PENNSYLVANIA ACADEMY of FAMILY PHYSICIANS

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1

Best Practices to Beat the Cardio-Renal-Metabolic Triad

Aaron King, MD

2

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4

CME/CE Information (Live Presentation)

The AAFP has reviewed Best Practices to Beat the Cardio-Renal-Metabolic Triad and deemed it acceptable for AAFP credit. Term of approval is from 04/01/2025, to 03/31/2026. Physicians should claim only the credit commensurate with the extent of their participation in the activity. This session is approved for 1.0 Live Activity AAFP Prescribed credits.

Following this CME activity, participants will have the opportunity to earn an additional two Prescribed credits for participation in each Translation to Practice® exercise. Information on Translation to Practice® will be shared within the activity.
1.00 Enduring AAFP Prescribed Credit(s) - Ambulatory Glucose Profile and Tie

5

Want Translation to Practice (T2P^{tm}) Credit?

- You may qualify for an additional 2.0 credits IF you make a commitment to change your practice behaviors in your post-presentation survey. In that survey, you will be asked
  - to commit to changes in your practice behaviors
  - to specify what those changes are, and
  - to provide your name and email address.
- If you do not enter the required data mentioned above, you will not be eligible for T2P credit, so please include all the information!
- Approximately six weeks later, we will contact you, asking if those changes were made, along with some additional questions. If you have completed those changes, you will be eligible to complete the survey and generate a certificate for the additional credits.

6

Faculty Disclosure Information

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7

Disclosures

- **Aaron King, MD,** presenter, **Austin Ulrich, PharmD,** medical writer, and **Michael Hanak**, **MD,** CME Reviewer, have no disclosures to report.

- All relevant financial relationships have been mitigated.

8

Learning Objectives

Participants in this presentation should be able to…
Apply strategies for diagnosing T2D, HF, and CKD early in the disease course to slow progression and reduce adverse outcomes.
Incorporate evidence-based, guideline-recommended therapeutic agents for treating CRM conditions across the spectrum of disease.
Engage the multidisciplinary health care team to promote optimal care of CRM diseases across care settings.

9

Introduction to Cardio-Renal-Metabolic (CRM) Diseases

10

T2D, CVD/HF, and CKD

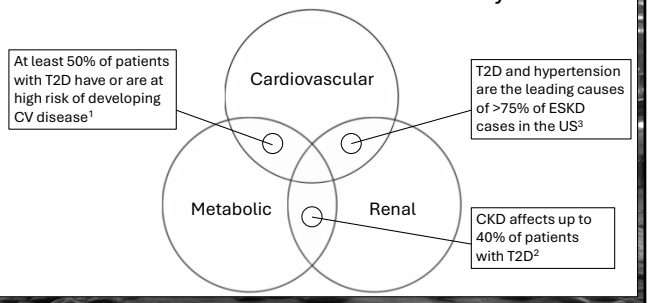
- Among the most disruptive public health issues of the century
- Strong interconnection between diseases affecting the three systems (metabolic, cardiovascular, renal)
- Coexistence of all three referred to as **"cardio-renal-metabolic"** diseases

T2D, type 2 diabetes; CVD, cardiovascular disease; CKD, chronic kidney disease; HF, heart failure

Marassi M and Fadini GP. *Cardiovasc Diabetol*. 2023;22:195.

11

Coexistence of Cardio-Renal-Metabolic Systems

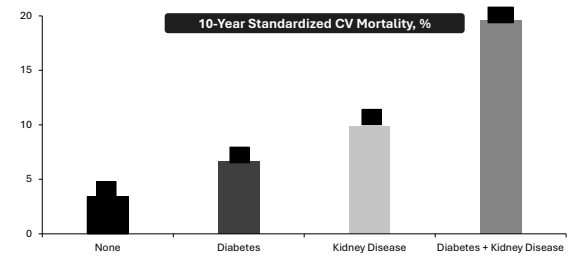


1. Wong K, et al. *J Diabetes Complications*. 2012;26:169-174. 2. Feng X, et al. *Kidney Med*. 2022;4(1):100385.
3. S Ramirez RR, et al. *MMWR Morb Mortal Wkly Rep*. 2022;71(11):412-415.

ESKD=End Stage Kidney Disease

12

CV Mortality in T2D is Magnified by CKD



Afkarian M, et al. *J Am Soc Nephrol*. 2013;24:302-308.

13

CKD Promotes the Pathogenesis of CVD in Diabetes

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

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

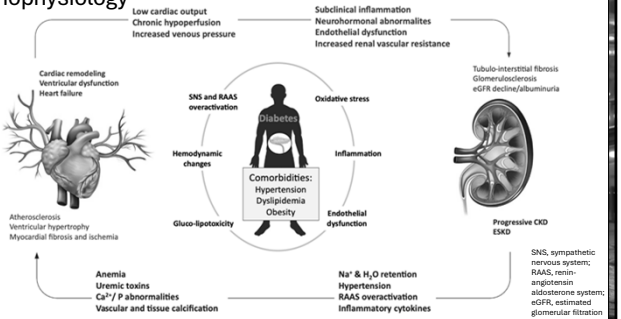
The risk of CV events in DKD increases as kidney function declines[1]

CV, cardiovascular; DKD, diabetes kidney disease

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.

