

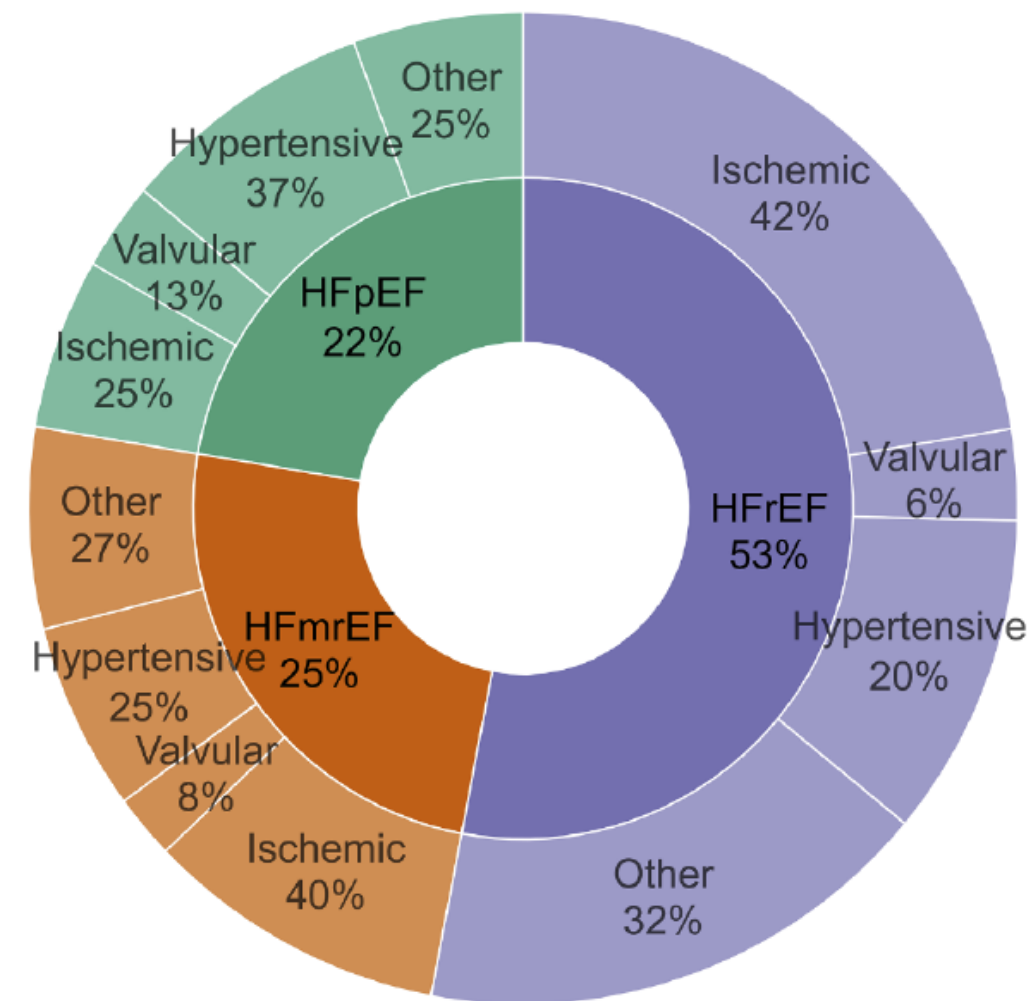
Ischemia Miocardica e Disfunzione Ventricolare Sinistra nella Sindrome Cardio-Nefro-Metabolica

Leonardo Bolognese, MD, FESC, FACC

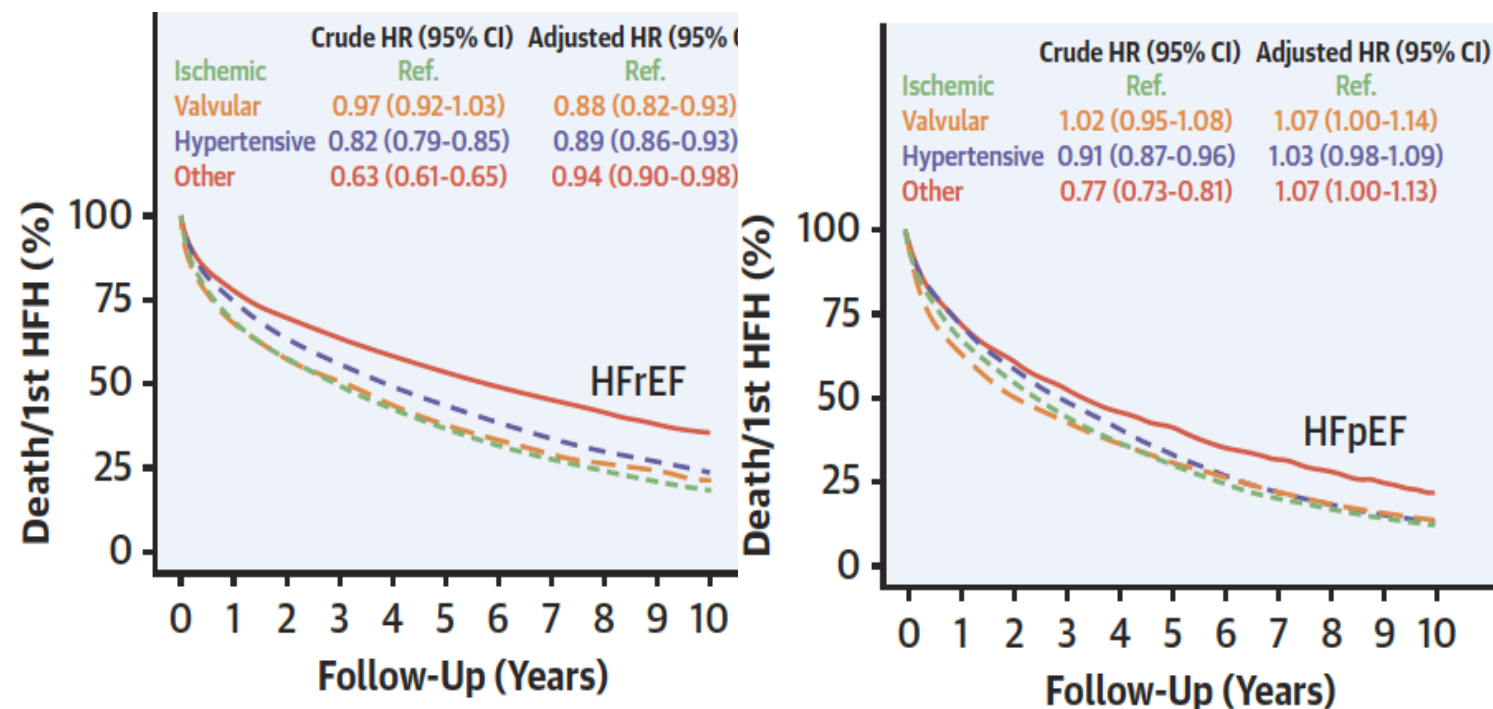
Myocardial Ischemia and LV Dysfunction

- Myocardial ischemia with obstructive CAD, LV dysfunction and HFrEF
- Myocardial ischemia without obstructive CAD, LV dysfunction and HFpEF

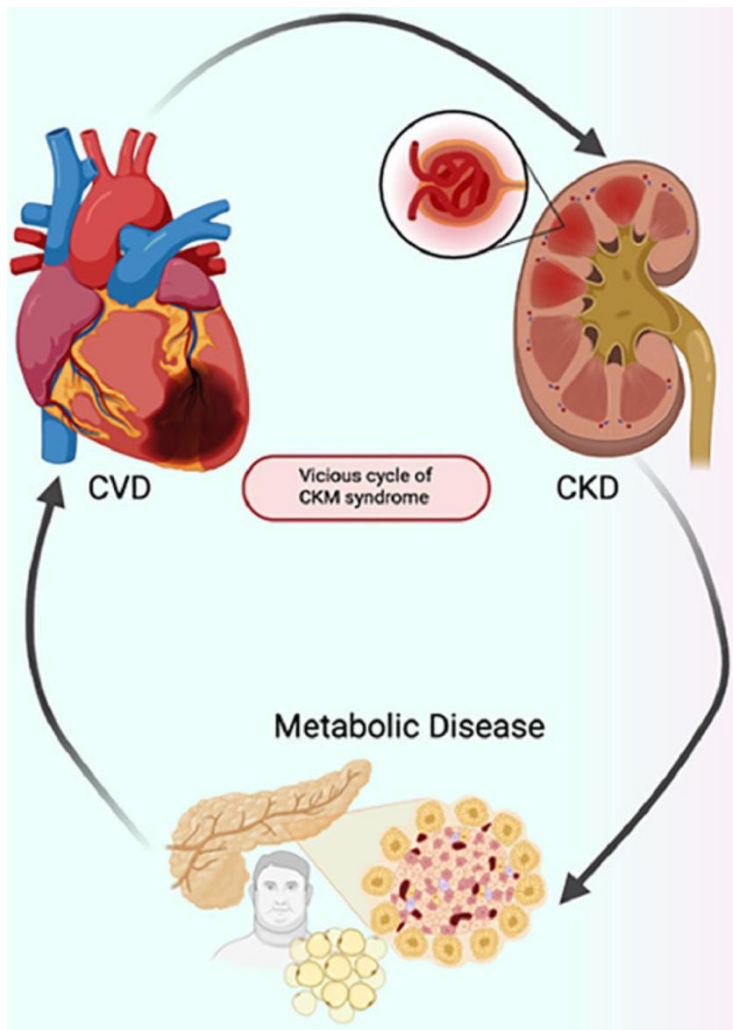
Prevalence and Prognosis of Ischemic LV Dysfunction in Heart Failure



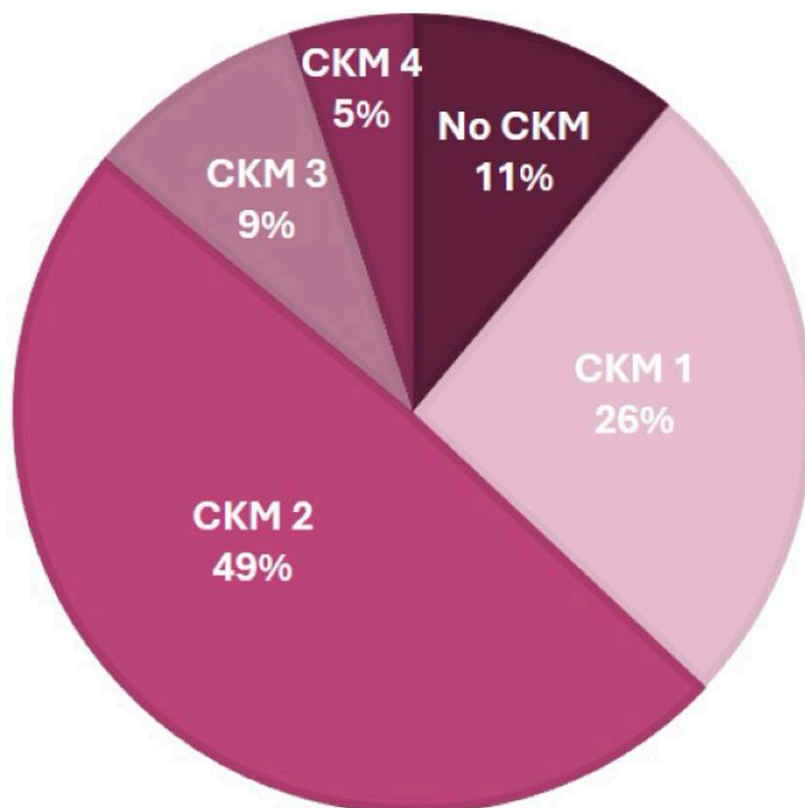
All-Cause Death and First HFHs According to Etiology



