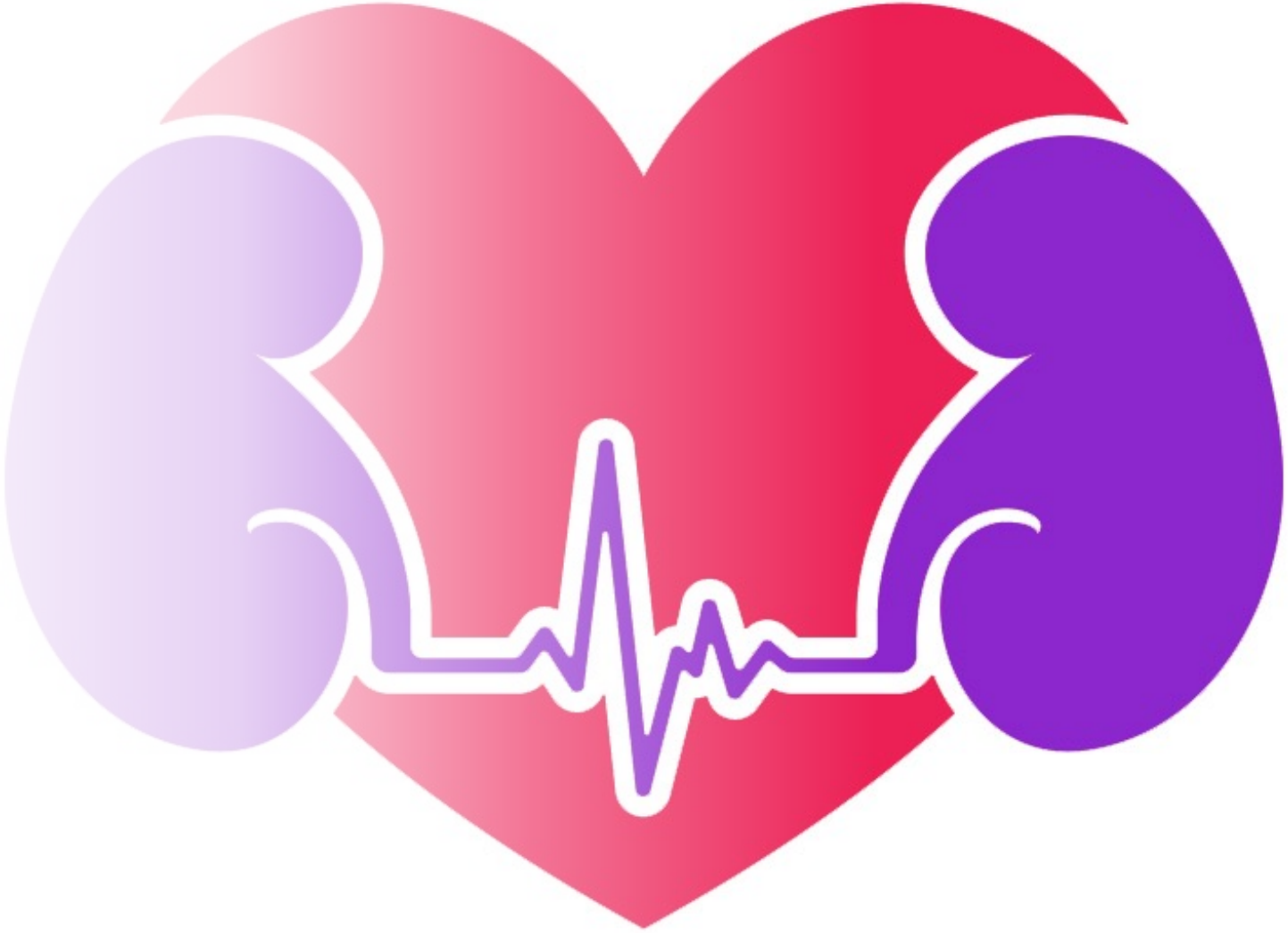
PRE-PRESENTATION Survey

Advances in the Treatment of Cardio-Renal-Metabolic Disorders

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/crm8

Advances in the Treatment of Cardio-Renal-Metabolic Disorders



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Executive Director

Primary Care Metabolic Group

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Disclosures

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

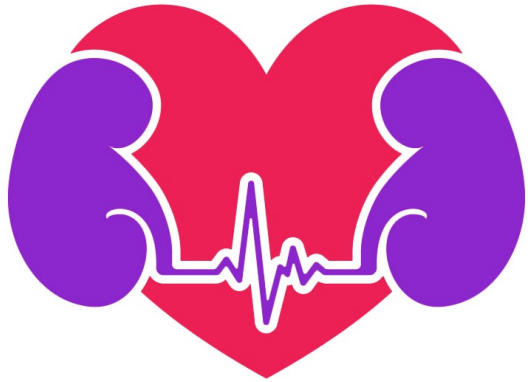
Austin Ulrich, PharmD, medical writer, and **Michael Hanak**, MD, CME Reviewer, have no disclosures to report.

- All relevant financial relationships have been mitigated.

Learning Objectives

Participants in this presentation should be able to…
Identify CKD in patients with reduced kidney function, including in early stages of disease.
Describe the link between DM and CVD, including the impact on health outcomes.
Select appropriate treatment for patients with DM, CVD, and/or CKD/DKD based practice guidelines and clinical evidence.
Recognize the importance of multidisciplinary care when managing patients with cardio-renal-metabolic conditions.

Association and Burden of T2D, CVD, and CKD



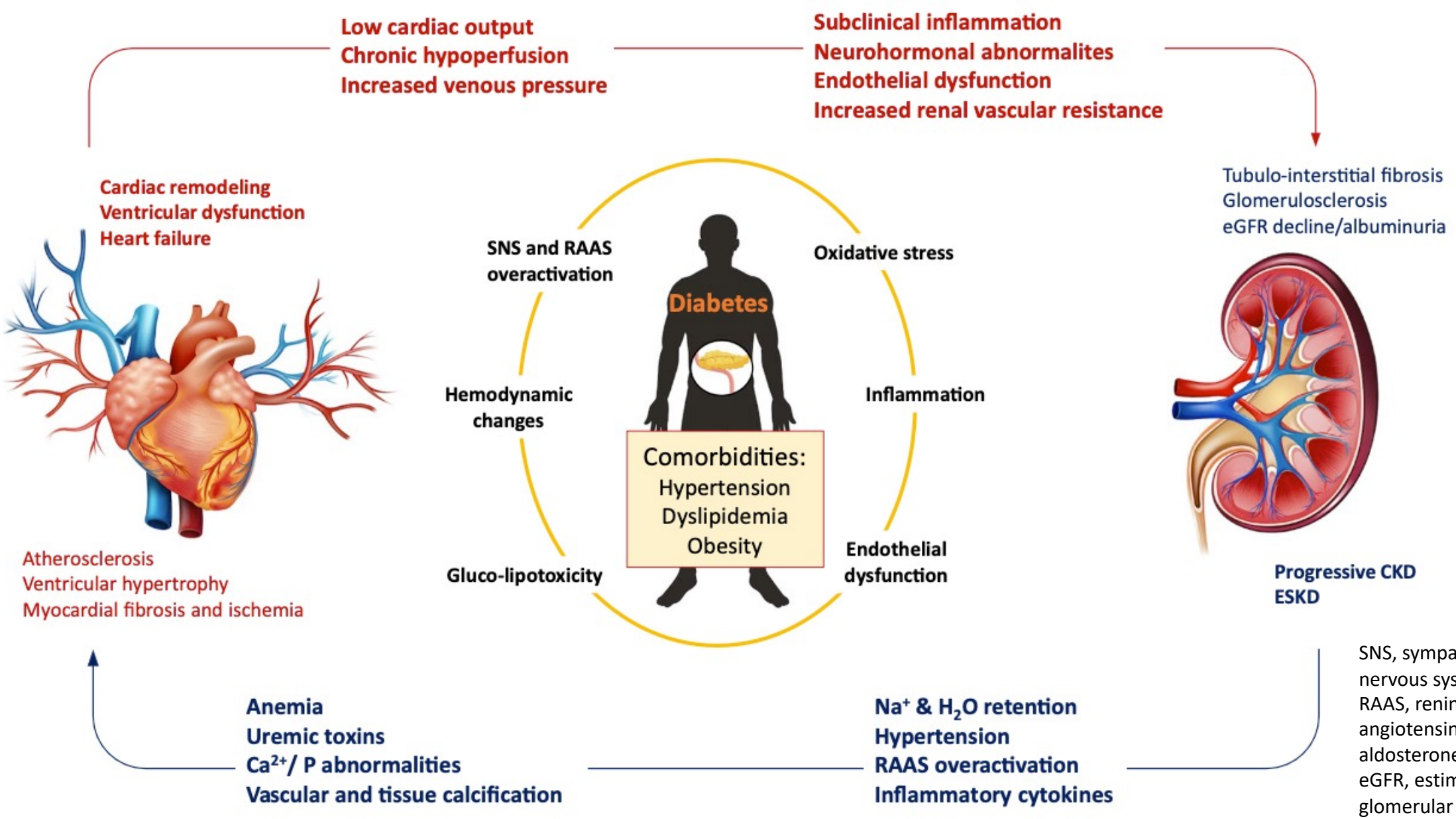
T2D, CVD, and CKD

- Among the most disruptive public health issues of the century
- Strong interconnection between the three diseases
- Coexistence of all three referred to as **”cardio-renal-metabolic”** diseases

