CMEO
BriefCase

Co-Management Strategies in CKD: The Role of the Pharmacist in Counseling Patients

Supported by an educational grant from Bayer Healthcare Pharmaceuticals Inc.

CME OUTFITTERS

Dhiren K. Patel, PharmD, CDCES, BC-ADM

Adjunct Associate Professor of Pharmacy Practice

Massachusetts College of Pharmacy and Health Sciences

Clinical Pharmacy Specialist

Boston, MA

Robert Busch, MD, FACE

Director of Clinical Research
Community Endocrine Group
Albany Med Faculty Practice
Albany, NY

Learning Objective 1

Describe the pathophysiological features of CKD giving rise to renal, CV, and mortality risks in patients with CKD and T2DM, despite optimized management according to current standards of care (SOC).

Learning Objective 2

Assess new efficacy and safety data for current and emerging therapies for CKD in patients with T2DM.

Patient Case: Endo Referral

Aliyah Washington:

- 43 YO Black female employed at local high school
- Referred from PCP to Endocrinology to optimize DM control
- **Past Medical History**: GDM, HTN
- **Family History**: MI, dialysis (father died at 62)
- **Medications:**
  - Losartan: 25 mg daily
  - Metformin: 1000 mg twice daily
- **Foot exam:**
  - Pulses in feet palpable
  - Pinprick sensation

BP: 132/82 mmHg Pulse: 75 bpm BMI: 32 kg/m^2 Height: 5'1" Weight: 160 lbs.	LDL: 112 mg/dL TG: 115 mg/dL HDL: 60 mg/dL HbA1c: 8.5%	Potassium: 4.2 mmol/L Bun: 24 mg/dL Creatinine: 1.0 mg/dL eGFR: 70 mL/min/1.73 m^2 UACR: 240 mg/g

A1C = Glycated hemoglobin. BMI = Body mass index. BP = Blood pressure. BPM = Beats per minute. BUN = Blood urea nitrogen. DM = Diabetes mellitus. eGFR = Estimated glomerular filtration rate. GDM = Gestational diabetes mellitus. Hb = Hemoglobin. HDL = High-density lipoprotein. HTN = hypertension. LDL = Low-density lipoprotein. MI = Myocardial infarction. mmHG = millimeters of mercury. Mmol/L = Millimoles per liter. PCP = Primary Care Provider. TG = Triglycerides. WNL = Within normal limits. UACR = Urine albumin-to-creatinine ratio. YO = Year old.

Given Ms. Washington's case and the following options on her formulary, what addition to her medication regimen will address both her uncontrolled blood sugar and her decreased eGFR/elevated UACR?

