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Obesity and Weight Loss Across the Spectrum of Heart Failure

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NUTRITION HF

May 18, 2026
Minneapolis Heart Institute Grand Rounds

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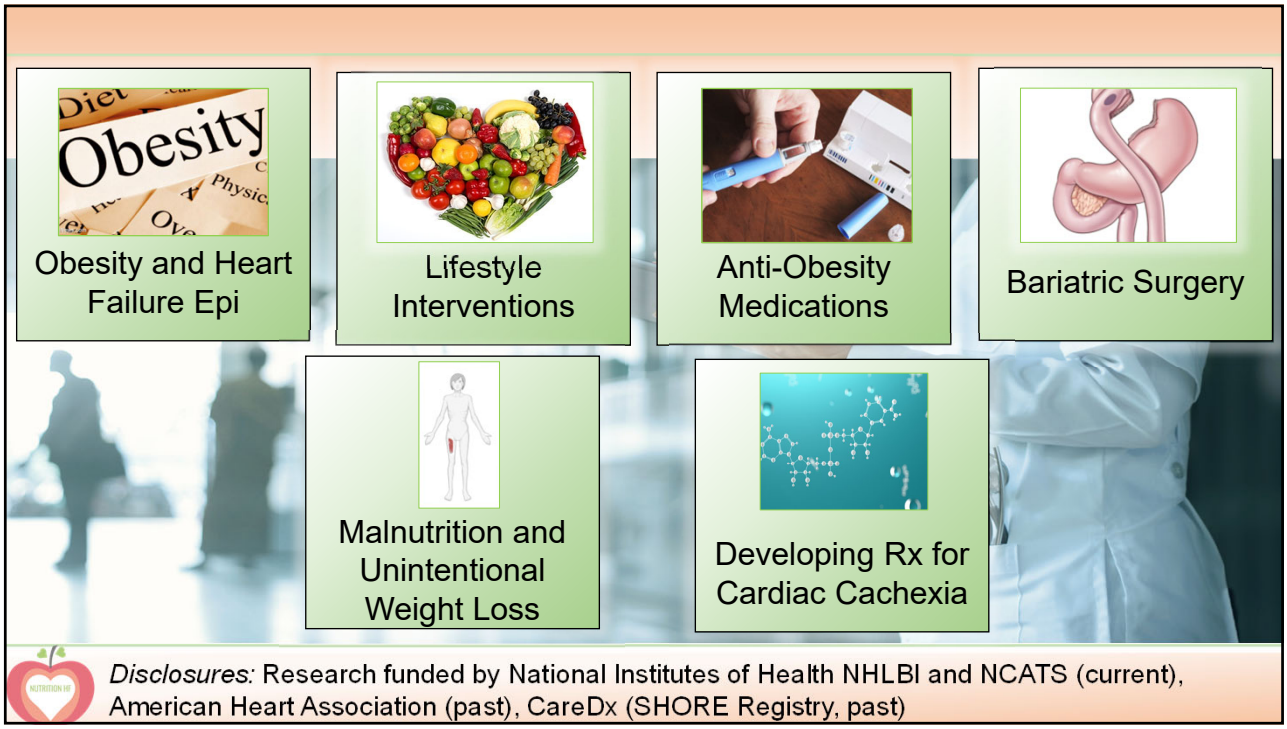

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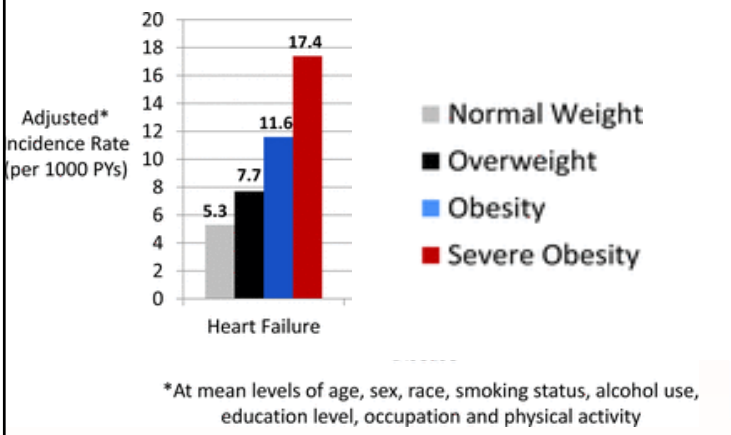
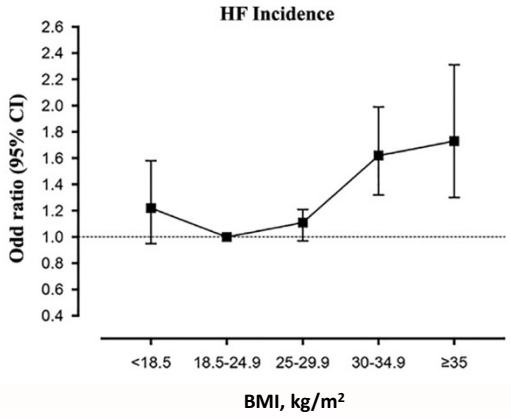
Clear Epidemiological Link Between Obesity and Heart Failure Development

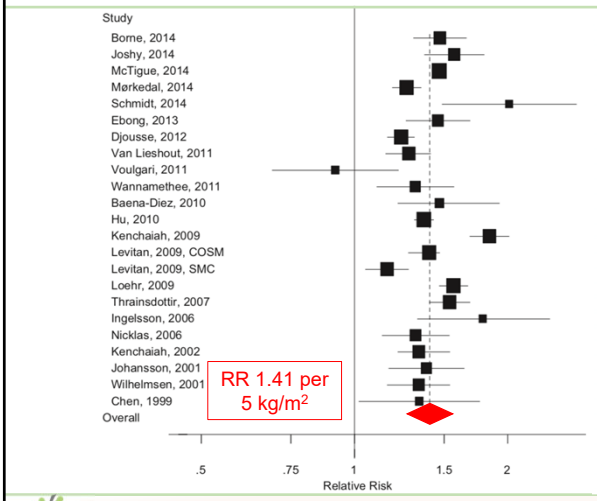


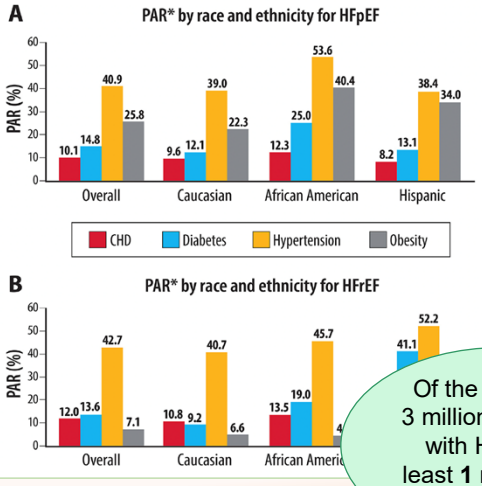


Ndumele, CE et al. Obesity and Subtypes of Incident Cardiovascular Disease. Journal of the American Heart Association. 2016;5:e003921
Mahajan R, et al. Complex Interaction Of Obesity, Intentional Weight Loss and Heart Failure. Heart. 2020;106:58-68.
Robertson J, et al. Body Mass Index in Young Women and Risk of Cardiomyopathy. Circulation. 2020;141:520-529.

4

Strongest Obesity Association is with Heart Failure with Preserved Ejection Fraction





HFpEF (heart failure with preserved ejection fraction)

HFrEF (heart failure with reduced ejection fraction)

Of the estimated 3 million US adults with HFrEF, at least **1 million** live with obesity

Aune D, et al. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systemat… Meta-Analysis of Prospective Studies. Circulation. 2016;133:639-49.
Bozkurt B, et al. HF STATS 2024: Heart Failure Epidemiology and Outcomes Statistics. *J Card Fail*. 2024;doi:10.1016/j.cardfail.2024.07.001.

5

Bariatric Surgery to Prevent Heart Failure: Retrospective Cohort Studies

Could speculate that HFpEF > HFrEF in these cohorts?

Author, journal, year	Surgical Group	Comparator Group
Benotti et al, JAHA 2017	RYGB, n=1724, U.S., 87% female, 6.3 yr f/up	Matched non-surgical primary care controls
Sundström et al, Circ 2017	RYGB, n=25,804, Sweden, 76% female, 4.1 yr f/up	Calorie-restricted diet program with exercise
Persson et al, JCF 2017	Mostly RYGB, n=22,295, Sweden, 70% female, 3.7 yr	Registry of patients with obesity
Aminian et al, JAMA 2019	RYGB/SG, n=2287, U.S., 66% female, 8 yr f/up	Matched 1:5 to patients with DM and obesity
Singh et al, BJS 2019	GB/RYGB/SG/DS, n=5170, U.K., 80% female, 3.9 yr	Matched 1:5 to EMR patients with obesity
Elsaid et al, JAMA Open 2022	GB/RYGB, n=30,300, U.S., 69% female, 21 mo f/up	Claims database non-surgical control

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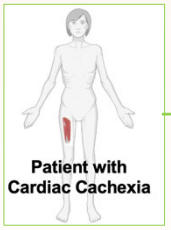
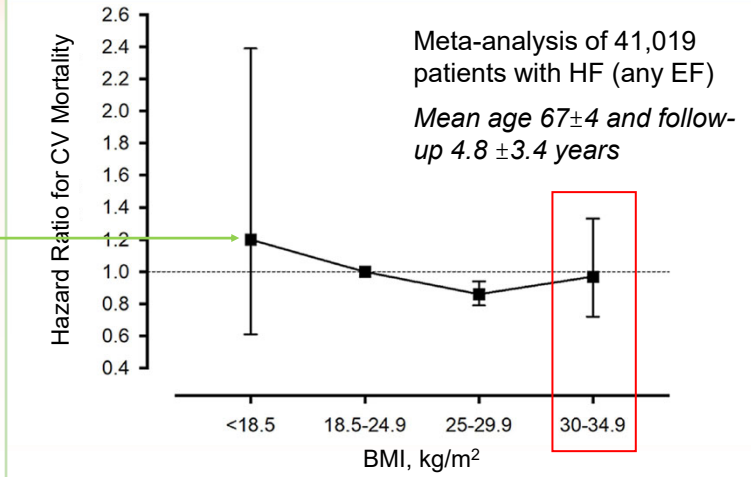
A HF Obesity Survival Paradox?: Higher Mortality with Lower BMIs

"Paradox" Contributors:

- Epidemiological phenomena e.g. healthy survivor bias
- Biology of cachexia
- Methodology of body comp assessment





Meta-analysis of 41,019 patients with HF (any EF)

Mean age 67±4 and follow-up 4.8 ±3.4 years

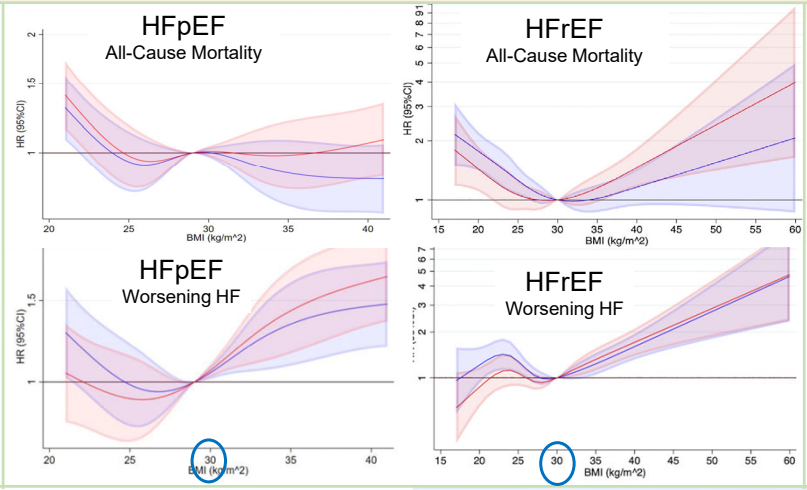
Mahajan R, et al. Complex Interaction Of Obesity, Intentional Weight Loss And Heart Failure. Heart. 2020;106:58-68.

