT2, responsible for ~90% of glucose reabsorption that occurs in the proximal tubule, promotes urinary excretion of glucose. However, SGLT2 inhibitors are associated with only modest HbA1c reductions, suggesting that the kidney effects are not driven by improved glycemic control. Rather, increased distal delivery of sodium to the macula densa (in tandem with glucose excretion) activates tubuloglomerular feedback, leading to vasoconstriction of the afferent arteriole and ultimately a reduction in intraglomerular pressure. SGLT2 inhibitors also reduce systolic and diastolic BP, likely due to osmotic diuresis (from glucosuria), natriuresis, and possibly inhibition of sympathetic nervous system activity. Other potential mechanisms for the renoprotective effects of SGLT2 inhibitors include weight loss, lowering of serum uric acid levels, and reduction of albuminuria.

Although SGLT2 inhibitors are generally well tolerated, some safety concerns warrant mentioning. Genitourinary fungal infections, particularly in women, are the most commonly reported adverse effect. Fournier gangrene, which occurs much more rarely, is another potential severe complication. The US Food and Drug Administration (FDA) issued a black box warning on canagliflozin regarding an increased risk of lower limb amputations based on a nearly 2-fold higher risk of amputations in the CANVAS Program. In contrast, there was no heightened amputation risk in CREDENCE. Still, it is prudent to perform regular foot examinations in all patients on SGLT2 inhibitors, particularly those with a history of neuropathy, peripheral vascular disease, and/or diabetic foot ulcers. An increased risk of fracture with SGLT2 inhibitors was reported in the CANVAS Program but not CREDENCE, EMPA-REG OUTCOME, or DECLARE-TIMI 58. The role of SGLT2 inhibitors as a precipitant for acute kidney injury remains controversial, with some published studies reporting protective effects.

For Question 6, SGLT2 inhibitors are associated with (a) a reduction in albuminuria and a 30% to 40% decreased risk of CKD progression. This class of medications is not commonly associated with hyponatremia or hyperkalemia and results in only a small reduction in HbA1c.

For Question 7, although all of the choices have been reported with the use of SGLT2 inhibitors, the most common is (a) genitourinary fungal infection.

Additional Readings

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GLP-1 Receptor Agonists

Case 6: *A 60-year-old man with type 2 diabetes mellitus and CKD G4A3 (eGFR 27 mL/min/1.73 m^2) has stable UACR (1,800 mg/g for 1 year). His BP is 126/70 mm Hg and HbA1c is 9.0%. His medications include lisinopril at 40 mg daily, diltiazem sustained release at 180 mg daily, and insulin glargine.*

Question 8: Which one of the following interventions would be appropriate to manage risk factors associated with CKD progression?

a) Addition of a GLP-1 receptor agonist to reduce HbA1c but at an increased risk for hypoglycemia
b) Addition of metformin rather than a GLP-1 receptor agonist due to the favorable side-effect profile of metformin
c) Addition of a GLP-1 receptor agonist to slow progression to KFRT without change in albuminuria
d) Addition of a GLP-1 receptor agonist to reduce BP to <120/80 mm Hg

For the answer to the question, see the following text.

The GLP-1 receptor agonists are another novel class of diabetes medications that improve kidney outcomes. In the AWARD-7 trial, dulaglutide 0.75 mg or 1.5 mg weekly resulted in slower eGFR decline over 52 weeks compared with daily insulin glargine among participants with type 2 diabetes, CKD G3-G4, and a UACR > 300 mg/g. Furthermore, UACR reduction occurred with dulaglutide in a dose-dependent manner. Among participants with a baseline UACR of ≤300 mg/g, no significant differences in eGFR decline were observed between the 3 treatment arms. In a meta-analysis of 5 cardiovascular outcome trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, and REWIND), Kristensen et al reported that GLP-1 receptor agonists were associated with a 17% lower risk of a composite kidney

outcome (new-onset UACR of >300 mg/g, a doubling of serum creatinine, and a ≥40% decline in eGFR, KFRT, or death from kidney disease), with an HR of 0.83 (95% CI, 0.78-0.89). However, when considering the more restrictive outcome of worsening kidney function, defined by a doubling of serum creatinine or a ≥40% eGFR decline (except for EXSCEL, which also included KFRT or death from kidney disease), there was no statistically significant protective effect of GLP-1 receptor agonists (HR, 0.87 [95% CI, 0.73-1.03]).

