Cardiac Cachexia: Intersection of Nutrition and Heart Failure

Amanda Vest, MBBS MPH FHFSA FAHA FACC

Cleveland Clinic, Ohio

Section Head, Heart Failure and Transplantation Cardiology

Diplomate, American Board of Obesity Medicine

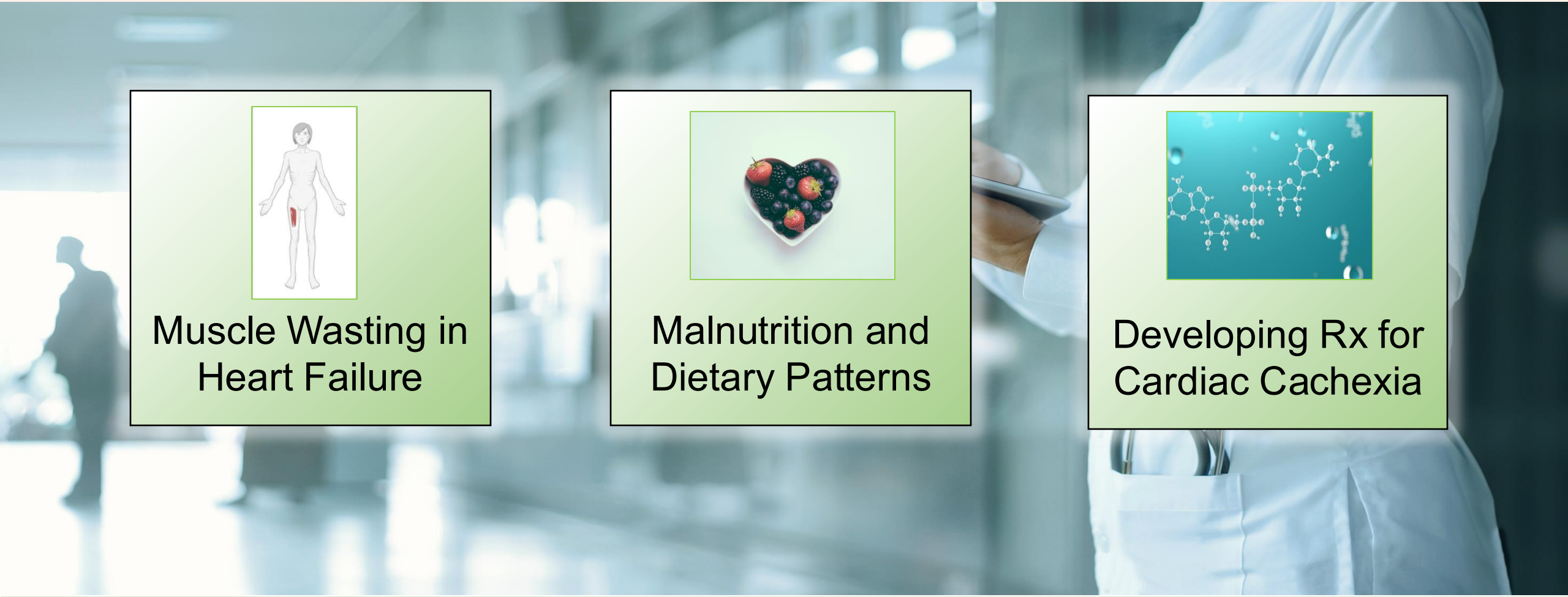
Site PI of SHORE Registry: CareDx

Cleveland Clinic

NUTRITION HF

December 4, 2025

55th Annual Robert D. Conn Heart Conference



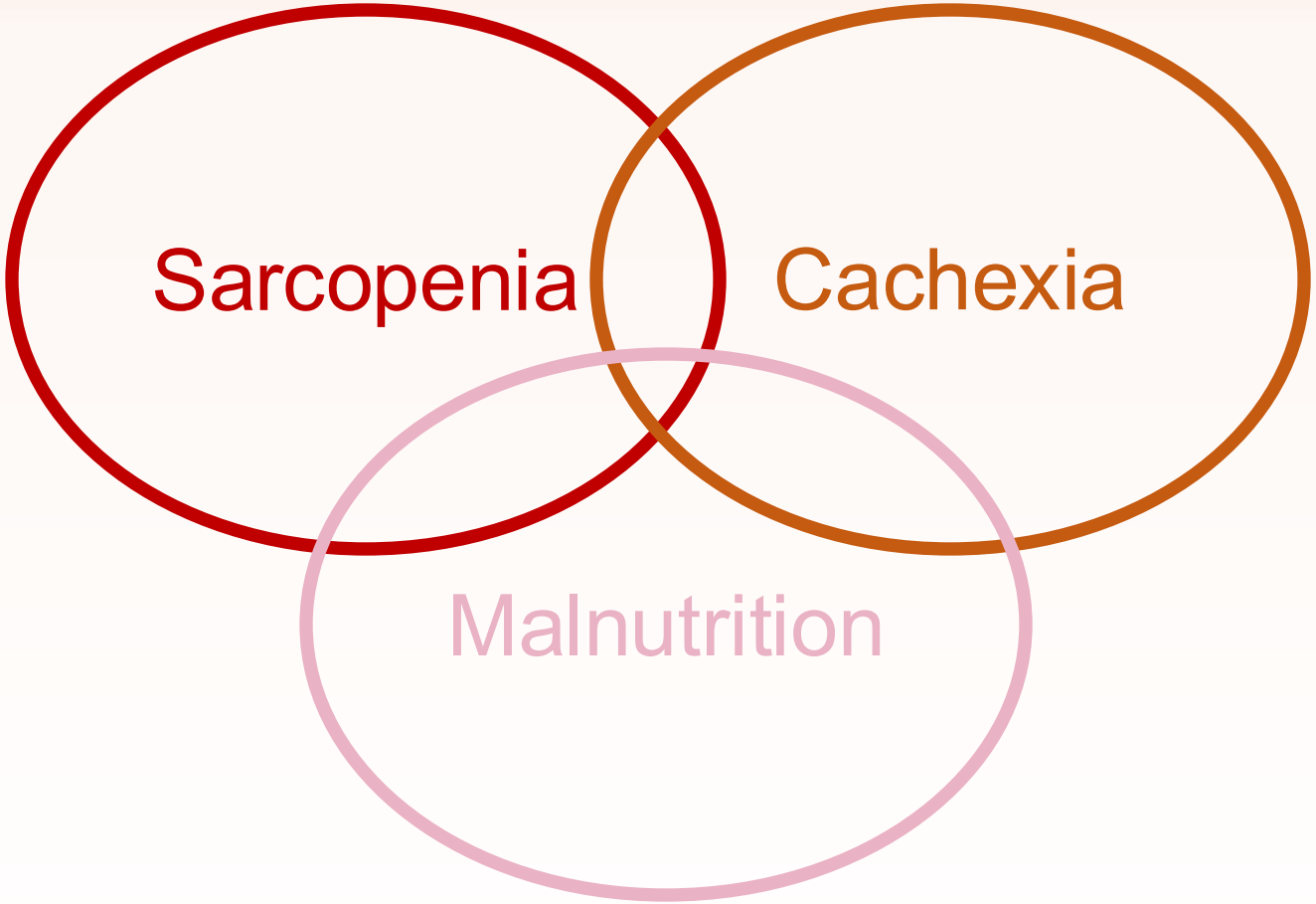
Muscle Wasting in Heart Failure

Malnutrition and Dietary Patterns

Developing Rx for Cardiac Cachexia

Disclosures: Research funded by National Institutes of Health NHLBI and NCATS (current), American Heart Association (past), CareDx (SHORE Registry, past)

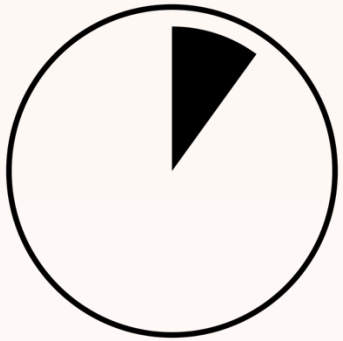
Disambiguation of Related Wasting Constructs



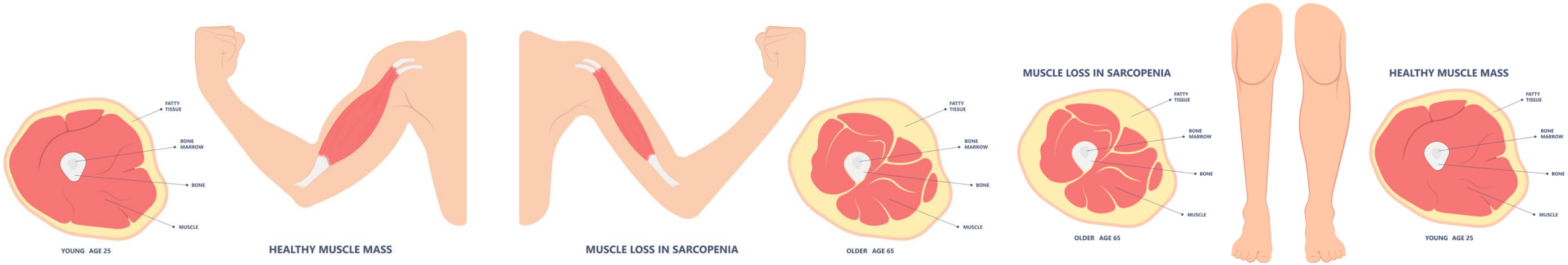
Sousa-Santos AR, Afonso C, Borges N, Santos A, Padrao P, Moreira P and T FA. Sarcopenia, Physical Frailty, Undernutrition And Obesity Cooccurrence Among Portuguese Community-dwelling Older Adults: Results From Nutrition UP 65 Cross-sectional Study. BMJ Open. 2020;10:e033661.

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)



~10% of healthy 60-70 year olds

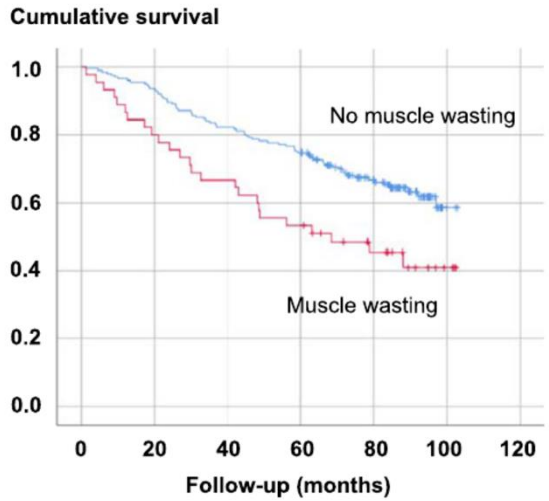


Anker SD et al. Wasting As Independent Risk Factor For Mortality In Chronic Heart Failure. *The Lancet.* 1997;349:1050-53.
von Haehling S, et al. Muscle Wasting As An Independent Predictor Of Survival In Patients With Chronic Heart Failure. *J Cachexia Sarcopenia Muscle.* 2020;11:1242-1249.

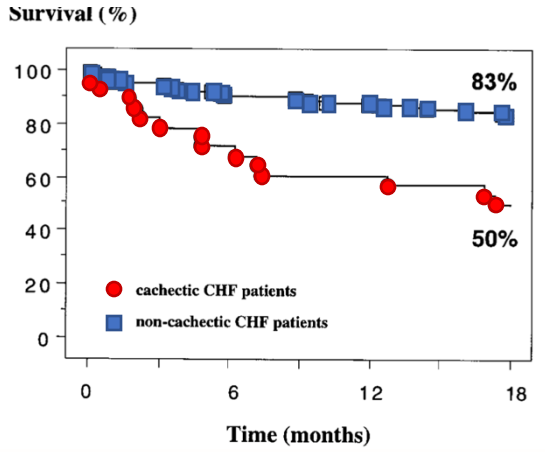
Muscle Wasting Disorders in Patients with HF

- **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.