Cardio-Kidney-Metabolic Syndrome

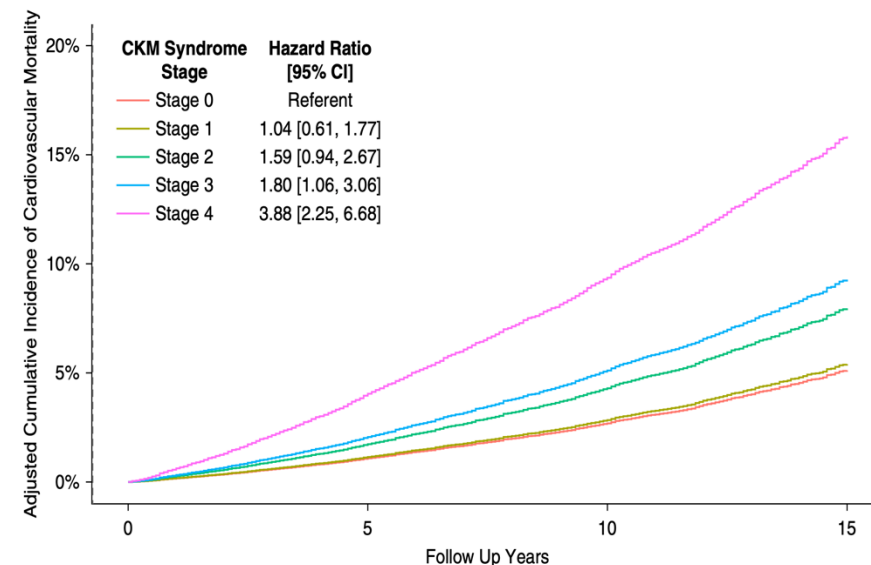


High Prevalence



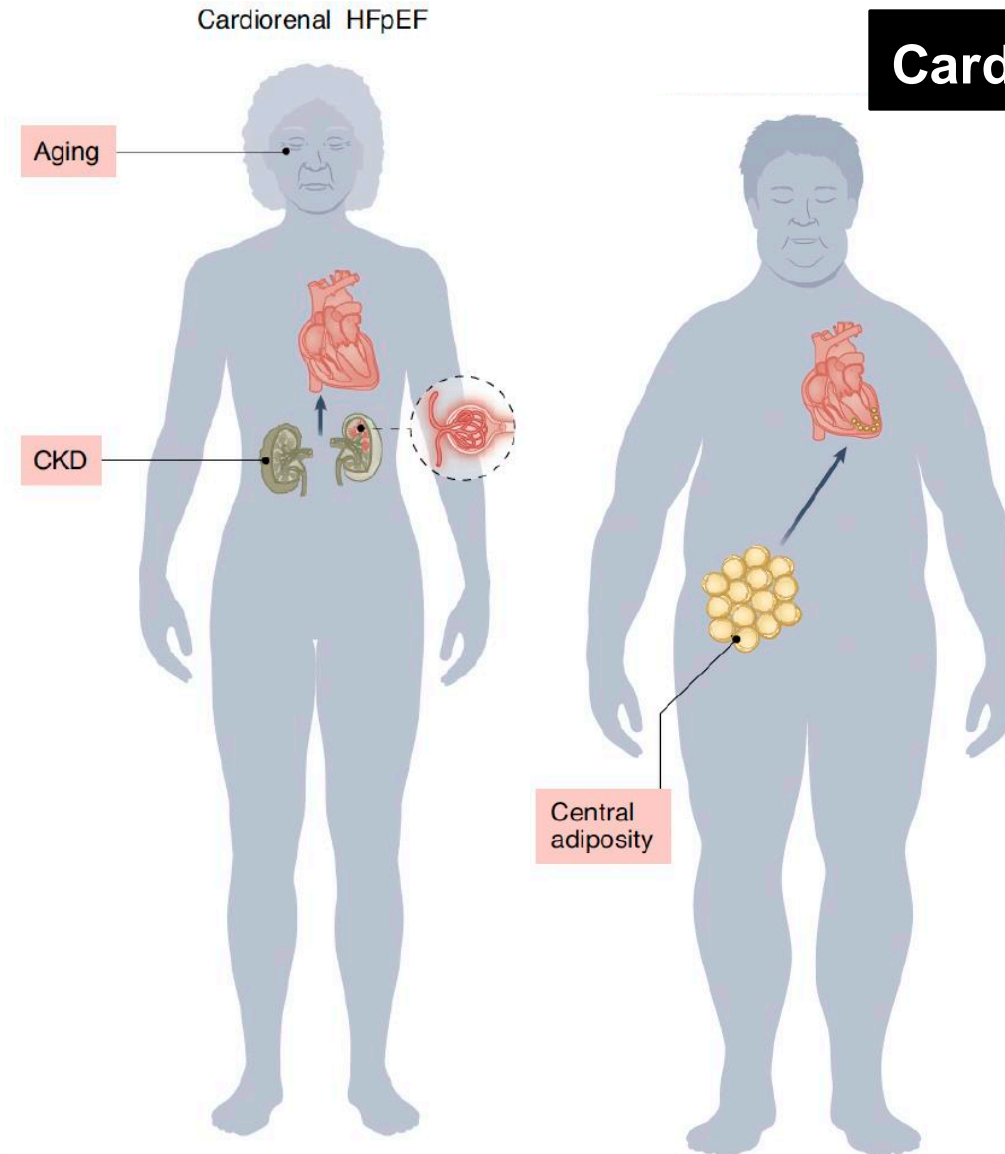
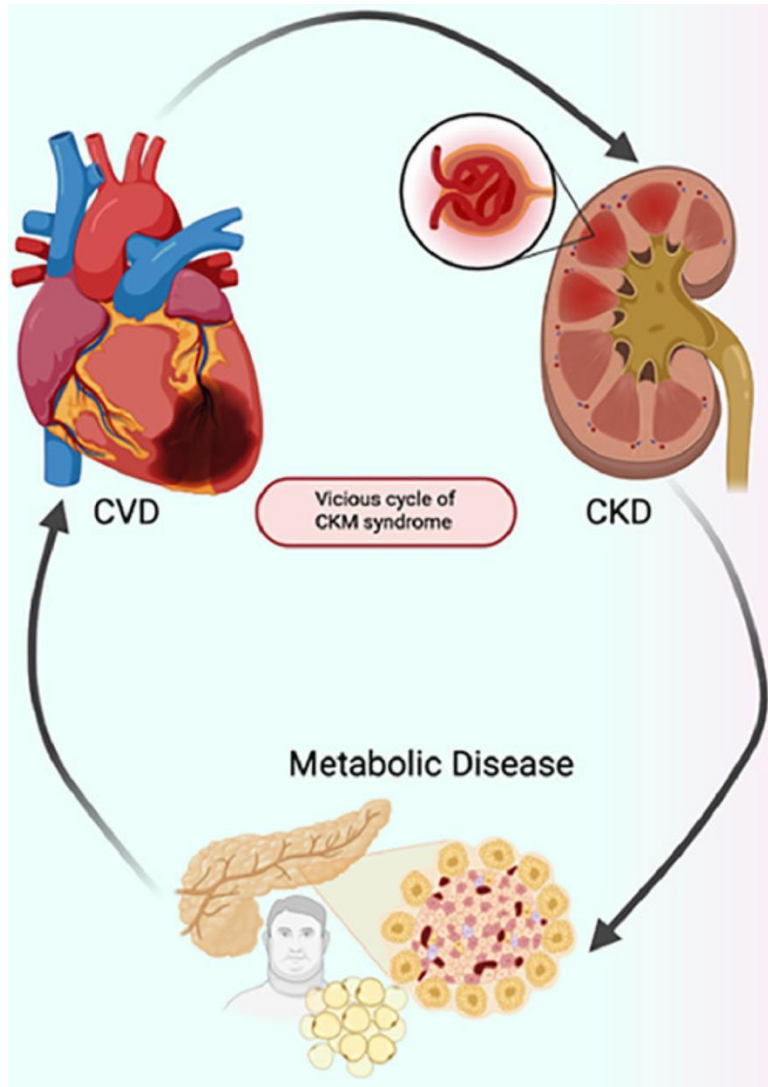
Aggarwal R et al JAMA 2024; 331:1858