7

A HF Obesity Survival Paradox?: BMI Insights from DAPA-HF & DELIVER

"Paradox" Contributors:

- Epidemiological phenomena e.g. healthy survivor bias
- Biology of cachexia
- Methodology of body comp assessment



Adamson C, et al. Efficacy of dapagliflozin in heart failure with reduced ejection fraction according to body mass index. *Eur J Heart Fail*. 2021;23:1662–1672.

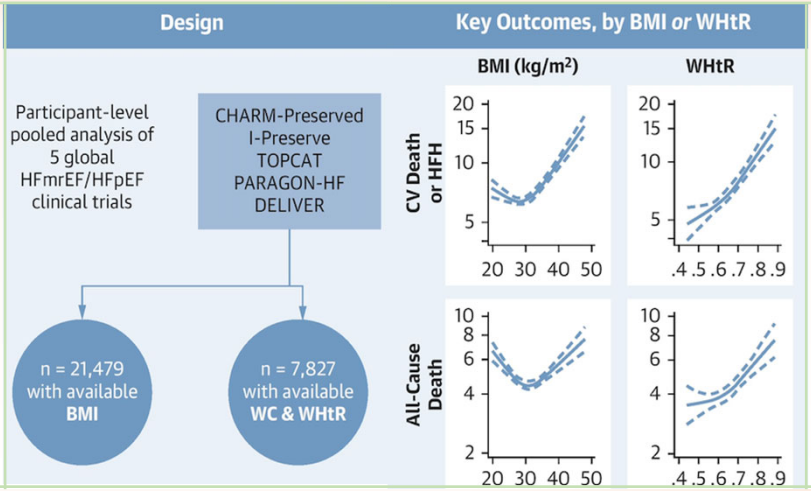
Adamson C, et al. Dapagliflozin for heart failure according to BMI: the DELIVER trial. *Eur Heart J*. 2022;43:4406–4417.

8

A HF Obesity Survival Paradox?: Attenuated with Waist Circumference Metrics

"Paradox" Contributors:

- Epidemiological phenomena e.g. healthy survivor bias
- Biology of cachexia
- Methodology of body comp assessment



Ostrominski JW, et al. Adiposity-Related Anthropometrics and Clinical Outcomes in Heart Failure With Mildly Reduced or Preserved Ejection Fraction: A Participant-Level Pooled Analysis of Randomized Clinical Trials. *J Am Coll Cardiol*. 2025;86:1760–1777.

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Potential Benefits of Intentional Rx Obesity in Patients with HF

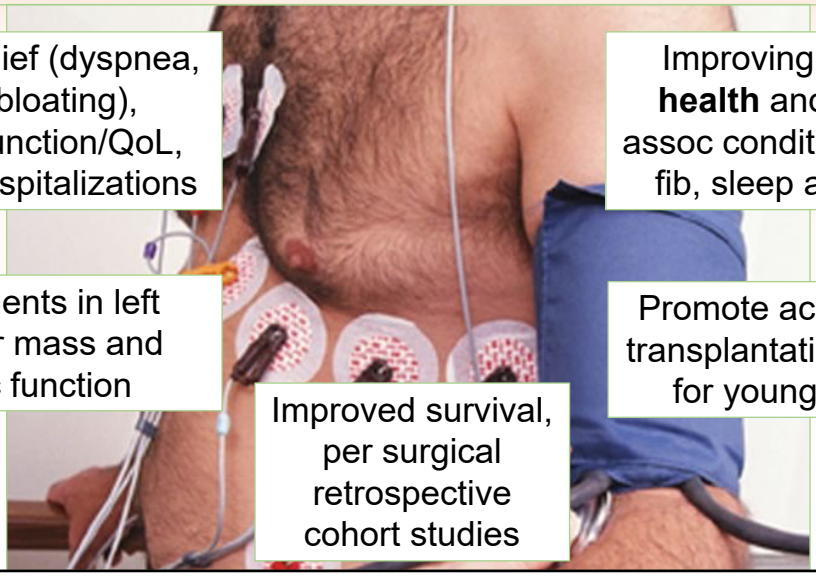
Symptom relief (dyspnea, edema, bloating), improved function/QoL, fewer HF hospitalizations

Improving **metabolic health** and managing assoc conditions incl atrial fib, sleep apnea, CAD

Improvements in left ventricular mass and diastolic function

Promote access to heart transplantation, especially for younger patients

Improved survival, per surgical retrospective cohort studies



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The 3 Domains of Obesity Management
Limited Data Specific to Patients with HF



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Study	N subjects	Cohort	Intervention	Outcome
Evangelista L, 2009	14 HFrEF	NYHA II-III, BMI >27 kg/m^2	High protein vs. standard protein vs conventional	-9.9 vs. -5.5 vs. 1.5 kg weight changes
Pritchett AM, 2012	20 HFrEF	Metabolic syndrome in all	Walking program + 2 Slim Fast vs. standard	No difference in weight loss or QoL, 6 min walk
Ritzel A, 2015	40 HFpEF	Metabolic syndrome or pre-DM in all	3-month lifestyle program	58% had ≥2% WL, associated with increased peak VO_2
Kitzman DW, 2016	100 HFpEF	>60 years, BMI >30 kg/m^2	20 weeks exercise vs. diet (400 kcal/day deficit) vs. exercise + diet (300 kcal/day deficit)	Best WL in ex+diet group of 11 kg (10%)
Gonzalez-Islas, 2017	88 HF any EF	NYHA I-III, 50% DM, 35% obesity	Low-carb standard diet	No significant weight loss
Evangelista L, 2021	76 HF any EF	DM and BMI >27 kg/m^2	High protein (30% protein, 40% carbohydrate, 30% fat) vs. standard-protein diet for 12 weeks	Body weight and adiposity; high-protein more effect on lipids and BP
Brubaker P, 2022	88 HFpEF	BMI ≥28 kg/m^2	300 kcal/day deficit diet plus aerobic activity, with vs. without resistance training	Body weight -8 versus -9 kg (8% vs. 9%); body fat -6.5 vs. -7.4 kg

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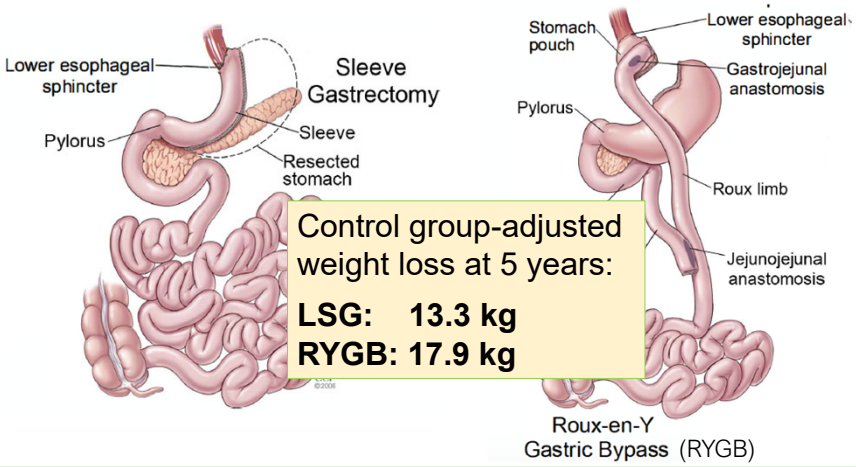
Bariatric Surgery Options: Laparoscopic Sleeve Gastrectomy or Gastric Bypass



Control group-adjusted weight loss at 5 years:

LSG: 13.3 kg
RYGB: 17.9 kg

2022 metabolic and bariatric surgical indications:

- BMI ≥ 35 kg/m^2 regardless of comorbidities
- BMI 30-34.9 kg/m^2 with metabolic disease
- BMI ≥ 27.5 kg/m^2 for Asian patients

And unable to achieve a sustained healthy weight with lifestyle ± medications

Vest AR, et al. Surgical Management of Obesity and the Relationship to Cardiovascular Disease. Circulation. 2013;127:945–959.
Eisenberg D, et al. 2022 American Society of Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) Indications for Metabolic and Bariatric Surgery. *Obes Surg*. 2023;33:3-14.

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Reduction in Mortality and HF Hospitalization after Bariatric Surgery for Patients with HF

Author, journal, year	Surgical Group	Comparator Group	Odds or Hazard Ratio for Mortality
Aleassa et al, Surg Obes Relat Dis 2019	Inpatients with primary diagnosis of HF and a prior bariatric surgery, n=2810	Matched 1:5 with similar inpatients with no history of bariatric surgery	OR 0.52 (95% CI 0.35-0.77)
Han et al, Surg Obes Relat Dis 2019	Inpatients with primary diagnosis of HF and a prior bariatric surgery, n=3617	Inpatients with primary diagnosis of HF and obesity without surgery	OR 0.47 (95% CI 0.37-0.74)

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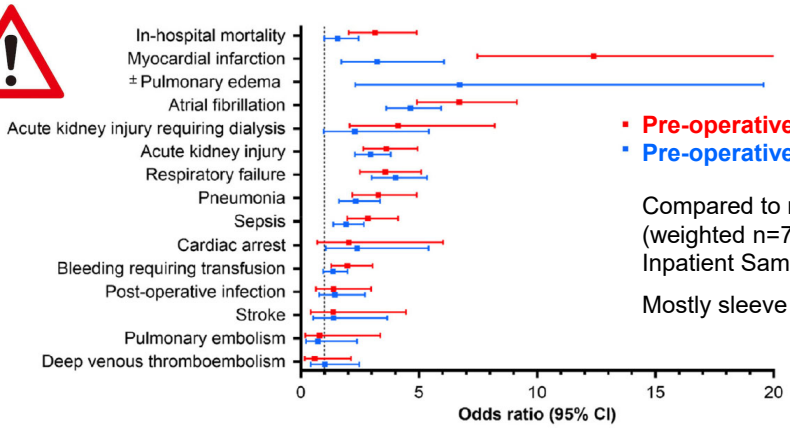
In-Hospital Mortality for Patients with Pre-existing HFrEF or HFpEF



- **Pre-operative HFrEF (weighted n=1915)**
- **Pre-operative HFpEF (weighted n=3301)**

Compared to no pre-operative HF (weighted n=788,195) in Nationwide Inpatient Sample

Mostly sleeve gastrectomy and RYGB

Blumer V…Vest AR. In-hospital Outcomes After Bariatric Surgery in Patients with Heart Failure. Am Heart J. 2020;230:59-62.