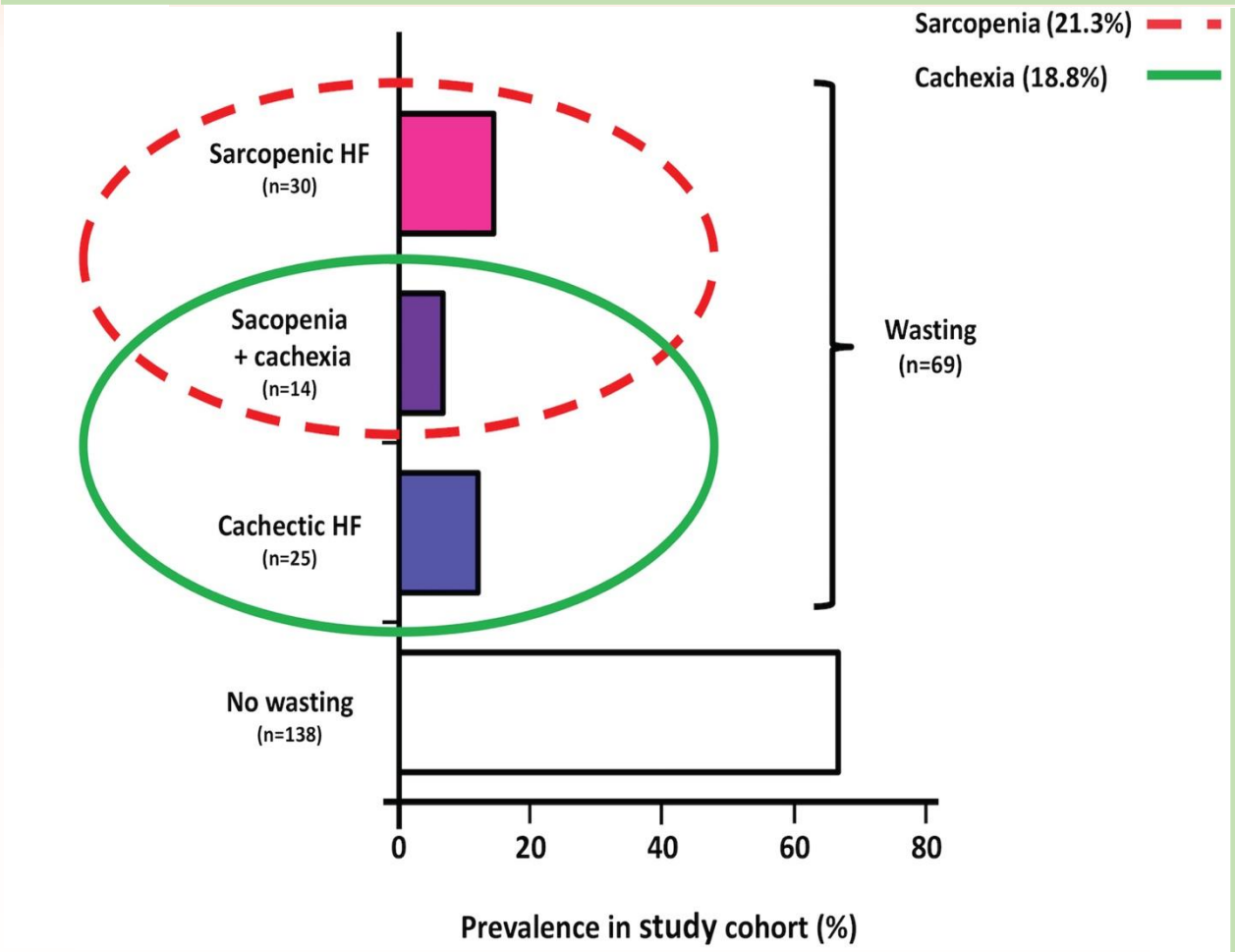
Prevalence of Muscle Wasting in HF

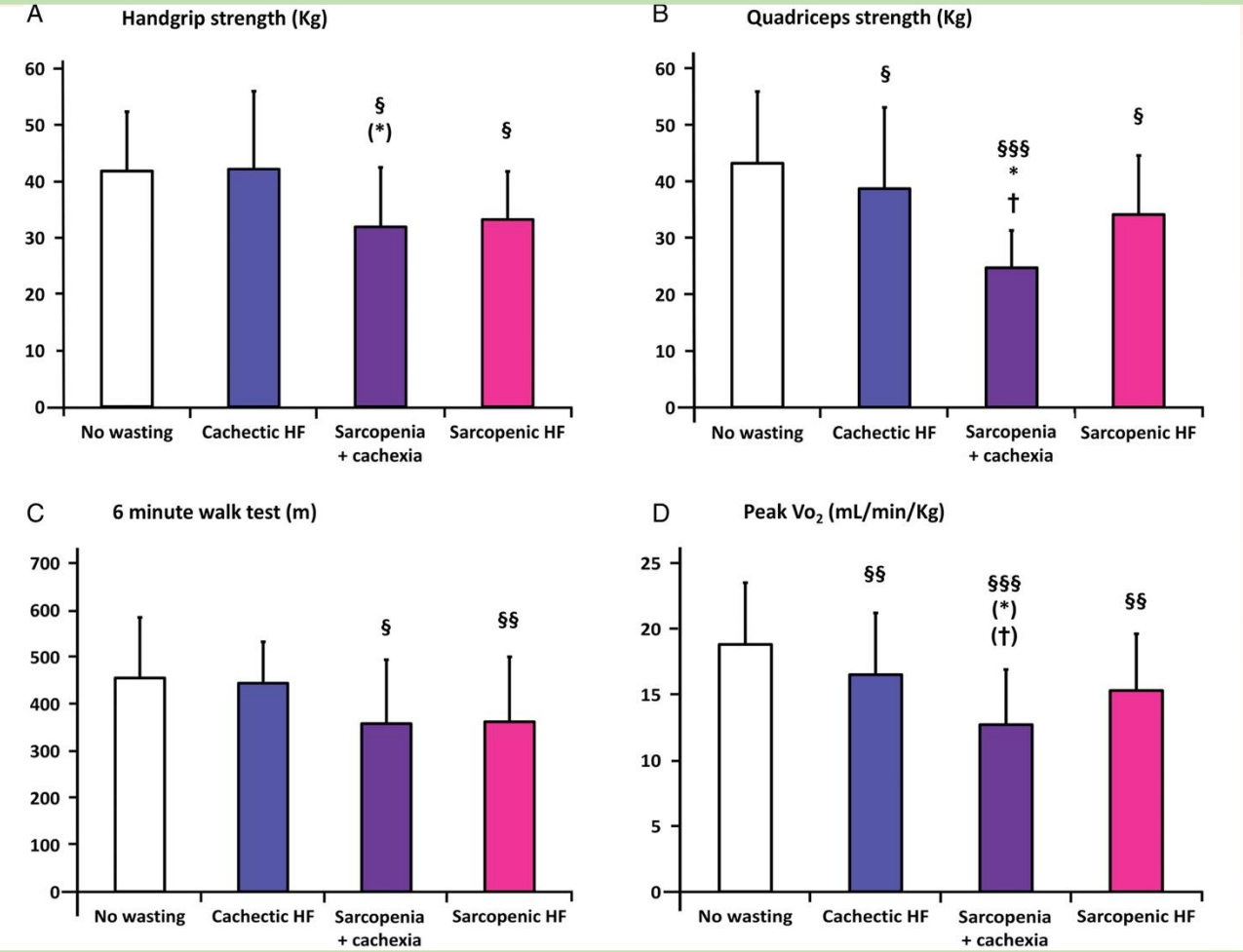
~20%

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

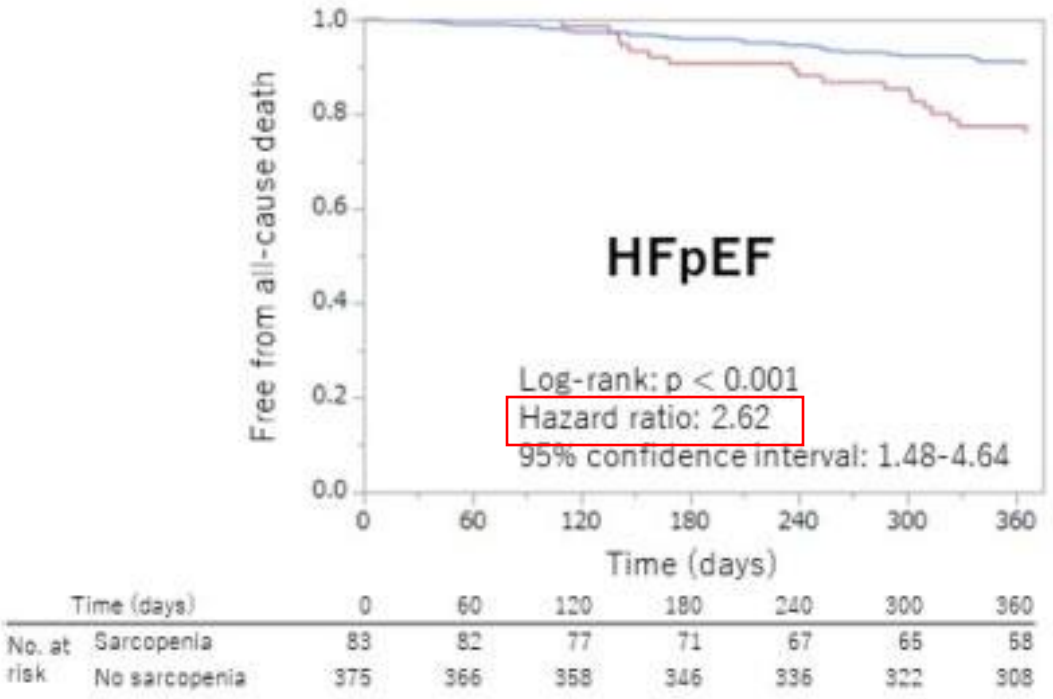
HF Functional Implications of Muscle Wasting

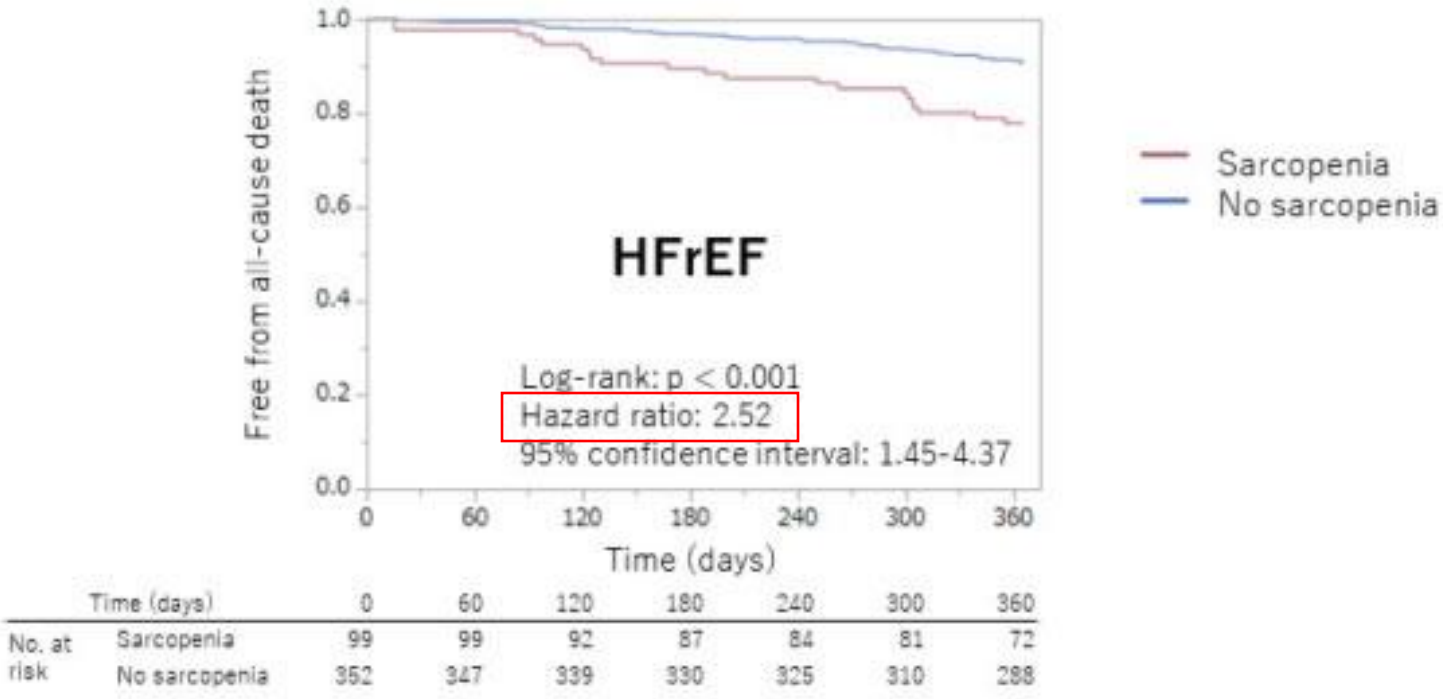




Emami A, Saitoh M, Valentova M, Sandek A, Evertz R, Ebner N, Loncar G, Springer J, Doehner W, Lainscak M, Hasenfuss G, Anker SD and von Haehling S. Comparison Of Sarcopenia And Cachexia In Men With Chronic Heart Failure: Results From The Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *Eur J Heart Fail*. 2018;20:1580-1587.