Poor Prognosis

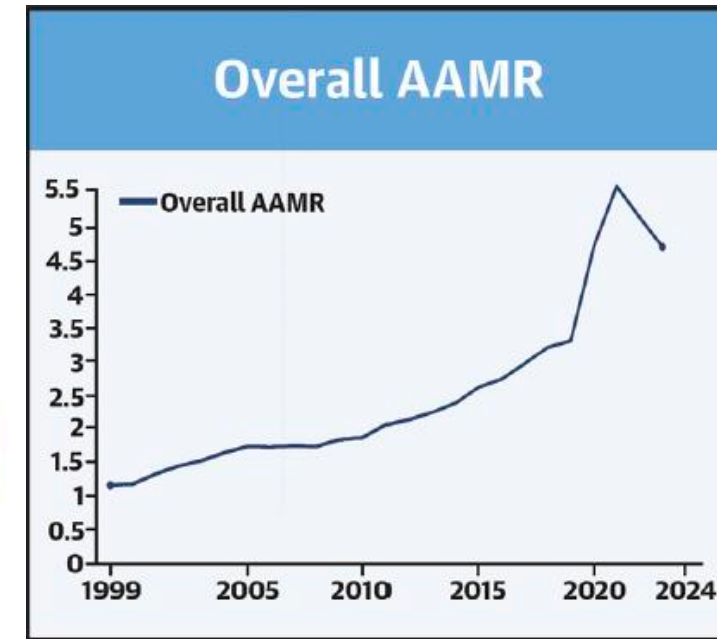


Chen Y, et al. JACC Adv. 2025;4(6):101843

HFpEF – CKM – Phenogroups - Prognosis



Cardiometabolic HFpEF



Sajid M, et al.
JACC Adv. 2025; 4:102303

HFpEF: The Prevailing Wisdom

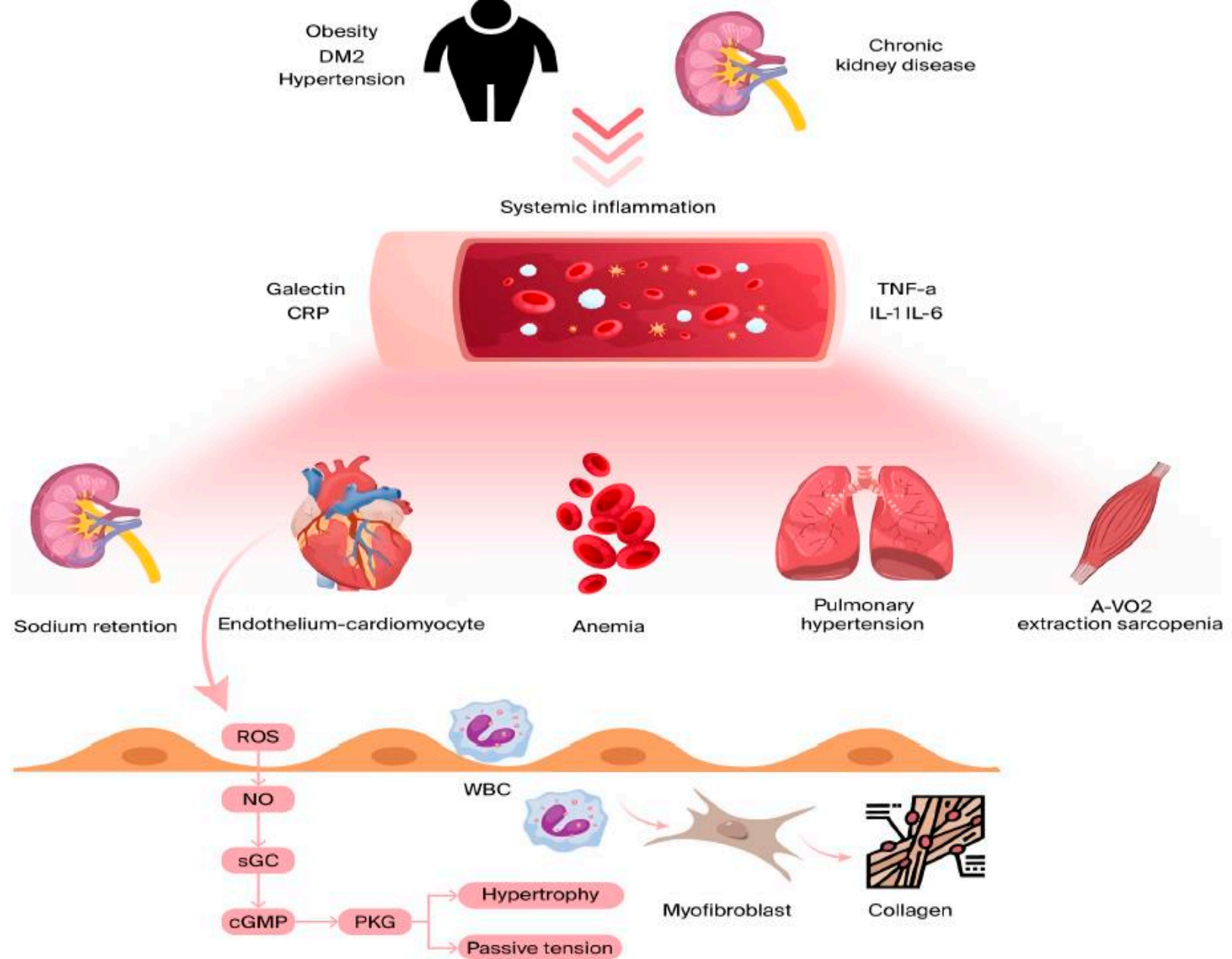
Comorbidities

Systemic low-grade inflammation

Coronary microvascular dysfunction

Myocardial Ischemia

Myocardial structural and functional changes





WORLD
HEALTH
SUMMIT

OCTOBER 12–14, 2025
BERLIN, GERMANY
& DIGITAL

Jeffrey Lazarus
The Barcelona Institute for
Global Health (ISGlobal)
Head of the Public Health
Liver Group Spain

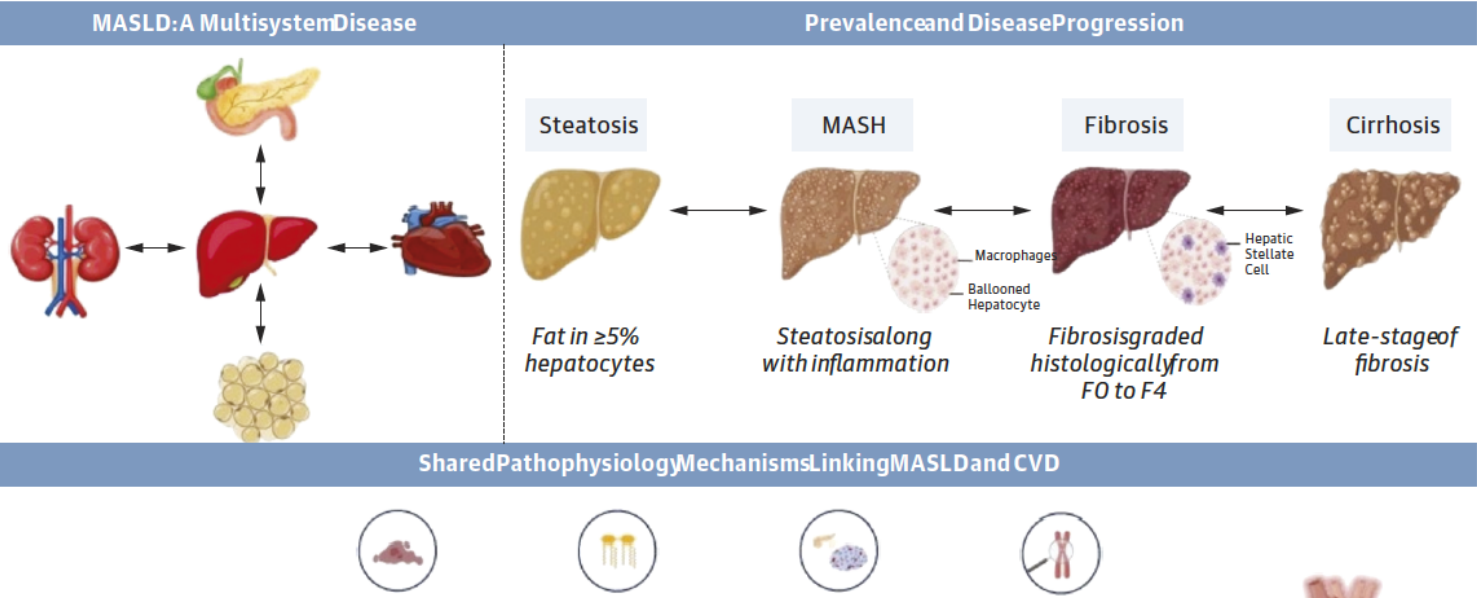
***“How many of you have
heard of MASLD?”***

***Less than half of the audience
members raised their hands.***



***“That’s good,” Lazarus said.
“That means I can keep
referring to it as the prevalent
NCD you’ve probably never
heard of.”***

Metabolic Dysfunction–Associated Steatotic Liver Disease and CV Disease



- MASLD is a major risk factor for cardiovascular mortality
- MASLD should be integrated into CKM staging enhancing early risk stratification

From Cardiovascular-Kidney-Metabolic Syndrome to Cardiovascular-Kidney-Hepatic-Metabolic Syndrome



Cardiovascular Disease

Diagnosis			CV Risk Stratification		Management		
Assessment of Steatosis			Risk Assessment Tools		Pharmacological		
MRI	Ultrasound	CT Scan	Framingham Risk Score Pooled Equation Cohort SCORE2-SCORE2OP PREVENT Calculator ASCVD Risk Score		FDA approved: Resmetirom	Statins and ACEi/ARBs (if CV indications are present)	SGLT2i and GLP-1 analogs
Assessment of Fibrosis					Non-pharmacological		
VCTE and MRE	NFS and FIB-4	Liver Biopsy			Healthy Diet	Exercise	Bariatric Surgery

MASLD in the cardiovascular–kidney– metabolic health framework: what does it add to the table?

- **MASLD requires metabolic dysfunction, which places nearly all patients at least in Stage 2 CKM thereby limiting potential additive value of MASLD**
- **It is unclear whether the association between MASLD and CVD is causal or largely mediated by shared risk factors**
- **Finally, does the integration change treatment decision?**

MASLD is a central player in the pathophysiology and clinical phenotype of cardiovascular disease

