Updates in the Management of CKD in Primary Care

Please take a moment to answer 3 quick questions using the QR code above or the URL below:

https://www.pcmg-us.org/survey/pre/updatesckd10

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Updates in the Management of Chronic Kidney Disease in Primary Care

Sponsorship and Support

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Stephen Brunton, MD, FAAFP, CDCES, has disclosed that he is on the advisory board and/or speakers bureau for Abbott Diabetes, AstraZeneca, Bayer, Biolinq, Boehringer Ingelheim, Lifescan, Lilly, Novo Nordisk, Sanofi, and holds stock options for Paracrine.

Joshua J. Neumiller, PharmD, Medical Writer, has disclosed that he is on the advisory board and/or speakers bureau for Sanofi, Bayer, Dexcom, Boehringer Ingelheim, and Eli Lilly. **Michael Hanak, MD,** CME Reviewer, and **Kim Zuber, PA-C,** have no disclosures to report.

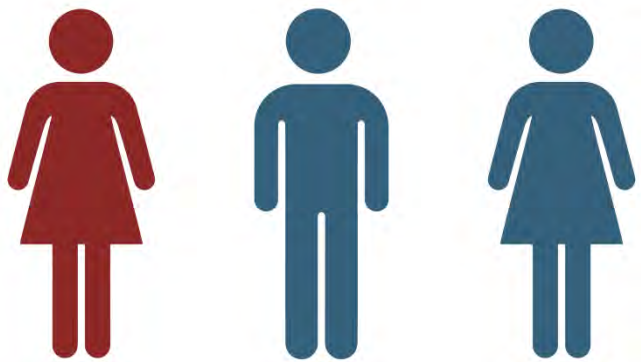
All relevant financial relationships have been mitigated.

Learning Objectives

At the end of the presentation, participants should be able to…
Detect and recognize CKD in patients with reduced kidney function, including in early stages of disease.
Implement screening for albuminuria in patients with diabetes in clinical practice to identify CKD as early as possible.
Initiate evidence-based therapies, including newer agents, for patients with CKD when indicated.
Discuss evidence for SGLT-2 inhibitors in patients with CKD, with or without diabetes.

Chronic Kidney Disease (CKD) and Diabetes in the United States

- More than 1 in 7 adults in the United States (U.S.) are estimated to have CKD, equating to ~37 million people
  - Approximately 1 in 3 adults with diabetes may have CKD
  - Approximately 1 in 5 adults with hypertension may have CKD
- Often asymptomatic, with ~90% of people with CKD unaware they have it



Centers for Disease Control and Prevention. Chronic kidney disease initiative. Available at: https://www.cdc.gov/kidneydisease/index.html.

Definition and Staging of CKD

- Risk of CKD progression, frequency of visits, and referral to nephrologist according to GFR and albuminuria shown.
- Risk of progression indicated by color grading.
- Numbers in boxes are a guide to how many times per year the patient should be seen.
- “Treat” suggests intervention is indicated and “Refer” suggests that nephrology referral is recommended.

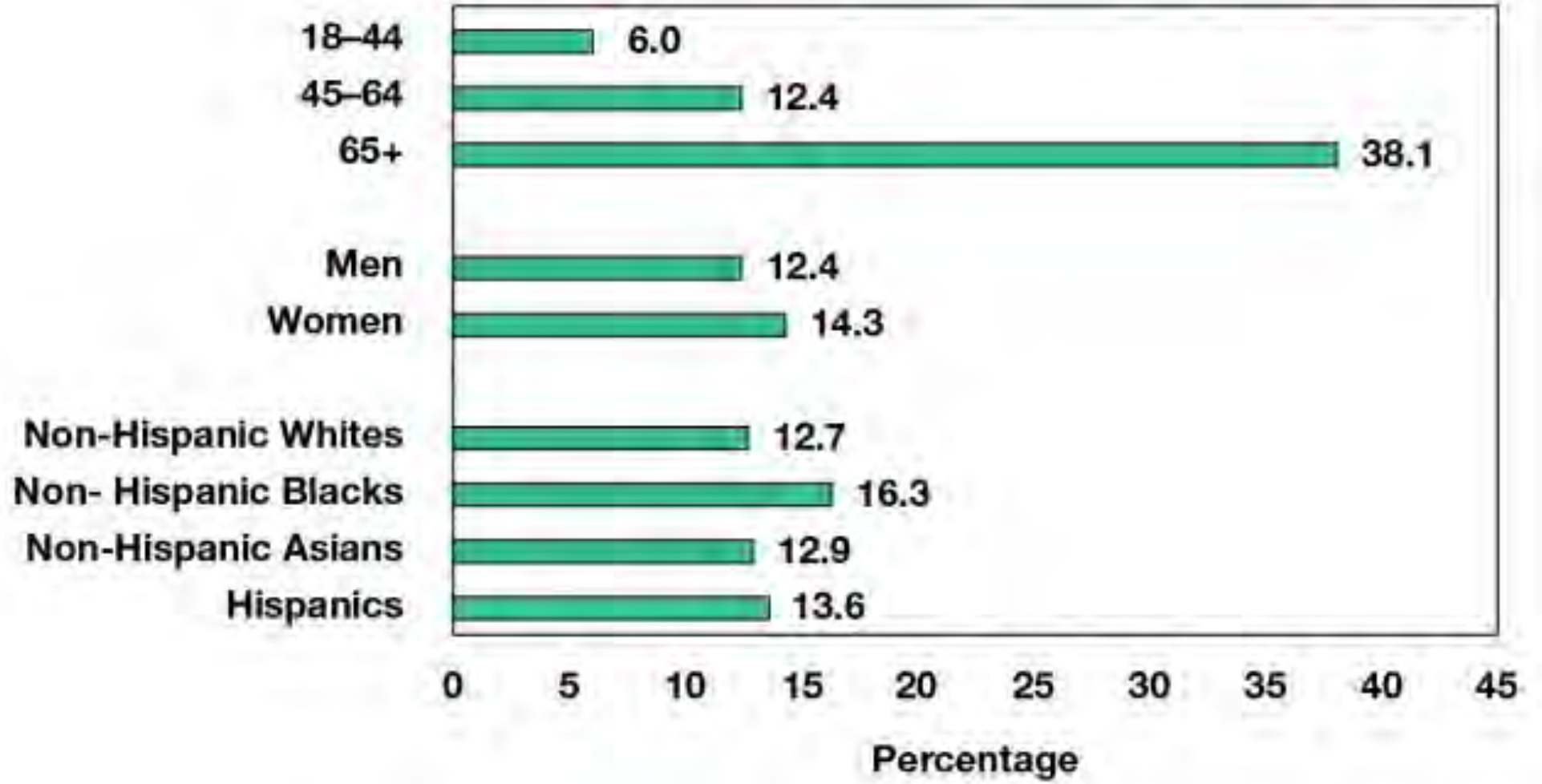
CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

