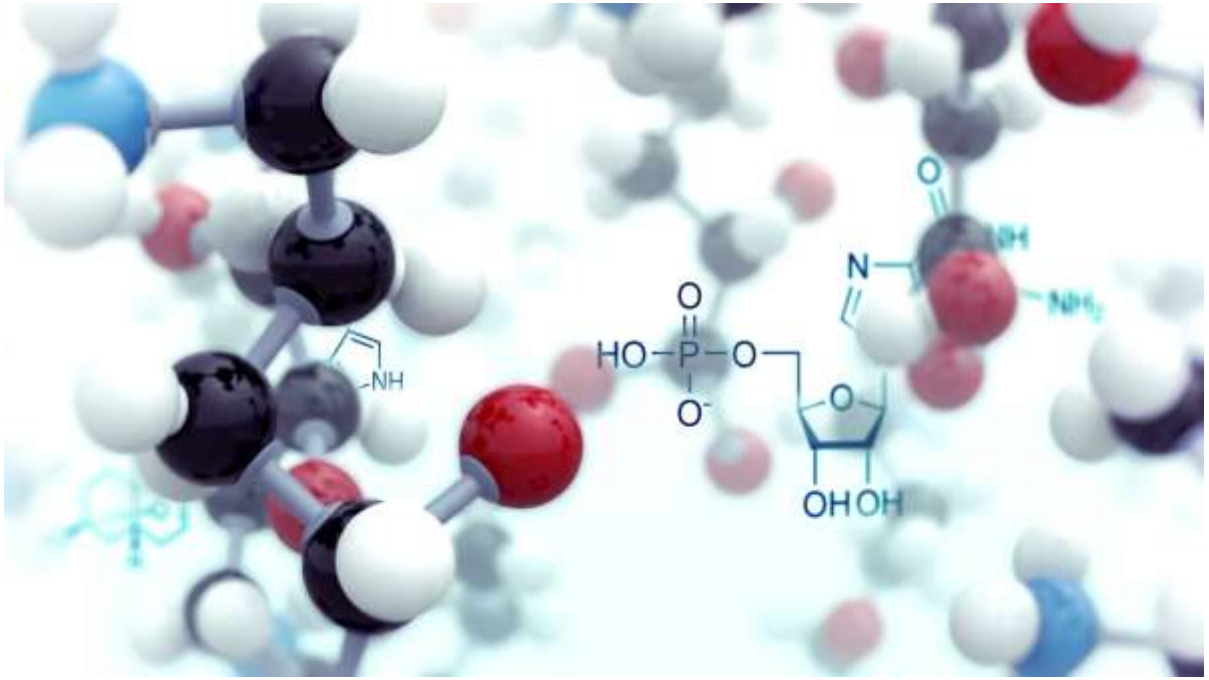
Cardiometabolic Medicine & Multimorbidity: A United Approach

Tora Sadigova

MD PhD

Associate Professor
Department of Internal Diseases

Azerbaijan Medical University



Why This Topic Matters

- Multimorbidity affects >70% of patients >55 years
- Hypertension, diabetes, obesity, CKD, dyslipidemia cluster together
- Fragmented care worsens outcomes
- Demand for integrated cardiometabolic pathways is growin

Definition: Cardiometabolic Medicine

- Integration of cardiology + endocrinology + nephrology

Focus on shared mechanisms: inflammation, insulin resistance, RAAS imbalance

- AHA introduces CKM health framework; ESC issues obesity–CVD consensus to guide integrated practice

- Aim today: synthesize CKM concept + ESC guidance + major trials into a single, pragmatic management strategy


Circulation

CURRENT ISSUE | ARCHIVE | JOUR

CORRECTION | Originally Published 25 March 2024 |

Correction to: Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association


ESC European Society of Cardiology

European Heart Journal (2024) 45, 4063–4098

SPECIAL ARTICLE

Diabetes and metabolic disorders

Obesity and cardiovascular disease: an ESC clinical consensus statement

Konstantinos C. Koskinas, Emeline M. Van Craenenbroeck, Charalambos Antoniades, Matthias Blüher, Thomas M. Gorter, Henner Hanssen, Nikolaus Marx, Theresa A. McDonagh, Geltrude Mingrone, Annika Rosengren, Eva B. Prescott, and the ESC Scientific Document Group

