GLP-1RA: BEYOND WEIGHT LOSS

— A NEW FRONTIER IN HEART FAILURE

April 17, 2026

Kumar Sarkar, MD, MA, FACC, DABOM
Assistant Professor of Cardiology
Preventive Cardiology & Cardiometabolic Medicine
Zucker School of Medicine at Hofstra/Northwell

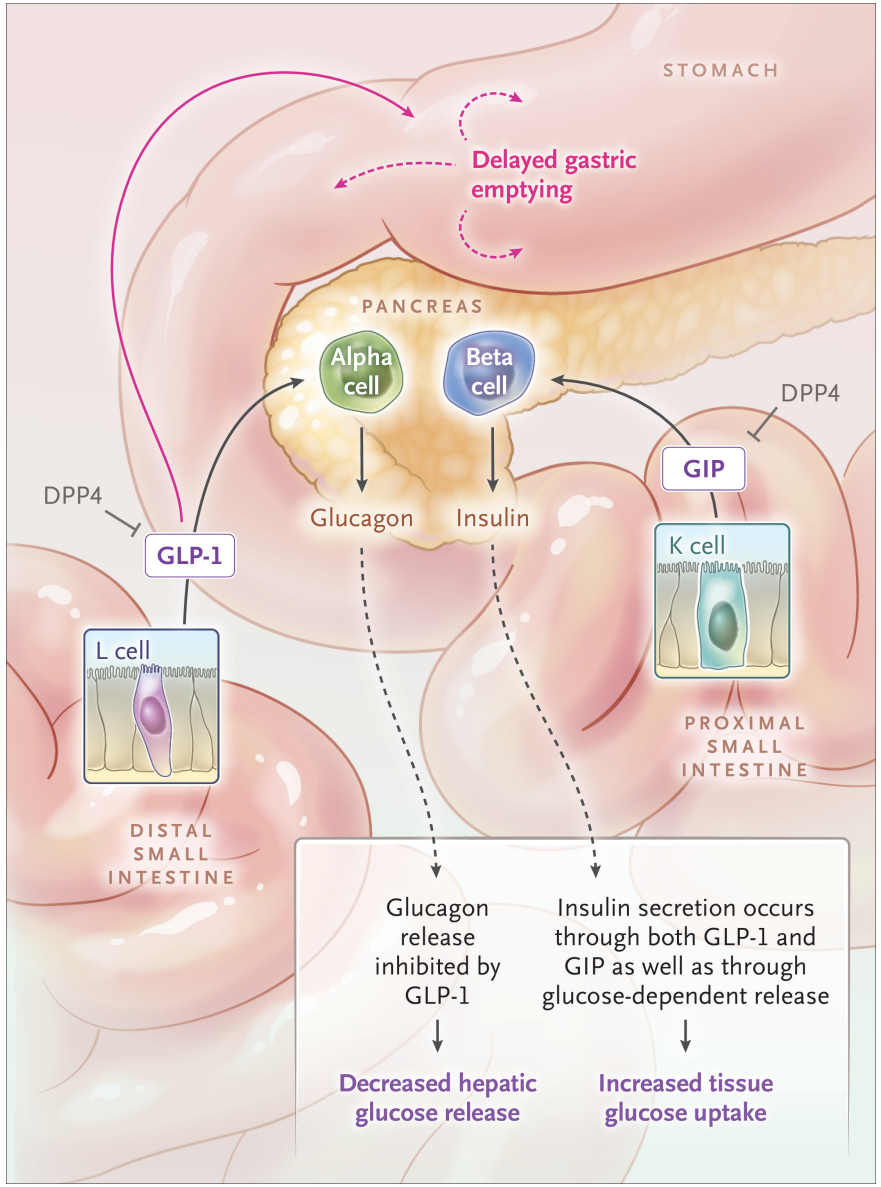
Northwell℠
Cardiovascular Institute

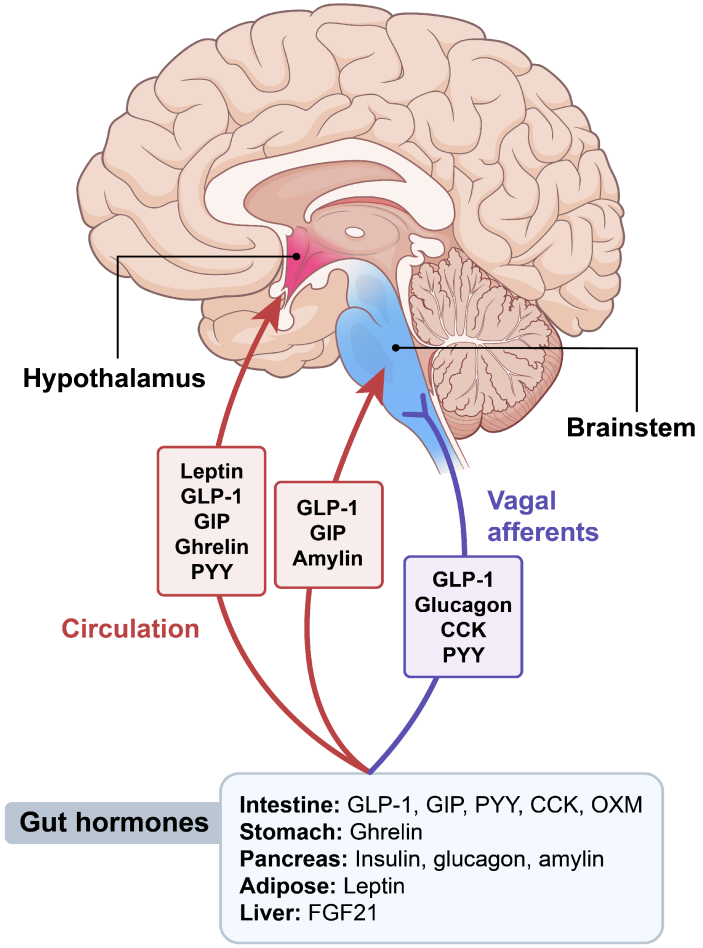
THE GILA MONSTER – A METABOLIC MIRACLE

- Exendin-4 from Gila monster venom mimics human GLP-1 but resists DPP-4 degradation.
- Single amino acid substitution at position 2 (Gly→Ala) extends half-life from <2 min to 2.4 hours
- Discovered in 1992 by Dr. John Eng at the Bronx VA — molecular foundation for all modern GLP-1 RAs

Eng J, et al. J Biol Chem. 1992; Diabetes Care 2005;28(5)

