Therapeutic Strategies for Cardiovascular-Kidney Metabolic Syndrome: Addressing the Interwoven Triad of Heart Failure, Chronic Kidney Disease, and Diabetes

22nd World Congress Insulin Resistance Diabetes & Cardiovascular Disease
Pre-Congress Breakfast CME Symposium
Thursday, December 12, 2024 | 7:00 AM - 8:00 AM

This activity is provided by MLI

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Activity Overview

Target Audience
This activity is intended for primary care physicians and other members of the multidisciplinary, interprofessional healthcare team in the U.S who care for patients with cardio-renal metabolic disease.

Educational Objectives
After completing this activity, the participant should be better able to:
- Describe the complex interplay between CKD, HF, and T2D in the context of CKM syndrome.
- Analyze the epidemiological trends and pathophysiological mechanisms underlying the interconnectedness of HF, CKD, and T2D, and their implications for patient prognosis and quality of life.
- Evaluate the current evidence base supporting emerging therapeutic strategies, including sodium-glucose cotransporter 2 (SGLT2) inhibitors and aldosterone synthase inhibitors (ASIs), for managing CKM syndrome, with a focus on their potential to mitigate morbidity and mortality.
- Formulate evidence-based treatment plans for patients with CKM syndrome that consider the complex interactions between HF, CKD, and T2D to enhance patient quality of life.

Agenda
- Introduction & Housekeeping
- Exploring the Connections Between CKD, HF, and T2D
- Unveiling Epidemiological Trends and Pathophysiological Links
- Emerging Therapeutic Strategies for CKM syndrome
- Tailoring Treatment for CKM syndrome
- Q&A with Expert Faculty
- Post-Test, Evaluation & Claim Your Credit

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Commission on Dietetic Registration
the credentialing agency for the Academy of Nutrition and Dietetics

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UAN: JA0007322-0000-24-091-L01-P

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Part 1

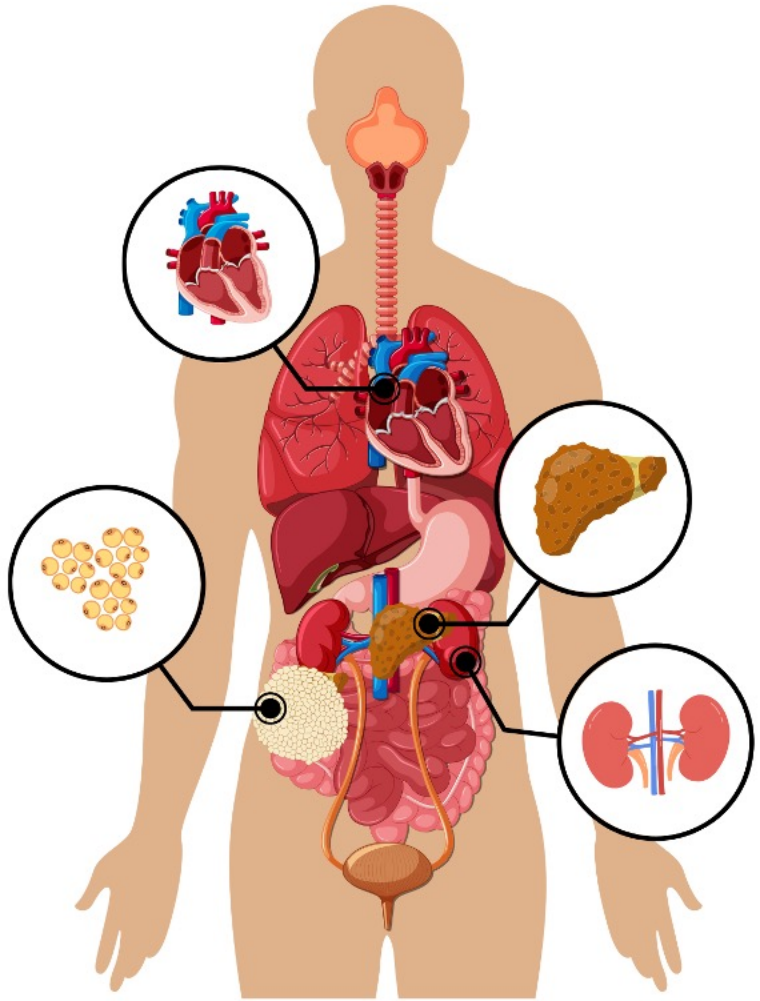
Exploring the Connections Between CKD, HF, and T2D

Educational Objective: Describe the complex interplay between CKD, HF, and T2D in the context of CKM syndrome.