A. Finerenone
B. Saxagliptin
C. Dapagliflozin
D. Pioglitazone
E. I am not sure

CKD Progression Heatmap: Visit 1

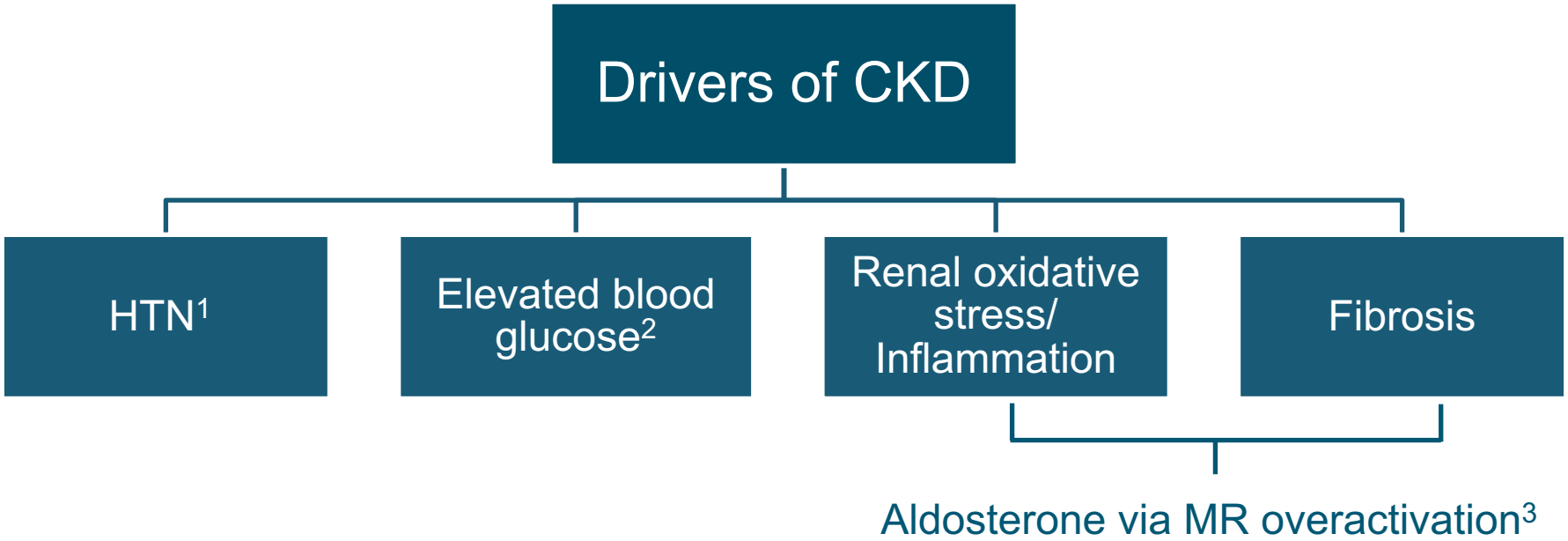
eGFR Categories			UACR Categories: A1 Normal to mildly increased (0-29 mg/g)	A2 Moderately increased (30-300 mg/g)	A3 Severely increased (> 300 mg/g)
Normal or high	G1	≥ 90 mL/min/1.73 m^2			
Mildly decreased	G2	60-89			
Mildly to moderately decreased	G3a	45-59			
Moderately to severely decreased	G3b	30-44			
Severely decreased	G4	15-29			
Kidney failure	G5	< 15			

Increasing risk of CKD progression

Increasing risk of CKD progression

CKD = Chronic Kidney Disease.
Adapted from Ciernik M. *Kidney Int Suppl*. 2013;3:1-150.

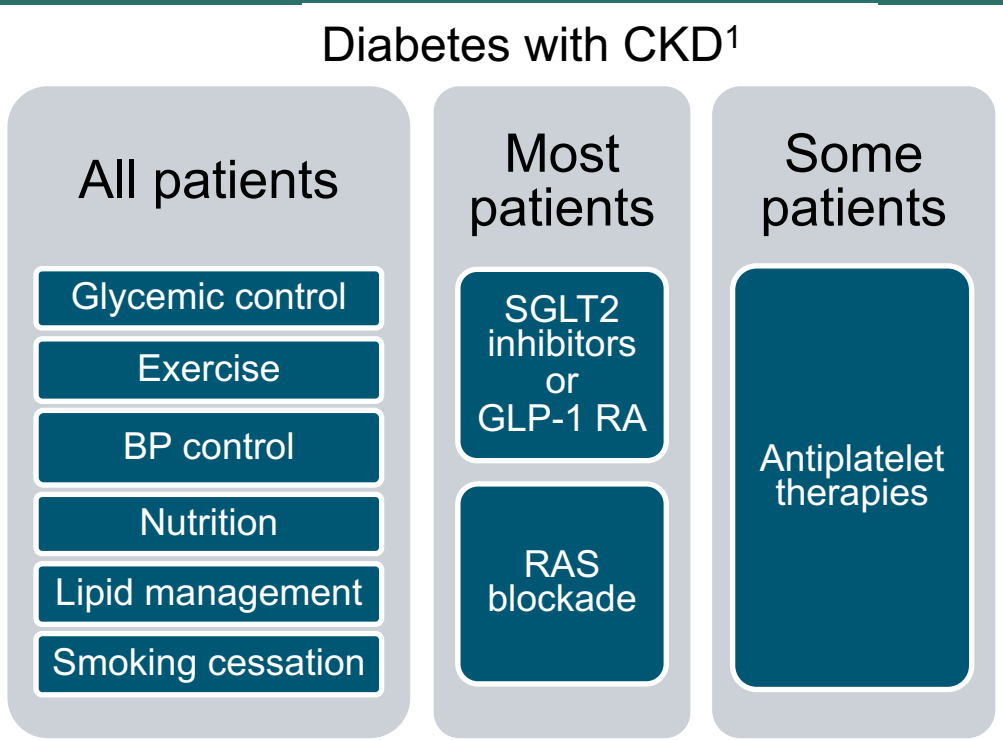
Addressing Control: CKD Drivers



MR =Mineralocorticoid receptor.