GLP-1 receptor agonists act by binding to the GLP-1 receptor, enhancing glucose-dependent insulin secretion, delaying gastric emptying, and decreasing appetite. Modest improvements in body weight, BP, and lipid parameters have also been reported. Prior studies suggest that multiple cell types (eg, glomerular, tubular, and vascular) within the kidney have GLP-1 receptors, but the mechanisms by which GLP-1 receptor agonists improve kidney outcomes are less clear. Altered renal hemodynamics, increased natriuresis, and reductions in inflammation and reactive oxidative species have all been proposed.

The most frequent side effect of GLP-1 receptor agonists is nausea, which usually resolves after 4 to 8 weeks of continued therapy. Diarrhea, hypoglycemia (particularly if used in combination with insulin therapy), tachycardia, gallbladder disease, pancreatitis, and retinopathy may also occur. Other major safety concerns include increased risks of pancreatic and thyroid cancer. Although Kristensen et al did not find an association of GLP-1 receptor agonist therapy with severe hypoglycemia, pancreatitis, or pancreatic or thyroid cancer, the trials excluded individuals with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, and the FDA label warns against the use of GLP-1 receptor agonists in these patients.

Although no trial has directly compared SGLT2 inhibitors with GLP-1 receptor agonists, a meta-analysis of 8 cardiovascular trials found a 38% (HR, 0.62 [95% CI, 0.58-0.67]) and 18% (HR, 0.82 [95% CI, 0.75-0.89]) lower risk of new-onset UACR > 300 mg/g, doubling of serum creatinine, a ≥40% decline in eGFR, KFRT, or death from kidney disease for SGLT2 inhibitors and GLP-1 receptor agonists, respectively. When an incident UACR of >300 mg/g was not included in the outcome, SGLT2 inhibitors were associated with a 45% lower risk (HR, 0.55 [95% CI, 0.48-0.64]) whereas no association was observed for GLP-1 receptor agonists (HR, 0.92 [95% CI, 0.80-1.06]). Thus, SGLT2 inhibitors appear to be more effective in slowing kidney disease progression and should be considered before GLP-1 receptor agonists (Fig 2).

For Question 8, studies best support (a) a reduction in UACR after addition of a GLP-1 receptor agonist. There is an increased risk of hypoglycemia when used concurrently with insulin, and a reduction in the rate of progression to KFRT has not been shown. While GLP-1 receptor agonists may result in a small reduction in BP, lowering to <120/80 mm Hg has not been shown to slow CKD progression. Initiating metformin would be inappropriate at this eGFR.

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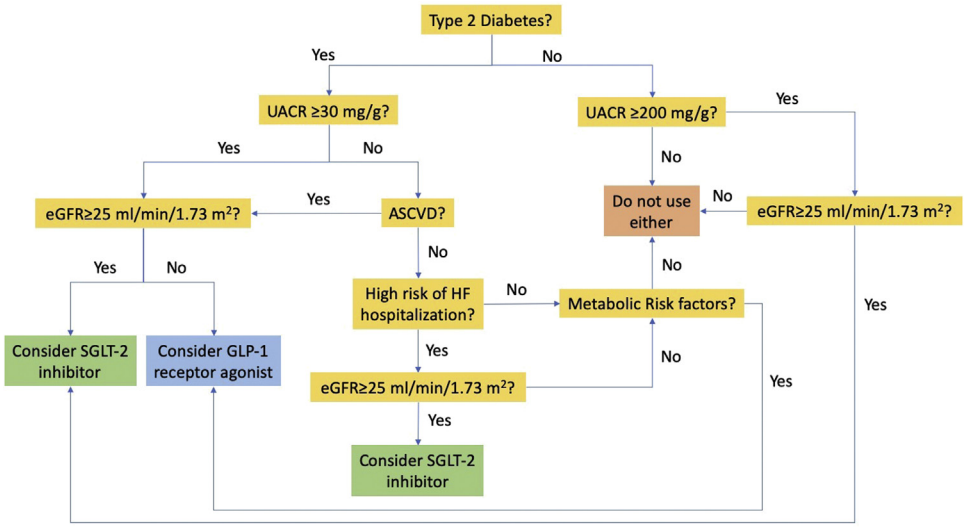