Setting The Stage: What We Already Know

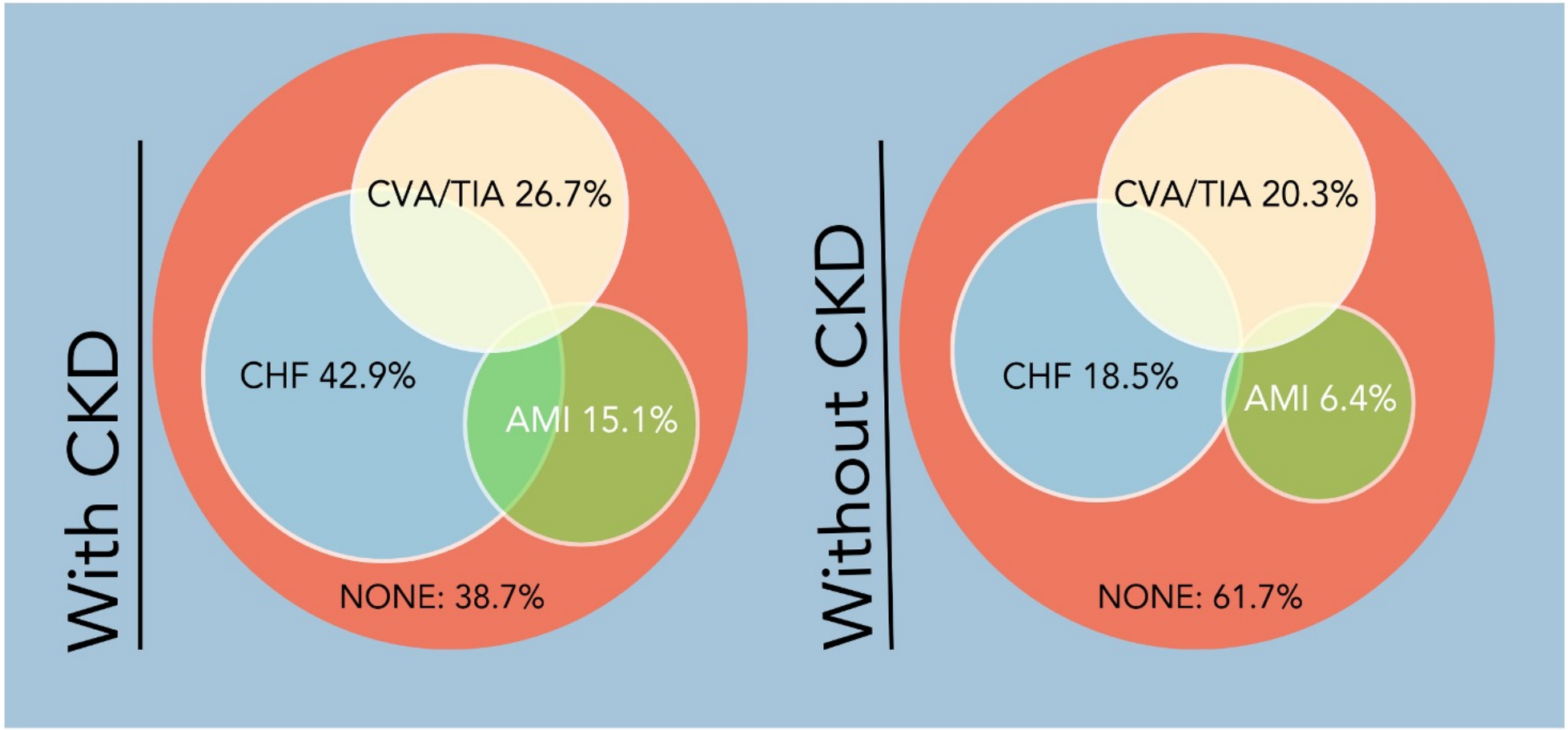
Cardiovascular-kidney-metabolic (CKM) syndrome is a health disorder that occurs due to connections among heart disease, kidney disease, diabetes, and obesity.

