Scientific Overview and Pharmacotherapeutic Options for CKM Syndrome

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Objectives

Discuss the science and clinical approach for prevention, screening, and management of individuals with cardiovascular-kidney-metabolic (CKM) syndrome.

Explain the pathophysiology of CKM syndrome and the underlying interplay of cardiovascular disease, chronic kidney disease and metabolic disease.

Describe the 4 stages of CKM and the recommended interventions at each stage.

Assess the optimal management strategies for CKM syndrome including lifestyle modifications, weight loss, emerging pharmacotherapies, and integrated multidisciplinary care approach.

Abbreviation	Meaning
ABI	Ankle-brachial index
ACEi	Angiotensin converting enzyme inhibitor
ADR	Adverse drug reaction
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor/neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CAC	Coronary artery calcium
CAD	Coronary artery disease
CHD	Coronary heart disease
CKD	Chronic kidney disease
CKM	Cardiovascular-kidney-metabolic
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease

Abbreviation	Meaning
FBG	Fasting blood glucose
GLP-1 RA	GLP-1 receptor agonist
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HIV/AIDS	Human immunodeficiency virus/ acquired immunodeficiency syndrome
MASLD	Metabolic dysfunction-associated steatotic liver disease
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
PAD	Peripheral artery disease
PCOS	Polycystic ovary syndrome
RA	Rheumatoid arthritis
SDOH	Social determinants of health
SLE	Systemic lupus erythematosus
TG	Triglyceride
TTE	Transthoracic echocardiogram
UA	Unstable angina
UACR	Urine albumin-to-creatinine ratio

CVD and CKD Connection

CVD → CKD

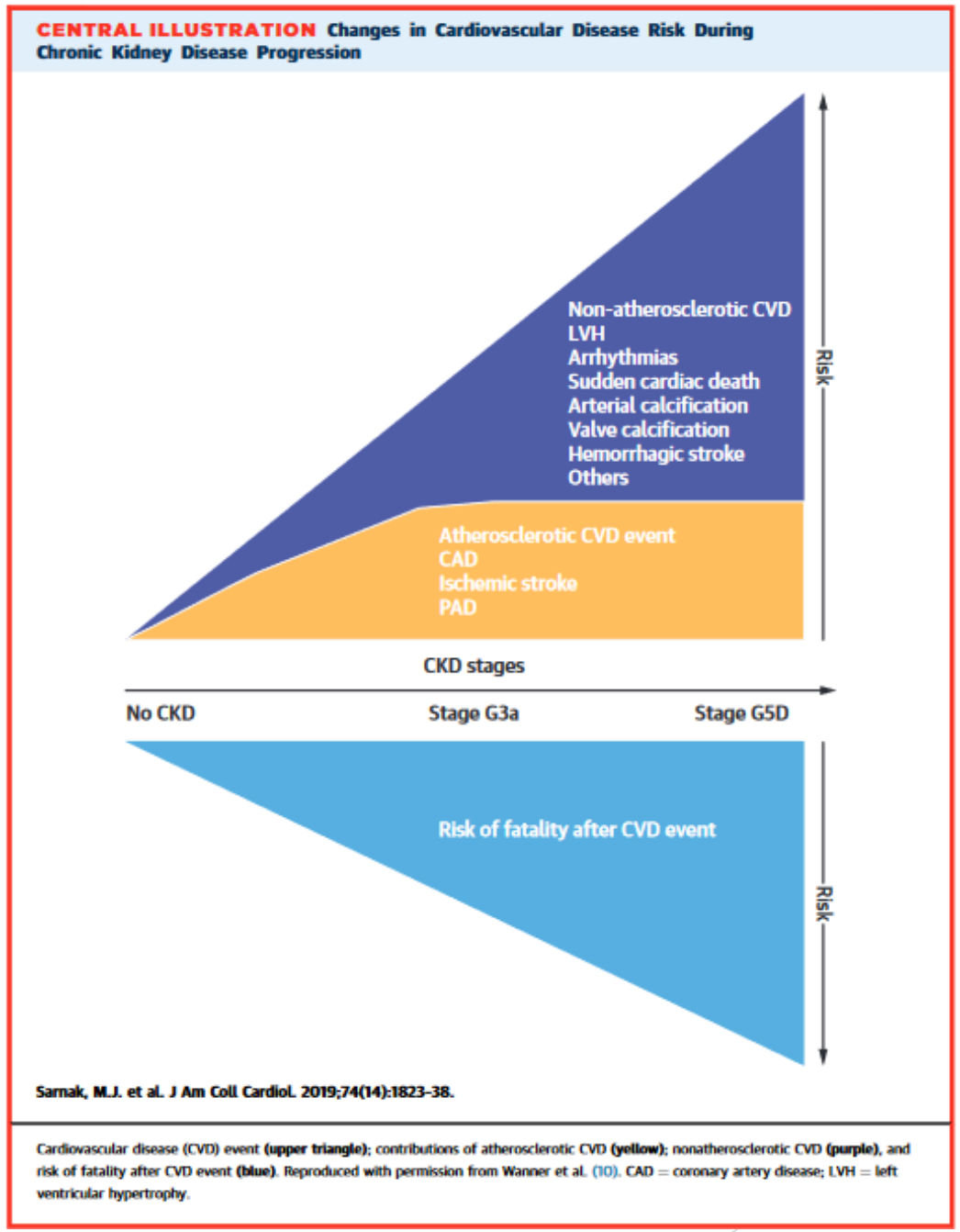
- CVD is primary cause of morbidity and mortality in CKD
- Linear rise in CAD diagnosis as eGFR drops below 60 mL/min/1.73m^2
- CVD mortality risk:
  - Doubles in CKD 3
  - Triples in CKD 4

CKD → CVD

- CKD associated with very high risk of CAD
- More advanced atherosclerotic plaques
- Increased management challenges
  - CAD symptoms may not be typical
  - Advanced CKD often excluded from trials
  - Medication ADRs risk higher

J Am Coll Cardiol. 2019;74:1823–38.