1. de Boer IH, et al. *Kidney Int*. 2020;98(4S):S1-S115. 2. American Diabetes Association. *Diabetes Care*. 2021;44(Suppl 1):S111-S124.
3. Buonafine M, et al. *Am J Hypertens*. 2018;31(11):1165-1174.

Standard of Care



Strategy to reduce risks of kidney disease and CV disease:

- ADA Guideline Recommendations[2]
- Standard of Care Timeline in CKD:
  - 2001 – RAS Blockade (ACEi or ARB)
  - 2008 – concomitant SGLT2 in patients with CKD and T2DM
  - 2021 – addition of MRA to SOC?

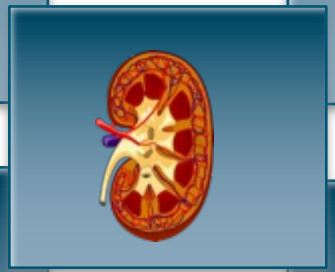
ACEi = Angiotensin-converting enzyme inhibitor. ADA = American Diabetes Association. ARB = Angiotensin receptor blocker. CV = Cardiovascular. GLP-1 RA = Glucagon-like peptide-1 receptor agonist. MRA =Mineralocorticoid receptor antagonist. RAS = Renin-angiotensin system. SGLT2 = Sodium-glucose transport protein 2. T2DM = Type 2 Diabetes Mellitus.

1. de Boer IH, et al. *Kidney Int*. 2020;98(4S):S1-S15. 2. American Diabetes Association. *Diabetes Care*. 2021;44(Suppl 1):S111-S124.

Renal Protective Mechanisms

SGLT2 Inhibitor[1]
Reduce sodium resorption, progressive recovery, and stabilization of renal function

RAS Inhibitor[3]
Modulate renal blood flow and tubular function



GLP-1 RA[2]
Reduce emergence/progression of proteinuria

MR Antagonist[4]
Prevents MR overactivation; decrease inflammation and kidney fibrosis

1. Fioretto P, et al. *Diabetes Care*. 2016;39 Suppl 2:S165-S171. 2. Greco EV, et al. *Medicina (Kaunas)*. 2019;55(6):233. 3. Weir MR. *Postgrad Med*. 2009;121(1):96-103. 4. Agarwal R, et al.. *Eur Heart J*. 2021;42(2):152-161. Kidney image: Wikimedia Commons. 2021. https://commons.wikimedia.org/w/index.php?title=Special:CiteThisPage&page=File%3AKidneyStructures.svg&id=465533896&wpFormIdentifier=titleform. Accessed September 29, 2021.

Statin Evidence in T2DM

- Primary prevention of CVD with atorvastatin in T2DM in the Collaborative Atorvastatin Diabetes Study (CARDS)
  - Atorvastatin 10 mg daily reduced CV events in T2DM patients without presence of high LDL[1]
    - ↓ acute coronary heart disease events by 36%
    - ↓ coronary revascularizations by 31%
    - ↓ rate of stroke by 48%
    - ↓ the death rate by 27%
- CARDS analysis of atorvastatin affects on diabetic kidney disease shows modest benefit on eGFR[2]
  - Reduced annual change in eGFR by 0.18 mL/min per 1.73m^2 per year

Colhoun HM, et al., *Lancet*. 2004;364(9435):685-696.

RAS Blocker Evidence in T2DM + CKD

- RENAAL Study
  - Effects of losartan on renal and CV outcomes in patients with T2DM and nephropathy
    - 16% (p = .02) reduction in the primary endpoint
      - Composite of a doubling of the base-line SCr concentration, ESRD, or death
    - Reduced the incidence of doubling SCr by 25% and ESRD by 28%
      - p = .006 and p = .002 respectively
    - Proteinuria declined by 35% with losartan
      - p < .001 for the comparison with placebo

ESRD = End-stage renal disease. SCr = Serum creatinine.
Brenner BM, et al. *N Engl J Med*. 2001;345:861-869.