HF Mortality Implications of Muscle Wasting

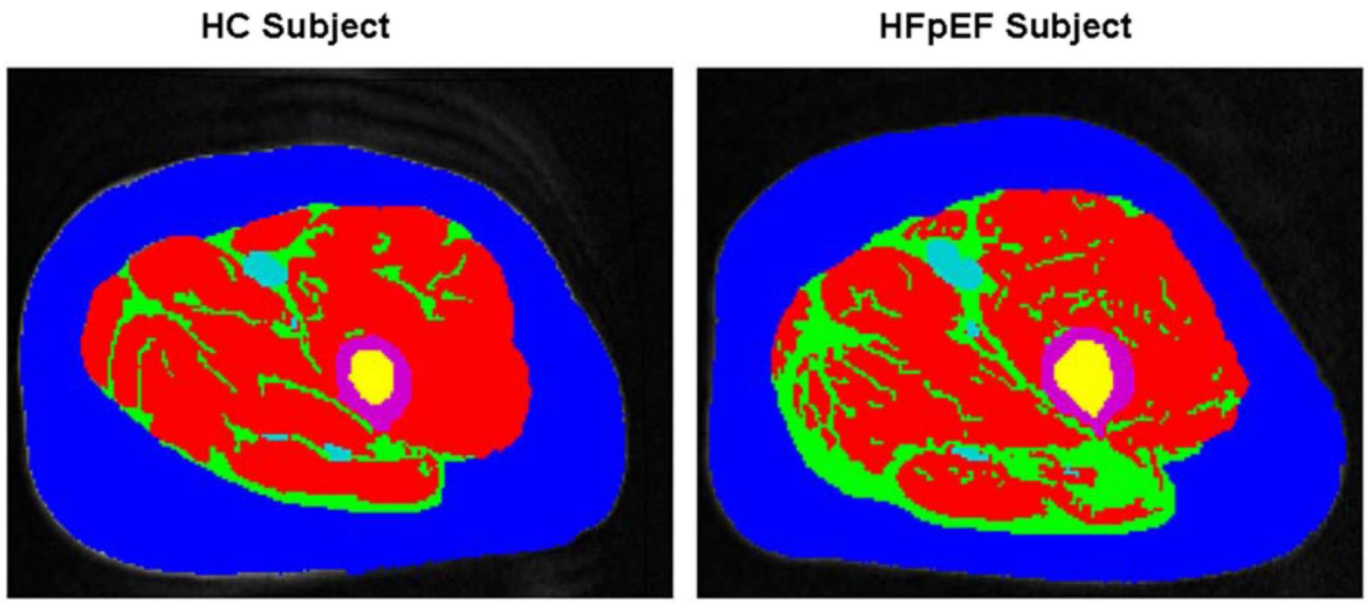




Sarcopenia independently associated with 1-year mortality in both HFpEF and HFrEF:
adjusted HR 2.42 (95% CI 1.36, 4.32) p=0.003 in HFpEF; and HR 2.02 (1.08, 3.75) p=0.027 in HFrEF

Konishi M, Kagiyama N, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Misumi T, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Makino A, Oka K, Momomura SI and Matsue Y. Impact Of Sarcopenia On Prognosis In Patients With Heart Failure With Reduced And Preserved Ejection Fraction. *Eur J Prev Cardiol.* 2021;28:1022-1029.

Muscle Wasting and Intermuscular Fat as a Component of HFpEF Multi-Organ Pathophysiology



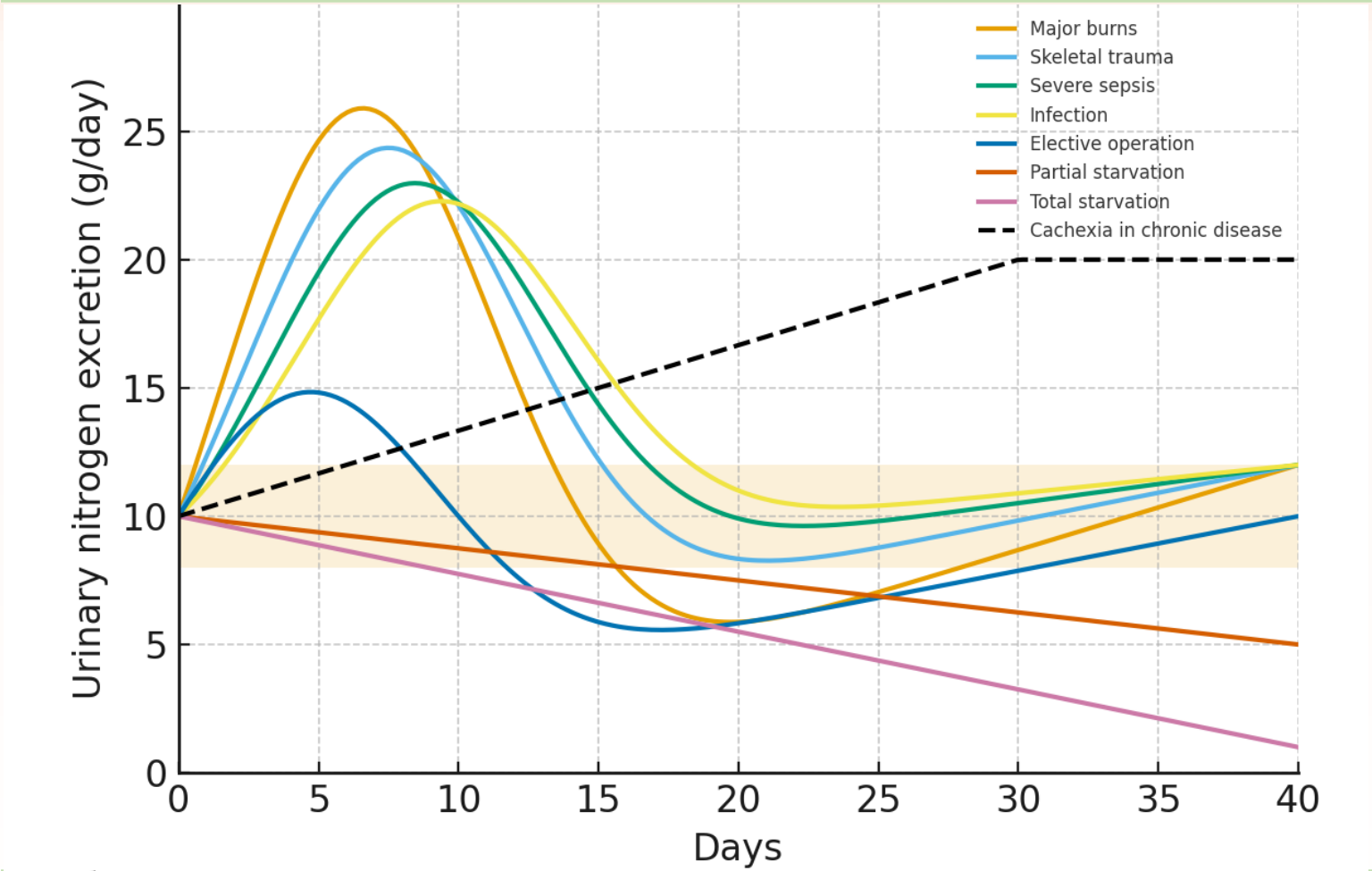
green = intermuscular fat
red = skeletal muscle

Also: **Reduced proportion of oxidative type I "slow twitch" muscle fibers vs glycolytic type II fibers**
Reduced muscle capillary density

Currently unclear if outcomes with **sarcopenia plus obesity** are any worse than for sarcopenia alone for patients with HF
(or general elderly populations)

Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J and Kitzman DW. Skeletal Muscle Composition And Its Relation To Exercise Intolerance In Older Patients With Heart Failure And Preserved Ejection Fraction. *Am J Cardiol.* 2014;113:1211-6.
Zakeri R and Cowie MR. Heart Failure With Preserved Ejection Fraction. *Heart.* 2018;104:377.

Muscle Protein Catabolism → Increased Nitrogen Excretion



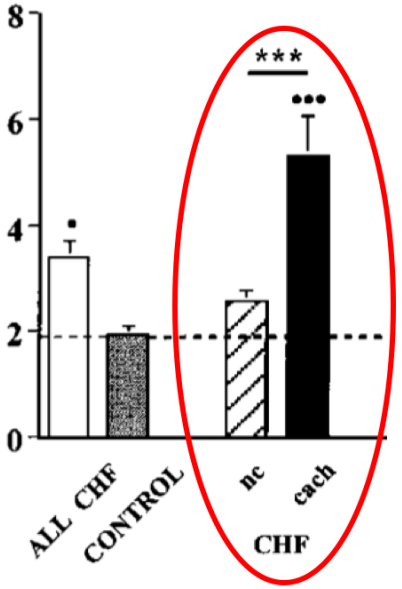
Cardiac cachexia: highly catabolic state, protein wasting into urinary nitrogen

Aka why Malnutrition and Cachexia are not the same process!

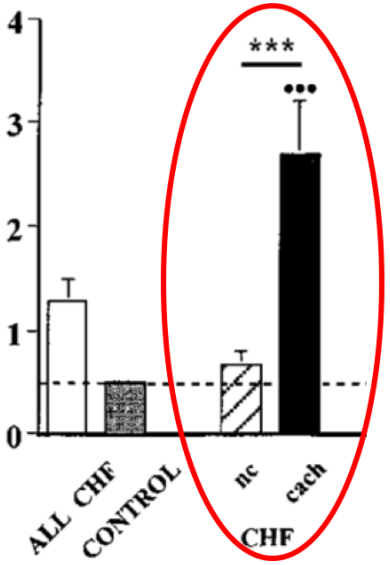
Adapted using ChatGPT 5.1 from: Long CL, et al. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. *JPEN J Parenter Enteral Nutr*. 1979;3:452–6.