CVD and CKD Connection



J Am Coll Cardiol. 2019;74:1823–38.

CKD + CVD Mechanisms

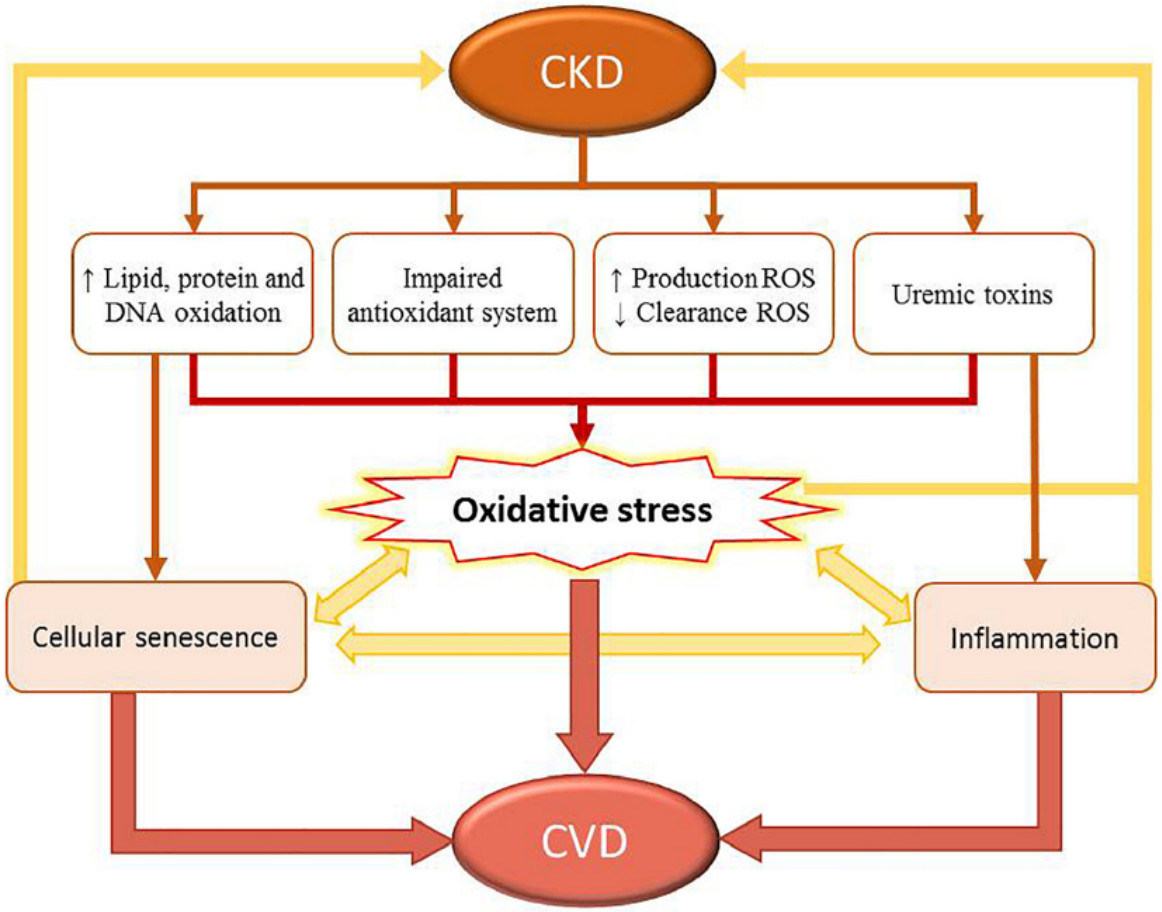


FIGURE 2 | Relationship between oxidative stress and CKD-associated cardiovascular disease (CVDs). CKD leads to increased damage of biomolecules (such as lipids, proteins, and DNA), impairment of the antioxidant system, increased levels of reactive oxygen species (ROS), decreased ROS clearance, and high concentration of uremic toxins in circulation. This process increases the levels of oxidative stress. CKD is also associated with systemic inflammation, mitochondrial dysfunction, loss of proteostasis, altered intercellular communication, and cellular senescence. Combined, these factors contribute to increased levels of oxidative stress in this patient population. However, cellular senescence and inflammation also participate in the development and progression of CVDs.

Front Cell Dev Biol. 2020;8:185.