Key Pathophysiological Links

Insulin Resistance

→ Endothelial Dysfunction:

Hyperinsulinemia impairs nitric oxide (NO) production, leading to impaired vasodilation, vascular stiffness, and microvascular damage, contributing to HF and CKD.

Obesity

→ Systemic Inflammation:

Dysfunctional adipose tissue releases inflammatory cytokines (e.g., leptin), activating immune cells, causing oxidative stress, and promoting insulin resistance, impacting heart and kidney.

CKD

→ RAAS Activation + Sympathetic Drive:

Reduced kidney perfusion (from HF or other causes) and intrinsic kidney damage activate the Renin-Angiotensin-Aldosterone System (RAAS) and sympathetic nervous system (SNS), causing vasoconstriction, sodium retention, and worsening kidney and heart function.

HF

→ Renal Hypoperfusion → Worsening CKD:

Decreased cardiac output in HF leads to reduced blood flow to the kidneys (renal hypoperfusion), triggering RAAS and SNS activation, worsening CKD and creating a dangerous feedback loop (Cardiorenal Syndrome).

From Cardiometabolic Risk to CKM Syndrome

- AHA: **Cardiovascular-Kidney-Metabolic (CKM) syndrome** = health disorder due to interconnected abnormalities of CV system, kidneys, and metabolism
- Staging model: CKM stages 0–4 (from risk factors to overt CVD/CKD)
- Emphasis on **early detection, risk stratification, and prevention** across the continuum
- CKM concept formalizes what we see daily as “cardiometabolic multimorbidity”

Definitions of CKM Syndrome Stages

CKM syndrome stages	Definition
Stage 0: No CKM risk factors	Individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if Asian ancestry), Waist circumference ≥88/102 cm in women/men (or if Asian ancestry ≥80/90 cm in women/men), or Fasting blood glucose ≥100–124 mg/dL or HbA1c between 5.7% and 6.4%*
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension, MetS,† diabetes), or CKD
Stage 3: Subclinical CVD in CKM	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs-troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk. Risk equivalents of subclinical CVD Very high-risk CKD (stage G4 or G5 CKD or very high risk per KDIGO classification) High predicted 10-y CVD risk
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic;

CT, computed tomography; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; hs-troponin, high-sensitivity troponin; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome; and NT-proBNP; N-terminal pro-B-type natriuretic peptide.

* Individuals with gestational diabetes should receive intensified screening for impaired glucose tolerance after pregnancy.

† MetS is defined by the presence of 3 or more of the following: (1) waist circumference ≥88 cm for women and ≥102 cm for men (≥80 cm for women and ≥90 cm for men if Asian ancestry); (2) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women; (3) triglycerides ≥150 mg/dL; (4) elevated blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg and/or use of antihypertensive medications); and (5) fasting blood glucose ≥100 mg/dL.

ESC Perspective: Obesity & CVD

- ESC clinical consensus: obesity is a **major, causal, and modifiable risk factor** for CVD across the life-course
- **~Two-thirds of deaths related to high BMI are cardiovascular**
- Interacts with hypertension, dyslipidemia, T2DM, HF, AF, CAD
- Calls for systematic **obesity assessment and treatment** within cardiology services

Definition: Multimorbidity

≥2 chronic conditions that interact and amplify each other

Typical cluster:

- Hypertension
- Diabetes / prediabetes
- Obesity
- Dyslipidemia
- NAFLD
- CKD
- Heart failure

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Multimorbidity Cluster in Clinical Practice