HFpEF: The Prevailing Wisdom

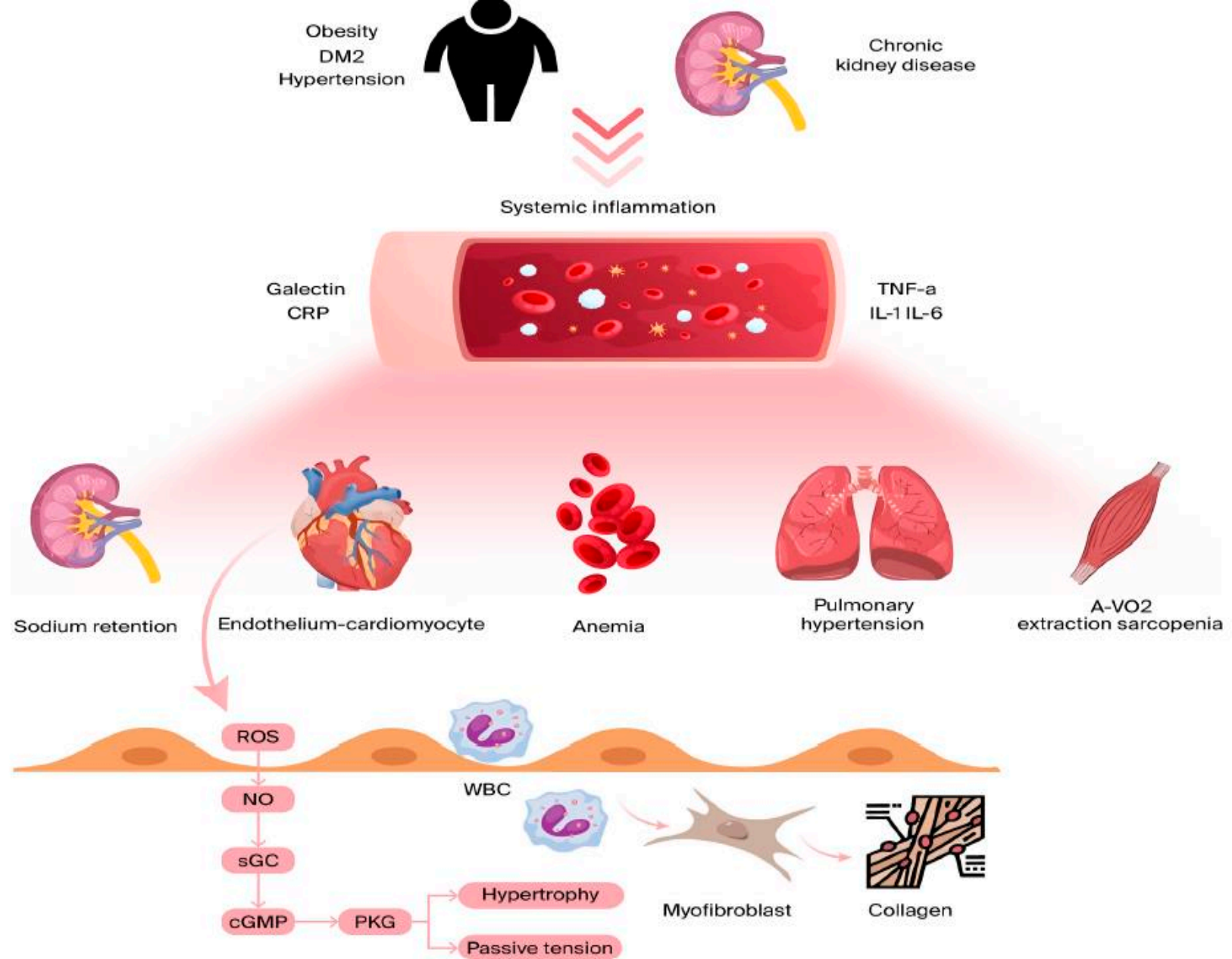
Comorbidities

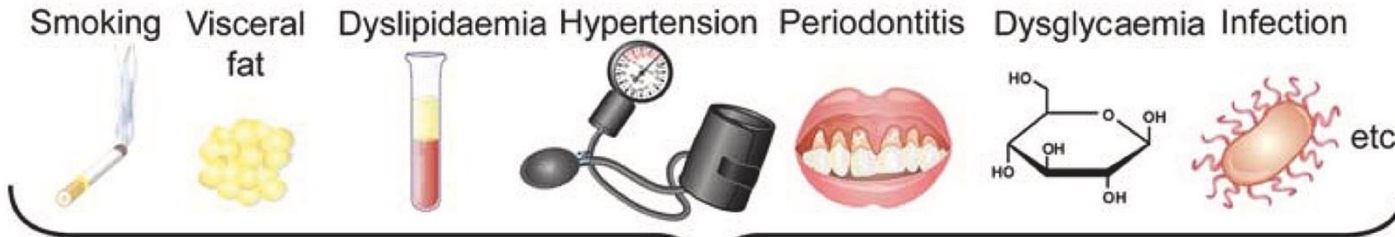
Systemic low-grade inflammation

Coronary microvascular dysfunction

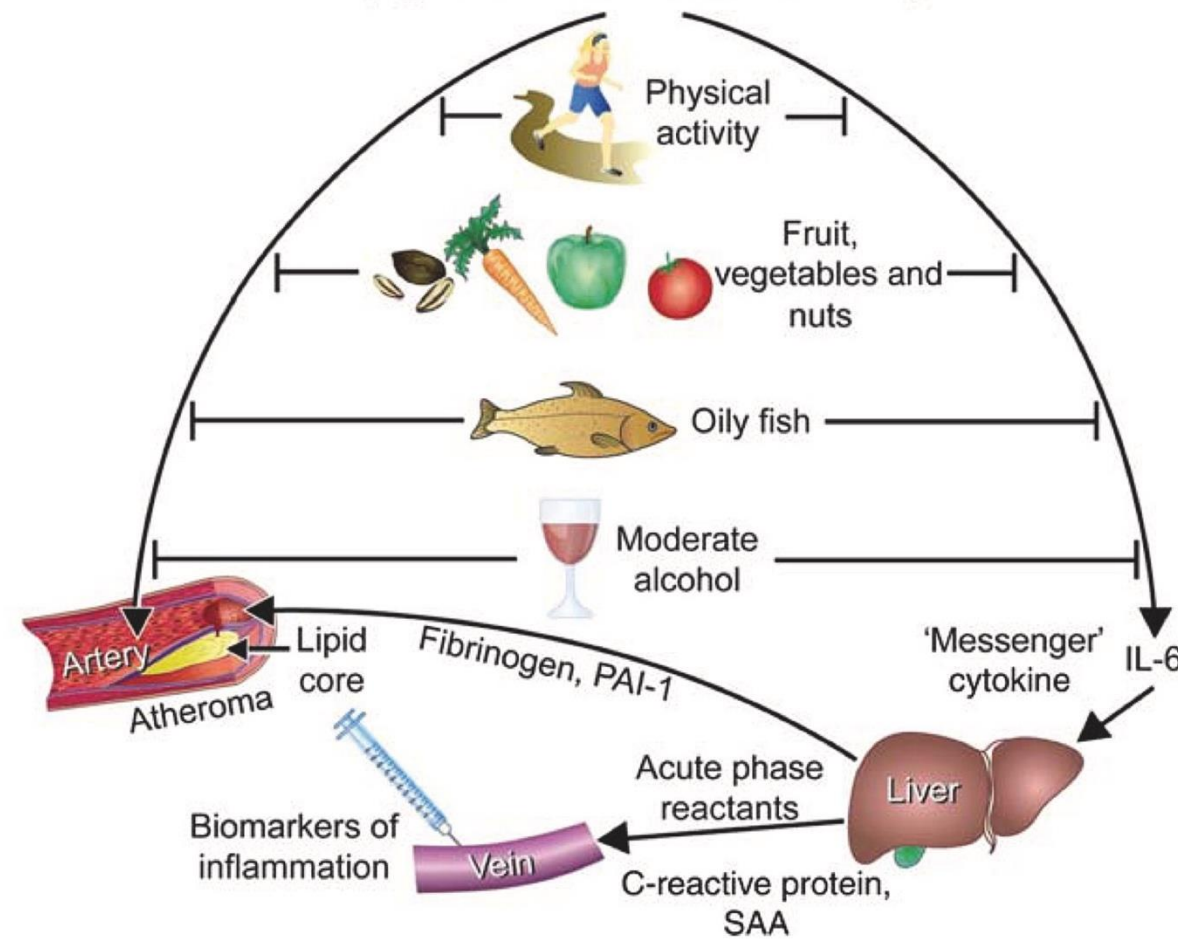
Myocardial Ischemia

Myocardial structural and functional changes



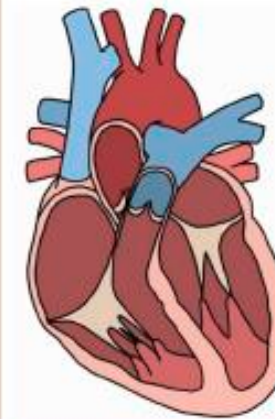


Proinflammatory cytokines
(e.g. IL-1, TNF, IL-18, CD40L, MCP-1)



Cytokines

- TNF- α
 - stimulates the production of other pro-inflammatory cytokines
 - progression and intensification of adverse remodeling and dysfunction
 - negative inotropic effects
 - extracellular matrix degradation
 - cardiomyocyte apoptosis
- Interleukin-1 family
 - stimulate apoptosis on cardiomyocytes
 - arterial stiffness
 - stimulate the expression of adhesion molecules in endothelial cells \rightarrow adhesive interactions with circulating leukocytes and \uparrow the recruitment of inflammatory cells into the myocardium
 - associated with worse functional capacity in patients with HF
- Interleukin-6
 - stimulatory effects of neurohormonal pathways
 - independent predictor of decompensation of HF and death
 - negative inotropic effects
 - hypertrophy and fibrosis myocardial stiffness



hs-CRP

- \uparrow myocardial tissue injury and scarring after infection
- \uparrow endothelial adhesion molecules
- triggering LDL cholesterol oxidation
- elevated hs-CRP in asymptomatic patients with HF \rightarrow worse outcomes and progression of HF

Myeloperoxidase

- affects vasomotor tone (\uparrow vasoconstriction and \downarrow vasodilation)
- \downarrow endothelial NO bioavailability
- \uparrow myocardial dysfunction

RAAS Biomarkers

- Ang 1-7 \rightarrow anti-inflammatory, antioxidant and antifibrotic effects
- elevated Ang II levels associated with mortality and HF

Neutrophils

- elevated levels are associated with major adverse cardiac events, chronic kidney disease and mortality

Ultrasound

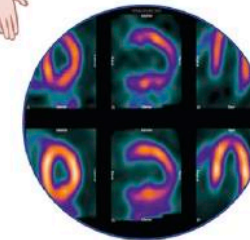
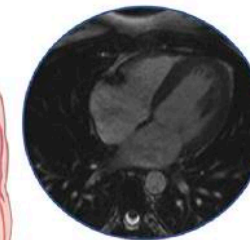
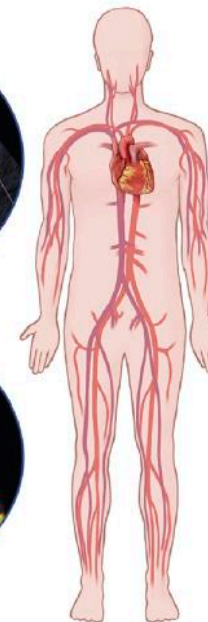
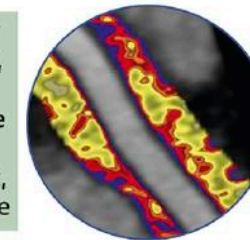
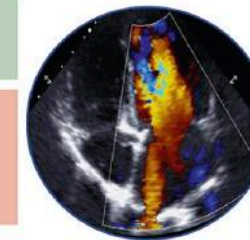
Low cost,
non-invasive

Low resolution,
no clinical use
currently for tissue
inflammation

Computed tomography

Validated methods for
inflammation detection,
currently used for
coronary artery disease
diagnosis and cardio-
vascular risk assessment,
growing usage in practice