CKD + CVD Mechanisms

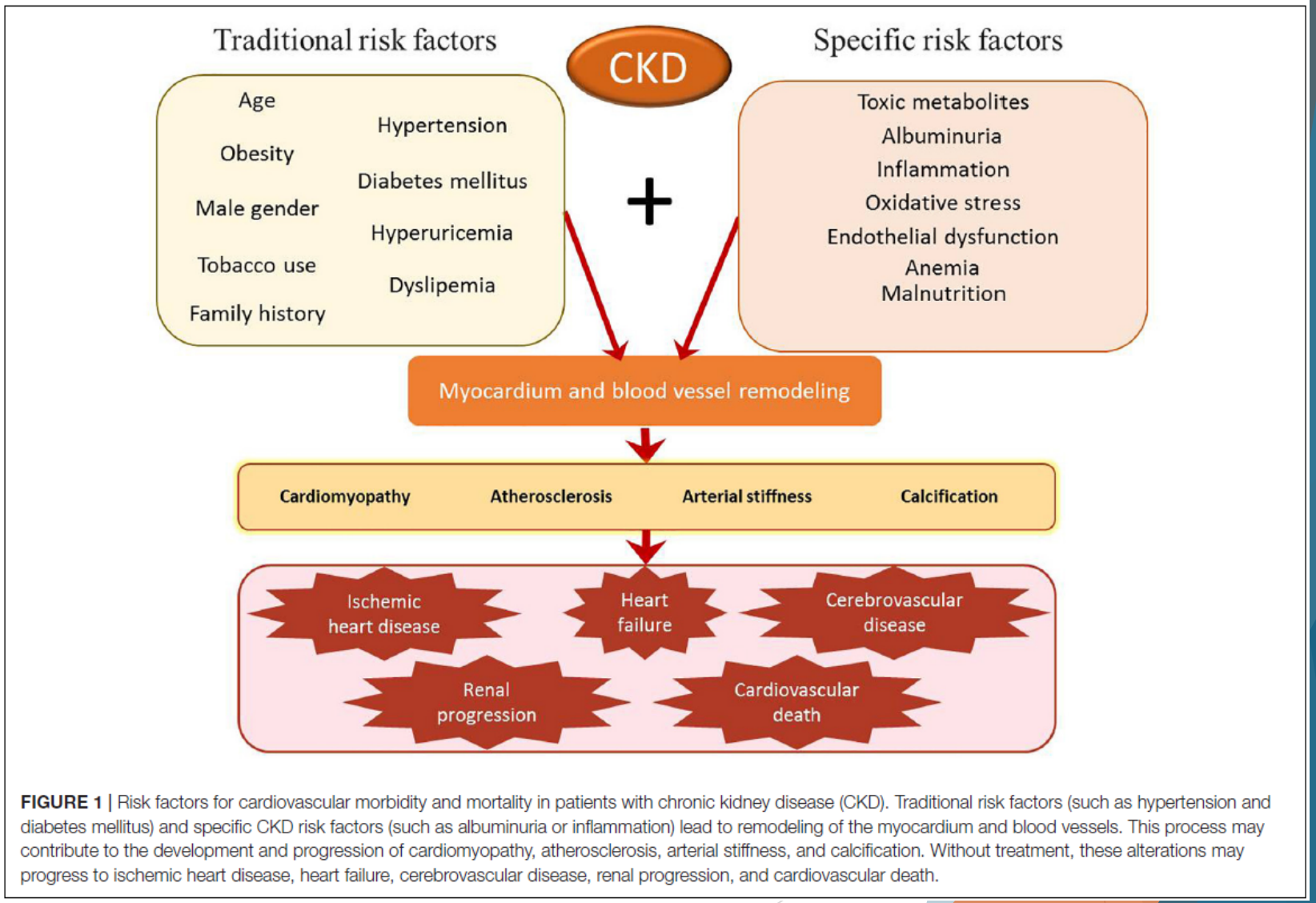


FIGURE 1 | Risk factors for cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). Traditional risk factors (such as hypertension and diabetes mellitus) and specific CKD risk factors (such as albuminuria or inflammation) lead to remodeling of the myocardium and blood vessels. This process may contribute to the development and progression of cardiomyopathy, atherosclerosis, arterial stiffness, and calcification. Without treatment, these alterations may progress to ischemic heart disease, heart failure, cerebrovascular disease, renal progression, and cardiovascular death.