Molecular Signals of Cardiac Cachexia Long Recognized

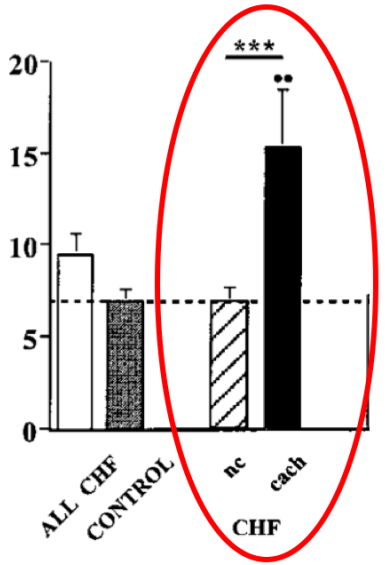
Norepinephrine



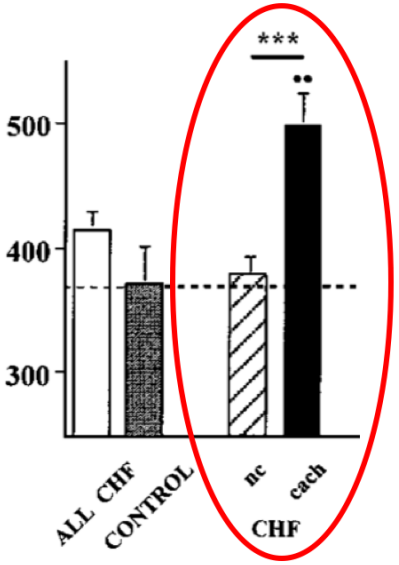
Epinephrine



Tumor Necrosis Factor-α

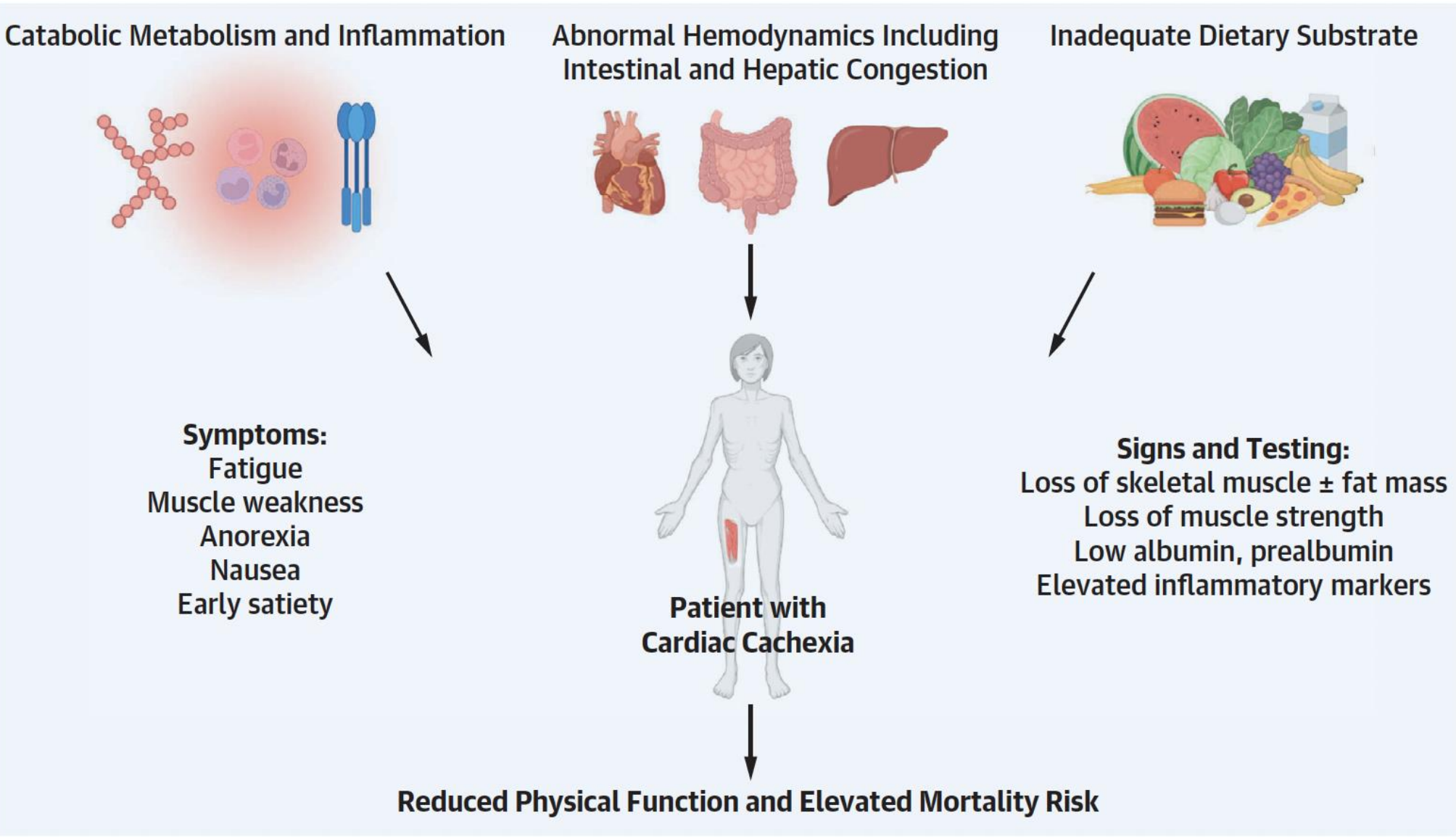


Cortisol



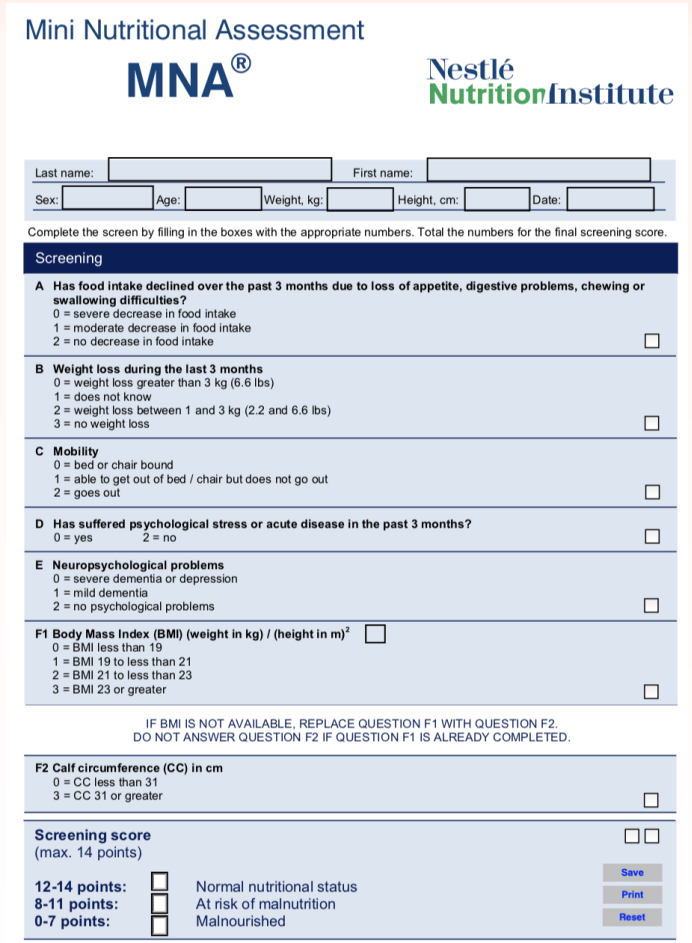
Anker SD and Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. *Chest*. 1999;115:836–47.

CENTRAL ILLUSTRATION Proposed Mechanisms, Symptoms, Signs, and Testing for Patients With Cardiac Cachexia



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;12:1645-60.

Malnutrition Screening for Patients with HF



Mini Nutritional Assessment

MNA®

Nestlé Nutrition Institute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers. Total the numbers for the final screening score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems

F1 Body Mass Index (BMI) (weight in kg) / (height in m)²
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater

IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2.
DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.

F2 Calf circumference (CC) in cm
0 = CC less than 31
3 = CC 31 or greater

Screening score
(max. 14 points)

12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished

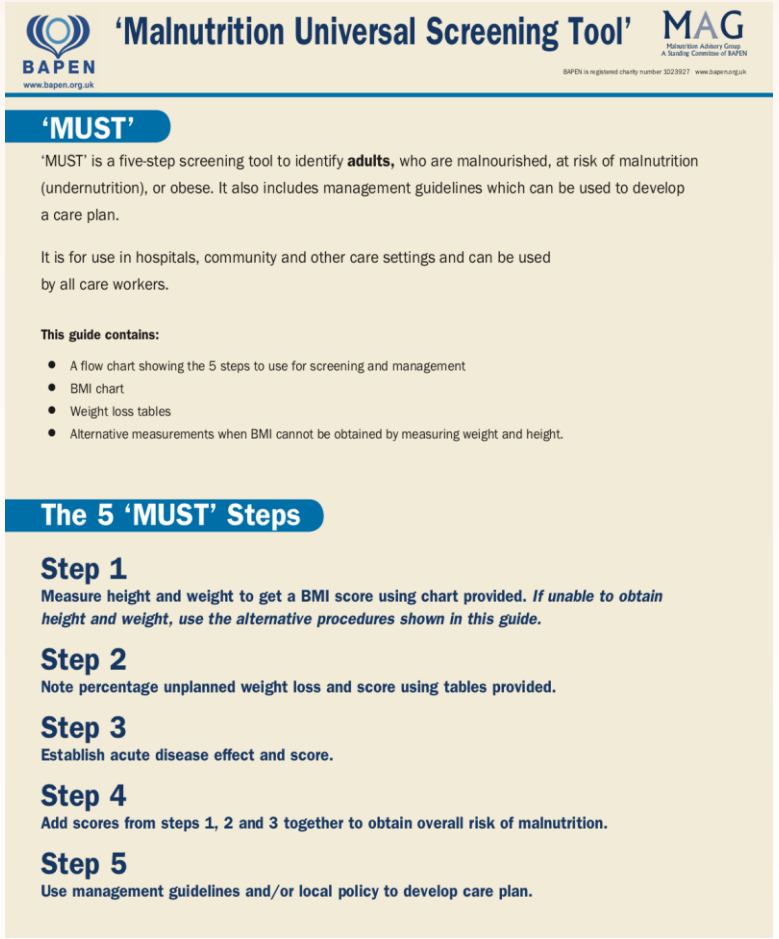
Save Print Reset

SNAQ

Short Nutritional Assessment Questionnaire

- Did you lose weight unintentionally?
  More than 6 kg in the last 6 months
  More than 3 kg in the last month
- Did you experience a decreased appetite over the last month?
- Did you use supplemental drinks or tube feeding over the last month?

● no intervention
●● moderately malnourished; nutritional intervention
●●● severely malnourished; nutritional intervention and treatment dietician



BAPEN www.bapen.org.uk

'Malnutrition Universal Screening Tool'

MAG Malnutrition Advisory Group A Standing Committee of BAPEN

BAPEN is registered charity number 1023927 www.bapen.org.uk

'MUST'

'MUST' is a five-step screening tool to identify **adults,** who are malnourished, at risk of malnutrition (undernutrition), or obese. It also includes management guidelines which can be used to develop a care plan.

It is for use in hospitals, community and other care settings and can be used by all care workers.

This guide contains:

- A flow chart showing the 5 steps to use for screening and management
- BMI chart
- Weight loss tables
- Alternative measurements when BMI cannot be obtained by measuring weight and height.

The 5 'MUST' Steps

Step 1
Measure height and weight to get a BMI score using chart provided. ***If unable to obtain height and weight, use the alternative procedures shown in this guide.***

Step 2
Note percentage unplanned weight loss and score using tables provided.

Step 3
Establish acute disease effect and score.

Step 4
Add scores from steps 1, 2 and 3 together to obtain overall risk of malnutrition.

Step 5
Use management guidelines and/or local policy to develop care plan.

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.

Malnutrition Diagnosis for Patients with HF

Clinical Nutrition: A.S.P.E.N./ Academy of Nutrition and Dietetics Consensus: Characteristics of Protein-Calorie Malnutrition	Malnutrition in the Context of Acute Illness or Injury		Malnutrition in the Context of Chronic Illness		Malnutrition in Context of Social/ Environmental Circumstances (starvation)	
Protein-Calorie Malnutrition Occurs at ALL Body Mass Index	**Moderate** Protein-Calorie Malnutrition (E44.0)	**Severe** Protein-Calorie Malnutrition (E43)	**Moderate** Protein-Calorie Malnutrition (E44.0)	**Severe** Protein-Calorie Malnutrition (E43)	**Moderate** Protein-Calorie Malnutrition (E44.0)	**Severe** Protein-Calorie Malnutrition (E43)
Clinical Characteristics: include all that apply						
1) **Energy Intake** Dietitian obtains diet history; calculates energy (and protein) demand. Suboptimal intake is calculated as percentage of estimated needs over time.	<75% of estimated energy requirement for >7 days	≤50% of estimated energy requirement for ≥5 days	<75% of estimated energy requirement for ≥1 month	≤75% of estimated energy requirement for ≥1 month	<75% of estimated energy requirement for ≥3 months	≤50% of estimated energy requirement for ≥1 month
2) **Weight Loss** Evaluate weight loss in light of other clinical findings, including hydration status. Weight change over time is reported as a percentage of weight lost (or weight change) from baseline. Equation: original weight minus current weight divided by original weight x 100 = % weight change	% Time 1-2 1 wk 5 1 mo 7.5 3 mo	% Time >2 1 wk >5 1 mo >7.5 3 mo	% Time 5 1 mo 7.5 3 mo 10 6 mo 20 1 yr	% Time >5 1 mo >7.5 3 mo >10 6 mo >20 1 yr	% Time 5 1 mo 7.5 3 mo 10 6 mo 20 1 yr	% Time >5 1 mo >7.5 3 mo >10 6 mo >20 1 yr
3) **Muscle Mass - Physical Assessment (all noted)** Muscle loss (e.g., wasting of the temples (temporalis muscle), clavicles (pectoralis and deltoids), shoulders (deltoids), interosseous muscles, scapula (latissimus dorsi, trapezius, deltoids), thigh (quadriceps), and calf (gastrocnemius).	Mild Depletion	Moderate Depletion	Mild Depletion	Severe Depletion	Mild Depletion	Severe Depletion
4) **Body Fat - Physical Assessment (all noted)** Loss of subcutaneous fat (e.g., orbital, triceps, overlying ribs).	Mild Depletion	Moderate Depletion	Mild Depletion	Severe Depletion	Mild Depletion	Severe Depletion
5) **Fluid Accumulation- Physical Assessment** Generalized or localized fluid accumulation evident on exam (extremities, vulvar/scrotal edema, or ascites). Weight loss is often marked by generalized fluid retention (edema), and fluid weight gain may be observed.	Mild	Moderate to Severe	Mild	Severe	Mild	Severe
6) **Functional Assessment**: Grip Strength American Society of Hand Therapists Method 3rd ed. 2016	NA	Measurably Reduced	NA	Measurably Reduced	NA	Measurably Reduced

White JV, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr*. 2012;36:275–83.