CKM leads to poor health outcomes.



Ndumele CE, et al. *Circulation*. 2023;148(20):1636-1664.

CVD in Patients With or Without CKD



AMI, acute myocardial infarction; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; TIA, transient ischemic attack.

House AA. *Am J Kidney Dis*. 2018;72(2):284-295.

Stages of CKM Syndrome

Learning Point!

Stage 0: No Risk Factors

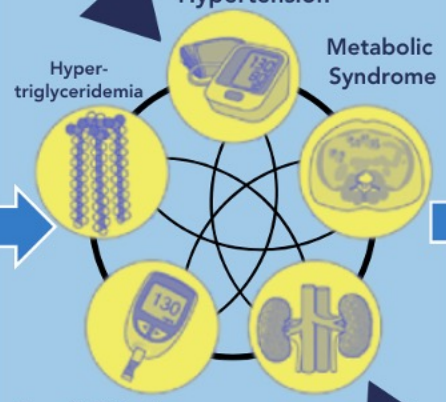
A focus on primordial prevention and preserving cardiovascular health

Stage 1: Excess/Dysfunctional Adipose Tissue

Overweight/obesity
Abdominal obesity
Impaired glucose tolerance

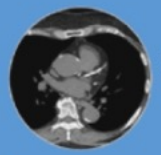
Nonmetabolic etiologies of hypertension

Stage 2: Metabolic Risk Factors and CKD



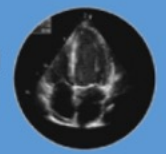
Nonmetabolic etiologies of CKD

Stage 3: Subclinical CVD in CKM Syndrome

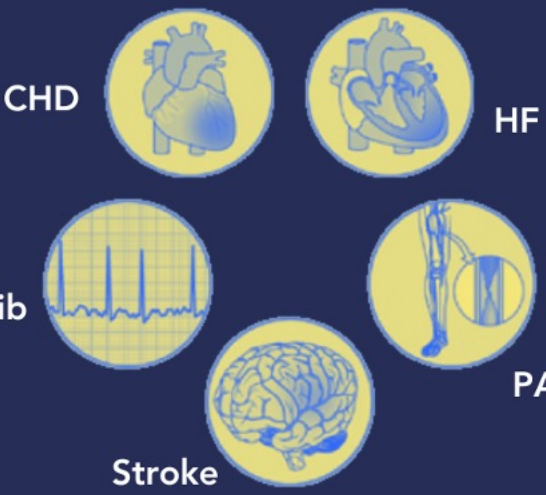


Subclinical ASCVD

Subclinical HF



Stage 4: Clinical CVD in CKM Syndrome



Risk equivalents of subclinical CVD in CKM Stage 3:
- Very high-risk CKD (G stage 4 and 5 CKD or by KDIGO heat map)
- High predicted risk for CVD using risk calculator

Afib, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CHD, coronary heart disease; KDIGO, Kidney Disease Improving Global Outcomes; PAD, peripheral artery disease.