- Typical cluster: HTN + T2DM/prediabetes + obesity + dyslipidemia + NAFLD + CKD + HF (HFrEF/HFpEF)
- Shared pathophysiology: insulin resistance, chronic inflammation, endothelial dysfunction, RAAS and SNS activation
- Multimorbidity ≈ “CKM Stage 2–4” (AHA) with high event rates
- Requires systems-based, not disease-based, management

The Need for a Unified Approach

- Traditional silo-based care fails in multimorbidity
- Leads to polypharmacy, conflicting treatments, poor adherence
- ESC guidelines emphasize integrated, risk-based management
- Focus on cross-beneficial therapies

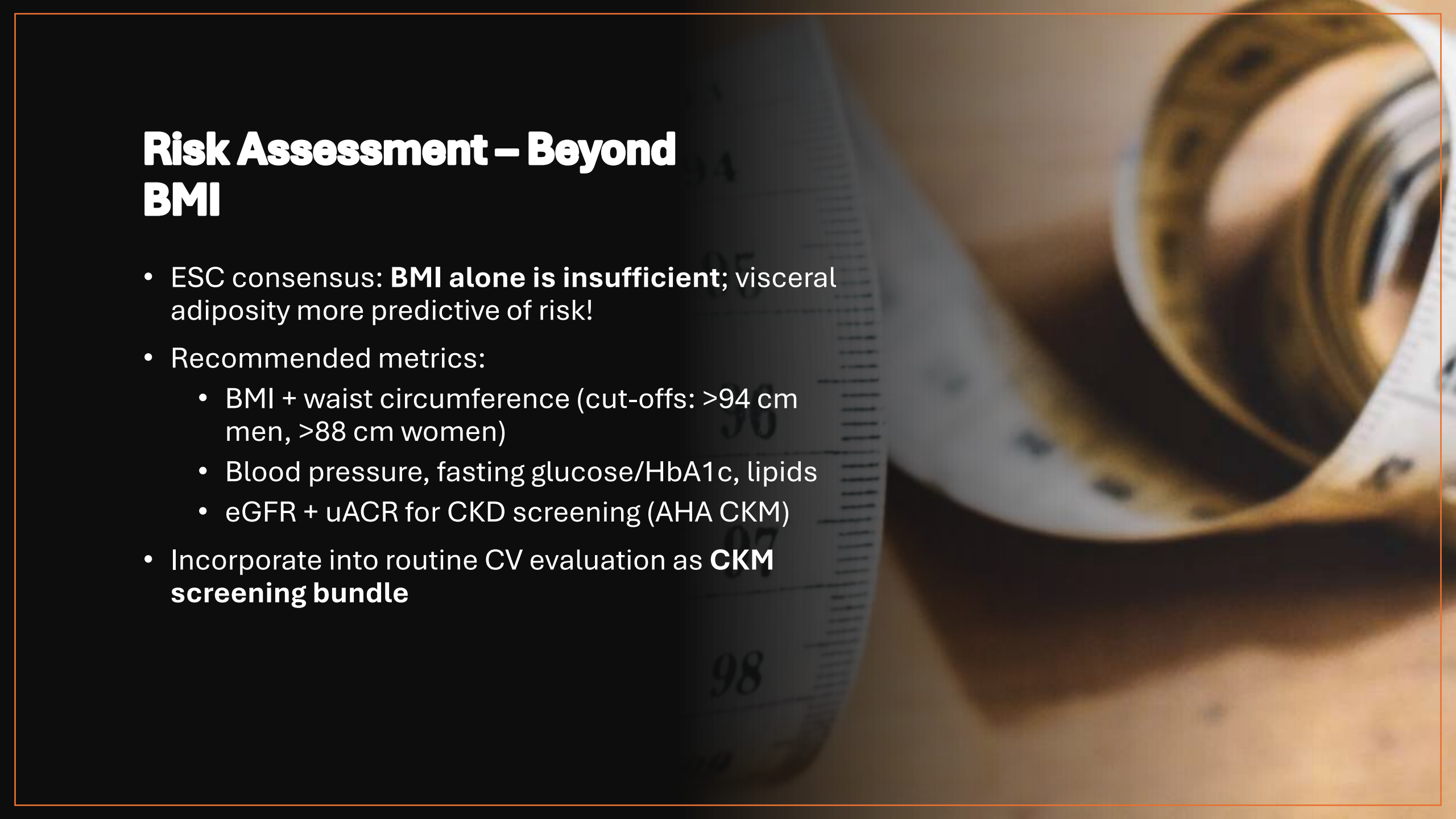
Diagnostic Work-Up

- BMI, waist circumference
- BP, ECG, Echo
- Fasting glucose, HbA1c
- Lipid panel
- ALT/AST, liver US
- eGFR, ACR
- Coronary calcium score (if available)

ESC 2023 endorses comprehensive cardiometabolic screening.

Risk Assessment – Beyond BMI

- ESC consensus: **BMI alone is insufficient**; visceral adiposity more predictive of risk!
- Recommended metrics:
  - BMI + waist circumference (cut-offs: >94 cm men, >88 cm women)