Malnutrition Prevalence in HFrEF

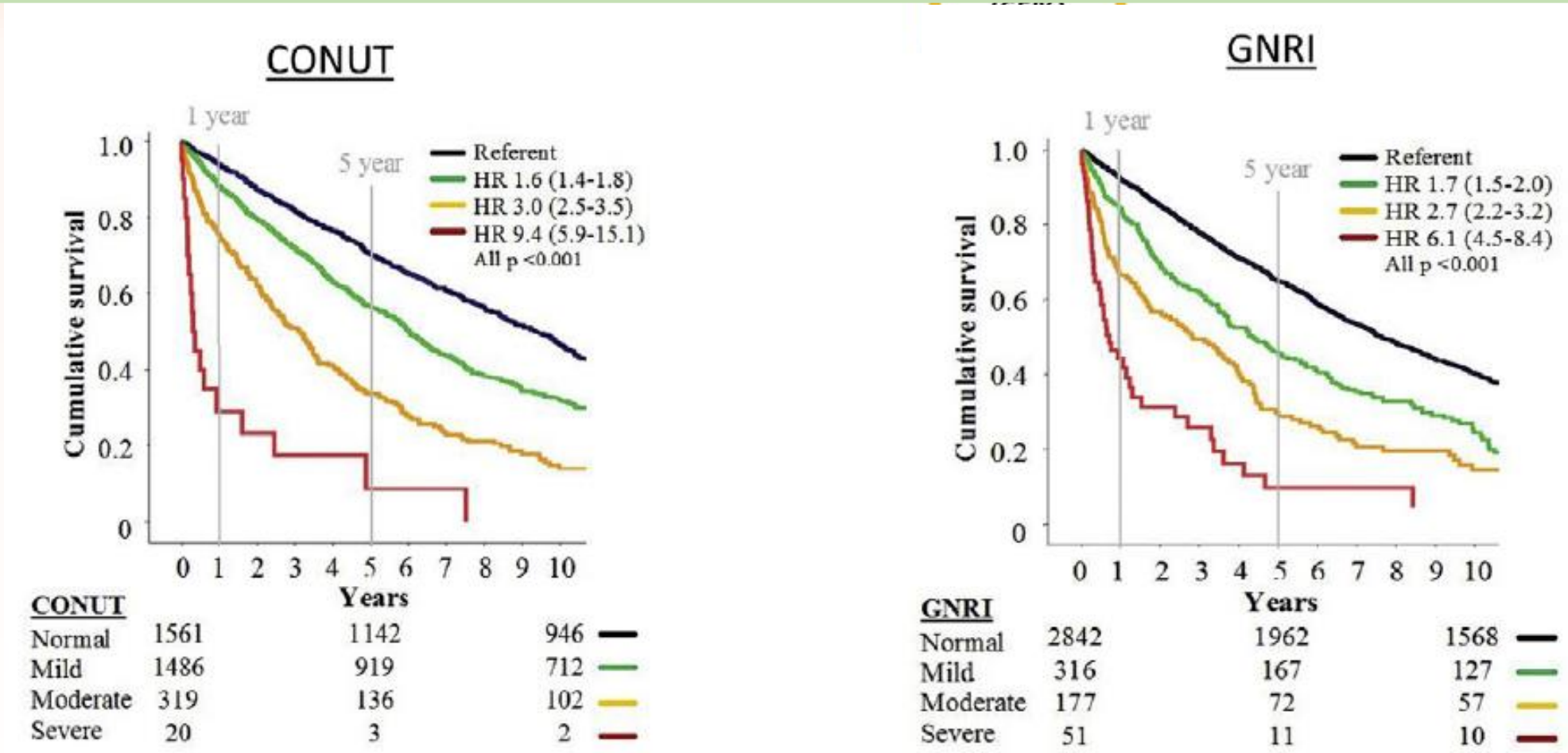
	Degree of malnutrition		
	Mild	Mod	Sev
CONUT	42%	11%	1%
GNRI	11%	6%	2%
PNI	-	4%	4%

MALNUTRITION PHENOTYPE

Elderly
Male
Anemia
Atrial fibrillation
↓Renal function
↓Mobility
↓BMI
↑NYHA class
↑NTproBNP
Takes loop diuretic

Sze S, et al. Prevalence and Prognostic Significance of Malnutrition Using 3 Scoring Systems Among Outpatients With Heart Failure: A Comparison With Body Mass Index. *JACC Heart Fail*. 2018;6:476–486.

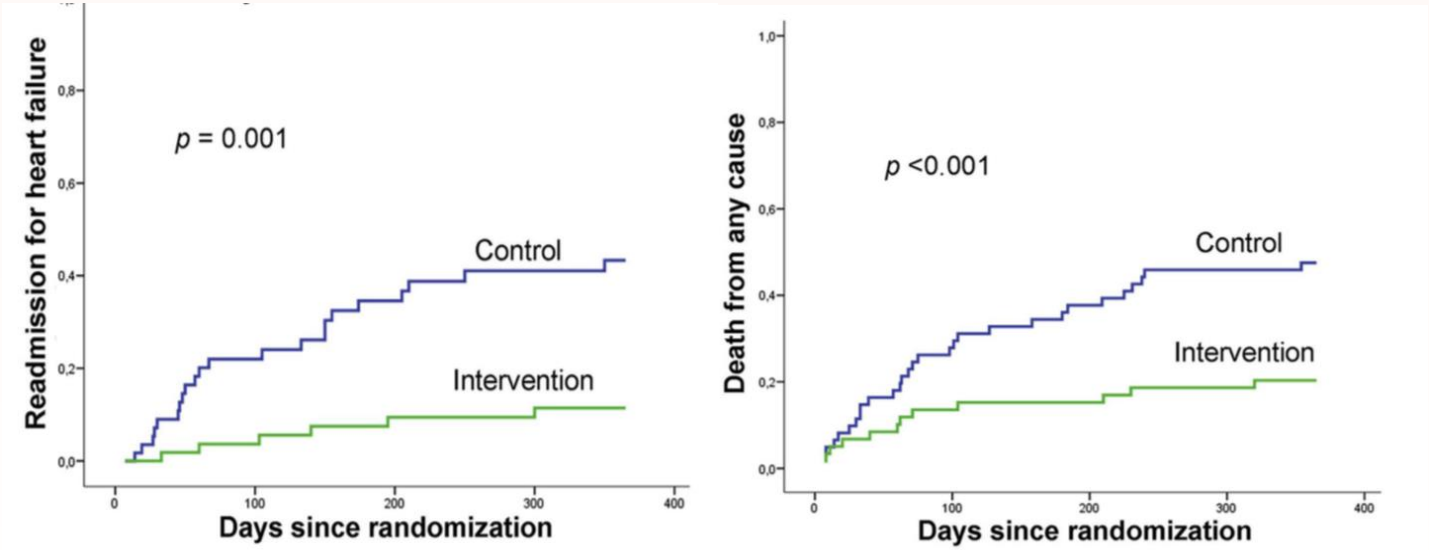
Malnutrition and Survival in Patients in with HF



Sze S, et al. Prevalence and Prognostic Significance of Malnutrition Using 3 Scoring Systems Among Outpatients With Heart Failure: A Comparison With Body Mass Index. *JACC Heart Fail*. 2018;6:476–486.

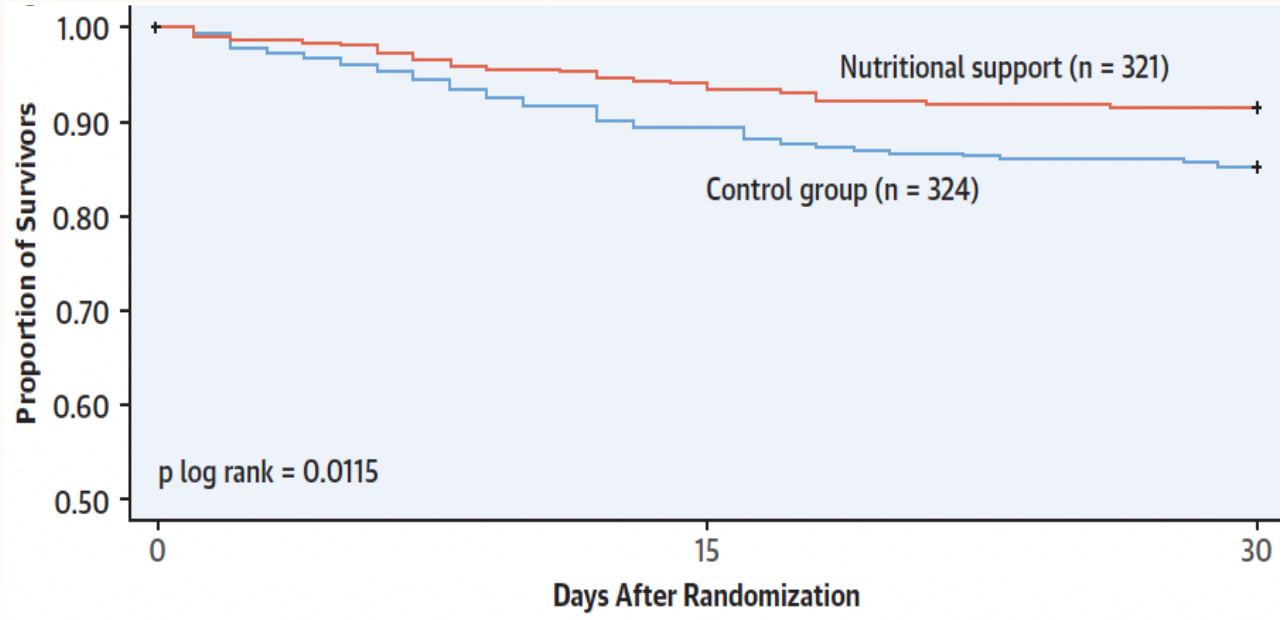
PICNIC: Treating Malnutrition Reduces Mortality and Readmissions after HF Hospitalization

- Spanish study recruiting 120 patients hospitalized with HF and screening in for malnutrition on MNA score <17 points
- Randomized 1:1 to standard of care vs 6 months nutritional intervention: *diet optimization, specific recommendations, nutritional supplement prescriptions when indicated*

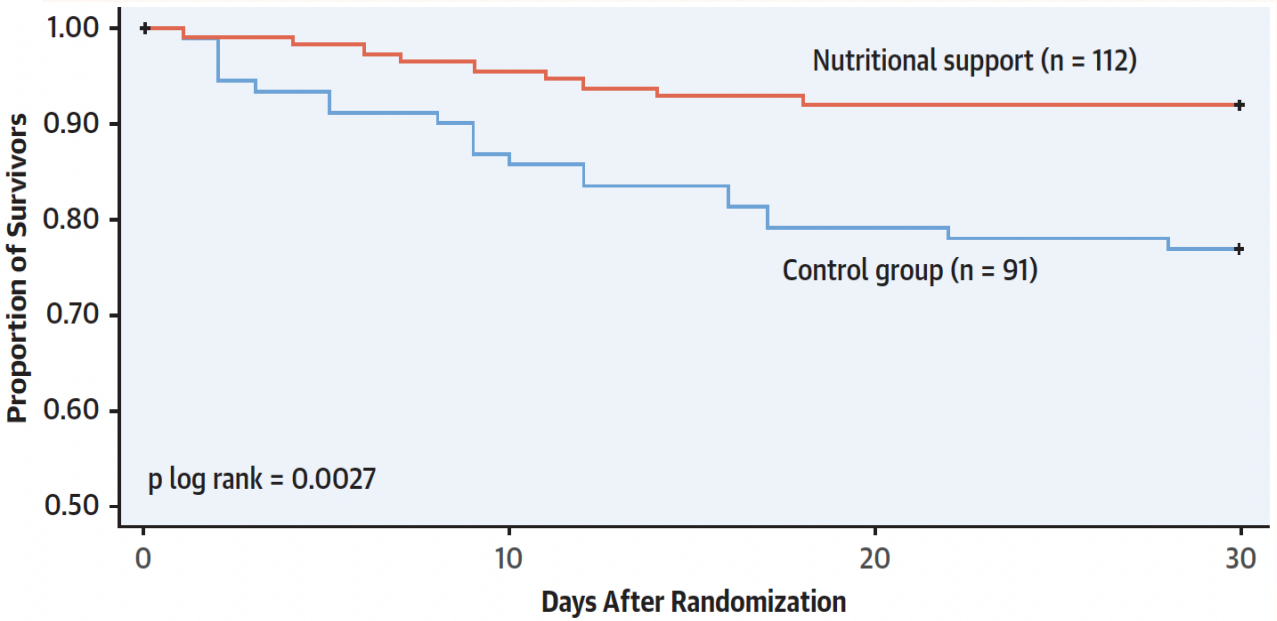


Bonilla-Palomas JL, et al. Nutritional Intervention in Malnourished Hospitalized Patients with Heart Failure. *Arch Med Res*. 2016;47:535–540.