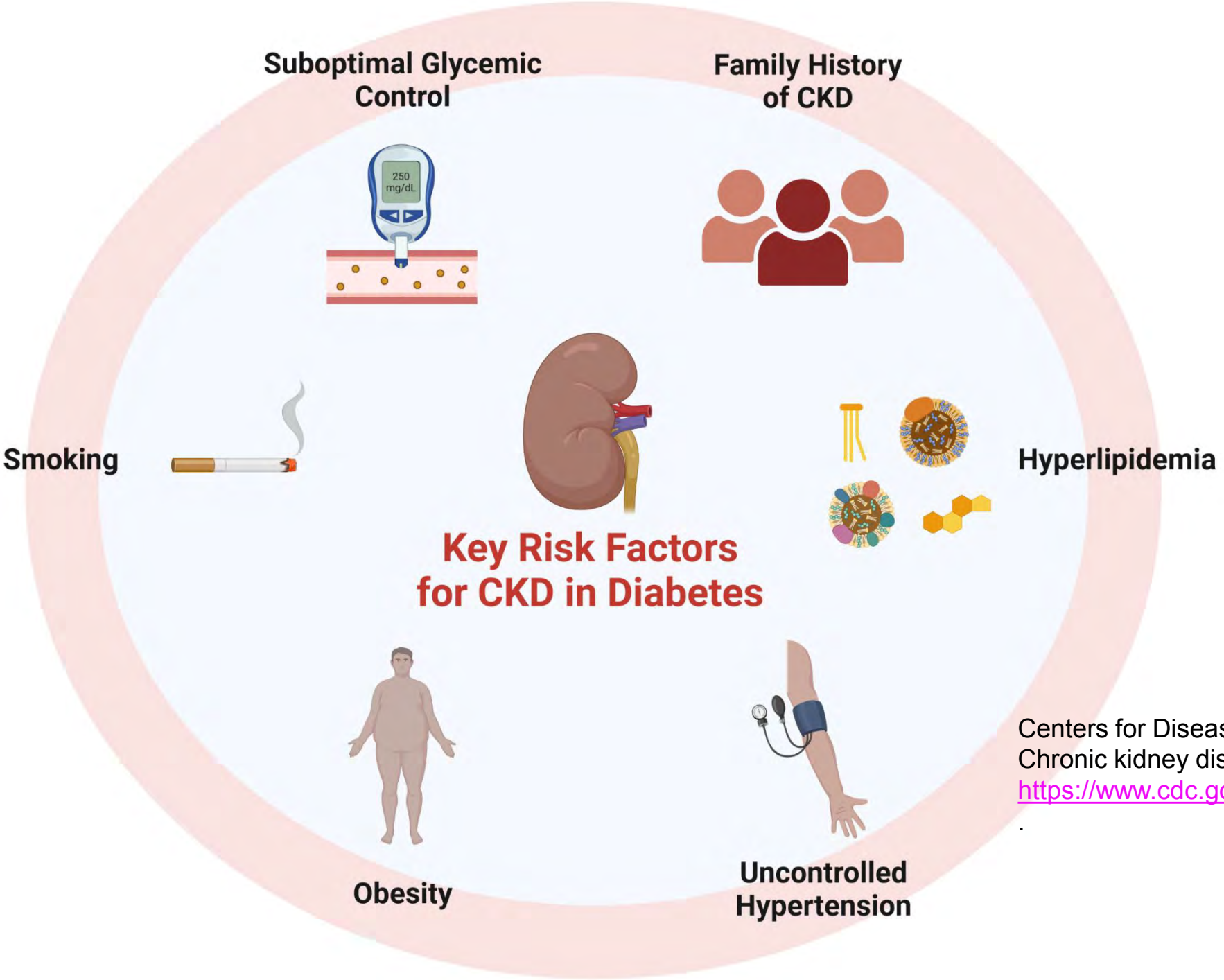
Introduction of the New eGFR Calculator

- February 28, 2022: All LabCorp moves to new calculator
  - Approx 51 million tests
- April 1, 2022: All VA labs move to new calculator
  - Largest integrated health system in the US
- July 11, 2022: All Quest labs move to new calculator
  - Approx 60 million tests
- July 2022: All transplant will be listed using the new calculator
- August 2022: All large universities changed (Mayo, Stanford, Univ of AL, Harvard, Yale, etc.)
- Fall 2022: EPIC moves to new calculator
- **By the end of 2022, 80% of all labs were using the new race neutral calculator**

CKD by Age, Sex, and Race/Ethnicity



Centers for Disease Control and Prevention. Chronic kidney disease initiative. Available at: https://www.cdc.gov/kidneydisease/index.html.



Centers for Disease Control and Prevention. Chronic kidney disease initiative. Available at: https://www.cdc.gov/kidneydisease/index.html
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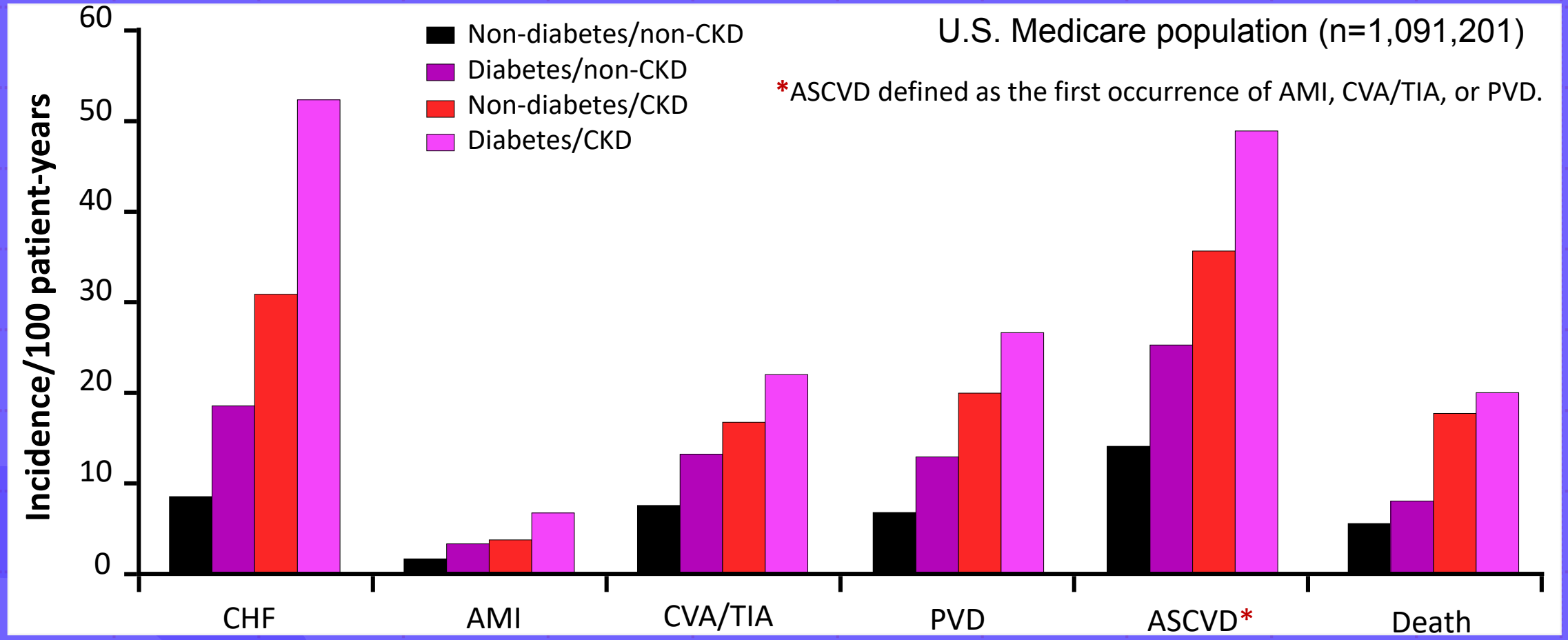
CV Event Risk in Diabetes is Amplified by CKD



Foley RN, et al. *J Am Soc Nephrol.* 2005;16:489-495.

CKD Promotes the Pathogenesis of Cardiovascular (CV) Disease in Diabetes

Patients with CKD and T2D have a very high risk of CV comorbidities[1-3]

- Endothelial dysfunction
- Inflammation and oxidative stress
- Hyper-coagulability
- Dyslipidemia
- Hypertension
- Myocardial infarction
- Stroke
- Heart failure
- Peripheral vascular disease

The risk of CV events in T2D increases as kidney function declines[1]

1. Sasso et al. *Nephrol Dial Transplant*. 2012;27:2269-2274; 2. Palsson, Patel. *Adv Chronic Kidney Dis*. 2014;21(3): 273-280.
3. Tuttle et al. *Diabetes Care*. 2014;37:2864-2883.

Role of the PCP

- Facilitate early screening and diagnosis
- Implement interventions early when indicated to prevent cardiovascular morbidity/mortality and slow CKD progression
  - Lifestyle interventions
  - Optimized risk factor management
  - Initiation of agents with evidence of cardiovascular and kidney benefit
    - ACE/ARB
    - SGLT2 inhibitors
    - Nonsteroidal mineralocorticoid receptor antagonists (ns-MRAs)
    - GLP-1 receptor agonists
- Refer to nephrology when appropriate

Shubrook JH, et al. *Postgrad Med.* 2022;134(4):376-387.