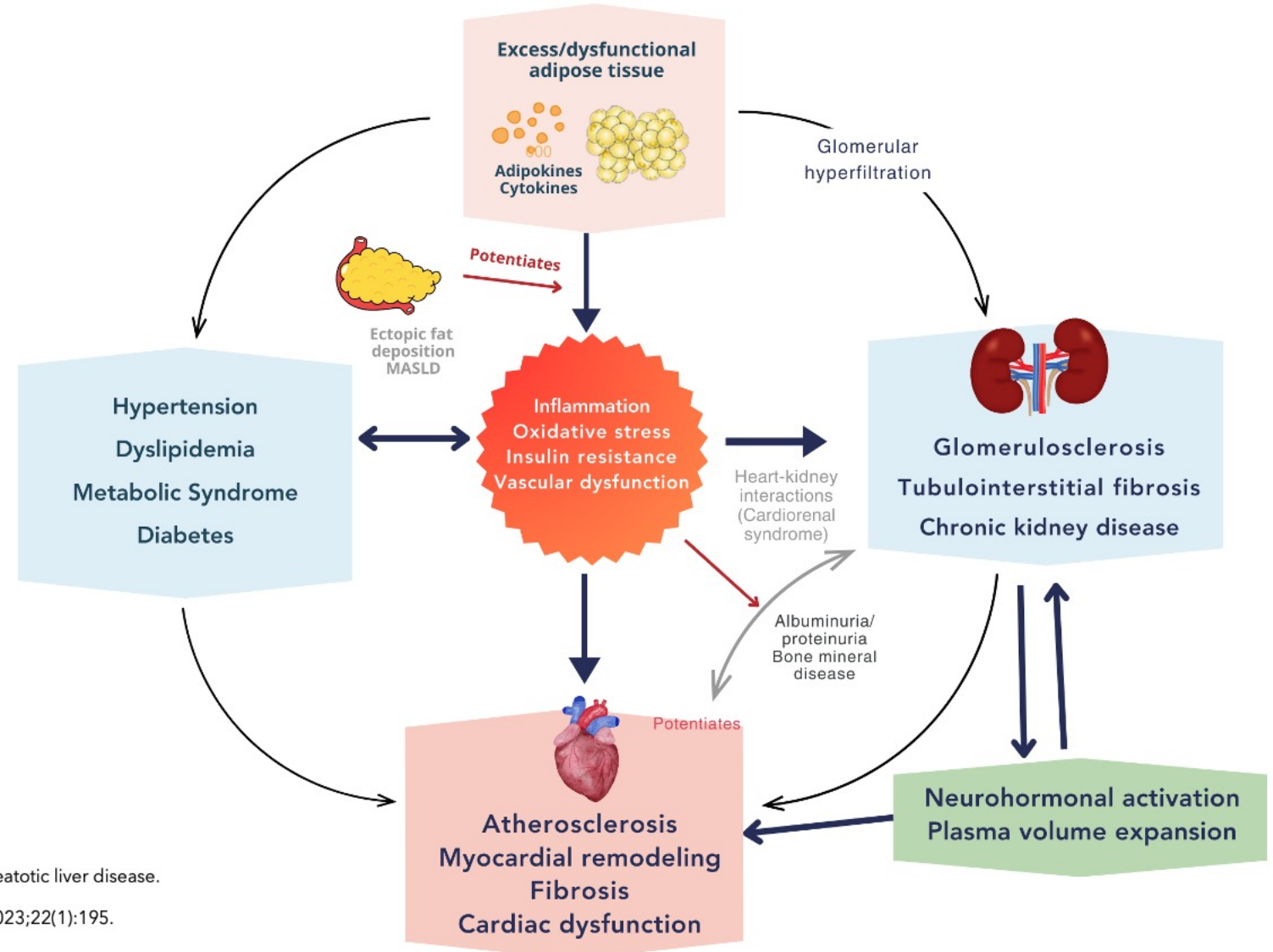
Ndumele CE, et al. *Circulation*. 2023;148(20):1606-1635.

Part 2

Epidemiological Trends and Pathophysiological Links

Educational Objective: Analyze the epidemiological trends and pathophysiological mechanisms underlying the interconnectedness of HF, CKD, and T2D, and their implications for patient prognosis and quality of life.