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

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

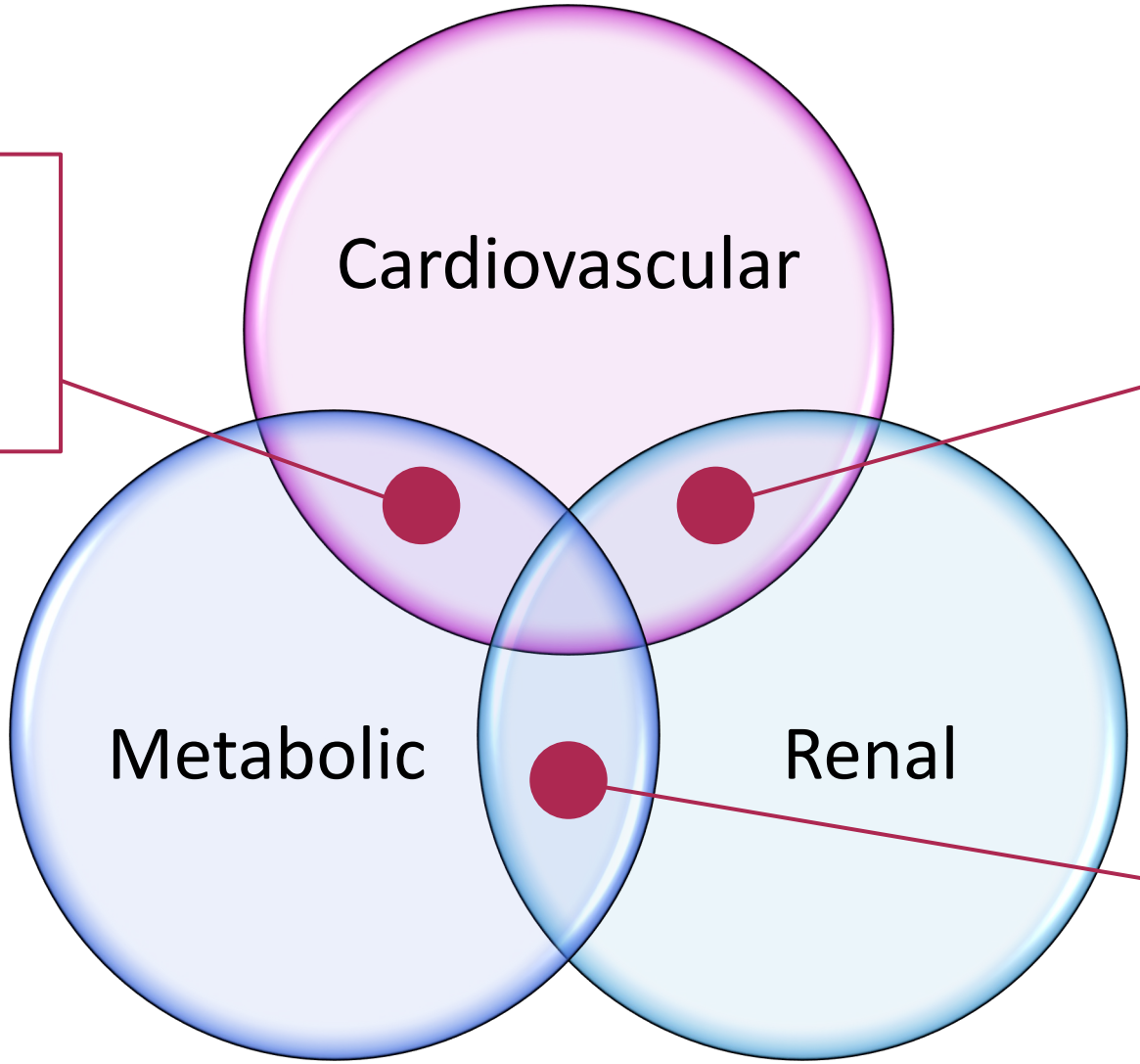
Pathophysiology



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

Coexistence of Cardio-Renal-Metabolic Systems

At least 50% of patients with T2D have or are at high risk of developing CV disease[1]

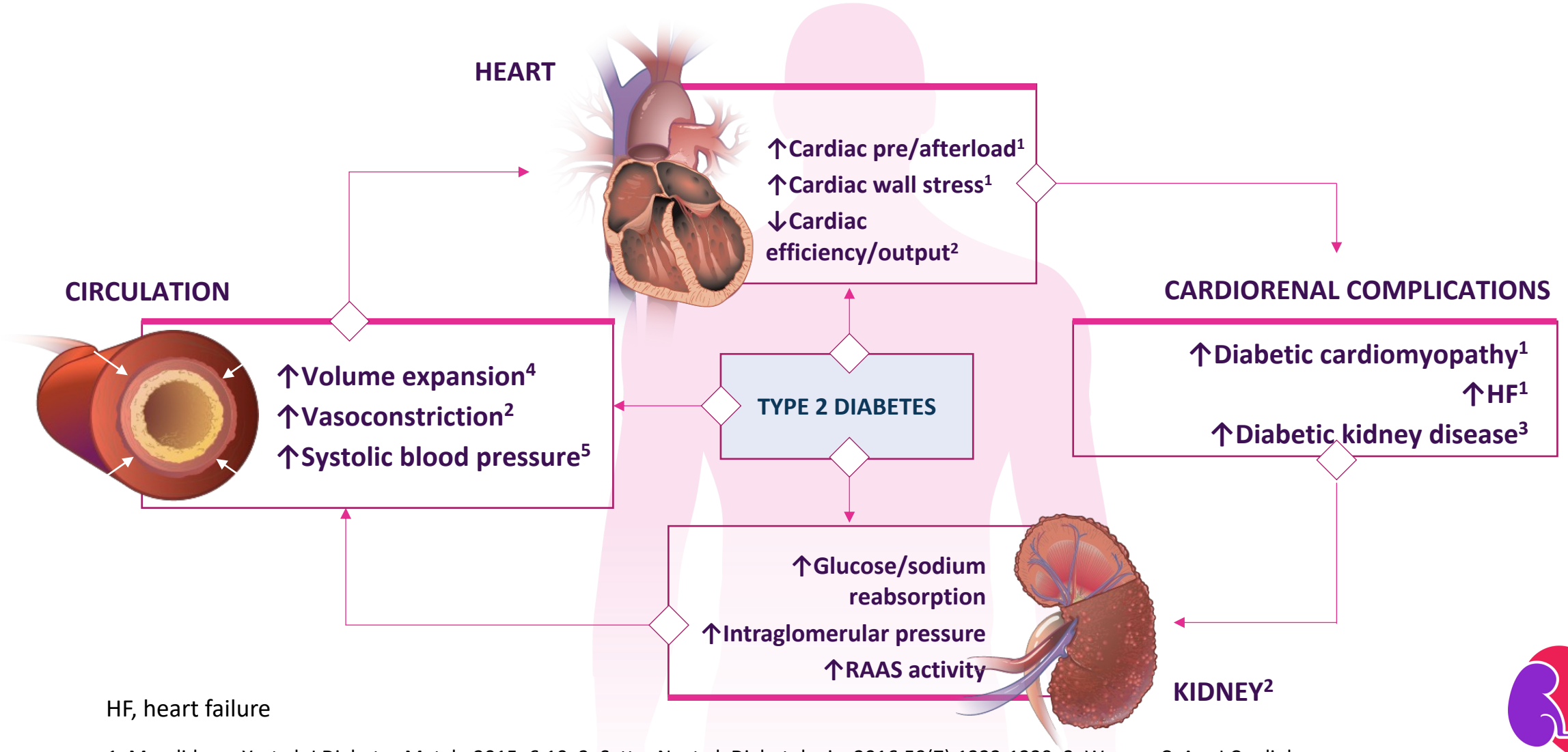


T2D and hypertension are the leading causes of >75% of ESKD cases in the US[3]

CKD affects up to 40% of patients with T2D[2]

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

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



HF, heart failure

1. Muralidaran Y, et al. J Diabetes Metab. 2015, 6:10. 2. Sattar N, et al. Diabetologia. 2016;59(7):1333-1339. 3. Wanner C, Am J Cardiol. 2017;120(1S):S59-S67. 4. Sattar N, et al. Circulation. 2018;138:7–9. 5. Mazidi M, et al. J Am Heart Assoc. 2017;6(6):e004007.

CKD Promotes the Pathogenesis of CVD in Diabetes

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

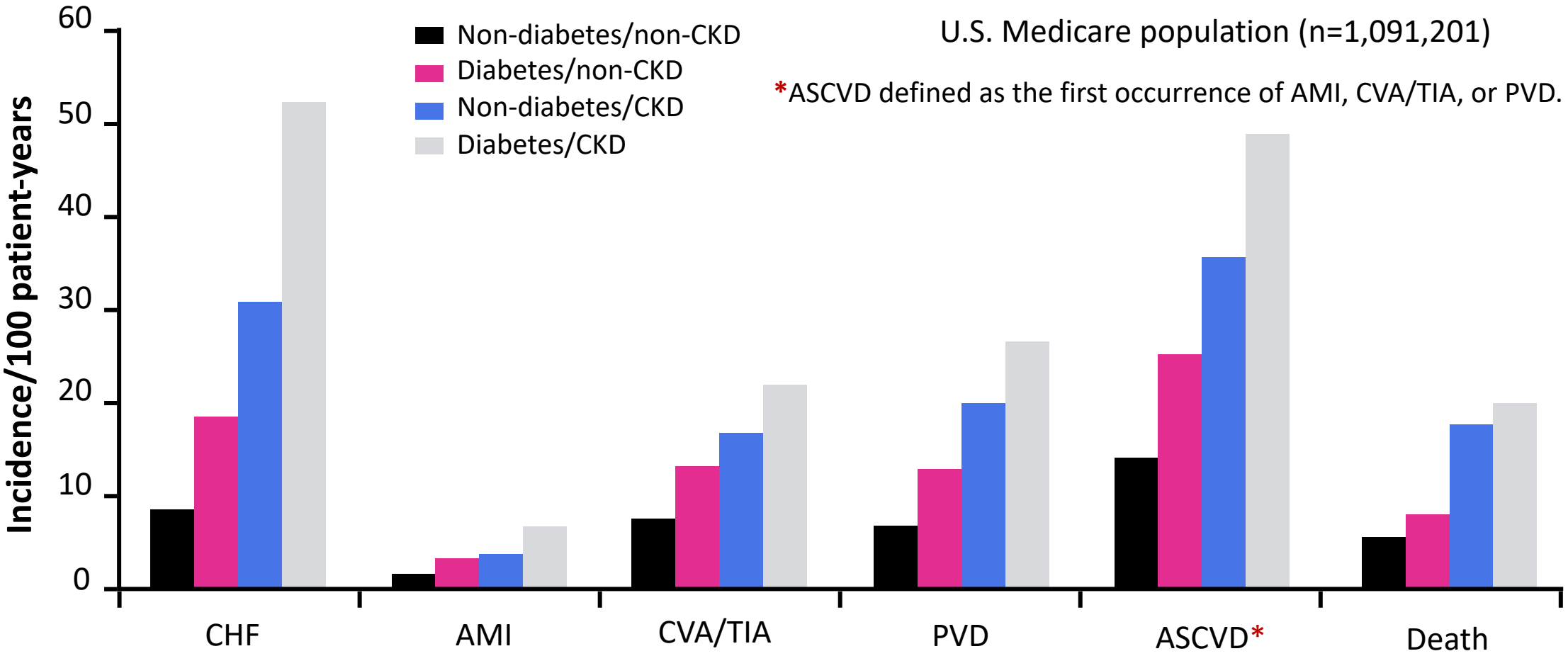
- Endothelial dysfunction
- Inflammation and oxidative stress
- Hyper-coagulability
- Dyslipidemia
- Hypertension
- Myocardial infarction
- Stroke
- Congestive heart failure
- Peripheral vascular disease

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.