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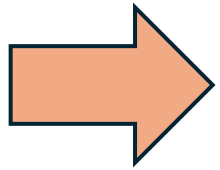
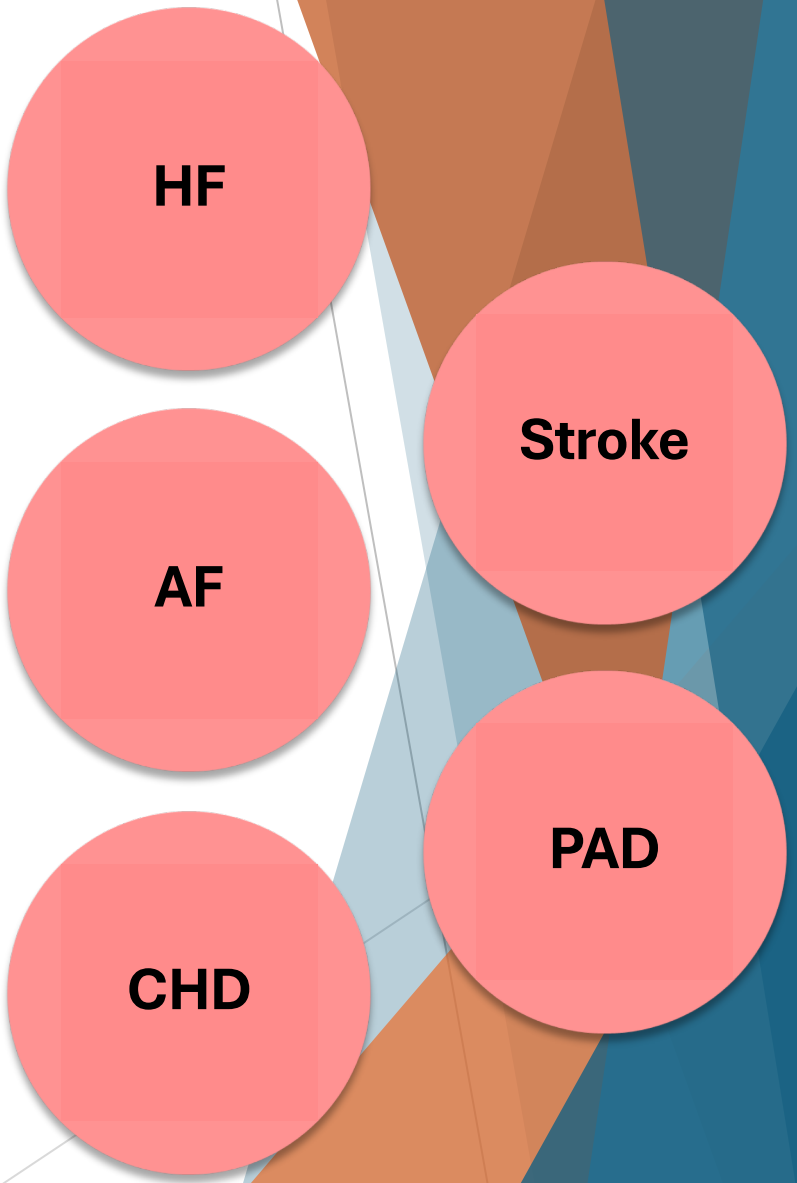
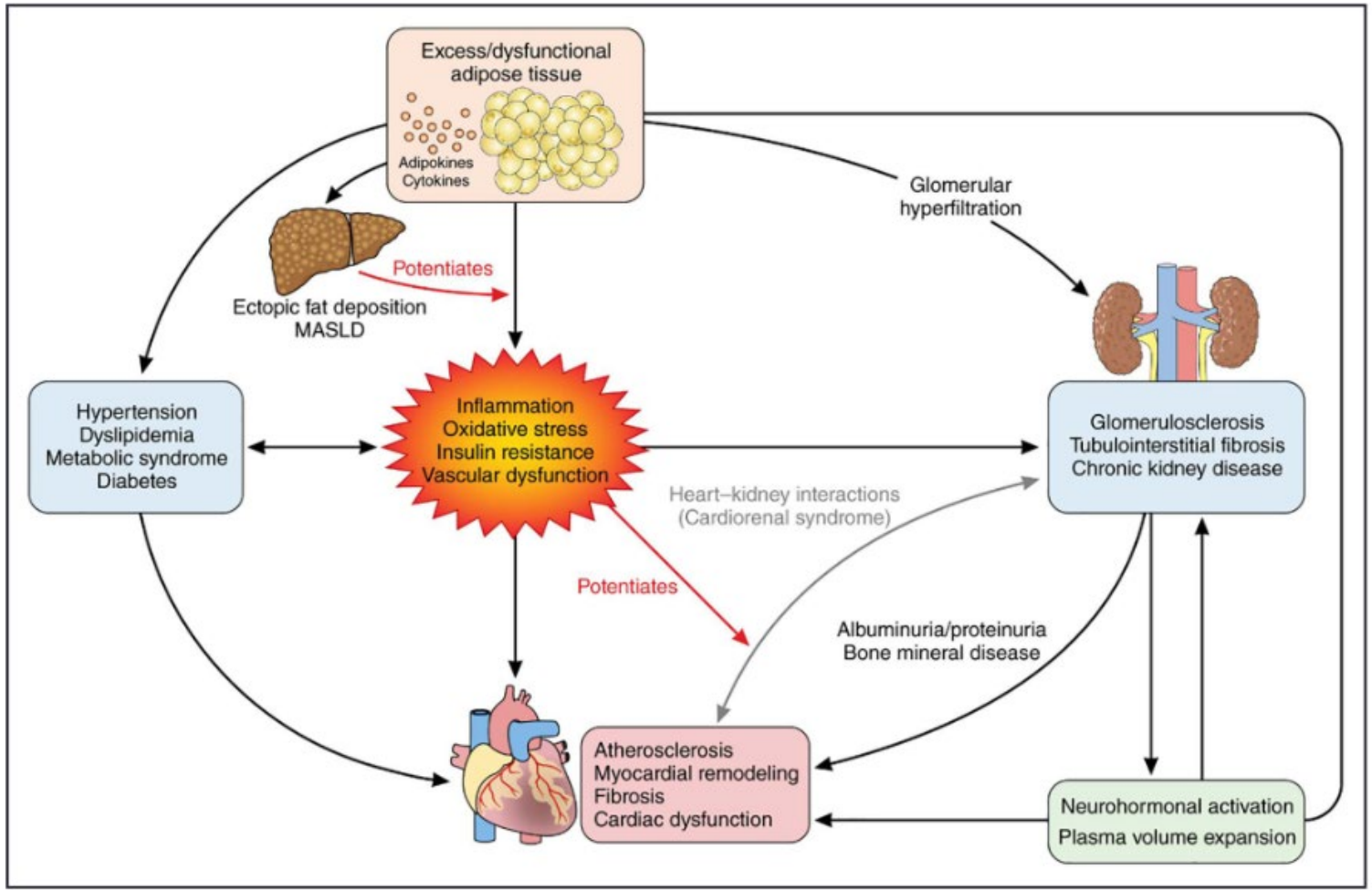