14

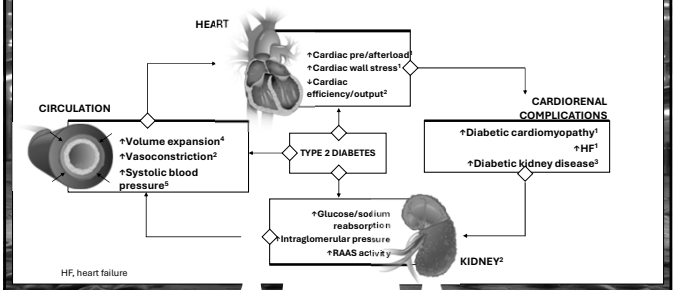
Pathophysiology



SNS, sympathetic nervous system; RAAS, renin-angiotensin aldosterone system; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease

15

Bidirectional, Pathophysiological Interaction Between Kidney and Heart in T2D: Potential for Multi-organ benefit



HF, heart failure

1. Munkenbeen V, et al. J Diabetes Metab. 2015;6:510. 2. Sattar N, et al. Diabetologia. 2016;59(7):1333-1339. 3. Wanner C, Am J Cardiol. 2017;120(1S):S89-S97. 4. Sattar N, et al. Circulation. 2019;139:7–9. 5. Mazidi M, et al. J Am Heart Assoc. 2017;6(6):e004007.

16

Cardiorenal Syndrome (CRS)

A "pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other"
- Includes CKD and HF, among other conditions

- 5 types of CRS identified
- Biomarkers can assist with early diagnosis of CRS and timely therapeutic intervention
  - Cardiac biomarkers, such as BNP
  - Kidney biomarkers, such as SCr, cystatin C, and albuminuria

BNP, B-type natriuretic peptide; SCr, serum creatinine

Ronco C, et al. *J Am Coll Cardiol*. 2008;52(19):1527-1539; Rangaswami J, et al. *Circulation*. 2019;139(16):e840-e878.

17

The 5 Subtypes of CRS

Type	Nomenclature	Description	Examples
Type 1 CRS	Acute CRS	HF resulting in AKI	• ACS leading to cardiogenic shock and AKI • Acute HF that leads to AKI
Type 2 CRS	Chronic CRS	Chronic HF resulting in CKD	• Chronic HF
Type 3 CRS	Acute renocardiac syndrome	AKI resulting in acute HF	• HF in the setting of AKI from volume overload • Inflammatory surge • Metabolic disturbances in uremia
Type 4 CRS	Chronic renocardiac syndrome	CKD resulting in chronic HF	• LVH and HF from CKD-associated cardiomyopathy
Type 5 CRS	Secondary CRS	Systemic process resulting in HF and kidney failure	• Amyloidosis • Sepsis • Cirrhosis

AKI, acute kidney injury; ACS, acute coronary syndrome; LVH, left ventricular hypertrophy

Ronco C, et al. *J Am Coll Cardiol*. 2008;52(19):1527-1539; Rangaswami J, et al. *Circulation*. 2019;139(16):e840-e878.

18

The Role of the Health Care Team in CRM Diseases[1-3]

- Health care team management of CRM diseases is recommended
- CKD is underdiagnosed, and many clinicians are not routinely screening patients with diabetes or hypertension for elevated UACR
  - Early screening and diagnosis leads to optimized kidney and CV care
- Primary care clinicians (PCCs) are often the first source for care
  - More than 60% of patients with CKD seen in primary care
  - PCCs can coordinate care to ensure coordinated, multidisciplinary management of CRM diseases

UACR, urine albumin-to-creatinine ratio

1. Rangaswami J, et al. *Circulation*. 2020;142(17):e265-e268. 2. Kushner PR, et al. *Clin Diabetes*. 2022; 40(4):401-412. 3. Alfego D, et al. *Diabetes Care*. 2021;44:2025-2032; Shin J, et al. *Hypertension*. 2021;78:1042-1052.

19

Role of the PCC

- Facilitate early screening and diagnosis
- Implement interventions early when indicated to prevent CV morbidity/mortality and slow CKD progression
  - Lifestyle interventions
  - Optimized risk factor management
  - Initiation of agents with evidence of cardiovascular and kidney benefit
- Refer to specialists as appropriate
- Coordinate multidisciplinary care

Boulware JH, et al. *Postgrad Med*. 2022;134(4):376-387; Kushner PR, et al. *Clin Diabetes*. 2022; 40(4):401-412.

20

Patient Case #1

58-year-old woman presents for a routine primary care visit follow up:

- History of T2D, HF, CKD, and hypertension
- Has been taking her medications for "years"
- BMI 31.2 kg/m^2
- Blood pressure today 156/80 mmHg
- HbA1c 8.5%
- eGFR 46 mg/mL/1.73 m^2, UACR 90 mg/g

Current Relevant Medications
Metformin 1,000 mg twice daily
Glipizide 10 mg twice daily
Lisinopril 40 mg once daily
Bisoprolol 5 mg once daily

What are the potential health risks for this patient, and what opportunities are there to improve disease management?