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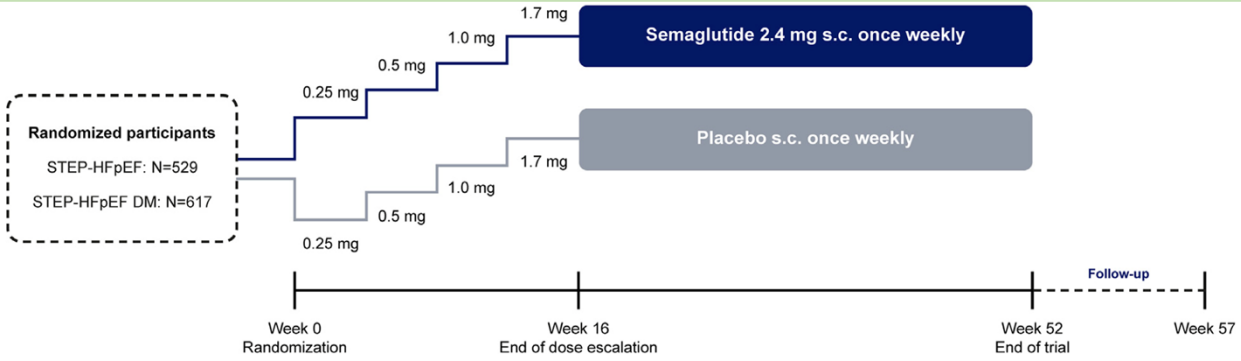
STEP-HFpEF: The *First* Large RCT of Obesity Treatment in Patients with HF

Enrolled HF patients with LVEF ≥45% and **BMI ≥30 kg/m²** and KCCQ <90

Median age 69 years (IQR 62-75)
56% female
96% White

Median BMI 37 kg/m² (IQR 33.7-41.1)
34% BMI 30-34.9 kg/m²
66% NYHA II, 81% diuretics



Kosiborod MN, et al. Design and Baseline Characteristics of STEP-HFpEF Program Evaluating Semaglutide in Patients With Obesity HFpEF Phenotype. *JACC Heart Fail.* 2023 Kosiborod et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *New England Journal of Medicine.* 2023;doi:10.1056/NEJMoa2306963.

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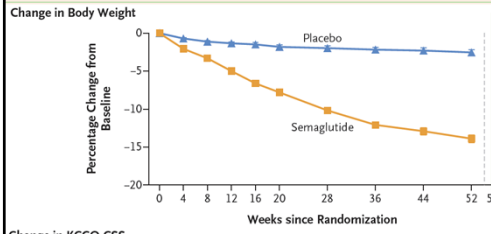
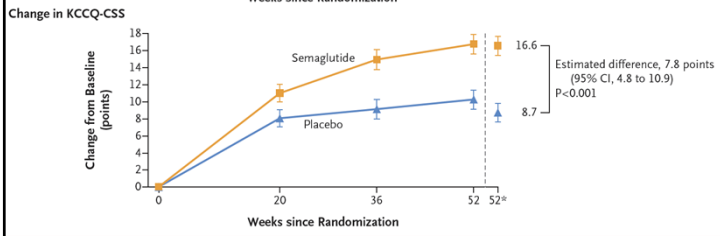
STEP-HFpEF: The *First* Large RCT of Obesity Treatment in Patients with HF





Control group-adjusted weight loss at 52 weeks:

11.3 kg

- ✅ Decrease in body weight
- ✅ Increase in KCCQ-CSS
- ✅ Increase in 6MWD
- ✅ Decrease in CRP
- ✅ Decrease in **NT-proBNP**

	Semaglu-tide (263)	Placebo (263)	P-value
SAE	13.3%	26.7%	<0.001
HF adj	0.4%	4.5%	
AF	1.1%	3.4%	
Death	1.1%	1.5%	
Pancreatitis	0%	0.4%	

Kosiborod et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *New England Journal of Medicine.* 2023;doi:10.1056/NEJMoa2306963.

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STEP-HFpEF: Consistency of Effects Across the BMI and LVEF Spectra

✅ No heterogeneity by **BMI category** in KCCQ, 6MWD, CRP, or clinical events

✅ Consistency of KCCQ, weight loss, 6MWD, CRP, and NT-proBNP improvements across the **≥45% LVEF range**

Similar findings, albeit with lesser weight loss, in STEP-HFpEF **DM**

Pooled studies: Reduced diuretic requirements and **fewer HF events** with semaglutide

Borlaug BA, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. *Nat Med*. 2023;29:2358-2365. Butler J, et al. Semaglutide in Patients With Obesity and Heart Failure Across Mildly Reduced or Preserved Ejection Fraction. *J Am Coll Cardiol*. 2023;82:2087-2096.

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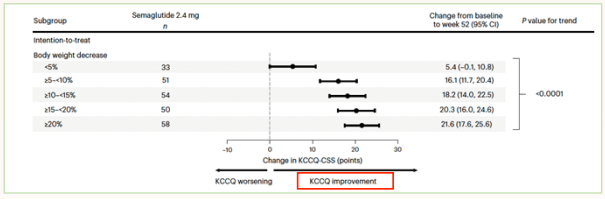
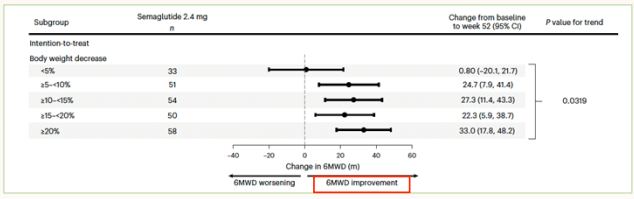
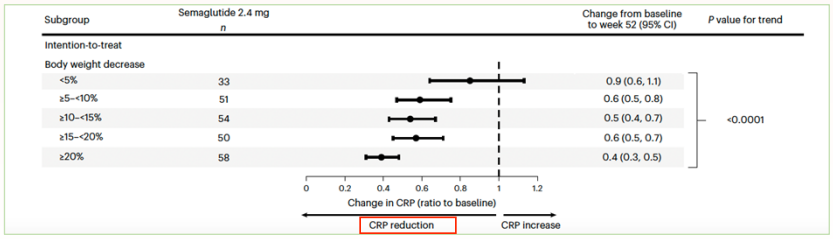
STEP-HFpEF: Dose-Response Relationship Between the Weight Change and Endpoints







Borlaug BA, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. *Nat Med*. 2023;29:2358-2365.

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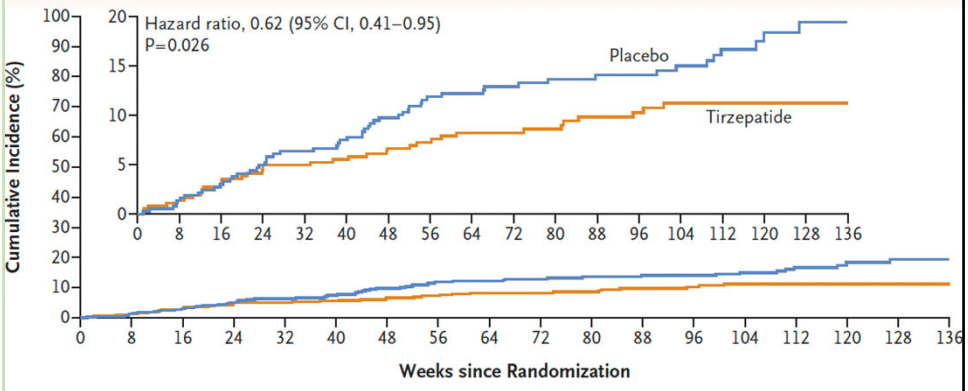
SUMMIT: Improved Clinical Outcomes for Patients with HFpEF-Obesity Receiving Tirzepatide

364 patients with HFpEF EF ≥ 50% and BMI ≥ 30 kg/m^2

Tirzepatide (GLP-1/GIP agonist) target 15 mg weekly vs. placebo

Average 11% WL



Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, Ge J, Weerakkody GJ, Ou Y, Bunck MC, Hurt KC, Murakami M, Borlaug BA. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2025;392:427-437.

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Notes on the GLP-1 Agonists in Advanced HFrEF (FIGHT, LIVE)

FIGHT Mortality or HF Rehospitalization

Excess risk: NYHA III-IV (vs I-II), no ICD/PPM

Outcome	Events placebo (N = 146)	Events liraglutide (N = 154)	Incidence rate ratio (95% CI)	*P* value
Total HHF or death	96	143	1.41 (0.98-2.04)	0.064
Total HHF	80	124	1.47 (0.98-2.20)	0.061
Death	16	19	1.13 (0.58-2.19)	0.72
Total HHF, urgent HF visit or death	102	153	1.48 (1.00-2.19)	0.056
Urgent HF visits	6	10	1.58 (0.52-4.81)	0.42
Total arrhythmic events[a]	21	39	1.76 (0.92-3.37)	0.088
Total events of interest[a,b]	196	295	1.43 (1.06-1.92)	0.018

Placebo-adjusted weight loss only 1.9 kg
Unknown if a liraglutide-specific issue; dose only 1.8 mg dose

Margulies KB, et al. Effects of Liraglutide on Clinical Stability Among Patients With Advanced HFrEF. *JAMA*. 2016;316:500-8. Neves JS, et al. Risk of adverse events with liraglutide in HFrEF: a post-hoc analysis from the FIGHT trial. *Diabetes Obes Metab*. 2023;25:189-197.