Pathophysiology

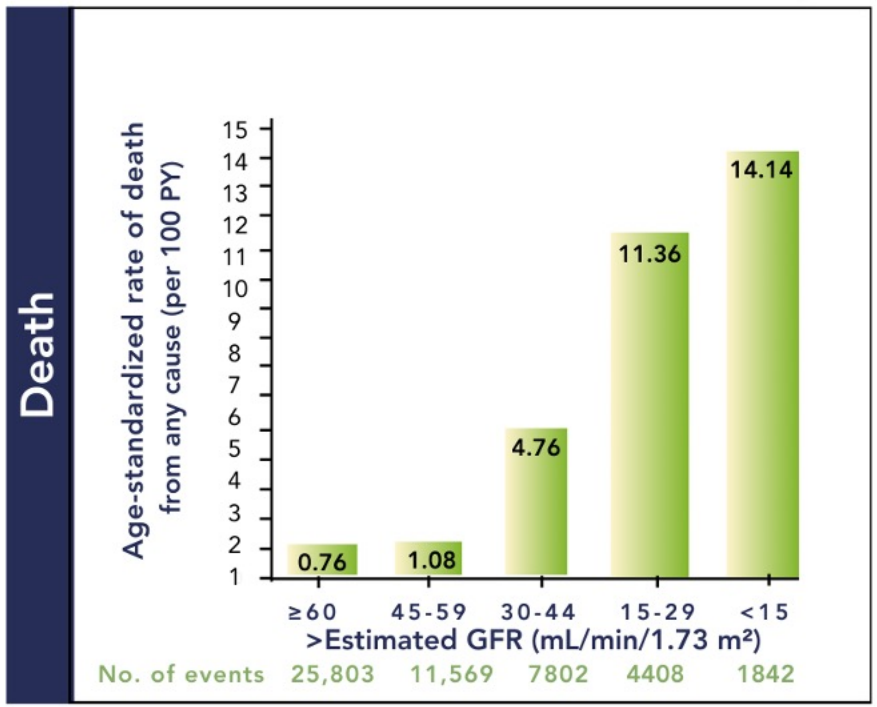


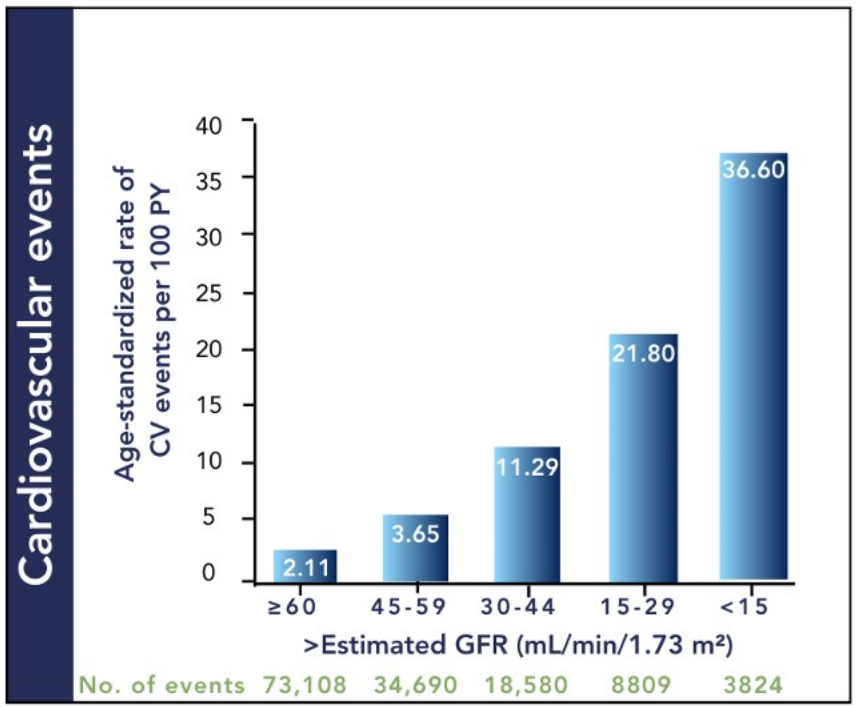
MASLD, metabolic dysfunction–associated steatotic liver disease.

