Kentucky
CHAPTER

OCTOBER 11, 2025 • CENTRAL BANK CENTER • LEXINGTON, KY

Track 1B
Cardio-Kidney-Metabolic
Breaking Down Silos

Kentucky
CHAPTER

OCTOBER 11, 2025 • CENTRAL BANK CENTER • LEXINGTON, KY

Trainee Presentation: Matthew Raymond

The Numbers Were Normal… Until They Weren’t

A Case for Screening for Metabolic Syndrome

Matthew Raymond, MD
Internal Medicine PGY-2
University of Kentucky

Our Case

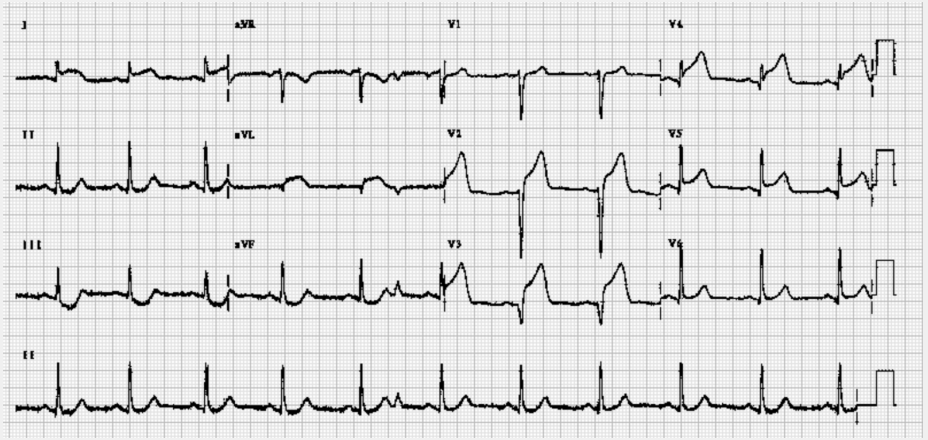
Age 49M, BMI 29, BP 134/86

Fasting Glucose 102, A1c 5.4%, TG 170, HDL 39

No diagnosis, routine follow-up in one year for his annual

Three Weeks Later

- This same gentleman presents to the emergency department diaphoretic with crushing chest pain.
- hsTroponin 230 -> 1000



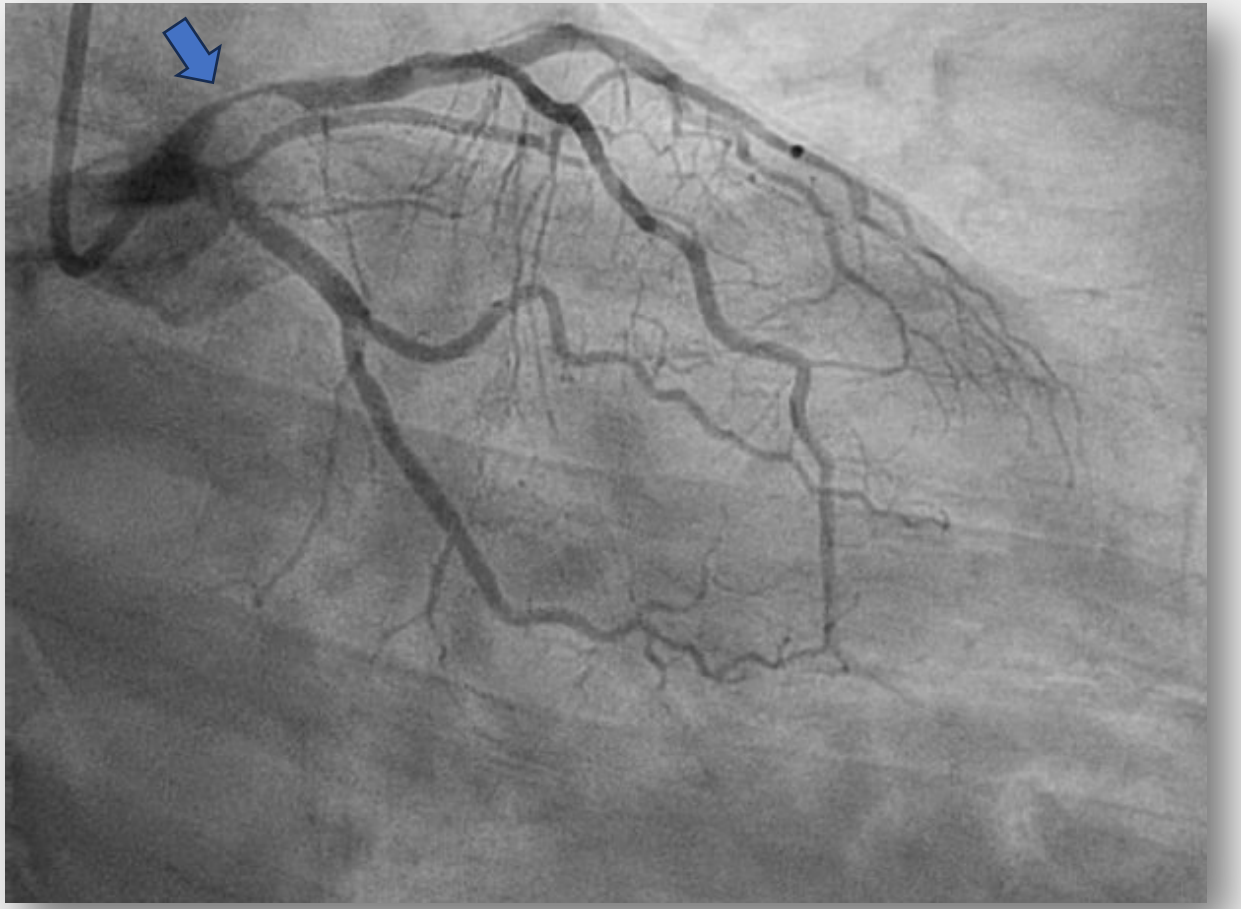


Image 1

Could this have been prevented?

Let’s Talk Metabolic Syndrome

Definition

- From the American College of Cardiology: **metabolic syndrome is a cluster of risk factors that increase the risk for atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes mellitus, and all-cause mortality**.

Let’s Talk Metabolic Syndrome

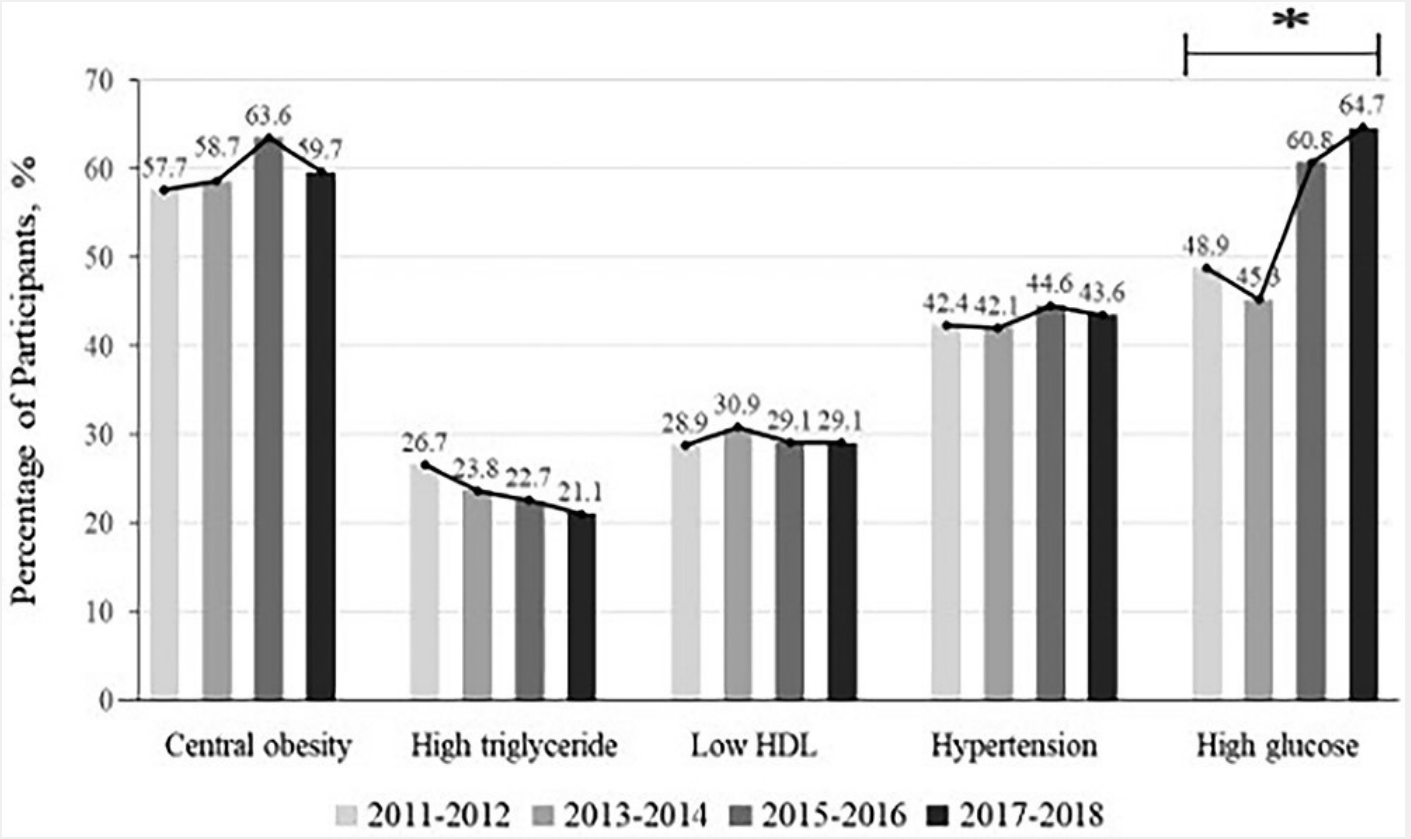
Diagnostic Criteria for NCEP ATP III Metabolic Syndrome[1]:

- Waist circumference >102 cm (M), > 89 cm (W)
- TG >150
- HDL <40 (M) < 50 (W)
- BP >130/85
- Fasting glucose >100

≥3 criteria = diagnosis

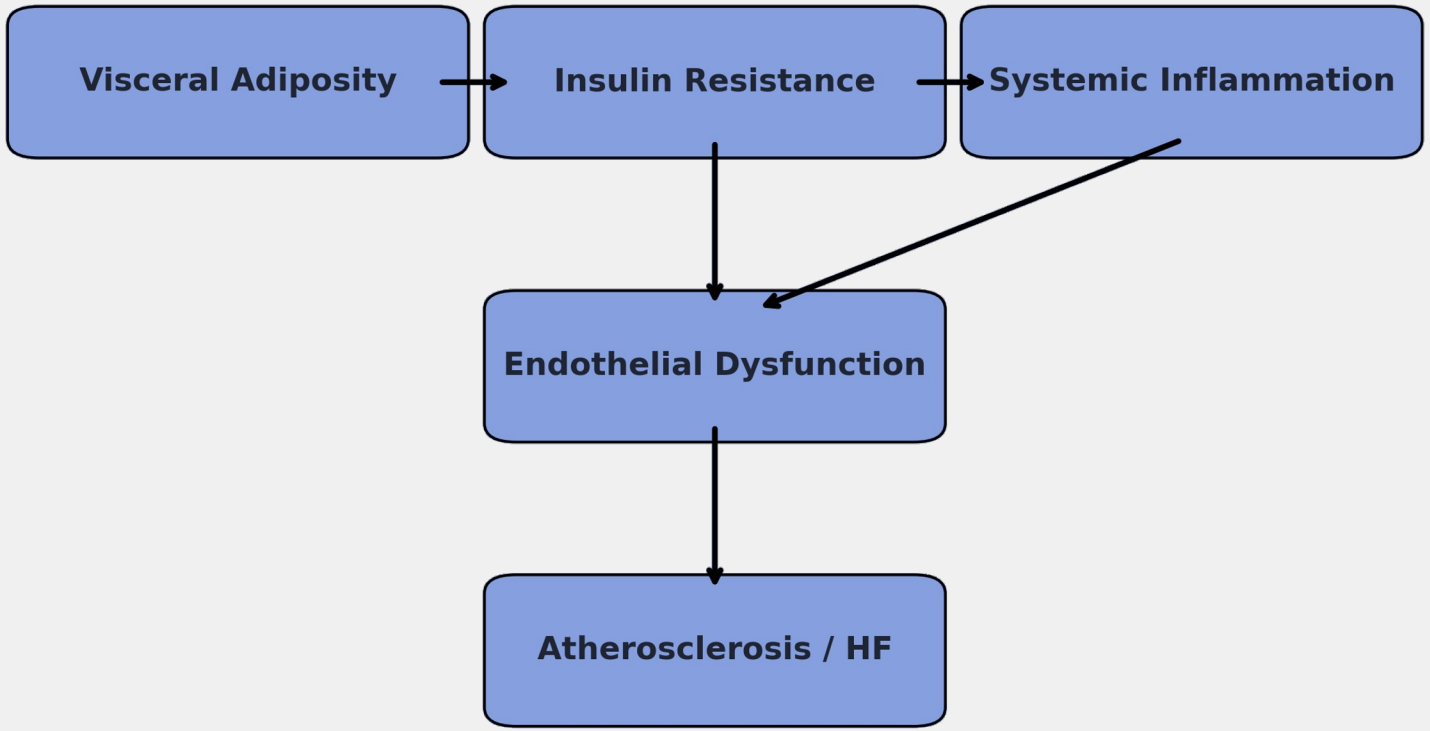
Epidemiology

- The total prevalence of MetS increased from 37.6% [95% confidence interval (CI): 34.0%-41.4%] in 2011-12 to 41.8% (95% CI: 38.1%-45.7%) in 2017-18 (P for trend = .028).[2]



Graph 1

The Metabolic Engine of Cardiovascular Disease



Why Does It Matter?

2-3x increased risk of cardiovascular events

Associated with:

HF, MI, CVA, CKD

Subclinical inflammation

Insulin resistance

Why Do We Miss It?

- Siloed care; too many cooks in the kitchen
- No EMR alerts; much easier to miss borderline values when they aren’t red
- Borderline labs dismissed; if everyone is sick, is anyone sick?
- Waist circumference rarely taken

What Should Be Done?

1. Screen intentionally
2. Document metabolic syndrome
3. Act before thresholds: lifestyle + meds
   - GLP1, SGLT2i, statins, antihypertensives
4. Don’t allow inertia to take the place of appropriate clinical judgement
5. Use blunt, honest language with patients

Acknowledgement

Special thanks to Dr. Vasili Katsadouros

References

1. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009 May-Jun;2(5-6):231-7. doi: 10.1242/dmm.001180. PMID: 19407331; PMCID: PMC2675814.

2. Liang, Xp & Or, Benjamin & Tsoi, Man Fung & Cheung, Ching-Lung & Cheung, Bernard. (2023). Prevalence of metabolic syndrome in the United States National Health and Nutrition Examination Survey 2011-18. Postgraduate medical journal. 99. 10.1093/postmj/qgad008.

Thank You

Talk 1: Korey Shotwell

Cardiovascular Kidney Metabolic Syndrome

Korey Shotwell, MD

University of Louisville

KY-ACC October 11th, 2025

Cardio-**K**idney **M**etabolic (CKM) syndrome

- The 2023 AHA Presidential Advisory redefines prevention as *multiorgan preservation*
- Recognizes CKM health as a major determinant of premature morbidity and mortality
- Represents systemic multiorgan dysfunction and ↑ adverse CV events
- Fragmented organ-based prevention fails to address cross-system injury

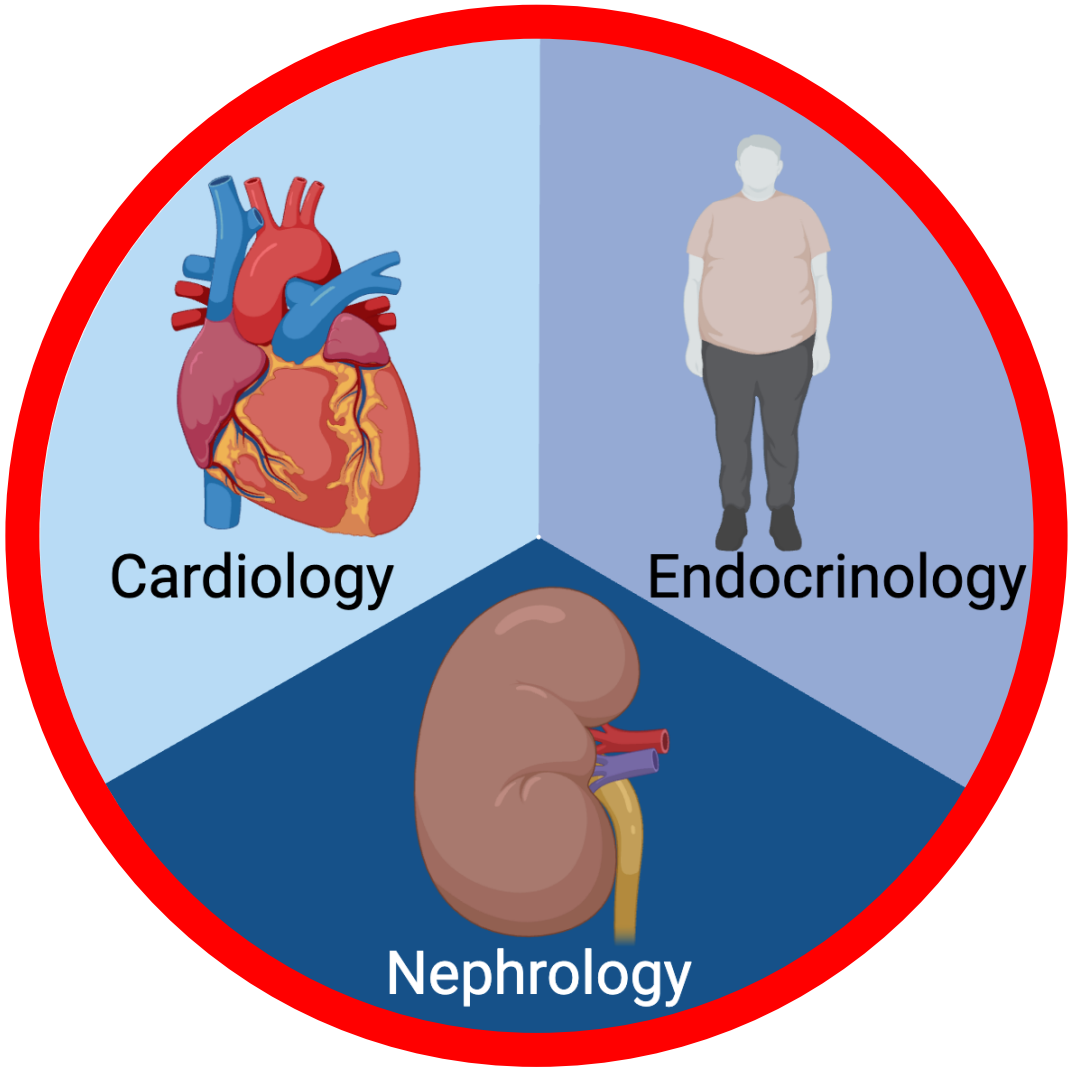
New Paradigm – Defragment the Specialties

Metabolic, renal, and cardiovascular axes are deeply intertwined [1]

- Metabolic risk and CKD have **multiplicative** rather than additive risk for CV events.

CVD prevention misses renal injury; CKM provides a framework to capture *subclinical* organ stress

- Nephrologists, cardiologists, and endocrinologists operate need to work together to treat the same condition
- The AHA Presidential Advisory calls for new **prediction algorithms** incorporating metrics beyond lipids and blood pressure [1]



[1] Ndumele et al., 2023 AHA Scientific Statement

Pathophysiologic Interplay: Mechanistic Triad

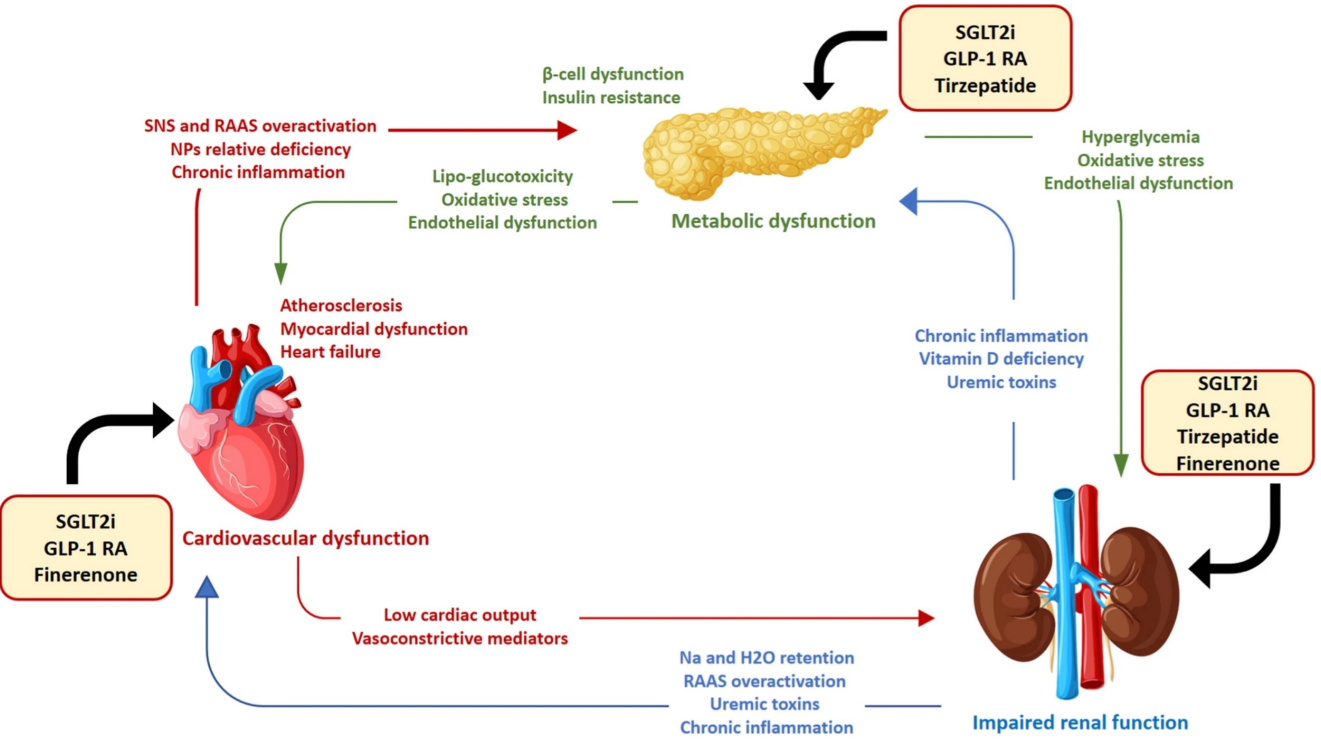
Adipose → Endothelium → Kidney → Heart Axis

Visceral inflammation → insulin resistance → endothelial dysfunction.

Microvascular injury → glomerular hyperfiltration → myocardial fibrosis.

Persistent RAAS, SNS, and NLRP3 activation perpetuate systemic injury.

Bidirectional organ failure cycle defines CKM.



Axis	Key Mediators	Consequence
Oxidative stress	NADPH oxidase ↑ → ROS → NF-κB activation	Endothelial injury + fibrosis
Inflammation	NLRP3 inflammasome ↑ → IL-1β → TGF-β ↑	CKD + HFpEF progression
Fibrosis loop	RAAS / MR → collagen I gene ↑	Interstitial fibrosis
Mitochondrial dysfunction	FA over-oxidation → ATP deficit	Diastolic dysfunction

Hotamisligil, Nature Rev Immunol 2022; Heerspink et al., NEJM 2020; Pitt et al., NEJM 2021)

Life-course Epidemiology

Pediatric origins to geriatric progression

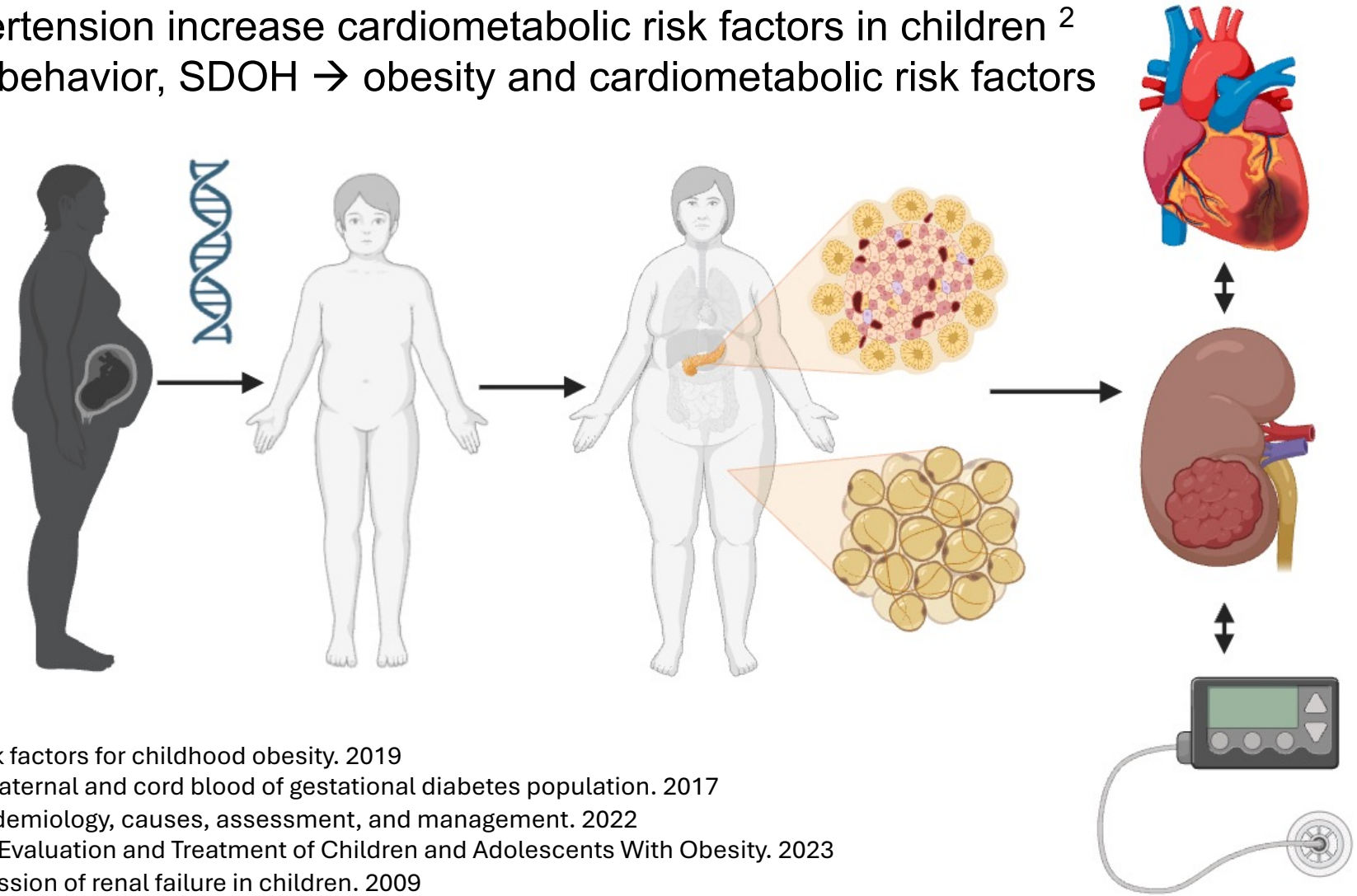
Risk factors begin even before en-utero via genomic imprinting [1]