Key Barriers to Optimal Management of CKD in Primary Care

- Clinical inertia
- Lack of practitioner awareness & knowledge of CKD
  - Suboptimal CKD screening and diagnosis
  - Suboptimal early initiation of evidence-based therapies
- Lack of practitioner time and resources
- Challenges associated with managing complex patients
- Barriers to specialist referral and collaboration
  - Lack of clear parameters for specialist referral and/or difficult referral processes

Shubrook JH, et al. *Postgrad Med.* 2022;134(4):376-387.

Screening in DM

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes; T2D, type 2 diabetes.

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

What to do with a positive result?

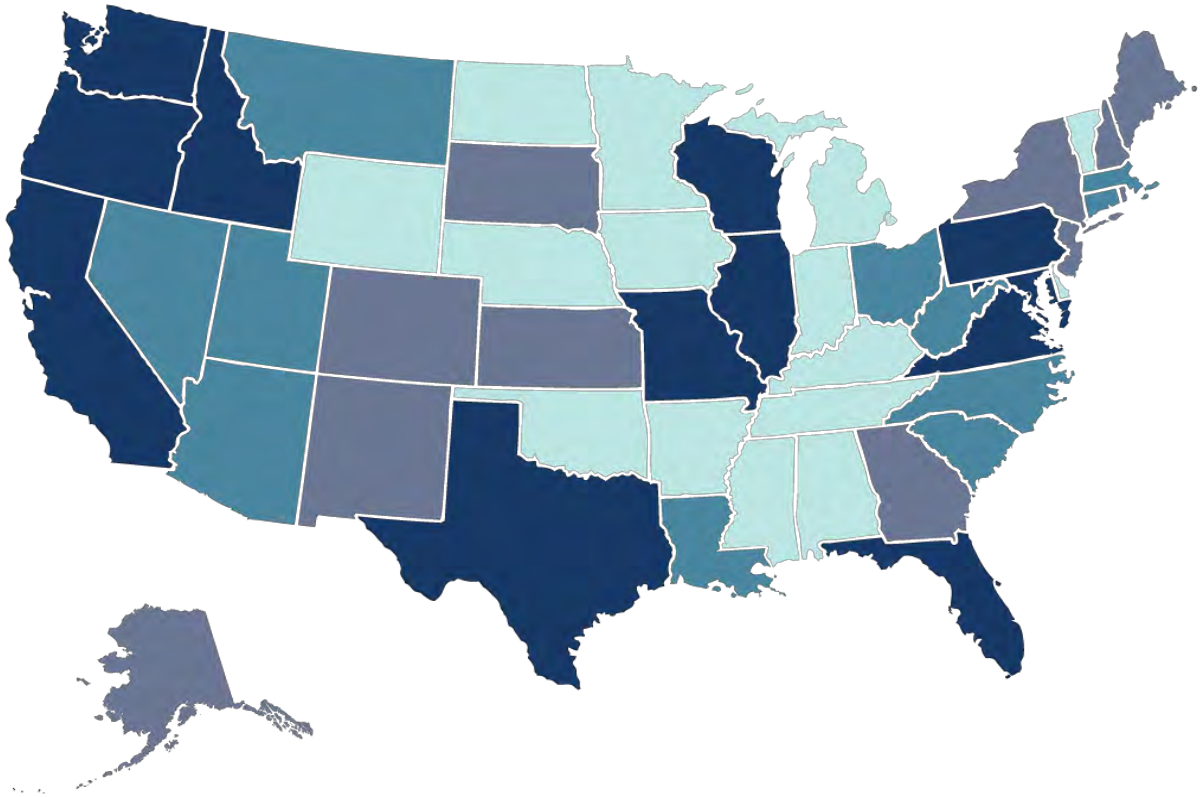
Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

LabCorp: Testing Rates of Patients at Risk for CKD Across U.S. (2013-2018)



Testing Percentage

- 5-9%
- 10-13%
- 14-15%
- 16-30%

Alfego D, et al. *Diabetes Care*. 2021;44(9):2025-2032.

Graphic provided by Kim Zuber, PA-C.

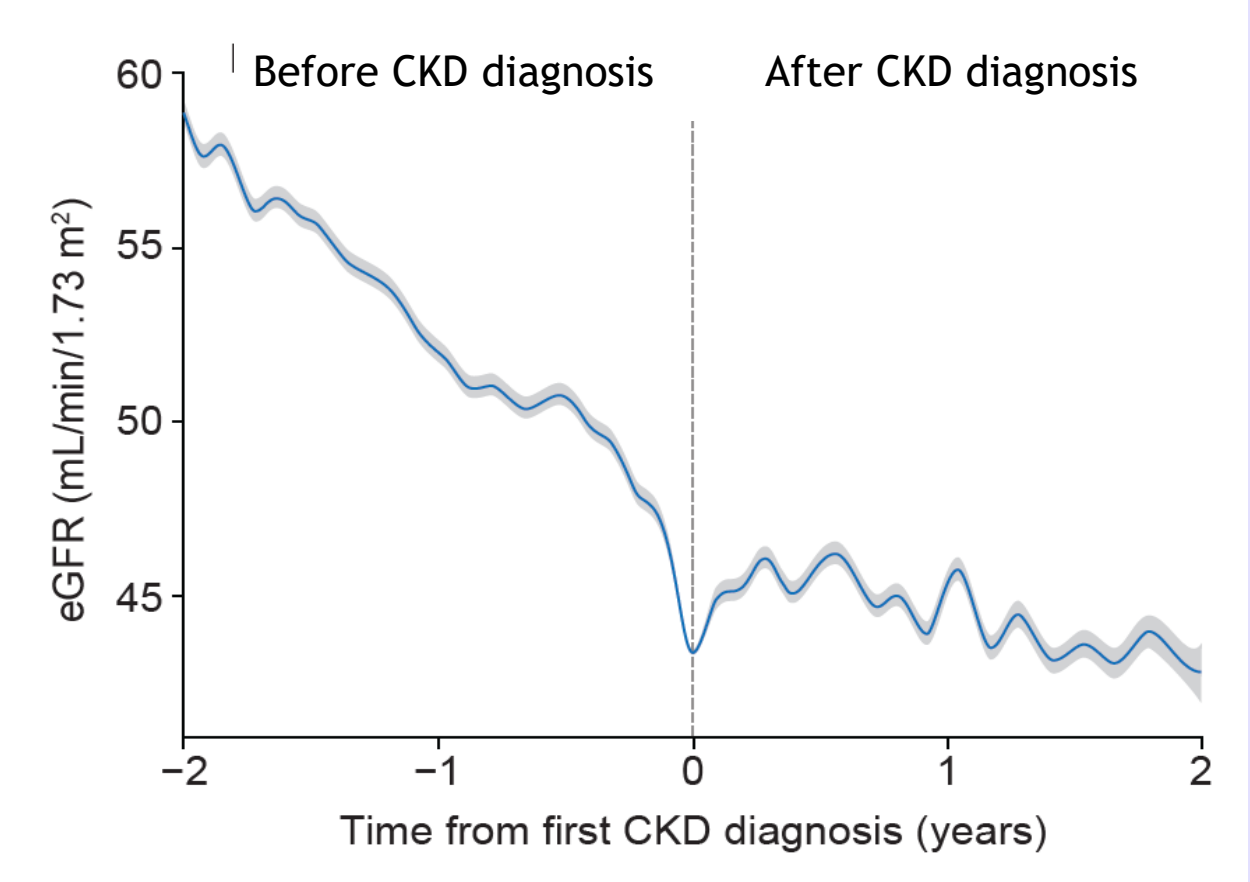
>80% of high-risk patients were not tested during the 6-year study.