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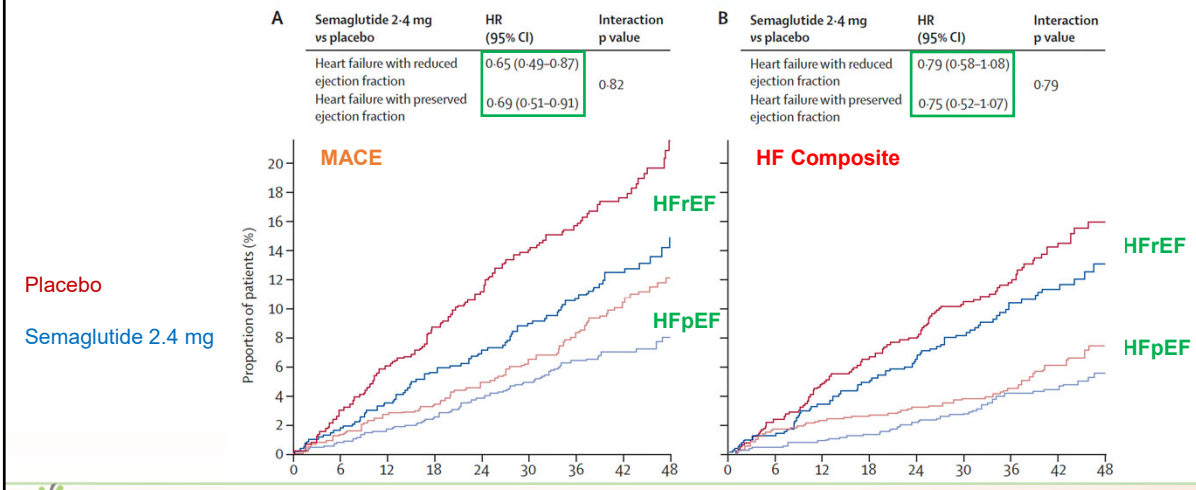
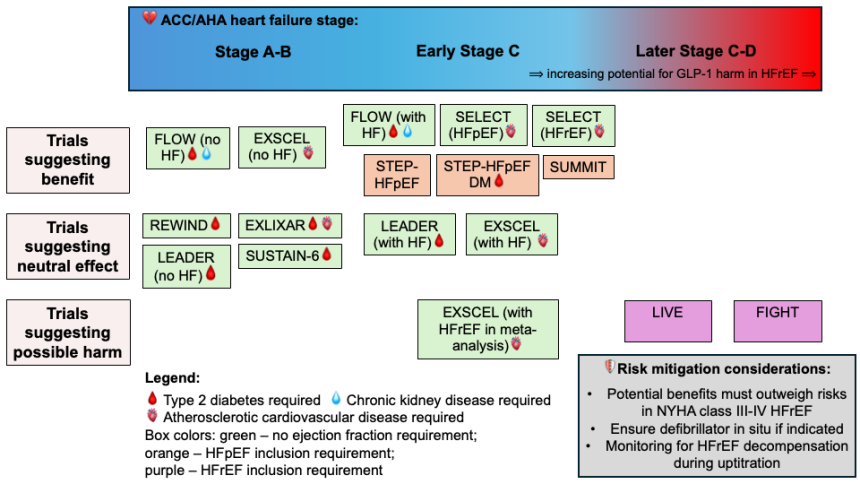
Some Reassurance from SELECT: Outcomes by Baseline HF Subtypes (~90% NYHA I-II)



Deanfield J, et al. Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial. *Lancet*. 2024;404:773-786.

25

Summary of Available Data Regarding GLP-1 RA by Indication and HF Stage



Vest AR and Deswal A. Thin Evidence, Heavy Need: The Case for GLP-1 Agonist Trials Specific to Patients With HFrEF. *JACC Heart Fail*. 2025:102715. doi:10.1016/j.jchf.2025.102715.

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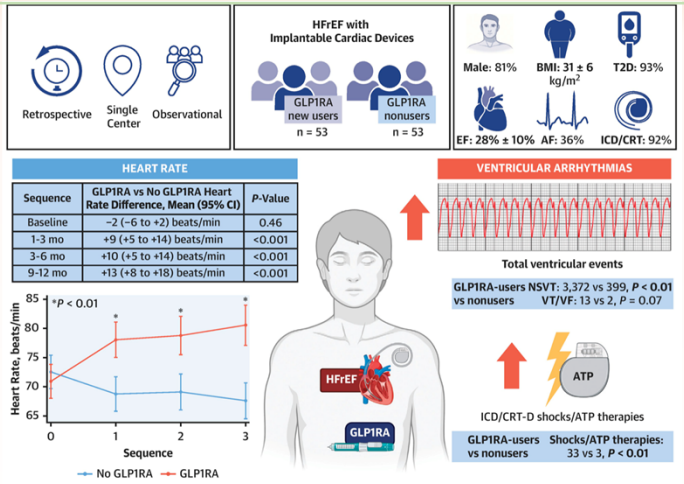
GLP-RA Use, Heart Rate and Ventricular Arrhythmias per HFrEF Device Monitoring

GLP-1 agonism has direct SA node effects via PKA-dependent calcium-clock pathways that increase HR



GLP-1 agonism augmentation of the myocardial glucose influx may be problematic in advanced HFrEF

Marques P, et al. Effects of Glucagon-Like Peptide 1 Receptor Agonist Initiation in Patients With Heart Failure With Reduced Ejection Fraction and Implantable Cardiac Devices. *JACC Heart Fail*. 2025;13:102573.

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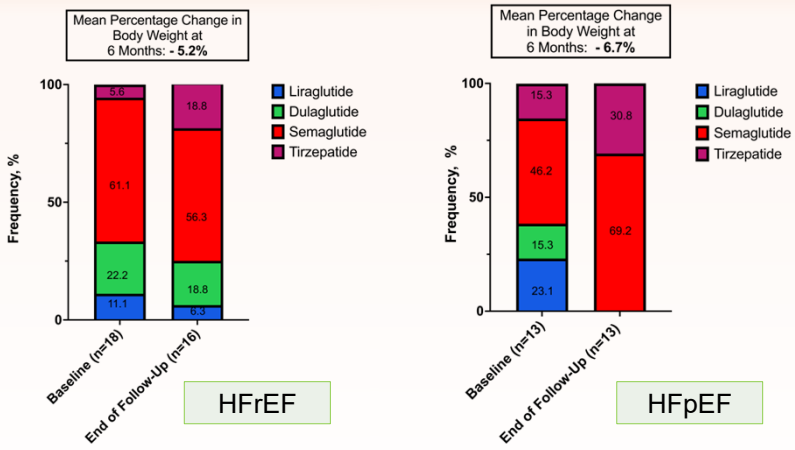
Real-World Experience with Incretin-Based Obesity Therapies in a Heart Failure Clinic

N=35, of which 31 started therapy

Table 1: Characteristics of the Study Cohort at Baseline and End of Study

Baseline Characteristics	All Subjects (n=35, unless stated)
Age, years	49.5 ±13.1
Female	14 (40.0%)
HFrEF (LVEF <50%)	21 (60.0%)
HFpEF (LVEF ≥50%)	14 (40.0%)
Average LVEF in patients with HFrEF, % (n=21)	26.8% ±9.9%
Etiology of HF, ischemic	5 (14.3%)
Duration of HF, months	63.2 ±61.4%
NYHA Class	
I	5 (14.3%)
II	12 (34.3%)
III	16 (45.7%)
IV	2 (5.7%)



Hussani SF, Nguyen K, Yu KM, Sinha D and Vest AR. Antiobesity Medications in Patients With Heart Failure: A Clinical Protocol and Preliminary Single-Center Experience. *JACC Heart Fail*. 2025;doi:10.1016/j.jchf.2024.10.018.

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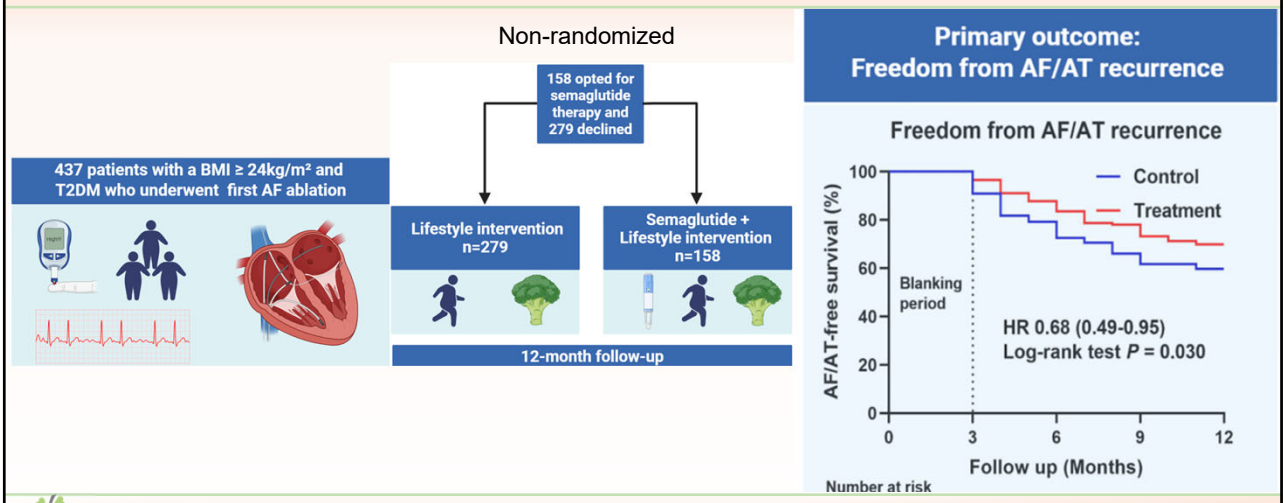
Real-World Experience with Incretin-Based Therapies for Atrial Fib Recurrence Prevention



Guo J, et al. Effect of Semaglutide on Atrial Arrhythmias Recurrence Following Ablation for Atrial Fibrillation: A Prospective Study. *Circ Arrhythm Electrophysiol*. 2025;18:e014069

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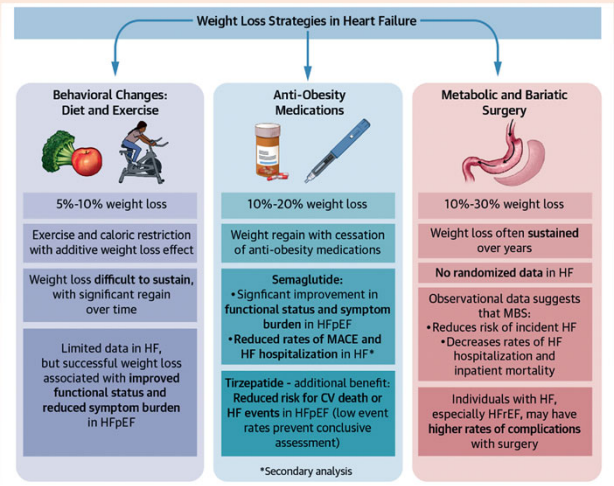
Goal: Safe and Effective Application of 3 Obesity Treatment Domains in Patients with Heart Failure



Kittleson MM, Benjamin EJ, Blumer V, Harrington J, Januzzi JL, McMurray JJV and Vest AR. **2025 ACC Scientific Statement on the Management of Obesity in Adults With Heart Failure**: A Report of the American College of Cardiology. *J Am Coll Cardiol*. 2025;doi:10.1016/j.jacc.2025.05.008.