- Maternal obesity, diabetes and hypertension increase cardiometabolic risk factors in children [2]

In youth, calorie-rich foods, sedentary behavior, SDOH → obesity and cardiometabolic risk factors [3]

CKD in pediatric populations increase CVD risk factors and excess CVD mortality [4]

Risk factor modification (especially hypertension) is linked to slower CKD progression.[5]



1: Larqué E, … Widhalm K. From conception to infancy - early risk factors for childhood obesity. 2019

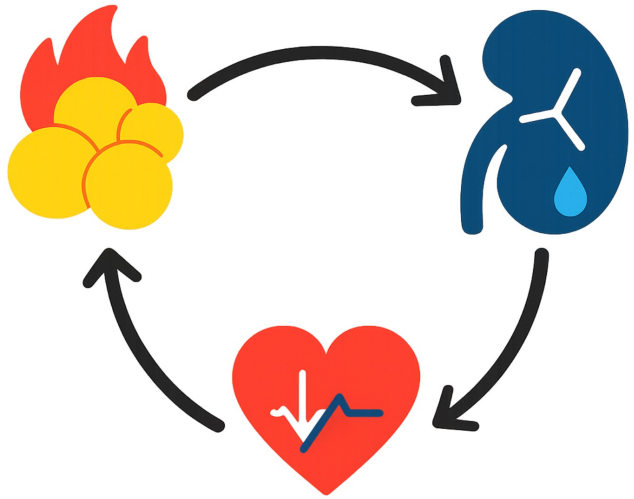
2: Kang J,… Lin SY. Genome-wide DNA methylation variation in maternal and cord blood of gestational diabetes population. 2017

3: Jebeile H,… Baur LA. Obesity in children and adolescents: epidemiology, causes, assessment, and management. 2022

4: Hampl SE,… Okechukwu K. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. 2023

5: Wühl E,… Schaefer F. Strict blood-pressure control and progression of renal failure in children. 2009

Risk Amplification



CKM = bidirectional disorder: metabolic stress → renal microvascular injury → cardiac dysfunction

30% of adults exhibit overlapping metabolic–renal–cardiac risk

- 75 % of ESRD from HTN + T2D
- CKD deaths in diabetes have ↑ > 100 % (1990–2013)

CKD and diabetes amplify CV mortality 2–4× before dialysis

- CKD → 2–3× ASCVD risk
- 10 % progress to dialysis, but > 50 % die of CVD first

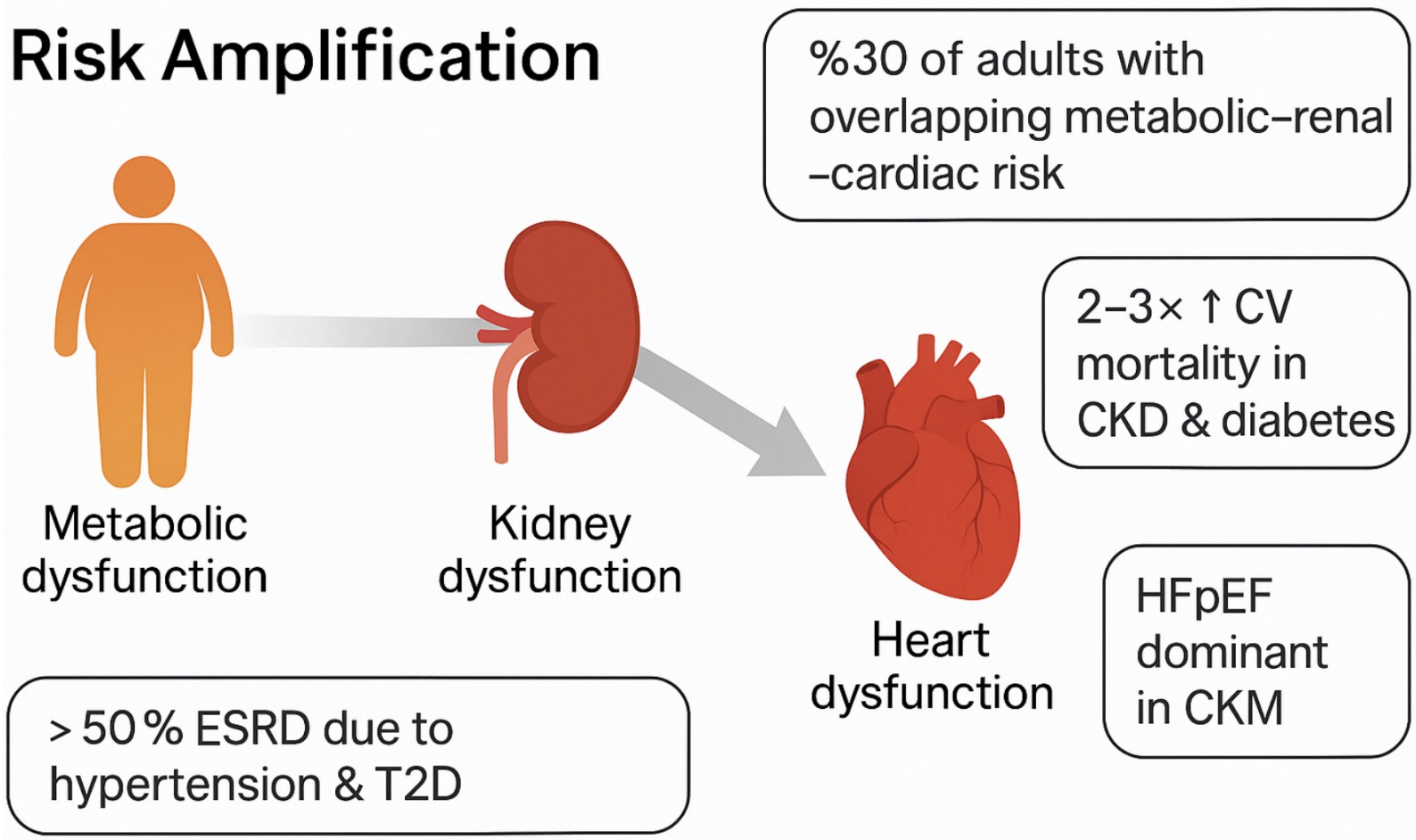
HFpEF is now the **dominant phenotype** of CKM progression

- The CKM overlap drives most heart failure and ASCVD hospitalizations

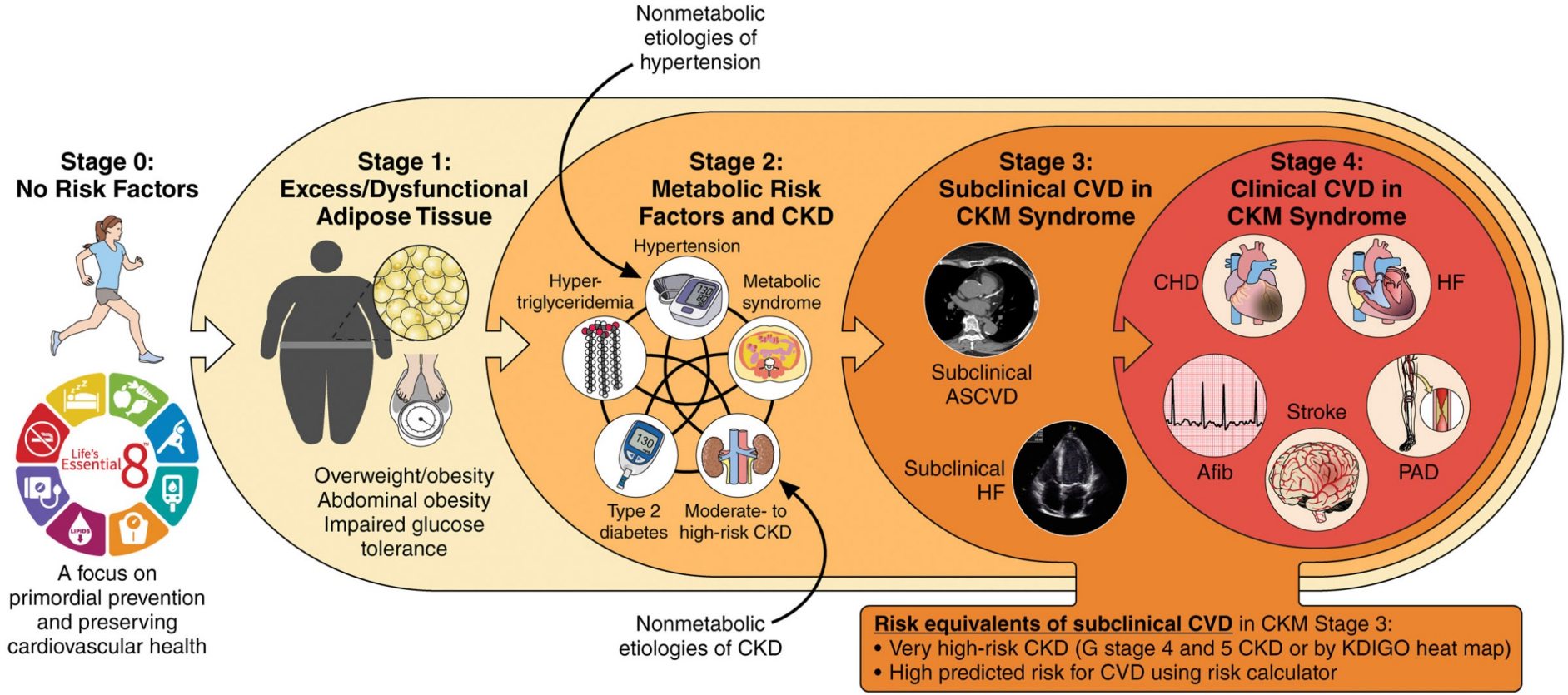
Risk Amplification

- CKD presence (moderate eGFR decline or low-grade albuminuria) independently predicts ASCVD events

- Obesity/BMI-attributable CKD burden has risen >3x in recent decades



CKM Staging



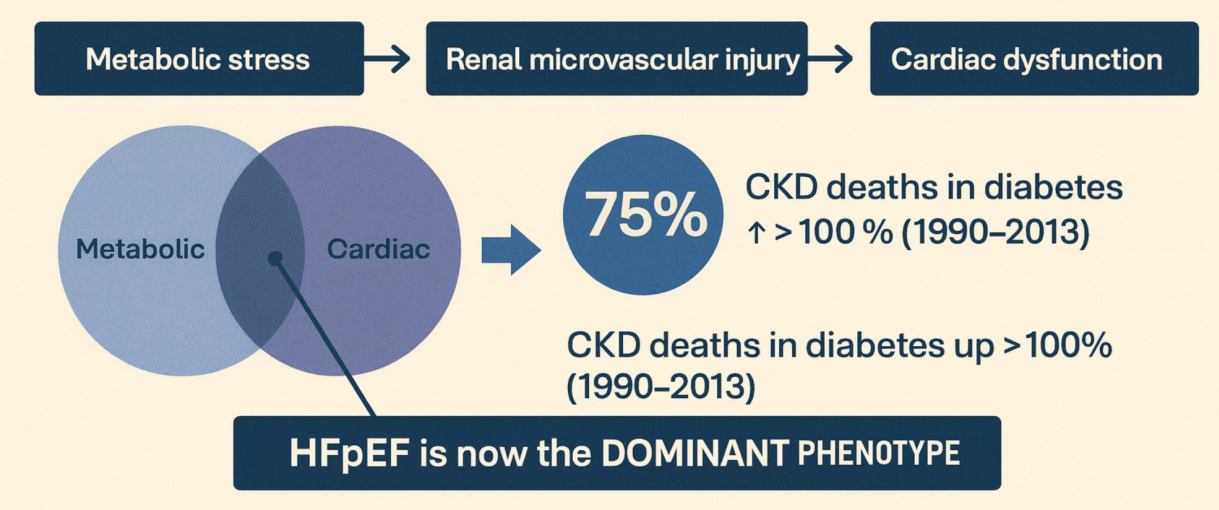
Stage	Clinical Definition	Example Interventions
0	Optimal health	Primordial prevention
1	Excess/dysfunctional adiposity	Weight loss ≥5 % → ↓ MetS risk 30 %
2	Metabolic RF ± CKD G1–3	BP <130/80; ACEi/ARB + statin ± SGLT2i
3	Subclinical CVD (CAC, hs-Tn, BNP)	ACEi + β-blocker ± SGLT2i initiation
4	Clinical CVD ± KF	GDMT HF + lipid/renal targeting

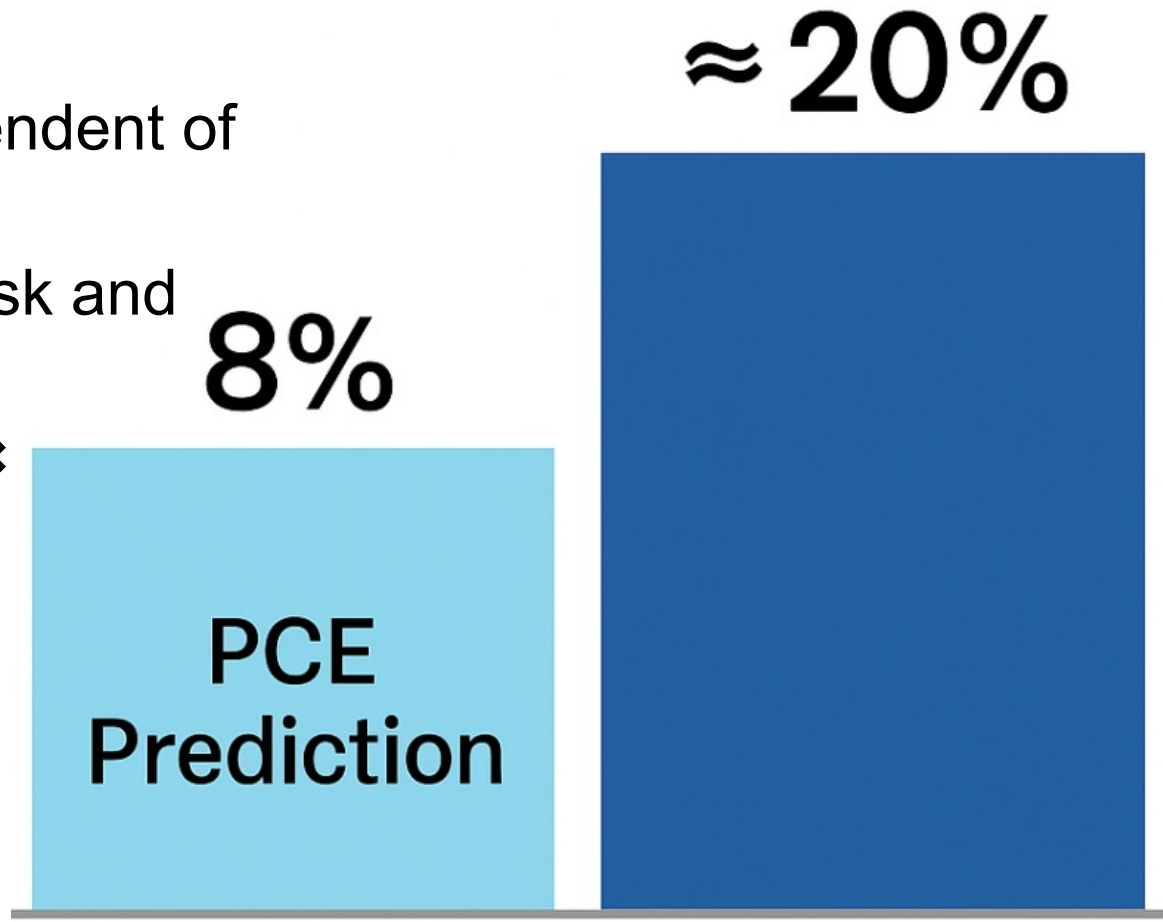
Limitations of Traditional Risk Calculators

ASCVD, Framingham, SCORE2 = lipid & BP centric.

•Omit renal and metabolic biomarkers.

- ↓eGFR and albuminuria predict MACE independent of lipid/BP/glucose.
- In diabetic CKD, ASCVD overestimates low-risk and underestimates high-risk groups
- Underpredict risk in CKM populations by **2–3×**





1: Ndumele et al., 2023 AHA Scientific Statement
2: Matsushita K et al. *Lancet*. 2020;

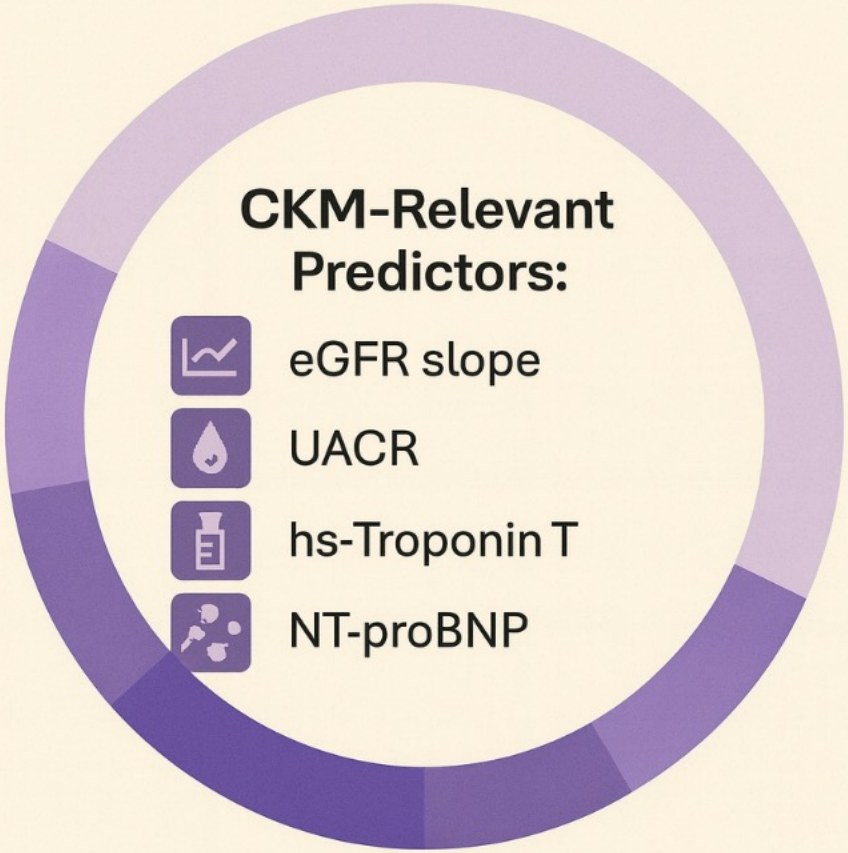
Multi-Marker Risk Stratification

CKM-Relevant Predictors:

- eGFR slope
- UACR
- hs-Troponin T
- NT-proBNP
- TNFR1/2, suPAR

Clinical Effect:

- Reclassifies ~15–20% of patients to higher risk
- Enhances discrimination and dynamic risk monitoring.
- Enables AI-based trajectory modeling. *(AHA CKM Statement 2023)*



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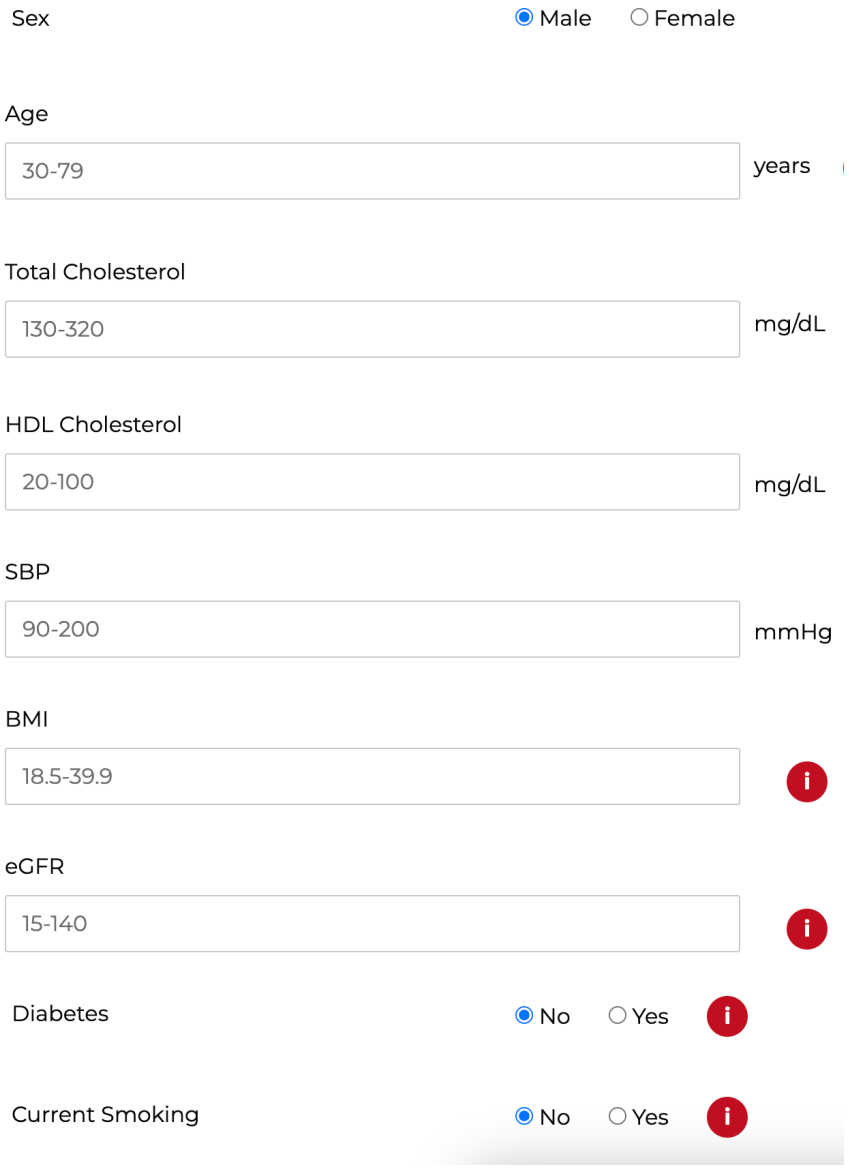
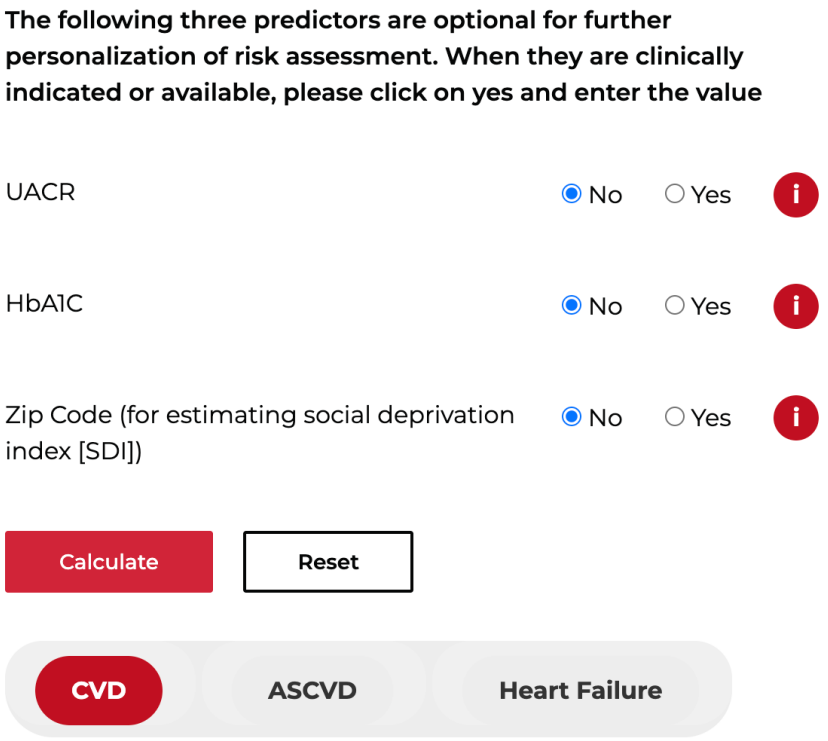
PREVENT™ Risk Calculator — Why It's Better

- U.S.-derived risk equations
- **10- and 30-year risk** of **CVD, ASCVD, and Heart Failure**
- Available online and on MDCalc



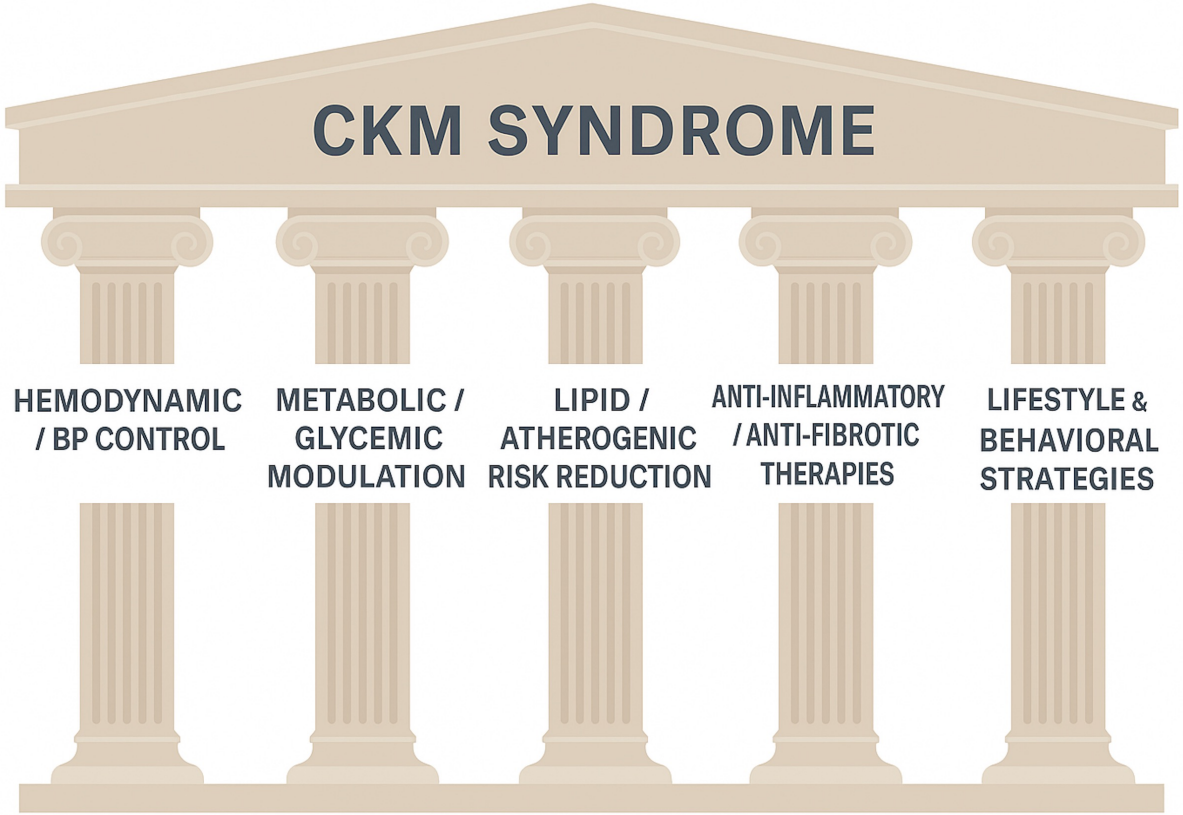


Therapeutic Pillars: Overview

Prevention must address multiple axes simultaneously:

1. **Hemodynamic / BP control**
2. **Metabolic / glycemic modulation**
3. **Lipid / atherogenic risk reduction**
4. **Anti-inflammatory / anti-fibrotic therapies**
5. **Lifestyle & behavioral strategies**

The order and combination depend on CKM stage and the individual phenotype.