REVEAL Trial: eGFR Decline Before & After a CKD Diagnosis

Median annual decline in eGFR (mL/min/1.73 m²) significantly decreased following a CKD diagnosis [a]

Before	**–3.20** 95% CI: –3.38, –3.00
After	**–0.74** 95% CI: –0.96, –0.53

eGFR trajectories before and after a CKD diagnosis



Shaded area represents 95% CIs

Tangri, N, et al. Patient Management and Clinical Outcomes Associated with a Recorded Diagnosis of Stage 3 CKD: The REVEAL-CKD Study. Adv Ther (2023)

Considerations for Nephrology Referral: ADA

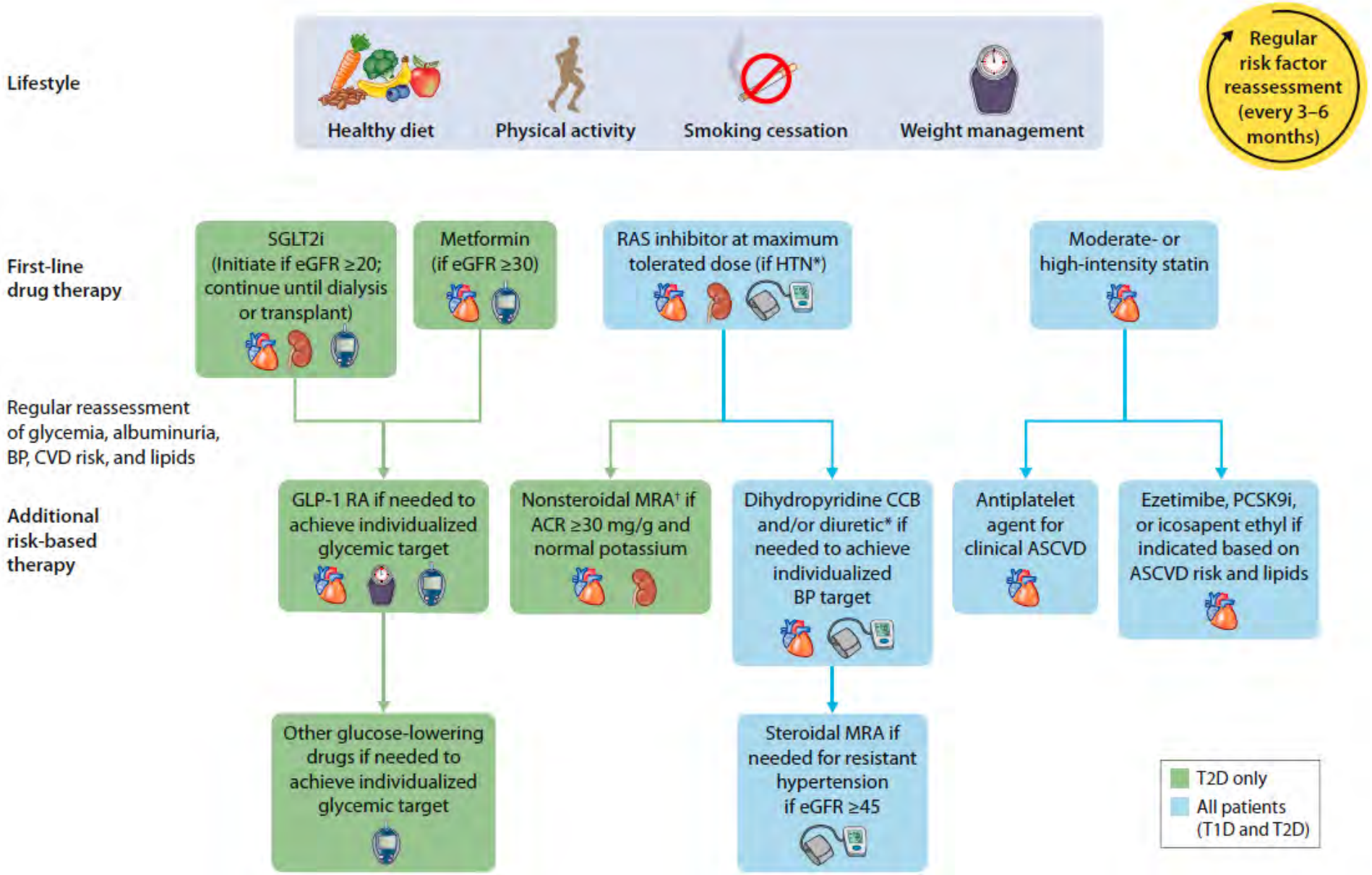
Uncertain etiology of kidney disease	Difficult management issues†
eGFR < 30 mL/min/1.73 m^2	Rapidly progressing kidney disease

*Referral threshold may vary.

†Anemia, secondary hyperparathyroidism, significant increase in albuminuria despite good BP management, metabolic bone disease, resistant hypertension, electrolyte disturbances.

American Diabetes Association Professional Practice Committee. *Diabetes Care*. 2024;47(Suppl. 1):S219-S230.

Approach to Improving Outcomes in Diabetes and CKD



Pathophysiology of CKD in Diabetes

- A variety of factors contribute to the development of CKD in diabetes:
  - Metabolic
    - Hyperglycemia
    - Elevated blood pressure
  - Inflammatory & Fibrotic factors
    - Pro-inflammatory state in kidney with fibrosis
  - Hemodynamic
    - Glomerular hyperfiltration
  - Overstimulation of the mineralocorticoid receptor (MR)
    - Promotion of inflammation and fibrosis in kidney

Alicic RZ, et al. *Clin J Am Soc Nephrol*. 2017;12(12):2032-2045.

Potential Consequences of CKD in T2D

- Kidney diseases are a leading cause of mortality in the United States
- CKD can progress to kidney failure, requiring dialysis or kidney transplantation
- CKD markedly increases cardiovascular risk
- CKD is associated with multiple additional complications:
  - Hypertension
  - Volume overload
  - Electrolyte abnormalities
  - Metabolic acidosis
  - Anemia
  - Metabolic bone disease

Centers for Disease Control and Prevention. Chronic kidney disease initiative. Available at: https://www.cdc.gov/kidneydisease/index.html.
ElSayed NA, et al. *Diabetes Care*. 2023;46(Suppl. 1):S191-S202.

Overall Management Goals for Patients with T2D and CKD

- **ADA/KDIGO Consensus Statement:**
  - All patients with type 1 or type 2 diabetes and CKD should be treated with a comprehensive plan, outlined and agreed upon by healthcare professionals and the patient together, to optimize nutrition, exercise, smoking cessation, and weight, upon which are layered evidence-based pharmacologic therapies aimed at preserving organ function and other therapies selected to attain intermediate targets for glycemia, blood pressure, and lipids.

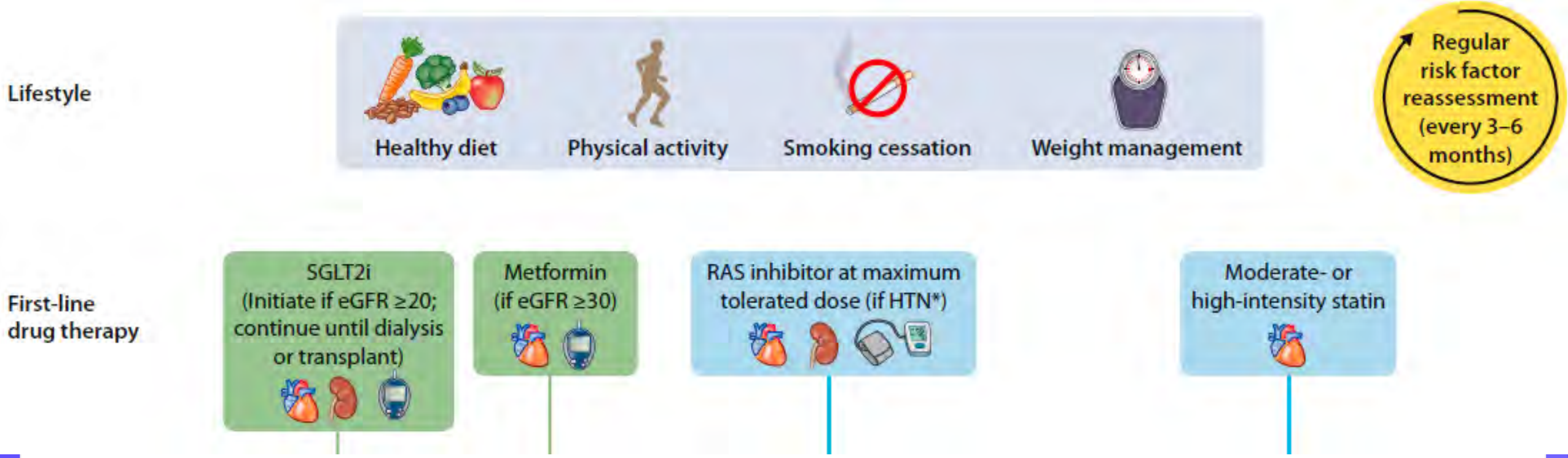
de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090.