  - Blood pressure, fasting glucose/HbA1c, lipids
  - eGFR + uACR for CKD screening (AHA CKM)
- Incorporate into routine CV evaluation as **CKM screening bundle**



ESC Guidelines – Core Therapeutic Pillars

- Summarize converging ESC recommendations (HF, diabetes-CVD, obesity):
- **SGLT2 inhibitors** for HF (HFrEF–HFpEF), CKD, T2DM with high CV risk
- **GLP-1 RAs** and new anti-obesity agents for weight and CV risk reduction
- **ARNI** as first-line in HFrEF (where feasible)
- **Finerenone/MRAs** in T2DM + CKD
- Intensive lipid-lowering and BP control as background “hygiene”

SGLT2 Inhibitors – Evidence Based cure

Key trials illustrating cross-organ benefits:

- **DAPA-HF, EMPEROR-Reduced:** ↓ CV death/HF hospitalization in HFrEF (with/without T2DM)
- **DELIVER, EMPEROR-Preserved:** benefit extended to HFpEF/HFmrEF
- **EMPA-Kidney, DAPA-CKD:** robust renal protection + HF benefit in CKD

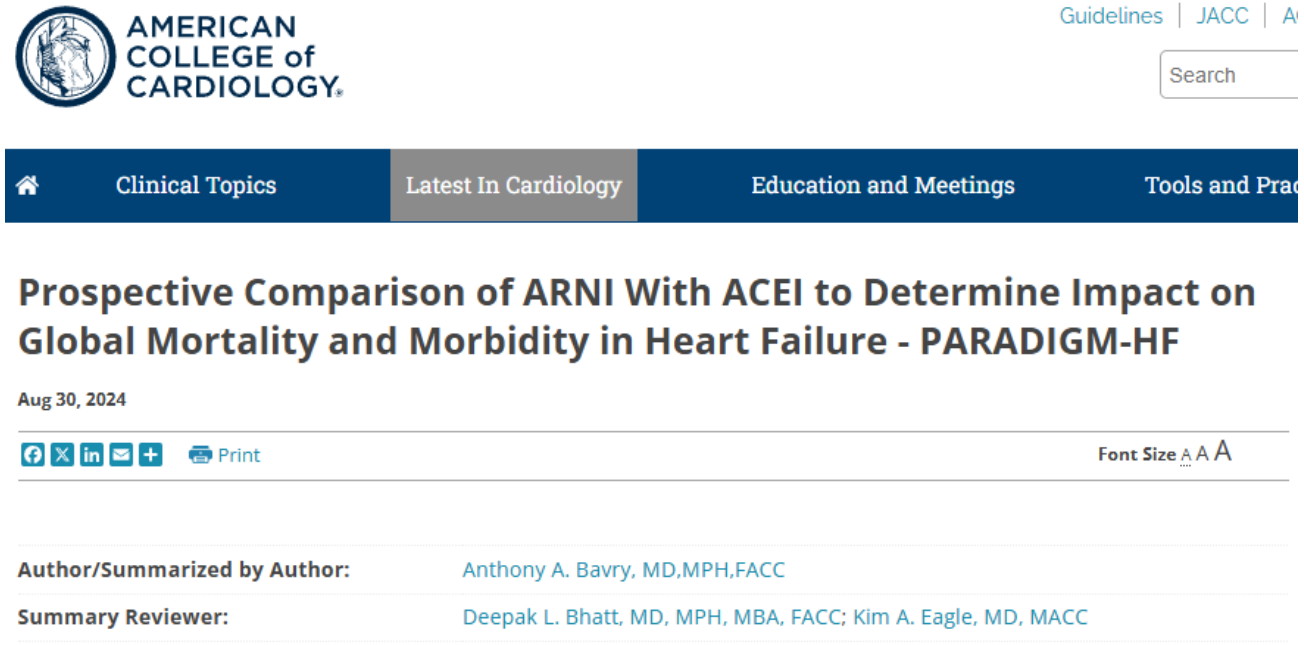
ESC/AHA: SGLT2i now **foundational therapy** for HF and CKM spectrum