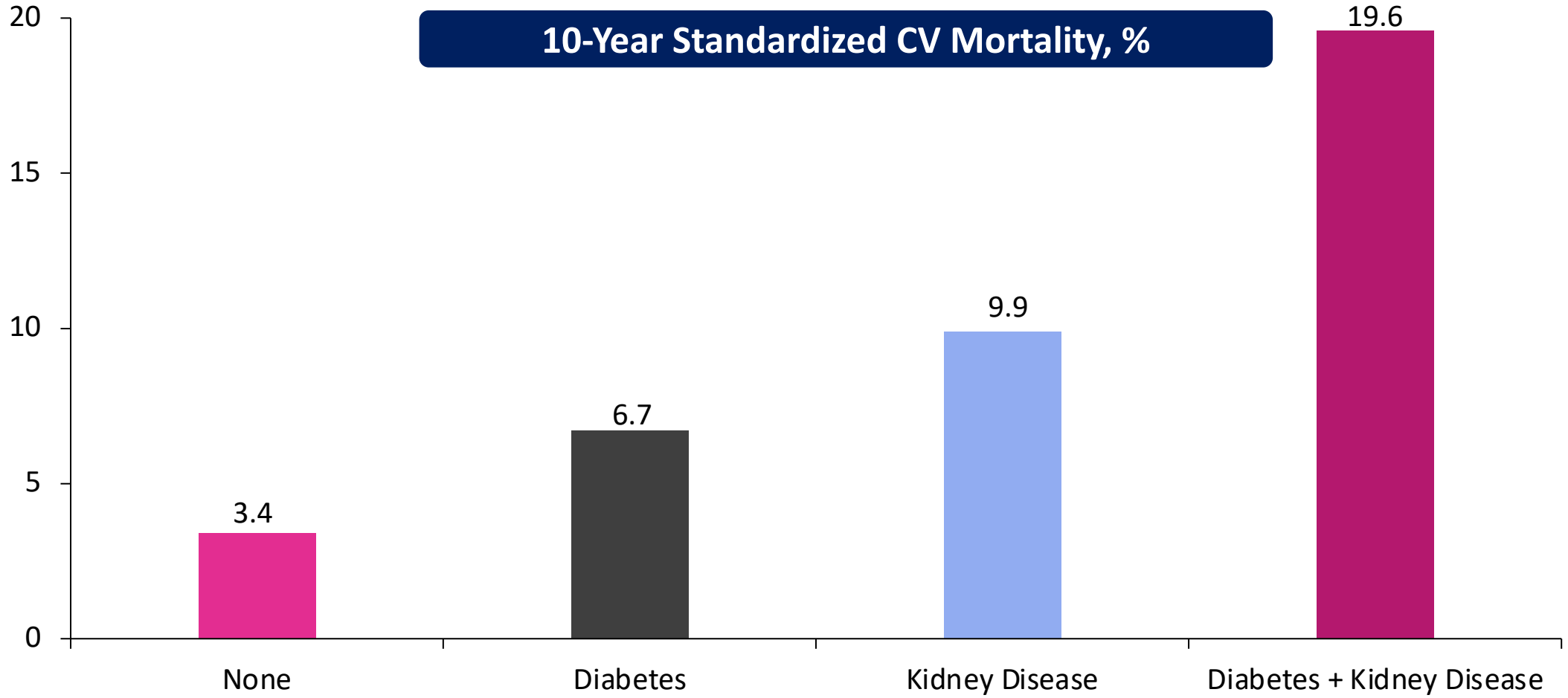
CV Event Risk in Diabetes is Amplified by CKD



CHF, heart failure; AMI, acute myocardial infarction; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; ASCVD, atherosclerotic cardiovascular disease

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

CV Mortality in T2D is Magnified by CKD



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

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”
- 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

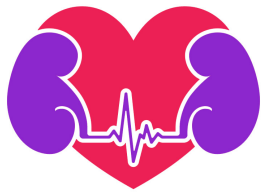
Ronco C, et al. *J Am Coll Cardiol*. 2008;52(19):1527-1539; Rangaswami J, et al. *Circulation*. 2019;139(16):e840-e878.

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.



PCP Often the First Source for Care

- More than 60% of patients with CKD seen in primary care
- Early screening and diagnosis leads to optimized kidney and CV care
- CKD is underdiagnosed, and many clinicians are not routinely screening patients with diabetes or hypertension for elevated UACR
- PCPs coordinate care to ensure coordinated, multidisciplinary management of cardio-renal-metabolic diseases

UACR, urine albumin-to-creatinine ratio

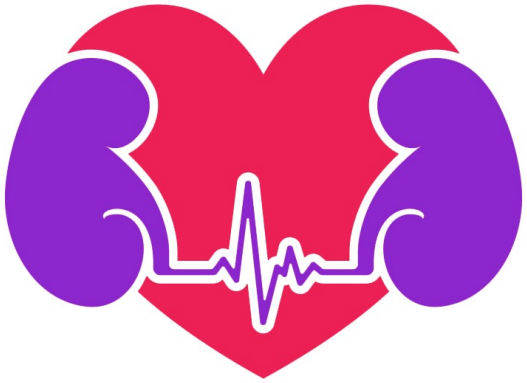
Kushner PR, et al. *Clin Diabetes*. 2022; 40(4):401-412; Alfego D, et al. *Diabetes Care*. 2021;44:2025-2032; Shin J, et al. *Hypertension*. 2021;78:1042-1052.

Role of the PCP

- 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

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

Screening and Diagnosis of CKD



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 DKD, UACR and eGFR should be monitored 1-4 times per year depending on the stage of disease.

ElSayed NA, et al. *Diabetes Care*. 2023;46(Suppl_1)S191-S202; ElSayed NA, et al. *Diabetes Care*. 2023;46(Suppl_1):S230-S253.

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

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

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

The new race-neutral eGFR Calculator

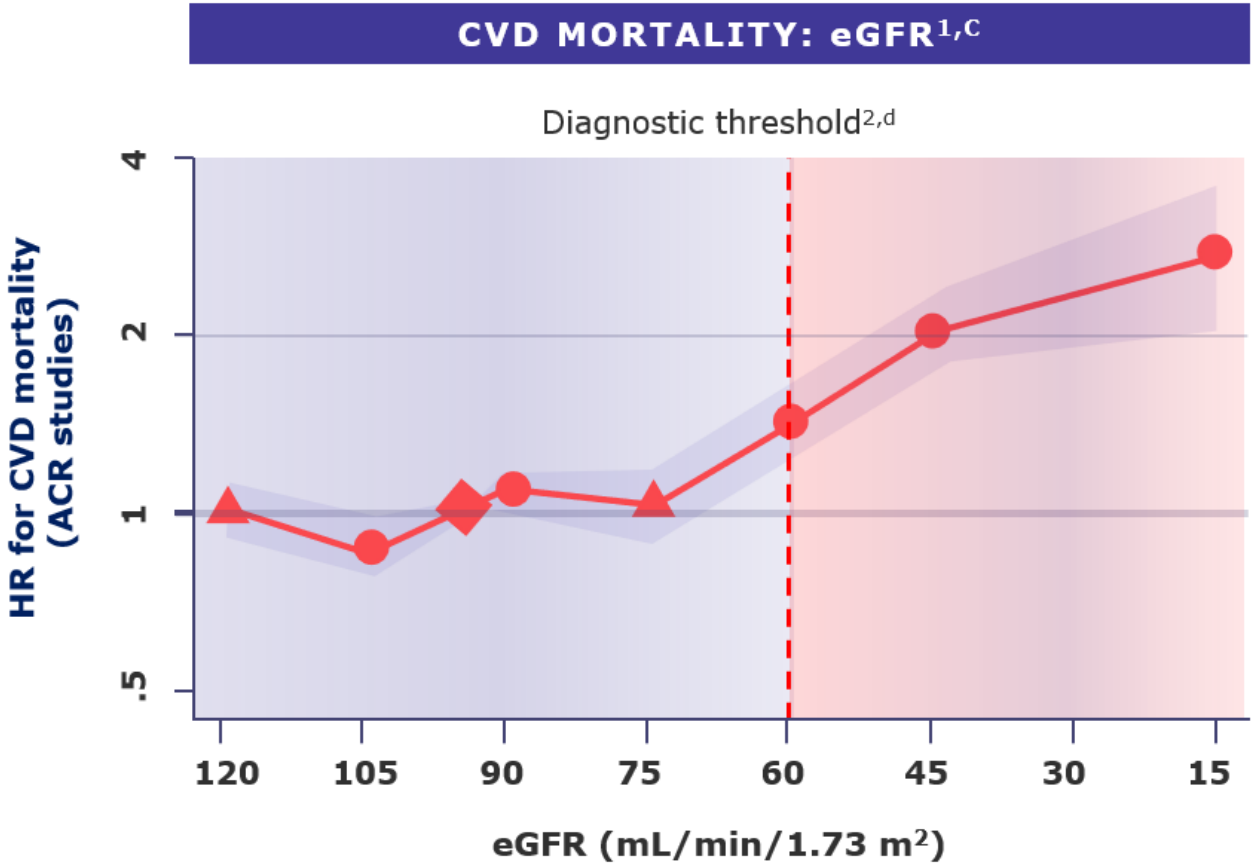
- February 28, 2022: All LabCorp moves to new calculator
    - Approx 51 million tests
- April 1, 2022: All VA labs move to new calculator
    - Largest integrated health system in the US
- July 11, 2022: All Quest labs move to new calculator
    - Approx 60 million tests
- July 2022: All transplant 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**

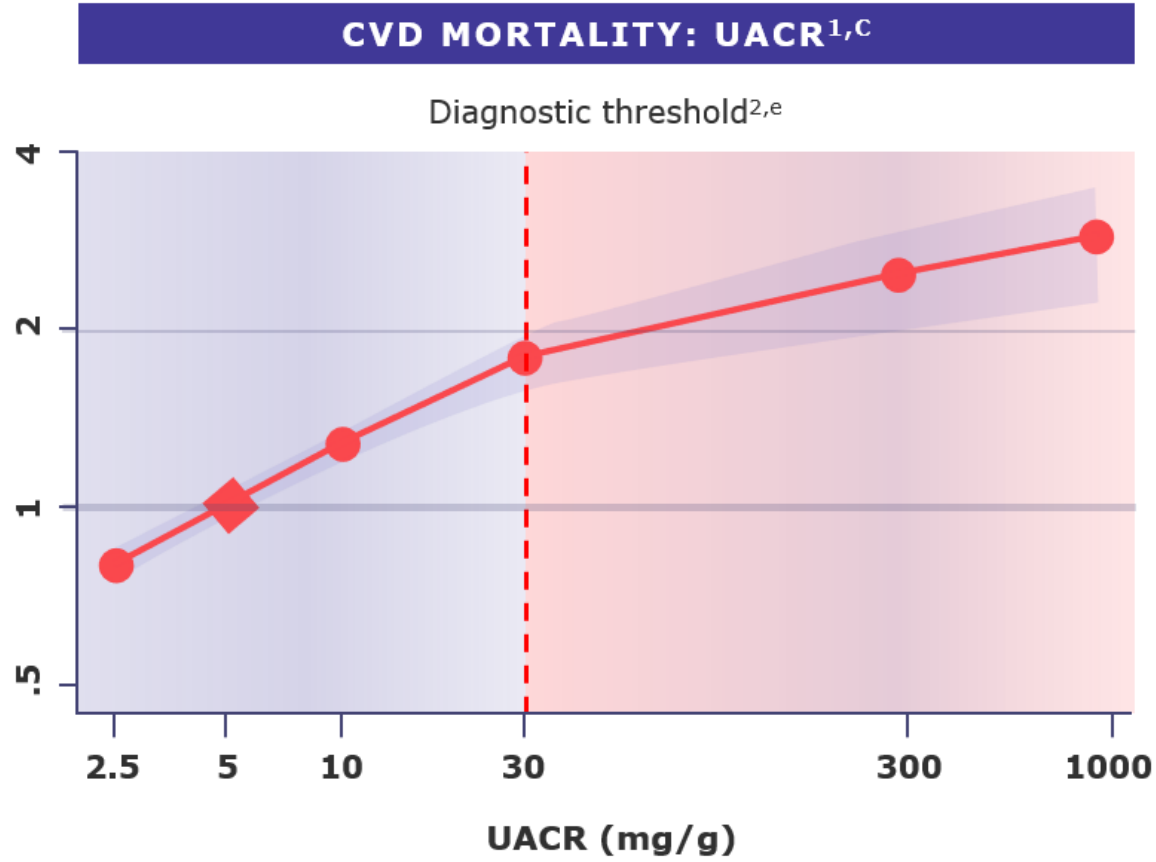
eGFR Test Change: Removal of Race from the Calculation | American Kidney Fund. www.kidneyfund.org. Published November 23, 2021. Accessed September 10, 2023. https://www.kidneyfund.org/all-about-kidneys/tests/egfr/egfr-test-change-removal-race-calculation#:~:text=Most%20US-based%20clinical%20lab%20companies%2C%20doctor%27s%20offices%2C%20and

Why both UACR and eGFR?