Other Management Goals for Patients with CKD

- **KDIGO[1]**
- KDIGO recommends a systolic blood pressure of < 120 mm Hg to slow progression in CKD.
- **DKD: ADA Standards of Care 2024[2]**
  - Optimize glucose control to reduce the risk or slow the progression of CKD.
  - Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD.

1. Kidney International (2024) 105 (Suppl 4S), S117–S314.
2. American Diabetes Association Professional Practice Committee. *Diabetes Care*. 2024;47(Suppl. 1):S219-S230.

Approach for Improving Outcomes in Diabetes and CKD



ADA/KDIGO: First Line Glucose-Lowering Therapies in T2D and CKD

- A SGLT2 inhibitor with proven kidney or CV benefit is recommended for patients with T2D, CKD, and eGFR ≥20 mL/min/1.73m^2. Once initiated, the SGLT2 inhibitor can be continued at lower levels of eGFR.
  - SGLT2 inhibitor therapy recommended to be continued until initiation of dialysis or transplant.
- Metformin is recommended for patients with T2D, CKD, and eGFR ≥30 mL/min/1.73m^2; the dose should be reduced to 1,000 mg daily in patients with eGFR 30-44 mL/min/1.73m^2 and in some patients with eGFR 45-59 mL/min/1.73m^2 who are at high risk of lactic acidosis.

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090.

What's Your Answer?

Which of the following is **TRUE** regarding current ADA/KDIGO recommendations for SGLT2 inhibitor use in CKD?

A. Recommended only in people with eGFR ≥45 mL/min/1.73m^2

B. Recommended for continuation until initiation of dialysis or transplant

C. Recommended only in patients with elevated A1C

D. Evidence of benefit is based on observational data only

SGLT2 Inhibitors: History and Evolution

- Originally investigated and approved as glucose-lowering agents
- Cardiovascular outcome trials (CVOTs) subsequently showed:
  - Benefit on major adverse cardiovascular events (MACE)
  - Consistent signals of benefit on key secondary outcomes:
    - Kidney disease outcomes
    - Heart failure (HF) outcomes
  - Subsequent study in dedicated kidney and HF outcome trials have led to expanded kidney and heart indications for agents in the class

Neumiller JJ, et al. *touchREV Endocrinol*. 2022;18(2):106-115.

Summary of Key SGLT2 Inhibitor Kidney Outcome Trials

Trial	CREDENCE (n = 4,401)	DAPA-CKD (n = 4,304)	EMPA-KIDNEY (n = 6,609)
Treatment	Canagliflozin vs. Placebo	Dapagliflozin vs. Placebo	Empagliflozin vs. Placebo
Key Inclusion Criteria	• T2D • A1C 6.5 to 12.0% • eGFR 30 to <90 mL/min/1.73m^2 • UACR >300 to 5000 mg/g • Treated with RAS inhibitor	• eGFR 25 to 75 mL/min/1.73m^2 • UACR of 200 to 5000 mg/g • Treated with RAS inhibitor	• eGFR 20 to <45 mL/min/1.73m^2 OR eGFR ≤45 to <90 mL/min/1.73m^2 with UACR ≥200 mg/g • Treated with RAS inhibitor
Baseline Diagnosis of T2D (%)	100	67	46
Median Follow-Up (Years)	2.6	2.4	2.0
Primary Outcome			
Primary Outcome; HR (95% CI)	ESKD, doubling of SCr, or renal or CV death **0.70** **(0.59-0.82)**	≥50% decline in eGFR, ESKD, or renal or CV death **0.61** **(0.51-0.72)**	≥40% decline in eGFR, sustained decrease in eGFR to <10 mL/min/1.73m^2, ESKD, or renal or CV death **0.72** **(0.64-0.82)**

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.; Heerspink HJL, et al. *N Engl J Med*. 2020;383:1436-1446.; Herrington WG, et al. *N Engl J Med*. 2023;388:117-127.

What's Your Answer?

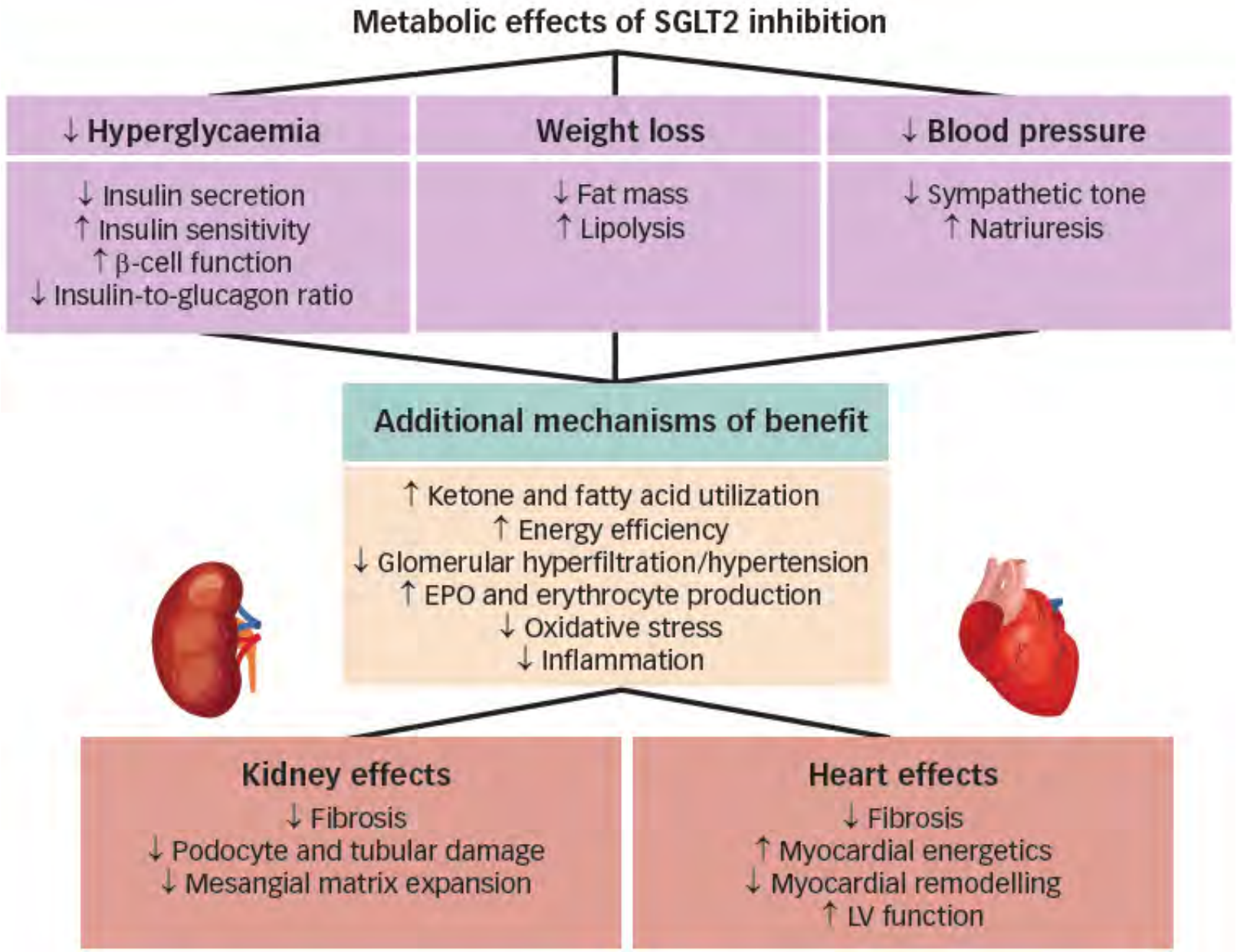
Which SGLT2 inhibitor has been studied in a population with CKD and low levels of albuminuria (e.g., <200 mg/g), without diabetes?