Radiation/contrast



Cardiac MRI

Can assess
structural disease

No use currently
validated for vascular
inflammation,
time consuming

PET CT/MRI

Gold standard for
inflammation with
high specificity

Lack of clinical
expertise and
availability outside
major centers

HFpEF: The Prevailing Wisdom

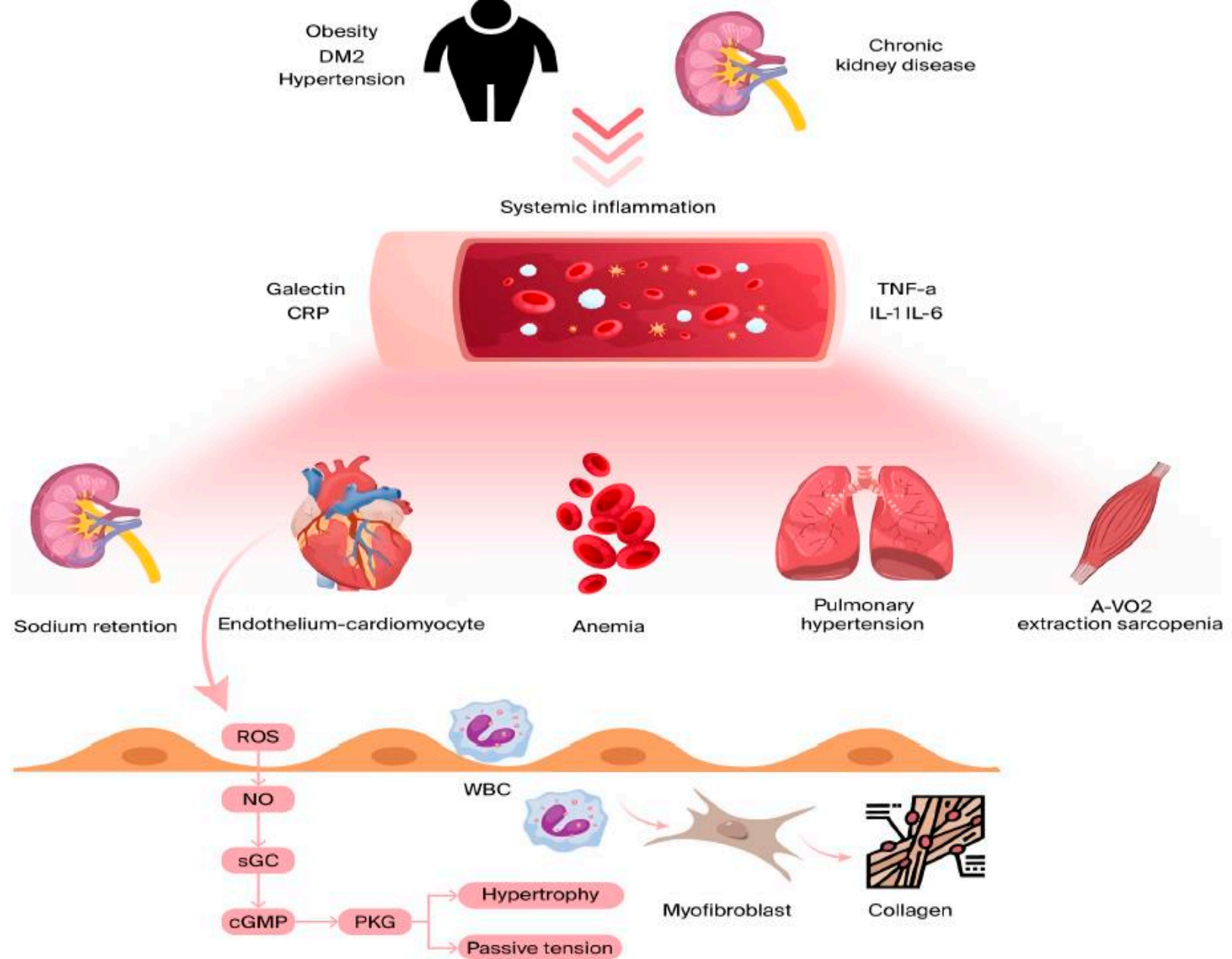
Comorbidities

Systemic low-grade inflammation

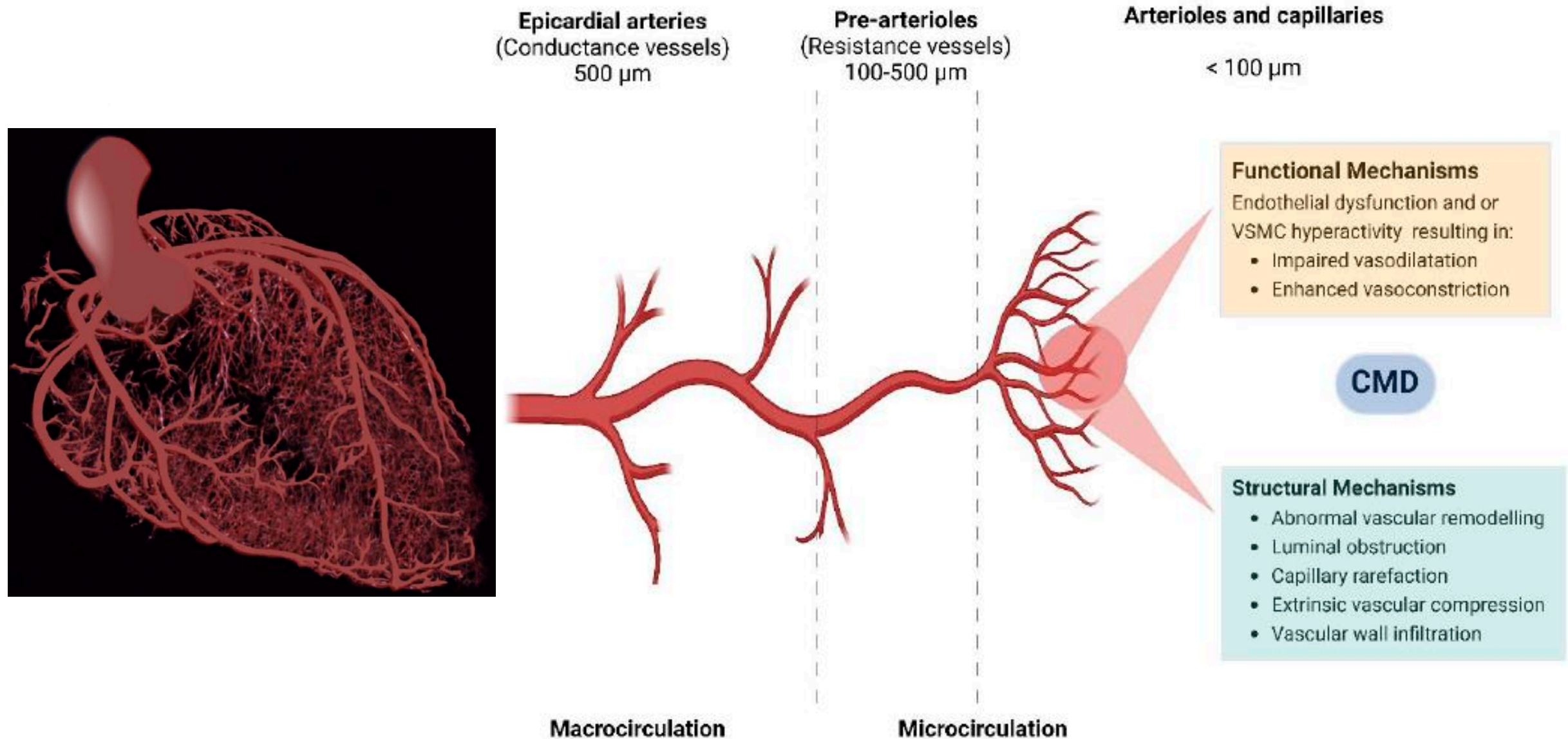
Coronary microvascular dysfunction

Myocardial Ischemia

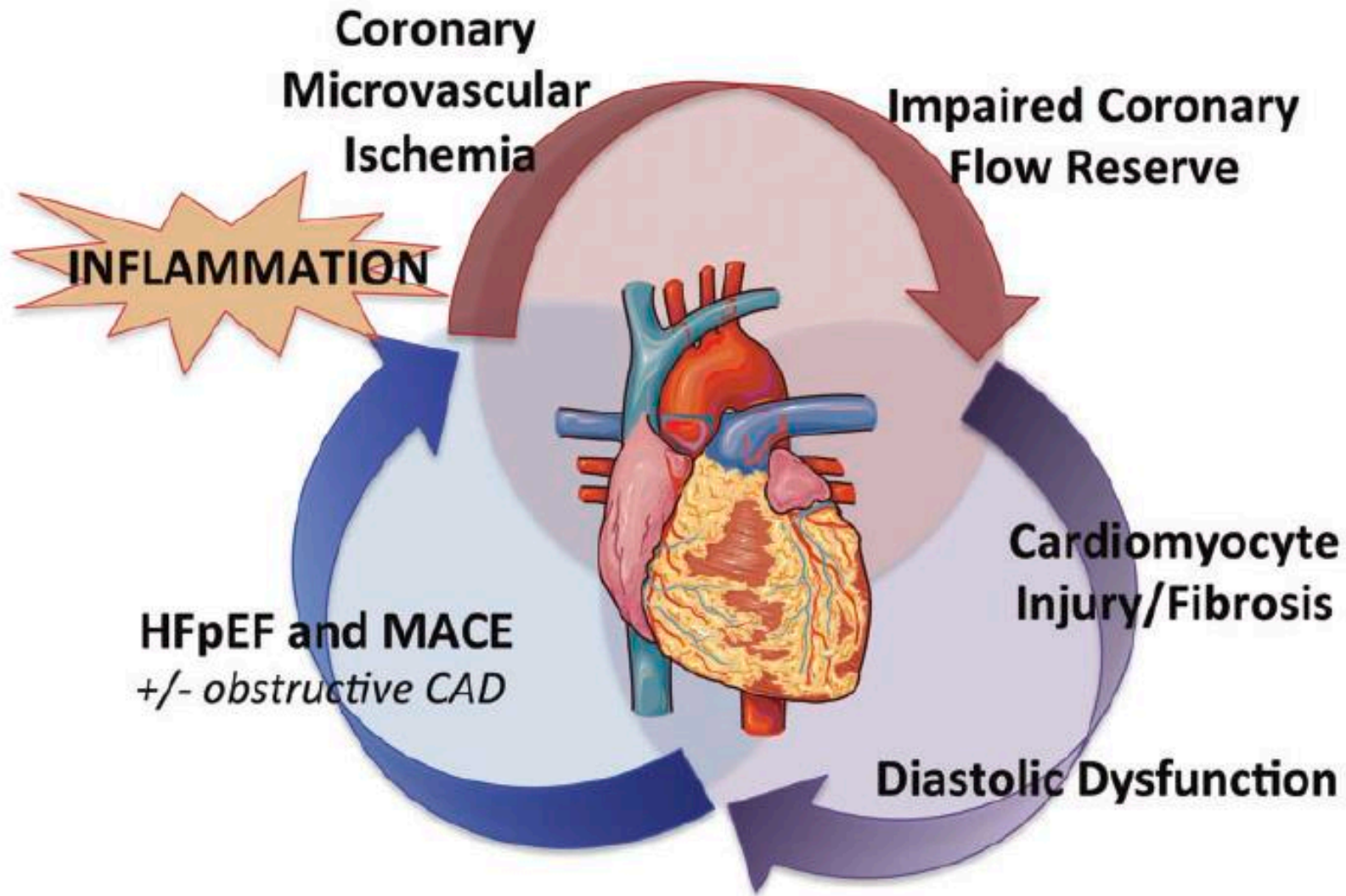
Myocardial structural and functional changes



Pathophysiology of coronary microvascular dysfunction

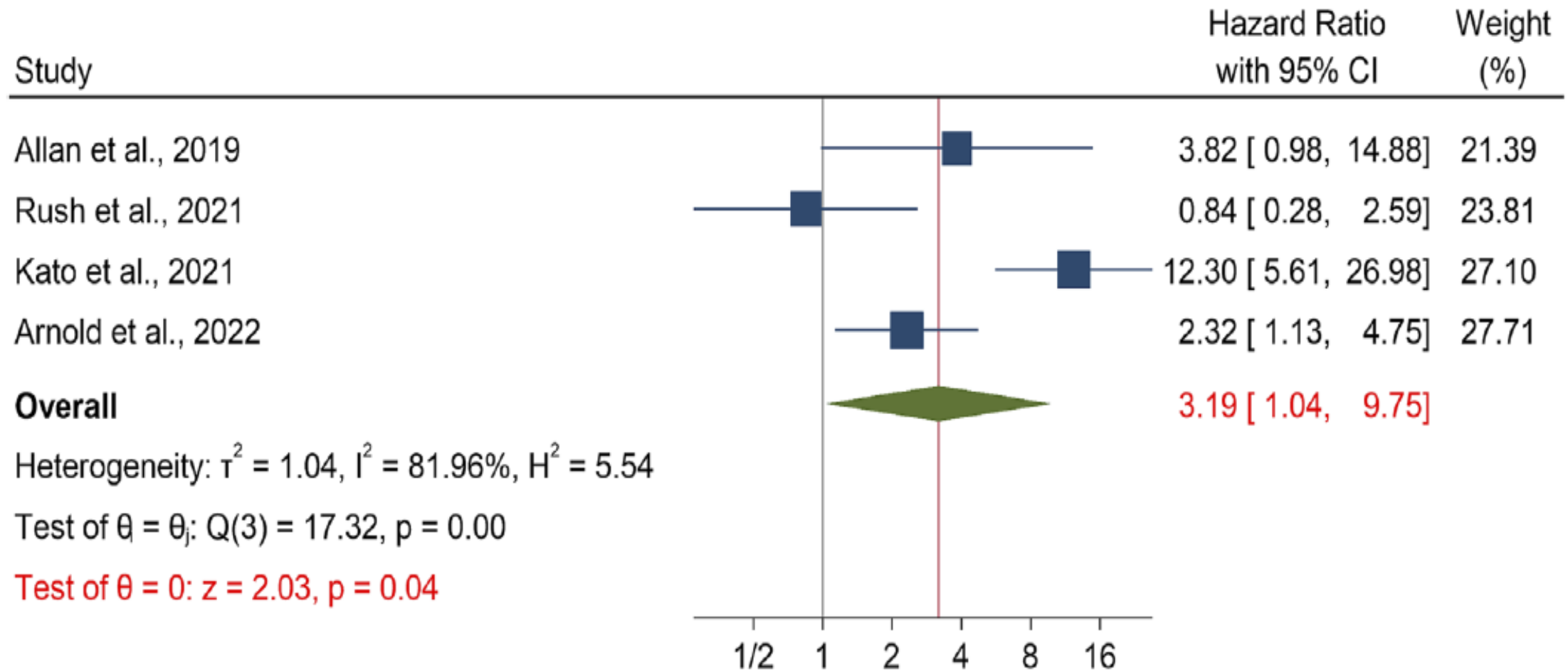


Conceptual model of the pathophysiology linking coronary microvascular ischaemia, low-level cardiomyocyte injury, and myocardial stiffness to HFpEF