GLP-1 RAs – CV Outcomes & Obesity

- CVOTs: **LEADER (liraglutide), SUSTAIN-6 (semaglutide), REWIND (dulaglutide)** → ↓ MACE in high-risk
- **SELECT trial**: semaglutide 2.4 mg in obesity without diabetes → **~20% MACE reduction** vs placebo
- Additional benefits: substantial and sustained weight loss, BP reduction, improved lipids, possible renal benefit
- ESC obesity consensus: GLP-1 RAs central in treatment algorithm for obesity with CVD

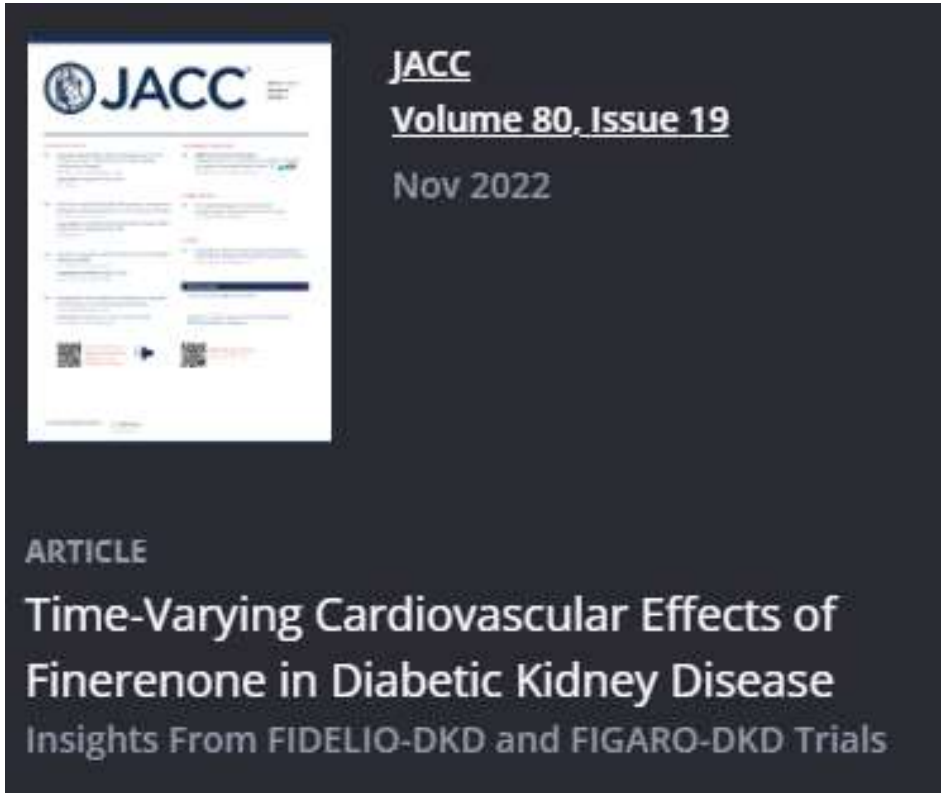
ARNI & HF – Structural Cornerstone

- **PARADIGM-HF:** sacubitril/valsartan vs enalapril → ~20% ↓ CV death or HF hospitalization in HFrEF
- 2023 ESC HF update: ARNI recommended as first-line in symptomatic HFrEF whenever possible
- Benefits particularly relevant in CKM patients with HFrEF (high event rates, remodeling)
- Integrates with SGLT2, MRAs, beta-blockers as part of **quadruple HF therapy**



Finerenone & MRAs – Linking CKD and HF

- **FIDELIO-DKD & FIGARO-DKD:** finerenone in T2DM + CKD → ↓ kidney failure progression and ↓ CV events (HF hospitalization, MI, stroke)
- ESC / KDIGO endorse finerenone as **preferred non-steroidal MRA** in CKD + T2DM to prevent HF and CKD progression
- Complements RAAS blockade + SGLT2i in CKM patients with albuminuric CKD



Obesity Treatment – Evidence & ESC Algorithm

Lifestyle interventions remain first-line, but **weight-loss pharmacotherapy** now evidence-based

GLP-1 RA (semaglutide) and dual agonists produce **15–20% weight loss** and CV benefit in SELECT

ESC consensus: for obesity with CVD or high risk, add **anti-obesity drugs and/or bariatric procedures** as part of cardiology care, not **“COSMETIC”** support

From Guidelines to Unified Regimen

Proposed **CKM-oriented core regimen** (***individualized***):

- **SGLT2 inhibitor** – HF + CKD + T2DM benefit
- **GLP-1 RA / anti-obesity agent** – weight + MACE reduction
- **ARNI** (if HFrEF)