GUT-BRAIN SIGNALING IN GLP-1





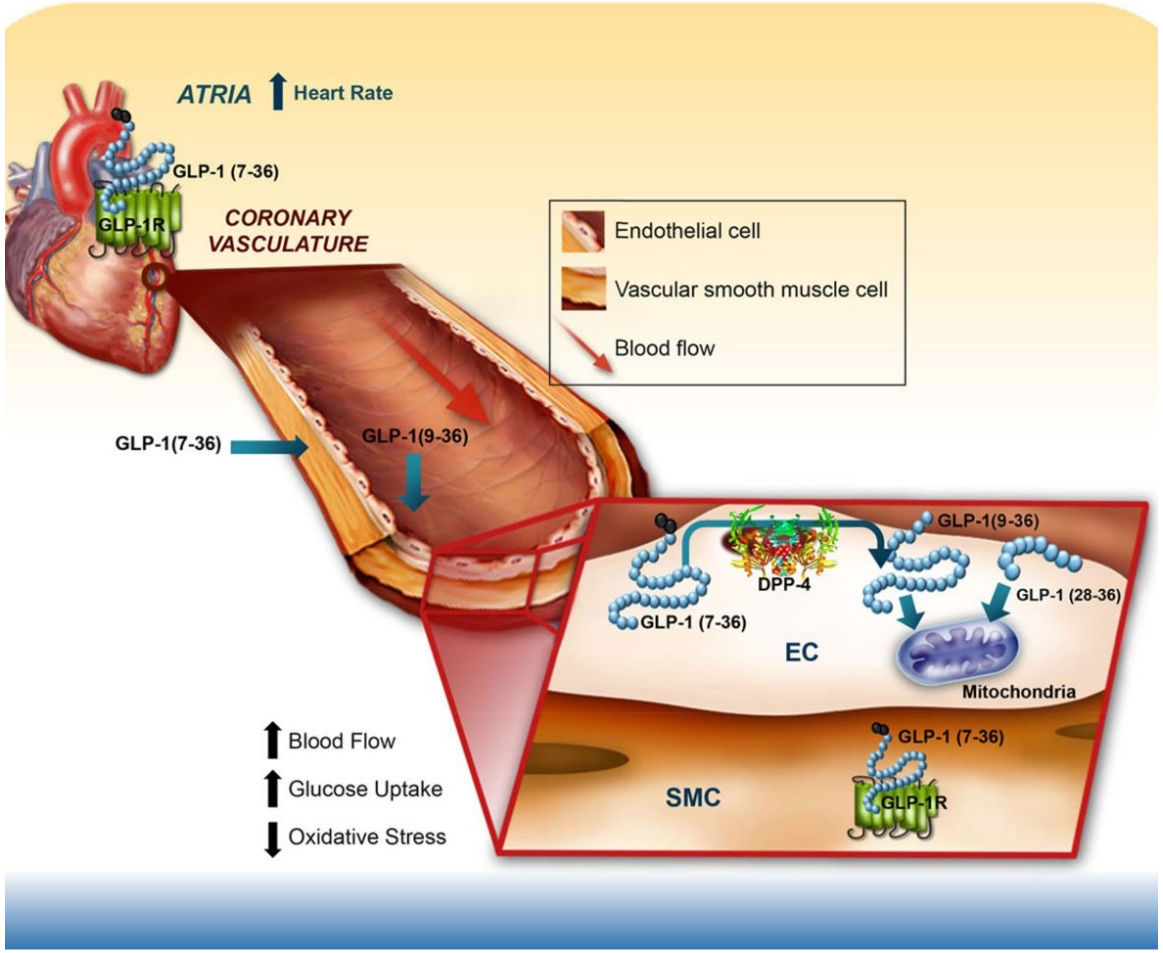
GLP-1 Based Therapies

- GLP-1 RA: Semaglutide (Wegovy)
- Dual Receptor Agonist (GLP-1/GIP): Tirzepatide (Mounjaro/Zepbound)
- Triple Receptor Agonist (GLP-1/GIP/Glucagon): Retatrutide (investigational)

N Engl J Med 2026;394:1313-1324
IJMS 2023;24:3384

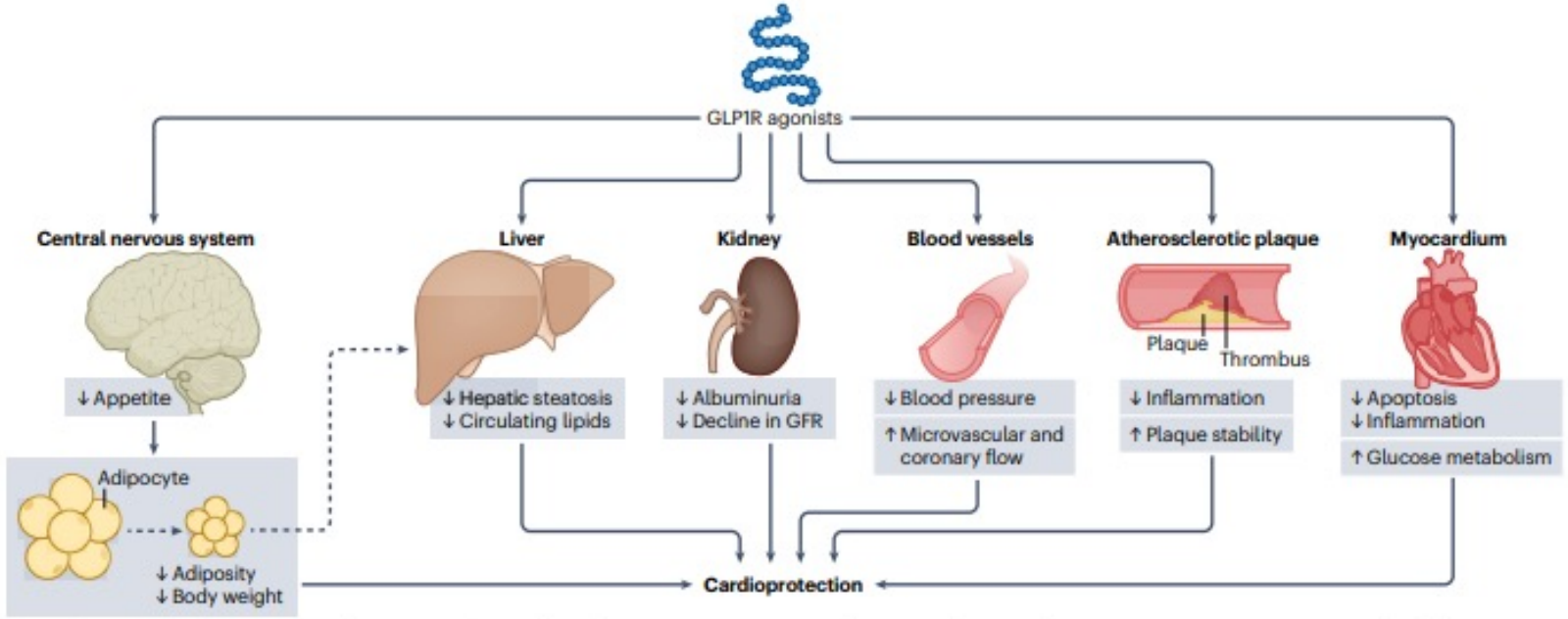
DIRECT GLP-1 EFFECT ON THE MYOCYTE AND MYOCARDIUM

- Present in atria and sinoatrial node — which explains the modest heart rate increase seen with all GLP-1 receptor agonists.
- The GLP-1 receptor is NOT expressed on ventricular cardiomyocytes.
  - Paracrine signaling from atrial GLP-1 receptors
  - GLP-1 receptors on vascular smooth muscle cells within the coronary vasculature
  - GLP-1R-independent pathways.