Both eGFR and UACR independently predict CVD mortality

CVD mortality increases with severity of renal impairment





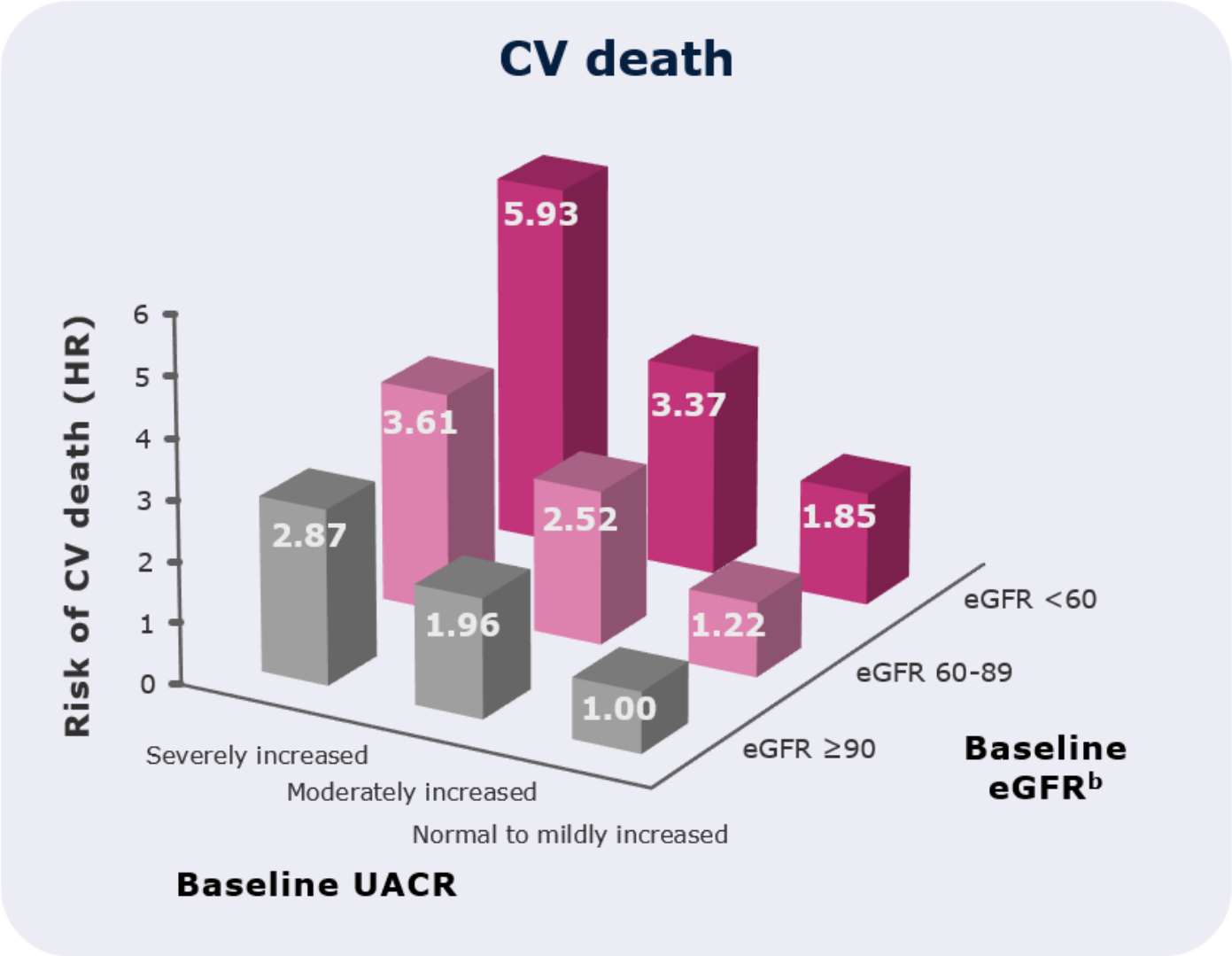
[a]Low eGFR was defined as eGFR <60 mL/min/1.73 m^2. [b]High albuminuria was defined as ACR ≥10 mg/g. [c]Reference points, represented by diamond shapes in graphs, were eGFR of 95 mL/min/1.73 m^2 and ACR of 5 mg/g. Circles represent statistically significant and triangles represent nonsignficiant values. [d]KDIGO guidelines recommend eGFR <60 mL/min/1.73 m^2 be reported as decreased and use this threshold as criteria for CKD diagnosis.[2] [e]KDIGO guidelines recommend albuminuria (ACR ≥30 mg/g) as a marker of kidney damage and criteria for CKD diagnosis.

CVD, cardiovascular disease

1. Matsushita K, et al. *Lancet*. 2010;375(9731):2073-2081. 2. KDIGO. *Kidney Int Suppl*. 2018;3:5-14. Figure reprinted from The Lancet, Vol 375, Matsushita et al, Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis, 2073-2081, Copyright 2010, with permission from Elsevier.

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 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

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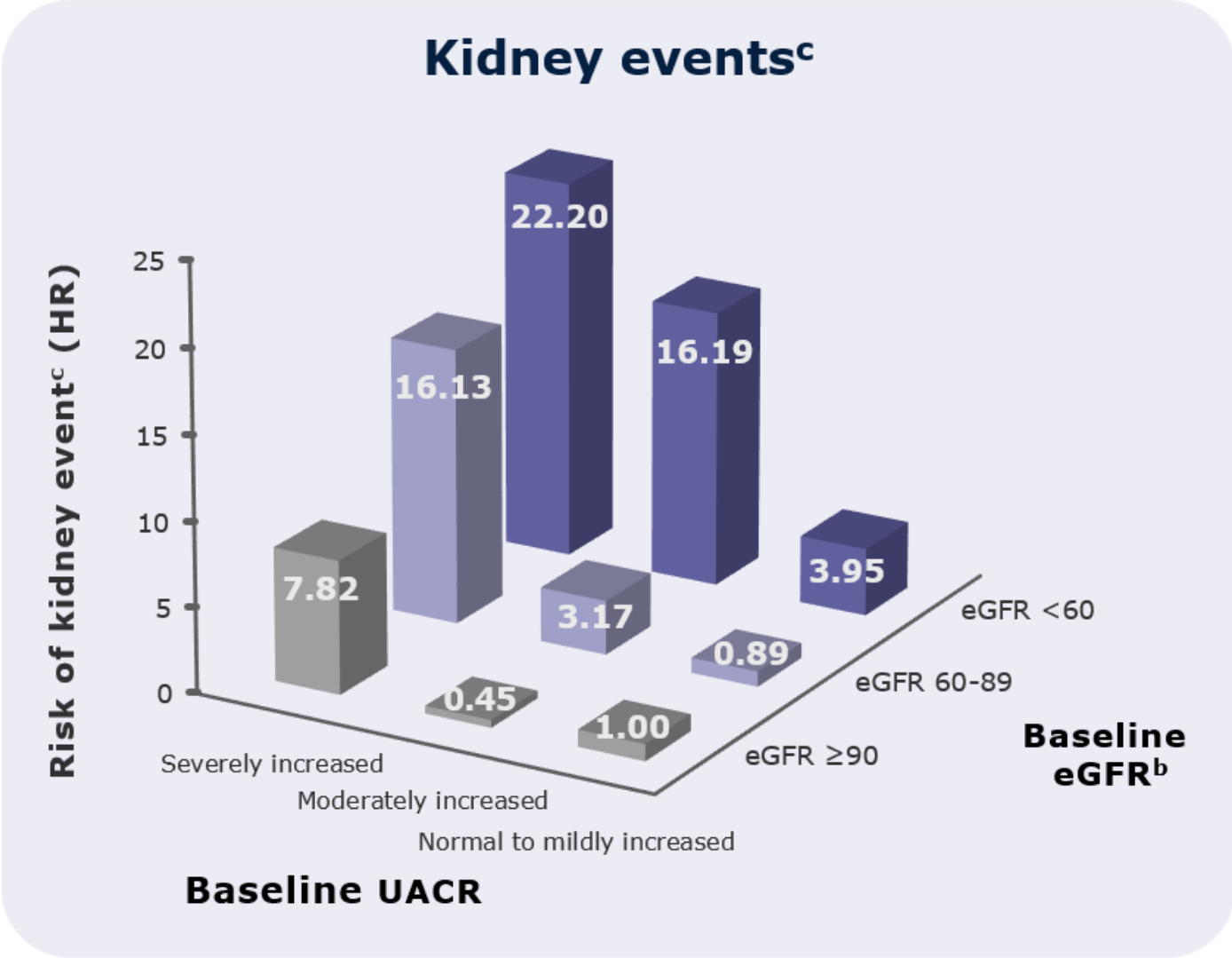


[a]Average time to follow-up for risk assessment was 4.3 years. [b]eGFR in mL/min/1.73 m^2. [c]A kidney event is defined as death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine to >2.26 mg/dL.

Ninomiya T, et al. *J Am Soc Nephrol*. 2009;20(8):1813-1821. Figure reprinted 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

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

A. Checking eGFR and UACR is recommended since both independently predict CVD mortality

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. Cystatin C and creatinine testing are preferred for initial CKD screening

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)**

GFR categories (mL/min/1.73 m²) Description and range			Albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
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

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

Patient Case: Patient History

59-year-old African American man presenting for a primary care visit

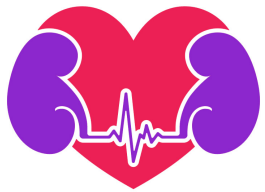
- Complaining of recent breathlessness and fatigue
- History of T2D
- BMI 31.2 kg/m^2
- Hypertension (blood pressure today 156/80 mmHg)

Current Relevant Medications
Lisinopril 20 mg daily
Hydrochlorothiazide 25 mg daily
Metformin 1,000 mg twice daily
Glipizide 10 mg twice daily

What are the opportunities for screening and diagnosis?

BMI, body mass index

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



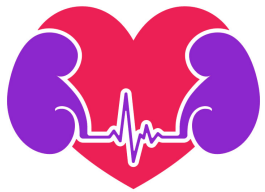
Patient Case: Patient History (cont)

59-year-old African American man presenting for a primary care visit

- Complaining of recent breathlessness and fatigue
- History of T2D
- BMI 31.2 kg/m^2
- Hypertension (blood pressure today 156/80 mmHg)

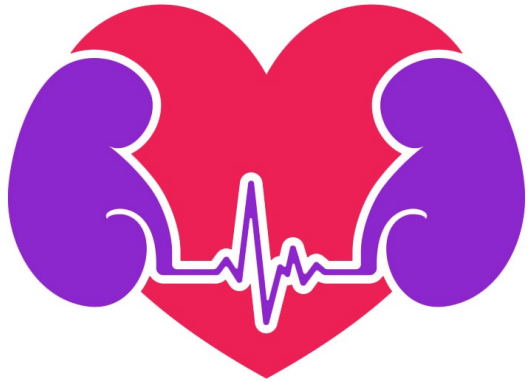
Current Relevant Medications
Lisinopril 20 mg daily
Hydrochlorothiazide 25 mg daily
Metformin 1,000 mg twice daily
Glipizide 10 mg twice daily

What are the opportunities for optimizing the treatment regimen?