Figure 2. Proposed algorithm for SGLT2 inhibitor and GLP-1 receptor agonist use in chronic kidney disease. Metabolic risks factors include uncontrolled diabetes or obesity/weight gain. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; HF, heart failure; SGLT2, sodium/glucose cotransporter 2; UACR, urinary albumin-creatinine ratio. Based on information in Li et al 2020 (*Clin J Am Soc Nephrol,* https://doi.org/10.2215/CJN.02690320).

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Chronic Metabolic Acidosis and Dietary Protein Restriction

Case 7: *A 63-year-old woman with CKD G4A2 and osteopenia returns for a follow-up visit, having been last seen 4 months ago. She underwent left nephrectomy 30 years ago after trauma. She reports no interval symptoms, and her weight has been stable. Her eGFR has slowly declined from 33 to 28 mL/min/1.73 m² over the past 2 years, with her last 2 total carbon dioxide values in the range of 19 to 21 mmol/L. On physical examination, her BP is 118/65 mm Hg, her lungs are clear, and she has trace pedal edema.*

Question 9: Which one of the following is most accurate in treating metabolic acidosis associated with CKD?

a) Modest dietary protein restriction should decrease urine ammoniagenesis
b) Dietary supplementation with sodium bicarbonate should decrease bone mineral density
c) Modest dietary protein restriction should increase skeletal muscle catabolism

Case 8: *A 58-year-old man with IgA nephropathy has had progressive CKD over the past 18 months. His eGFR is 29 mL/min/1.73 m² with total carbon dioxide ranging between 18 and 20 mmol/L.*

Question 10: Which one of the following interventions has the greatest efficacy in improving metabolic acidosis?

a) Increase daily fruit intake to 4 servings
b) Add sodium bicarbonate as a 650-mg tablet once daily
c) Ensure 2 servings of pasta daily
d) Replace one serving of red meat with one serving of fish daily

For the answers to the questions, see the following text.

Metabolic acidosis is a common complication of CKD due to impairments in the kidney's ability to excrete acid. Dietary composition also influences acid-base balance, with animal-derived proteins contributing primarily hydrogen ions, and fruits and vegetables contributing alkali. Thus, treatment of metabolic acidosis in patients with CKD typically relies on 3 strategies: reduction of dietary animal protein, increased consumption of fruits and vegetables, and administration of oral alkali salts. Metabolic acidosis is a risk factor for KFRT, decreased bone mineralization, and sarcopenia. Correction of metabolic acidosis may slow CKD progression. A systematic review of 13 small, primarily open-label clinical trials suggested that both oral alkali supplementation and dietary interventions slow GFR decline, with a meta-analyzed effect on mean GFR decline of >3 mL/min/1.73 m² per year for both strategies. However, only 4 of the 13 studies had durations more than 1 year, and 4 had durations of 6 months or less. The largest randomized controlled trial of dietary protein restriction to date (MDRD Study) suggested a more modest effect size that failed to demonstrate statistical significance. Among the participants randomized to usual-protein, low-protein, or very-low-protein diet (1.3 vs 0.58 vs 0.28 grams per kilogram of body weight per day), the difference in mean GFR decline over a mean follow-up of 2.2 years was 0.8 mL/min per year for very-low-protein versus low-protein ($P = 0.07$) and 0.4 mL/min per year for the low-protein versus usual-protein diets ($P = 0.30$).