BMI, body mass index; HbA1c, glycated hemoglobin

21

22

Screening for CKD in Diabetes

	Adults	Children/Adolescents
Who?	T1D: Duration ≥5 years T2D: All	At puberty or age >10 years, whichever is earlier, once the child has had diabetes ≥5 years
How?	Urinary albumin (eg, spot UACR) and eGFR	Urinary albumin (morning preferred) with spot UACR
When?	At least once a year	At least once a year

Note: The ADA (American Diabetes Association) recommends that patients with established T2D and CKD, UACR and eGFR should be monitored 1-4 times per year depending on the stage of disease.

American Diabetes Association Professional Practice Committee. *Diabetes Care*. 2024;48(Suppl. 1):S239-S251.

23

Screening for CKD in patients with diabetes

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

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

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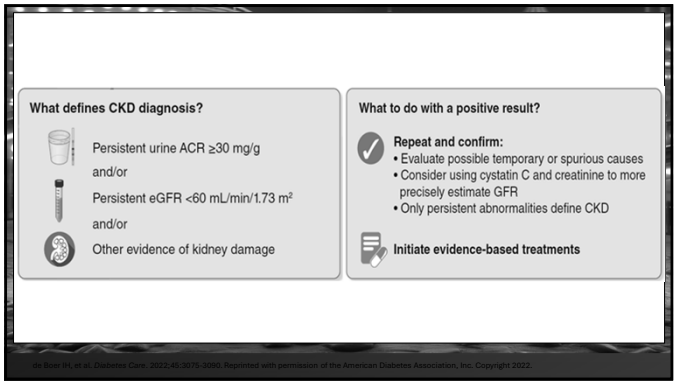


de Boer IH, et al. Diabetes Care. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

25

The race-neutral 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**

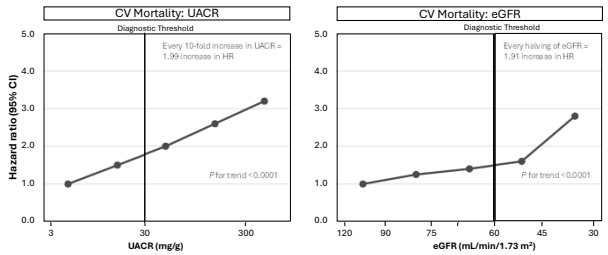
eGFR Test Change: Removal of Race from the Calculation | American Kidney Fund. www.kidneyfund.org. November 23, 2021. Accessed March 17, 2022. https://www.kidneyfund.org/all-about-kidneys/tests/egfr/egfr-test-change-removal-race-calculation

26

Why both UACR and eGFR?

Both eGFR and UACR independently predict CVD mortality

CVD mortality increases with severity of renal impairment



Ninomiya T, et al. *J Am Soc Nephrol*. 2009;20(8):1813-1821. Figure reprinted with permission from Ninomiya et al, Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes, Journal of the American Society of Nephrology, 20(8):1813-1821, https://journals.lww.com/jasn/fulltext/2009/08000/albuminuria_and_kidney_function_independently.25.aspx

27

Which of the following is true about screening for CKD in patients with diabetes?

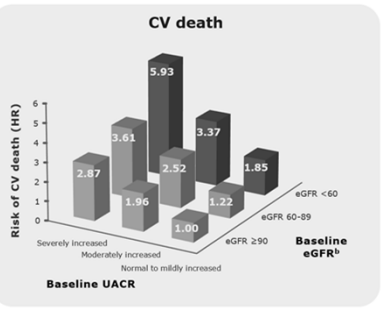
A. Cystatin C and creatinine testing are preferred for initial CKD screening
B. Only checking eGFR is recommended since it independently predicts CVD mortality
C. Only checking UACR is recommended since it independently predicts CVD mortality
D. Checking eGFR and UACR is recommended since both independently predict CVD mortality

28

Why both UACR and eGFR?

Having both abnormal UACR and eGFR compounds the risk of CV death and kidney events[a]

[a]Average time to follow-up for risk assessment was 4.3 years. [b]eGFR in mL/min/1.73 m^2.



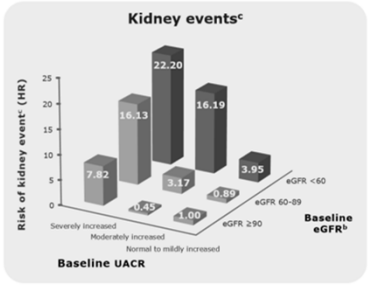
Ninomiya T, et al. *J Am Soc Nephrol*. 2009;20(8):1813-1821. Figure reprinted with permission from Ninomiya et al, Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes, Journal of the American Society of Nephrology, 20(8):1813-1821, https://journals.lww.com/jasn/fulltext/2009/08000/albuminuria_and_kidney_function_independently.25.aspx

29

Why both UACR and eGFR?

Having both abnormal UACR and eGFR compounds the risk of CV death and kidney events[a]

[a]Average time to follow-up for risk assessment was 4.3 years. [b]eGFR in mL/min/1.73 m^2. [c]A kidney event is defined as death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine to >2.26 mg/dL.



Ninomiya T, et al. *J Am Soc Nephrol*. 2009;20(8):1813-1821. Figure reprinted with permission from Ninomiya et al, Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes, Journal of the American Society of Nephrology, 20(8):1813-1821, https://journals.lww.com/jasn/fulltext/2009/08000/albuminuria_and_kidney_function_independently.25.aspx

30

Definition and Staging of CKD

Risk of CKD progression, frequency of visits, and referral to nephrologist according to GFR and albuminuria shown.