A. Canagliflozin

B. Dapagliflozin

C. Empagliflozin

D. All of the above



Reprinted with permission from: Neumiller JJ, et al. *touchREV Endocrinol*. 2022;18(2):106-115.

SGLT2 Inhibitors: Recommended Dosing by eGFR†

	Stage 3b (eGFR 30-44)	Stage 4 (eGFR 15-29)	Stage 5 (eGFR <15)
Canagliflozin*	Maximum 100 mg daily	• Initiation not recommended • May continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin*	10 mg daily†	• Initiation not recommended with **eGFR <25 mL/min/1.73 m²** • May continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin*	10 mg daily¶	• Initiation not recommended with **eGFR <20 mL/min/1.73 m²** • May continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	**Use not recommended with eGFR <45**		

†Glucose-lowering efficacy is reduced with SGLT2 inhibitors as eGFR declines, but kidney and cardiovascular benefits are preserved.

†Dapagliflozin approved for use at 10mg once daily with an eGFR of 25 to <45 mL/min/1.73 m².

¶Initiation not recommended with eGFR <30 for glycemic control or <20 mL/min/1.73m² for HF.

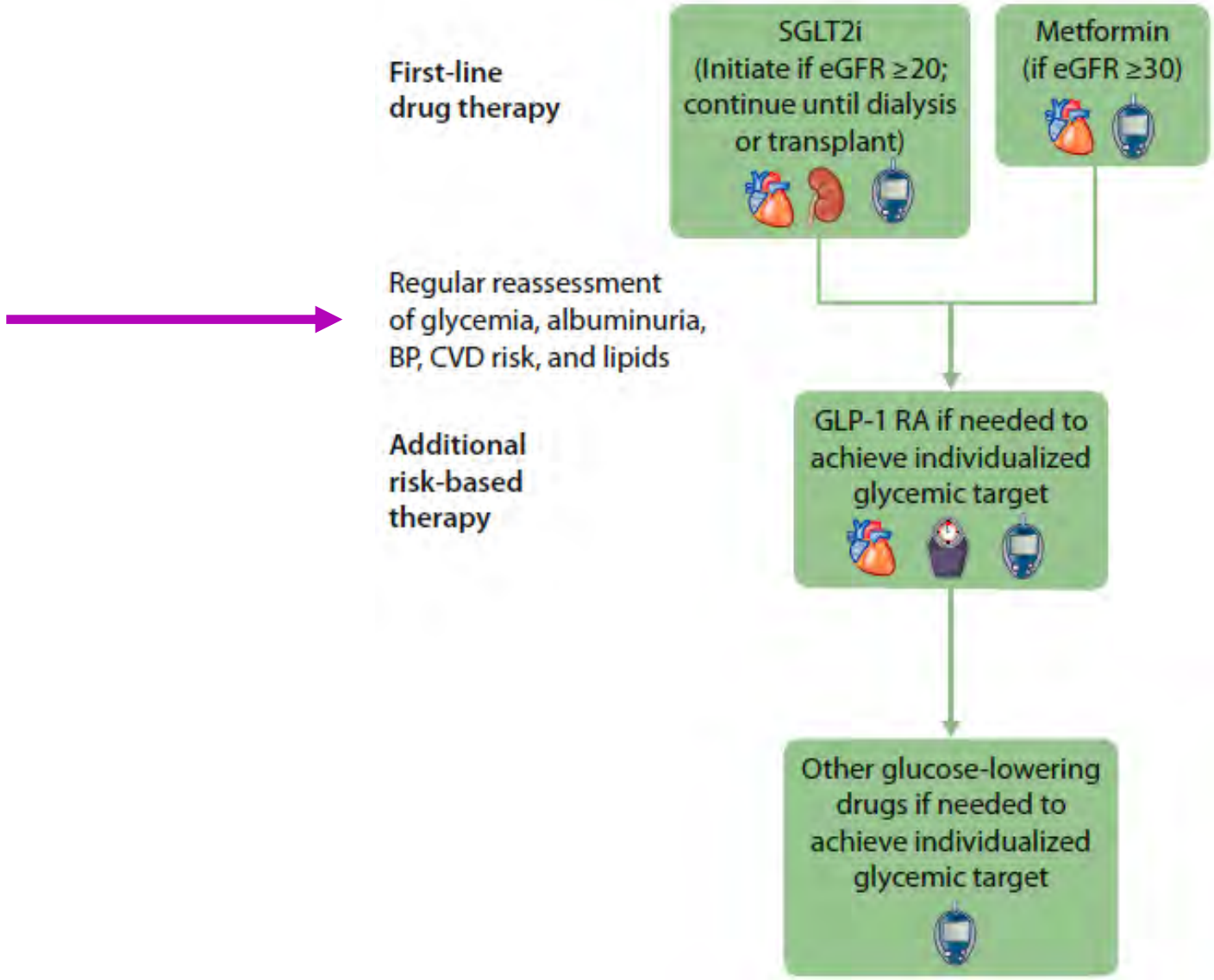
***Agents with primary evidence of kidney benefit**

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT2 sodium-glucose cotransporter-2

ADA/KDIGO: Additional First Line Therapies

- An ACE inhibitor (ACEi) or angiotensin II receptor blocker (ARB) is recommended for patients with type 1 or type 2 diabetes who have hypertension and albuminuria, titrated to the maximum antihypertensive or highest tolerated dose.
- A statin is recommended for all patients with type 1 or type 2 diabetes and CKD, moderate intensity for primary prevention of atherosclerotic cardiovascular disease (ASCVD) or high intensity for patients with known ASCVD and some patients with multiple ASCVD risk factors.

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090.