Proposed Workflow / Algorithm

Step 1: Screen broadly (BMI/adiposity, BP, fasting glucose, lipids, creatinine, UACR)

Step 2: Assign CKM stage → baseline risk estimate (multi-marker + calculator)

Step 3: Initiate backbone therapy (lifestyle, BP, statin)

Step 4: Add CKM-specific therapy (SGLT2i, GLP-1, finerenone) based on phenotype

Step 5: Monitor trajectories (eGFR slope, albuminuria, biomarkers, imaging)

Step 6: Escalate or de-escalate based on response; reassess social determinants

Step 7: Integrate multidisciplinary care and quality metrics

Metabolic Axis

SGLT2 inhibitors and GLP-1 RAs = cornerstone CKM agents.

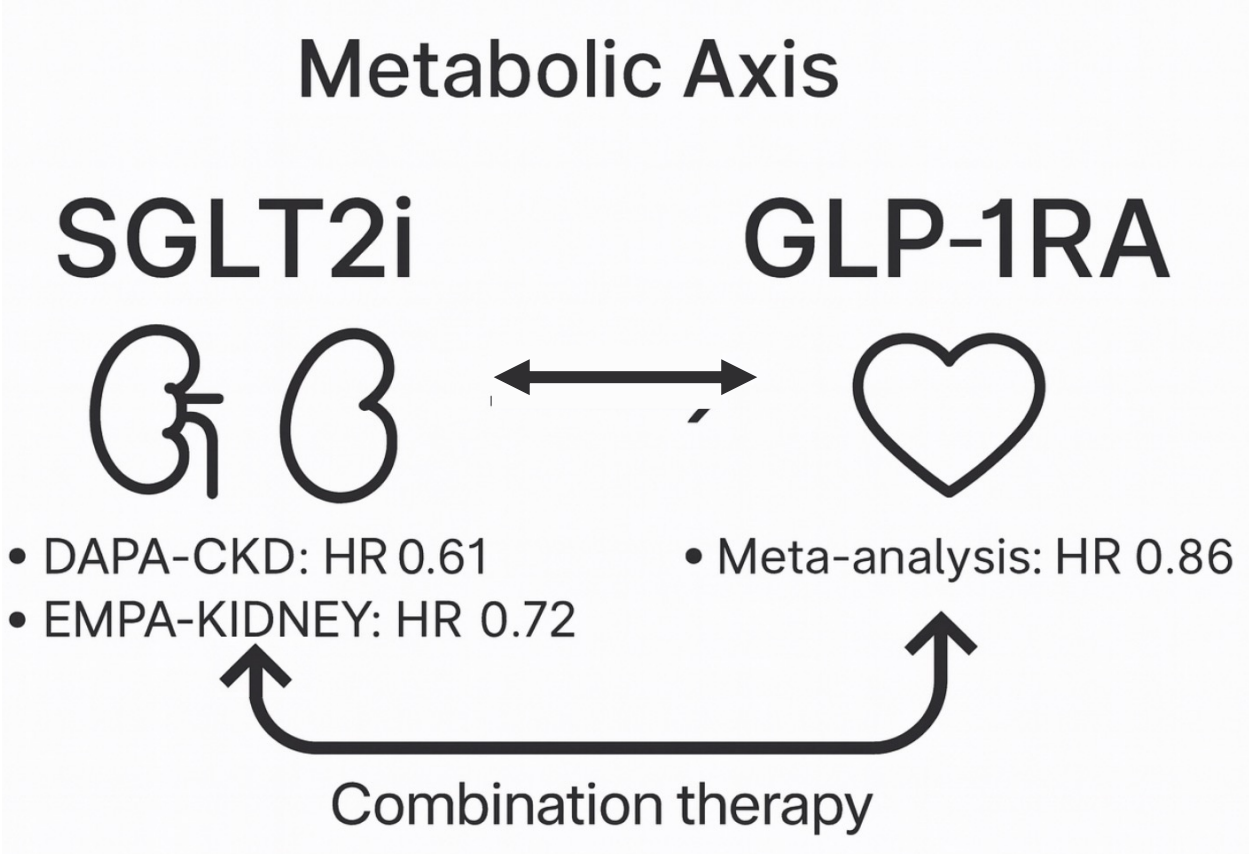
SGKT2i: DAPA-CKD, EMPA-KIDNEY: ~25–40% relative risk reductions in CKD progression or cardiovascular death, in diabetic and non-diabetic CKD.

GLP-1s: ↓ MACE 14%, ↓ HHF 14% (Kristensen et al., *Diabetes Care 2025*).

- meta-analyses: MACE reduction ~14% in high-risk cohorts, plus benefits on weight, lipids, and inflammation.

Combination therapy provides an additive benefit.

- Additive or synergistic benefit (small-scale observational support) *(Cardiovasc Diabetol 2025)*



Hemodynamic Axis

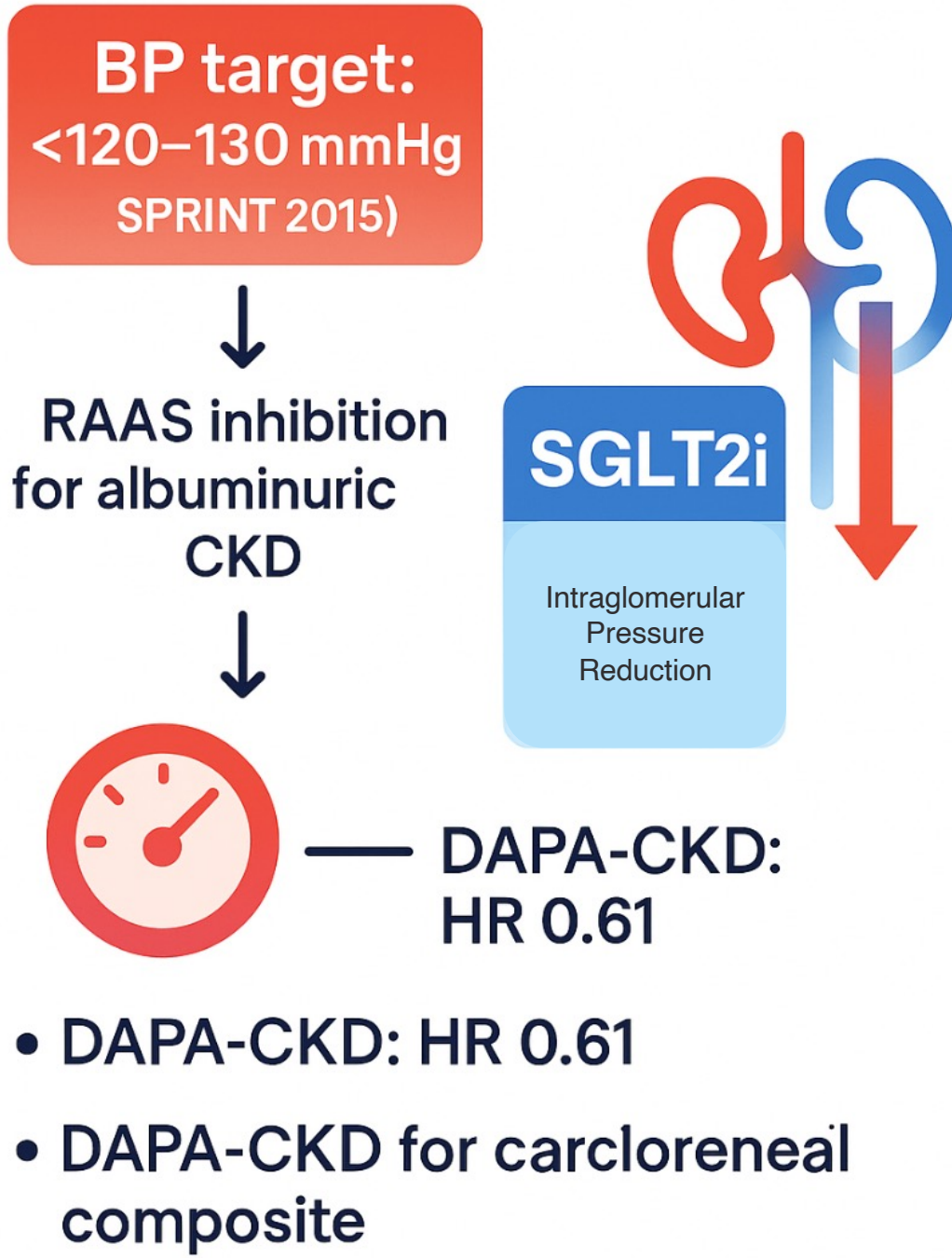
BP target: <120–130 mmHg systolic [1]

- ↓CV outcome by ~25% and all-cause mortality by ~27%

RAAS inhibition remains foundational for albuminuric CKD

SGLT2i improves renal hemodynamics by ↓ intraglomerular pressure

- DAPA-CKD: HR 0.61 for cardiorenal composite



SPRINT Research Group, *NEJM* 2015
Heerspink et al., *NEJM 2020*
DAPA-CKD, *NEJM* 2020

Lipid / Atherogenic Axis

CKD is a **high-risk state** for ASCVD; guidelines recommend statins in non-dialysis CKD

- Atherogenic dyslipidemia = residual risk driver in CKM.

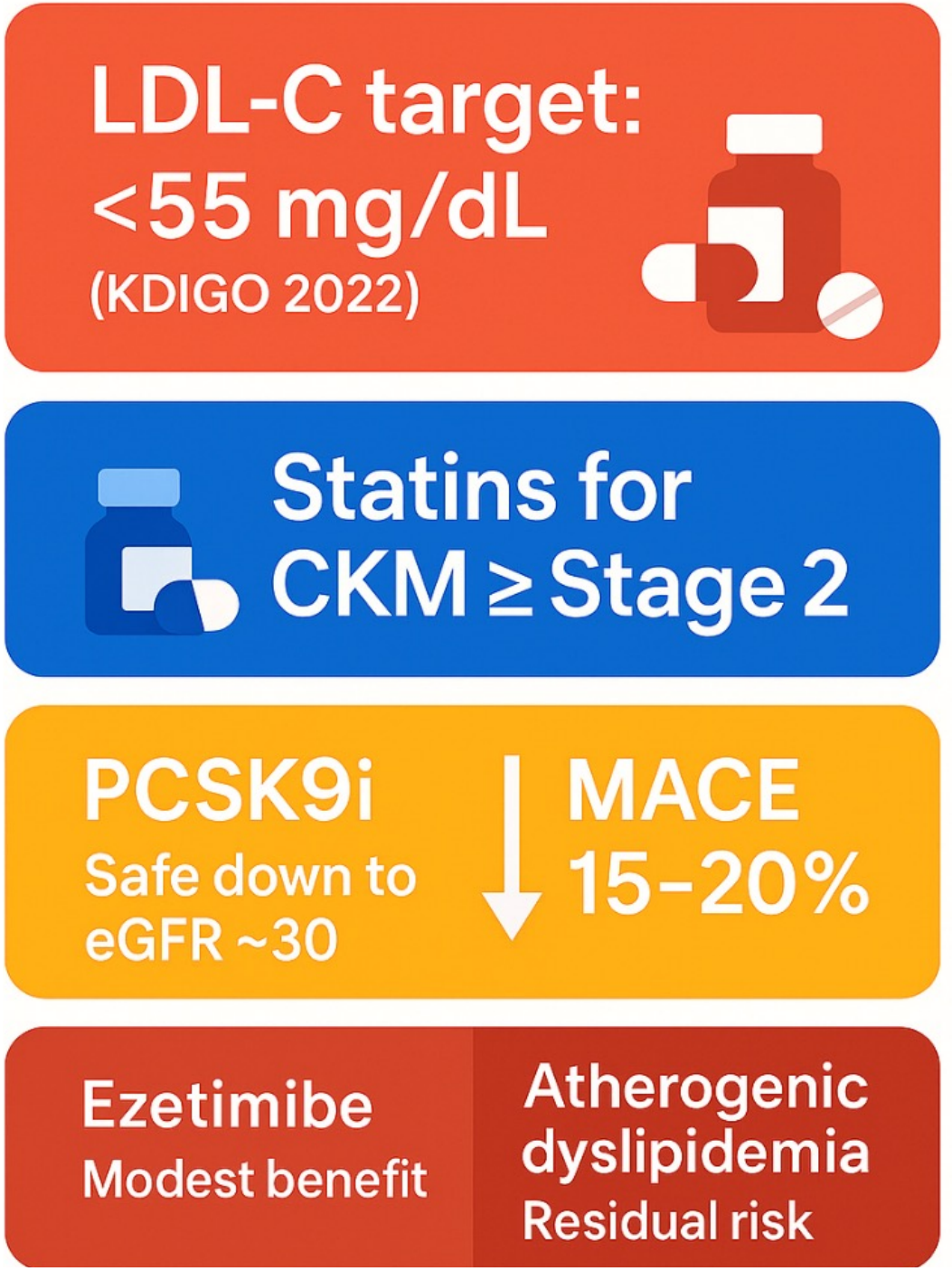
Lipid-lowering in CKD reduces MACE

- Absolute benefit is attenuated compared to the general population
- Statins are indicated for all CKM ≥ Stage 2

LDL-C target: <55 mg/dL (KDIGO 2022, ESC 2021)

PCSK9i (FOURIER, ODYSSEY): ↓ MACE 15–20%
•Safe down to eGFR ~30

Ezetimibe: modest incremental benefit (IMPROVE-IT)



Anti-Inflammatory / Anti-Fibrotic Axis

Pathobiology: chronic low-grade inflammation and fibrosis driving cardiorenal remodeling [1]

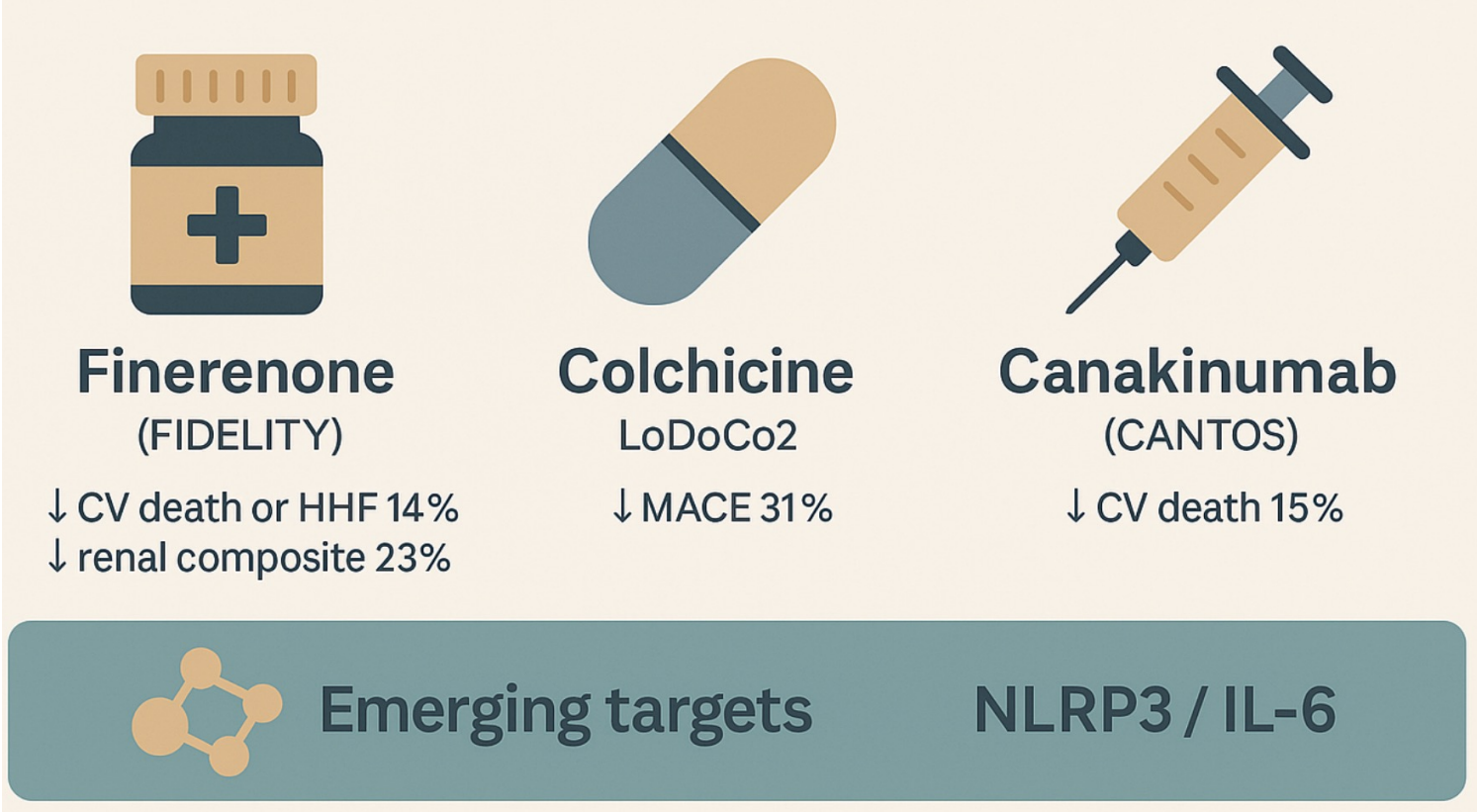
Finerenone: CV death or HHF ↓14%, renal composite ↓23% [2]

Colchicine: MACE ↓31% in stable CAD [3]

Canakinumab: CV death ↓15% in prior MI with elevated hs-CRP [4]

Ziltivekimab (IL-6 ligand mAb): Phase 2 **RESCUE** in CKD/high-risk patients ↓hsCRP; large CV outcomes trial **ZEUS** ongoing

Dapansutrile (oral NLRP3 inhibitor): Early-phase studies show ↓ inflammatory signaling in HFrEF/arthritis; CV outcomes trials pending.



1: Hotamisligil, Nat Rev Immunol 2022
2: FIDELITY, Eur Heart J 2021; Pitt et al., NEJM 2021.
3: LoDoCo2, NEJM 2020.
4: CANTOS, NEJM 2017

Lifestyle & Behavioral Axis

“Life’s Essential 8”: diet, activity, sleep, BMI, BP, lipids, glucose, tobacco

Weight loss ≥7% → 70% reduction in CKM transition risk

Physical activity: 150 min/wk → ↓ HF and renal progression

Mediterranean / DASH diet: ↓ ASCVD and CKD progression *(AHA 2023)*

Clinical Vignette

52-year-old male

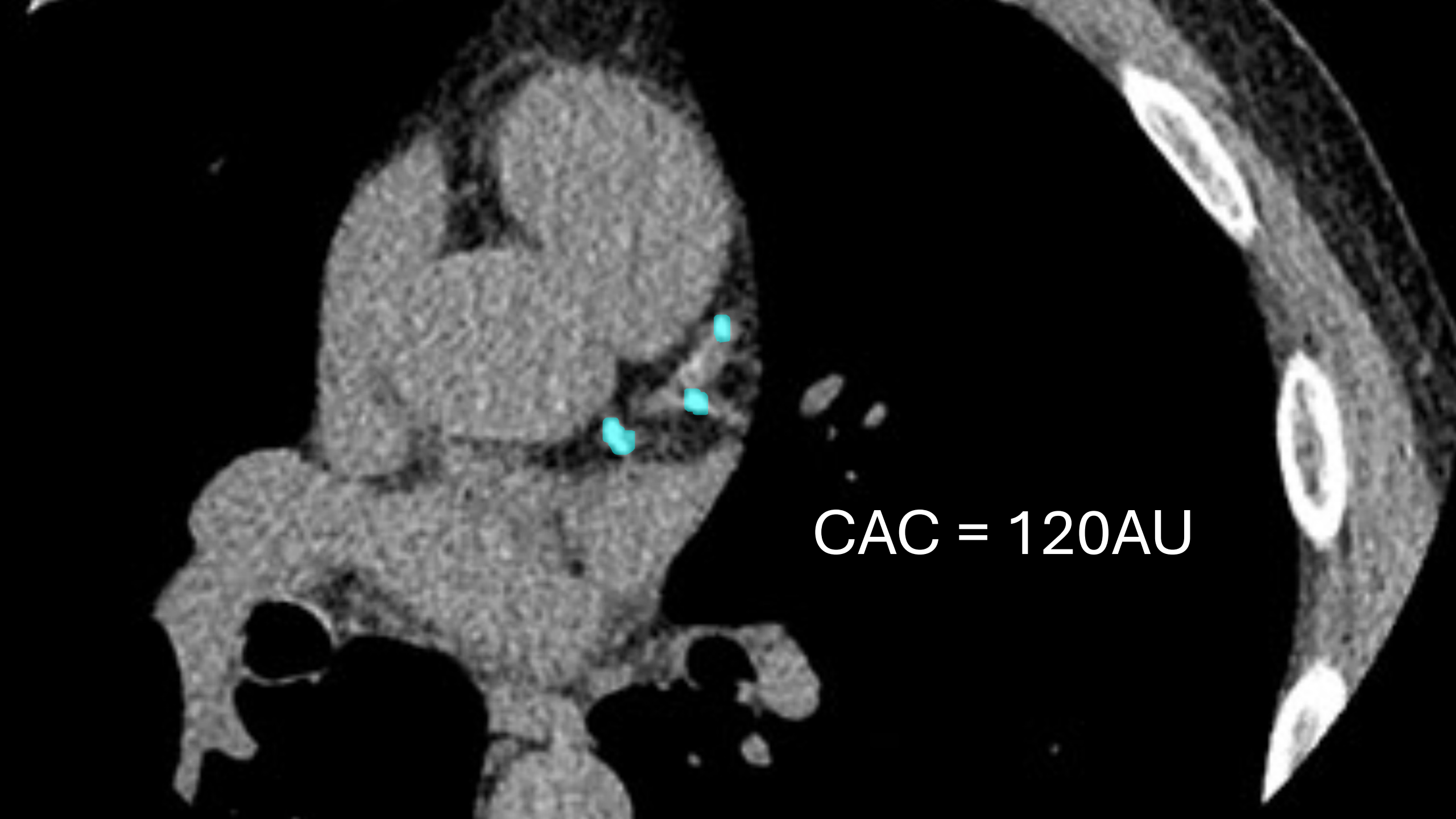
BMI 33 kg/m², T2DM × 8 yrs, HTN, no overt CVD

Meds: metformin, amlodipine, HCTZ

eGFR = 78 mL/min/1.73 m², UACR = 56 mg/g

LDL = 86 mg/dL, HDL = 37 mg/dL, TG = 196 mg/dL

HbA1c = 7.3 %, hs-TnT = 16 ng/L (elevated), NT-proBNP = 180 pg/mL


CAC = 120AU

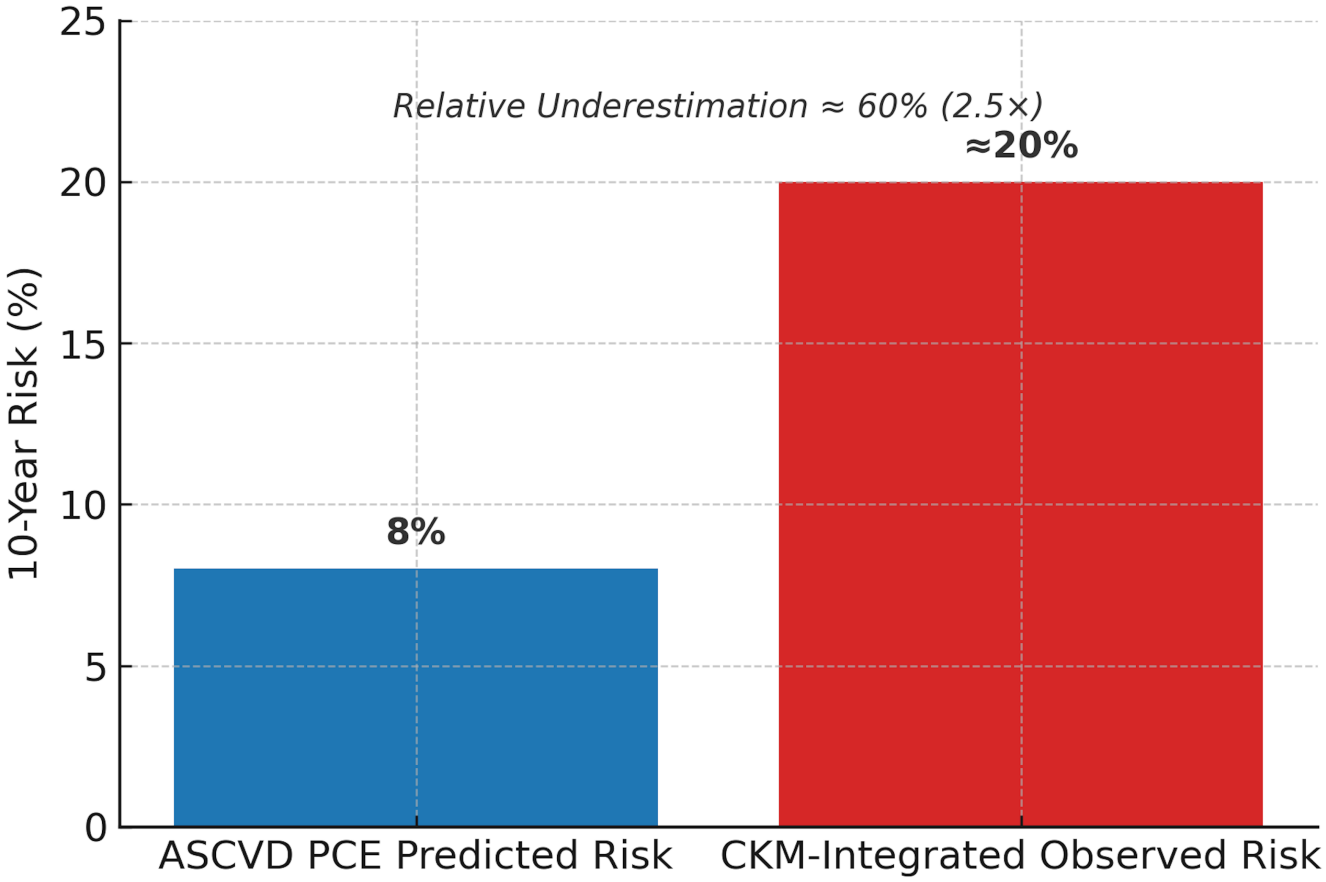
What Is This Patient's Risk Assessment?

Stage 2 → early Stage 3 CKM
•*Subclinical CVD with metabolic-renal stress*: mild albuminuria, early biomarker elevation, metabolic syndrome phenotype

ASCVD score underestimates true risk
•10-yr ASCVD ≈ 8 %

CKD-Prognosis Consortium
•Integration of albumin:creatinine 56 mg/g, eGFR 78, and hs-TnT 16 ng/L → **10-yr MACE ≈ 18–22 %**

<u>Predicted 8 % (ASCVD) → Observed ~20 % (CKM)</u>
•*Relative underestimation ≈ 60%*



1: Matsushita K,... Woodward M; Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis. *Lancet.* 2020.
2: Neuen BL,...Perkovic V. Cardiovascular risk prediction in patients with type 2 diabetes and chronic kidney disease: calibration of current tools and need for CKD-specific models. *Circulation.* 2022.
3: Ndumele CE,... Carnethon MR, et al.; AHA Presidential Advisory: A Cardiorenal–Metabolic Health Framework for Prevention. *Circulation.* 2023.