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"Essential" Components of a Metabolic HF Clinic Protocol

Registered Dietitian

Cardiac and Obesity Experience
Virtual availability

Exercise Physiologist

Heart Failure Experience
Ideally, HFpEF Access

Clinical Pharmacist

Heart Failure
Virtual availability
Collaborative practice agreement

Physician with Heart Failure and Obesity Experience

Elkind MSV, et al. The American Heart Association at 100: A Century of Scientific Progress and the Future of Cardiovascular Science: A Presidential Advisory From the American Heart Association. *Circulation*. 2024;149:e964–e985.

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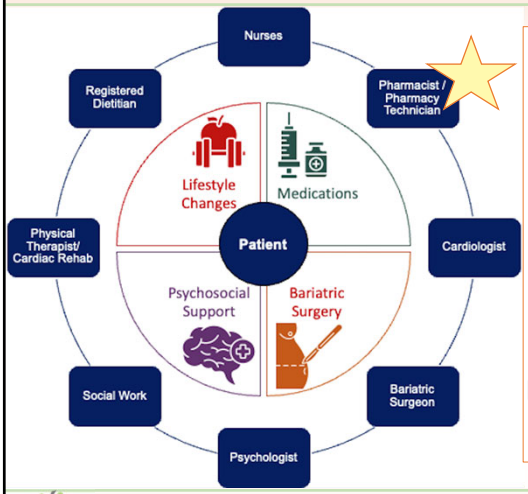
The "Metabolic-HF Clinic" Construct with Pharmacy Team Collaboration



Send to CCF Home Delivery if patient resides in service area & okay with receiving from CCF HD

Patient appropriate to start GLP1^

Send for 1 month supply + 1 refill if referring for GLP1 titration/monitoring in HF Pharmacy Clinic (will titrate monthly)

History of DM?

Yes / No

Preferred

Mounjaro® (tirzepatide)
Ozempic® (semaglutide)

Mounjaro®	2.5 mg	2 mL	28 days
Ozempic®	0.25 mg	3 mL	42 days

Use Ozempic (aka new start or continuation) order for initial pen: 0.25 mg x4 wk then 0.5 mg x2 wk

Consider if OH Medicaid or preferred agents not covered

Trulicity® (dulaglutide)

0.75 mg	2 mL	28 days

Established CV disease (history of MI/CAD, CVA, or PAD)?

Yes / No

Wegovy® (semaglutide)

0.25 mg	2 mL	28 days

History of mod-severe OSA?*

Yes / No

Zepbound® (tirzepatide)

2.5 mg	2 mL	28 days

Insurance may not cover, consider manufacturer discount programs

Starting Dose	Quantity	Day Supply

^Contraindications: Personal or family history of MTC or MEN2
Relative contraindication: History of pancreatitis
*Submit sleep study documenting AHI (apnea-hypopnea index). Cutoff is typically ≥15
Due to variable absorption with PO Wegovy®, SC formulations preferred

Harrington J, Gale SE and Vest AR. Anti-Obesity Medications in Patients With Heart Failure: Current Evidence and Practical Guidance. *Circ Heart Fail*. 2024:e011518.

CC Quick Start and Protocol: **Emily McElhaney, PharmD BCCP & Julianne Fallon, PharmD BCCP**

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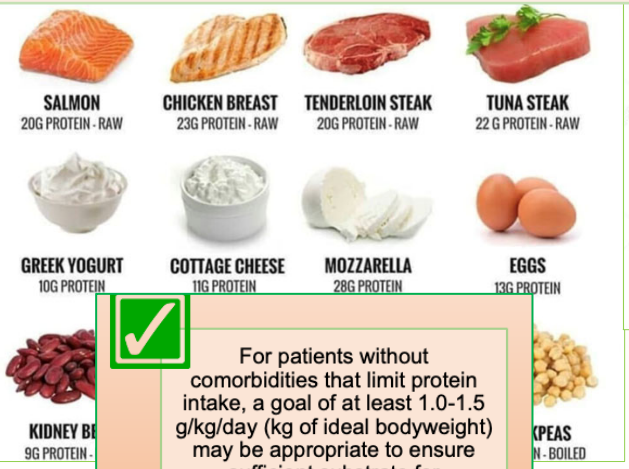
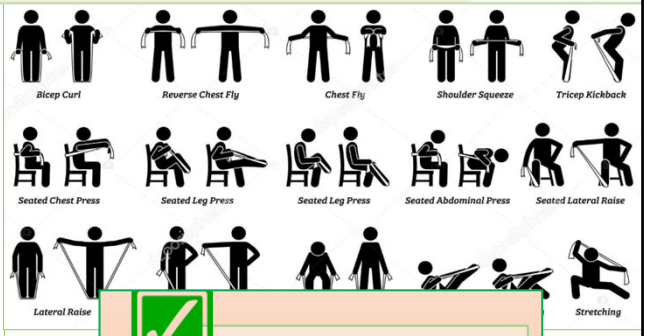
Lean Mass Maintenance Suggestions, Pending Further Study

TONEIC HFpEF
Targeting Optimal Nutrition and Exercise to Improve Composition in Heart Failure with Preserved Ejection



For patients without comorbidities that limit protein intake, a goal of at least 1.0-1.5 g/kg/day (kg of ideal bodyweight) may be appropriate to ensure sufficient substrate for maintenance of muscle mass during weight loss



For patients able to participate in physical activity it is reasonable to recommend 20 minutes of upper and lower body resistance exercises 2-3 times per week, with additional walking activity for 40 minutes 3 times per week, as tolerated

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TONEIC-HFpEF
Study Design (~July 2026)

TONEIC HFpEF
Targeting Optimal Nutrition and Exercise to Improve Composition in Heart Failure with Preserved Ejection

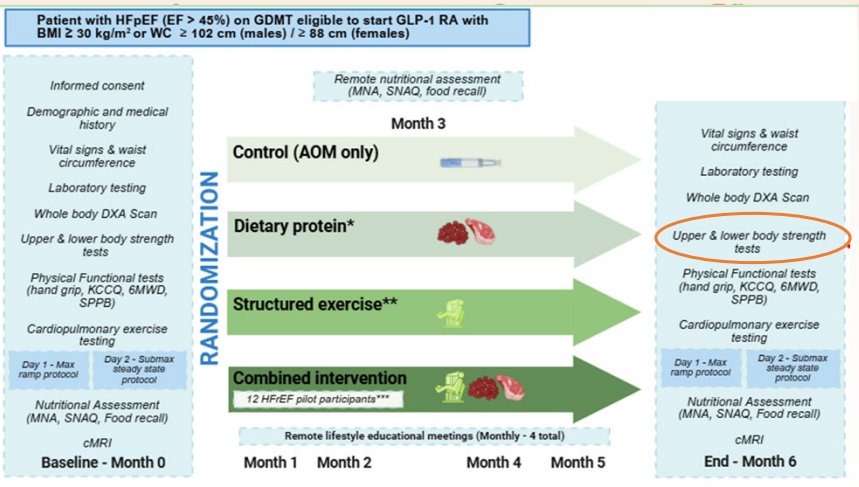

Figure credit: HF Research Fellow **Andrey Sanko Posada** MD MS
Heart, Vascular and Thoracic Institute, Cleveland Clinic, Ohio

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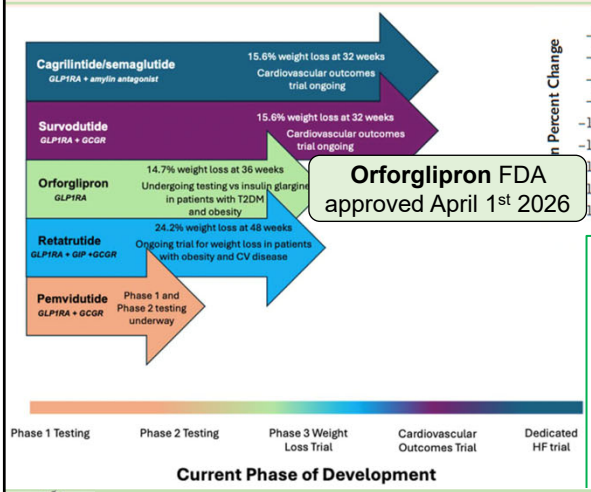
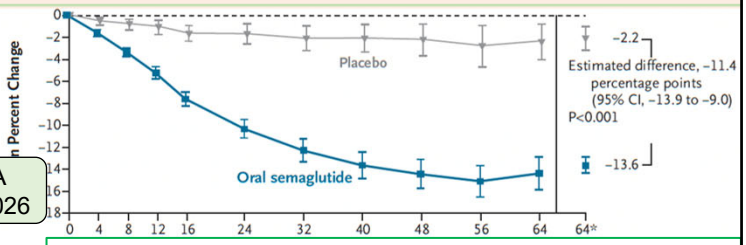
Next Steps in Obesity Pharmacotherapy



Orforglipron FDA approved April 1st 2026



Maridebart cafraglutide: GLP-1 RA/GIP *antagonist*
Under study in phase 3 **MARITIME-HF** trial in patients with obesity and HFpEF/HFmrEF
- GIP antagonism may remove a weight-promoting/storage signal and amplify GLP-1 effect on weight loss
- (vs Tirzepatide, where GIP agonism may synergize with GLP-1 to reduce intake and improve energy balance)

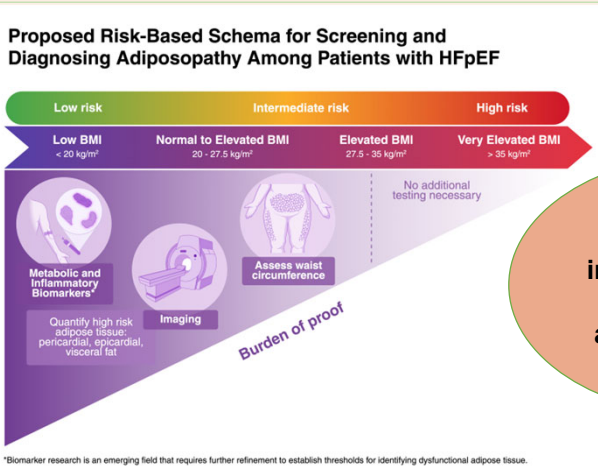
Opposite GIP effects, similar anticipated direction on weight

Harrington J, Gale SE and Vest AR. Anti-Obesity Medications in Patients With Heart Failure: Current Evidence and Practical Guidance. *Circ Heart Fail*. 2024:e011518. doi:10.1161/CIRCHEARTFAILURE.124.011518.
Wharton S, et al. Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity. *NEJM*. 2025;393:1077–1087

35

Re-Visiting the Diagnosis of Obesity-Related HFpEF

Limitations of BMI: Sex and race calibration, ignores fluid retention, insensitive to adipose distribution, overlooks metabolic and end-organ dysfunction



What does this mean for the inclusion criteria of future adiposity-associated HFpEF trials?