Marassi M, Fadini GP. *Cardiovasc Diabetol*. 2023;22(1):195.

Association of eGFR and Risk of Death and CV Events

Large integrated health system including 1,120,295 patients who had serum creatinine measured between 1996 and 2000 and median follow-up of 2.84 years





eGFR, estimated glomerular filtration rate; PY, person/patient years.

Go AS, et al. *N Engl J Med*. 2004;351:1296-1305.

Role of Mineralocorticoid Receptor Activation

Heightened MR activity plus inappropriate MR activation ultimately lead to increased myocardial stiffness, left ventricular hypertrophy, and the development of glomerular and interstitial fibrosis in the kidneys.

MR, mineralocorticoid receptor.

Buonafine M, et al. *Am J Hypertens*. 2018;31(11):1165-1174; Jia G, et al. *Biochim Biophys Acta Mol Basis Dis*. 2017;1863(8):2012-2018; Lother A, Hein L. *Hypertension*. 2016;68(1):6-10; Mihai S, et al. *J Immunol Res*. 2018;2018:2180373.

Part 3

Emerging Therapeutic Strategies for CKM syndrome

Educational Objective: Evaluate the current evidence base supporting emerging therapeutic strategies, including sodium-glucose cotransporter 2 (SGLT2) inhibitors and aldosterone synthase inhibitors (ASIs), for managing CKM syndrome, with a focus on their potential to mitigate morbidity and mortality.

KDIGO: Comprehensive Treatment Approach

LIFESTYLE

- Healthy Diet

- Physical Activity

- Smoking Cessation

- Weight Management

FIRST-LINE DRUG THERAPY

- **SGLT2i** (continue until dialysis or transplant)
- RAS inhibitor at maximum tolerated dose (if HTN)
  - ns-MRA in patients with diabetes and an indication for use
  - Dihydropyridine CCB and/or diuretic if needed to achieve individualized BP target
    - Steroidal MRA if needed by resistant HTN if eGFR 245 mL/ min/1.73 m²
- Moderate or high-intensity statin
  - ASCVD risk, lipids
    - Antiplatelet agent for clinical ASCVD
      - Ezetimibe, PCSK9i, if indicated based on ASCVD risk and lipids
        - Diagnose and manage ASCVD and atrial fibrillation similarly to those without CKD
    - Manage anemia, CKD-MBD, acidosis, and potassium abnormalities, where indicated