Management Strategies

Cardio-Renal protection:
• ACEi → add SGLT2 inhibitor (dapagliflozin) (EMPA-KIDNEY, *NEJM 2022*)
• Finerenone for anti-fibrotic/anti-inflammatory benefit (FIDELITY, *Eur Heart J 2021*)

Metabolic modulation:
• Tirzepatide (dual GLP-1/GIP) for weight, glycemia, and CV risk (SURPASS CVOT ongoing)
• Icosapent ethyl if TG > 135 mg/dL (REDUCE-IT, *NEJM 2019*)

Lipid intensification:
• If LDL > 55 mg/dL → add PCSK9 inhibitor (evolocumab); maintain LDL < 55 mg/dL

HFpEF optimization:
• SGLT2i ± MRA

Inflammatory axis:
• Colchicine 0.5 mg daily (LoDoCo2, *NEJM 2020*)

Follow-up:
• Serial eGFR slope, UACR, NT-proBNP, CRP every 6–9 mo; echo every 12–18 mo

Questions?

Talk 2: Craig Beavers

Pharmacotherapy of Cardio-Kidney-Metabolic Syndrome

Craig J. Beavers, PharmD, FACC, FAHA, FCCP, BCCP, BCPS, CACP

Adjunct Associate Professor, University of Kentucky College of Pharmacy

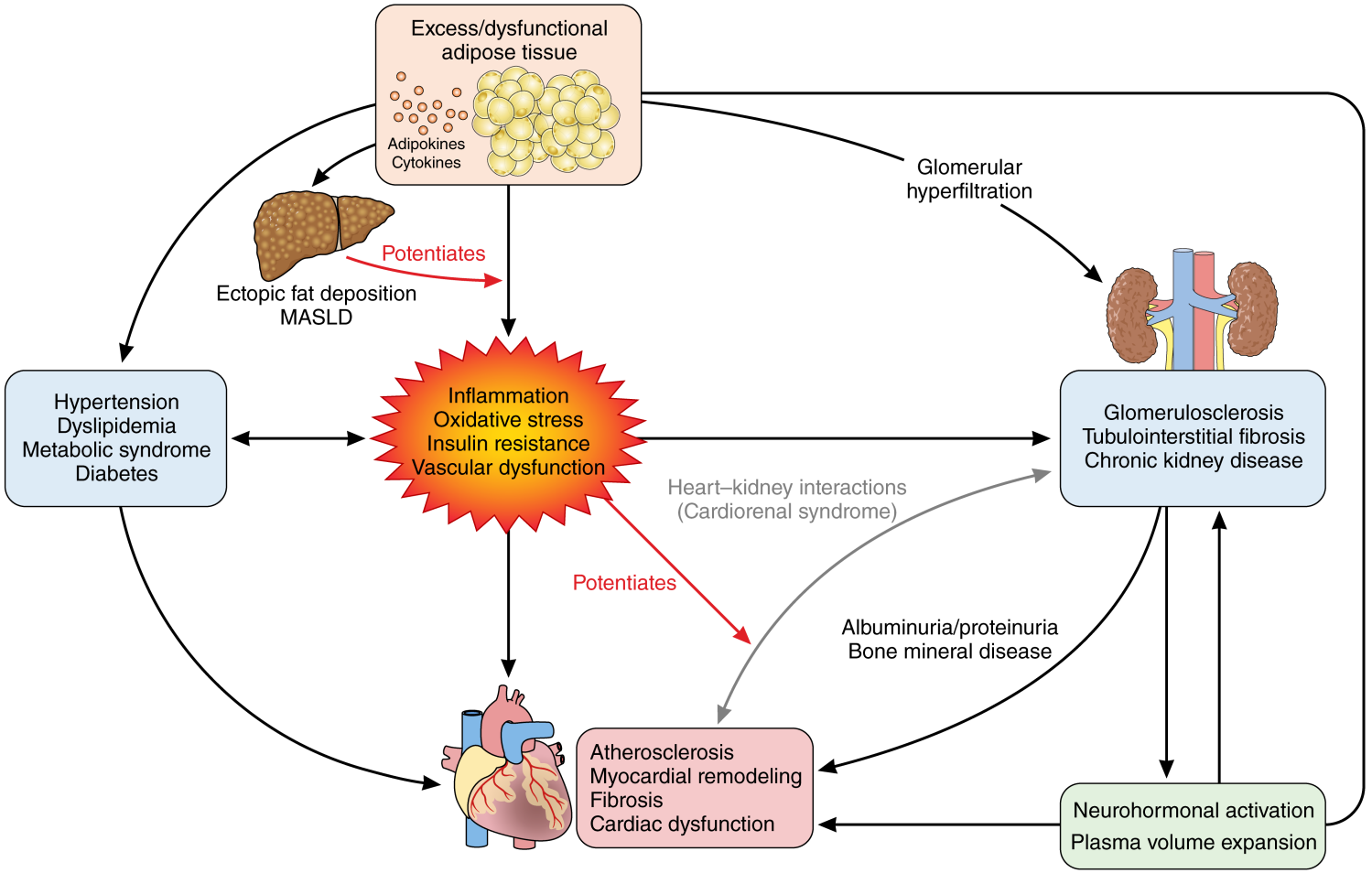
Cardiovascular Clinical Pharmacist/Vice President of Operations Baptist Health Paducah/Cardiovascular Serviceline Executive Sponsor

Objective and Conflicts of Interest

- Devise an evidence-based pharmacotherapy regiment of cardio-kidney-metaboic disease

- Conflict:
  - American Heart Association Grant for CKM Implmentation, Bayer (PI for Moonraker)

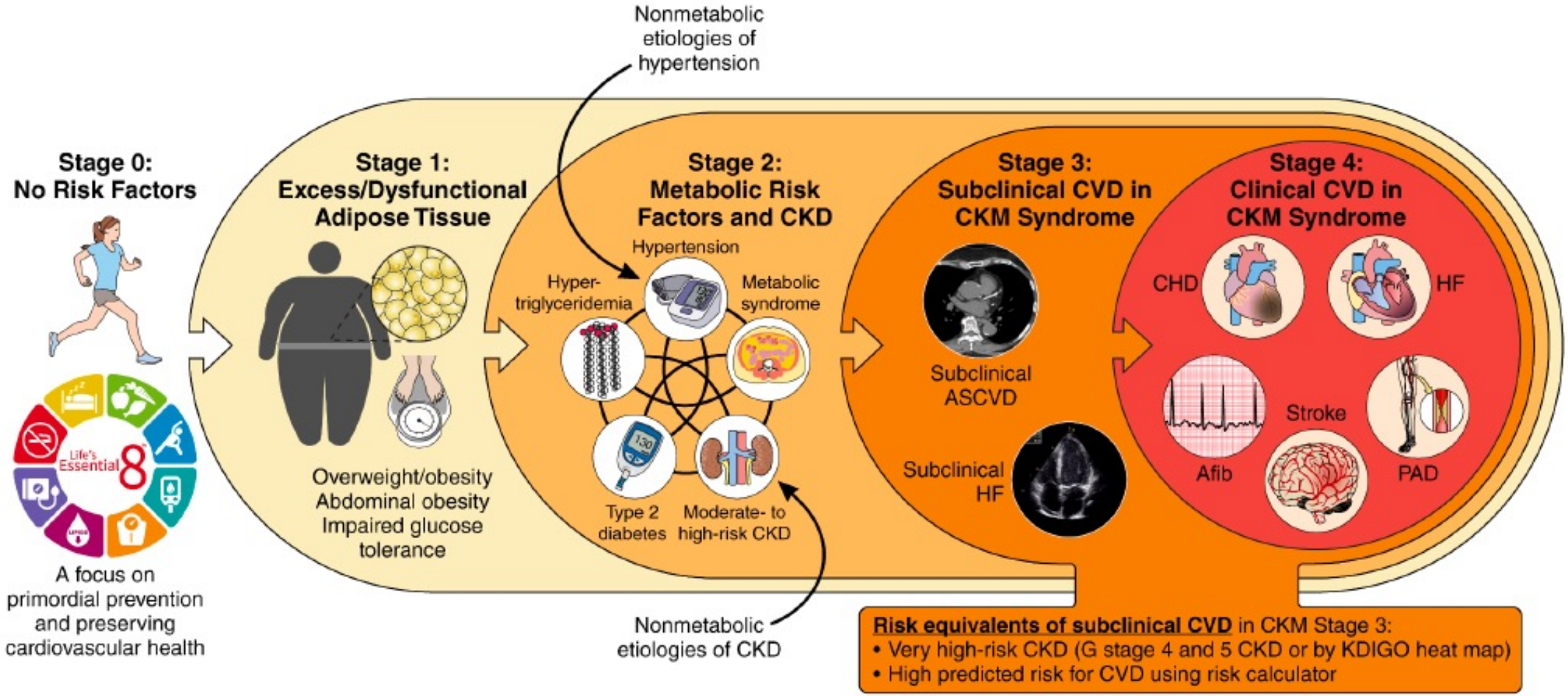
Cardio-Kidney-Metabolic (CKM) Syndrome Defined



- a health disorder due to connections among heart disease, kidney disease, diabetes, and obesity leading to poor health outcomes.

Ndumele, C.E. et al., A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic Syndrome: A Scientific Statement From the American Heart Association. 2023. *Circulation*.

CKM Syndrome Staging Definitions



Ndumele, C.E. et al., A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic Syndrome: A Scientific Statement From the American Heart Association. 2023. *Circulation*.

Stage 0: No Risk Factors

Stage 0

STAGE 0[72,79,197,198]
- Attaining and maintaining ideal CVH linked to decreased CVD and mortality
- Multilevel school-based and family-based interventions increase likelihood of ideal CVH
- Avoiding weight gain with aging decreases likelihood of developing CKM risk factors

Ndumele, C.E. et al., A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic Syndrome: A Scientific Statement From the American Heart Association. 2023. *Circulation*.

Stage 1: Excess/Dysfunction Adipose Tissue

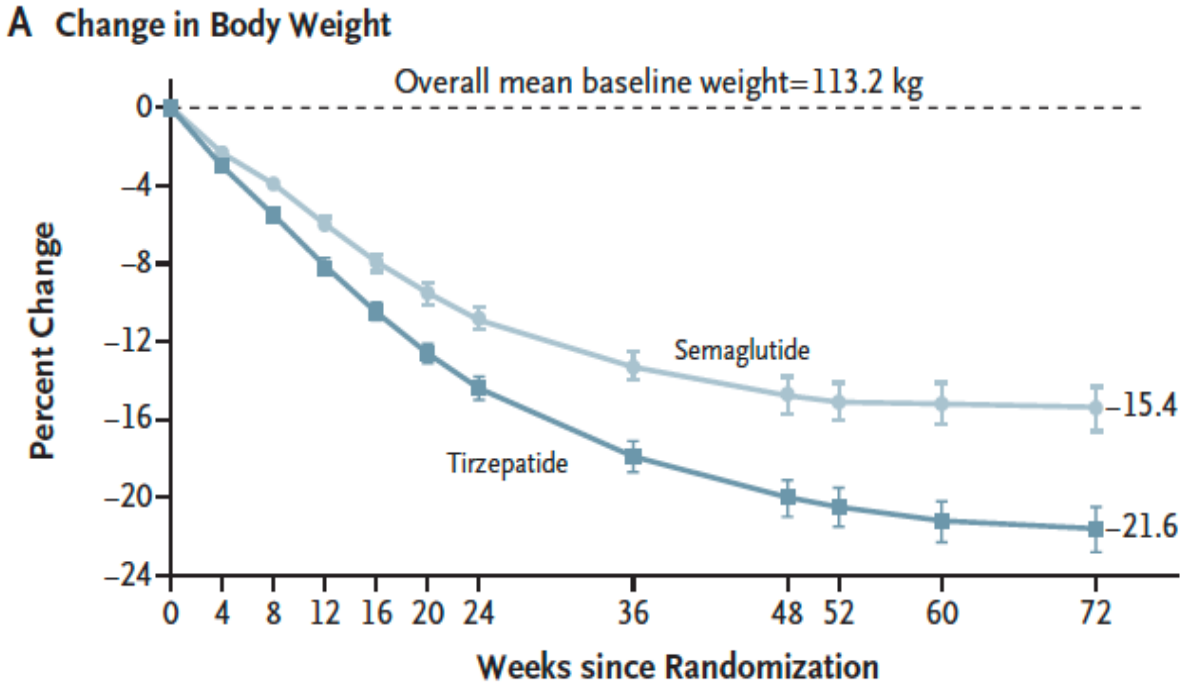
Stage 1

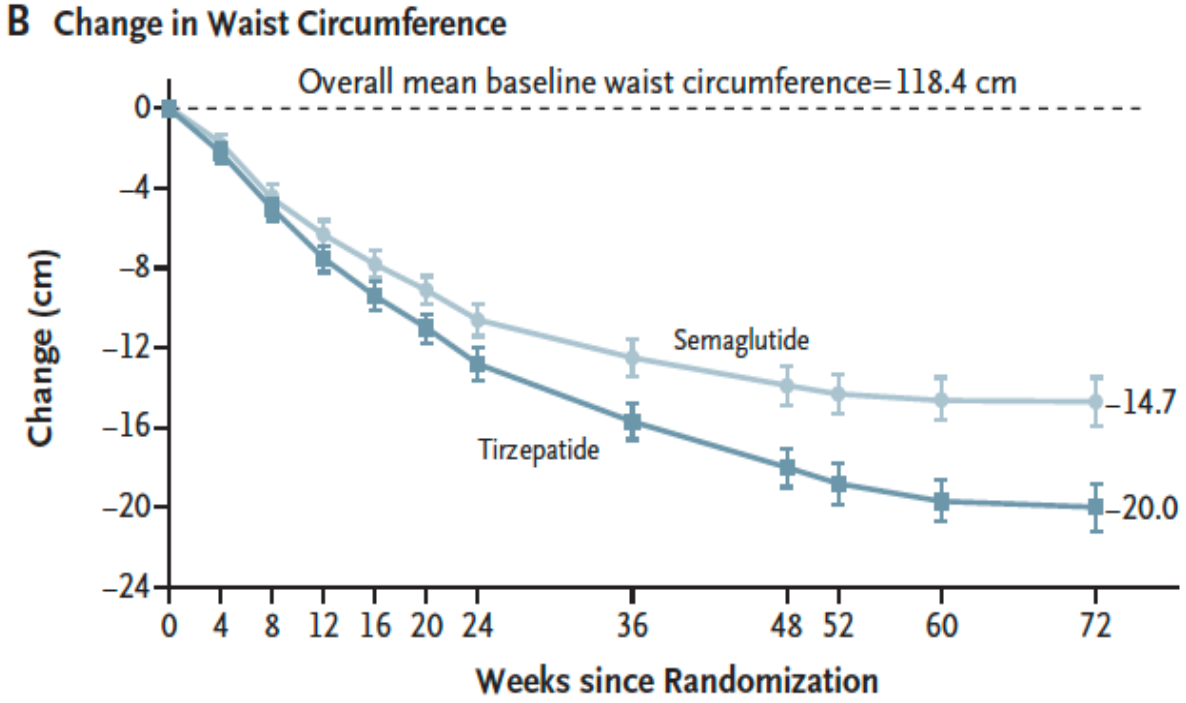
Can consider weight loss support via integrated teams to facilitate lifestyle changes/navigate weight loss options:

- Intensive lifestyle intervention
- Pharmacotherapies (BMI≥ $30kg/m^2$) $without\ comorbidites$
- Bariatric surgery

Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-like Peptide-1 (GLP-1) Receptor Antagonist

SURMOUNT-5 Trial





N Engl J Med 2025;393:26-36

Not Just Weight Loss Alone!

Lilly's Mounjaro (tirzepatide), a GIP/GLP-1 dual agonist, demonstrated cardiovascular protection in landmark head-to-head trial, reinforcing its benefit in patients with type 2 diabetes and heart disease

July 31, 2025

Mounjaro met the primary objective of non-inferiority vs. Trulicity with an 8% lower rate of MACE-3 events, while delivering greater reductions in A1C and weight

Download PDF

In the trial, Mounjaro was associated with a 16% lower rate of all-cause death compared to Trulicity, suggesting more comprehensive health benefits

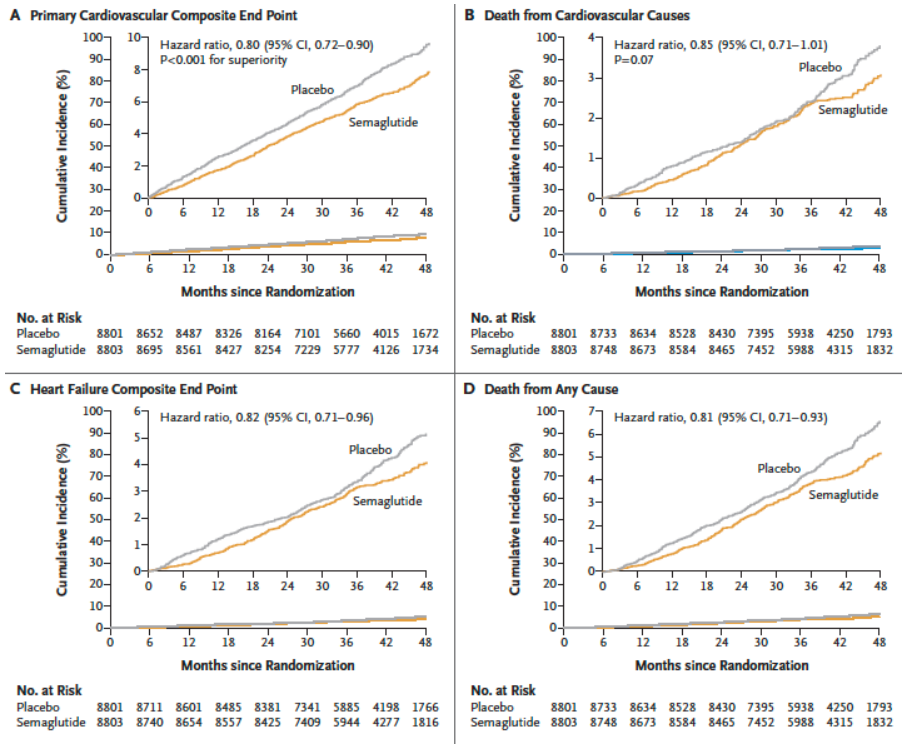
Results from the largest and longest Mounjaro trial to date reaffirm its established safety and tolerability profile

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*



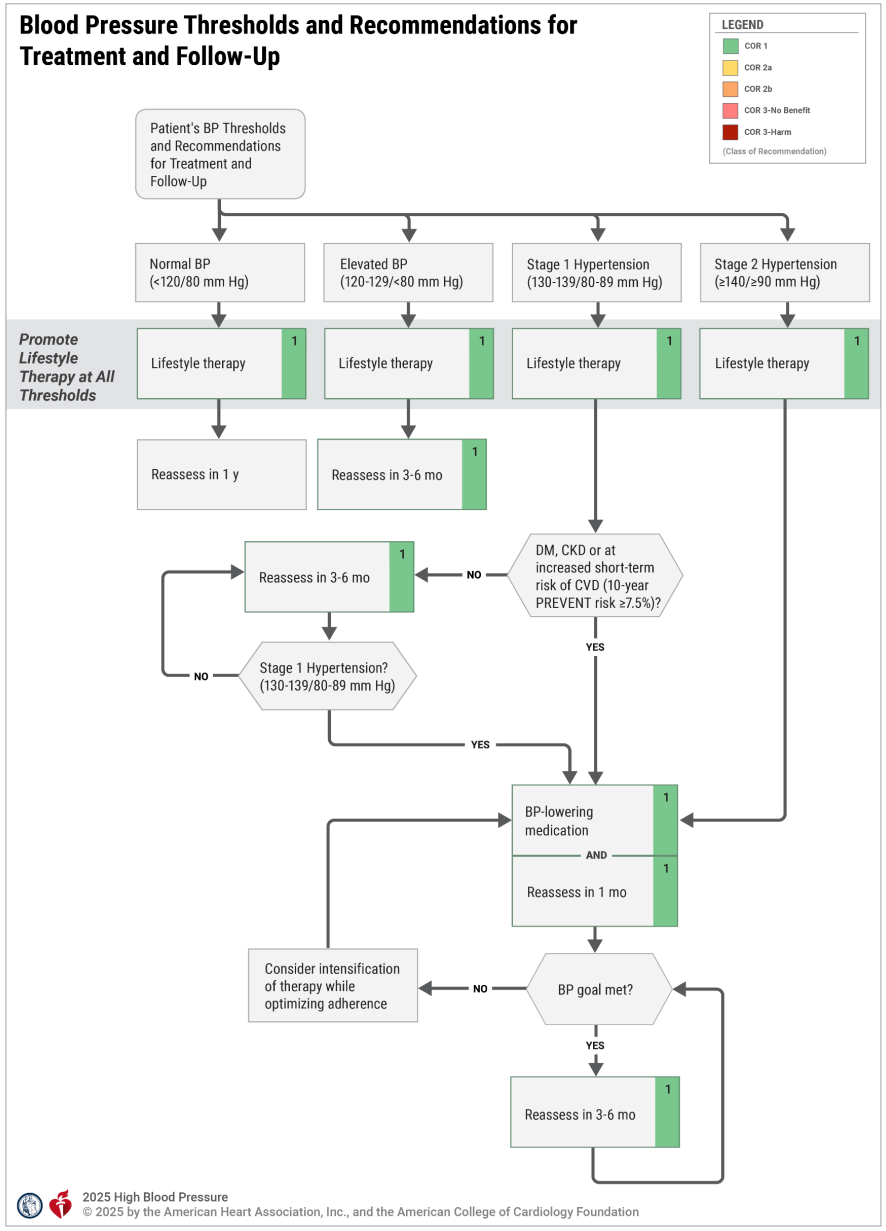
N Engl J Med 2023;389:2221-2232

Stage 2: Metabolic Risk Factors and CKD

Stage 2

- Hypertension
- Hypertriglyceridemia
- Moderate-to-High-Risk Chronic Kidney Disease
- Diabetes
- Metabolic Syndrome

2025 Hypertension Guidelines



- The overarching blood pressure treatment goal is <130/80 mm Hg for all adults.
- ACE-I/ARB for those with diabetes/albuminuria or with CKD

https://doi.org/10.1016/j.jacc.2025.05.007

2025 Hypertension Guidelines

Recommendations for Lifestyle and Psychosocial Approaches

Referenced studies that support the recommendations are summarized in the evidence table.

COR	LOE	Recommendations
		Weight
1	A	**1. In adults who have overweight or obesity, weight loss is recommended with a goal of at least 5% of body weight reduction to prevent or treat elevated BP and hypertension.**

Recommendations for Obesity and Metabolic Syndrome

Referenced studies that support the recommendations are summarized in the evidence table.

COR	LOE	Recommendations
2b	B-R	**1. In adults with hypertension who also have overweight or obesity with a BMI ≥27 kg/m², incretin mimetics (eg, GLP-1RA) when used for weight management may be effective as an adjunct to lower BP.**
2b	B-R	**2. In adults with hypertension who have obesity with a BMI ≥35.0 kg/m², bariatric surgery (when considered for weight loss) in combination with behavioral interventions and antihypertensive therapies may be effective at lowering BP.**

https://doi.org/10.1016/j.jacc.2025.05.007

Hypertriglyceridemia

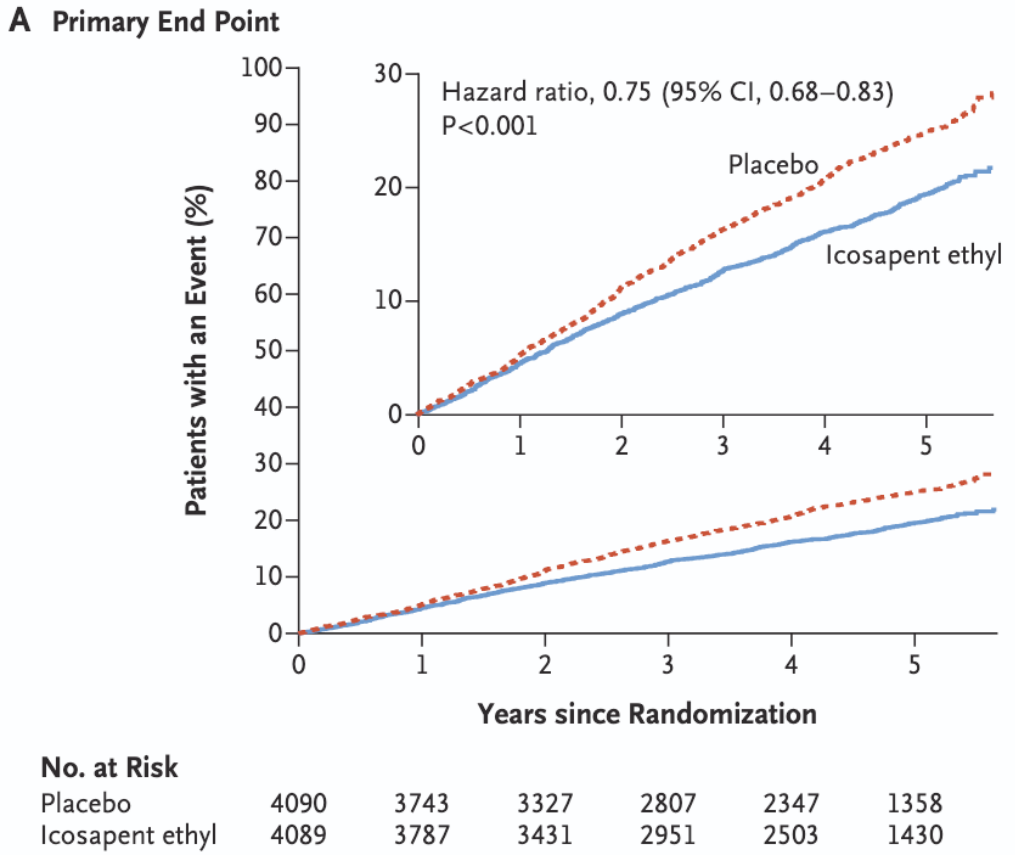
- Maximize statin therapy with elevated ASCVD
- Levels 135-499mg/dL plus diabetes + risk factors --> eicosapentaenoic acid (EPA)
- Greater than 500mg/dL --> fibrates

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

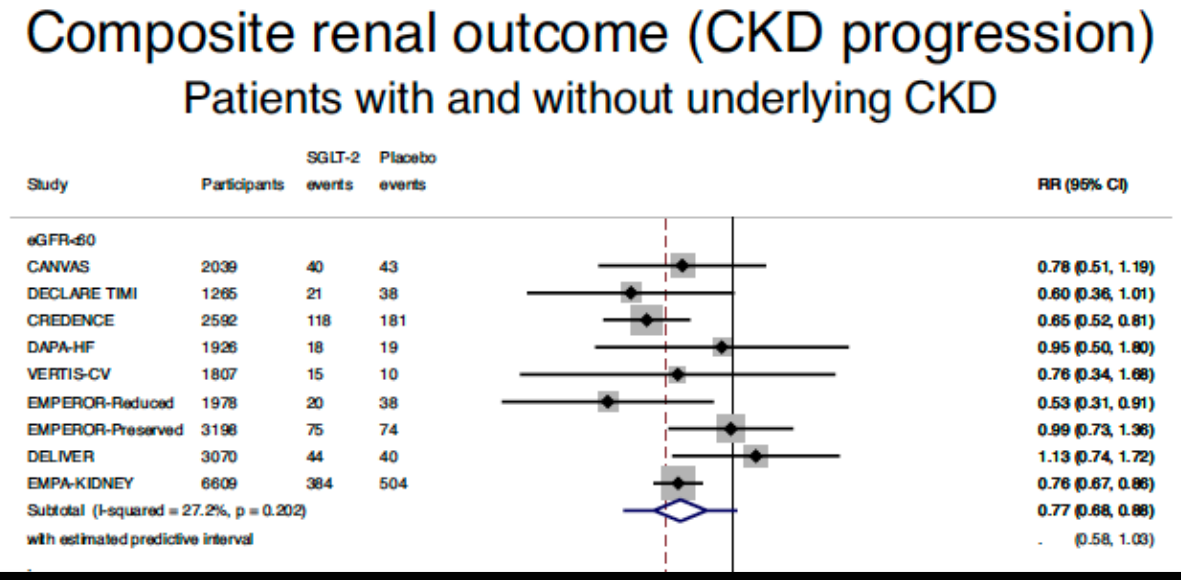


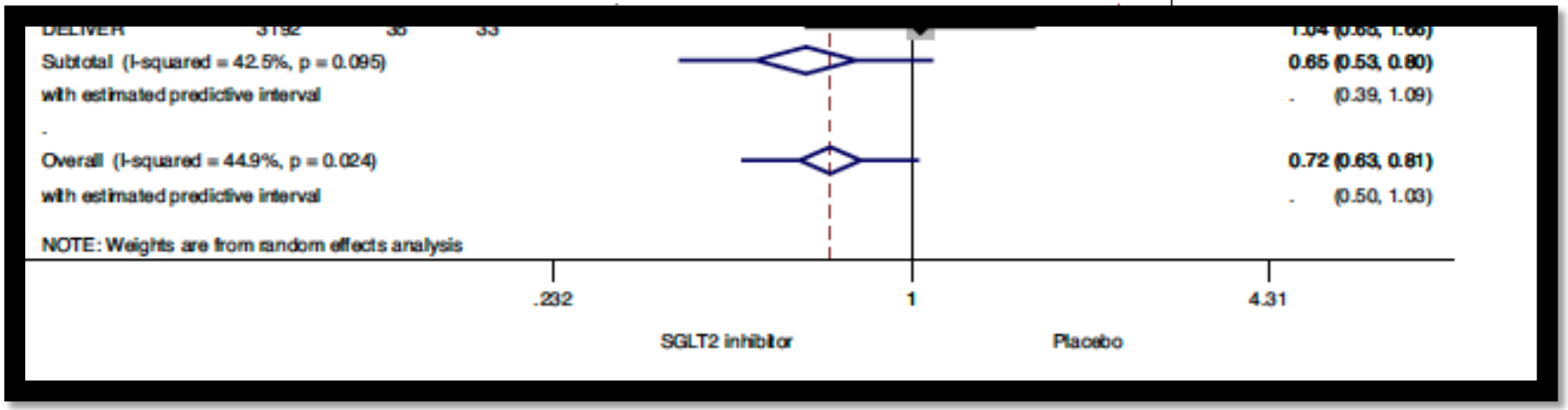
Moderate-to-High-Risk Chronic Kidney Disease (CKD)

- Albuminuria → ACE-I/ARB
- CKD (with or without diabetes) → Sodium Glucose Transporter Type 2 Inhibitor (SGLT2-Inhibitor)
- Diabetic Kidney Disease with residual albuminuria on ACEI/ARB (+/- SGLT2-Inhibitor) → finerenone

Moderate-to-High-Risk Chronic Kidney Disease (CKD)

SGLT-2 inhibitors were associated with a lower incidence of CKD progression among patients with pre-existing CKD: RR 0.77 (95% CI 0.68–0.88), compared with placebo.