EFFORT: Treating Malnutrition Reduces In-Hospital Mortality for Patients with Heart Failure



All inpatients with HF and malnutrition



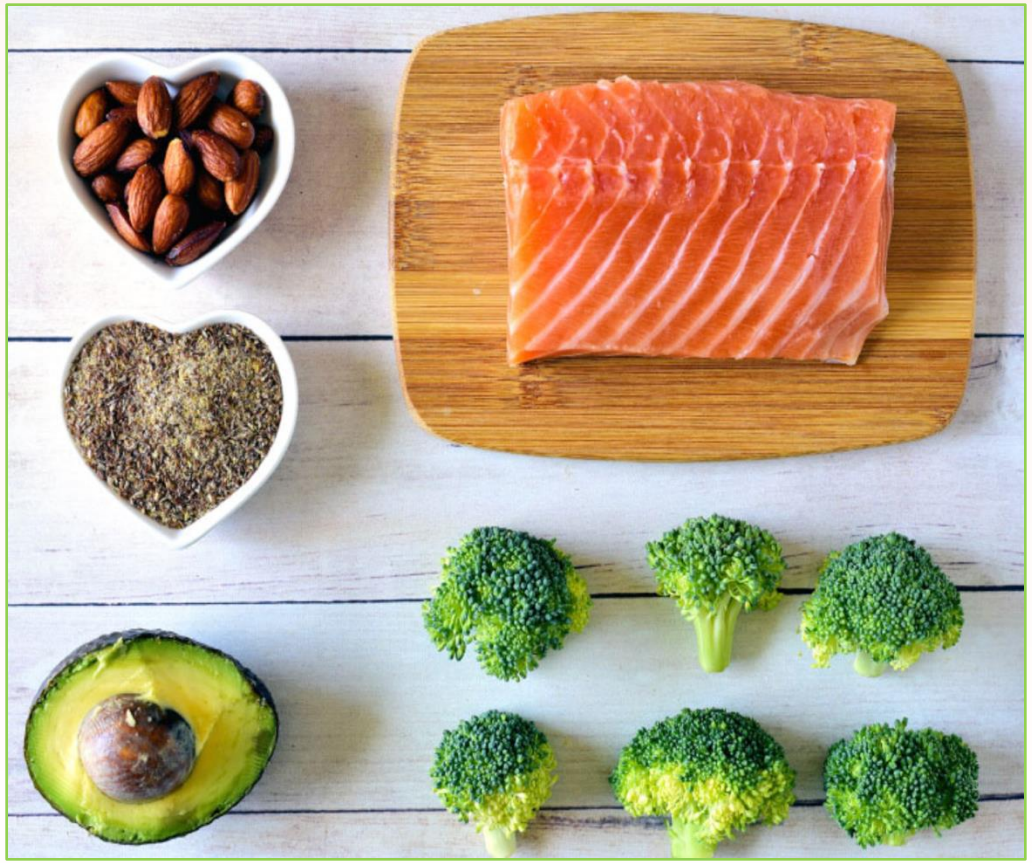
Subgroup with Nutritional Risk Score >4

Hersberger L, et al. Individualized Nutritional Support for Hospitalized Patients With Chronic Heart Failure. *J Am Coll Cardiol*. 2021;77:2307-2319.

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.

Outpatients with HF

At least one diet evaluation/counselling session by RDN (or other health professional with specialist nutrition knowledge)

Criteria for RDN consultation:

- BMI <20 or ≥30 kg/m² or unintentional edema-free weight loss >7.5% in prior 6-12 months
- Patients reporting <50% prior nutritional intake or 'at risk of malnutrition' on assessment tool e.g. SNAQ
- Diabetes or chronic kidney renal disease
- History of malabsorption or bariatric surgery
- Consideration for heart transplantation or mechanical circulatory support

Inpatients with HF

Criteria for RDN consultation:

- BMI <20 or ≥30 kg/m² or unintentional edema-free weight loss >7.5% in prior 6-12 months
- Patients reporting <50% prior nutritional intake or 'at risk of malnutrition' on assessment tool e.g. SNAQ
- Diabetes or chronic kidney disease
- History of malabsorption or bariatric surgery
- Consideration for heart transplantation or mechanical circulatory support
- Receiving/considered for tube feeds or TPN
- Hospitalized ≥7 days

Initial RDN HF evaluation should include: medical/surgical, diet, weight and social histories, at least 24-hour food and supplement intake record

Initial RDN HF counselling should include: sodium restriction, healthy diet composition, interventions for specific problems identified

HF + Cachexia or Malnutrition

- RDN develops individualized nutrition plan with patient, caregivers, clinicians; may include protein-calorie supplementation for at least 1.1 g/kg/day intake and specific weight gain goals
- RDN reassessment every 4-12 weeks, as indicated
- If dietary/weight gain goals not met, RDN initiates consideration of appetite stimulants and/or tube feeing/TPN with HF clinicians
- If meeting sarcopenia criteria and physically able, consider referral for graded exercise

Routine HF monitoring

- RDN, or other health professional with specialist nutrition knowledge, remains a resource to enhance optimal dietary composition
- Ideally, annual nutrition re-evaluation as above

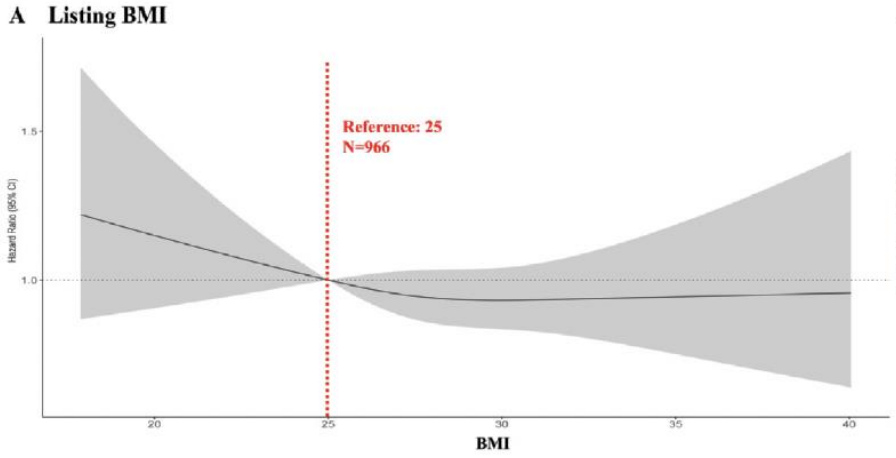
HF + Obesity

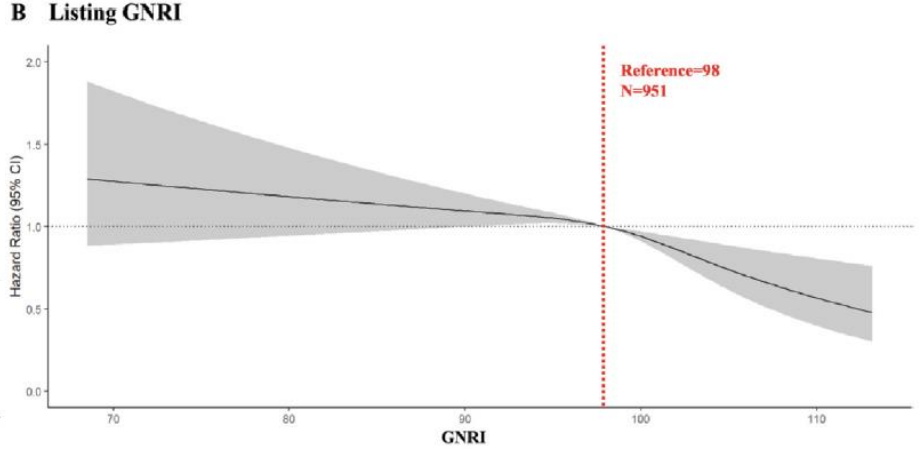
- RDN develops individualized nutrition plan with patient, caregivers, clinicians; may include low-calorie meal replacement with specific dietary/weight loss goals
- If physically able, consider referral for graded exercise
- RDN reassessment every 4-12 weeks, as indicated
- If dietary/weight loss goals not met, RDN initiates consideration of specialist medical and/or surgical weight loss consultation in an experienced program

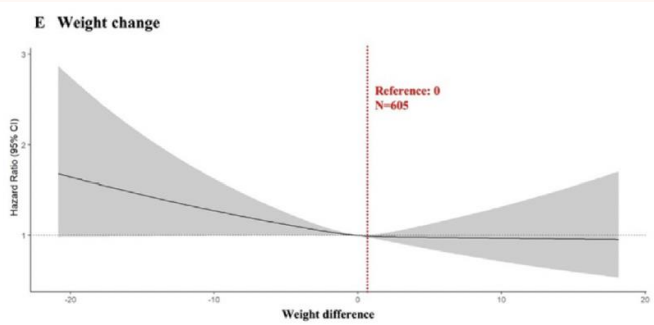
Abbreviations: HF, heart failure; RDN, Registered Dietician Nutritionist; SNAQ, short nutritional assessment questionnaire; TPN, total parenteral nutrition

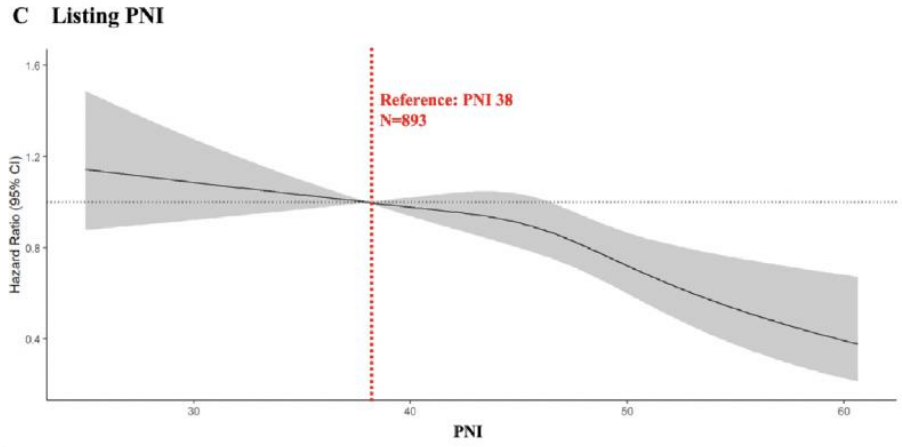
Limitations: Access to RDN, insurance coverage

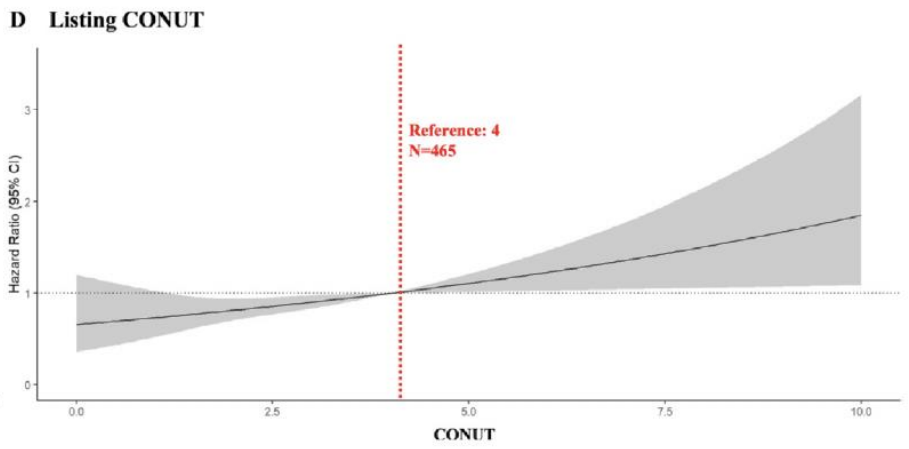
Malnutrition Risk at Heart Transplant *Listing* and Mortality