TARGETED THERAPIES FOR COMPLICATIONS

- GLP-1 RA if needed to achieve individualized glycemic target

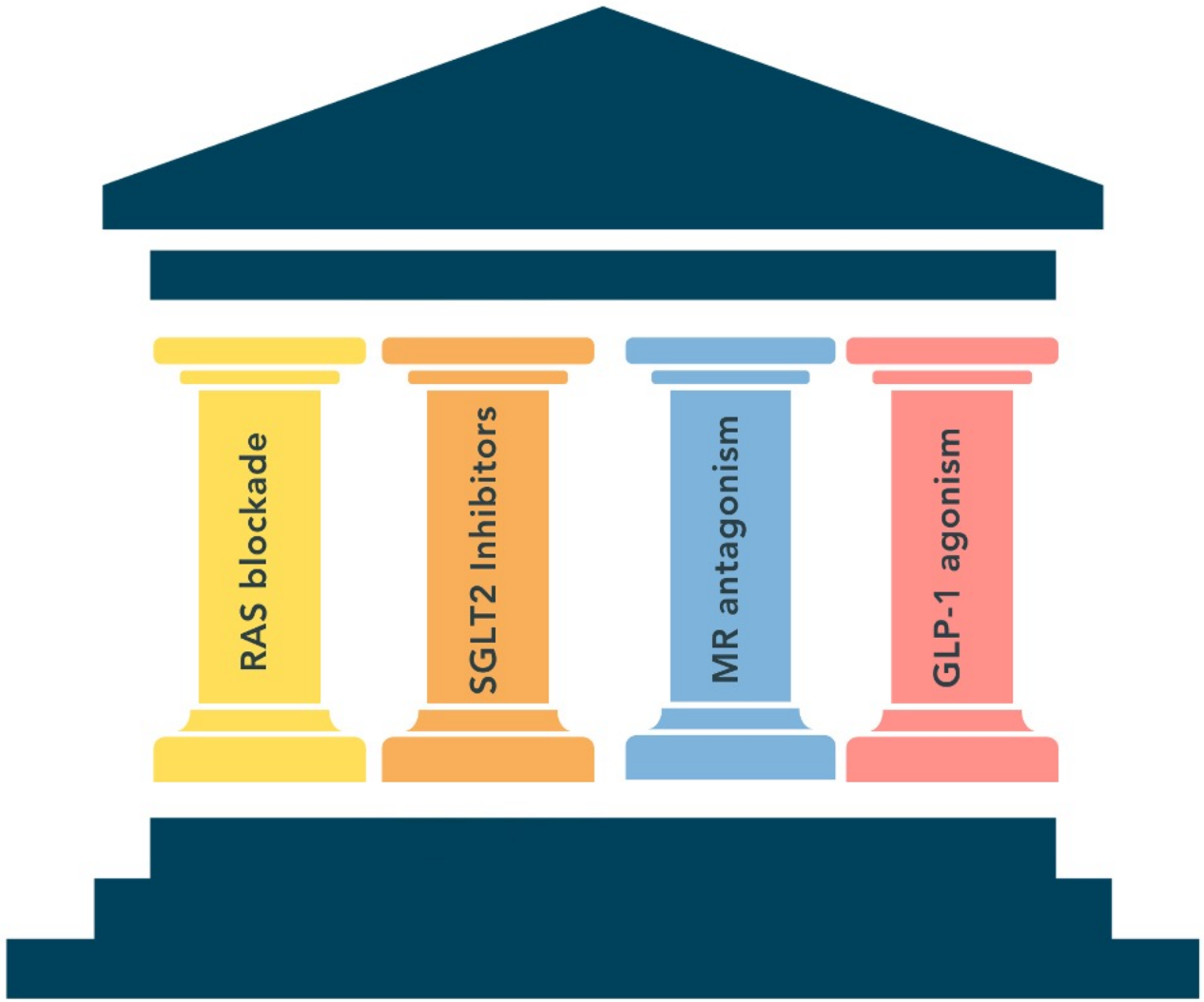
KEY

- T2D only
- T1D and T2D

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CKD-MBD, Chronic kidney disease–mineral and bone disorder; GLP-1 RA, Glucagon-like peptide-1 receptor agonists; HTN, hypertension; ns-MRA, Non-steroidal mineralocorticoid receptor antagonists; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium-glucose cotransporter 2 inhibitors; T1D, type 1 diabetes, T2D, type 2 diabetes.

Modified from KDIGO CKD Work Group. *Kidney Int*. 2024;105(4S):S117-S314.

Four Pillars of Care CKM



Modified from Blazek O, Bakris GL. *Am Heart J Plus.*

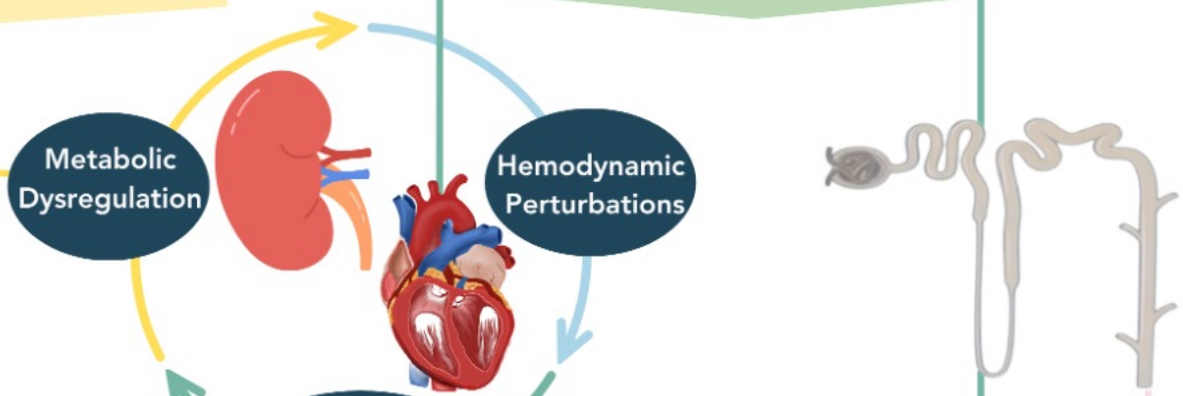
GLP-1, Glucagon-like peptide-1; MR, mineralocorticoid receptor antagonist; RAS, Renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2.