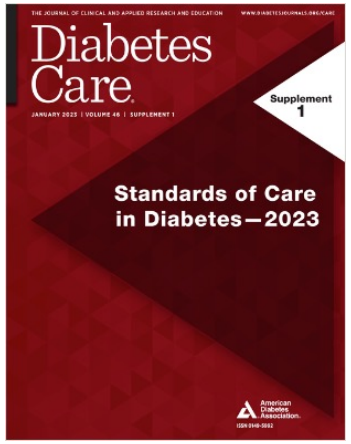
Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412.

Guideline-Directed Management of Cardio-Renal-Metabolic Diseases

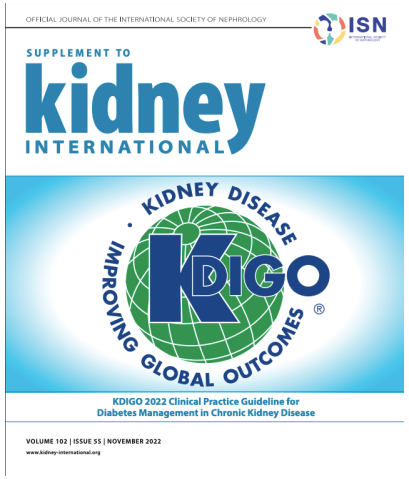


ADA, KDIGO, and AHA Recommendations

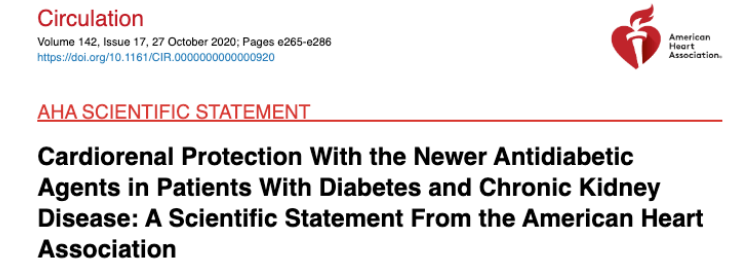
Early screening, diagnosis, and comprehensive, coordinated care optimize outcomes in T2D, CVD, and CKD



2023 ADA Standards of Care in Diabetes



2022 Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for Diabetes and CKD Management

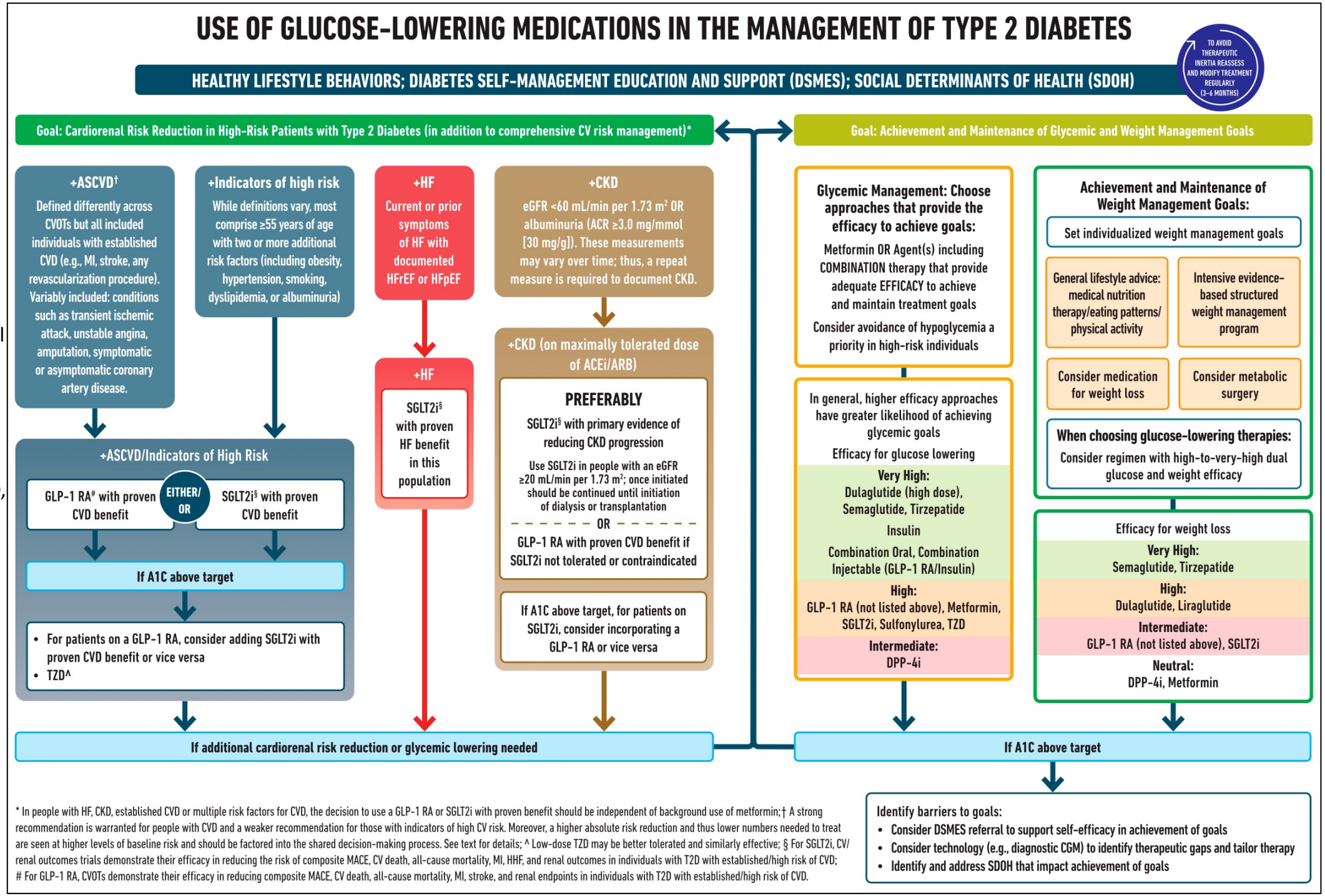


2020 American Heart Association (AHA) Scientific Statement

ElSayed NA, et al. *Diabetes Care*. 2022;46(Suppl_1):S1-S291; KDIGO Diabetes Work Group. *Kidney Int*. 2022;102(5S):S1-S127; Rangaswami J, et al. *Circulation*. 2020;142:e265-e286.

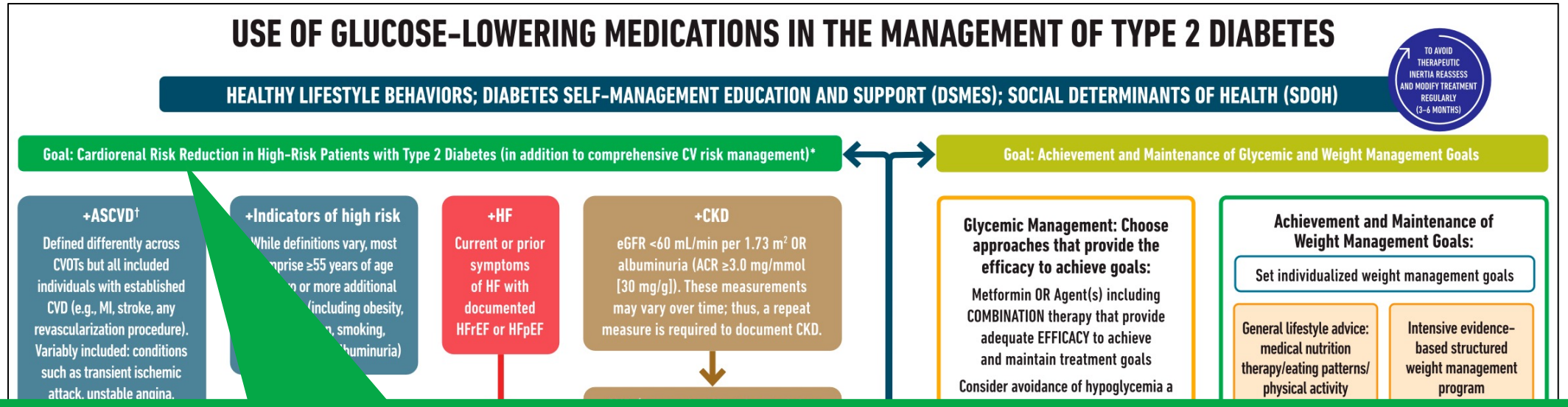
ADA 2023 Pharmacologic Therapy Algorithm

CGM, continuous glucose monitoring; DPP-4i, dipeptidyl peptidase 4 inhibitor; HHF, hospitalization for heart failure; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, thiazolidinedione



American Diabetes Association. *Diabetes Care.* 2023;46(Suppl_1):S140-S157. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2023.

Use of Glucose-Lowering Medications in the Management of T2D



Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

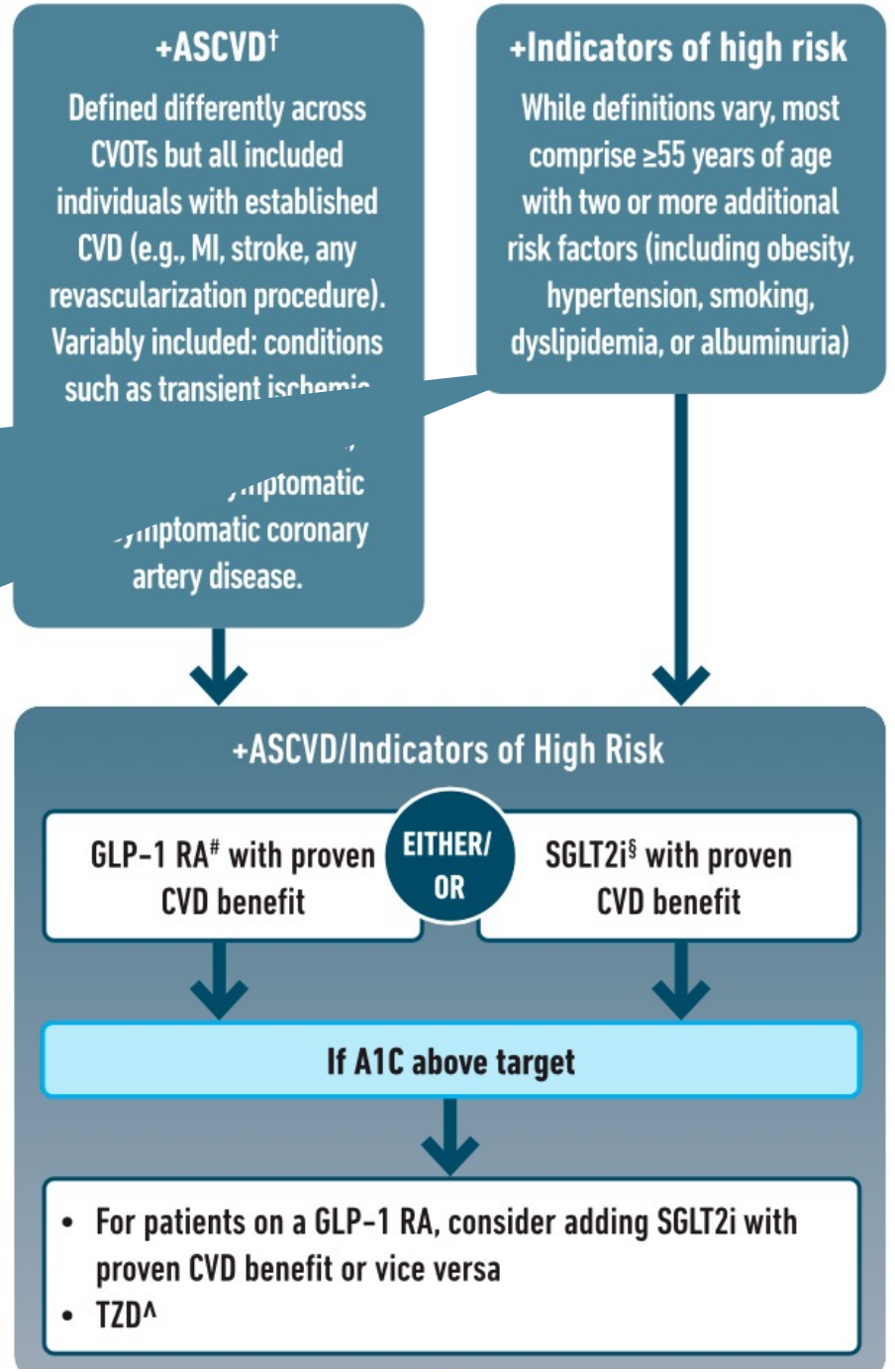
*In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin

American Diabetes Association. *Diabetes Care*. 2023;46(Suppl_1):S140-S157. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2023.