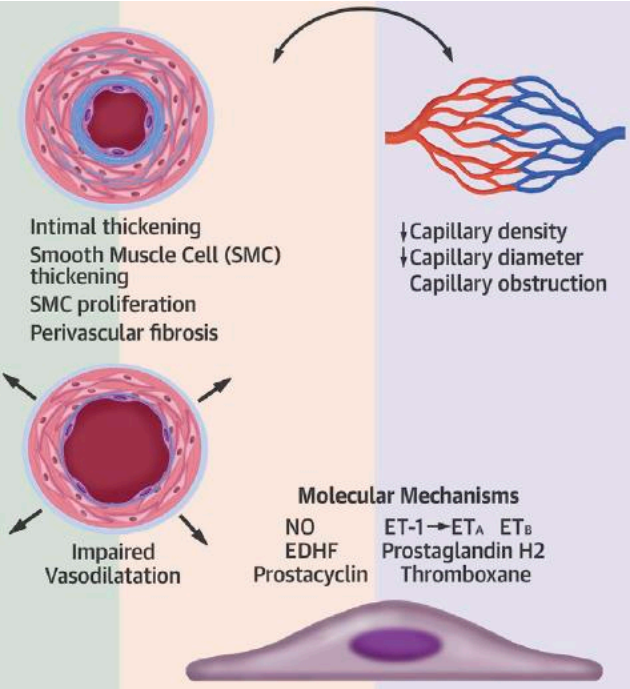


Prognostic Impact of CMD and Diastolic LV Dysfunction

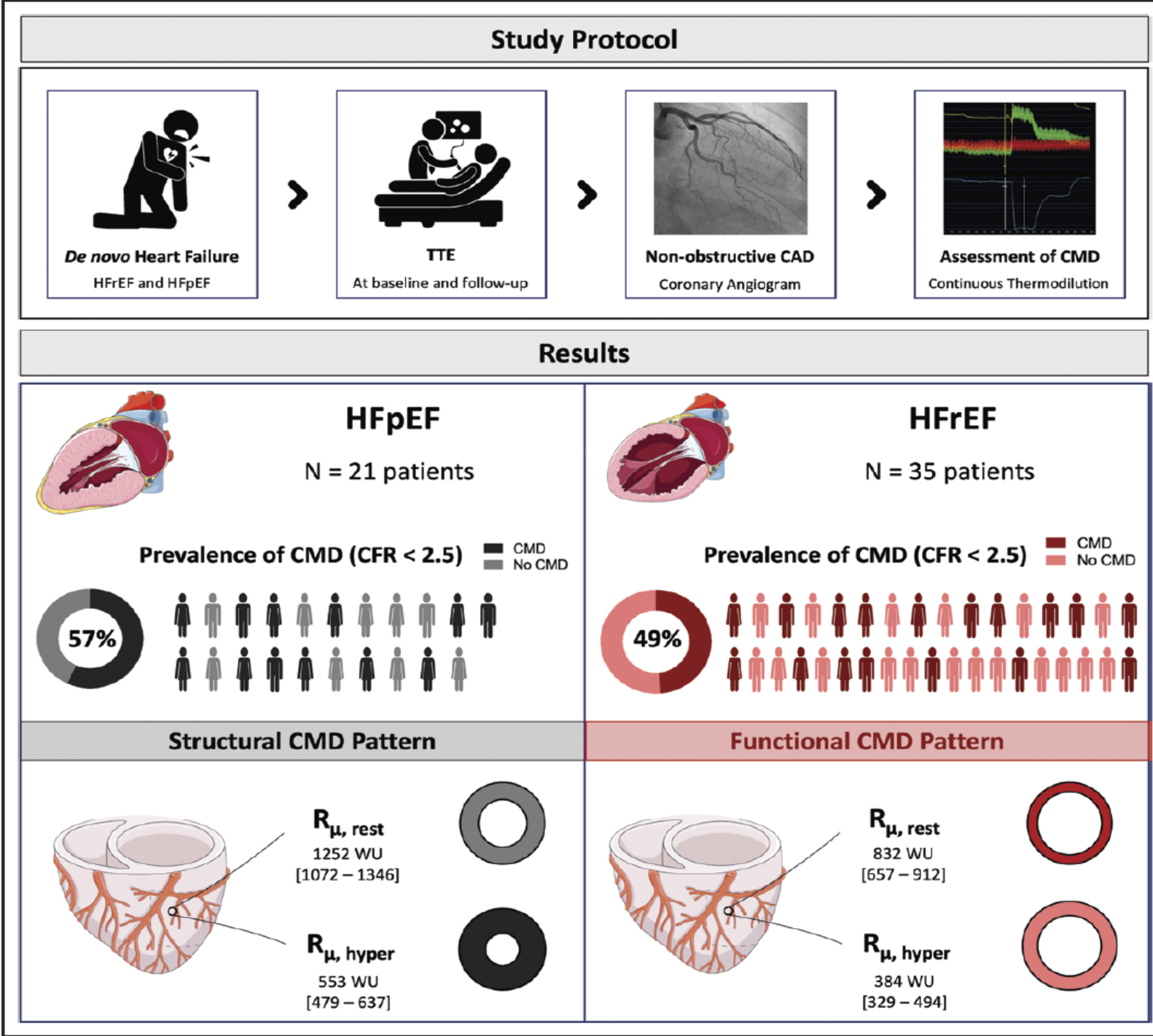
Death or hospitalization for heart failure



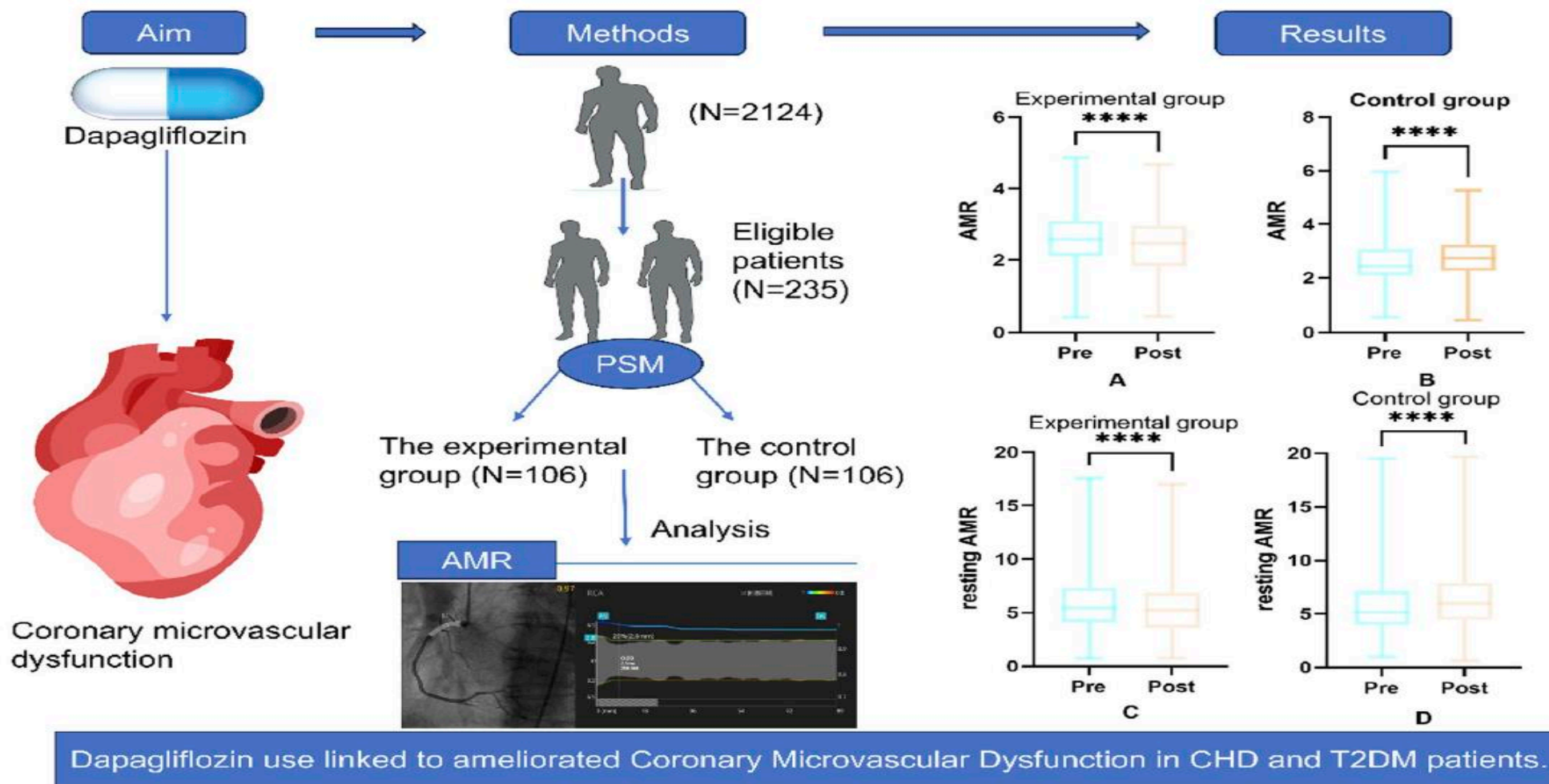
Coronary Microvascular Dysfunction in Patients With Heart Failure



Paolisso P et al. *Circ Heart Fail.* 2024;17:e010805



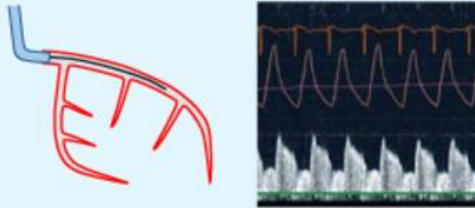
Effects of SGLT2 inhibitors on coronary microcirculatory resistance in patients with CAD and type 2 diabetes



WISE Pre-HFpEF: Study Design and Hypothesis

Baseline

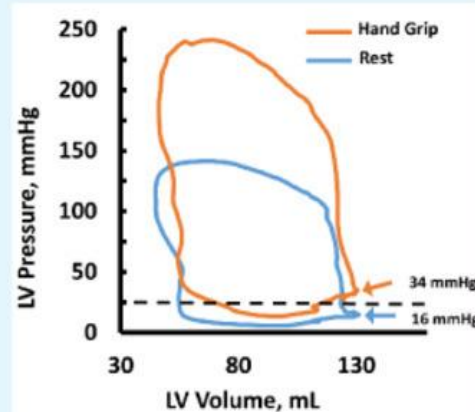
Coronary function testing



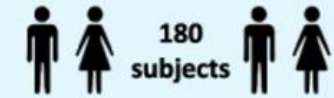
Myocellular ischemia detection

- I. Ultra-high-sensitivity-cTnl
- II. Transmyocardial O₂ gradient
- III. Transmyocardial lactate

Invasive PV loop analysis



Hypothesis at baseline



CFT-based diagnosis

CMD (+)

CMD (-)

Myocellular ischemia/damage

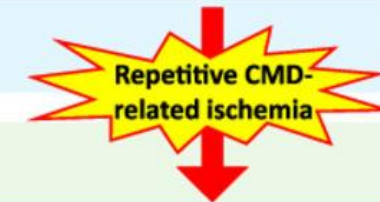
+

-

Provocative stress-related LV relaxation

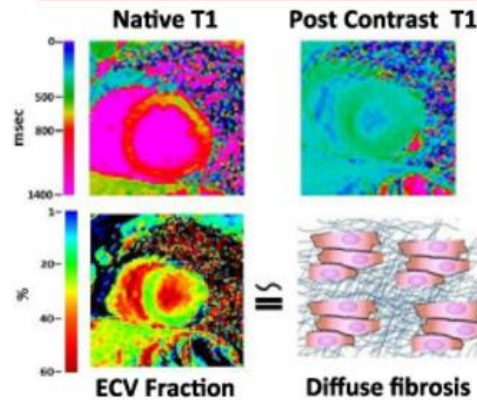
Impaired or normal

normal

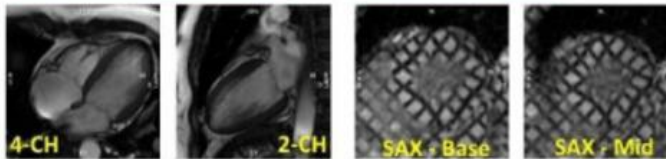


Follow-up: 1-year vs baseline cardiac MRI

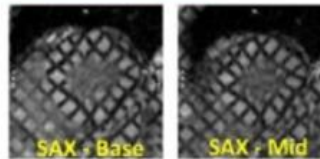
Tissue Characterization: Diffuse Fibrosis