Circulation. 2023;148:1606–1635.

Stage	Definition		
0	No risk factors or CKM disease		
1	Excess and/or dysfunctional adiposity • BMI ≥25 kg/m2 • Waist circumference ≥88 cm (women) or 102 cm (men) • FBG ≥100–124 mg/dL **OR** A1c 5.7-6.4%		
2	Metabolic risk factors • Hypertriglyceridemia (≥135 mg/dL) • Hypertension • Metabolic syndrome • Diabetes	OR	CKD
3	Subclinical ASCVD or subclinical HF in individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD	OR	Risk equivalent of subclinical CVD • Very high-risk CKD (G4 or G5) • High predicted 10-year CVD risk
4	Clinical CVD (CHD, HF, stroke, PAD, AF) among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD • 4a: no kidney failure • 4b: kidney failure		

Circulation. 2023;148:1606–1635.



CKM Syndrome Pathophysiology

Circulation. 2023;148:1636–1664.

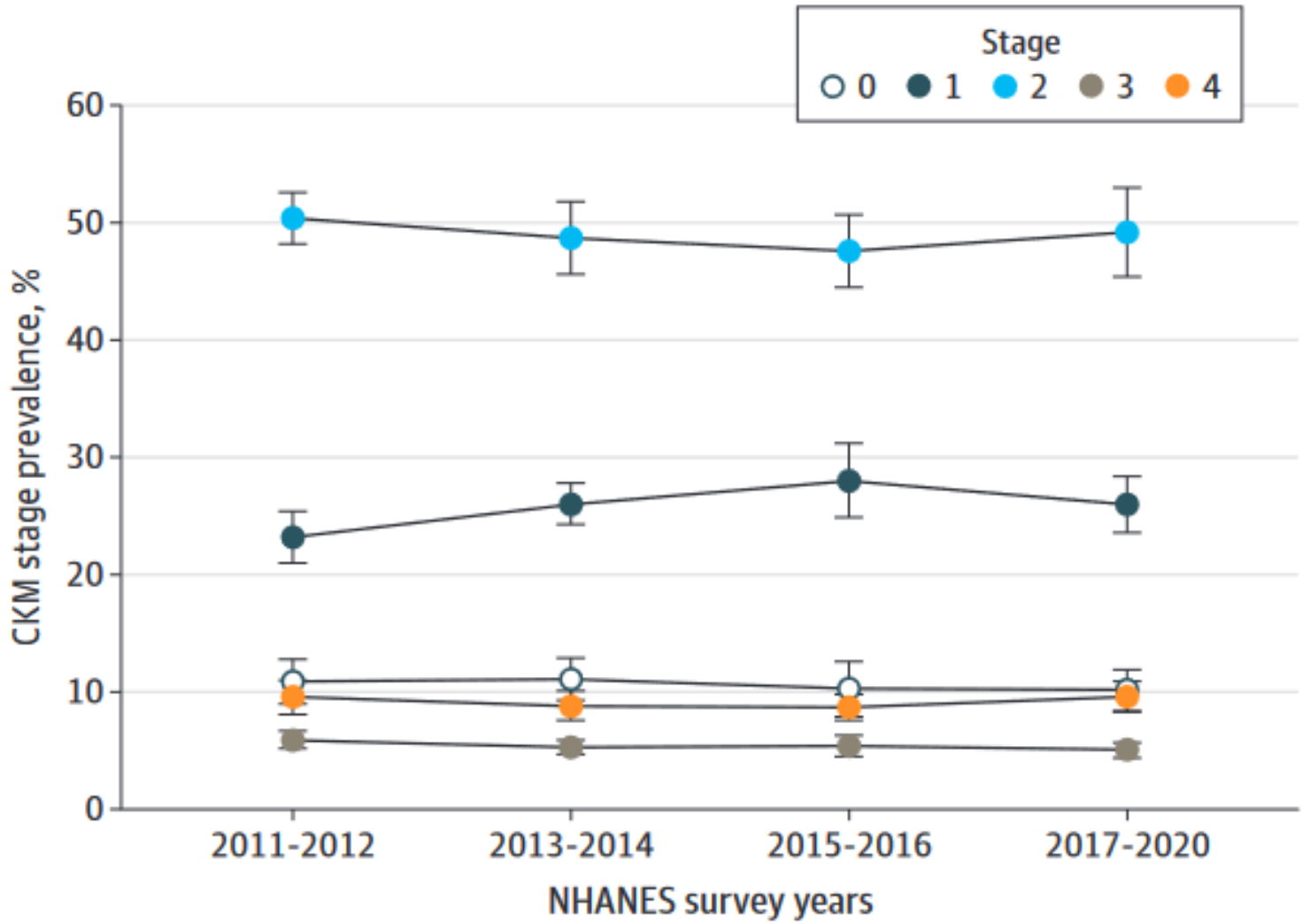
Epidemiology

- 1 in 3 US adults have ≥ 3 CKM syndrome risk factors
- Therapies exist (many newer), but often care is fragmented
- CKM syndrome leads to poor health outcomes
- CKM diseases affect > 25% of US adults between 2015-2020
- CKM disease leading causes of death in 2021 in US (> 1 million deaths (29%))

https://www.heart.org/en/professional/cardiovascular-kidney-metabolic-health

Circulation. 2023;147(8):e93-e621. *JAMA*. 2024;331(21):1858-1860. *JAMA*. 2023;330(21):2042-2043.

Figure. Temporal Trends of Cardiovascular-Kidney-Metabolic Syndrome Stages Among US Adults, 2011-March 2020

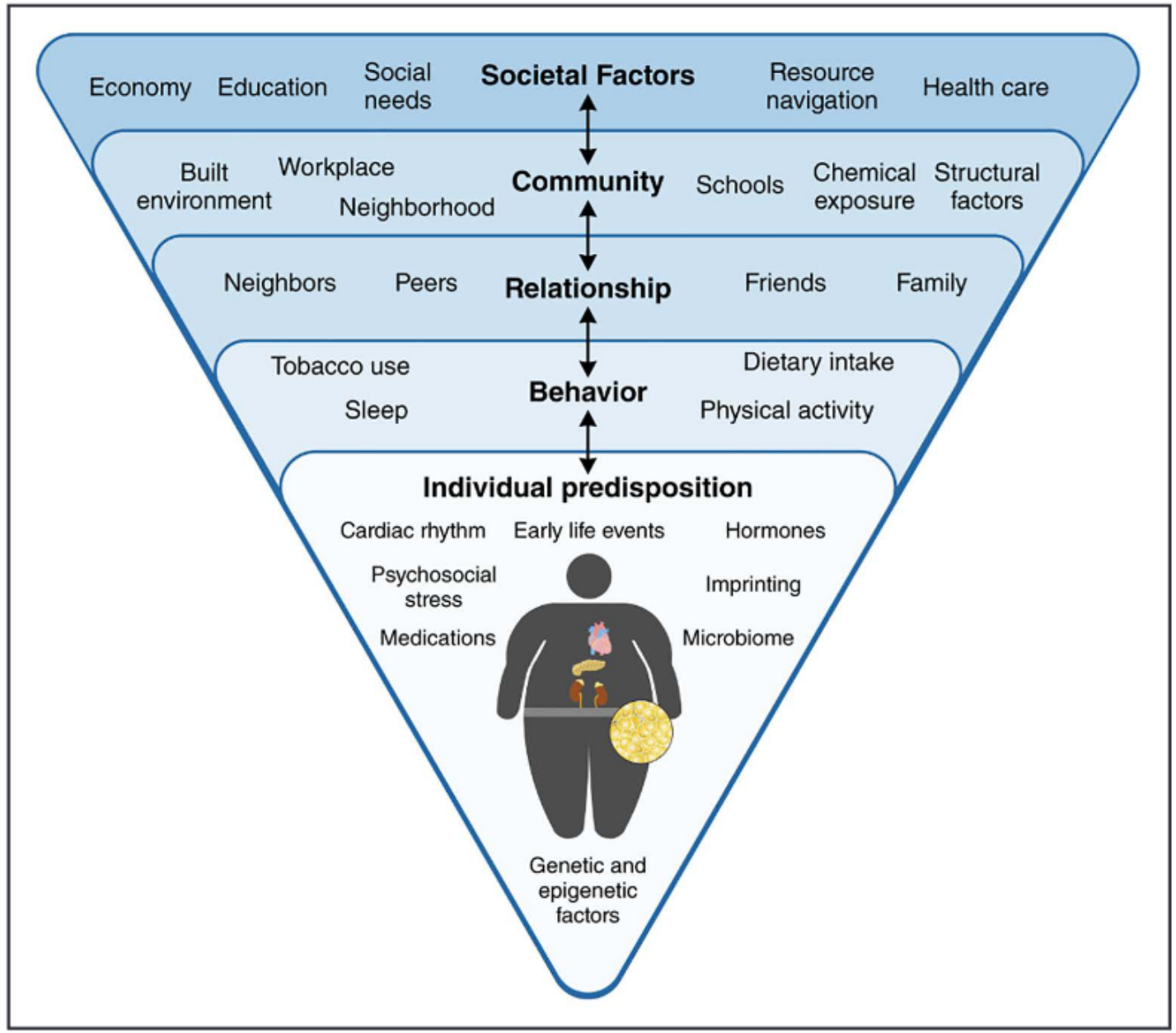


JAMA. 2024;331(21):1858-1860.