Vest AR, Ilonze OJ, Umapathi P and Harrington J. Body Composition and Treatment Response in Heart Failure With Preserved Ejection Fraction: Interpreting the Adipokine Hypothesis. *J Am Coll Cardiol*. 2025;86:1256–1259.

36

2025 ACC Scientific Statement on Management of Obesity in Adults with Heart Failure

A Report of the American College of Cardiology

WRITING COMMITTEE

Michelle M. Kittleson, MD, PhD, FACC, Chair

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Josephine Harrington, MD
James L. Januzzi, MD, FACC
John J.V. McMurray, MD, FACC
Amanda R. Vest, MBBS, MPH, FACC

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HFSA Dietary Recommendations for Patients with Heart Failure

Endorse diets based on DASH, Mediterranean, or plant-based patterns; calorie-restricted for patients with excess weight or diabetes

'Whole food approach' more valuable than supplementation of single nutrients

Beware risks of restrictive dietary counselling which may prompt micronutrient inadequacies, wasting

Recommend at least population minimum of 0.8 g/kg protein intake, potentially more if skeletal muscle wasting, but red meat concerns

Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C, Lennie T, Litwin SE, Parsly L, Rodgers JE, Rich MW, Schulze PC, Slader A and Desai A. Nutrition, Obesity, and Cachexia in Patients With Heart Failure: A Consensus Statement from the Heart Failure Society of America Scientific Statements Committee. J Card Fail. 2019;25:380-400.

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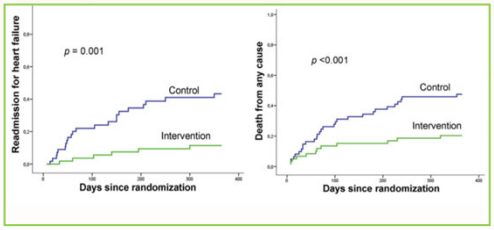
Malnutrition is Prevalent and Worsens Outcomes But Modifiable: PICNIC and EFFORT trials

Depending on screening tool or diagnostic criteria used, approx 30-40% of patients with HF have **malnutrition**

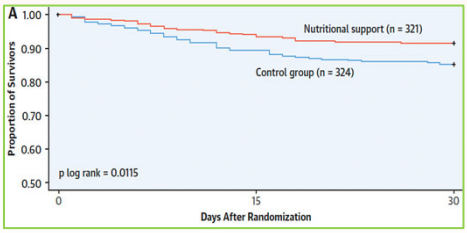
Significant independent association with mortality over 2-4 years

PICNIC: Spanish n=120 patients hospitalized with HF with MNA score <17 points, randomized 1:1 to standard of care vs 6 months intervention with *dietary optimization, specific recommendations, nutrition supplement prescriptions (RD, MD)*



Reduction in 6-month HF readmission and mortality

EFFORT: n=645 subgroup with chronic HF in a Swiss RCT of hospitalized patients with malnutrition per NRS score, randomized 1:1 to standard of care inpatient food vs *individualized nutrition support incl protein 1.2-1.5 g/kg/day (RD)*



Reduction in 30-day mortality

Bonilla-Palomas JL, et al. Nutritional Intervention in Malnourished Hospitalized Patients with Heart Failure. *Arch Med Res*. 2016;47:535–540.
Hersberger L, et al. Individualized Nutritional Support for Hospitalized Patients With Chronic Heart Failure. *JACC*. 2021;77:2307-2319.

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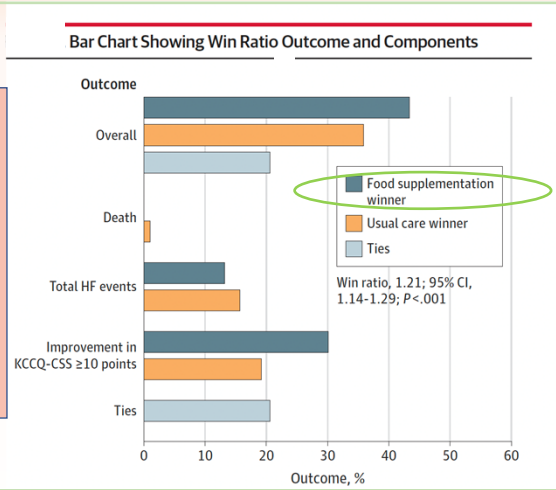
FOOD-HF: 90-day Food Supplementation Feasible and Acceptable after a HF Hospitalization

FOOD-HF: Open-label, 2-center, factorial RCT in Dallas, TX recruiting adults with HF within 14 days of discharge

1:1:1 to receive MTM, vs Fresh Produce, vs usual care with dietary counseling for 90 days

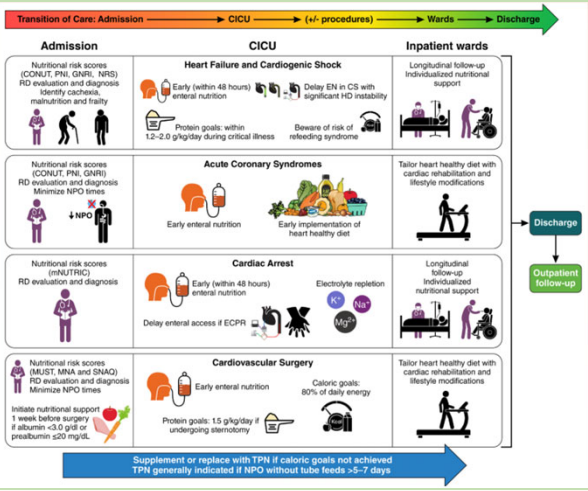


Participant rated meal adherence, acceptability and satisfaction were all greater with **Fresh Produce** than Medically Tailored Meals

Pandey A, Keshvani N, Coellar JD, Jain AK, Segar MW, Bustillo-Rubio M, Rizvi SK and Peterson ED. Food Supplementation in Patients Hospitalized for Heart Failure: A Randomized Clinical Trial. *JAMA Cardiol*. 2026:doi:10.1001/jamacardio.2026.0435.

40

AHA Statement: Malnutrition and Cachexia in Inpatients with Acute Cardiac Conditions



Vest AR, DiDomenico RJ, Lichtenstein L, Slater T, Ekpo E, Damluji AA, Bohula E, Alviar CL. Malnutrition and Cachexia in Inpatients With Acute Cardiac Conditions: A Scientific Statement From the American Heart Association. *Circulation*. 2026;doi:10.1161/CIR.0000000000001405.

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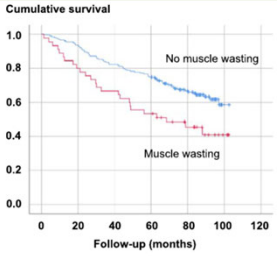
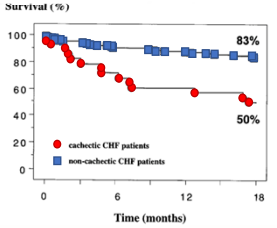
Muscle Wasting Definitions and Epidemiology

- **Sarcopenia:** Age-related decline in skeletal muscle mass and function that can be accelerated by chronic diseases (per sex-specific DXA lean mass thresholds or strength measures)
- **Cachexia:** A complex wasting syndrome in chronic disease, characterized by unintentional edema-free weight loss (e.g. ≥7.5%), sarcopenia, inflammation and abnormal biochemistry



Adjusted HR 1.80
(95% CI 1.01-3.19)
p=0.04



Adjusted HR 3.73
(95% CI 1.93-7.23)
p=0.0003

Anker SD et al. Wasting As Independent Risk Factor For Mortality In Chronic Heart Failure. *The Lancet.* 1997;349:1050-1053.
von Haehling S, et al. Muscle Wasting As An Independent Predictor Of Survival In Patients With Chronic Heart Failure. *J Cachexia Sarcopenia Muscle.* 2020;11:1242-1249.

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Prevalence of Muscle Wasting in HF

~20%

Fulster 2013 SICA-HF Cohort	Y. Zhang 2021 Meta-analysis	Konishi 2021 Japan Cohort
200 ambulatory pts with HF, 80% male, mean 67 yrs	965 ambulatory pts with HF	475 older pts with HFpEF (EF ≥45%) 49% male, 81 yrs
19.5%	**26%**	**18.1%**

Each study used similar DXA ALM sarcopenia diagnostic criteria

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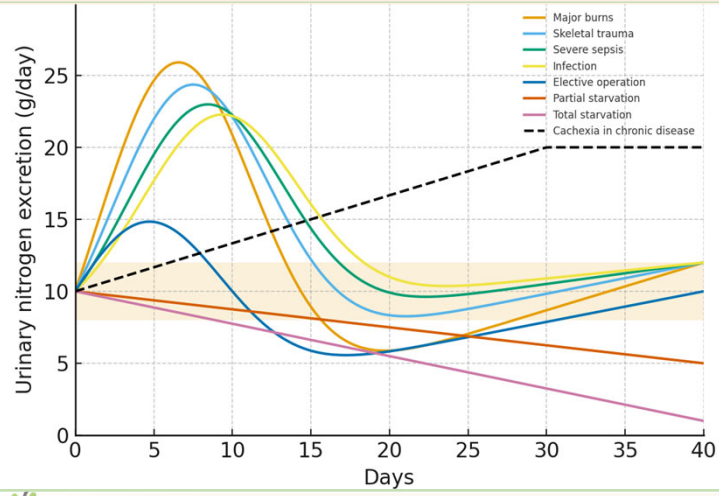
Muscle Protein Catabolism → Increased Nitrogen Excretion



Cardiac cachexia: highly catabolic state, protein wasting into urinary nitrogen

Aka why Malnutrition and Cachexia are not the same process!

Adapted using ChatGPT 5.1 from: Long CL, et al. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. *JPEN J Parenter Enteral Nutr*. 1979;3:452–6.