Numbers in boxes are a guide to how many times per year the patient should be seen.

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

31

CV Risk by KDIGO Stages

Observational study assessing CV and renal risk in 543,606 individuals using an electronic database in Japan

KDIGO	A1	A2	A3	Without urine protein test
(a) MACE1 (primary outcome)				
G2	1.00 (reference)	1.17 (1.12–1.21)	1.59 (1.52–1.67)	1.39 (1.36–1.42)
G3a	1.16 (1.12–1.20)	1.37 (1.29–1.46)	1.78 (1.68–1.89)	1.46 (1.42–1.50)
G3b	1.43 (1.34–1.51)	1.68 (1.53–1.84)	2.02 (1.88–2.17)	1.82 (1.74–1.90)
G4	1.86 (1.65–2.09)	2.25 (1.96–2.59)	2.44 (2.24–2.66)	2.64 (2.46–2.83)
G5	2.08 (1.46–2.96)	2.37 (1.69–3.33)	2.83 (2.54–3.15)	3.18 (2.90–3.47)
(b) MACE2 (ad hoc primary outcome)				
G2	1.00 (reference)	1.35 (1.28–1.43)	1.97 (1.85–2.09)	1.50 (1.45–1.55)
G3a	1.17 (1.11–1.23)	1.47 (1.35–1.59)	2.13 (1.97–2.30)	1.59 (1.52–1.66)
G3b	1.61 (1.49–1.73)	1.99 (1.78–2.22)	2.46 (2.25–2.69)	2.18 (2.07–2.31)
G4	2.35 (2.04–2.70)	2.62 (2.21–3.11)	3.12 (2.81–3.46)	3.60 (3.31–3.90)
G5	3.48 (2.31–5.25)	3.63 (2.42–5.44)	3.43 (3.00–3.93)	4.68 (4.20–5.21)

Data are HR (95% CI).

MACE1: composite of myocardial infarction, stroke, heart failure hospitalization, and in-hospital death
MACE2: myocardial infarction hospitalization, stroke hospitalization, heart failure hospitalization, and in-hospital death

KDIGO, Kidney Disease: Improving Global Outcomes; MACE, major adverse cardiovascular events

32

Patient Case #2

42-year-old man with newly-diagnosed T2D presents to the primary care clinic for a diabetes follow-up visit

- History of hypothyroidism, T2D
- BMI 27.5 kg/m^2

Current Relevant Medications
Metformin 1,000 mg twice daily
Insulin glargine 15 units daily
Levothyroxine 50 mcg daily

When and how should this patient be screened for CVD/HF and CKD?

33

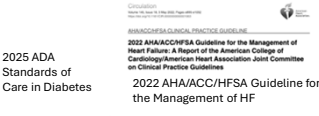
Guideline-Directed Management of CRM Diseases

34

Guideline Recommendations

Early screening, diagnosis, and comprehensive, coordinated care optimize outcomes in T2D, CVD/HF, and CKD

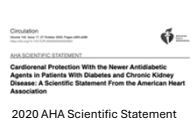
2025 ADA Standards of Care in Diabetes



2022 AHA/ACC/HFSA Guideline for the Management of HF

2024 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD

2022 KDIGO Guidelines for Diabetes and CKD Management

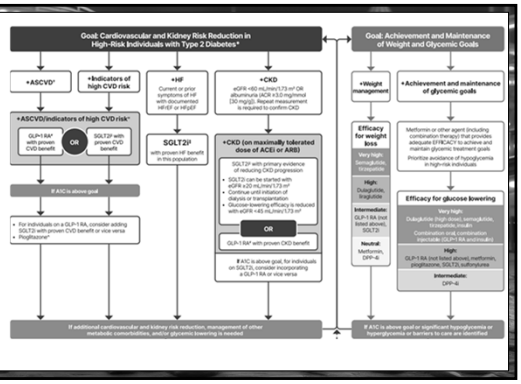


2020 AHA Scientific Statement

ACC, American College of Cardiology; AHA, American Heart Association; HFSAA, Heart Failure Society of America

35

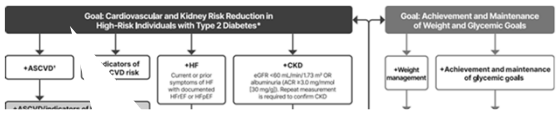
ADA 2025 Pharmacologic Therapy Algorithm



CGM, continuous glucose monitoring; DPP-4i, dipeptidyl peptidase 4 inhibitor; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium-glucose cotransporter 2 inhibitor

36

Use of Glucose-Lowering Medications in the Management of T2D



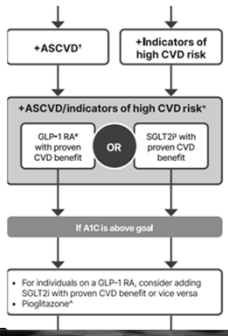
Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*