Characteristic/Stage	0	1	2	3	4
Total	10.6	25.9	49.0	5.4	9.2
Age					
20-44	18.2	36.6	43.2	0.1	1.9
45-64	5.4	21.2	62.7	1.4	9.2
≥ 65	1.3	7.2	36.2	27.4	27.9
Sex					
Male	7.9	24.9	50.3	6.5	10.4
Female	13.1	26.8	47.7	4.4	8.0
Race/Ethnicity					
Asian	12.2	26.2	50.2	6.5	11.4
Black	6.7	23.9	50.5	7.5	18.9
Hispanic	6.5	26.9	52.0	7.2	7.5
White	12.2	26.1	47.9	4.6	9.2

JAMA. 2024;331(21):1858-1860.

Social Determinants of Health



Circulation. 2023;148:1636–1664.

CKM Syndrome Risk Factors

- Obesity
- Hypertension
- Hypertriglyceridemia
- Diabetes

Circulation. 2023;148:1636–1664.

Risk-Enhancing Factors

- Chronic inflammatory conditions (psoriasis, RA, SLE, HIV/AIDS)
- High-risk demographic groups (South Asian ancestry, lower socioeconomic class)
- High burden of adverse social determinants of health
- Mental health disorders
- Sleep disorders
- Elevated high-sensitivity CRP
- Family history of kidney failure
- Family history of diabetes

- Female specific
  - Premature menopause (age < 40)
  - Adverse pregnancy outcome
  - PCOS

- Male specific
  - Erectile dysfunction

Circulation. 2023;148:1606–1635.

Clinical Guidelines

Primary Prevention of ASCVD

- 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults
- 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease
- 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice

Hypertension

- 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults
- 2021 AHA Scientific Statement on Weight-Loss Strategies for Prevention and Treatment of Hypertension

Dyslipidemia

- 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

Diabetes

- 2022 AHA Scientific Statement: Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes
- 2023 Standards of Medical Care in Diabetes

CKD

- 2013 KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease
- 2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

Heart failure

- 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure
- 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Atrial fibrillation

- 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation
- 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration With the EACTS

Screening

Biologic Factors

- Metabolic risk factors
- Renal function
- Subclinical atherosclerosis
- Cardiac dysfunction

Selection and intensity of interventions/ management

SDOH

- Social and structural barriers
  - Health lifestyle
  - Self-care
  - Healthcare access
  - Disease prevention
  - Disease management

Identification of CKM risk factors and outcomes

Circulation. 2023;148:1606–1635.

Age	Parameters	Frequency
< 21	Weight	Annually
	Blood pressure	Annually (or every health encounter if CKM risk factors)
	Lipid panel	9-11 years old, 17-21 years old
	Glucose/A1c	9-11 years old (repeat every 2-3 years if overweight/obese)
	Mental/behavioral health	Continually
	SDOH	Continually
≥ 21	Weight	Annually
	Metabolic syndrome	Stage 0 CKM: every 3-5 years Stage 1 CM: every 2-3 years Stage 2 CKM: Annually
	Liver fibrosis/MASLD	Diabetes/prediabetes/≥2 metabolic risk factors: every 1-2 years
	UACR + SCr	Stage 2-4 CKM: annually (more frequently if higher KDIGO risk)
	Coronary artery calcium	10-year ASCVD risk – intermediate
	Subclinical HF + TTE ± cardiac biomarkers	Not yet defined but deemed important
	SDOH	Continually

Screening

Circulation. 2023;148:1606–1635.

Stage	Recommendations	Considerations
0	• Attain and maintain CV health • Maintain healthy weight • School-based and family-based intervention	• Start and intervene young/early • Healthy diet • Regular physical activity

1	• Weight loss counseling + 5-10% weight loss
	  ○ Lifestyle interventions to reach sustainable behavioral changes
	  ○ BMI ≥ 30 kg/m^2: GLP-1 RA
	  ○ BMI ≥ 40 kg/m^2: Bariatric surgery
		• Importance of shared decision making
		• Setting attainable goals
		• Avoid “fad” diets
		• GLP-1 RA access/cost

2	• Weight loss
	• HTN: BP < 130/80 mmHg
	• Hypertriglyceridemia: statin, icosapent ethyl
	• Diabetes: SGLT2 inhibitors, GLP-1 RA, metformin
	• CKD: ACEi/ARB, SGLT2 inhibitors, finerenone
		• HTN medication choice
		  ○ Mortality reduction
		  ○ ASCVD reduction
		• Diabetes medication choice
		  ○ CKD: SGLT2 inhibitor
		  ○ Obesity: GLP-1 RA
		• Medication access/cost
		• Medication adherence

Management

Circulation. 2023;148:1606–1635.