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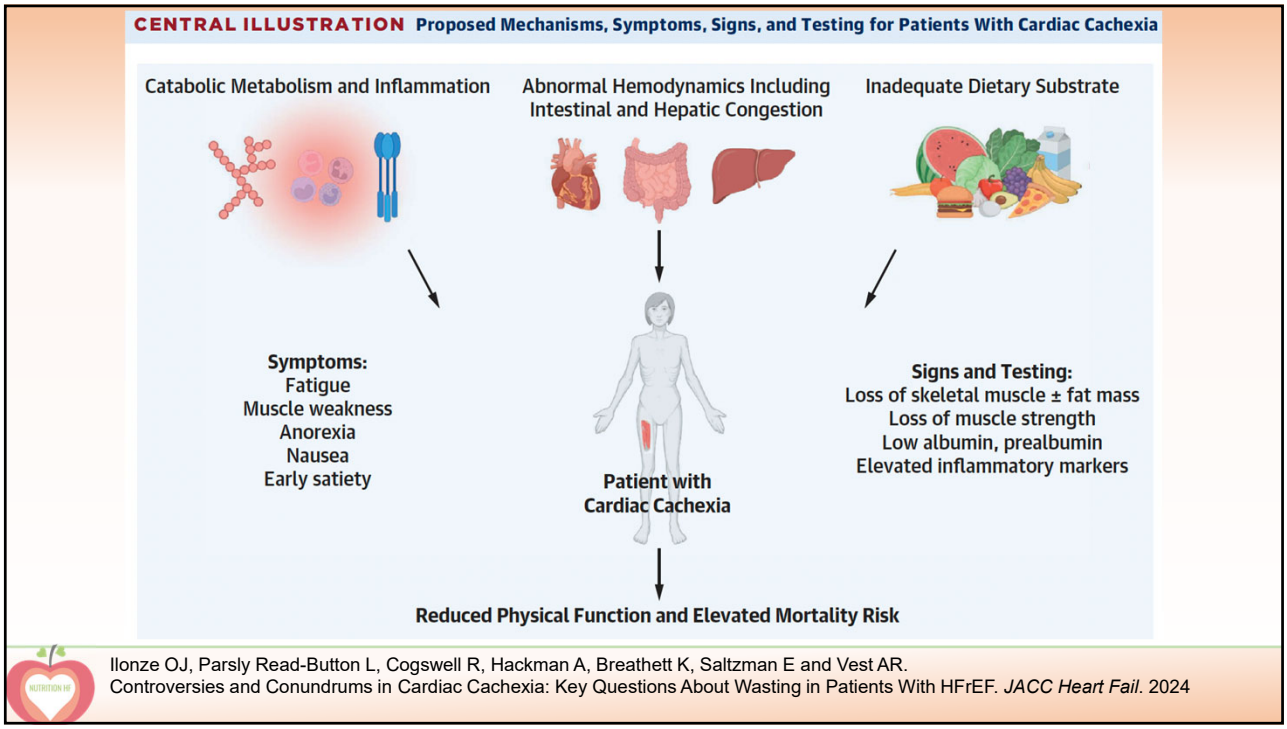

Ilonze OJ, Parsly Read-Button L, Cogswell R, Hackman A, Breathett K, Saltzman E and Vest AR.
Controversies and Conundrums in Cardiac Cachexia: Key Questions About Wasting in Patients With HFrEF. *JACC Heart Fail*. 2024

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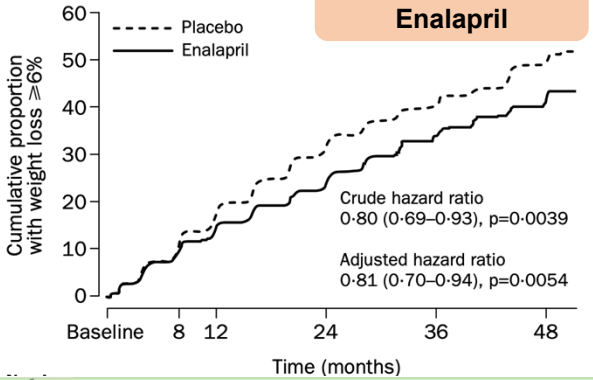
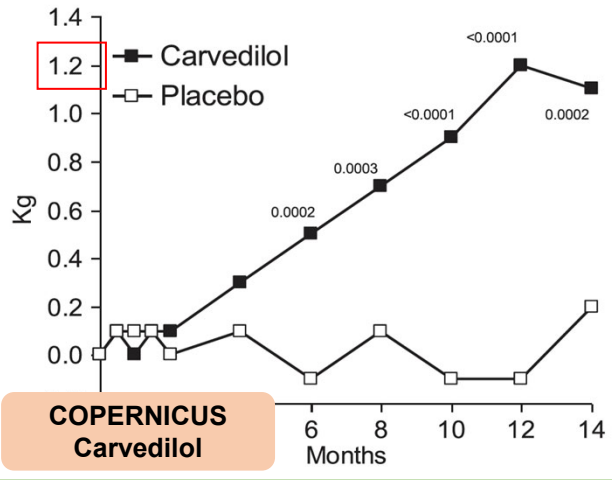
What Therapies Reverse Cardiac Cachexia?

Figure 2: **Cumulative incidence of weight loss ⩾6% in patients with chronic heart failure treated with enalapril or placebo in the SOLVD treatment study**

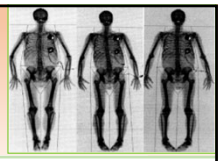


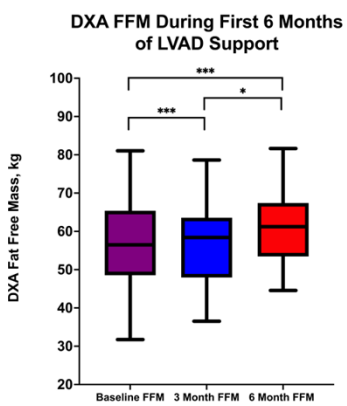


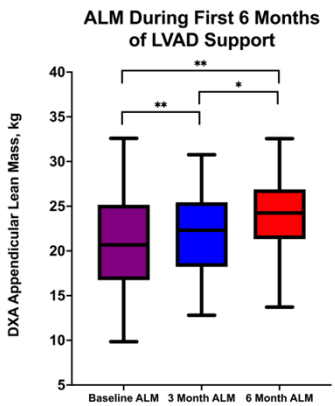
Anker SD, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet. 2003;361:1077-1083.
Coats AJS, et al. Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic HF. J Cachexia Sarc Muscle. 2017;8:549-

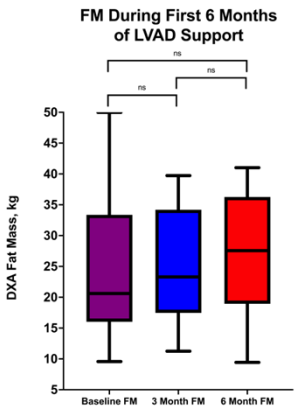
46

Skeletal Muscle Mass Recovery Early After LVAD Implant in Advanced HFrEF









Vest AR et al. Skeletal Muscle Mass Recovery Early After Left Ventricular Assist Device Implantation in Patients with Advanced Systolic Heart Failure. Circ Heart Fail. 2022:101161CIRCHEARTFAILURE121009012.

Funded by an American Heart Association Scientist Development Grant

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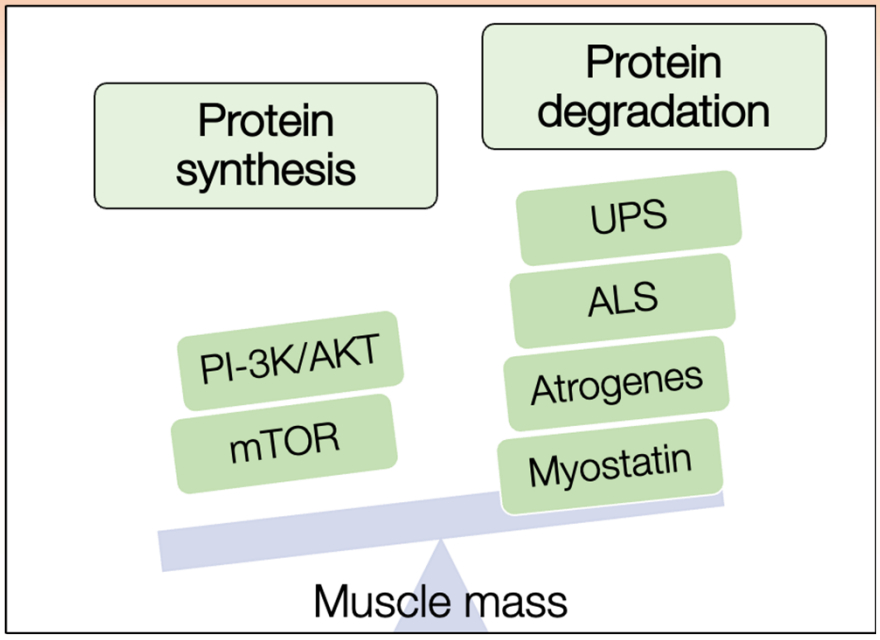