*In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or HbA1c

GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin

37

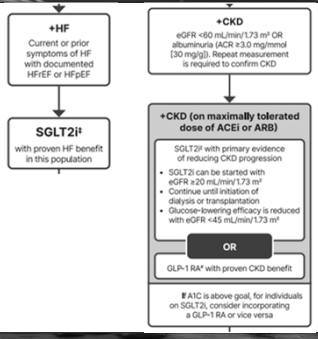
High-risk or established ASCVD



CVOTs, cardiovascular outcomes trials

38

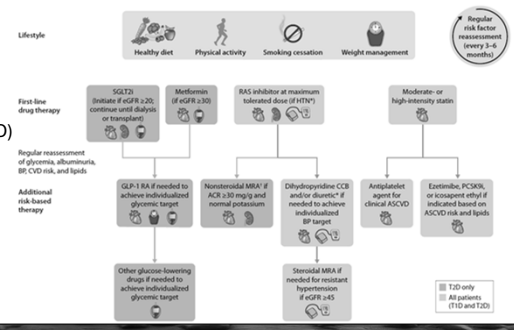
HF or CKD



39

Approach for Improving Outcomes in Diabetes and CKD

(ADA and KDIGO)



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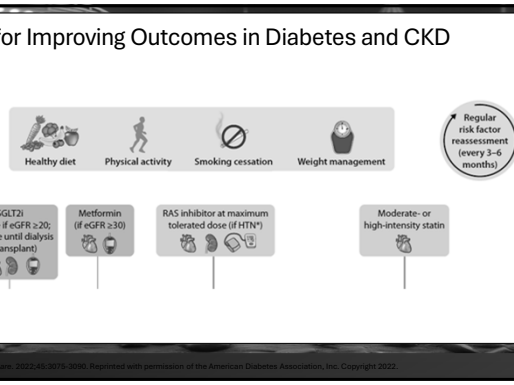

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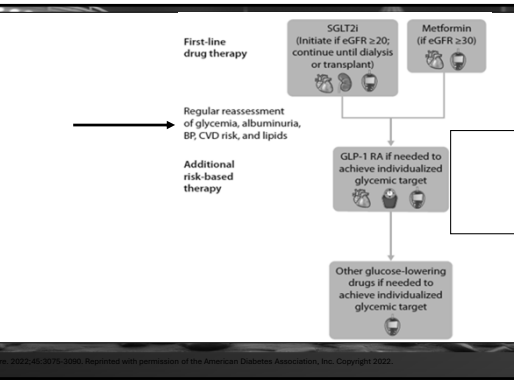

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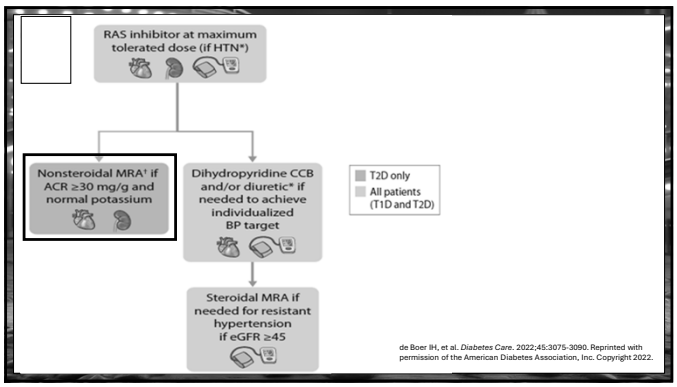

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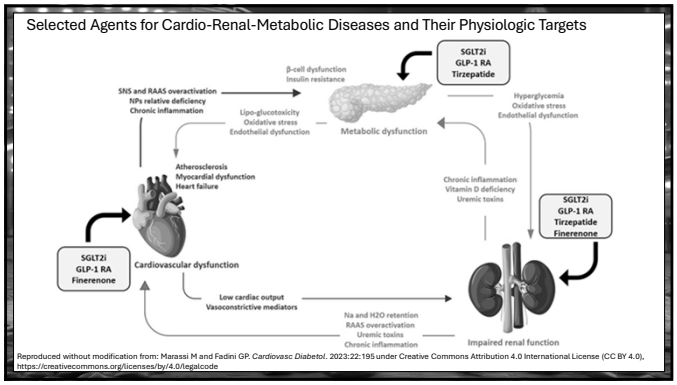


44

SGLT2 Inhibitors: Kidney Outcome Trial Results

Agent	Canagliflozin	Dapagliflozin	Empagliflozin
Study	CREDENCE (n = 4,401)	DAPA-CKD (n = 4,304; **2,906 w/diabetes**)	EMPA-KIDNEY (n = 6,609; **3,040 w/diabetes**)
Median follow-up (years)	2.6	2.4	2.0
Key kidney-related enrollment criteria	eGFR 30 to < 90 UACR: > 300 to 5000 mg/g	eGFR 25 to 75 UACR: 200 to 5000 mg/g	eGFR 20 to 45 (any UACR) eGFR 45 to 90 (UACR ≥200 mg/g)
Mean baseline eGFR	56 mL/min/1.73 m^2	43 mL/min/1.73 m^2	37 mL/min/1.73 m^2
Median Baseline UACR	927 mg/g	949 mg/g	329 mg/g
Kidney outcome(s)	**Primary Outcome** • ESKD (dialysis, transplantation, or sustained eGFR < 15 mL/min/1.73m^2), doubling of SCr, or death from renal causes **HR: 0.70 (0.59-0.82)**	**Primary Outcome** • ≥ 50% decrease in eGFR, ESKD, or death from renal or cardiovascular causes **HR: 0.61 (0.51-0.72)**	**Primary Outcome** • ≥ 40% decrease in eGFR, decrease in eGFR to <10 mL/min/1.73 m^2, ESKD, or death from renal causes **HR: 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; The EMPA-KIDNEY Collaborative Group. *N Engl J Med*. 2023;388:117-127.