High-risk or established ASCVD

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic asymptomatic coronary artery disease.

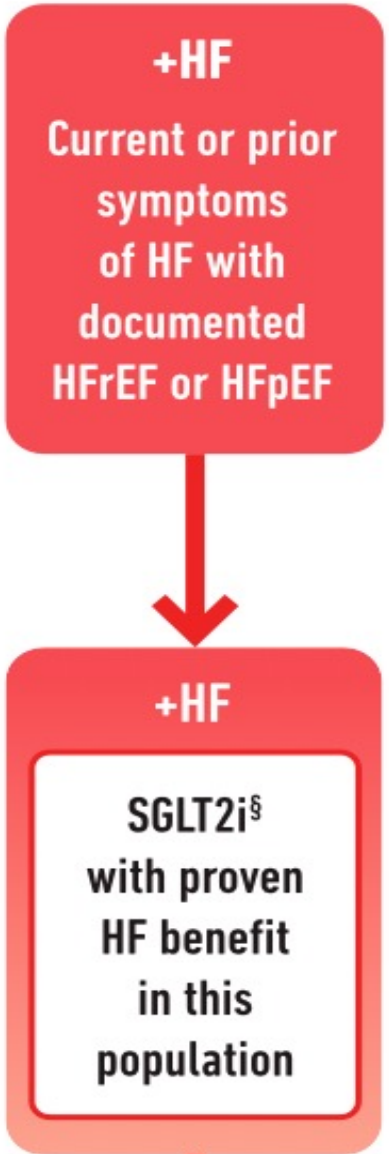
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

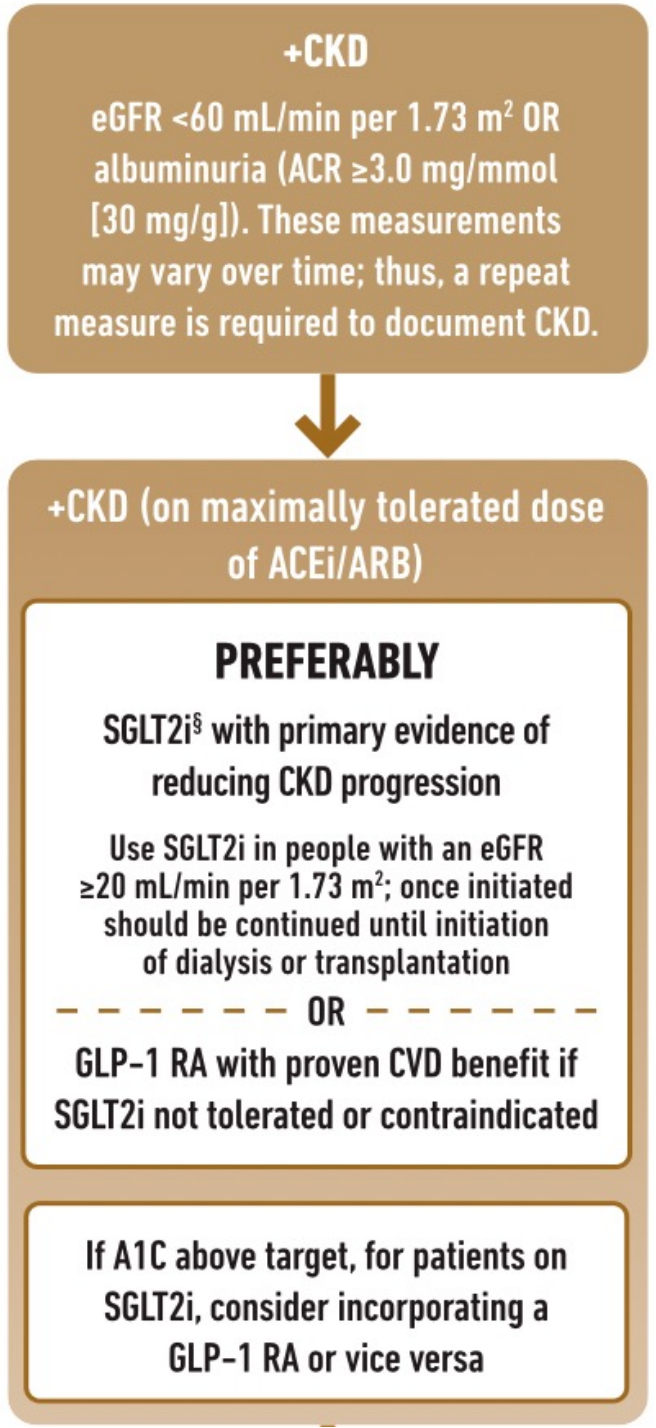


†A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk; ^Low-dose TZD may be better tolerated and similarly effective.

CVOTs, cardiovascular outcomes trials

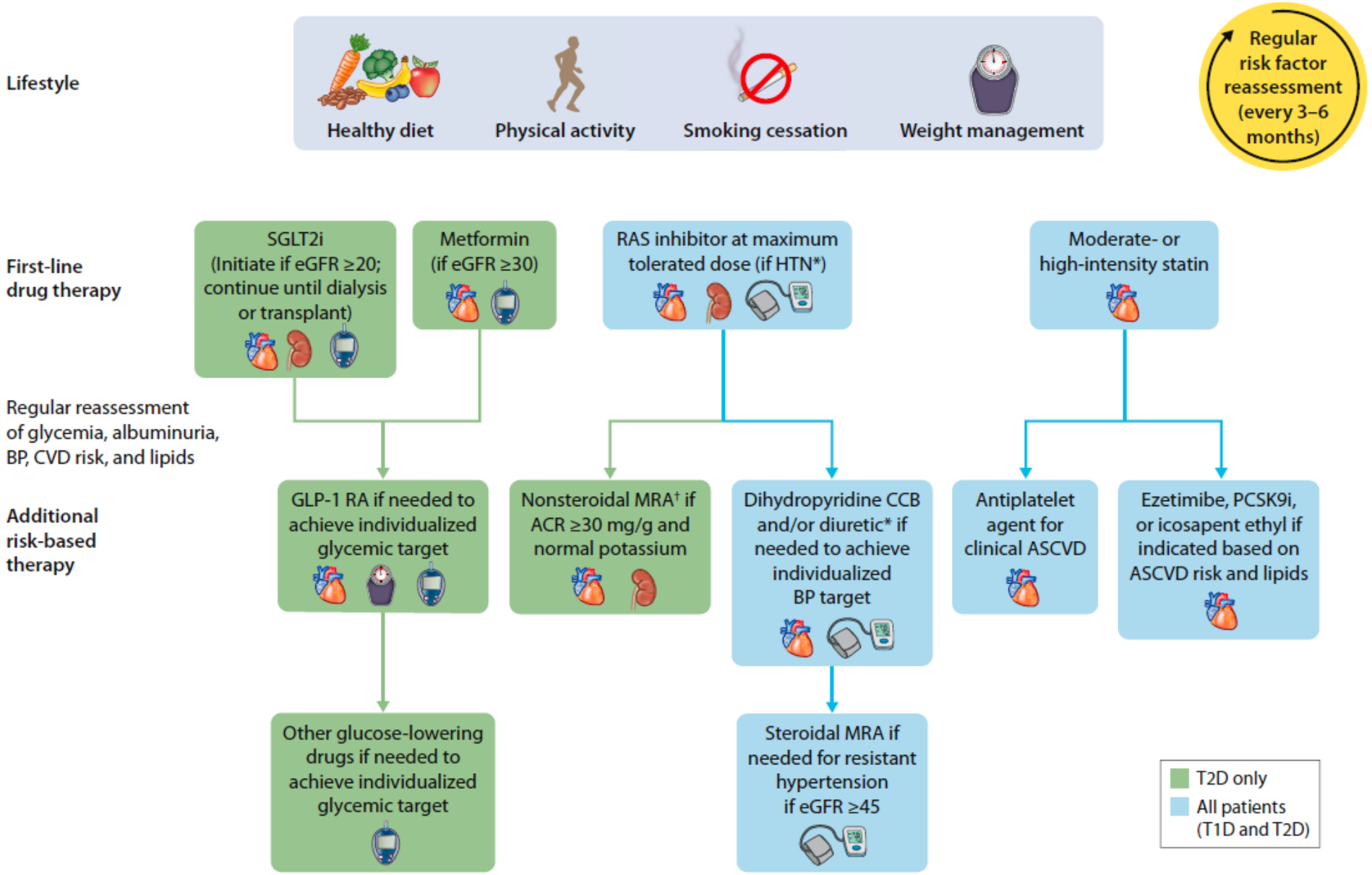
HF or CKD





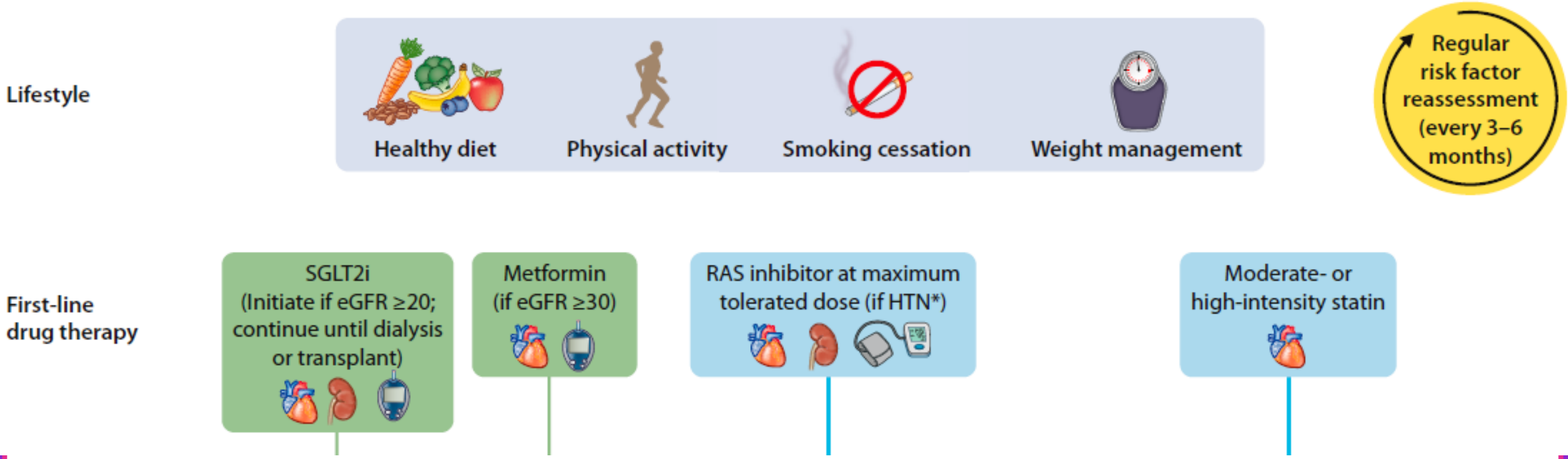
Approach for Improving Outcomes in Diabetes and CKD