Despite little clinical trial evidence, the KDIGO guidelines suggest consideration of dietary protein restriction to < 1.3 grams per kilogram of body weight per day for patients with or at risk for CKD G3 and 0.8 grams per kilogram of body weight per day for patients with CKD G4-G5, given the theoretical benefit. Patients with CKD and bicarbonate of <22 mmol/L should also be treated with oral alkali therapy to maintain their bicarbonate concentrations in the normal range, recognizing the risks of increased BP and edema. Diets enriched in fruits and vegetables may provide as much or more alkali than bicarbonate supplementation and, in one small study, were similarly effective in slowing eGFR decline (Fig 3).

Returning to Question 9, chronic metabolic acidosis is associated with progression of CKD, stimulates increased renal ammoniagenesis, increases bone resorption, and is associated with the development of sarcopenia. Therefore, the best answer is (a) as reducing protein intake will decrease dietary acid production. For Question 10, the best answer is (a) since 4 servings of fruits and vegetables provide more alkali than low-dose sodium bicarbonate. Carbohydrates and animal meats contribute to net acid production, although replacing servings of red meat with fish may have other health benefits.

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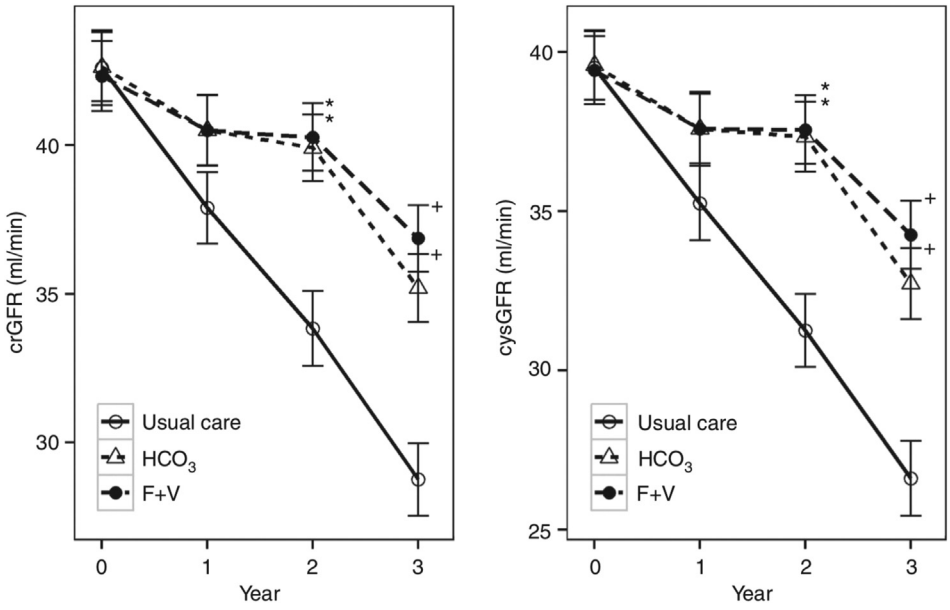

Figure 3. Mean (± SE) estimated glomerular filtration rates among patients with CKD G3 randomized to usual care, sodium bicarbonate supplementation, or base-producing fruits and vegetables. Abbreviations: CKD, chronic kidney disease; crGFR, plasma creatinine-based glomerular filtration rate; cysGFR, plasma cystatin C-based glomerular filtration rate; F+V, fruits and vegetables; HCO_3, sodium bicarbonate supplementation. Reproduced from Goraya et al 2014 (*Kidney Int,* https://doi.org/10.1038/ki.2014.83) with permission of the copyright holder. Original graphic © 2014 International Society of Nephrology.