45

SGLT2 Inhibitors: HF Trial Results

Agent	Dapagliflozin	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
Study	DAPA-HF (n = 4,744)	DELIVER (n = 6,263)	EMPEROR-Reduced (n = 3,730)	EMPEROR-Preserved (n = 5,988)	SOLOIST-WHF (n = 1,222)
Median follow-up (years)	1.5	2.3	1.33	2.2	0.75*
Patients	NYHA class II, III, or IV HF and EF ≤40%	HF and EF >40%	NYHA class II, III, or IV HF and EF ≤40%	NYHA class II, III, or IV HF and EF >40%	T2D, recently hospitalized for worsening HF
HF outcomes	Composite of worsening heart failure or CV death **HR: 0.74 (0.65-0.85)**	Composite of worsening heart failure or CV death **HR: 0.82 (0.73-0.92)**	Composite of hospitalization for heart failure or CV death **HR: 0.75 (0.65-0.86)**	Composite of hospitalization for heart failure or CV death **HR: 0.79 (0.69-0.90)**	Composite of urgent visits or hospitalizations for HF and CV death **HR: 0.67 (0.52-0.85)**

NYHA, New York Heart Association; EF, ejection fraction

*Trial ended early due to lack of funding

McMurray JJV, et al. *N Engl J Med.* 2019;381:1995-2008; Solomon SD, et al. *N Engl J Med.* 2022;387:1089-1098; Packer M, et al. *N Engl J Med.* 2020;383:1413-1424; Anker SD, et al. *N Engl J Med.* 2021; 385:1451-1461; Bhatt DL, et al. *N Engl J Med.* 2021;384:117-128.

46

SGLT2 Inhibitors: Expanded Indications

Medication	Expanded Indications
Canagliflozin	...to reduce to reduce the risk of MACE* in adults with T2D and established CVD ...to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for HF in adults with T2D and diabetic nephropathy with albuminuria
Dapagliflozin	...to reduce the risk of hospitalization for HF in adults with T2D and established CVD or multiple CV risk factors ...to reduce the risk of CV death and hospitalization for HF, and urgent HF visit in adults with heart failure ...to reduce the risk of sustained eGFR decline, ESKD, CV death, and hospitalization for HF in adults with CKD at risk of progression
Empagliflozin	...to reduce the risk of CV death and hospitalization for HF in adults with HF ...to reduce the risk of CV death in adults with T2D and established CVD
Sotagliflozin	...to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF or T2D with CKD and other CV risk factors

*Composite of CV death, nonfatal MI, nonfatal stroke

Farxiga [Package Insert]. Updated December 2024. Accessed March 17, 2025. Farxiga [Package Insert]. Updated October 2024. Accessed March 17, 2025. Jardiance [Package Insert]. Updated September 2024. Accessed March 17, 2025. Ingvoti [Package Insert]. Updated January 2024. Accessed March 17th, 2025.

47

FDA approval

Certain agents from which of the following drug classes have FDA approval for indications of T2D, HF (regardless of ejection fraction), and CKD (with or without diabetes)?

A. ACE inhibitors

B. SGLT2 inhibitors

C. GLP-1 receptor agonists

D. Nonsteroidal MRAs

48

SGLT2 Inhibitors and AKI Hospitalization

- SGLT-2 inhibitors often withheld during AKI among patients hospitalized with acute HF
- Retrospective study of 3305 patients
  - 356 patients received SGLT-2 inhibitor following AKI diagnosis
  - **Rate of renal recovery not significantly different** between those exposed and unexposed to SGLT-2 inhibitors following AKI (HR 0.94, 95% CI 0.79-1.11, *P*=0.46)
  - SGLT-2 inhibitor exposure associated with **lower risk of 30-day mortality** (HR 0.45, 95% CI 0.23-0.87, *P*=0.02)

Conclusion: in adults with hospitalized with AKI and acute HF, exposure to SGLT-2 inhibitors leads to decreased mortality and no delay in recovery of kidney function

Akilu AM, et al. *Kidney360*. 2023. doi:10.3406/KID.0000000000000250 AKI, acute kidney injury

49

Treatment for Cardiorenal Syndrome (CRS)

Treatment Strategy	Comments
Diuretics	Cornerstone of CRS management (though not supported by data from large clinical trials)
Ultrafiltration	Allows decongestion without use of loop diuretics
ACE inhibitors/ARBs/angiotensin-neprilysin inhibitor	Primary blood pressure-lowering agents
Aldosterone receptor antagonists	Improve RAAS suppression, but caution with risk for hyperkalemia; nonsteroidal MRAs (finerenone) have lower risk of hyperkalemia
Evidence-based beta blockers	Improve NYHA class, LVEF, and HF symptoms, and reduce hospitalizations
SGLT-2 inhibitors	SGLT-2 inhibitors indicated for HF (empagliflozin, dapagliflozin, canagliflozin, sotaglifl ozin) or CKD (dapagliflozin, canagliflozin; empagliflozin granted FastTrack designation by FDA)
Cardiac device therapy	Subcutaneous implantable cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT) are options for certain patients

Rangaswami J, et al. *Circulation*. 2019;139(16):e840-e878. LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MRA, [illegible]

50

Pillars of T2D/CKD Management

Foundation	Lifestyle intervention (diet/exercise)
1st Pillar	ACE inhibitor/ at maximum tolerated dose
2nd Pillar	SGLT-2 inhibitor with primary evidence of reducing CKD progression
3rd Pillar	Nonsteroidal-MRA (finerenone)
4th Pillar	GLP-1 RAs

Agarwal A, Fogue D. *Nephrol Dial Transplant*. 2023;38(2):253-267.