Morphology & Function



Myocardial Strain



MPRI



Tissue Characterization: Focal Scar

Hypothesis at 1 year

Adverse LV remodeling

+

±

Diffuse myocardial fibrosis

+

±

LV diastolic dysfunction

+

±

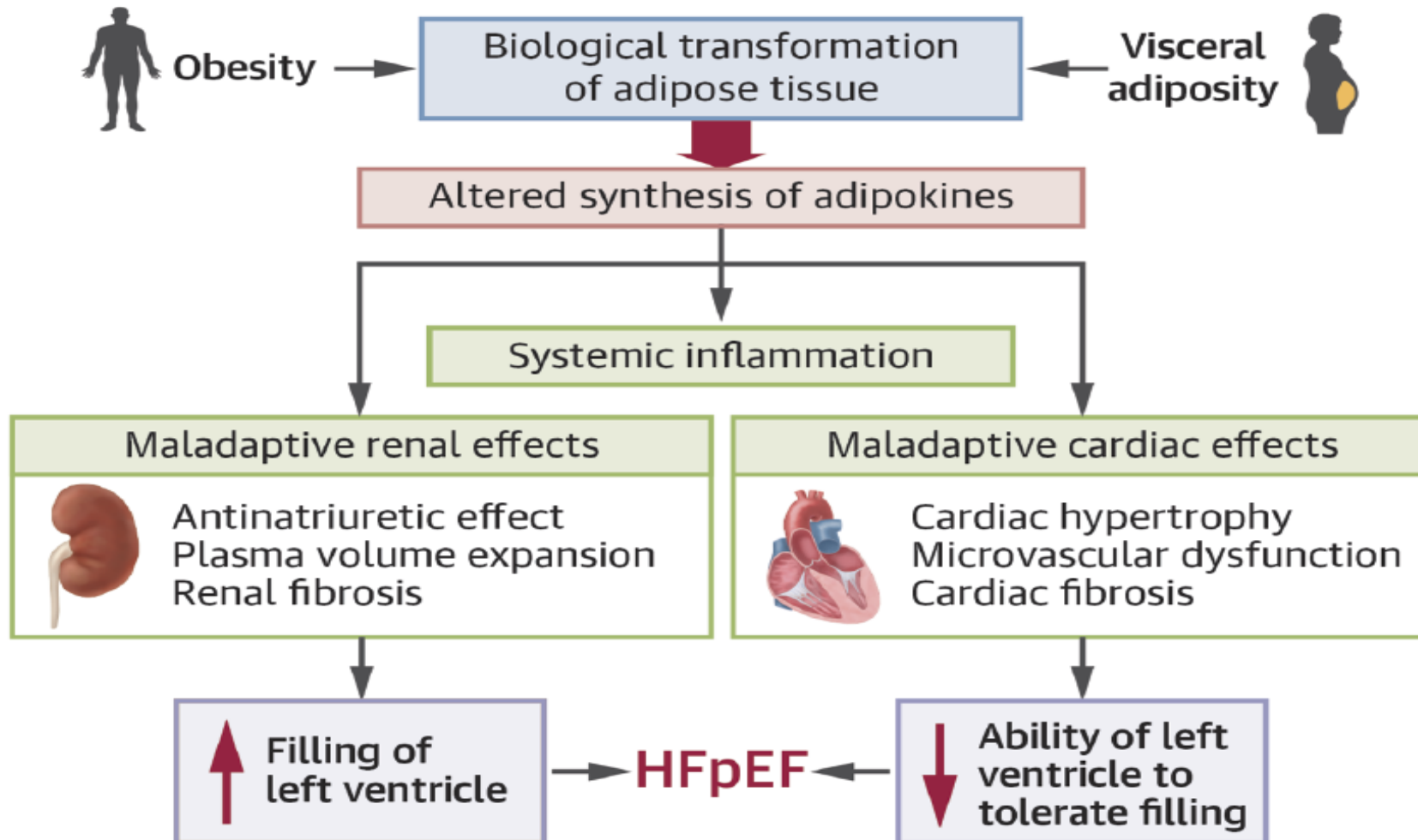
Myocardial perfusion reserve index

↓

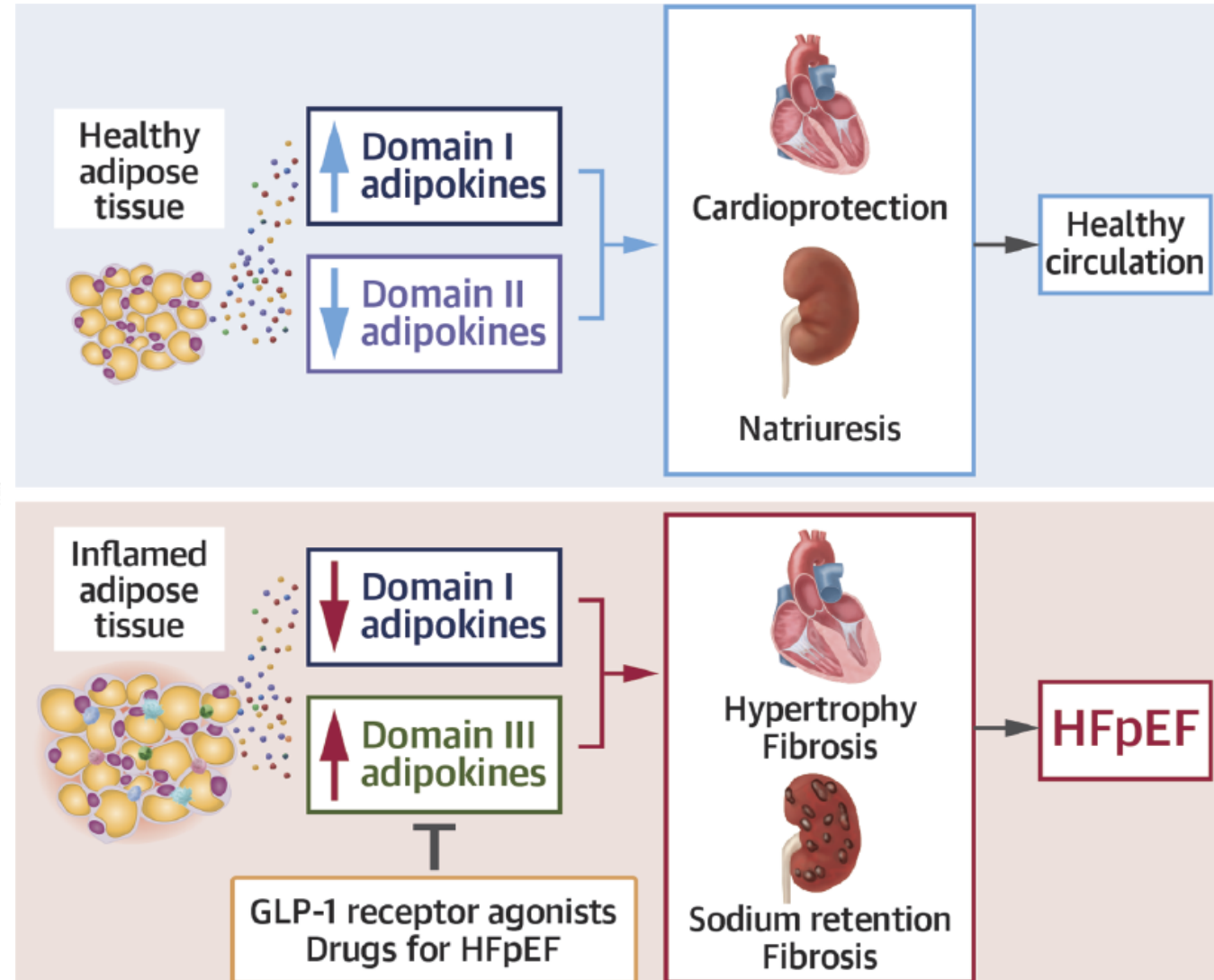
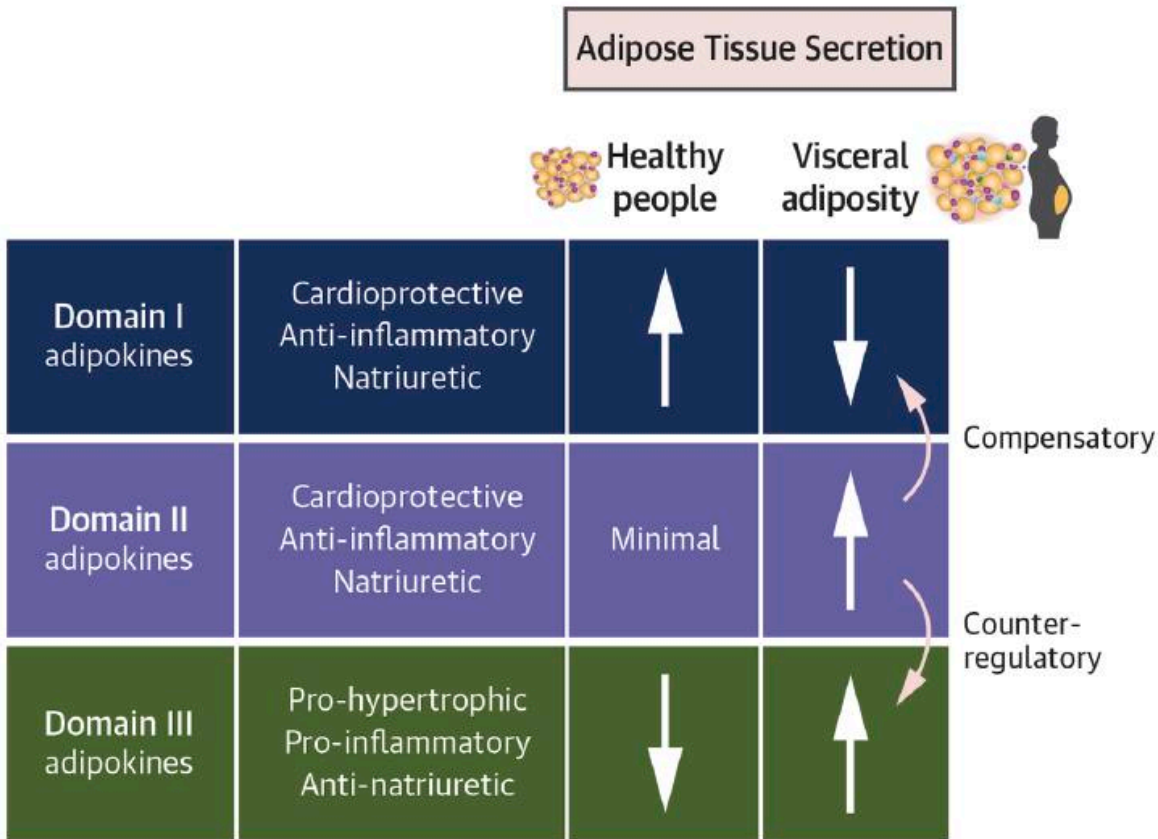
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HFpEF: A Novel Unifying Hypothesis

The Adipokine Hypothesis: Secretion of Adipokines From Biologically Transformed Visceral Adipose Tissue Leads to HFpEF