Sci Rep **13**, 15922 (2023).

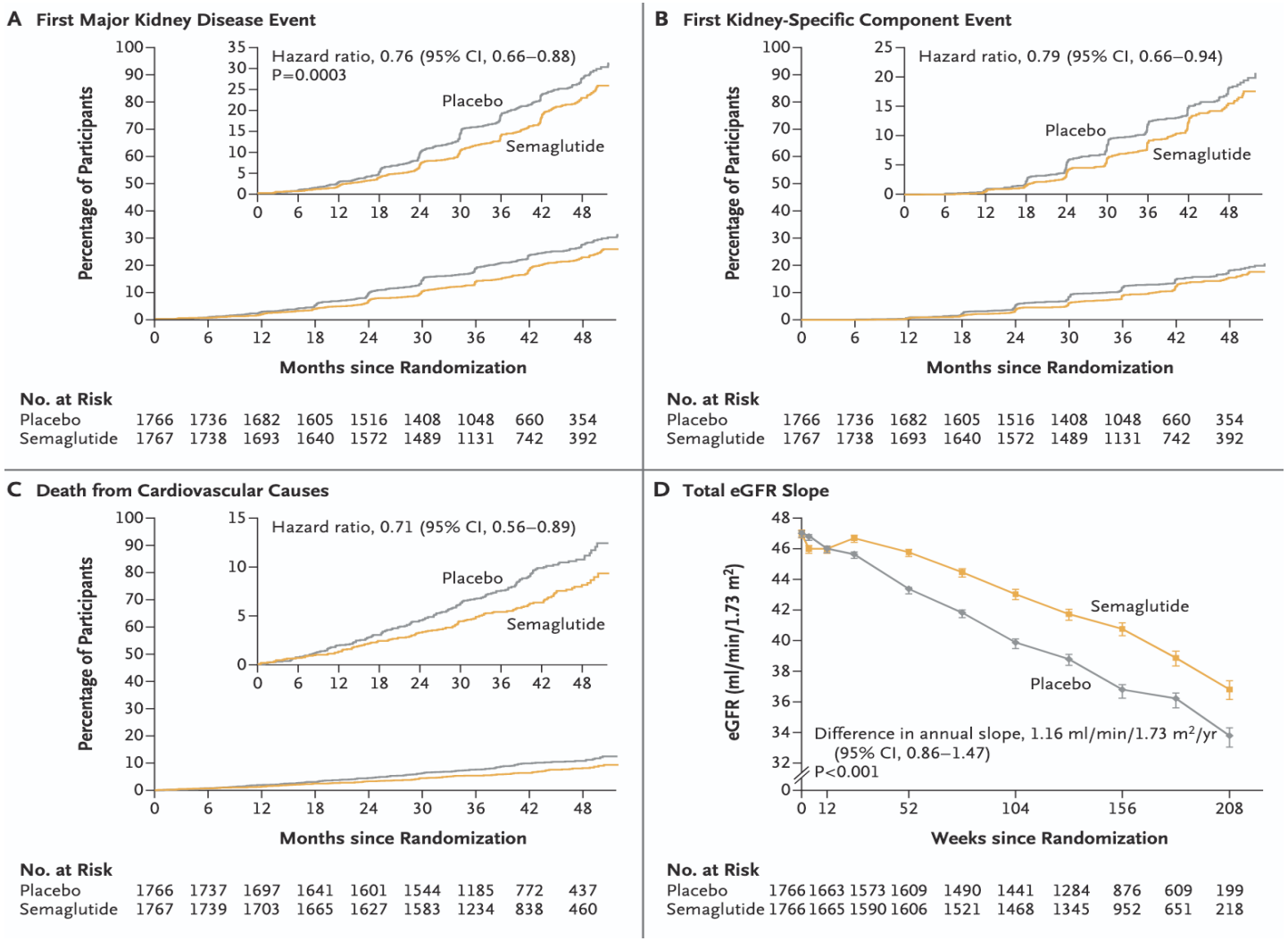
Moderate-to-High-Risk Chronic Kidney Disease (CKD)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*



Moderate-to-High-Risk Chronic Kidney Disease (CKD)

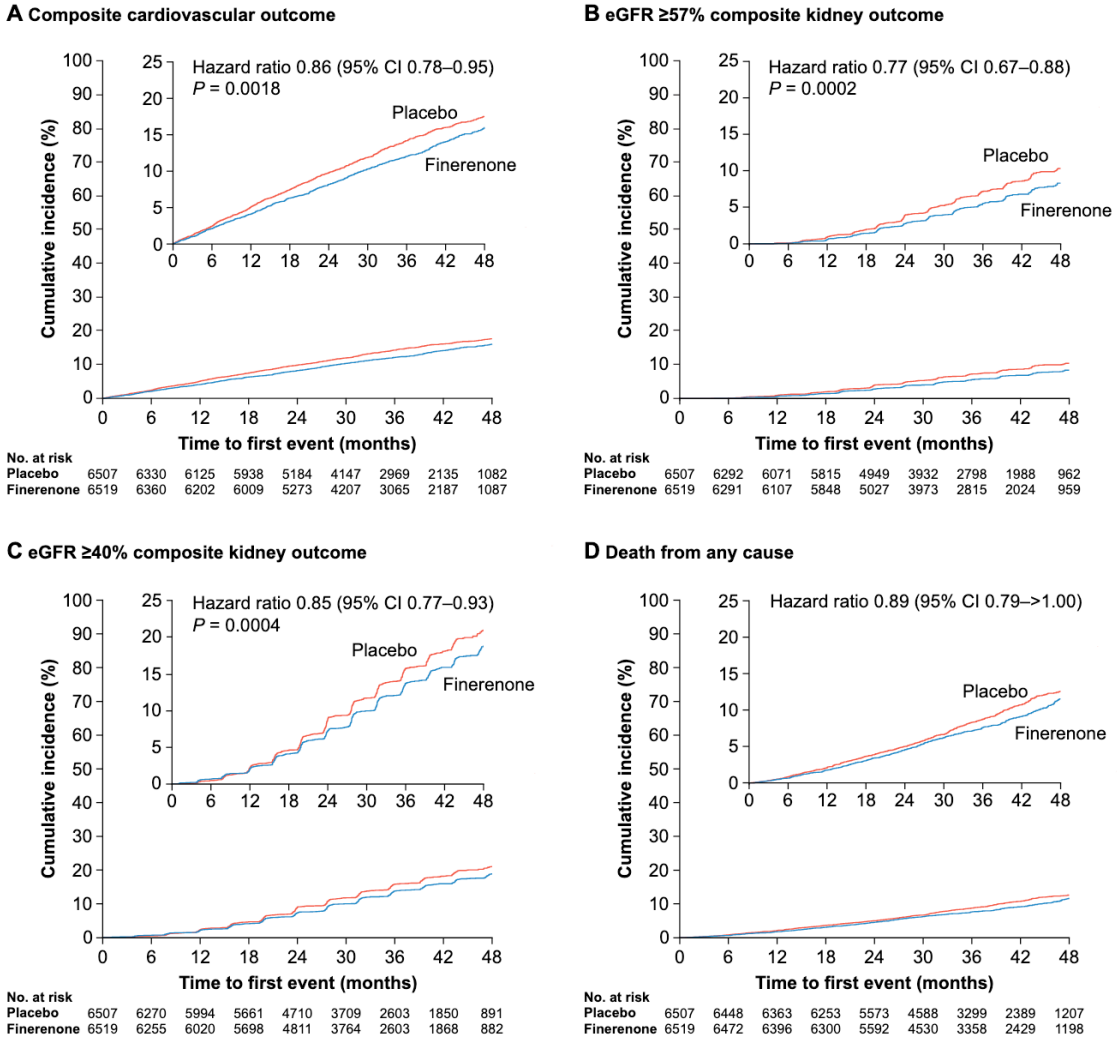
ESC European Society of Cardiology

European Heart Journal (2022) **43**, 474–484
https://doi.org/10.1093/eurheartj/ehab777

FASTTRACK CLINICAL RESEARCH
Diabetes and metabolic disorders

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

Rajiv Agarwal [1*†], Gerasimos Filippatos [2*†], Bertram Pitt [3], Stefan D. Anker [4], Peter Rossing [5,6], Amer Joseph [7], Peter Kolkhof [8], Christina Nowack [9], Martin Gebel [10], Luis M. Ruilope [11,12,13], and George L. Bakris [14]; on behalf of the FIDELIO-DKD and FIGARO-DKD investigators [‡]



Stage 3: Subclinical CVD in CKM Syndrome

Stage 3

Subclinical Atherosclerosis

-Aspirin/Statin/Non-Lipid

Subclinical Heart Failure

-Guideline Directed Medical Therapy

CVD Risk Equivalents for Stage 3 CKM

Stage 4: Clinical CVD in CKM Syndrome

Stage 4

- CKD
- Hypertension (Compelling Indications)
- Hypertriglyceridemia
- Diabetes

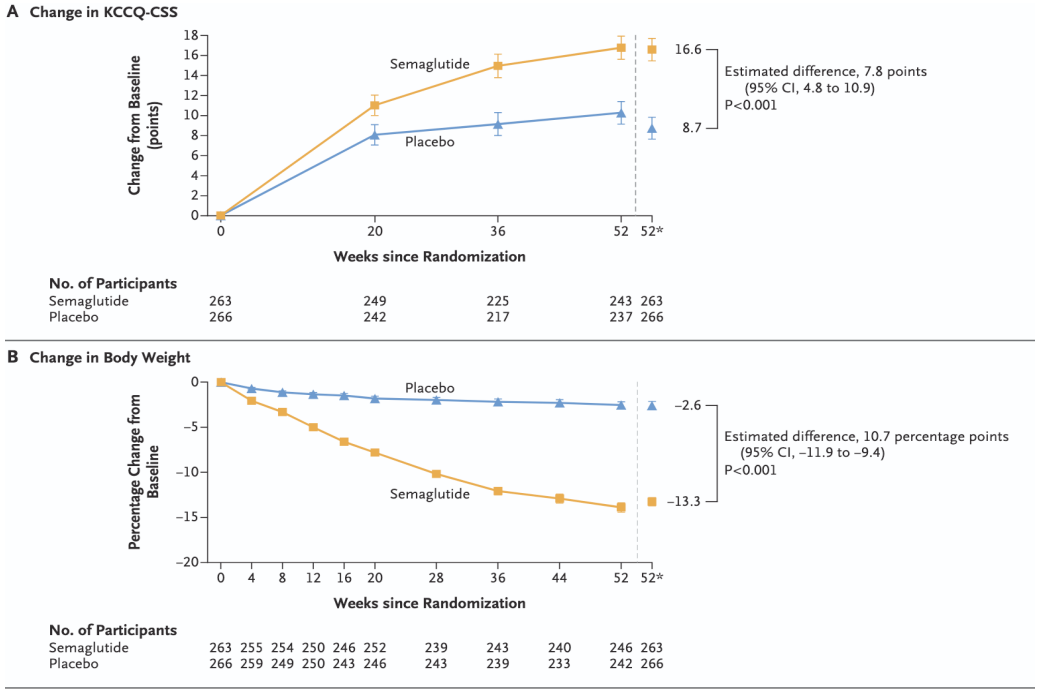
Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

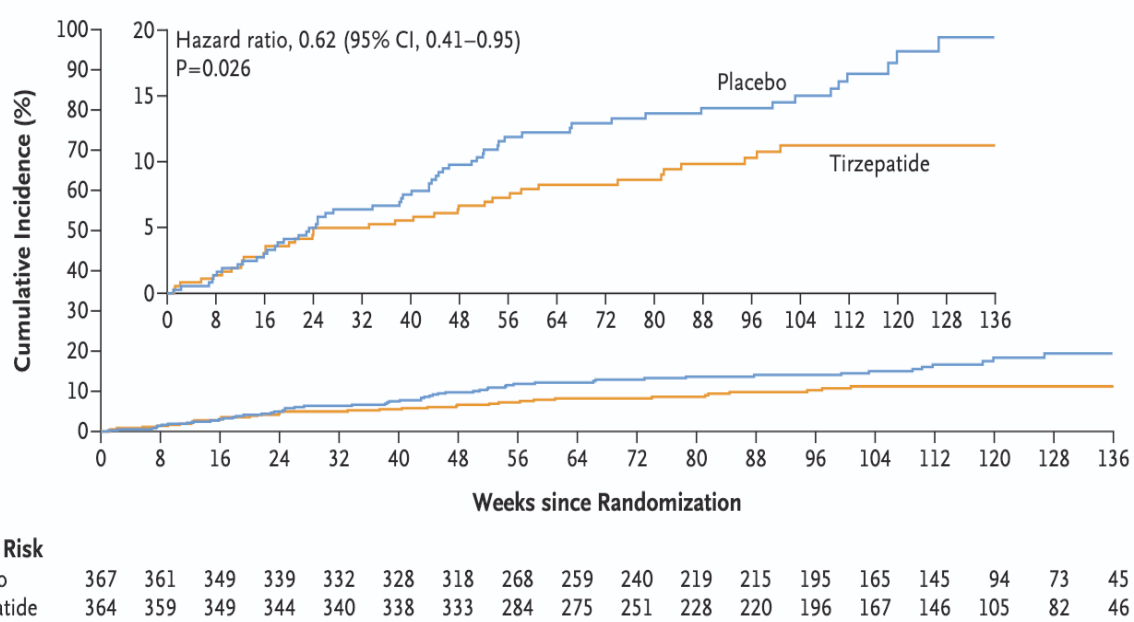


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2025 VOL. 392 NO. 5

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

Milton Packer, M.D., Michael R. Zile, M.D., Christopher M. Kramer, M.D., Seth J. Baum, M.D., Sheldon E. Litwin, M.D., Venu Menon, M.D., Junbo Ge, M.D., Govinda J. Weerakkody, Ph.D., Yang Ou, Ph.D., Mathijs C. Bunck, M.D., Karla C. Hurt, B.S.N., Masahiro Murakami, M.D., and Barry A. Borlaug, M.D., for the SUMMIT Trial Study Group*



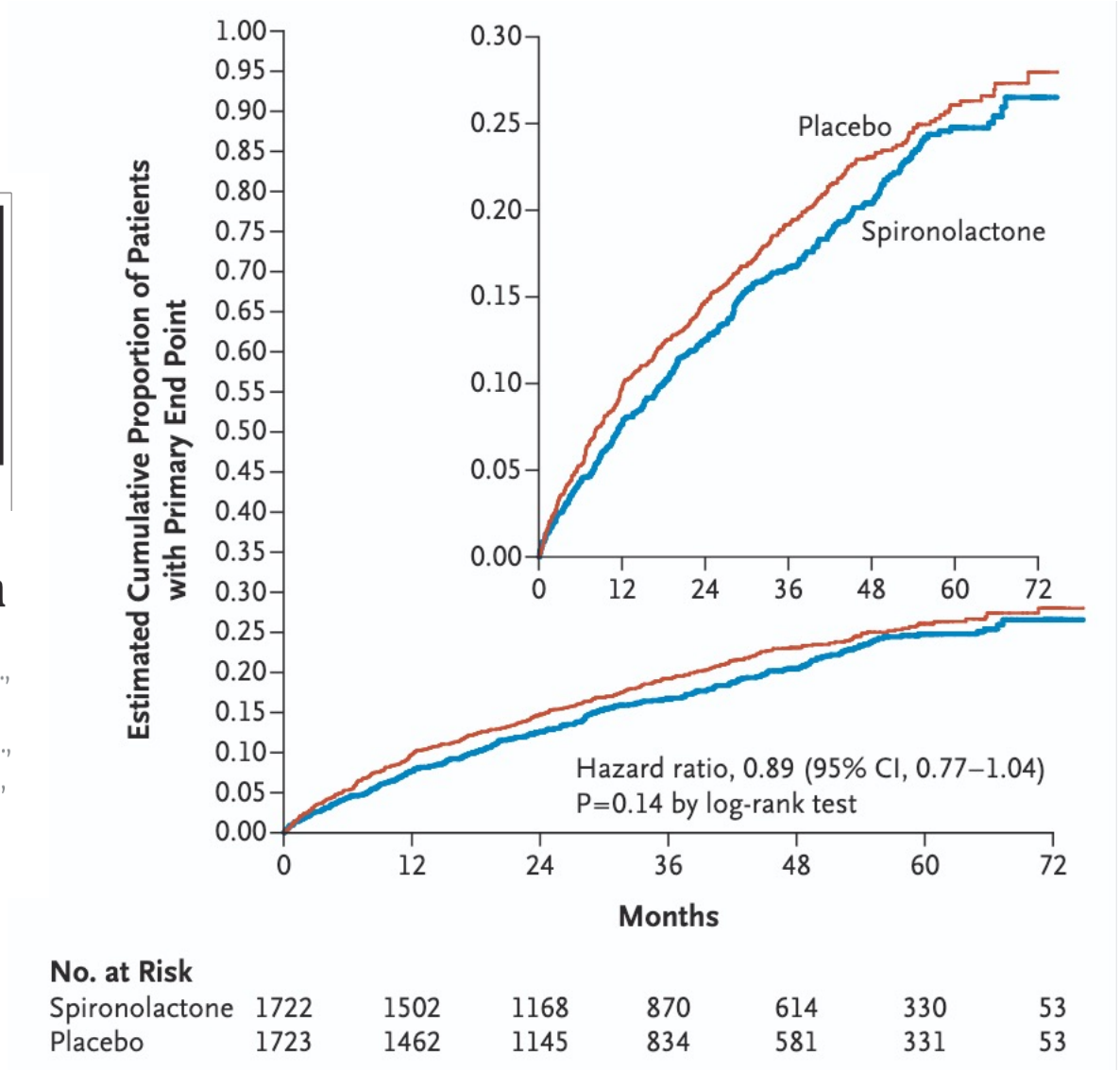
Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2014 VOL. 370 NO. 15

Spironolactone for Heart Failure with Preserved Ejection Fraction

Bertram Pitt, M.D., Marc A. Pfeffer, M.D., Ph.D., Susan F. Assmann, Ph.D., Robin Boineau, M.D., Inder S. Anand, M.D., Brian Claggett, Ph.D., Nadine Clausell, M.D., Ph.D., Akshay S. Desai, M.D., M.P.H., Rafael Diaz, M.D., Jerome L. Fleg, M.D., Ivan Gordeev, M.D., Ph.D., Brian Harty, M.A., John F. Heitner, M.D., Christopher T. Kenwood, M.S., Eldrin F. Lewis, M.D., M.P.H., Eileen O'Meara, M.D., Jeffrey L. Probstfield, M.D., Tamaz Shaburishvili, M.D., Ph.D., Sanjiv J. Shah, M.D., Scott D. Solomon, M.D., Nancy K. Sweitzer, M.D., Ph.D., Song Yang, Ph.D., and Sonja M. McKinlay, Ph.D., for the TOPCAT Investigators*



Conclusions

- CKM reflects the interrelationships among metabolic risk factors, CKD, and cardiovascular disease.
- Poor CKM health has implications on adverse clinical outcomes.
- Growth, and growing options, for CKM pharmacotherapies can improve outcomes with patients with CKM.

Talk 3: Sonali Arora

GLP-1 RECEPTOR AGONISTS IN HFPEF

SONALI ARORA MD FACC FHFSA

ADVANCED HEART FAILURE AND CARDIAC TRANSPLANT

DIVISION OF CARDIOVASCULAR MEDICINE

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

NO DISCLOSURES

OBJECTIVES

1. Definition and Stages of CKM (Cardiovascular-Kidney-Metabolic) syndrome
2. Overlap of CKM with HFpEF (Heart Failure with preserved Ejection fraction)
3. Mechanism of Action of GLP-1 RAs (Glucagon-Like Peptide-1 Receptor agonists)
4. Clinical evidence of GLP-1 RAs in HFpEF

CARDIOVASCULAR-KIDNEY-METABOLIC (CKM) DEFINITION

- CKM syndrome is a novel construct which reflects the pathophysiological interplay of excess and/or dysfunctional adiposity, metabolic derangements, chronic kidney disease (CKD), and cardiovascular disease (CVD)
- A recent American Heart Association (AHA) Presidential Advisory defines a new staging system for CKM syndrome that integrates novel risk prediction equations to both qualitatively and quantitatively stratify patients for total CVD risk and determine optimal strategies for targeted interventions based on absolute risk and net benefit across each stage
- Nearly 90% of adults in the United States have CKM syndrome (stage 1 or higher), with more than 50% of adults over 65 having advanced disease (stages 3-4)
- CKM syndrome progression is the strongest predictor of cardiovascular disease, and it drives persistent inequities in morbidity and mortality rates