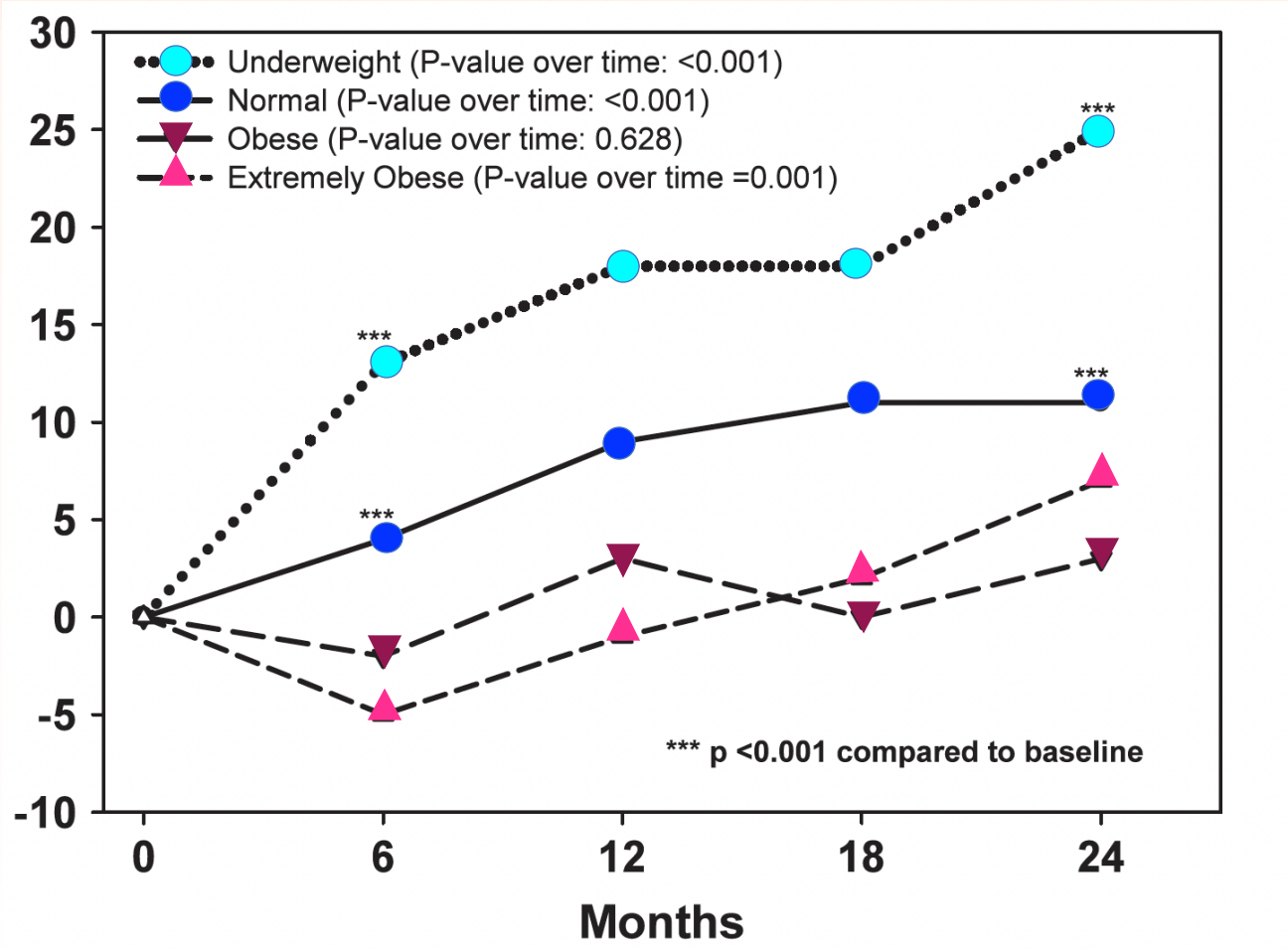




Yoo TK, Miyashita S, Stein A, Wu M, Read-Button LP, Kawabori M, Couper GS, Saltzman E and Vest AR. Malnutrition risk, weight loss, and subsequent survival in patients listed for heart transplantation. *JHLT Open*. 2025;7:100162.

LVAD Recipients Tend to Gain Weight During Support

% Change in BMI by baseline weight category for LVAD recipients in the HMII clinical trials



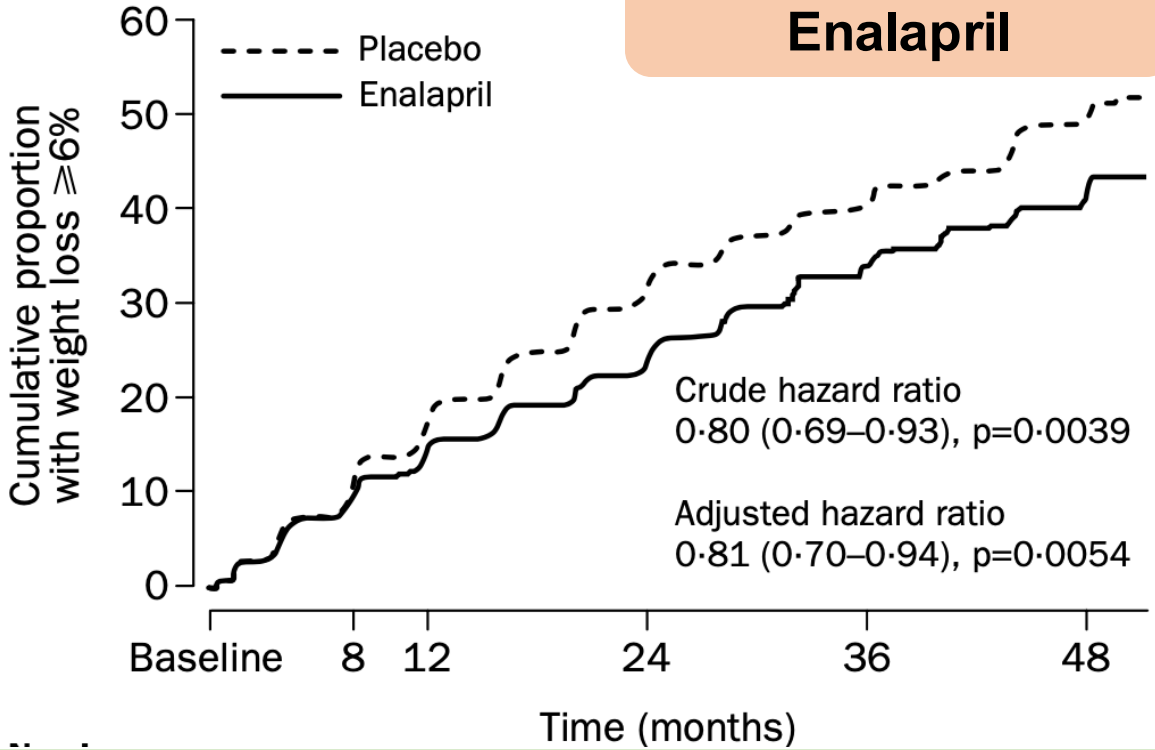
Emani S, et al. Patients With Low Compared With High BMI Gain More Weight After Implantation of a CF-LVAD. J Heart Lung Transplant 2013;32:31-35.

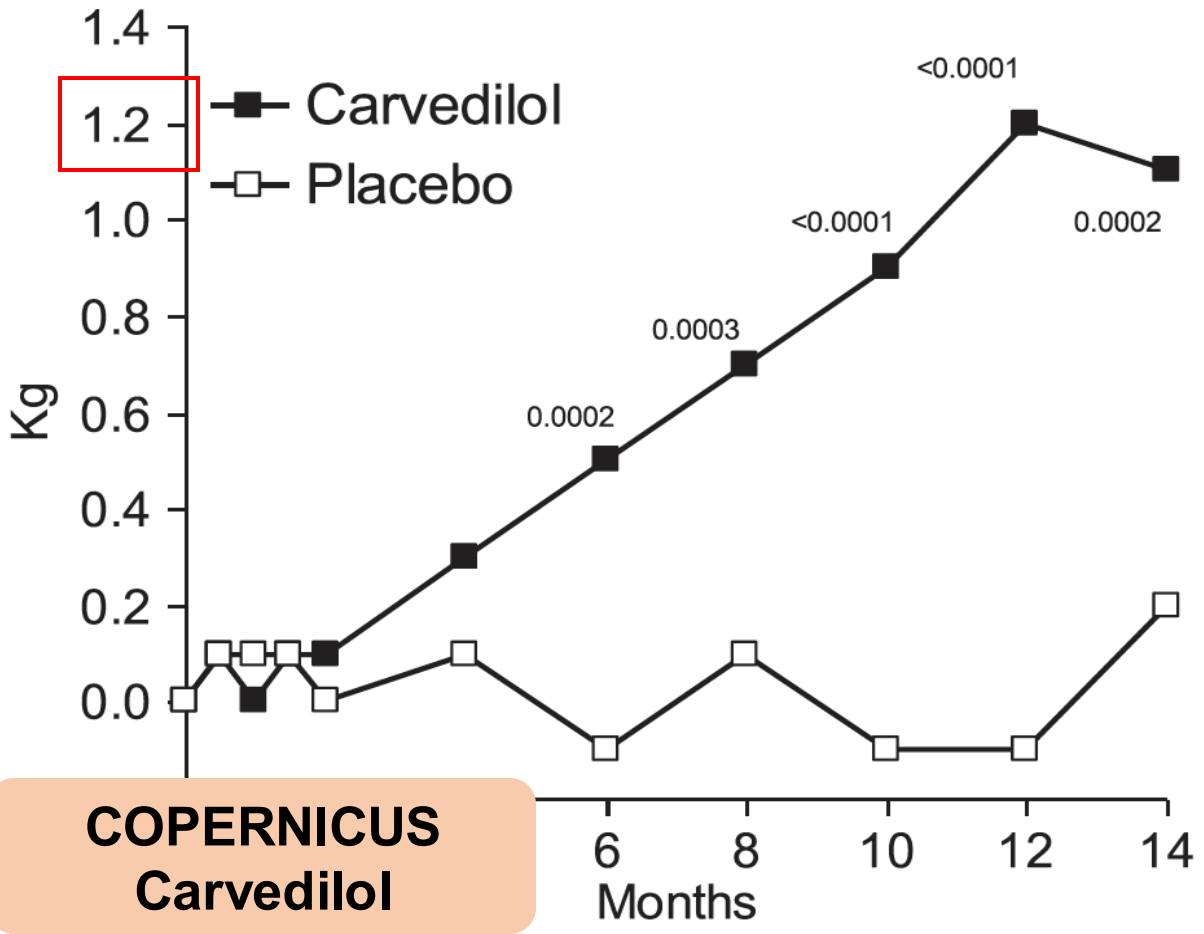
Jaiswal A, et al. Impact of Obesity on VAD Outcomes. J Card Fail. 2020;26:287-297.