Ussher JR, et al. Circ Res. 2014;114(11):1788-1803.

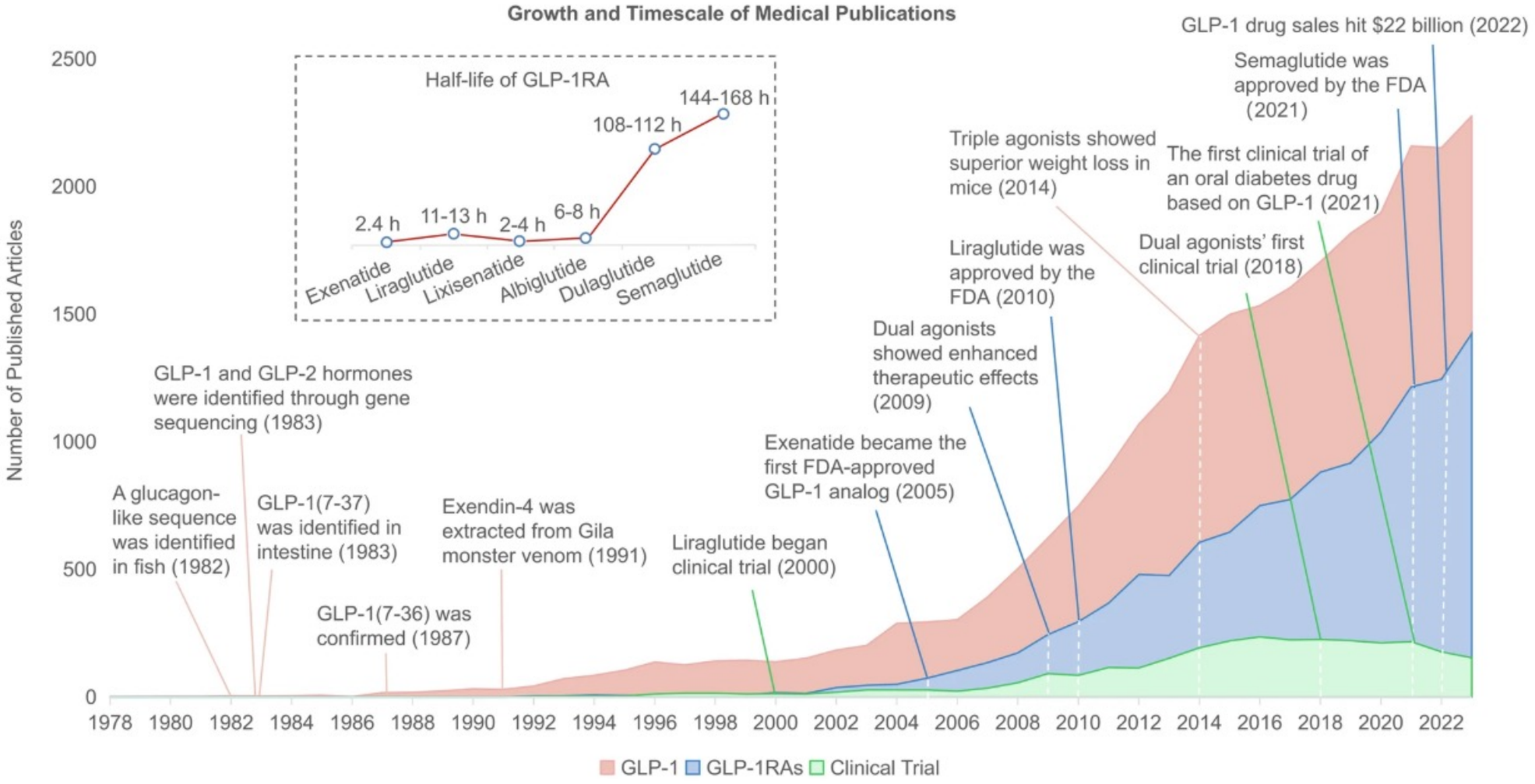
INDIRECT CARDIOVASCULAR EFFECTS OF GLP-1RA



- Direct vascular and myocardial effects are likely dominant mechanism ~60%
- Pleiotropic actions: hepatic steatosis reduction, renal protection, anti-atherosclerotic effects

Nature Reviews Cardiology. 2023;20:463-474.