Residual Risk Despite RAS Blockade

- Despite SOC guidelines of RAS blockade (since 2001) and concomitant SGLT2i in patients with CKD + T2DM (since 2008), kidney diseases are a leading cause of death in the U.S.[1]
- Patients most likely to be treated with RAS blockade still develop and continue to show decline in kidney function
  - Estimated that about 1 in 3 adults with diabetes and 1 in 5 adults with hypertension have CKD[1]
- A decrease in eGFR decline is not enough
- Multi-modal approach to CKD is necessary to slow progression

1. Centers for Disease Control and Prevention [CDC]. *Chronic kidney disease basics.* 2021. www.cdc.gov/kidneydisease/basics.html. Reviewed August 19, 2021. Accessed September 29, 2021.

SGLT2i or GLP-1 RA in T2DM + CKD

Guideline Recommended Use in the Presence of:

- High ASCVD risk
- Established ASCVD
- Established CKD
- or HF guides selection of glucose-lowering agent
- Independency of baseline
- or individualized A1C level
- or metformin use

If ASCVD predominates[1,2]

- GLP-1 RA with proven CVD benefit
- SGLT2i with proven CVD benefit, if eGFR is adequate

If HF or CKD predominates[1,2]

- SGLT2i with evidence of reducing HF and/or CKD progression, if eGFR is adequate
- GLP-1 RA with proven CVD benefit if SGLT2 inhibitor is contraindicated, not tolerated, or eGFR not adequate

ASCVD = Atherosclerotic cardiovascular disease. HF = Heart failure.

1. American Diabetes Association. *Diabetes Care*. 2021;44(suppl 1):S1-S232. 2. Garber AJ, et al. *Endocr Pract*. 2020;26:107-139. Kidney image: Wikimedia Commons. 2021. https://commons.wikimedia.org/w/index.php?title=Special:CiteThisPage&page=File%3AKidneyStructures.svg&id=465533896&wpFormIdentifier=titleform. Accessed September 29, 2021. Heart image: Wikimedia Commons. 2021. https://commons.wikimedia.org/wiki/File:Human_Heart.png. Accessed September 29, 2021.

SGLT2i Evidence in CKD

CREDENCE: canagliflozin in T2DM + CKD

- Reduced primary endpoint of ESKD, doubling of SCr, and renal or CV death by 30%.[1]
- Reduced secondary (renal specific) endpoint of ESKD, doubling of SCr, or renal death by 34%.[1]
- Effect on eGFR and UACR benefit in all stages of CKD (eGFR 30 to < 90 and UACR < or > 1000).[1]

DAPA-CKD: dapagliflozin in CKD ± T2DM

- Reduced primary composite endpoint of ≥ 50% eGFR decline, ESKD, and renal or CV death by 39%.[2]
- Reduced secondary (renal specific) endpoint of sustained ≥ 50% eGFR decline, ESKD, or renal death by 44%.[2]
- Subgroup analysis of patients with CKD + T2DM
  - Reduced UACR by 35.1%.[3]
  - Reduced eGFR decline of total eGFR slope by 1.18 mL/min per 1.73m^2 per year.[4]

1. Perkovic V, et al. *N Engl J Med*. 2019;380(24):2295-2306. 2. Heerspink HJL, et al. *N Engl J Med*. 2020;383:1436-1446. 3. Jongs N, et al. *Lancet Diabetes Endocrinol*. 2021. In press. 4. Heerspink HJL, et al. *Lancet Diabetes Endocrinol*. 2021. In press.

GLP-1 RA Evidence in CKD

Secondary endpoints from multiple trials suggest kidney protection

- ELIXA, EXSCEL, LEADER, and REWIND show benefit due to effects on reducing albuminuria[1,2]
- EXSCEL and LEADER show benefit on composite renal outcomes[1,2]

FLOW: Semaglutide in T2DM & CKD[3]

- Ongoing prospective study specifically evaluating a GLP-1 RA in patients with T2DM + CKD
- Aim to evaluate renal outcomes to confirm previously suggested benefit
- Primary endpoint: Composite of eGFR decline of ≥ 50%, ESRD, renal or CV death

1. Mosterd CM, et al. *J Nephrol*. 2020;33:965-975. 2. Yin WL, et al. *Diabetes Ther*. 2020;11:835-844 3. Williams DM, et al. *Diabetes Ther*. 2020;11(10):2221-2235.