51

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, ESKD, CV death, nonfatal myocardial infarction, and hospitalization for HF in adult patients with CKD associated with T2D.

Agarwal R, et al. Nephrol Dial Transplant. 2022;37(6):1014-1023. Kerendia. Prescribing information. Bayer HealthCare Pharmaceuticals Inc.; 2022. Accessed July 2, 2025. https://labeling.bayerhealthcare.com/html/products/pi/Kerendia_PI.pdf

52

Finerenone Phase 3 Trials in T2D and CKD

	FIDELIO-DKD[1]	FIGARO-DKD[2]
Design	Randomized, double-blind, placebo-controlled, multicenter, phase 3, event-driven	
Subjects	Adults (N = 5734) with: • T2D • Treated with ACE-I or ARB • UACR 30-300 eGFR 25-60 and diabetic retinopathy or UACR ≥300 and eGFR 25-75	Adults (N = 7437) with: • T2D • Treated with ACE-I or ARB • UACR 30-300 and eGFR 25-90 or UACR ≥300 and eGFR ≥60
Randomized treatment	Finerenone 10 or 20 mg/d or placebo Titration based on potassium level and change in eGFR	
Primary endpoint	Composite of time to first occurrence of kidney failure, sustained decrease of eGFR ≥40% over ≥4 wks, or kidney-related death	Composite of time to first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or HF hospitalization
Median follow up	2.6 years	3.4 years
Results published	October 2020	August 2021

UACR in mg/g and eGFR in mL/min/1.73 m²

1. Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229. 2. Pitt B, et al. *N Engl J Med*. 2021;385(24):2252-2263.

53

FLOW Trial: T2D/CKD Outcomes with Semaglutide

- Patients: 3533 adults with T2D and CKD randomized 1:1 to semaglutide 1.0 mg once weekly or placebo
- Trial stopped early at median follow-up of 3.4 years
- Results (all statistically significant in favor of semaglutide):

Outcome	Semaglutide vs Placebo
Primary outcome: major kidney disease events, a composite of the onset of kidney failure, at least a 50% reduction in the eGFR from baseline, or death from kidney or cardiovascular causes	**HR 0.76**; 95% CI, 0.66 to 0.88; *P* = .0003
Kidney-specific components of the primary outcome	**HR 0.79**; 95% CI, 0.66 to 0.94
Death from cardiovascular causes	**HR 0.71**; 95% CI, 0.56 to 0.89
Risk of major adverse cardiovascular events	**HR 0.82**; 95% CI, 0.68 to 0.98; *P* = .029
Risk of death from any cause	**HR 0.80**; 95% CI, 0.67 to 0.95; *P* = 0.01

Conclusion: semaglutide reduced the risk of clinically important kidney outcomes and death from CV causes in patients with T2D and CKD

Perkovic V, et al. *N Engl J Med*. 2024; May 24 online ahead of print. doi:10.1056/NEJMoa2403347

54

GLP-1 RAs and Kidney Benefits in Patients Without T2D

SELECT trial analysis

- Long-term kidney outcomes in patients with obesity/overweight and cardiovascular disease who did not have diabetes
- Kidney composite endpoint:
  - Death from kidney disease, initiation of chronic kidney replacement therapy, onset of persistent eGFR < 15 mL/min/1.73 m^2, persistent ≥50% reduction in eGFR or onset of persistent macroalbuminuria
- Semaglutide 2.4 mg compared to placebo
  - 22% reduction in the kidney composite endpoint
  - 1.8% with semaglutide, 2.2% with placebo, *P* = 0.02

Cothon HM, et al. *Nat Med*. May 25, 2024; online ahead of print. doi:10.1038/s41591-024-03015-5

55

Combined SGLT-2 Inhibitor and MRA Benefit

Joint analysis of randomized trials (CREDENCE, FIDELIO-DKD, and DAPA-CKD)

Outcome	Combination Treatment Events/Patients	Conventional Treatment Events/Patients	Hazard Ratio (95% CI)
Doubling of SCr, ESKD, or death due to kidney failure	405/5035	550/5040	**0.50 (0.44–0.57)**
ESKD	324/5035	400/5040	**0.59 (0.51–0.69)**
All-cause mortality	387/5035	445/5040	**0.75 (0.65–0.86)**

- Patients had T2D and CKD
- Conventional Treatment: ACE inhibitor or ARB
- Combination treatment: SGLT-2 inhibitor and nonsteroidal MRA

Estimated event-free survival from composite kidney outcome incremental gain was 6.7 years with combination treatment

Heerspink HJL, et al. *Diabetes Obes Metab*. 2023. doi:10.1111/dom.15232

56

Combined SGLT2 Inhibitor and MRA Benefit

The CONFIDENCE trial

- Patients had T2D and CKD (eGFR 30 to 90 mL/min/1.73 m^2 and UACR of 100 to ≤5000 mg/g)
  - Protocol required that patients were taking an ACE inhibitor or ARB
- Randomized 1:1:1 to finerenone + placebo, placebo + empagliflozin, or finerenone + empagliflozin
- Stratified by eGFR and UACR

Safety Outcome	Empagliflozin and Finerenone	Empagliflozin Alone	Finerenone Alone
Hyperkalemia	9.3%	11.4%	3.8%
>30% drop in eGFR at day 30	6.3%	3.8%	1.1%

Agarwal R, et al. *N Engl J Med*. 2025;393(6):533-543.