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Avoidance of Nephrotoxins

Case 9: *A 62-year-old woman with recently diagnosed ovarian cancer has presented to the emergency department with a urinary tract infection and atrial fibrillation. Her medical history is notable for CKD G4A1 in the setting of hypertension and chronic hepatitis B. Her home medications include lisinopril, tenofovir disoproxil fumarate, and multivitamin. Computed tomography imaging of her abdomen/pelvis demonstrates a large ovarian mass with peritoneal carcinomatosis.*

Question 11: Which one of the following medications is safest to use in the setting of CKD G4?

a) Gentamicin
b) Amiodarone
c) Tenofovir disoproxil fumarate
d) Cisplatin

Case 10: *A 74-year-old man with CKD G4A2 in the setting of diabetes mellitus and IgA nephropathy is hospitalized for a nonhealing lower extremity ulceration. His eGFR is currently 23 mL/min/1.73 m^2, as compared with 26 mL/min/1.73 m^2 1 month before. You are consulted before the planned lower extremity angiography for recommendations to reduce the risk for contrast-associated acute kidney injury.*

Question 12: Which one of the following interventions is most appropriate before administration of intra-arterial intravenous iodinated contrast in hospitalized patients with diabetes and CKD?

a) Oral *N*-acetylcysteine
b) 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor
c) Vitamin C
d) Normal saline hydration

For the answers to the questions, see the following text.

Nephrotoxins can contribute to CKD progression by causing acute kidney injury, chronic interstitial nephritis, tubular dysfunction, or glomerular changes. Avoidance of nephrotoxins is not always possible, especially in the hospital or acute care setting; thus, an individualized approach that carefully weighs the risks versus benefits for

each patient is necessary. Many chemotherapeutic (eg, platinum-based agents, gemcitabine, immunotherapies) and antimicrobial (eg, aminoglycosides, colistin, amphotericin B, tenofovir disoproxil fumarate) agents require special attention in CKD given their potential for harm to the kidney and/or need for dose adjustments. Despite known toxicities, alternative drug options may not be appropriate due to susceptibility patterns or decreased efficacy. In such cases, counseling patients on the potential worsening of CKD, close monitoring of kidney function, and dose adjustments as needed is a reasonable approach. Other potential nephrotoxins include gastrointestinal agents (eg, phosphate-containing bowel preparations, proton-pump inhibitors), pain relievers (eg, nonsteroidal anti-inflammatory agents), and herbal supplements or remedies. Although proton-pump inhibitors do not necessarily need to be stopped in patients with CKD, providers should review need and candidacy for alternative therapy (eg, H2 blockers) regularly.

Contrast-associated acute kidney injury remains a concern among patients with CKD, particularly those with eGFR < 30 mL/min/1.73 m^2 or diabetes. Proposed mechanisms of injury include vasoconstriction leading to renal ischemia, direct tubular toxicity, and oxidative stress from free radical generation. High-osmolar (>1,200 mOsm/kg) ionic contrast agents are more likely to be nephrotoxic than low-osmolar (700-850 mOsm/kg) or iso-osmolar (~290 mOsm/kg) nonionic agents. The risk for acute kidney injury is thought to be higher with arterial compared with venous contrast administration. However, patients with CKD should not be denied necessary tests that require contrast for diagnosis and management. Fundamental risk reduction measures include (1) use of minimum dose of contrast necessary; (2) use of low-osmolar or iso-osmolar agents; (3) expansion of intravascular volume as tolerated with intravenous normal saline before, during, and after the procedure; and 4) avoidance of concurrent nephrotoxins.

Returning to Question 11, the best answer is (b) because amiodarone does not require discontinuation or dose adjustment in CKD G4. For Question 12, although all the listed agents have been reported to reduce the risk of contrast-associated kidney injury, the best answer is (d) because periprocedural hydration with normal saline is the most widely accepted prophylaxis.