Telehealth Visit 2

Patient Case Telehealth Call:

Aliyah Washington:

- Follow-up visit with pharmacist after medication changes
- **Medications:**
  - Losartan: 50 mg daily (dose increased from 25 mg)
  - Metformin: 1000 mg twice daily
  - Atorvastatin: 10 mg daily (new medication)
  - Dapagliflozin: 5 mg daily (new medication)
- **Notable changes since previous labs:**
  - Microalbuminuria elevated: 320 mg/g

After hearing the follow up call, now what would you recommend for Ms. Washington's medication regimen?

A. Addition of meloxicam
B. Addition of finerenone
C. Encourage adherence to therapy as prescribed
D. Change the SGLT-2 inhibitor to a GLP-1
E. I am not sure

CKD Progression Heatmap

eGFR Categories			UACR Categories: A1 Normal to mildly increased (0-29 mg/g)	A2 Moderately increased (30-300 mg/g)	A3 Severely increased (> 300 mg/g)
Normal or high	G1	≥ 90 mL/min/1.73 m^2			
Mildly decreased	G2	60-89			
Mildly to moderately decreased	G3a	45-59			
Moderately to severely decreased	G3b	30-44			
Severely decreased	G4	15-29			
Kidney failure	G5	< 15			

Increasing risk of CKD progression

Adapted from Ciernik M. *Kidney Int Suppl*. 2013;3:1-150.

FIDELITY: Pooled Analysis of FIDELIO-DKD and FIGARO-DKD

FIDELITY evaluated relationship between stage of kidney disease and efficacy of finerenone on composite CV and renal endpoints in 13,026 patients followed for 3 years[1]

FIDELIO-DKD found finerenone slowed kidney disease progression and improved CV outcomes in patients with predominantly advanced kidney disease and T2DM[2]

FIGARO-DKD found finerenone reduced risk of CV events in patients with mild-to-moderate kidney disease and T2DM[3]

1. European Society of Cardiology Website. 2021. https://www.escardio.org/The-ESC/Press-Office/Press-releases/Finerenone-benefits-patients-with-diabetes-across-spectrum-of-kidney-disease. Accessed September 29, 2021. 2. Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229. 3. Pitt B, et al. *N Engl J Med*. August 28, 2021 [Epub ahead of print].

Thinking back to Ms. Washington's initial visit, when she had uncontrolled blood sugar and decreased eGFR/elevated UACR, which option below could be added to her medication regimen to address both issues?

A. Finerenone
B. Saxagliptin
C. Dapagliflozin
D. Pioglitazone
E. I am not sure

After the follow-up telehealth call, which of the following would you recommend for Ms. Washington's medication regimen?

A. Addition of meloxicam
B. Addition of finerenone
C. Encourage adherence to therapy as prescribed
D. Change the SGLT-2 inhibitor to a GLP-1 RA
E. I am not sure

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Recognize that the pathophysiology of CKD, as well as its relationship with increasing renal and CV risk, is complex and requires early management to improve outcomes.
- In patients with T2DM + CKD, remember to treat MR overactivation, which leads to kidney damage via fibrosis and inflammation in addition to treating the drivers HTN and ↑ HbA1C.
- Because RAS blockade is not enough to slow the progression of CKD, consider a multimodal approach including ACEi or ARB, SGLT-2i, GLP-1 RA, and finerenone, in addition to lifestyle modifications.

CMEO BriefCase 1

Identifying Patients at Risk of CKD in Pharmacy Settings

CMEO BriefCase 2

Co-Management Strategies in CKD: The Role of the pharmacist in Counseling Patients

www.CMEOutfitters.com/virtual-education-hub

Virtual Education Hub

A robust hub of patient education and resources for your patients

https://www.cmeoutfitters.com/virtual-education-hub/

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.