- **Finerenone / MRA** in albuminuric CKD + T2DM
- Statin ± ezetimibe/PCSK9i; ACEi/ARB where indicated

This reflects convergence of AHA CKM advisory + ESC HF/diabetes/obesity documents

Reducing Polypharmacy & Fragmentation

- AHA CKM advisory: priority to **reduce fragmented, organ-specific care** and align specialists within shared pathways
- Use **cross-benefit drugs** instead of adding organ-specific agents without prognostic gain
- Simplify regimens (fix-dose combinations, once-weekly injectables) to enhance adherence
- Embed lifestyle and weight management within cardiology follow-up

Practical Algorithm – CKM Patient

Stepwise ESC/AHA-aligned approach:

- **Stage & stratify** (CKM stage, obesity grade, HF/CKD presence)
- Initiate **foundational therapies** (SGLT2, ARNI, MRA, statin, BP control)
- Add **GLP-1 RA / anti-obesity therapy** when BMI and risk profile justify
- Regularly reassess eGFR, uACR, HbA1c, lipids, weight, and HF status
- Involve multidisciplinary team (cardio-nephro-endo, dietitian, bariatric)

Research Gaps & Future Directions

- Optimal sequencing/combination of GLP-1, SGLT2, dual agonists in CKM
- Long-term outcomes in non-diabetic obesity with multi-organ disease **(post-SELECT era)**
- Integration of **omics, imaging, and AI risk engines** into CKM staging
- Need for trials with **multimorbidity endpoints**, not single-organ outcomes only

Key Messages

- CKM/obesity statements from **AHA and ESC** provide a **conceptual and practical framework** for cardiometabolic multimorbidity.
- Major trials (SGLT2, GLP-1, ARNI, finerenone) deliver **cross-organ risk reduction** and should be positioned as core therapy.
- Move from **organ-centric** to **unified CKM-centric** management to reduce events and improve survival.
- **Call to action**: implement CKM staging and ESC-aligned obesity/HF/diabetes algorithms in everyday cardiology practice.