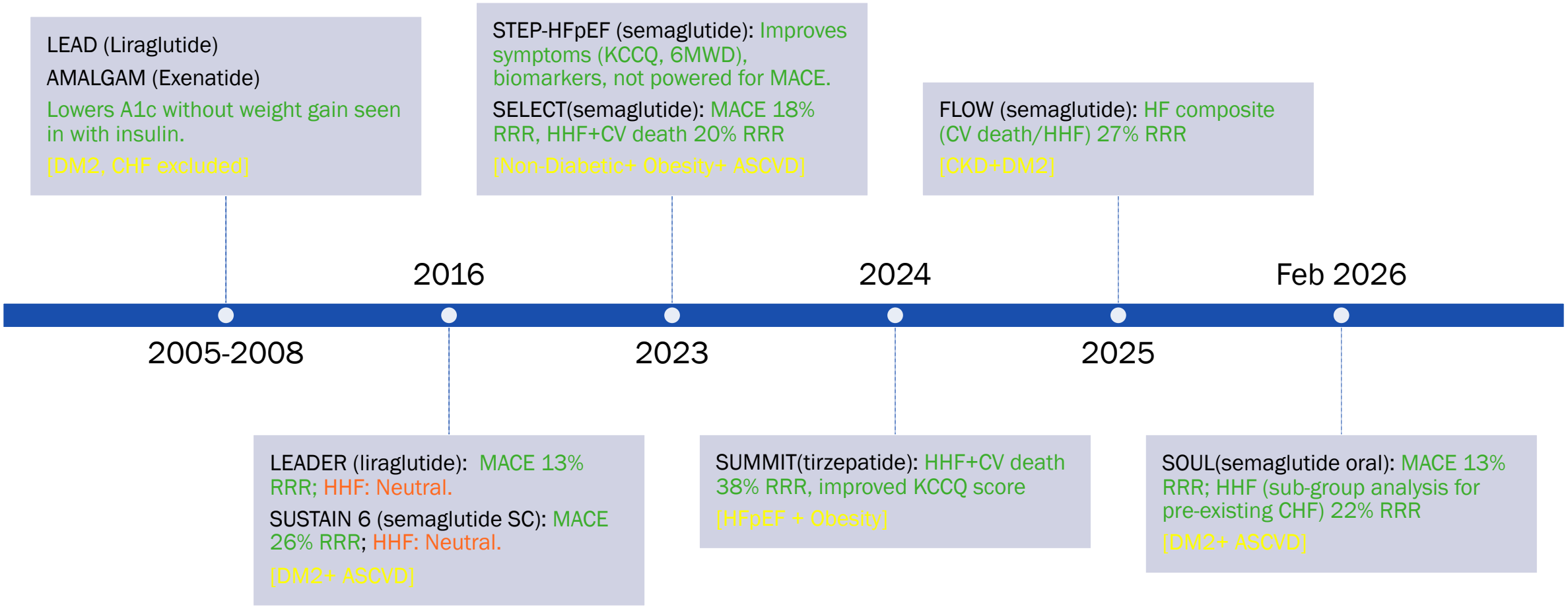
EXPANDING LANDSCAPE OF GLP1 RA AND HEART FAILURE



Zheng, Z., Zong, Y., Ma, Y. et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Sig Transduct Target Ther 9, 234 (2024)

EVOLUTION OF GLP-1RA IN HEART FAILURE

Buse JB, et al. *Lancet* 2009;374:39-47 (LEAD)
Nathanson D, et al. *Circ Heart Fail* 2012;5:452-458 (AMALGAM)
Marso SP, et al. *NEJM* 2016;375:311-322 (LEADER)
Marso SP, et al. *NEJM* 2016;375:1834-1844 (SUSTAIN-6)
Kosiborod MN, et al. *NEJM* 2023;389:1069-1084 (STEP-HFpEF)
Lincoff AM, et al. *NEJM* 2023;389:2221-2232 (SELECT)
Lingvay I, et al. *NEJM* 2023;389:2073-2084 (SOUL)
Packer M, et al. *NEJM* 2024;391:685-699 (SUMMIT)