57

Combined SGLT2 Inhibitor and MRA Benefit

The CONFIDENCE trial – primary outcome

Outcome	Empagliflozin and Finerenone	Empagliflozin Alone	Finerenone Alone
Reduction in UACR from baseline to 180 days	52%	32%	29%
Least-squares mean ratio of the difference in change from baseline (vs combination)	—	0.71; 95% CI, 0.61 to 0.82; **P<.001**	0.68; 95% CI, 0.59 to 0.79; **P<.001**

Combination therapy reduced UACR by 29% more than finerenone alone and by 32% more than empagliflozin alone over 180 days of treatment

Agarwal R, et al. *N Engl J Med*. 2025;393(6):533-543.

58

Utilization of Therapies for Cardio-Renal-Metabolic Diseases

There is low utilization of therapies that reduce CKD and CV risk[1]

Agent(s)	Implementation Rate
ACE inhibitors/ARBs	25-40%[2,3]
SGLT-2 inhibitors	13%[4]
Nonsteroidal MRA	Not yet known

Access to care and implementation of evidence-based therapies can save millions of lives by mitigating kidney failure, CV events, and premature death[5]

1. Tuttle KR, et al. *Clin J Am Soc Nephrol*. 2022;17:1082-1103. 2. Tuttle KR, et al. *JAMA Netw Open*. 2019;2:e1918169. 3 Murphy DP, et al. *J Am Soc Nephrol*. 2021;32(11):2761-2769. 4. Patel MJ, et al. *Diabetol Metab Syndr*. 2018;10:62. 5. Bilinski NA, et al. *PharmacoEcon Open*. 2022;6(3):413-431.

59

Overcoming Barriers to Use of Evidence-Based Therapies

Barriers in Primary Care	Potential Solutions
Lack of clinician awareness and knowledge of cardiometabolic conditions	• Concise and consistent practice guidelines • Actionable and patient-centered recommendations • Automated decision support tools integrated into electronic health records • Improved team-based care
Complex patient characteristics	
Lack of clinician time and resources	
Inadequate collaboration with and access to specialists	
Lack of clear parameters for specialist referral and difficult referral processes	

Nee R, et al. *Nephrol Dial Transplant*. 2023;38(3):532-541.

60

Patient Case #2 (continued 2 years later)

42-year-old man with a T2D, hyperthyroidism, CKD, and sudden weight gain

- Blood pressure 150/92 mmHg
- LVEF 45%
- LVH, grade 1 diastolic dysfunction
- NT-proBNP 2,789 pg/mL
- eGFR 52 mL/min/1.73 m^2
- UACR 110 mg/g
- A1C 7.5%
- Normal complete blood count, electrolytes, and TSH; antibody testing negative for type 1 diabetes
- BMI 35.5 kg/m^2

Current Relevant Medications
Metformin 1,000 mg twice daily
Insulin glargine 25 units daily
Levothyroxine 50 mcg daily
Valsartan 320 mg daily

How should this patient's conditions be managed? How can treatment be optimized to reduce CV risk?

61

Multidisciplinary Care for CRM Diseases

62

Need for Multidisciplinary Care

- Multidisciplinary approach for CRM diseases is recommended[1]
- Patients often have access to specialized care only at a late stage in the disease trajectory[2]
- PCCs are uniquely positioned to facilitate multidisciplinary management of cardio-renal metabolic diseases[2]

1. Rangaswami J, et al. *Circulation*. 2020;142(17):e265-e268. 2. Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412.

63

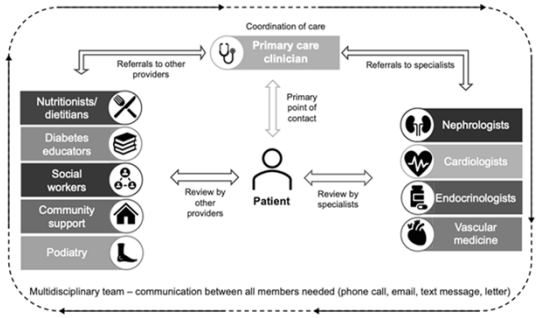
PCC Coordination of Multidisciplinary Care

- Ensure T2D, CVD/HF, and CKD are not treated as separate problems
- Expertise of each specialty should be maximized
- Refer patients in a timely manner when appropriate
- Team includes:
  - Nephrologists
  - Cardiologists
  - Endocrinologists
  - Diabetes educators
  - Social workers
  - Community support
- Establish a clear chain of communication between PCCs and specialists
- Changes to monitoring or treatment plan should be made clear to the multidisciplinary team

Kushner PR, et al. Clin Diabetes. 2022;40(4):401-412.

64

Multidisciplinary care for patients with cardio-renal-metabolic disease



Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

65

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67