ADA/KDIGO: Additional Glucose-Lowering Therapies

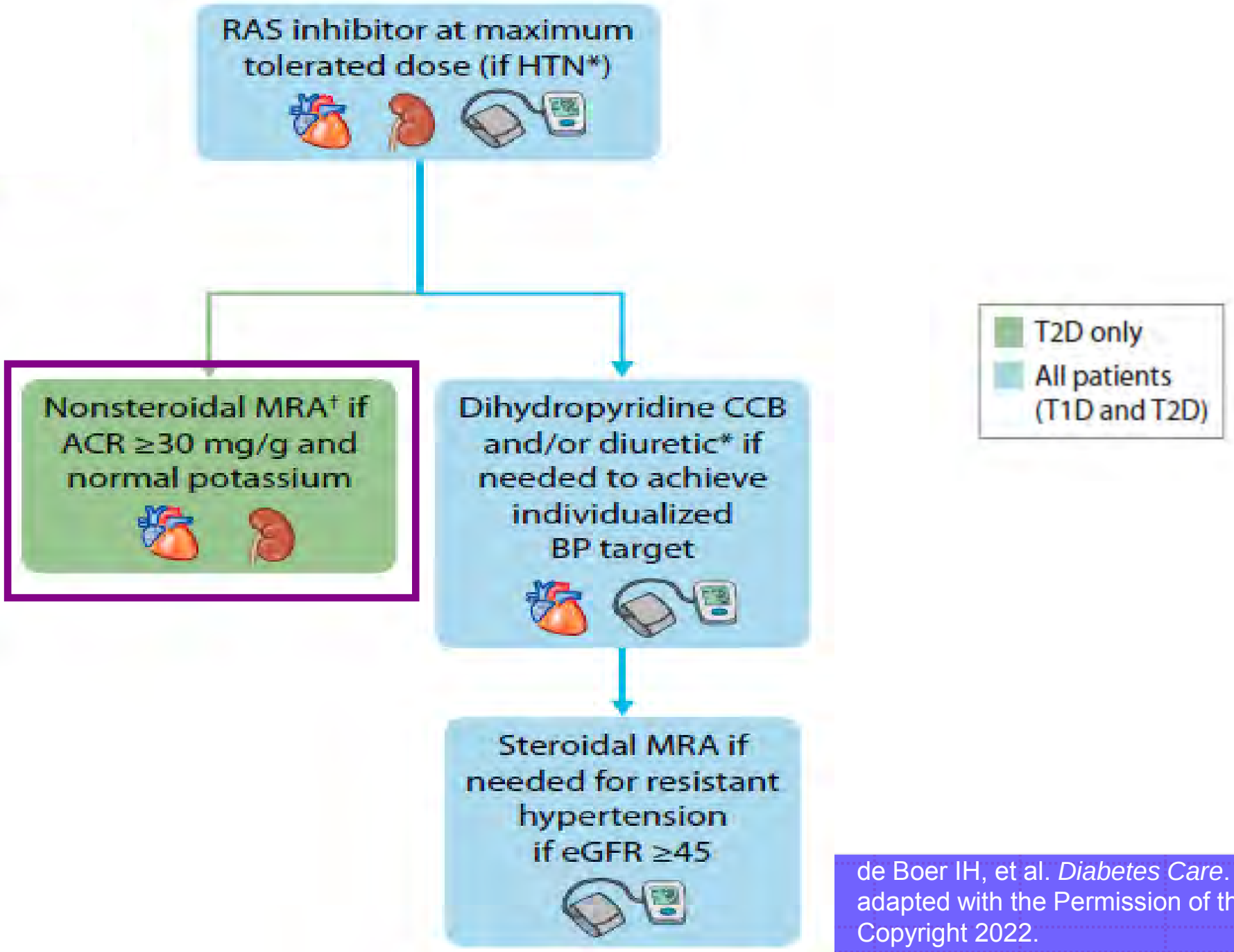
- A glucagon-like peptide 1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended for patients with T2DM and CKD who do not meet their individualized glycemic target with metformin and/or an SGLT2 inhibitor or who are unable to use these drugs.

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090.

GLP-1 Receptor Agonists: Dosing in CKD

	Stage 3b (eGFR 30-44)	Stage 4 (eGFR 15-29)	Stage 5 (eGFR <15)
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide*	No dose adjustment required		
Liraglutide*	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide*†	No dose adjustment required		
Tirzepatide	No dose adjustment required		

*GLP-1 RAs with expanded indications for CVD; †Injectable semaglutide carries a CVD indication



ADA/KDIGO: Nonsteroidal Mineralocorticoid Receptor Antagonist

- A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2DM, eGFR ≥25 mL/min/1.73m^2, normal serum potassium concentration, and albuminuria (ACR ≥30 mg/g) despite maximum tolerated dose of renin-angiotensin system (RAS) inhibitor.

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090.

Comparison of Mineralocorticoid Receptor Agonists (MRAs)

	Potency	Selectivity	Metabolites	Tissue Distribution* (Kidney/Heart)	FDA-Approved Indications
Steroidal					
Spironolactone	High	Low	Multiple, active	Higher in kidney	• Hypertension • Heart failure • Edema • Primary hyperaldosteronism
Eplerenone	Low	Medium	No active metabolites	Higher in kidney	• Hypertension • Heart failure post-MI
Non-Steroidal					
Finerenone	High	High	No active metabolites	Balanced in heart and kidney	• To improve kidney and CV outcomes in T2DM and CKD

*Based on standard whole-body quantitative analysis in healthy rats.

Agarwal R, et al. *Eur Heart J*. 2021;42(2):152-161.
Clinical Pharmacology Online. Available at: https://www.clinicalkey.com.

Finerenone

- **FDA approved in 2021**
- **Non-steroidal MRA**

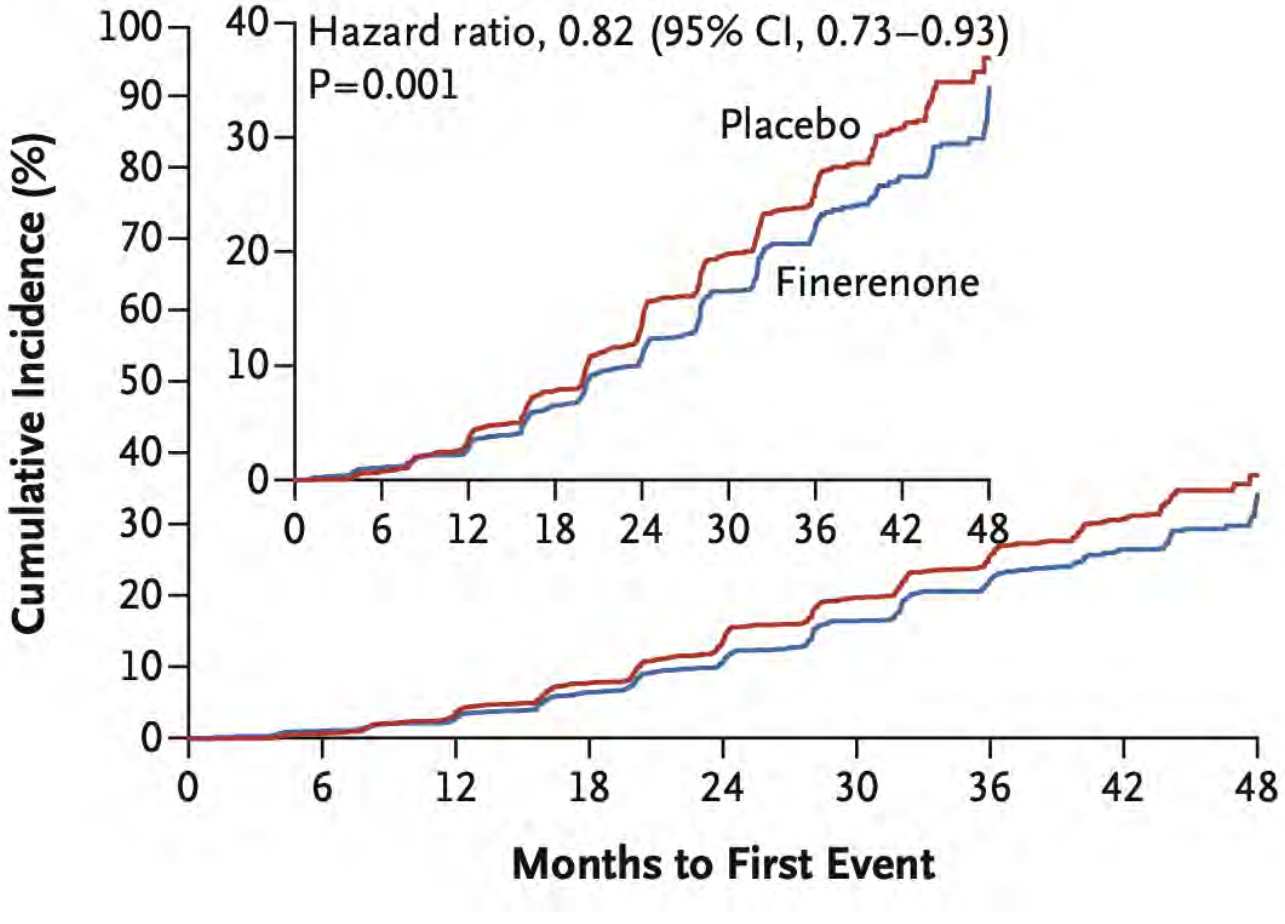
  Less steroidal side effects (e.g., gynecomastia) and hyperkalemia when compared to steroidal MRAs
- **Indication:**

  To reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, nonfatal MI, and hospitalization for heart failure in adult patients with CKD associated with type 2 diabetes.

Agarwal R, et al. *Nephrol Dial Transplant*. 2022;37(6):1014-1023.
Finerenone tablets (Kerendia). Prescribing Information. Bayer HealthCare Pharmaceuticals Inc.; Whippany, NJ. September 2022.