Four Pillars of Care

Learning Point!

POTENTIAL PILLAR 4: GLP-1RAS
- Decrease weight
- Decrease dyslipidemia
- Decrease oxidative stress
- Decrease endothelial dysfunction

PILLAR 1: RAS blockers
- Decrease efferent arteriole tone
- Decrease hyperfiltration
- Decrease endothelial dysfunction
- Decrease cardiac remodeling



PILLAR 3: Finerenone
- Decreases inflammation
- Decreases fibrosis
- Decreases endothelial dysfunction
- Decreases tissue remodeling
- Decreases proteinuria

PILLAR 2: SGLT2 inhibitors
- Increase afferent arteriole tone
- Improve tubuloglomerular feedback
- Decrease hyperfiltration
- Decrease proteinuria
- Decrease oxidative stress
- Increase anti-inflammatory and anti-fibrotic effects

Awosika A, et al. *Cureus*. 2023;15(3):e36184; McMurray et al. *N Engl J Med*. 2019;381(21):1995-2008; Naaman SC, Bakris GL. *Diabetes Care*. 2023;46(9):1574-1586; Packer M, et al. *Circulation*. 2021;143(4):326-336; Sattar N, et al. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662; Wilcox, CS, et al. *Hypertension*. 2020;75(4):894-901.

Novel Approaches in CKM Syndrome

RAAS: Pivotal in regulating BP and fluid-electrolyte balance, aldosterone synthesis is a crucial step

ASIs: Novel approach to modulating aldosterone, with potential advantages over MRAs in HTN and its complications, including CKD

Baxdrostat (CIN-107): Shown promise in treating treatment-resistant HTN

- Phase 3 trials underway, with a focus on uncontrolled HTN, CKD, and primary aldosteronism

Lorundrostat: Target-HTN: reduces systolic BP, especially in patients with suppressed plasma renin activity

- Lower doses showed significant BP reduction with fewer AEs

Vicadrostat (BI 6905170): Potent ASI in patients with CKD, aiming to address the AEs associated with RAAS inhibition

- Dose-dependent reductions in albuminuria
- Vicadrostat + empagliflozin: additive benefits, including kidney protection and reduced hyperkalemia

ASI, Aldosterone synthase inhibitor; HTN, hypertension; MRA, mineralocorticoid receptor antagonist.

Awosika A, et al. *Cureus*. 2023;15(3):e36184; Laffin LJ, et al. *JAMA*. 2023;330(12):1140-1150; Tuttle KR, et al. *Am J Nephrol*. 2024;55(2):262-272; Tuttle KR, et al. *Lancet*. 2024;403(10424):379-390.

Part 4

Tailoring Treatment for CKM Syndrome: Navigating Complex Interactions

Educational Objective: Formulate evidence-based treatment plans for patients with CKM syndrome that consider the complex interactions between HF, CKD, and T2D to enhance patient quality of life.

Collaboration in CKM Syndrome Management

"Cardiorenal disease is an important and potentially fatal complication in T2D, representing an unmet clinical need which should be considered when choosing future optimal preventive strategies in the management of these patients, adding a cardiorenal preventive approach to an already existing and quietly successful atherosclerotic preventive approach."

Birkeland KI, et al. *Diabetes Obes Metab.* 2020;22(9):1607-1618.

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