Stage	Recommendations	Considerations

3	• Weight loss
	• Subclinical ASCVD: statin, consider aspirin
	• Subclinical HF: ACEi/ARB, beta-blocker, SGLT2 inhibitors (diabetes)
		• HTN medication choice
		  ○ Comorbidity drives selection
		• Aggressive LDL and TG reduction
		  ○ Additional LDL reduction: ezetimibe, PCSK9 inhibitors, inclisiran, bempedoic acid
		• Medication access/cost
		• Medication adherence

4	• Weight loss
	• Hypertriglyceridemia: statin, icosapent ethyl
	• Diabetes: SGLT2 inhibitors, GLP-1 RA, metformin
	• ASCVD: high intensity statin, aspirin ± P2Y12 inhibitors
	• HFrEF: 4 pillars (ACEi/ARB/ARNI, beta-blocker, MRA, SGLT2 inhibitor)
	• CKD: ACEi/ARB, SGLT2 inhibitors, finerenone
		• HTN medication choice
		  ○ Comorbidity drives selection
		• Aggressive LDL and TG reduction
		  ○ Additional LDL reduction: ezetimibe, PCSK9 inhibitors, inclisiran, bempedoic acid
		• Medication access/cost
		• Medication adherence

Management

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GLP-1 RA

- A1c reduction
  - Tirzepatide > semaglutide > liraglutide = dulaglutide > exenatide
- Weight loss
  - Tirzepatide > semaglutide > liraglutide > dulaglutide = exenatide
- Reduce CV outcomes in diabetics and advanced CKD
  - Dulaglutide, liraglutide, semaglutide
- Considerations
  - ADRs
  - Dose titration
  - Duration of use (weight loss alone)

Medication	Administration Frequency
Dulaglutide	Weekly
Exenatide	BID or weekly (based on formulation)
Liraglutide	Daily
Semaglutide	Weekly (subQ)
Tirzepatide	Weekly

BMJ. 2024;384:e076410. Diabetes Care. 2024;47(Suppl 1):S158-S178.

Finerenone

ADA Standards of Care (2024)

- Type 2 diabetes + CKD with albuminuria on ACEi/ARB – recommended to improve CV outcomes and reduce CKD progression
- Type 2 diabetes + diabetic kidney disease – recommended to reduce HF hospitalization

Diabetes Care. 2024;47(Suppl 1):S179-S218.

Trial	FIDELIO-DKD	FIGARO-DKD

Population	• Type 2 diabetes
	• Maximally tolerated ACEi/ARB
	• CKD
	  ○ eGFR 25-59mL/min + albuminuria (UACR 30-299) + retinopathy
	  ○ eGFR 25-74mL/min + albuminuria (UACR 300-5000)
		• Type 2 diabetes
		• Maximally tolerated ACEi/ARB
		• CKD
		  ○ eGFR 25-90mL/min + albuminuria (UACR 30-299)
		  ○ eGFR >60mL/min + albuminuria (UACR 300-5000)

Intervention	Finerenone 10-20 mg daily	Finerenone 10-20 mg daily
Comparator	Placebo	Placebo

Outcomes	• Kidney failure, eGFR decrease ≥40%, or death from renal cause: 17.8% vs. 21.1% (p=0.001)
	  ○ Driven by reduction in eGFR decrease ≥40%
	• ≥57% eGFR decrease: 5.9% vs. 8.6% (HR 0.68 (0.55-0.82))
		• CV death, nonfatal MI, nonfatal stroke, or HF hospitalization: 12.4% vs. 14.2% (p=0.03)
		  ○ Driven by reduction in HF hospitalization
		• ESRD: 0.9% vs. 1.3% (HR 0.64 (0.41-0.995))
		• Kidney composite with ≥57% eGFR decrease: 2.9% vs. 3.8% (HR 0.77 (0.6-0.99))
		• Hyperkalemia: 10.8% v. 5.3%

N Engl J Med. 2020;383(23):2219-2229. N Engl J Med. 2021;385(24):2252-2263.

Icosapent Ethyl

- Icosapent ethyl 2g BID recommended to reduce CV risk

Option 1	Option 2

• Age > 45
• ASCVD
• Fasting TG 135 to 499 mg/dL
• High intensity or maximally tolerated statin (+/- ezetimibe)
• LDL goals achieved
	• Age > 50 + diabetes + ≥1 risk factor
	  ○ Age (≥55 yo for men, ≥65 yo for women)
	  ○ Smoker
	  ○ HTN
	  ○ HDL (≤40 mg/dL for men, ≤50 mg/dL for women)
	  ○ Hs-CRP>3.0 mg/L
	  ○ CrCl 30-60 mL/min
	  ○ Retinopathy
	  ○ Microalbuminuria or macroalbuminuria
	  ○ ABI <0.9 without claudication
	• TG 135-499 mg/dL
	• High intensity or maximally tolerated statin (+/- ezetimibe)

J Clin Lipidol. 2019;13(6):860-872.

Trial	REDUCE-IT
Population	• Age ≥ 45 + established CVD **OR** ≥ 50 + diabetes + ≥ 1 risk factor • TG 150-499 mg/dL • LDL 41-100 mg/dL • Stable statin dose
Intervention	Icosapent ethyl 2g BID
Comparator	Placebo
Outcomes	• CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or UA: 17.2% vs. 22% (p<0.001) ○ CV death: 4.3% vs. 5.2% (HR 0.80 (0.66-0.98)) ○ Nonfatal MI: 5.8% vs. 8.1% (HR 0.70 (0.59-0.82)) ○ Nonfatal stroke: 2.1% vs. 2.9% (HR 0.71 (0.54-0.94)) ○ Coronary revascularization: 9.2% vs. 13.3% (HR 0.66 (0.58-0.76)) ○ UA: 2.6% vs. 3.8% (HR 0.68 (0.53-0.87))

N Engl J Med 2019;380:11-22.

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