AHA PRESIDENTIAL ADVISORY

Circulation

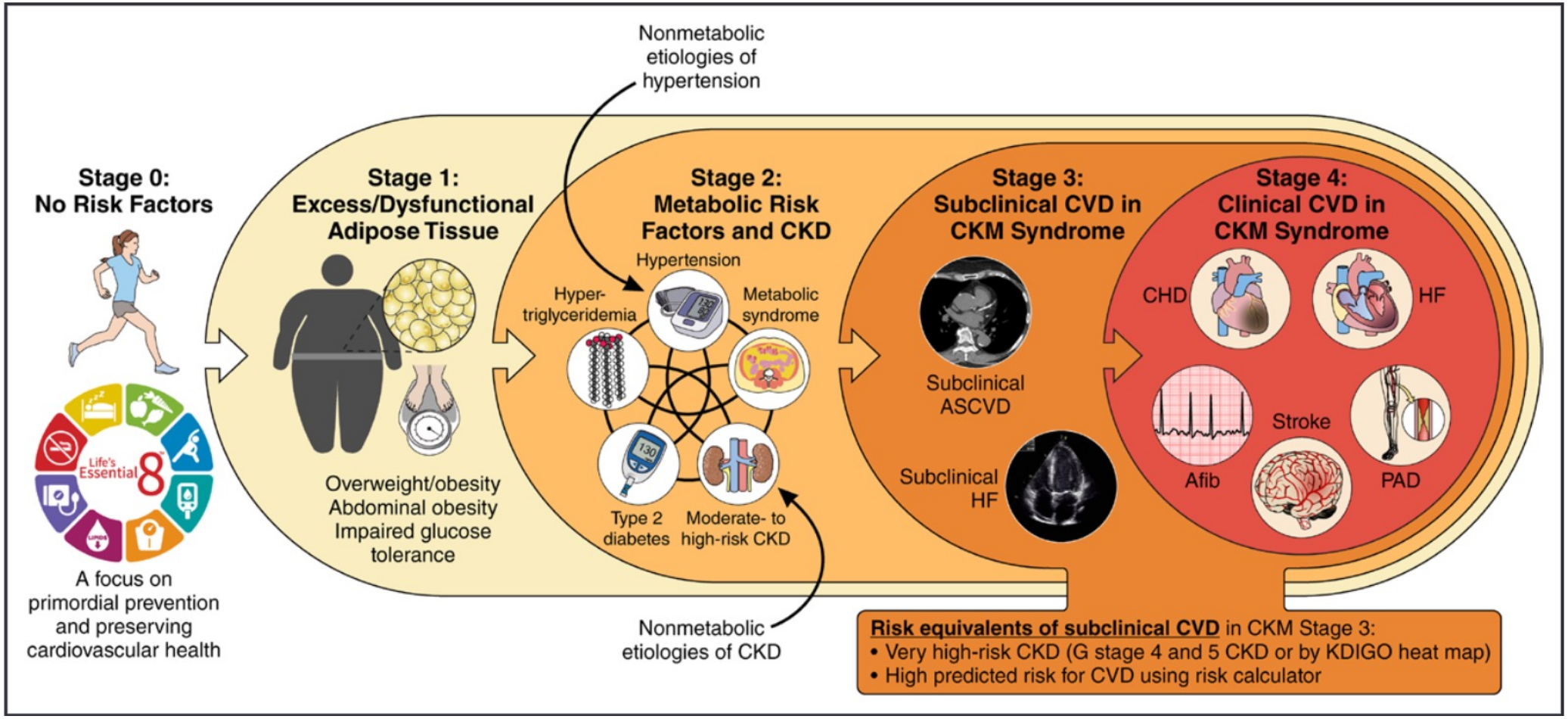
AHA PRESIDENTIAL ADVISORY

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

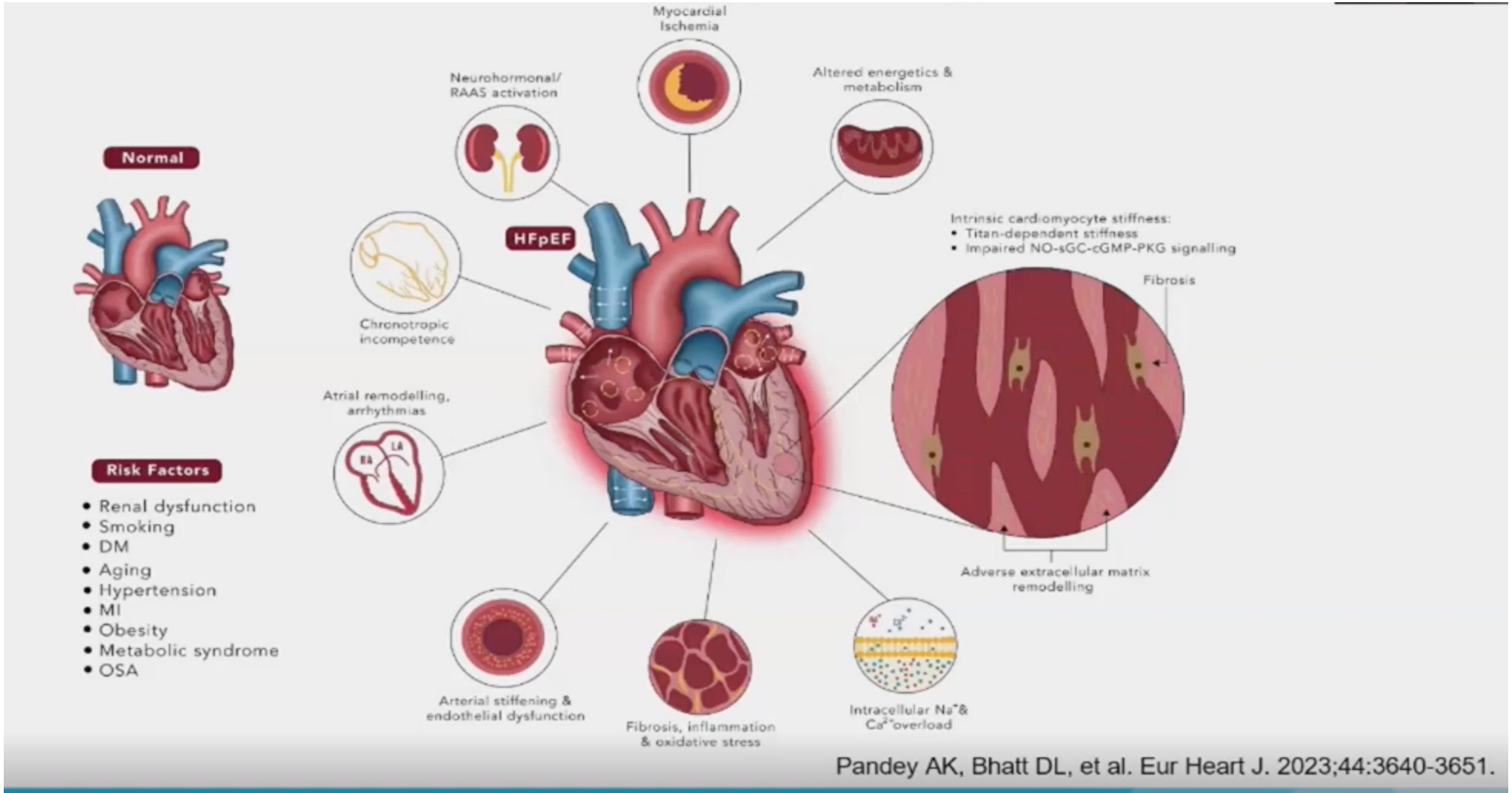
Summary

There is a high burden of poor cardiovascular-kidney-metabolic health in the population, which affects nearly all organ systems and has a particularly powerful impact on the incidence of cardiovascular disease. More guidance is needed on definitions, staging, prediction strategies, and algorithms for the prevention and treatment of cardiovascular-kidney-metabolic syndrome to optimize cardiovascular-kidney-metabolic health across diverse clinical and community settings.

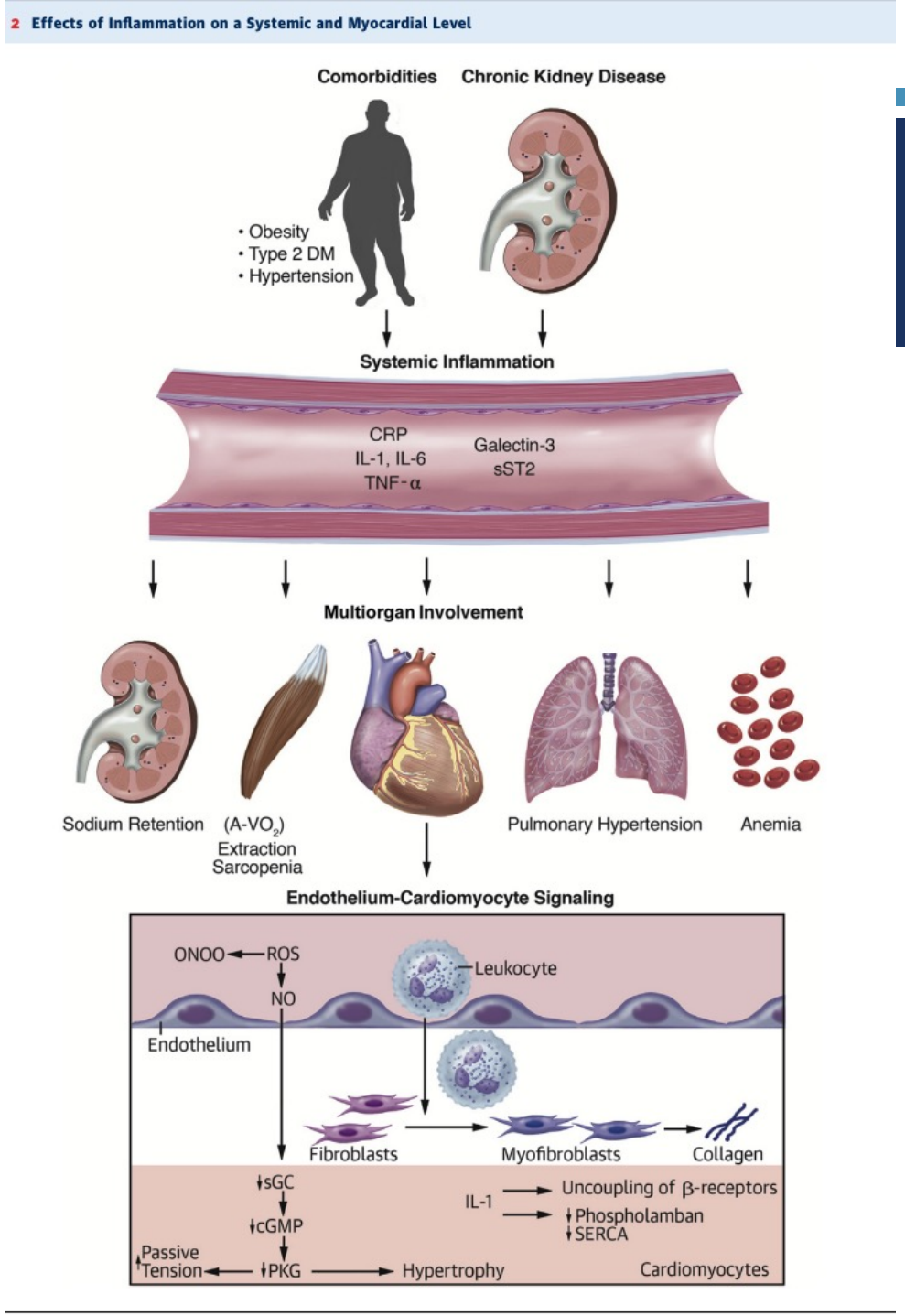
STAGES OF CKM SYNDROME



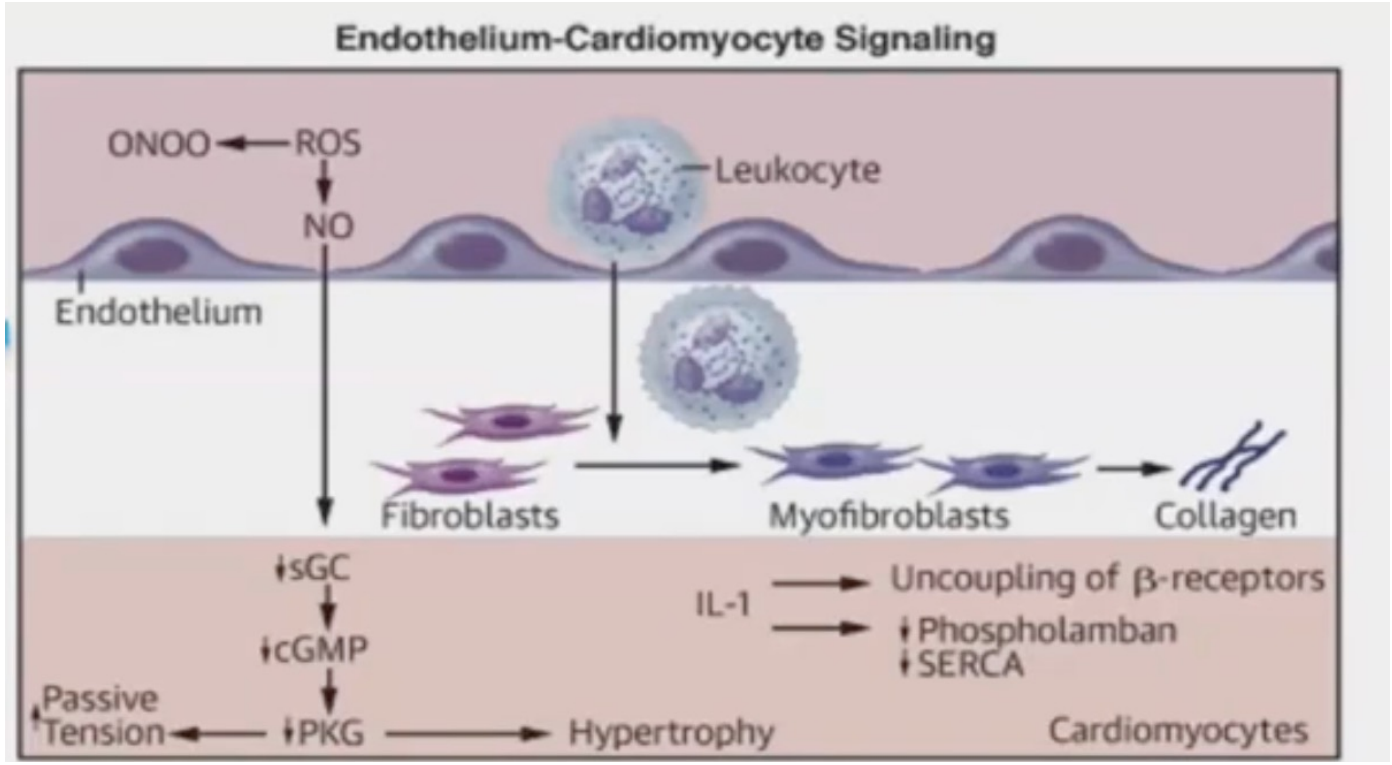
HFPEF RISK FACTORS AND PATHOPHYSIOLOGICAL MECHANISMS



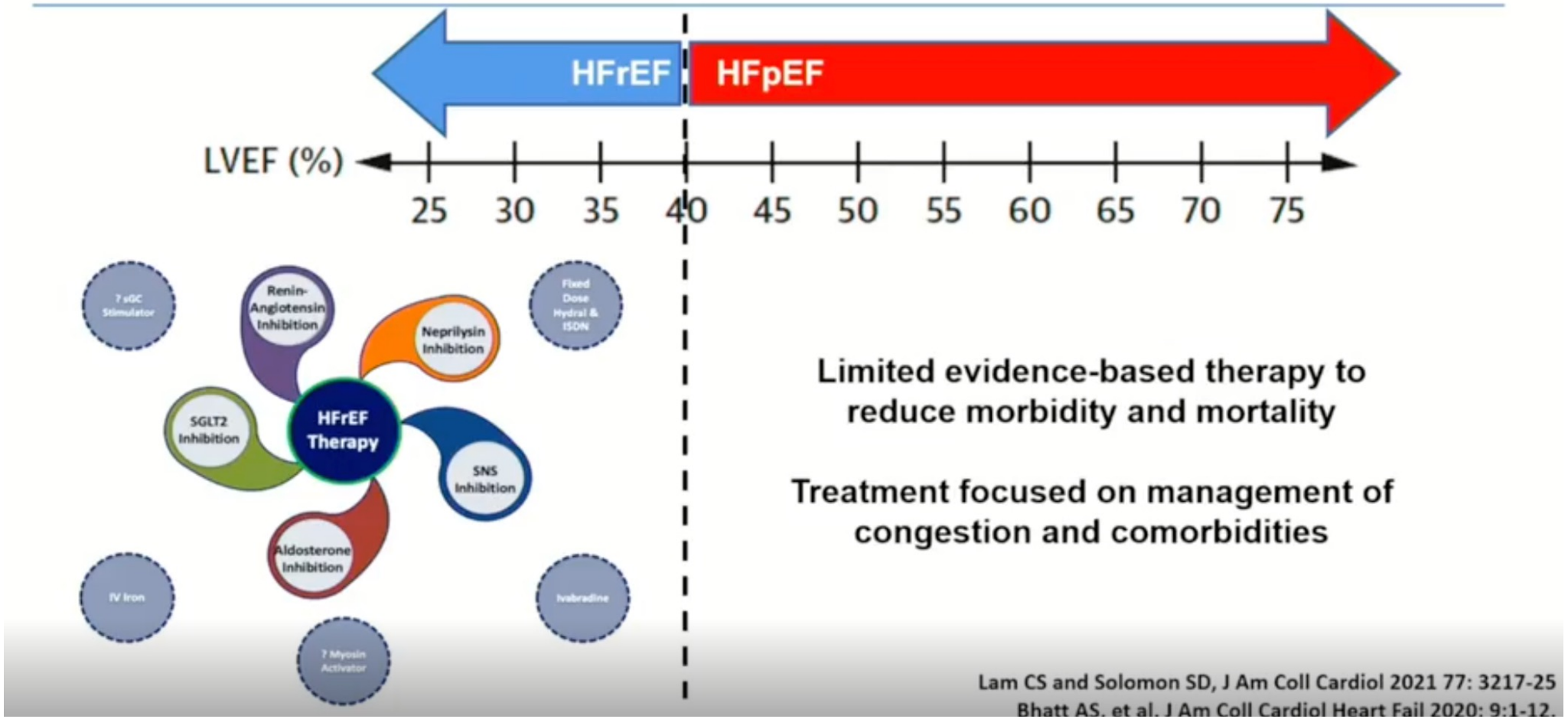
Pandey AK, Bhatt DL, et al. Eur Heart J. 2023;44:3640-3651.



EFFECTS OF INFLAMMATION ON MYOCARDIUM

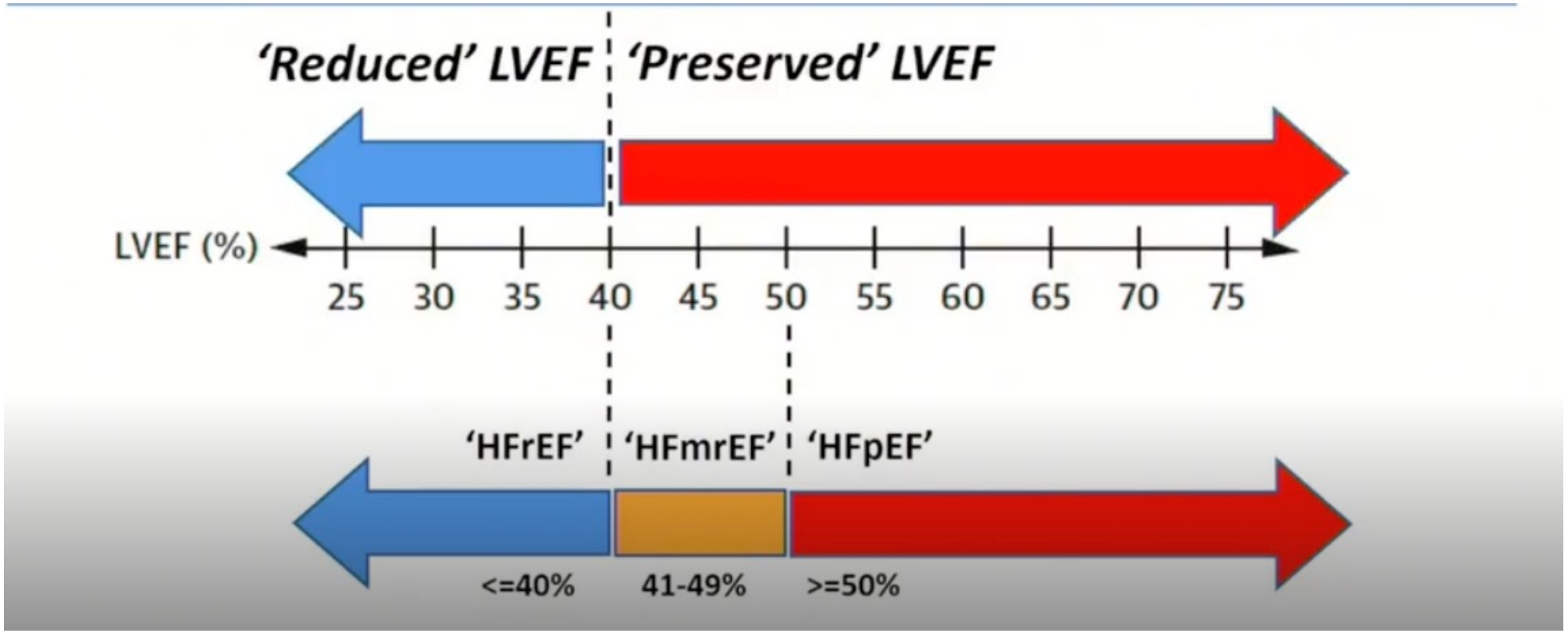


UNMET NEEDS OF HFPEF



Lam CS and Solomon SD, J Am Coll Cardiol 2021 77: 3217-25
Bhatt AS, et al. J Am Coll Cardiol Heart Fail 2020; 9:1-12.

HEART FAILURE CLASSIFICATION BY EJECTION FRACTION

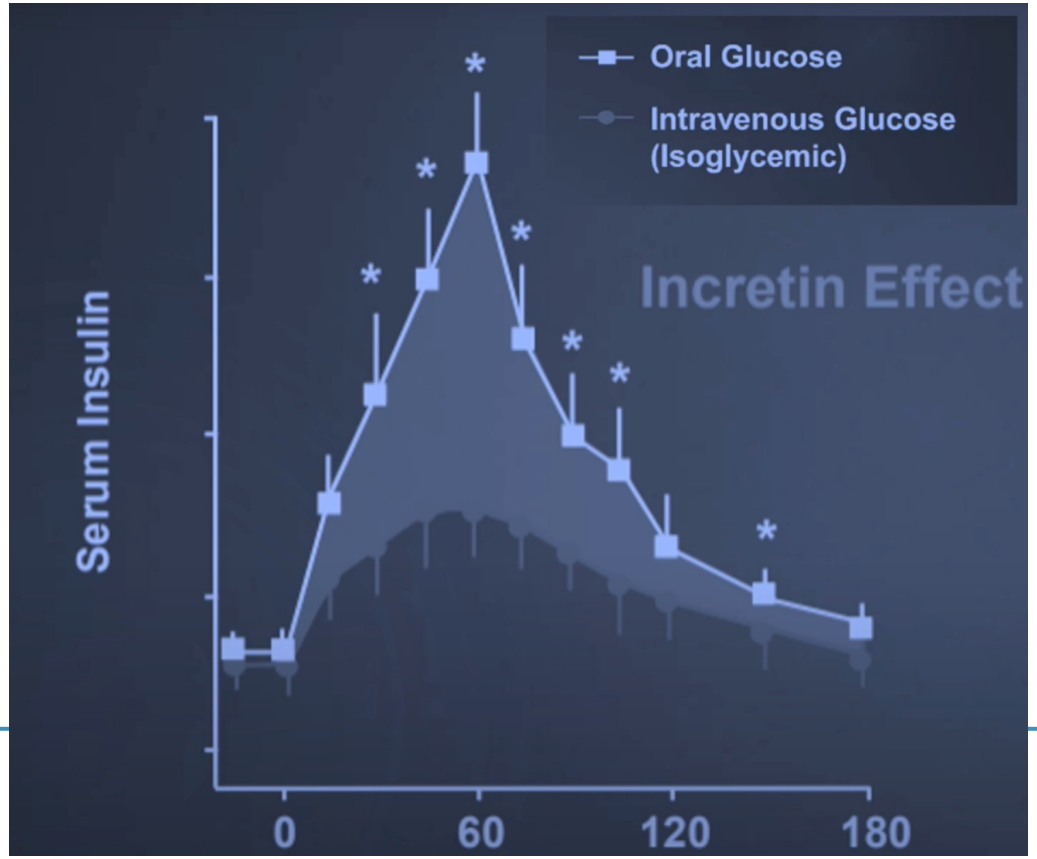


GLP-1 RECEPTOR AGONISTS AND THEIR MECHANISM OF ACTION IN HEART FAILURE

- GLP-1 RAs are synthetic analogues of the incretin hormone GLP-1, which is secreted by intestinal L cells in response to nutrient ingestion
- Physiological actions of GLP-1 include
  - stimulation of glucose-dependent insulin secretion
  - inhibition of glucagon release,
  - slowing of gastric emptying and the promotion of satiety
  - contributing to both reducing glycemic levels and weight loss
- Unlike endogenous GLP-1, which is rapidly degraded by dipeptidyl peptidase-4, GLP-1 receptor agonists are resistant to degradation and have longer half-lives, particularly for modern long-acting agents, such as liraglutide, dulaglutide, semaglutide and tirzepatide

GLP-1 RECEPTOR AGONISTS AND THEIR MECHANISM OF ACTION IN HEART FAILURE

- GLP-1 receptor agonists exhibit several cardioprotective mechanisms that make them interesting candidates for the treatment of HF
- Obesity and insulin resistance are major contributors to HF
- Chronic hyperglycemia is strongly related to the risk of cardiovascular disease (CVD) and death by inducing oxidative stress and inflammation and promoting atherosclerosis and endothelial dysfunction
- GLP-1 RAs are an antidiabetic class of drugs, but their effect on the relative reduction in HbA1c compared with placebo was moderate (0.4–1.2%) in the cardiovascular outcomes trials (CVOTs)
- The effect of GLP-1 RAs on major adverse cardiovascular events (MACE) goes beyond glycemic control



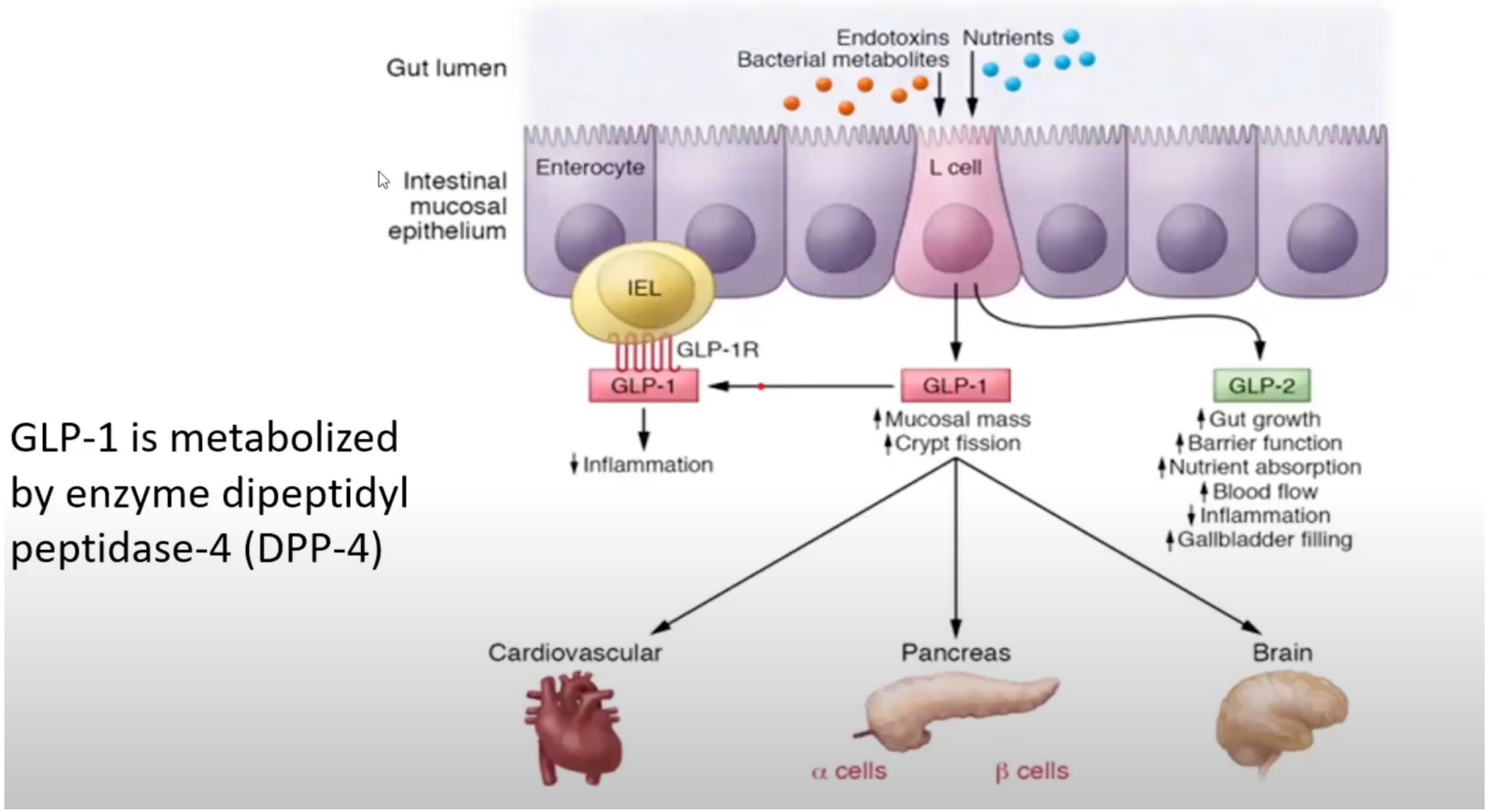
- A phenomenon where delivery of oral glucoses elicits a higher insulin secretion compared to intravenous glucose.
- Conclusion: A humoral substance is released from intestinal wall during glucose absorption which stimulates release of insulin from the pancreatic islet cells.