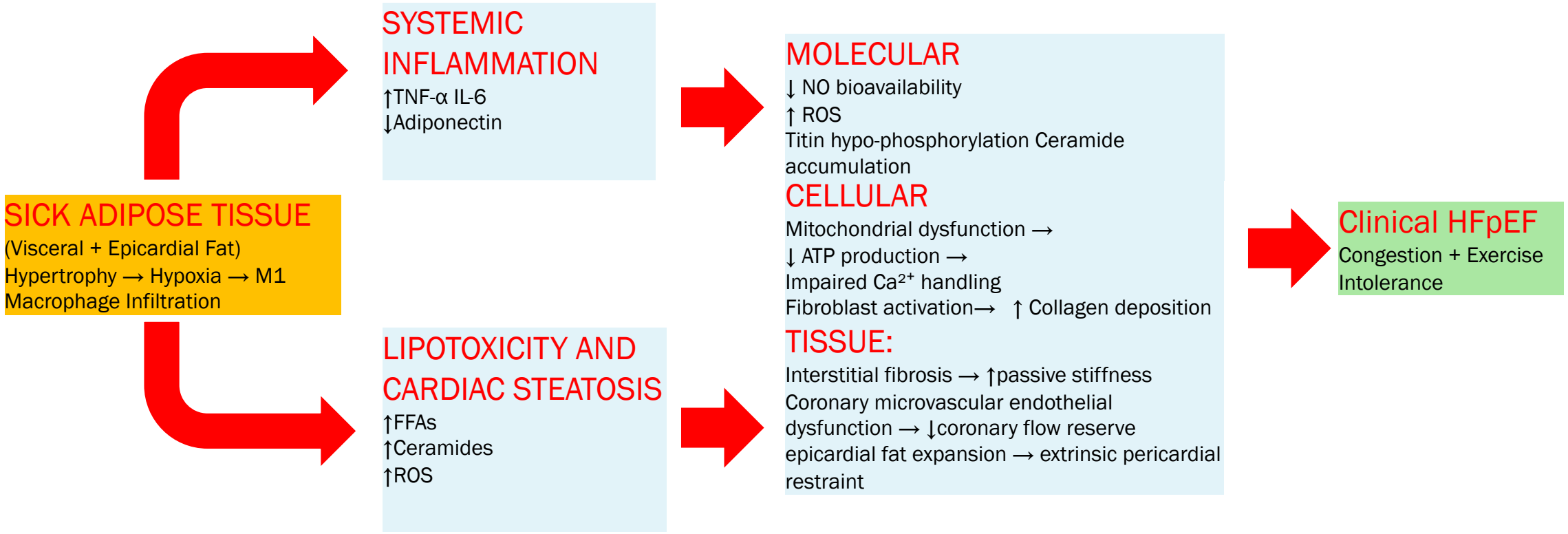
LANDMARK TRIALS OF GLP-1 RAS IN HFPEF

Feature	STEP-HFpEF (2023)	SUMMIT (2024)
Publication	NEJM 2023	NEJM 2024
Drug	Semaglutide 2.4 mg (GLP-1 RA)	Tirzepatide 15 mg (GLP-1/GIP)
Mechanism	Single Agonist	Dual Agonist
Population	HFpEF + BMI ≥30 (EF ≥45%)	HFpEF + BMI ≥30 (EF ≥40%)
N / Follow-up	529 / 52 weeks	731 / 104 weeks (longer durability)
Primary Endpoint	Dual: KCCQ-CSS & Body Weight	Composite: CV Death or Worsening HF
HF Events (HHF)	Not powered for events	HR 0.62 (38% Reduction)
KCCQ-CSS Δ	+7.8 points vs. placebo	+6.9 points vs. placebo
Weight Loss Δ	−10.7% (net of placebo)	−9.8% (net of placebo)
NT-proBNP Δ	−20.9% vs. placebo	−20.0% vs. placebo
CRP (Inflam.)	−38.8% vs. placebo	−33.9% vs. placebo
6MWD Δ	+21.5 m vs. placebo	+18.4 m vs. placebo
Safety	GI events (18% Nausea)	GI events (17% Nausea)

- **Class effect:** two different molecules (semaglutide, tirzepatide) → concordant benefits in symptoms, exercise capacity, and CV outcomes
- **Biomarker improvements** (NT-proBNP ↓20%, CRP ↓35%) disproportionate to weight loss → direct cardiometabolic mechanism beyond hemodynamic unloading
- **"Obese" HFpEF is now a pharmacologically treatable disease.** Benefit in "Lean" HFpEF unknown.
  - Mean BMI ~37 in STEP-HFpEF and ~38 in SUMMIT — no trials have enrolled HFpEF patients with BMI <27.