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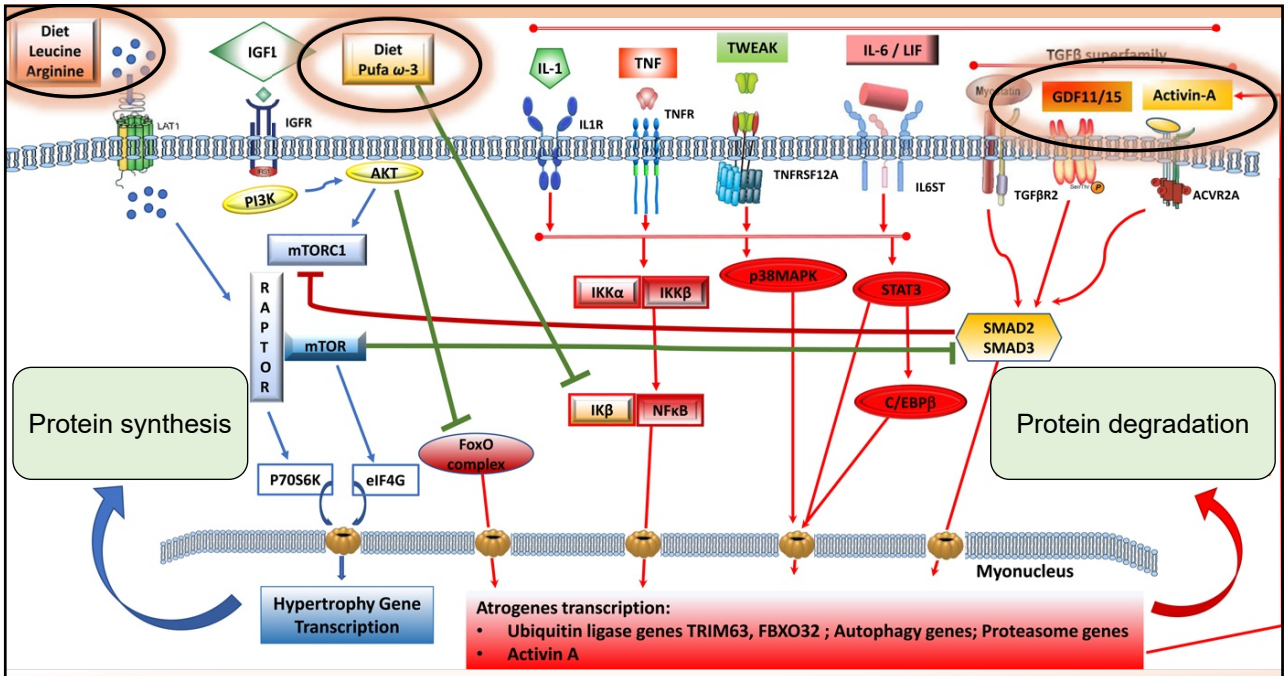
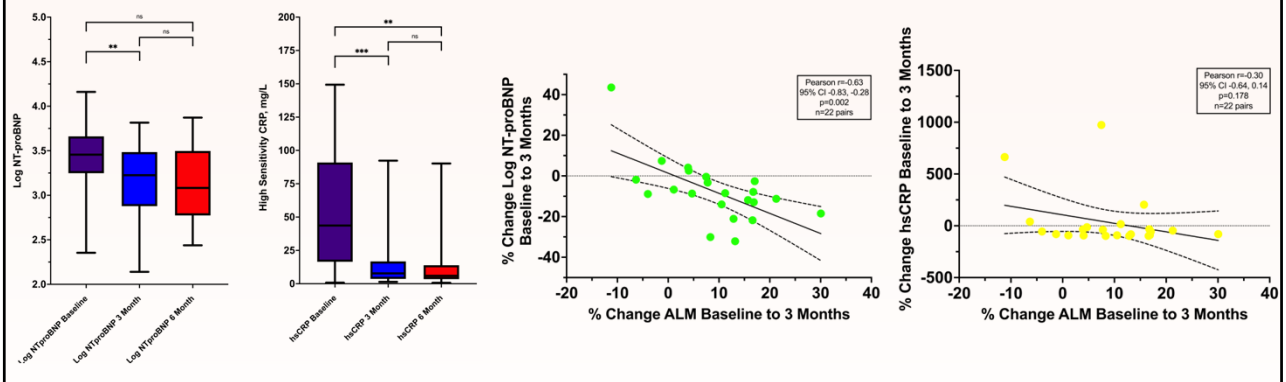


Schiessel DL and Baracos VE. Barriers to cancer nutrition therapy: excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. Proc Nutr Soc. 2018;77:394-402. doi:10.1017/S0029665118000186.

49

Concepts in Skeletal Muscle Mass Recovery from our LVAD Cohort: NTproBNP and hsCRP



Celkupa D, Sweigart BA, Chery J, Coston A, Telfer L, Lawrence M, Kiernan MS, Couper GS, Kawabori M, LeBrasseur N, Saltzman E and Vest AR. Evaluation of potential mechanisms for skeletal muscle mass recovery early after left ventricular assist device implantation. *JHLT Open*. 2025;9:100338.

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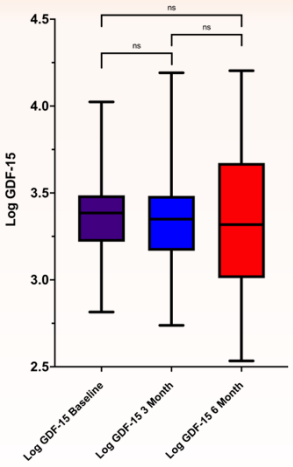
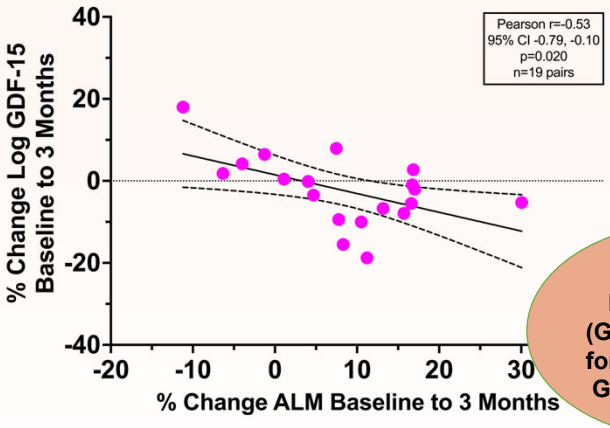
Concepts in Skeletal Muscle Mass Recovery from our LVAD Cohort: GDF-15





Example: Ponsegromab (GDF-15 inhibitor) for heart failure in GARDEN TIMI 74

Celkupa D, Sweigart BA, Chery J, Coston A, Telfer L, Lawrence M, Kiernan MS, Couper GS, Kawabori M, LeBrasseur N, Saltzman E and Vest AR. Evaluation of potential mechanisms for skeletal muscle mass recovery early after left ventricular assist device implantation. *JHLT Open*. 2025;9:100338.

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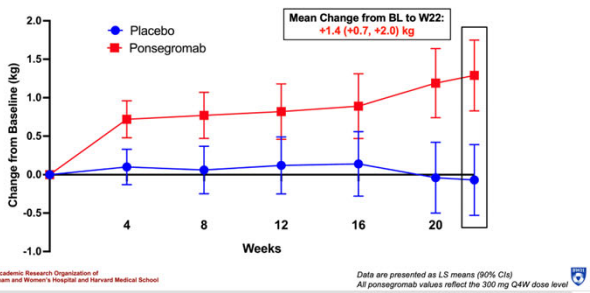
GDF-15 Inhibitor Ponsegromab in HFrEF in GARDEN-TIMI 74

Garden TIMI 74

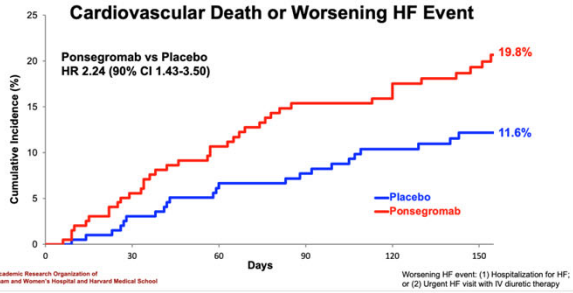
Body Weight



An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

Data are presented as LS means (90% CIs)
All ponsegromab values reflect the 300 mg Q4W dose level

Clinical Composite Outcome



An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

Worsening HF event: (1) Hospitalization for HF; or (2) Urgent HF visit with IV diuretic therapy

Courtesy of: **David D. Berg, MD, MPH, John D. Groarke, MBBCh, MPH**
on behalf of the GARDEN-TIMI 74 Investigators, September 29th 2025, HFSA ASM, Minneapolis MN

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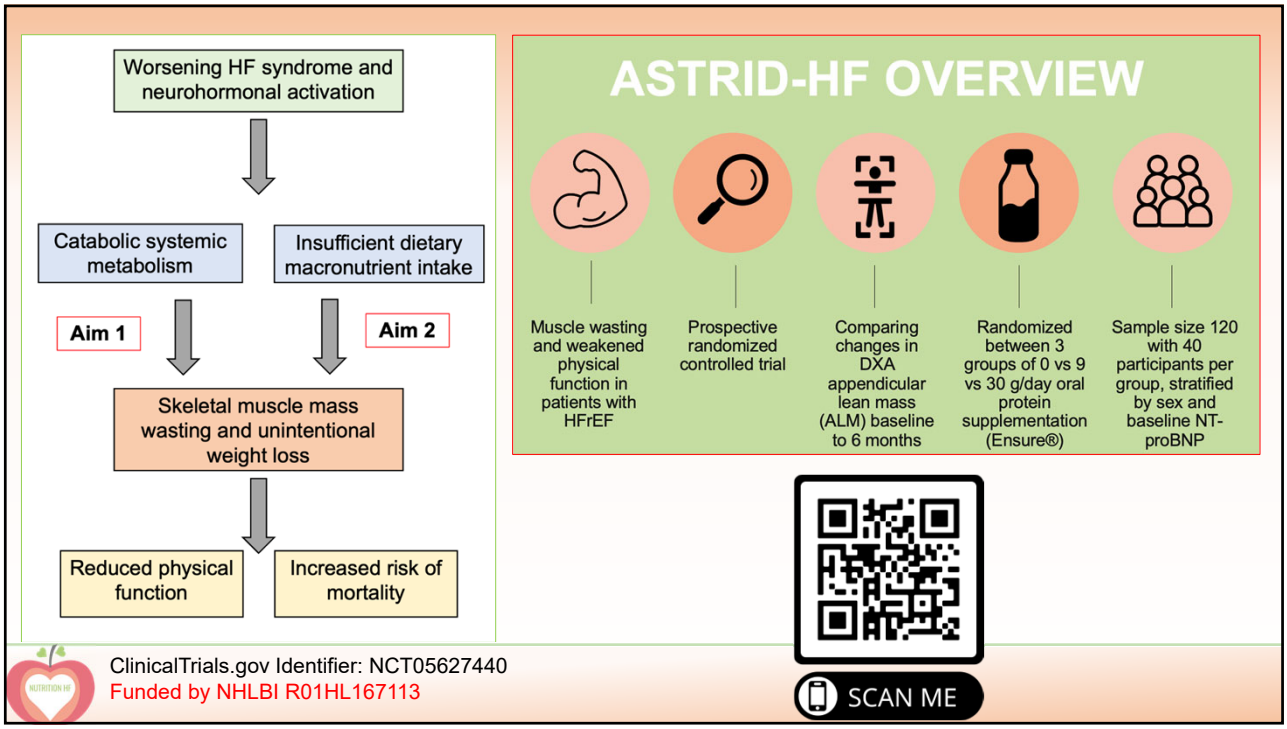

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Moving Towards Treatments for Cachexia as Therapies for Heart Failure

- *Key Points:*
  - Wasting appears tightly coupled to the degree of neurohumoral activation in patients with HF, and strongly associated to excess mortality
  - Unlikely that dietary substrate alone can prevent or reverse cachexia
  - Uncertain if reversal of cachexia will improve outcomes in HFrEF
- *Current Projects:*
  - Skeletal muscle US for bedside assessment of wasting
  - RCT of protein supplementation in advanced HFrEF: *ASTRID-HF*
  - Dietary protein and resistance exercises during GLP-1RA: *TONEIC-HFpEF*

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