(ADA and KDIGO)

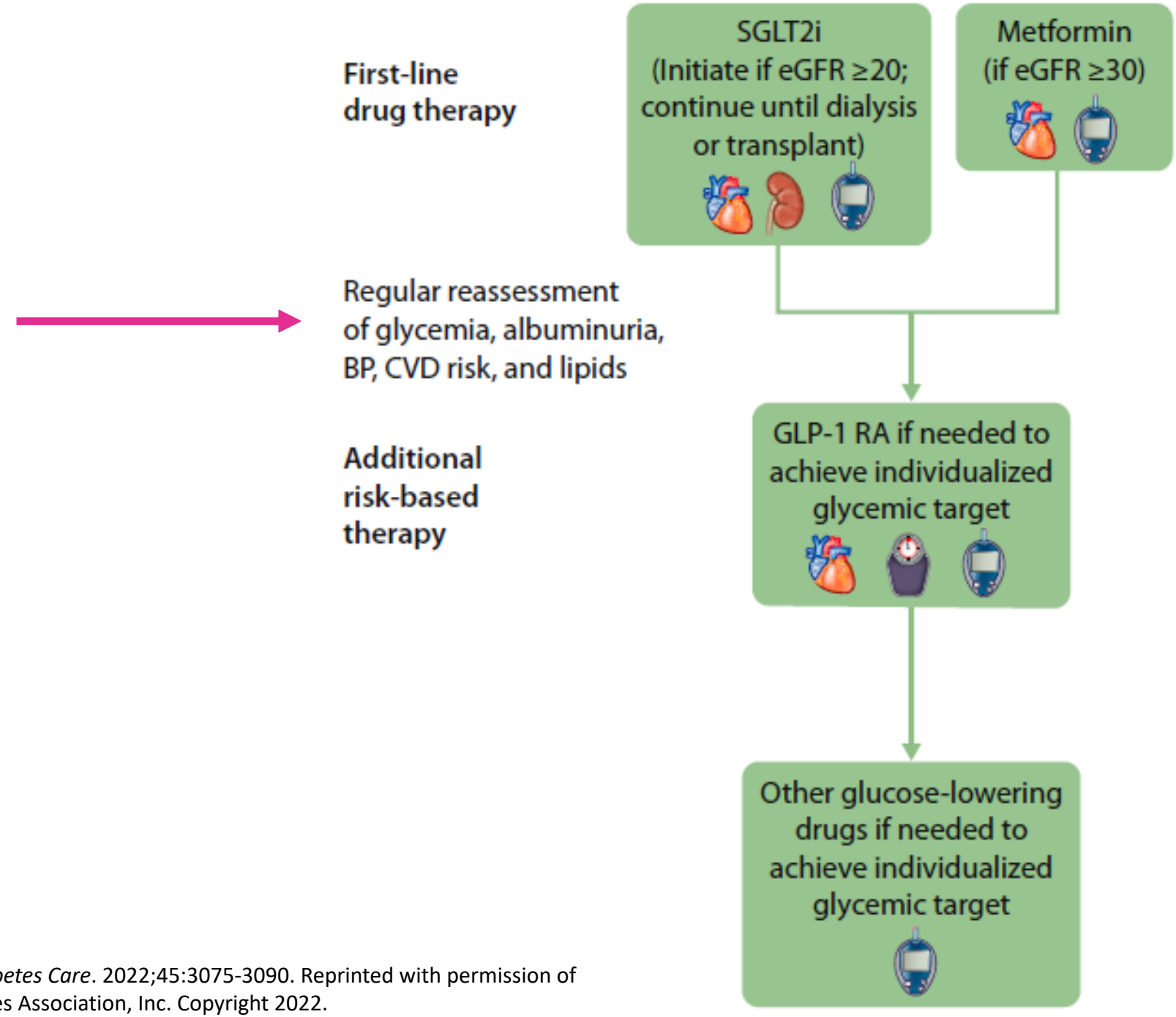


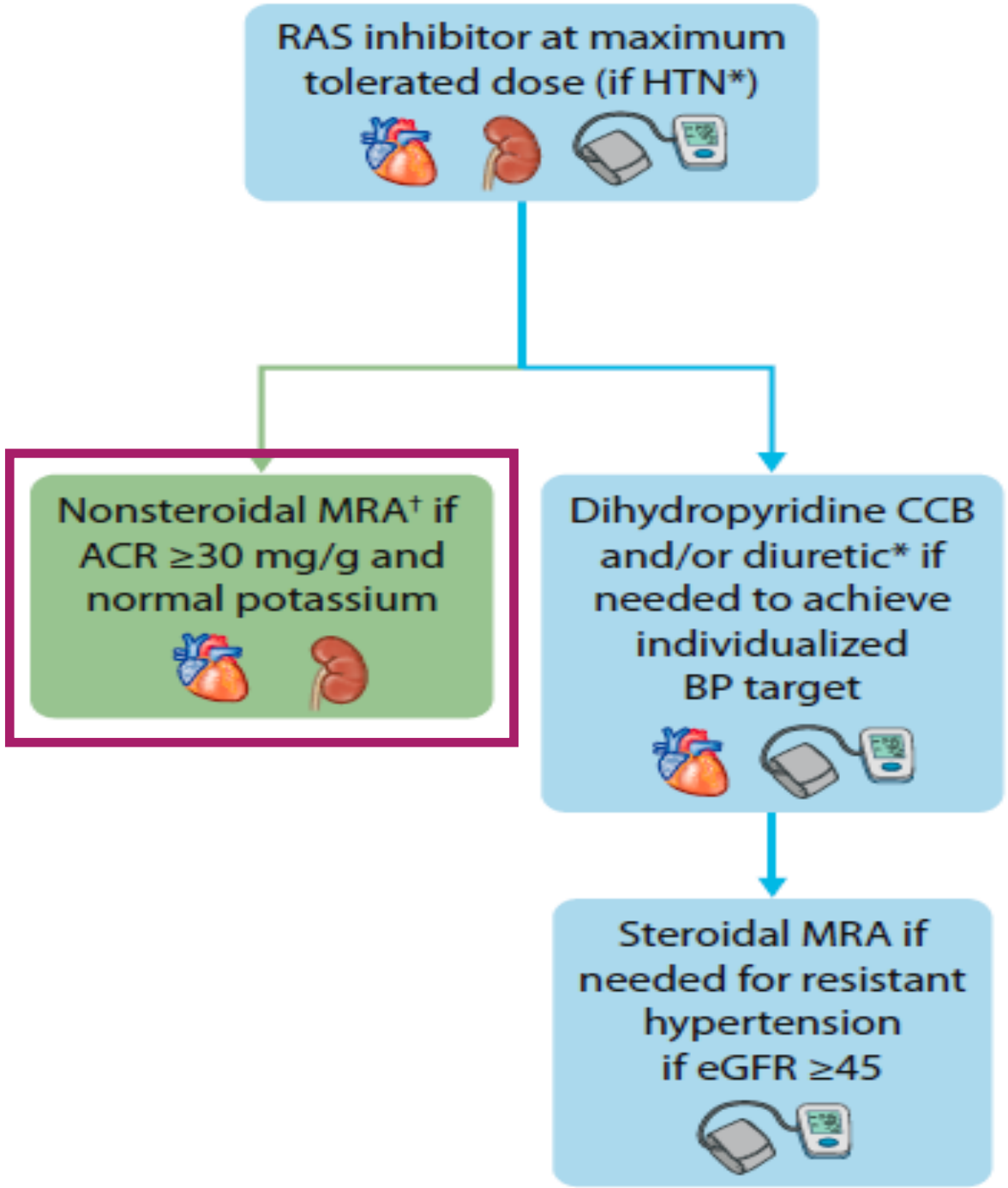
de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

Approach for Improving Outcomes in Diabetes and CKD

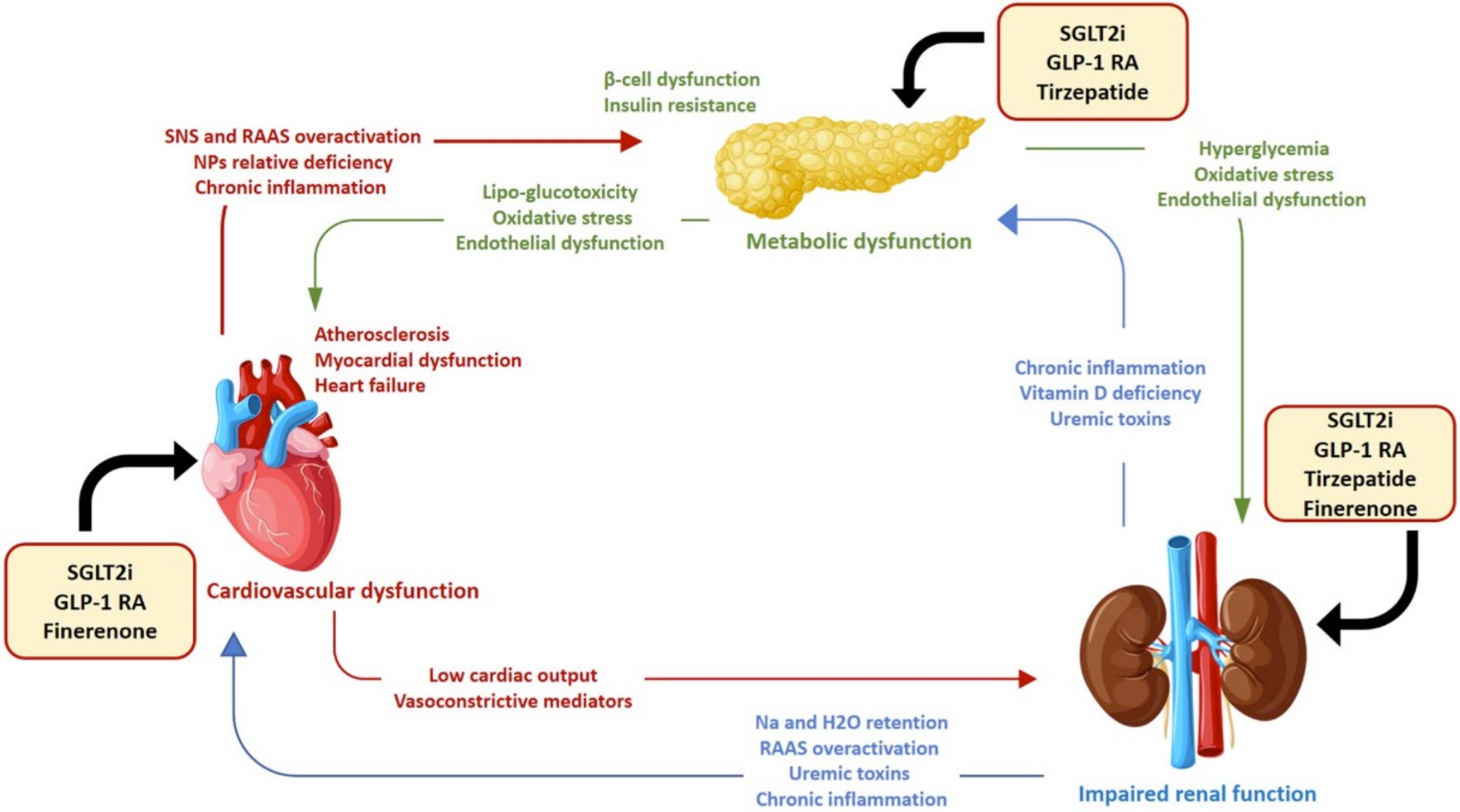


de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.