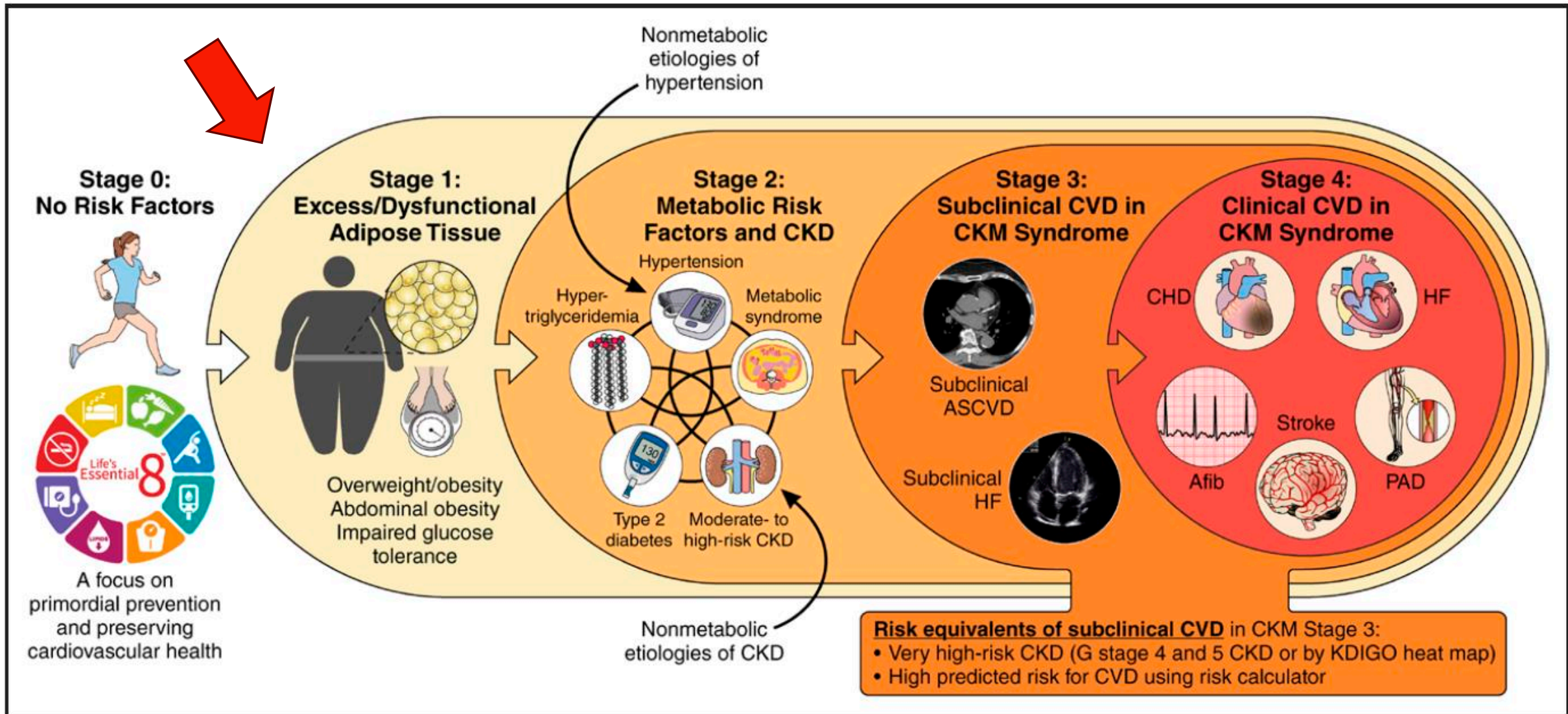


Characterization of Adipokine Domains and Shifts in the Balance in the Healthy Circulation and in HFpEF

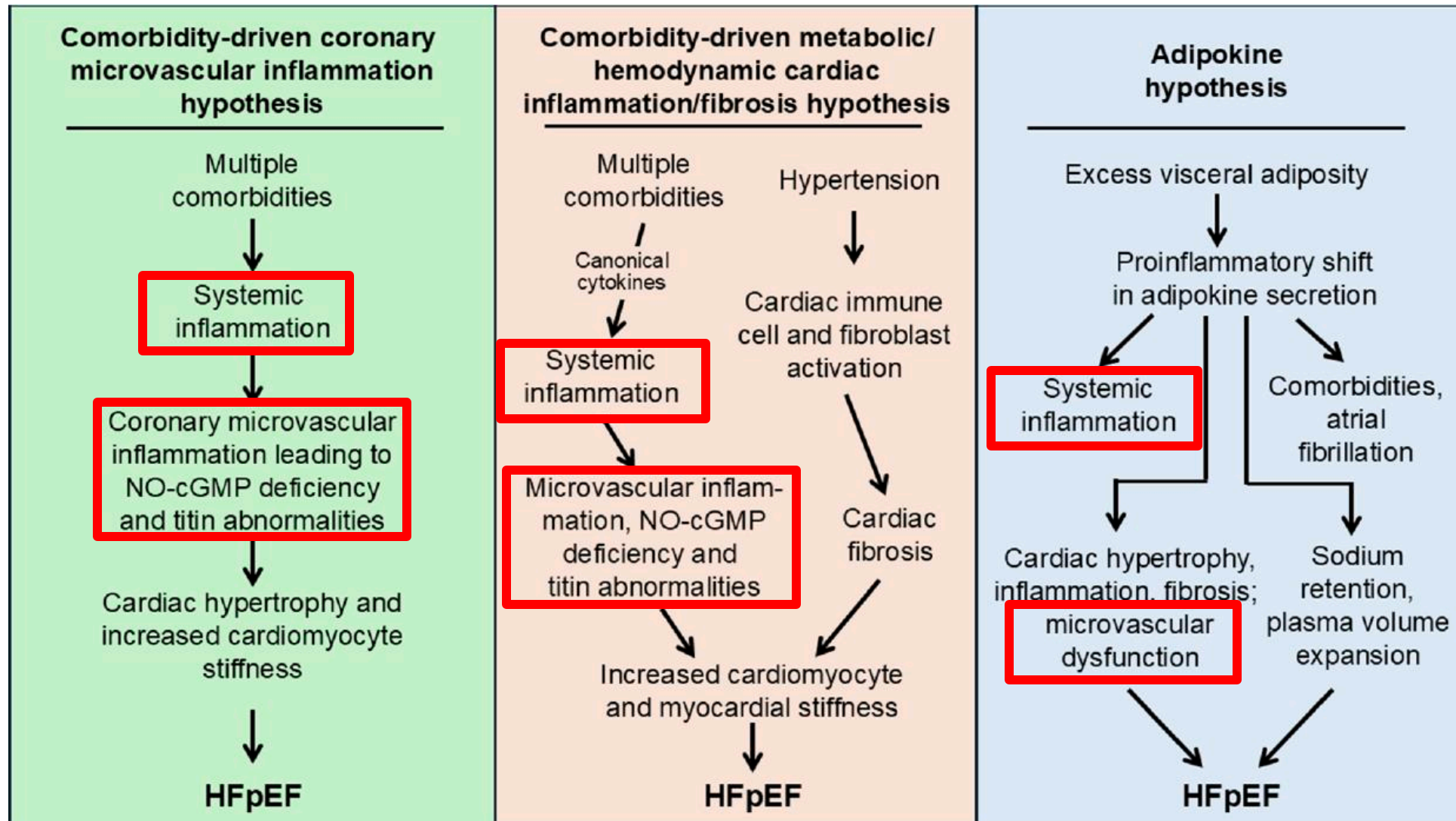


Cardiovascular-Kidney-Metabolic Health

A Presidential Advisory From the American Heart Association



Conceptual Frameworks to Explain the Pathogenesis of Heart Failure With Preserved Ejection Fraction

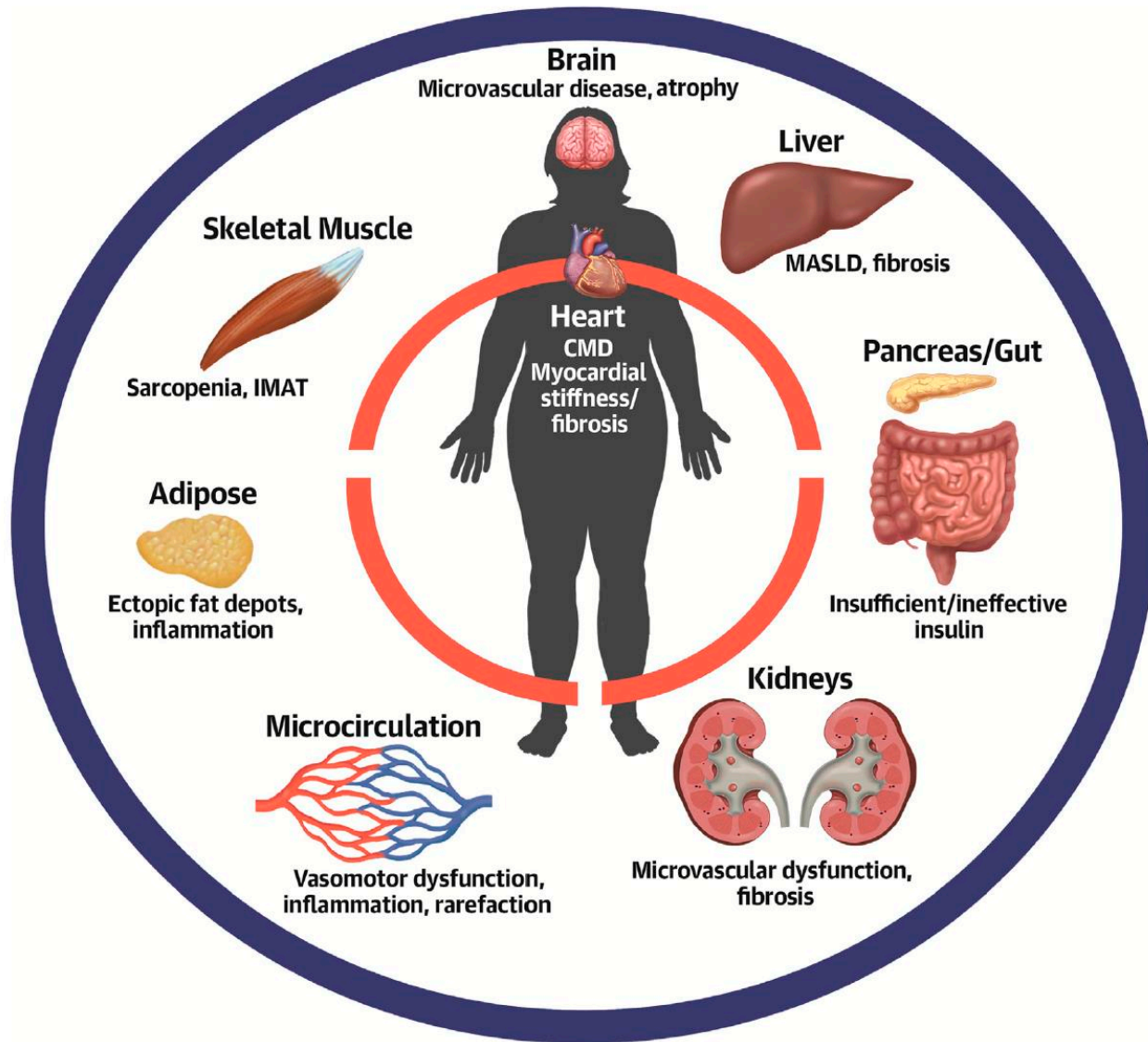


Myocardial Ischemia, LV Dysfunction, CKM and HF

Conclusive Remarks

- **Over the last decade, there has been a rise in CV mortality reflecting the surging contribution of key metabolic risk factors**
- **Microcirculation of the heart and other organs is a critical factor impacting individual cardiometabolic health outcomes**
- **Coronary microvascular dysfunction is associated with cardiometabolic diseases and future risk of HF, MI, and death in a manner that is independent of traditional CV risk factors.**
- **We are now at the precipice of transformative change in our understanding of pathophysiology of cardiometabolic science and clinical outcome such HF and the role of myocardial ischemia.**

Overlap of Cardiometabolic Diseases and Microvascular Dysfunction



***The Rise of 2 Interacting
Subspecialties in Cardiology
Cardiometabolic Diseases and
the Microcirculation***

Taqueti, V, Fuster, V. JACC. 2024; 83:1821–1823.