INCRETIN EFFECT

Nauck M et.al Reduced incretin effect in Type 2 Diabetes. Diabetologia 29,46-52(1986)

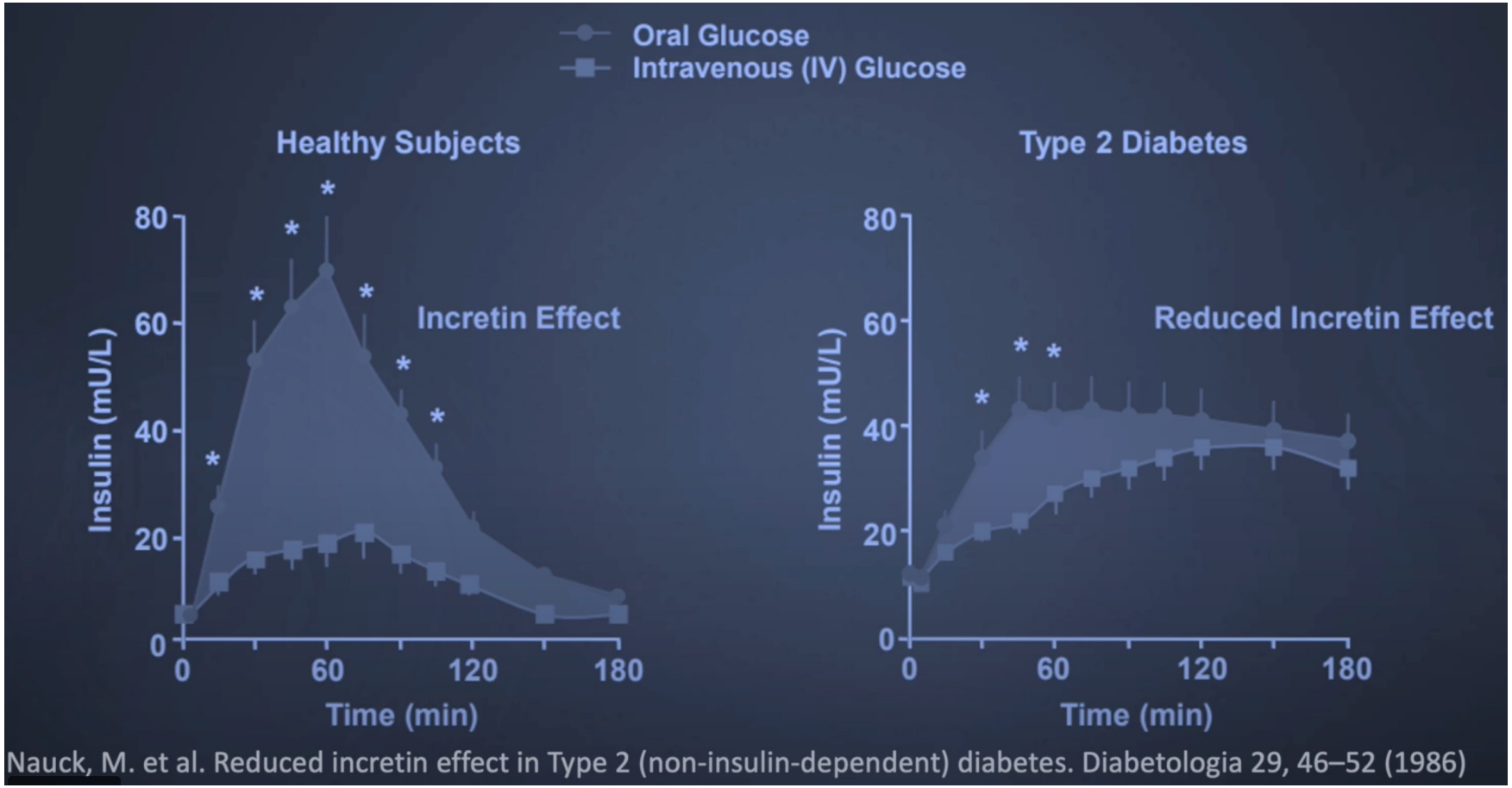
HUMAN GLP-1

GLP-1 is metabolized by enzyme dipeptidyl peptidase-4 (DPP-4)



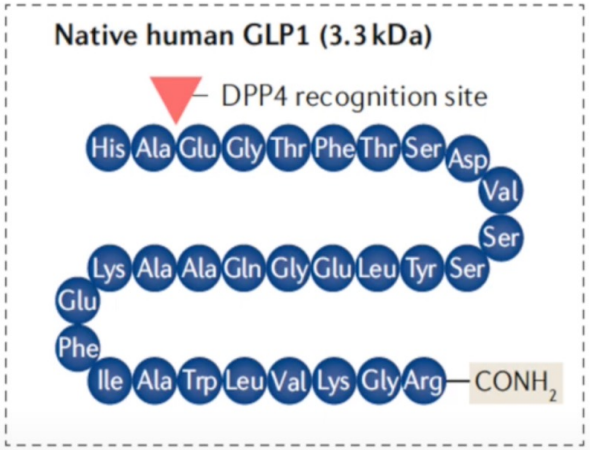
Drucker DJ et.al J Clin invest

INCRETIN EFFECT IS BLUNTED IN TYPE 2 DM

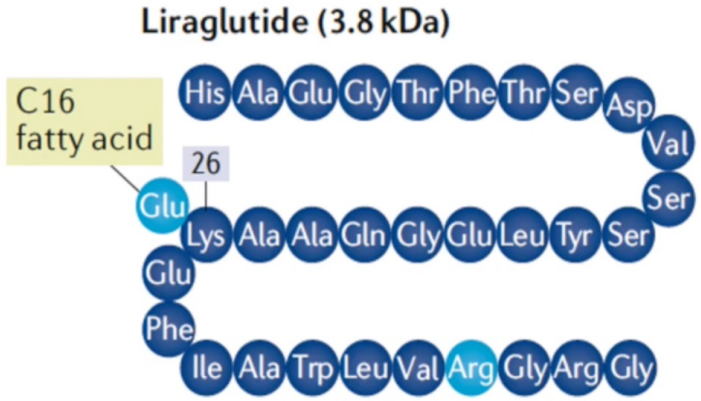


Nauck, M. et al. Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes. Diabetologia 29, 46–52 (1986)

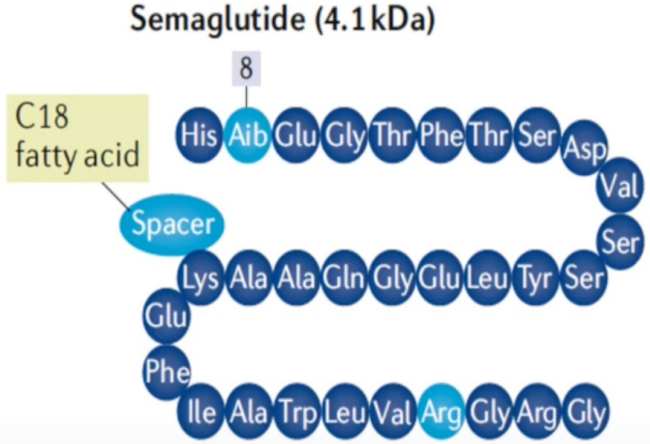
STRUCTURE OF NATIVE GLP-1 COMPARED TO APPROVED GLP-1 RAS



- Half life = 1-2 minutes



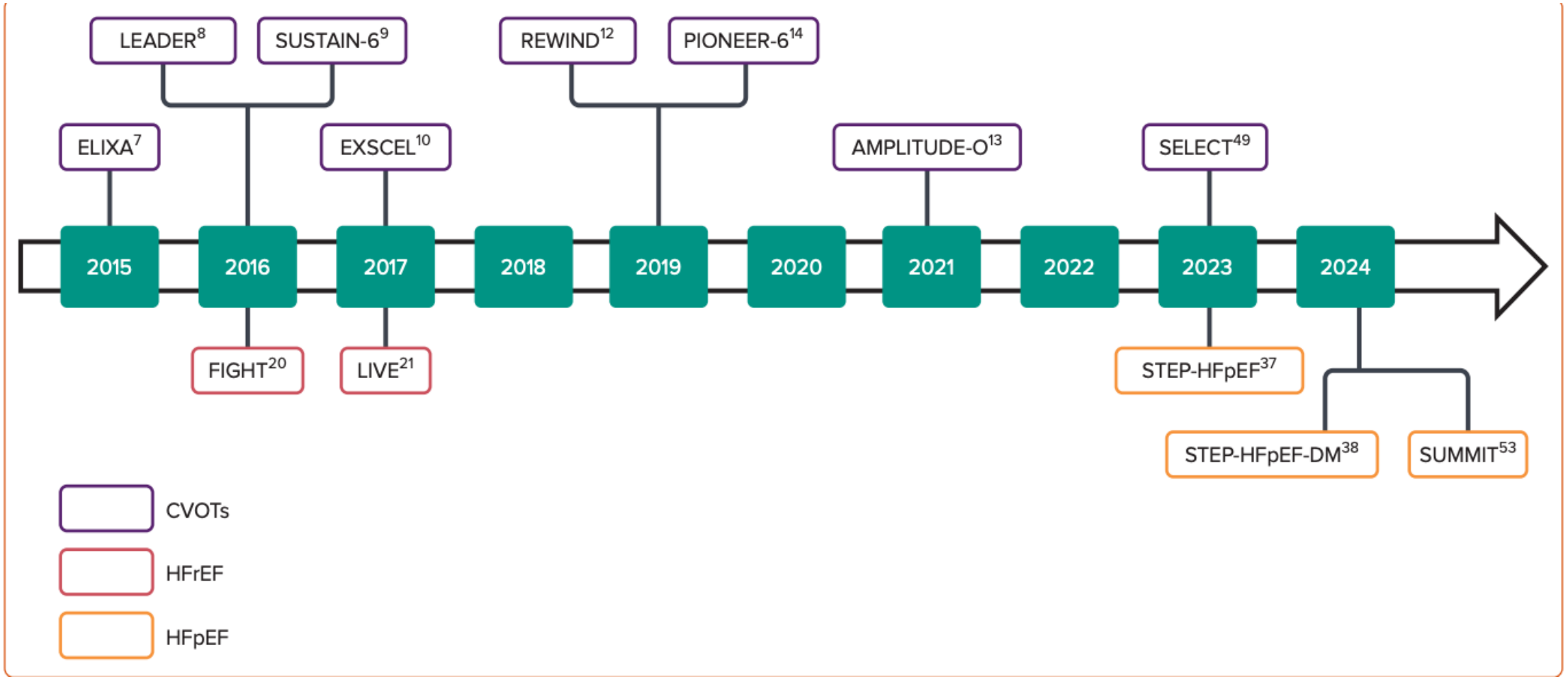
- Half life = 13 hours



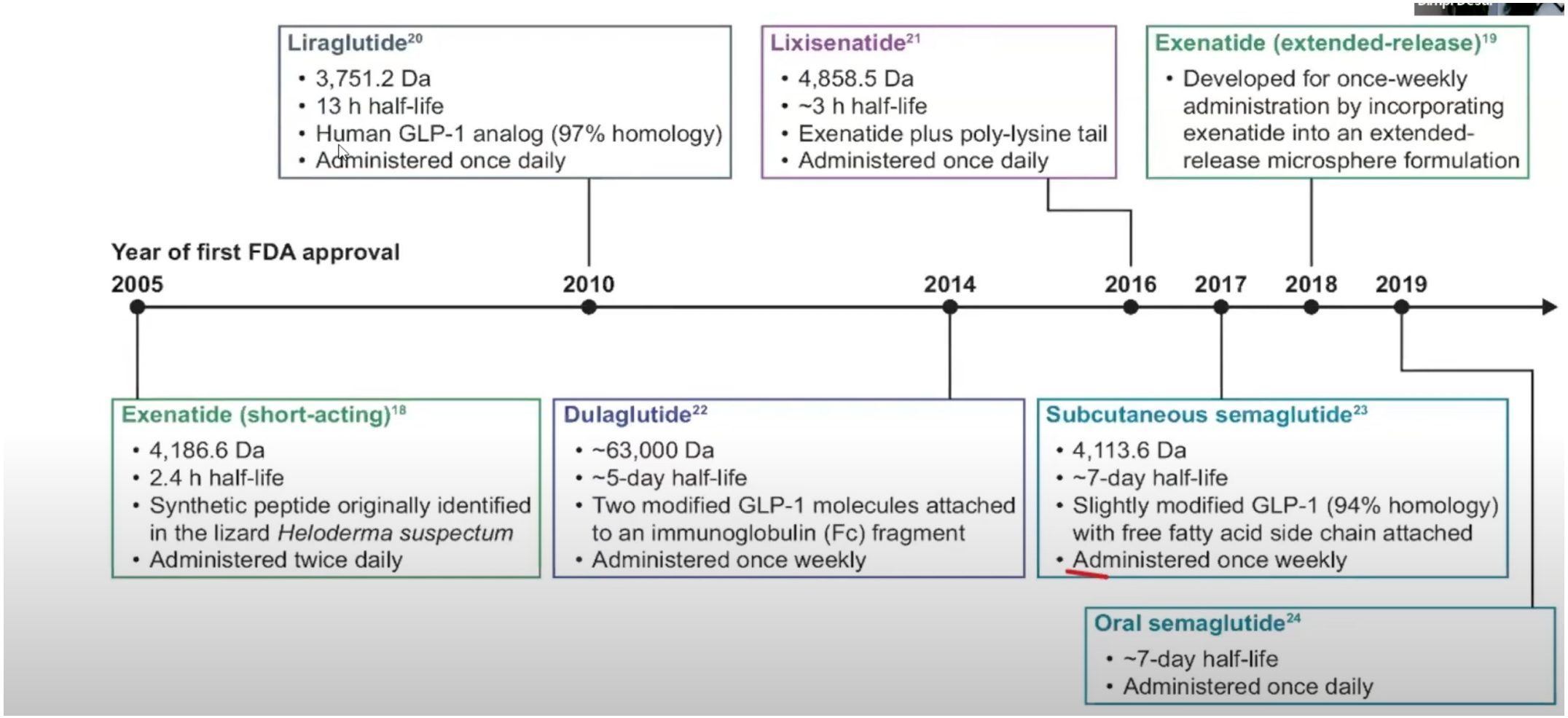
- Half life = 165 hours

Andersen, A., Lund, A., Knop, F.K. *et al.* Glucagon-like peptide 1 in health and disease. *Nat Rev Endocrinol* **14**, 390–403 (2018).

TIMELINE OF RANDOMIZED CLINICAL TRIALS OF GLP-1 RA

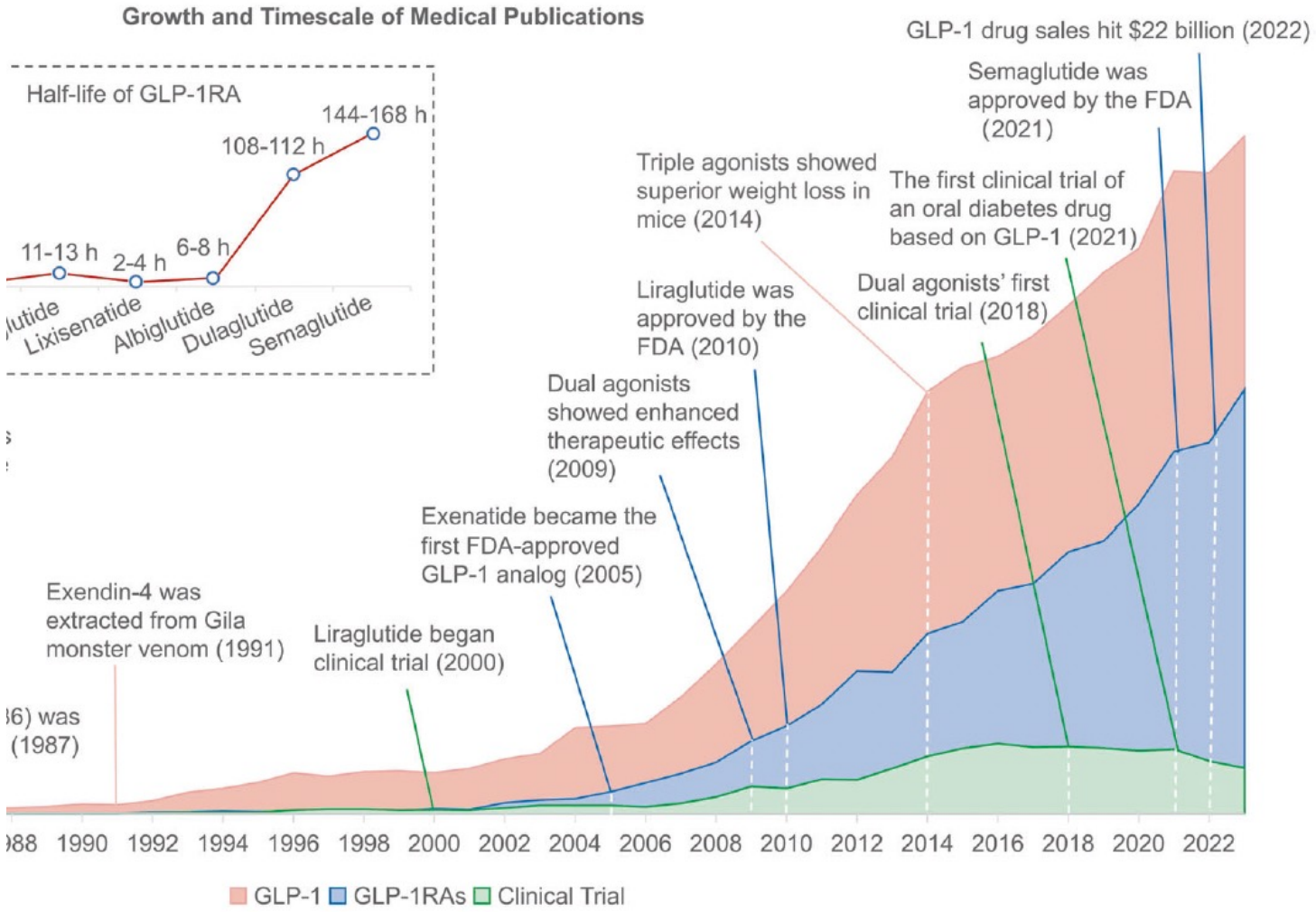


TIMELINE OF DIFFERENT GLP-1 AGONISTS



TIMELINE

Glucagon-like peptide-1 receptor: mechanisms and advances in therapy
Zheng et al.



OBESITY

- Obesity is a strong cardiovascular risk factor and it is strictly related to HF, particularly HFpEF
- Induce significant weight loss through appetite suppression and consequent reduced caloric intake
- Weight loss was significant in outcome trials, ranging from a 0.6 kg reduction at 12 weeks in the ELIXA trial to a 4.3 kg reduction at 2 years with injectable semaglutide in the SUSTAIN-6 trial
- Semaglutide resulted in the most significant weight reduction.
- Tirzepatide, a dual agonist of glucose dependent insulinotropic polypeptide and GLP-1 receptors, resulted in even more pronounced weight loss effects, suggesting a potential advantage over traditional GLP-1 Ras

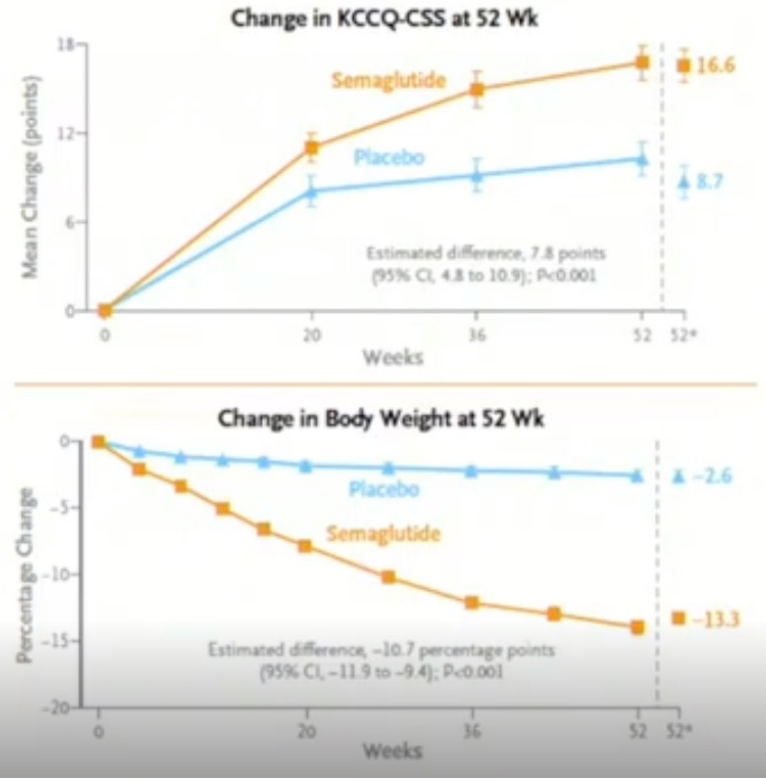
OBESITY

- Weight loss did not always correlate with improved clinical outcomes in patients with HF
- LIVE and FIGHT trials, in which liraglutide, despite leading to significant weight loss , failed to demonstrate any beneficial effects on clinical outcomes in patients with HFrEF
- Patients with obesity have an of epicardial adipose tissue which causes proinflammatory activity and worse hemodynamic/metabolic profile in patients with HFpEF
- GLP-1 RAs produces a rapid, substantial and dose-dependent reduction in epicardial adipose tissue thickness

GLP-1 RA FOR HFPEF WITH OBESITY

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

Kosiborod MN et al. DOI: 10.1056/NEJMoa2306963

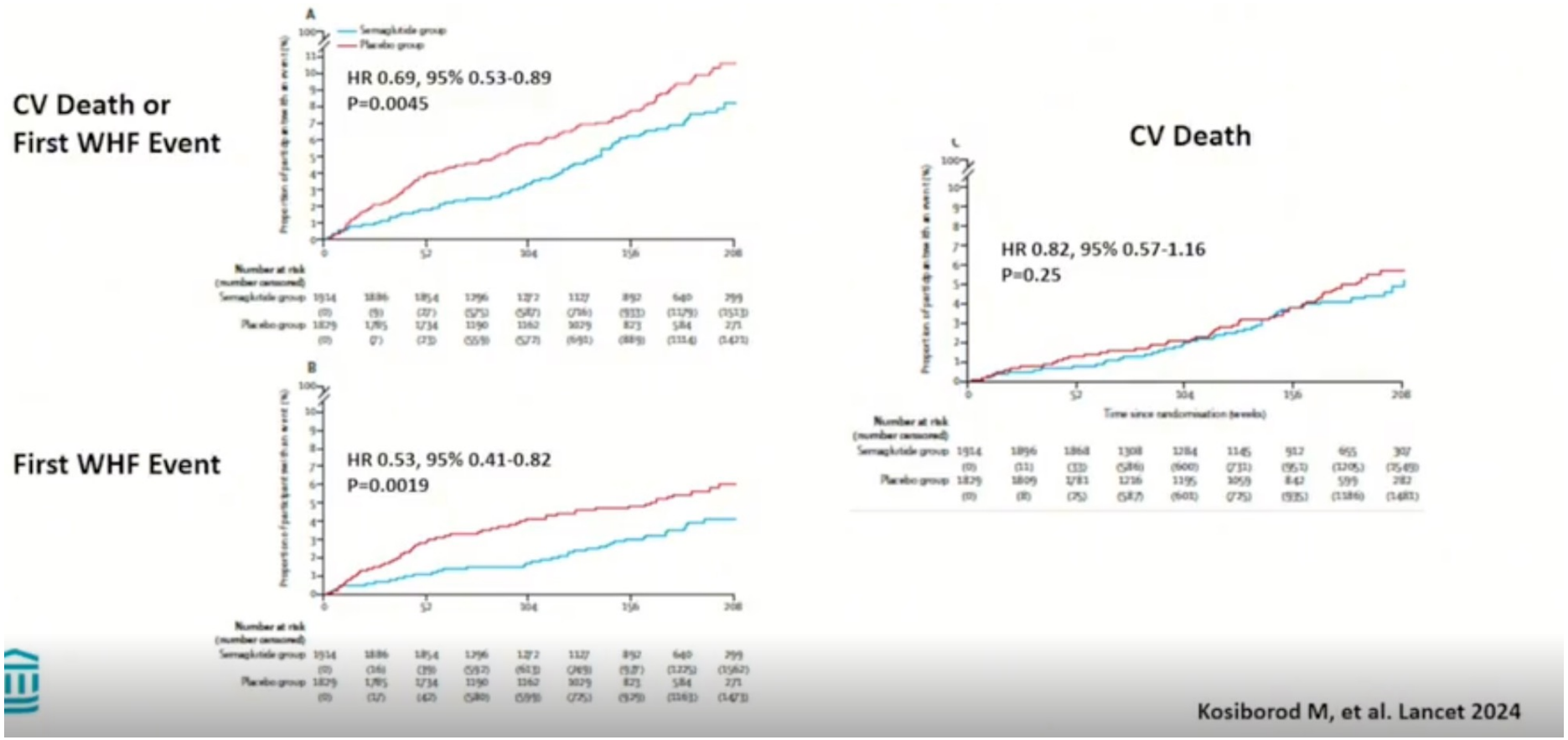


Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

Kosiborod MN et al. DOI: 10.1056/NEJMoa2313917

POOLED ANALYSIS

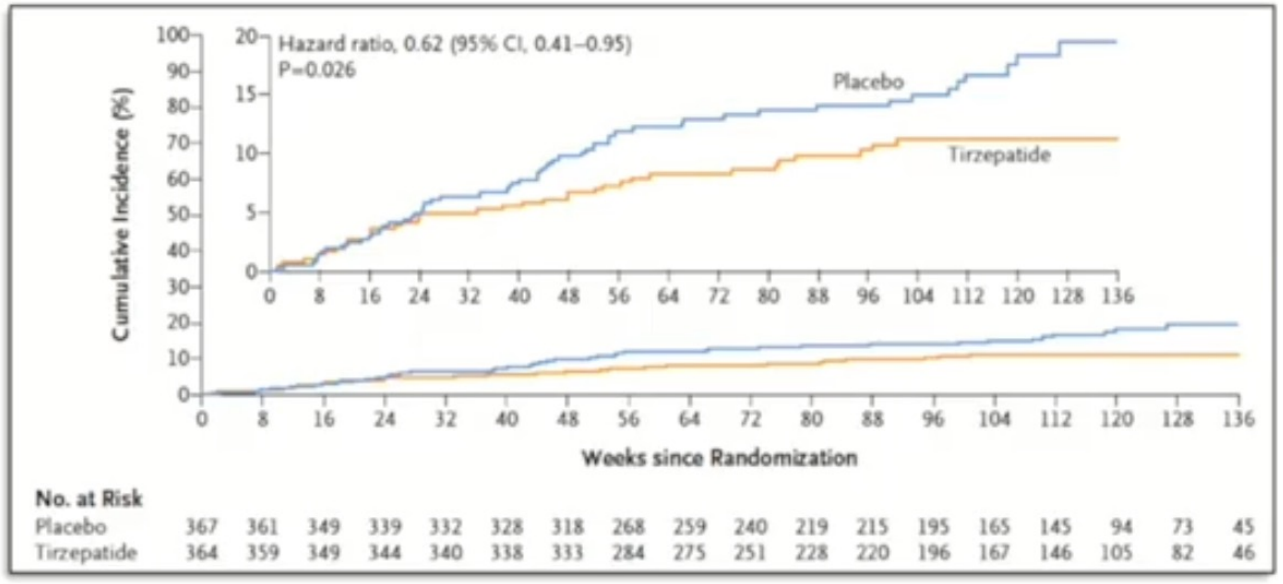
SELECT
FLOW
STEP-HFpEF
STEP-HFpEF DM

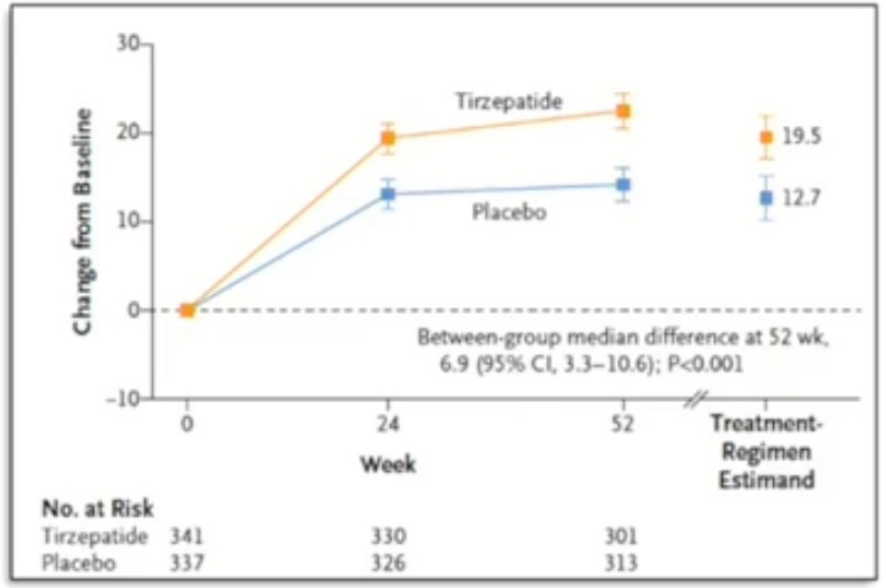


Semaglutide reduced risk of combined endpoint of CV death or worsening HF events and worsening HF events alone