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Uric Acid–Lowering Therapies

Prior studies have reported an association between elevated serum uric acid levels and increased risk of CKD progression. Whether uric acid directly causes CKD progression or is an indirect marker of some other process is unclear. Two recent trials, PERL and CKD-FIX, investigated whether treatment with allopurinol slowed eGFR decline. The PERL study enrolled patients with type 1 diabetes and early diabetic kidney disease (mean GFR 68 mL/min/1.73 m^2 and median urine albumin excretion rate of 60 mg/d) and showed no difference in GFR slope over 3 years between the allopurinol and placebo groups. The CKD-FIX study, which included individuals with more advanced CKD (mean eGFR 32 mL/min/1.73 m^2 and median UACR 717 mg/g), also reported no significant difference in eGFR change between allopurinol and placebo over 2 years (−3.33 and −3.23 mL/min/1.73 m^2 per year; mean difference, −0.10 [95% CI, −1.18 to 0.97] mL/min/1.73 m^2 per year). Of note, baseline uric acid levels in both trials were not markedly elevated (PERL: 6.1 mg/dL; CKD-FIX: 8.2 mg/dL). Another randomized clinical trial of febuxostat in patients with CKD G3 and asymptomatic hyperuricemia (mean uric acid ~7.8 mg/dL) similarly found no difference in eGFR slopes compared with placebo.

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Weight Loss and Bariatric Surgery

Case 11: *A 54-year-old man has CKD G4A1 in the setting of diabetes mellitus and hypertension. His weight has been stable for the past year after losing 15 pounds. His medications include lisinopril at 40 mg daily and a GLP-1 receptor agonist. His BP is 125/70 mm Hg and BMI is 32 kg/m². His laboratory tests demonstrate an eGFR of 27 mL/min/1.73 m², a UACR of 25 mg/g, HbA1c 7.2%, and serum uric acid of 8.1 mg/dL. The kidney failure risk equation predicts a 4.6% risk of kidney failure at 2 years.*

Question 13: Which one of the following interventions would be most appropriate to reduce his risk of progression to kidney failure?

a) Referral for bariatric surgery
b) Starting allopurinol treatment

c) Starting treatment with a second antihypertensive agent to lower his BP to <120/80 mm Hg
d) No additional therapy

For the answer to the question, see the following text.

In observational studies, higher BMI has been associated with substantially greater risk of developing hypertension and diabetes and a more modest risk for CKD. Mechanisms for the latter association may be through the development of hypertension/diabetes, or there may independent effects through inflammation and hemodynamic alterations in the glomerulus. Weight loss through lifestyle modification or bariatric surgery may improve kidney outcomes.

A meta-analysis of 4 small studies suggested a benefit of weight loss achieved through nonsurgical interventions on reduction in albuminuria; however, only 2 of the studies were clinical trials, with 40 and 18 participants each. A post hoc analysis of the Look AHEAD trial of people with type 2 diabetes who were overweight or had obesity suggested a 31% reduction in risk of developing very-high-risk CKD (defined as G4, G3bA2-3, or G3aA3) associated with intensive lifestyle intervention, which aimed to reduce caloric consumption and increase physical activity. Interestingly, the effect of the intervention was only partially mediated by weight loss and reductions in HbA1c and systolic BP. A propensity-matched study of 985 patients who underwent bariatric surgery compared with 985 controls with obesity suggested that long-term GFR decline was attenuated in the bariatric surgery group, with a 57% lower risk of doubling of serum creatinine, an eGFR <15 mL/min/1.73 m^2, or KFRT over a median follow-up period of 4 years. Thus, it appears that weight loss may confer benefits for both GFR decline and worsening albuminuria, although clinical trial evidence is lacking.

In Question 13, of the options shown, response (d), or no additional therapy, would be the most appropriate intervention. Bariatric surgery at this BMI or a BP goal of <125/70 mm Hg have not been shown to slow the progression to KFRT. And, as discussed in the previous section, randomized controlled trials have not shown a benefit of uric acid–lowering therapy in preserving kidney function.

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