N Engl J Med. 2023;389(12):1069-1084
N Engl J Med 2024;391:1512-1524

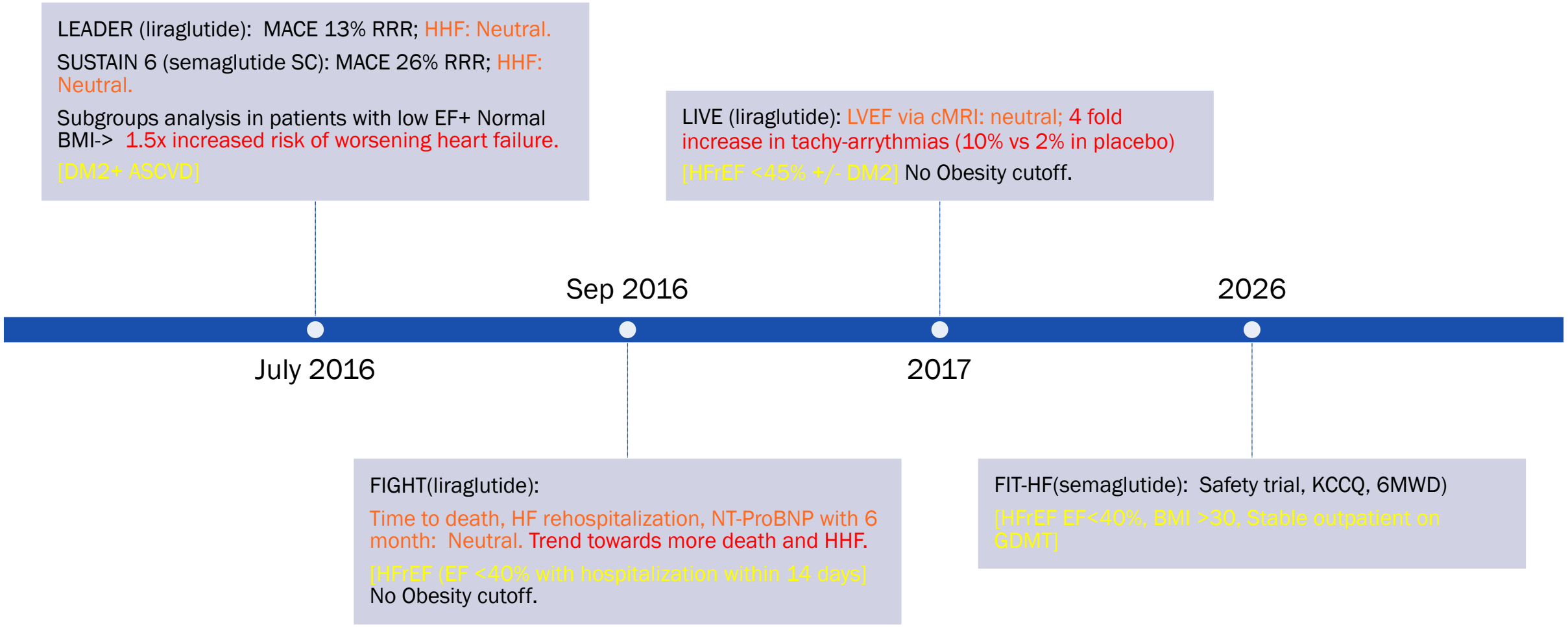
OBESITY AND HFPEF



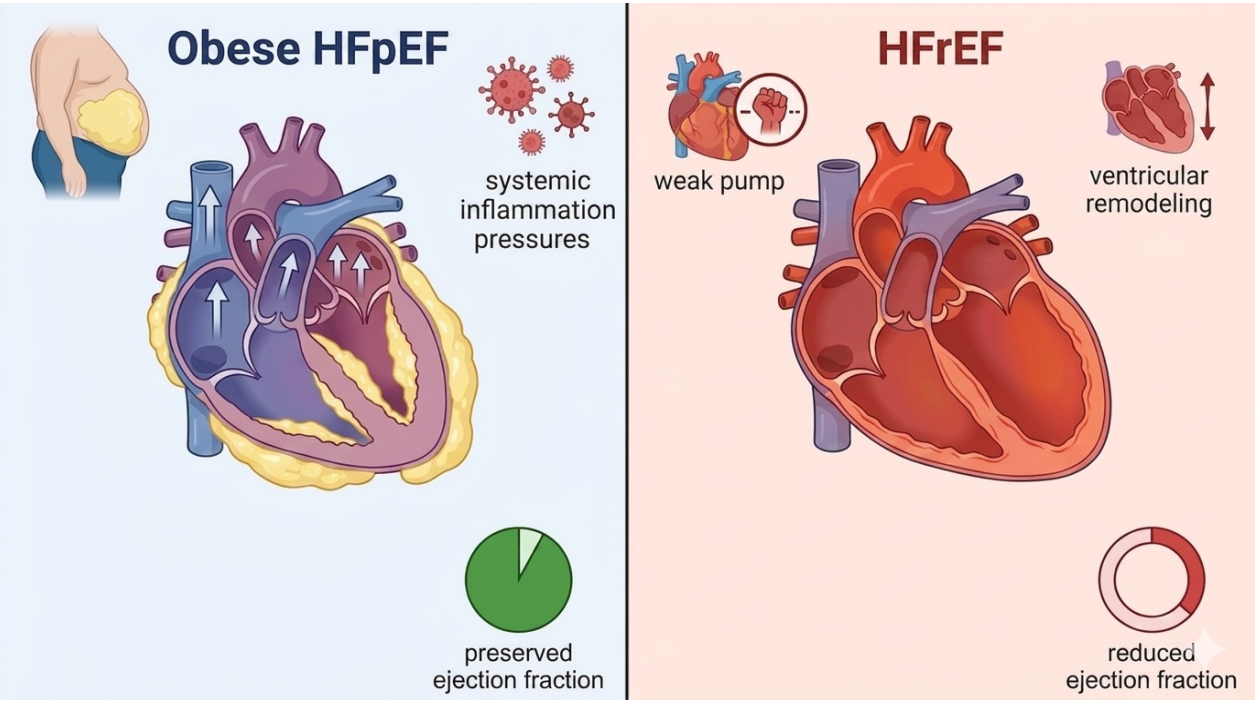
HOW DO GLP-1 RA COMPARE WITH OTHER STANDARD TREATMENTS OF HFPEF IN OBESITY?