FIDELIO-DKD

Primary Composite Outcome[1]



1. Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229.; 2. Filippatos G, et al. *J Am Coll Cardiol*. 2021;78(2):142-152.

FIDELIO-DKD

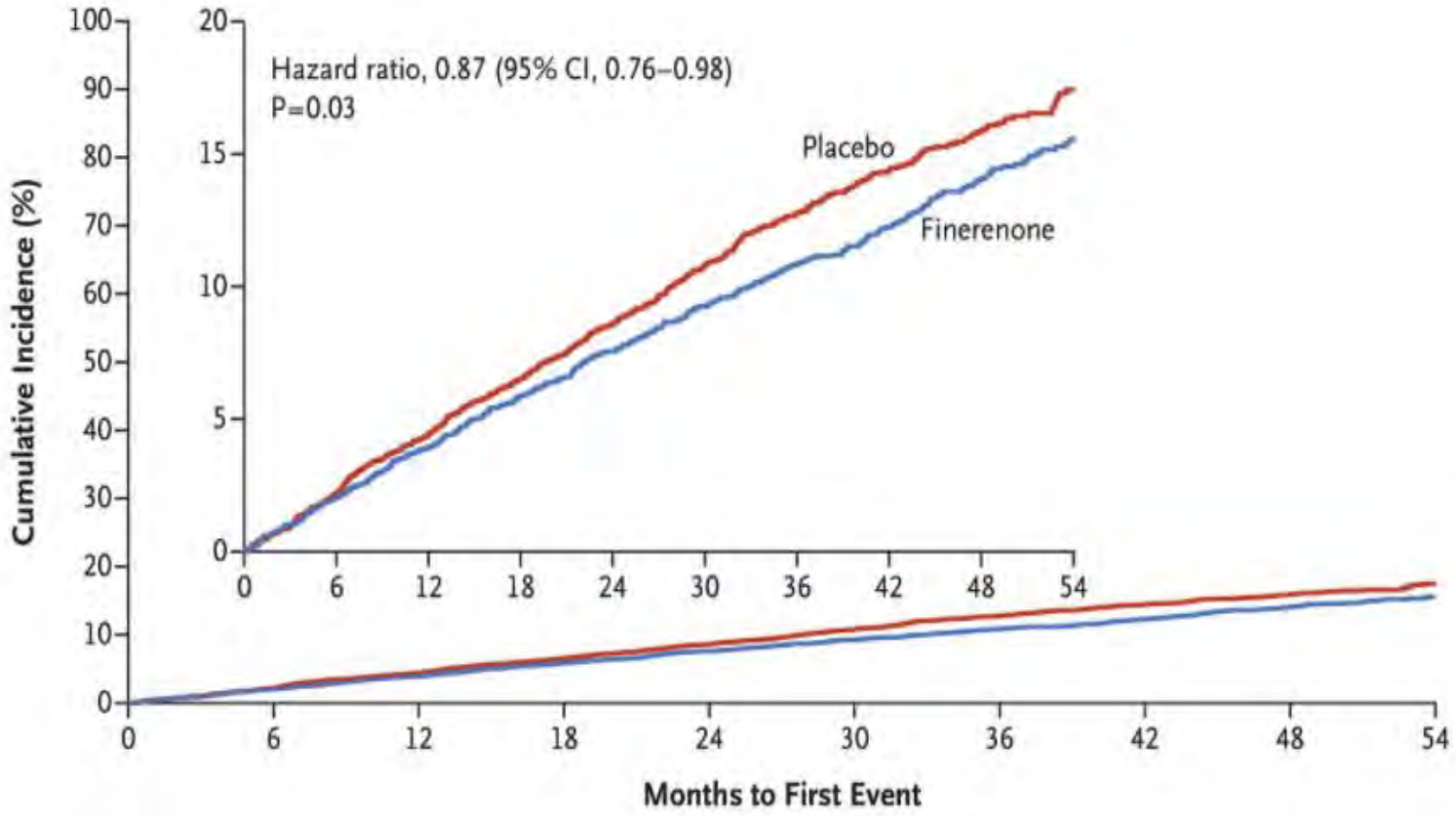
All Outcomes[1,2]

Outcome	Hazard ratio (95% CI)	*P* value
Primary composite[1]	0.82 (0.73-0.93)	0.001
Sustained decrease ≥40% in eGFR[1]	0.81 (0.72-0.92)	–
Secondary composite[1]	0.86 (0.75-0.99)	0.03
Secondary kidney composite[1]	0.76 (0.65-0.90)	–
Sustained doubling of SCr for ≥4 wks[1]	0.68 (0.55-0.82)	–
New-onset atrial fibrillation/atrial flutter*[2]	0.71 (0.53-0.94)	0.016

1. Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229.; 2. Filippatos G, et al. *J Am Coll Cardiol*. 2021;78(2):142-152.

FIGARO-DKD

Primary Composite Outcome[1]



1. Pitt B, et al. *N Engl J Med*. 2021;385(24):2252-2263; Image from *N Engl J Med*, Pitt B, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. 385:2252-2263. Copyright 2021 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

FIGARO-DKD

All Outcomes[1,2]

Outcome	Hazard ratio (95% CI)	*P* value
Primary composite[1]	0.87 (0.76-0.98)	0.03
Hospitalization for heart failure[1]	0.71 (0.56-0.90)	–
Secondary composite[1]	0.87 (0.76-1.01)	–
Secondary kidney composite[1]	0.77 (0.60-0.99)	–
End-stage kidney disease[1]	0.64 (0.41-0.995)	–
New-onset heart failure*[2]	0.68 (0.50-0.93)	0.016

1. Pitt B, et al. *N Engl J Med*. 2021;385(24):2252-2263; Filippatos G, et al. *Circulation*. 2022;145:437-447.

Case Vignette

- 65-year-old female presenting to PCP to establish care after moving to the area to be closer to family
- **PMH:** T2D, hypertension, dyslipidemia, obesity, history of MI
- **Vitals:** BMI: 34 kg/m^2, BP: 138/90 (average of 3 seated measures)
- **Key Labs:** A1C: 7.5%, eGFR: 52 mL/min/1.73m^2, UACR: 220 mg/g, lipid panel and electrolytes all within normal range. Medical records indicate an eGFR of 58 mL/min/1.73m^2 measured 13 months prior.
- **Medications:** metformin 1,000 mg BID, linagliptin 5 mg once daily, lisinopril 40 mg once daily, aspirin 81 mg daily

Case Vignette

- The patient has CKD in addition to T2D and established atherosclerotic cardiovascular disease.

What short-term management goals would be appropriate in this patient?

Case Vignette: Plan

- Optimized management would include interventions aimed at reducing her cardiorenal risk:
  1. Optimize A1C and blood pressure management to slow CKD progression
  2. Initiation of SGLT2 inhibitor therapy to slow CKD progression and reduce cardiovascular risk
  3. Referral for diabetes self-management education to reinforce healthy lifestyle and receive education about her CKD diagnosis and management options

After addressing initial goals, additional interventions to further reduce her cardiorenal risk can be considered

(e.g., addition of GLP-1 receptor agonist for additional glucose-lowering to meet A1C goal and/or addition of finerenone to further reduce albuminuria if ACR remains ≥30 mg/g despite treatment with first-line agents)

Summary

- CKD is associated with increased risk for cardiovascular events, kidney disease progression, and mortality.
- Annual CKD screening is recommended for patients with T2D, including albuminuria and eGFR assessment.
- Risk factor management, including optimization of glycemia and blood pressure, are recommended to prevent and/or slow progression of CKD.
- Use of RAS inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists and/or finerenone are recommended for organ protection in patients with T2D and CKD.

Resource Toolkit:

You'll find links to every reference from the presentation and more.

Updates in the Management of
Chronic Kidney Disease in Primary Care

https://www.pcmg-us.org/toolkit/updatesckd

Post-presentation Survey:

Please complete the survey by using the QR code to the right or the URL below.

Updates in the Management of Chronic Kidney Disease in Primary Care

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