Selected Agents for Cardio-Renal-Metabolic Diseases and Their Physiologic Targets



SGLT-2 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)**

SGLT-2, sodium-glucose cotransporter 2

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.

SGLT-2 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.

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SGLT-2 Inhibitors: Expanded Indications

Medication	Expanded Indications
Bexagliflozin	—
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
Ertugliflozin	—
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

Invokana [Package Insert]. Updated July 2023. Accessed July 31, 2023. Farxiga [Package Insert]. Updated May 2023. Accessed July 31, 2023. Jardiance [Package Insert]. Updated June 2023. Accessed July 31, 2023. Inpefa [Package Insert]. Updated May 2023. Accessed July 31, 2023.

SGLT-2 Inhibitors and AKI Hospitalization

- SGLT-2 inhibitors often withheld during AKI among patients hospitalized with acute HF
- Retrospective study of 3305 patients*
  - **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)
- Retrospective study of 10,036 Veterans with AKI restarted on SGLT2i after hospitalization**
  - Post-AKI SGLT2i use was associated with a **reduced risk for progression of CKD** and recurrent AKI

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

*Aklilu AM, et al. *Kidney360*. 2023. ** Murphy DP, et al. *Kidney 360*, Jan 2024

SGLT-2 Inhibitors and AKI Hospitalization

2024 KDIGO Guidelines released 3/14/24

- If medications (metformin, ACEi/ARB and SGLT2i) are discontinued during an acute illness or fasting, a clear plan to restart must be implemented and documented in the medical record

- **Failure to restart these medications may lead to unintentional harm**

*Aklilu AM, et al. *Kidney360*. 2023. ** Murphy DP, et al. *Kidney 360*, Jan 2024

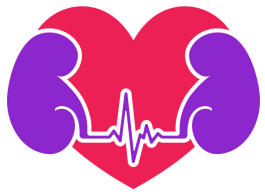
What is the most appropriate action to take for a patient with T2D and CKD who is taking an SGLT-2 inhibitor and is admitted to the hospital for acute heart failure with acute kidney injury?

A. Discontinue the SGLT-2 inhibitor since it likely caused the acute kidney injury

B. Hold the SGLT-2 inhibitor during hospitalization to avoid worsening kidney function

C. Continue the SGLT-2 inhibitor to lower mortality risk without excess risk of worsened kidney function

D. Increase the dose of the SGLT-2 inhibitor to maximize kidney-protective benefit in acute kidney injury



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, sotagliflozin) 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

LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MRAs

Rangaswami J, et al. *Circulation*. 2019;139(16):e840-e878.

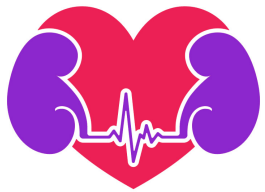
Combined SGLT-2 Inhibitor and MRA Benefit

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



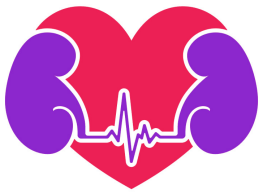
Heerspink HJL, et al. *Diabetes Obes Metab*. 2023. doi:10.1111/dom.15232

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;17:1092-1103. 2. Tuttle KR, et al. *JAMA Netw Open*. 2019;2;e1918169. 3 Murphy DP, et al. *J Am Soc Nephrol*. 2019;30:1314-1321. 4. Tuttle KR, et al. *Lancet Diabetes Endocrinol*. 2018;6:605-617. 5. Burrows NR, et al. *MMWR Morb Mortal Wkly Rep*. 2022;71:412-415.

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.

Patient Case (cont): Now Hospitalized

59-year-old African American man admitted for breathlessness

- Blood pressure 220/105 mmHg
- LVEF 45%
- LVH, grade 1 diastolic dysfunction
- NT-proBNP 2,789 pg/mL
- SCr 1.16 mg/dL (eGFR 60 mL/min/1.73 m^2)
- UACR 80 mg/g
- A1C 7.1%
- Normal complete blood count, electrolytes, and TSH
- Pulmonary edema
- Moderately increased cardiac size

Current Relevant Medications
Intravenous furosemide
Lisinopril 40 mg once daily
(hydrochlorothiazide, metformin, and SGLT-2 inhibitor held on admission)

What are the opportunities for optimizing the treatment regimen?

NT-proBNP, N-terminal pro-B-type natriuretic peptide; A1C, glycated hemoglobin; TSH, thyroid stimulating hormone

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

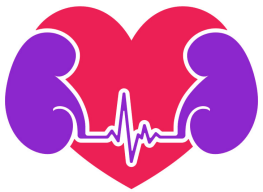
Patient Case (cont): At Discharge

59-year-old African American man now feeling well

- DKD
- Hypertension
- Obesity
- T2D
- HFmrEF
- Blood pressure 110/70 mmHg
- Diuresed 4 L
- 3 kg weight loss

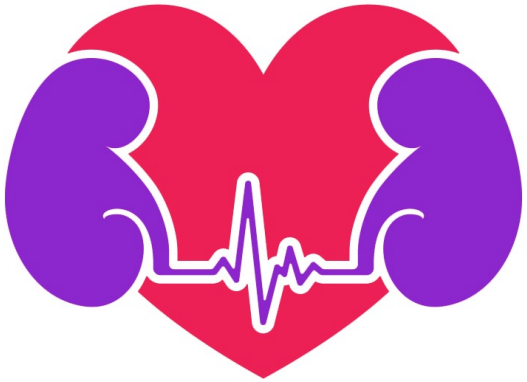
Current Relevant Medications
Furosemide 40 mg once daily
Lisinopril 40 mg once daily
Metformin 500 mg twice daily
Glipizide 10 mg twice daily

What are the opportunities for optimizing the treatment regimen?



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

Multidisciplinary Care for Cardio-Renal-Metabolic Diseases



Need for Multidisciplinary Care

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

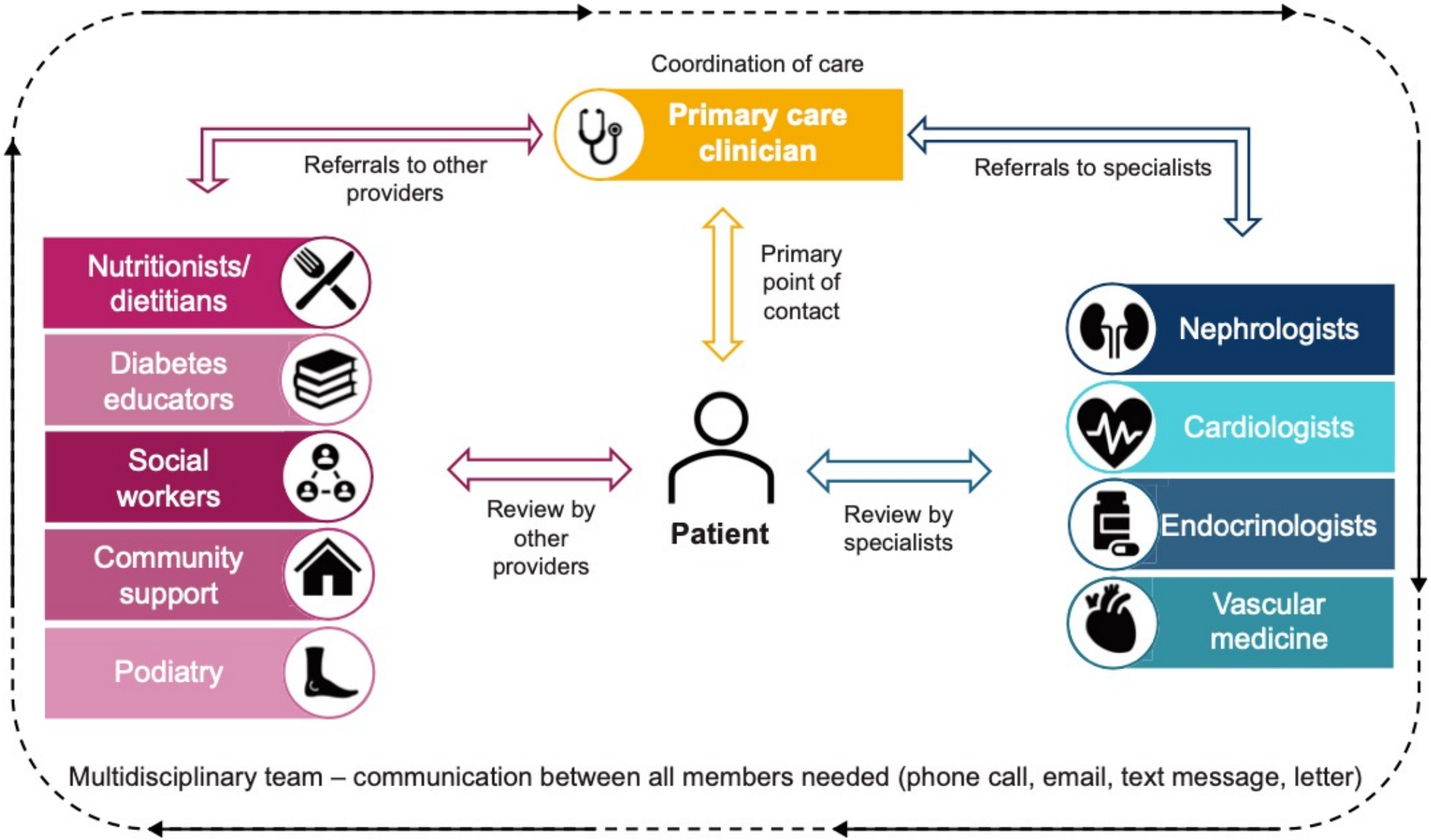
1. Rangaswami J, et al. *Circulation*. 2020;142(17):e265-e268. 2. Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412.

PCP Coordination of Multidisciplinary Care

- Ensure T2D, CVD, and CKD are not treated as separate problems
- Expertise of each specialty should 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 PCPs 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.

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.

Patient Case (cont): Follow-up and outpatient treatment

59-year-old African American man

- DKD
- Hypertension
- Obesity
- T2D
- HFmrEF

Current Relevant Medications
Furosemide 40 mg once daily
Lisinopril 20 mg once daily
Metformin 500 mg twice daily
Empagliflozin 10 mg daily

What are the opportunities for optimizing care?

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

Resource Toolkit

Advances in the Treatment of Cardio-Renal-Metabolic Disorders

URL:https://www.pcmg-us.org/toolkit/CRMD

POST-PRESENTATION Survey

Advances in the Treatment of Cardio-Renal-Metabolic Disorders

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

https://www.pcmg-us.org/survey/post/crm8