SUMMIT: TERZIPATIDE FOR HFPEF WITH OBESITY

731 patients with symptomatic HF, LVEF>50%, BMI>=30 kg/m²





Kosiborod M, NEJM 2024

RENAL PROTECTION

- GLP-1 RAs exhibit significant nephroprotective effects
  - reducing albuminuria
  - improving renal hemodynamics
  - attenuating oxidative stress and inflammation in the kidneys
- LEADER trial, liraglutide resulted in a 22% reduction in adverse renal outcomes (HR 0.78; 95% CI [0.67–0.92]; p=0.003) compared with placebo in 9,340 patients with T2D and a high risk of CVD
- SUSTAIN-6 Trial, semaglutide reduced macroalbuminuria by 46% and resulted in a lower rate of new or worsening nephropathy in patients with T2D and risk factors for CVD
- AMPLITUDE-O and FLOW Trials

ANTI INFLAMMATORY AND ANTI FIBROTIC EFFECTS

- Chronic inflammation and myocardial fibrosis are hallmarks of HF progression
- Reduction in meta-inflammation, defined as a low-grade chronic inflammatory status
- Downregulate proinflammatory cytokines by suppressing nuclear factor (NF)-κB signaling
- STEPHFpEF and STEP-HFpEF-DM trials, semaglutide resulted in a significant reduction in C-reactive protein levels versus placebo in a pooled analysis of the two trials (−43% versus −10%, respectively)
- Meta-analysis of 40 RCTs that included patients with T2D, GLP-1 RAs significantly reduced levels of inflammatory markers and oxidative stress

JACC STATE-OF-THE-ART REVIEW

Inflammation in Heart Failure

JACC State-of-the-Art Review

Sean P. Murphy, MB, BCH, BAO,[a] Rahul Kakkar, MD,[b] Cian P. McCarthy, MB, BCH, BAO,[c] James L. Januzzi, JR, MD[c]

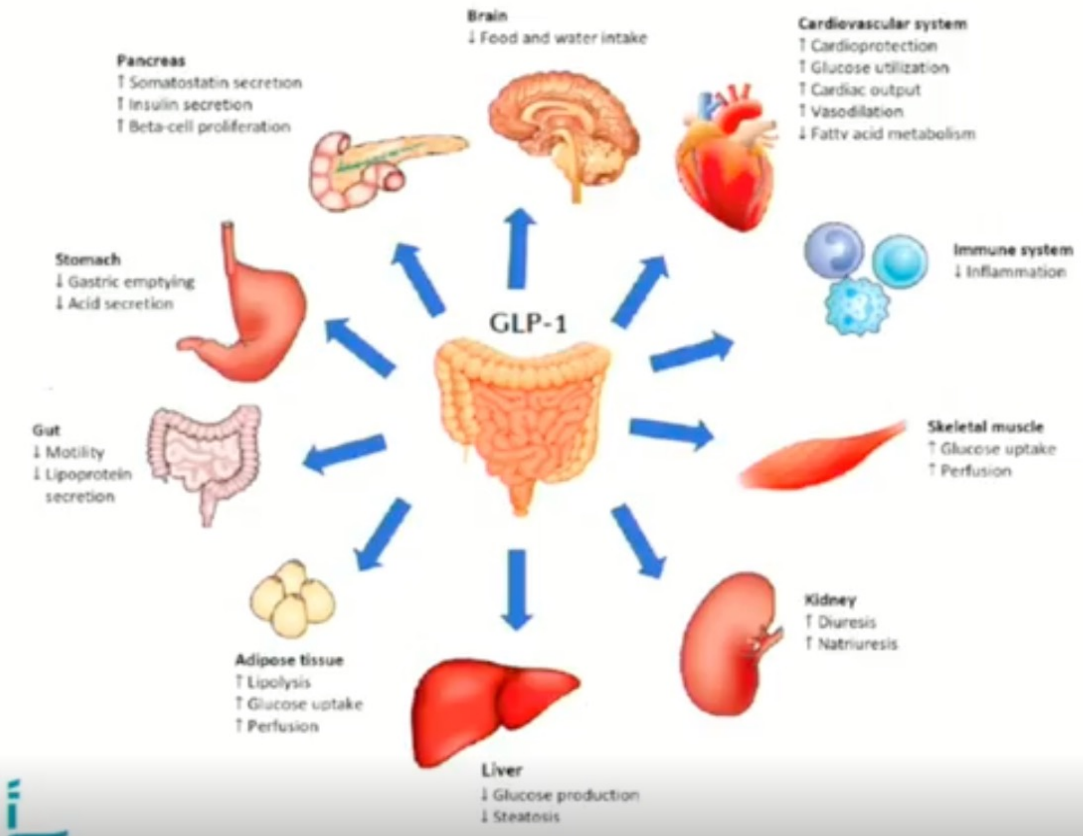
ABSTRACT

It has long been observed that heart failure (HF) is associated with measures of systemic inflammation. In recent years, there have been significant advancements in our understanding of how inflammation contributes to the pathogenesis and progression of HF. However, although numerous studies have validated the association between measures of inflammation and HF severity and prognosis, clinical trials of anti-inflammatory therapies have proven mostly unsuccessful. On this backdrop emerges the yet unmet goal of targeting precise phenotypes within the syndrome of HF; if such precise definitions can be realized, and with better understanding of the roles played by specific inflammatory mediators, the expectation is that targeted anti-inflammatory therapies may improve prognosis in patients whose HF is driven by inflammatory pathobiology. Here, the authors describe mechanistic links between inflammation and HF, discuss traditional and novel inflammatory biomarkers, and summarize the latest evidence from clinical trials of anti-inflammatory therapies. (J Am Coll Cardiol 2020;75:1324–40) © 2020 by the American College of Cardiology Foundation.

ENDOTHELIAL FUNCTION AND VASODILATATION

- In patients with HF, the nitric oxide pathway is downregulated, producing a vasoconstrictor effect
- Nitric oxide has vasodilator properties, which reduce systemic vascular resistance and improve artery compliance, thus alleviating hemodynamic burden in HF
- Endothelial function combined with their anti-inflammatory properties may explain the positive effects of GLP-1 RAs on atherogenesis, and consequently on MACE

SYSTEMIC EFFECTS OF GLP-1 RA



- Weight loss
- Reduced Blood Pressure
- Improved Glycemic Control
- Reduction in hepatic fat/NASH
- Renal Protection/Reduced albuminuria

Khan MS, et al. Circulation 2020; 142:1205-1218

CLINICAL EVIDENCE

- GLP-1 RAs were associated with a reduction in new-onset HF among patients with cardiovascular risk factors, but neutral effects were observed on HF events among patients with already diagnosed and stable HF
- Effect appears to differ according to baseline LVEF, with worse results in patients with reduced ejection fraction
- Meta-analysis including 68,653 patients from 10 trials showed that GLP-1 RAs reduce HF hospitalizations only in patients without history of previously diagnosed HF

SELECT TRIAL

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

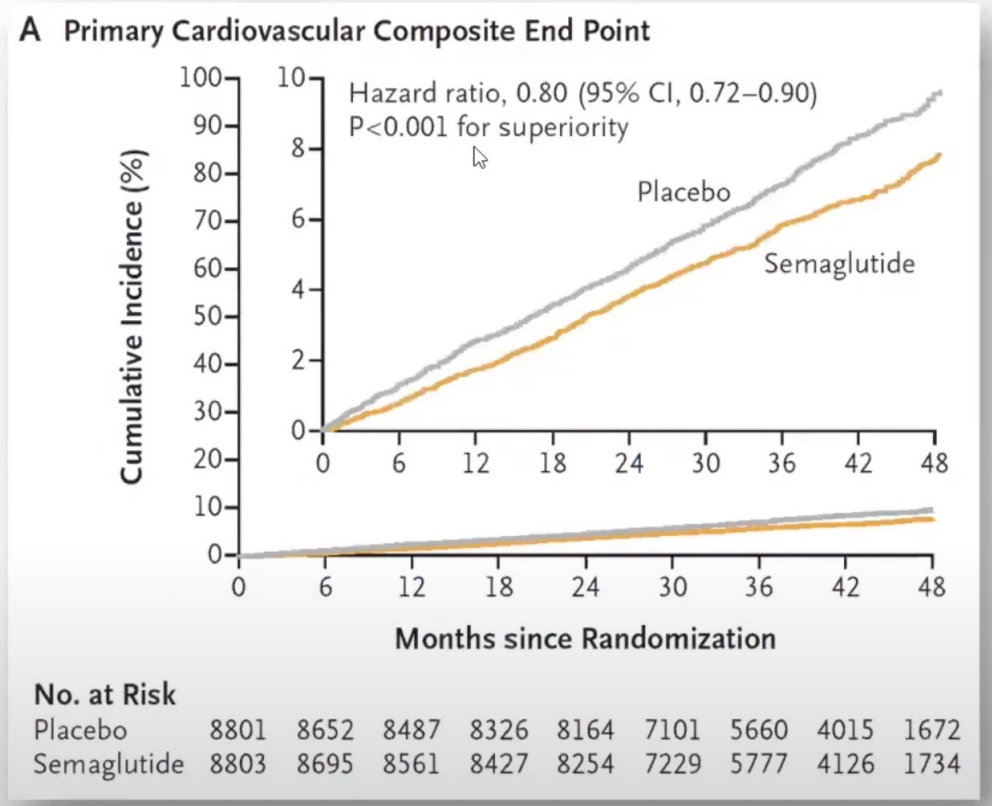
- Patients older than 45 years with pre-existing cardiovascular disease
- BMI more than 27
- NO history of diabetes

Patients were randomly assigned in a 1:1 ratio to receive once-weekly semaglutide 2.4mg weekly or placebo.

Mean duration 39.8 months

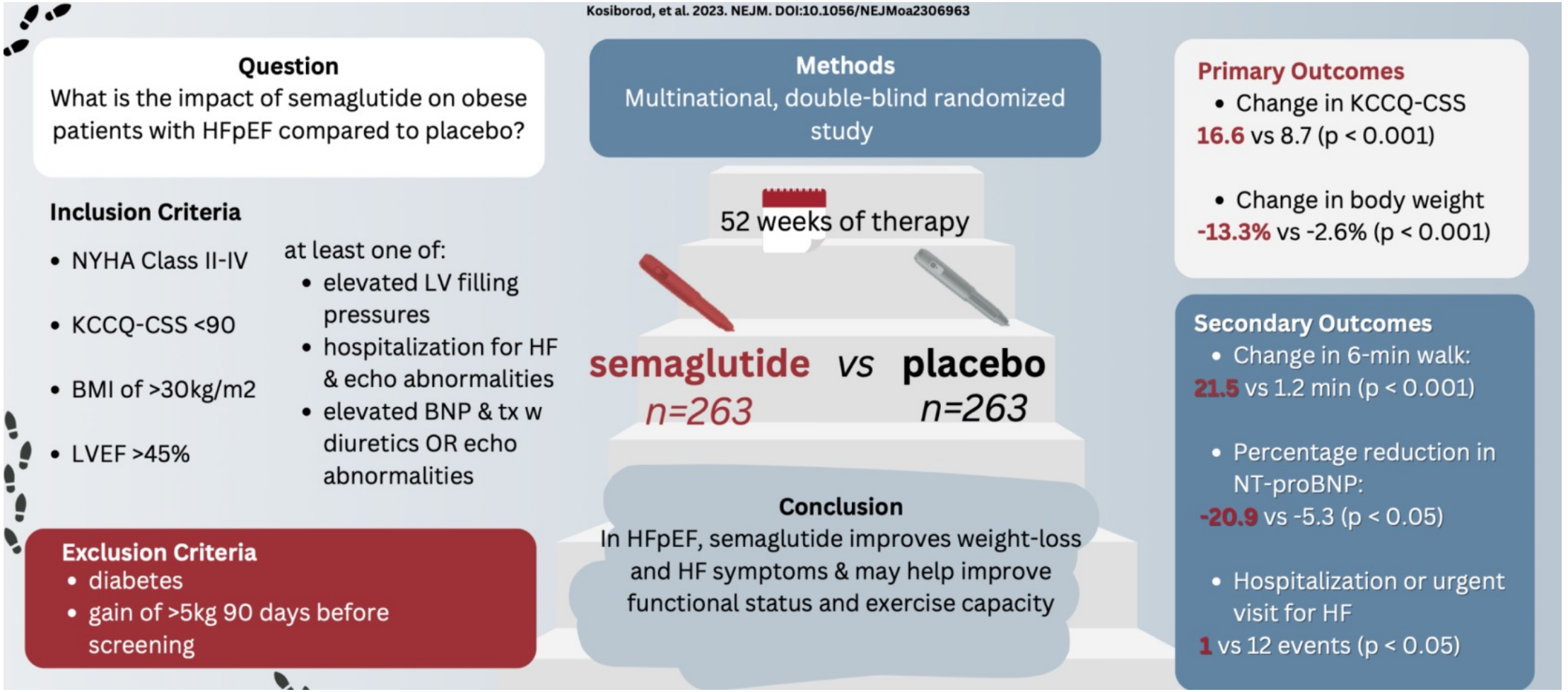
A Michael lincoff et al NEJM 2023

SELECT TRIAL

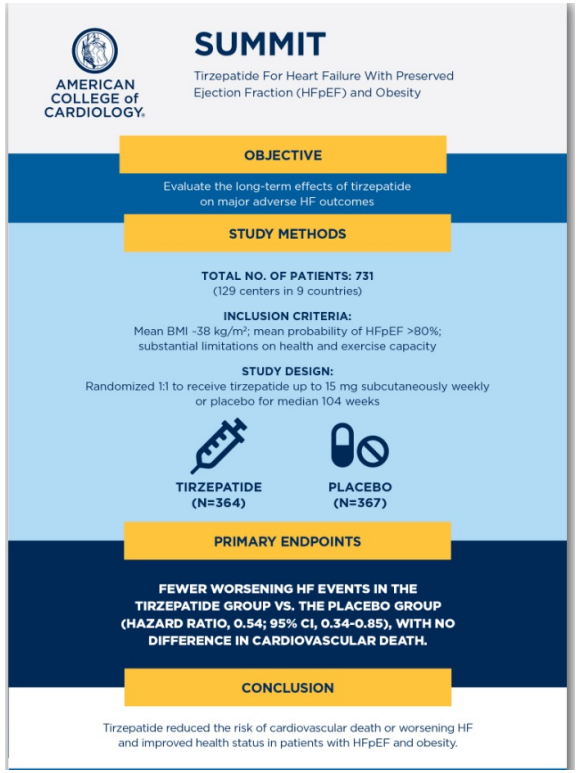


Endpoint	Semaglutide (N:8803)	Placebo (N: 8801)	Hazard Ratio	P value
Primary	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Death from CV causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA

STEP-HFPEF TRIAL , NEJM 2023



SUMMIT-HF TRIAL



- Tirzepatide was evaluated in the SUMMIT trial
- 731 patients with HFpEF and BMI ≥30 kg/m2 were randomized to receive tirzepatide or placebo for at least 52 weeks
- Unlike the STEP-HFpEF trials, cardiovascular outcomes were included as a co-primary endpoint in the SUMMIT trial
- Tirzepatide showed significant benefits on both co-primary endpoints, namely adjudicated death from cardiovascular causes or worsening HF events (HR 0.62; 95% CI [0.41–0.95]; p=0.026), as well as on mean changes in the KCCQ-CCS scores (6.9 difference versus placebo; p<0.001)
- Worsening HF events occurred in 29 (8.0%) patients in the tirzepatide group and 52 (14.2%) patients in the placebo group (HR 0.54; 95% CI [0.34–0.85])
- SURMOUNT-5 trial demonstrated that tirzepatide was superior to semaglutide in obese patients without diabetes with respect to reductions in body weight and waist circumference at week 72

- Overview of Randomized Clinical Trials Analyzing the Effectiveness of Glucagon-like Peptide-1 Receptor Agonists With Specific Focus on Heart Failure Outcomes

Trial	Inclusion Criteria	Drug	No. Patients	Primary Endpoint	HF Outcome
ELIXA[12]	T2D and an acute coronary event within 180 days before screening	Lixisenatide versus placebo	6,068	Time-to-event of any of: death from CV causes, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina	HFH: HR 0.96; 95% CI [0.75–1.23]
LEADER[10]	T2D with ≥1 CV coexisting condition or age ≥60 years with ≥1 CV risk factor	Liraglutide versus placebo	9,340	Time-to-event of first occurrence of death from CV causes, non-fatal MI or non-fatal stroke	HFH: HR 0.87; 95% CI [0.73–1.05]
SUSTAIN-6[11]	T2D with CV disease or age ≥60 years with at least one CV risk factor	Subcutaneous semaglutide versus placebo	2,735	Time-to-event of first occurrence of death from CV causes, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for unstable angina or HF	HFH: HR 1.11; 95% CI [0.77–1.61]
FIGHT[29]	HFrEF with recent HFH (≤14 days) despite OMT	Liraglutide versus placebo	300	Hierarchical outcome: time to death, time to rehospitalisation for HF, time-average change in NT-proBNP	Primary endpoint: not significant (p=0.31) HFH: HR 1.30; 95% CI [0.89–1.88]
EXSCEL[13]	T2D with previous CV events: 70% T2D without previous CV events: 30%	Exenatide versus placebo	14,752	Time-to-event analysis of first occurrence of death from CV causes, non-fatal MI or non-fatal stroke	HFH: HR 0.94; 95% CI [0.78–1.13]
LIVE[30]	Chronic HF with LVEF≤45%, NYHA Class I–III, OMT for ≥3 months	Liraglutide versus placebo	241	Change in LVEF	Mean difference −0.8% (−2.1, 0.5; p=0.24)
REWIND[15]	T2D and BMI ≥23 kg/m^2 with vascular disease or age ≥60 years and ≥2 CV risk factors	Dulaglutide versus placebo	9,901	Time-to-event analysis of death from CV causes, non-fatal MI or non-fatal stroke	HFH or urgent visit: HR 0.93; 95% CI [0.77–1.12]
PIONEER-6[17]	Established CVD or CKD or age ≥60 years and ≥1 CV risk factor	Oral semaglutide versus placebo	3,183	Time-to-event analysis of first occurrence of death from CV causes, non-fatal MI or non-fatal stroke	HFH: HR 0.86; 95% CI [0.48–1.55]
Amplitude-O[16]	T2D and history of CVD or age ≥50 years if male and ≥55 years if female and CKD and ≥1 CV risk factor	Efpeglenatide versus placebo	4,076	Time-to-event analysis of first occurrence of death from CV causes, non-fatal MI or non-fatal stroke	HFH: HR 0.61; 95% CI [0.38–0.98]
SELECT[57]	Age ≥45 years and BMI ≥27 kg/m^2 and established CVD	Subcutaneous semaglutide versus placebo	17,604	Time-to-event analysis of death from CV causes, non-fatal MI or non-fatal stroke	Hospitalisation or urgent visit for HF: HR 0.79; 95% CI [0.60–1.03]

- Overview of Randomised Clinical Trials Analysing the Effectiveness of GLP-1 Ras With Specific Focus on Heart Failure Outcomes

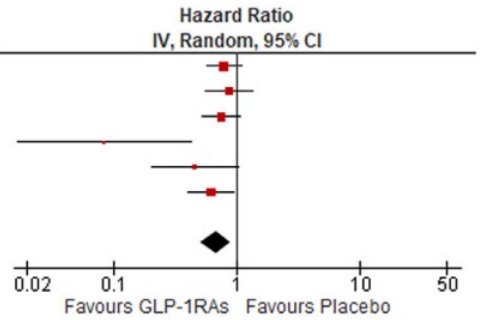
STEP-HFpEF[45]	Chronic HF with LVEF ≥45% and BMI ≥30 kg/m^2	Subcutaneous semaglutide versus placebo	529	Change in KCCQ-CSS and percentage change in body weight	Estimated difference change in KCCQ-CSS: 7.8 points (p<0.001) Hierarchical composite outcome of death from any cause, number and timing of HF events, difference in KCCQ-CCS and difference in 6MWT: HR 1.72; 95% CI [1.37–2.15]
STEP-HFpEF-DM[46]	Chronic HF with LVEF ≥45%, T2D and BMI ≥30 kg/m^2	Subcutaneous semaglutide versus placebo	616	Change in KCCQ-CSS and percentage change in body weight	Estimated difference change in KCCQ-CSS: 6.4 points (p<0.001) Hierarchical composite outcome of death from any cause, number and timing of HF events, difference in KCCQ-CCS and difference in 6MWT: HR 1.58; 95% CI [1.29–1.94]
SUMMIT[59]	Chronic HF with LVEF ≥50% NYHA Class II–IV and BMI ≥30 kg/m^2	Tirzepatide versus placebo	731	Hierarchical composite of death from any cause or worsening HF	Primary endpoint: HR 0.62; 95% CI [0.41–0.95] Change in KCCQ-CSS: 6.9 (p<0.001)

- Forest plot evaluating the effect of GLP-1 RAs vs placebo on the composite outcome of cardiovascular death or worsening heart failure events, as well as the individual components of a worsening heart failure event and cardiovascular death

A) Composite of CV Death or Worsening HF event

Study or Subgroup	log[Hazard Ratio]	SE	GLP-1RAs Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
EXSCEL	-0.2357	0.1674	499	561	25.0%	0.79 [0.57, 1.10]
FLOW	-0.1462	0.224	167	158	19.5%	0.86 [0.56, 1.34]
SELECT	-0.2877	0.183	1174	1099	23.4%	0.75 [0.52, 1.07]
STEP HFpEF	-2.4663	0.8216	263	266	2.7%	0.08 [0.02, 0.42]
STEP HFpEF DM	-0.7853	0.4082	310	306	9.1%	0.46 [0.20, 1.01]
SUMMIT	-0.478	0.216	364	367	20.2%	0.62 [0.41, 0.95]
Total (95% CI)			**2777**	**2757**	**100.0%**	**0.68 [0.51, 0.89]**

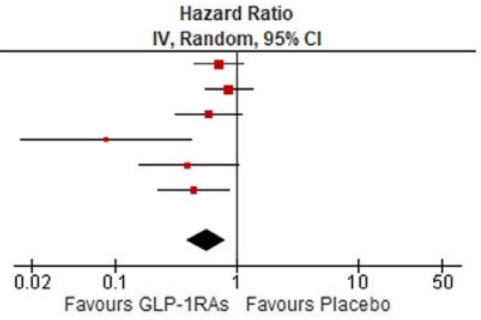
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 9.51$, df = 5 (P = 0.09); $I^2 = 47\%$
Test for overall effect: Z = 2.77 (P = 0.006)



B) Worsening HF event

Study or Subgroup	log[Hazard Ratio]	SE	GLP-1RAs Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
EXSCEL	-0.3425	0.2327	499	561	23.8%	0.71 [0.45, 1.12]
FLOW	-0.1473	0.2243	167	158	24.4%	0.86 [0.56, 1.34]
SELECT	-0.5344	0.3183	1174	1099	18.5%	0.59 [0.31, 1.09]
STEP HFpEF	-2.4769	0.826	263	266	4.9%	0.08 [0.02, 0.42]
STEP HFpEF DM	-0.9263	0.4819	310	306	11.4%	0.40 [0.15, 1.02]
SUMMIT	-0.821	0.349	364	367	16.9%	0.44 [0.22, 0.87]
Total (95% CI)			**2777**	**2757**	**100.0%**	**0.56 [0.38, 0.82]**

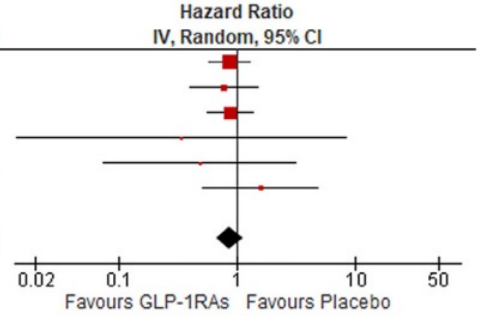
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 10.22$, df = 5 (P = 0.07); $I^2 = 51\%$
Test for overall effect: Z = 2.95 (P = 0.003)



C) CV Death

Study or Subgroup	log[Hazard Ratio]	SE	GLP-1RAs Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
EXSCEL	-0.1485	0.2057	499	561	41.3%	0.86 [0.58, 1.29]
FLOW	-0.2485	0.3369	167	158	15.4%	0.78 [0.40, 1.51]
SELECT	-0.1393	0.2221	1174	1099	35.4%	0.87 [0.56, 1.34]
STEP HFpEF	-1.0873	1.6307	263	266	0.7%	0.34 [0.01, 8.24]
STEP HFpEF DM	-0.7215	0.9541	310	306	1.9%	0.49 [0.07, 3.15]
SUMMIT	0.4574	0.57	364	367	5.4%	1.58 [0.52, 4.83]
Total (95% CI)			**2777**	**2757**	**100.0%**	**0.86 [0.67, 1.12]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.91$, df = 5 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 1.10 (P = 0.27)



CONCLUSION

- Strict relationship between CKM syndrome and HF has led to the development of different therapeutic strategies targeting multifaceted pathophysiological aspects
- GLP-1 RAs and SGLT2i have different and synergistic effects in CKM syndrome
- Beyond body weight reduction, GLP-1 RAs have anti-inflammatory and antioxidative effects which show strong promise in HF, particularly HFpEF
- Anticipate incorporation of GLP-1RAs in guidelines in treatment of HFpEF/CKM spectrum

THANK YOU

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CHAPTER