Feature	GLP-1 RA	SGLT2i	MRA / ARNi	NS-MRA
Trial	STEP-HFpEF; SUMMIT	EMPEROR-P, DELIVER	TOPCAT, PARAGON-HF	FINEARTS-HF
HFH Reduction	+++	++	+	+
QOL (KCCQ)	+++	++	+	++
Exercise (6MWD)	+++	+	Neutral	Neutral
Weight Loss	+++	+	Neutral	Neutral
Anti-Inflammatory	+++	+	Neutral	Neutral

GLP1 RA IN HFREF



HFPEF VS HFREF



- Tachycardia Tax: +4–7 bpm increases oxygen demand in hearts with minimal contractile reserve.
- Coronary perfusion deficit: Faster heart rates shorten diastole and compromise coronary flow.
- Pro-arrhythmic cAMP: Elevated atrial cAMP mimics Milrinone, lowering the threshold for AFib.
- Preload Paradox: Rapid volume loss triggers compensatory tachycardia in preload-dependent patients

Circulation
Volume 145, Issue 18, 3 May 2022; Pages e895-e1032
https://doi.org/10.1161/CIR.0000000000001063

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

CURRENT GUIDELINES

INDICATION	ACC/AHA GUIDELINE Level of Evidence
HFpEF + Obesity EF ≥45%, BMI ≥30 NYHA II-III	Class IIa LOE B-R
T2DM + ASCVD EF ≥45% (CV risk, not HF)	Class I LOE A
HFmrEF + Obesity EF 40-49%	N/A (Data emerging)
NYHA IV	N/A (Lacks Evidence)
HFrEF EF <40%	No recommendation

Kittleson, JACC 2023;81:1835
Aggarwal, JACC 2024
Circ 2023;148:1606

KNOWLEDGE GAPS AND GUIDELINE INTEGRATION

HFrEF + Obesity	FIT-HF ongoing (NCT06128005) — safety, KCCQ, 6MWD in stable outpatients with EF <40% and BMI >30
"Lean" HFpEF	No trial data in non-obese, non-diabetic HFpEF — does the metabolic pathway apply without excess adiposity?
Long-term Durability	SUMMIT's 38% RRR demonstrated at 2 years — 5-year data unknown
Combination Therapy	SGLT2i + MRA + GLP-1 RA — biologically additive but no trial testing the combination
Semaglutide vs Tirzepatide	Head-to-head in HFpEF (~2027)

PIPELINE: NEXT GENERATION THERAPEUTICS

Retatrutide	Triple agonist (GLP-1/GIP/Glucagon)	Glucagon component preferentially targets hepatic and epicardial fat via thermogenesis and lipolysis
CagriSema	Dual Agonist GLP-1 RA + long-acting amylin analog	Dual satiety pathway with potential muscle-sparing effect; REDEFINE-3 trial (MACE + HF composite)
Survodutide	Dual Agonist GLP-1 RA + Glucagon	Currently in Phase 3 trials (SYNCHRONIZE) for obesity and MASH, with potential availability around 2027.

KEY POINTS

- In HFpEF (EF ≥45%, BMI ≥30), STEP-HFpEF and SUMMIT confirm a class effect — SUMMIT's 38% reduction in CV death/worsening HF is the strongest outcome signal ever in HFpEF.
- In HFrEF (EF <40%), GLP-1 RAs are neutral to potentially harmful on earlier studies.
  - FIGHT/LIVE were short, underpowered, used lower doses, and enrolled acutely ill patients without BMI criteria.
  - FIT-HF (semaglutide 2.4 mg in stable, obese HFrEF on optimized GDMT) ongoing.
- The future is combination therapy (SGLT2i + MRA + GLP-1 RA) and next-generation molecules (retatrutide, CagriSema)
- Guidelines anticipated 2026 pending completion of several key trials.

THANK YOU

Northwell[SM]
Cardiovascular Institute