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**

SOLVD
Enalapril





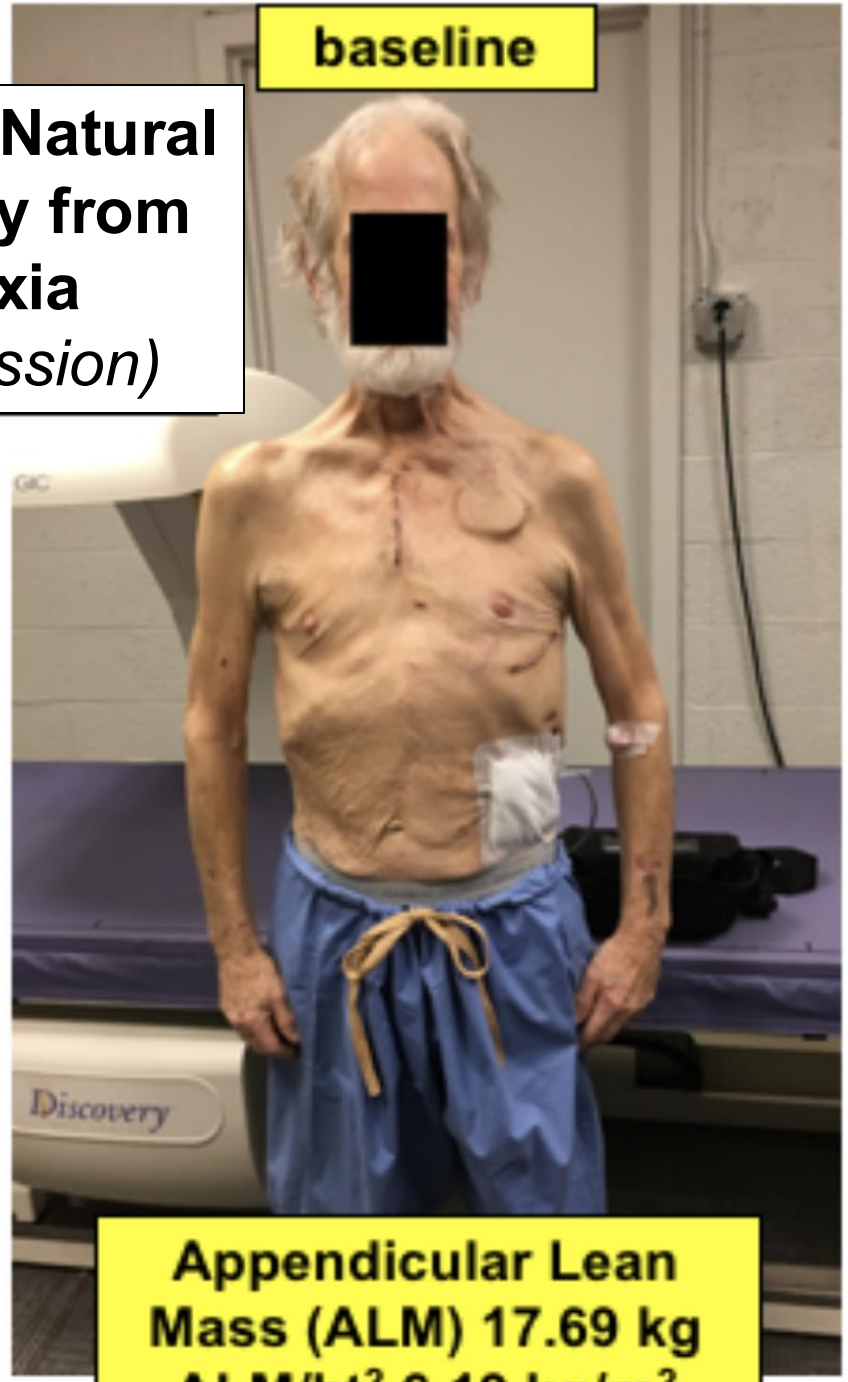
COPERNICUS
Carvedilol

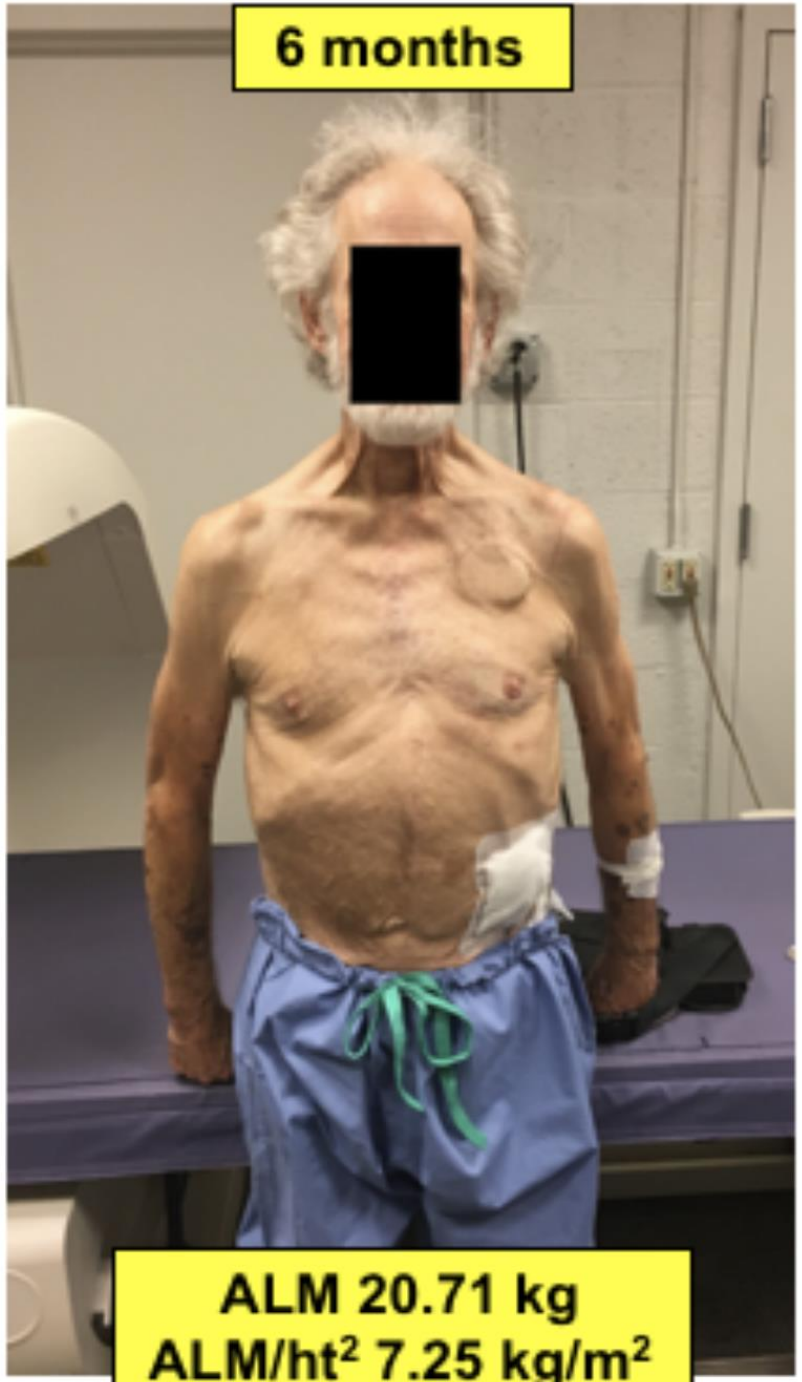
Anker SD, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet. 2003;361:1077-1083.

Coats AJS, et al. Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic HF. J Cachexia Sarc Muscle. 2017;8:549-

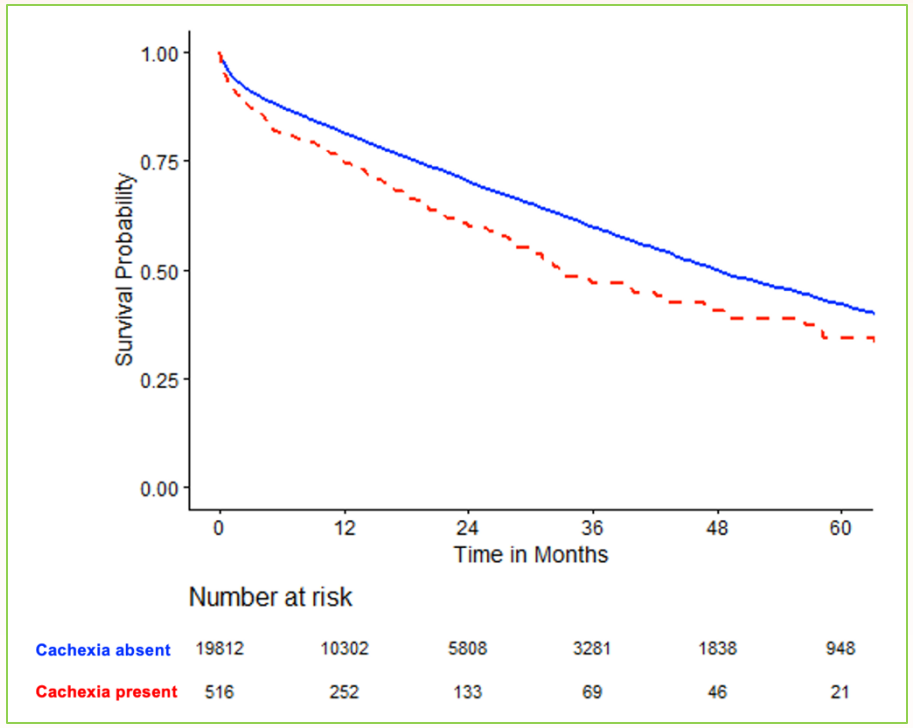
LVAD Support as a Natural Model for Recovery from Cardiac Cachexia

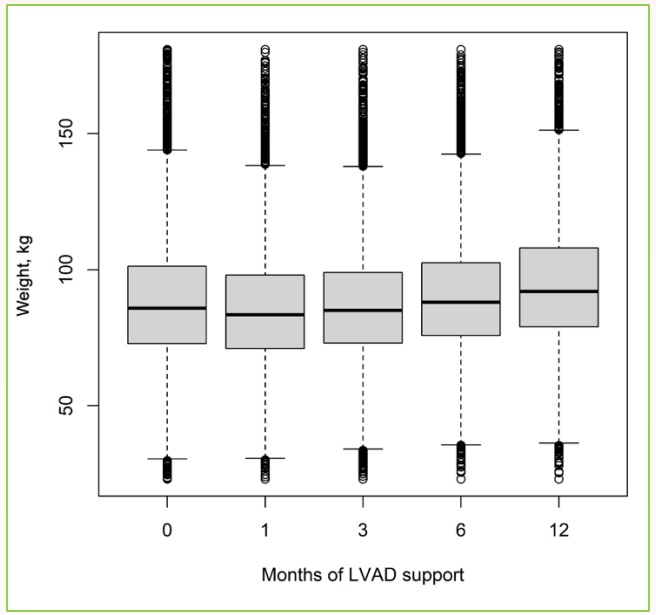
(with patient permission)

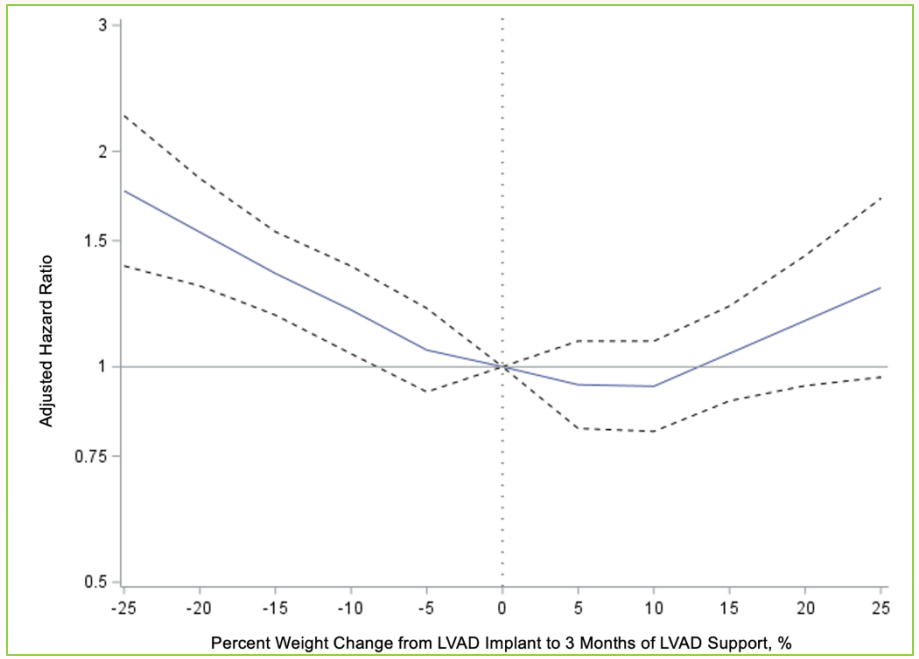




Does LVAD Therapy Improve Cardiac Cachexia?







Cachexia mortality aHR 1.23 (1.0-1.42)

Body weight increase during LVAD support

Early weight gain ≥5% assoc with survival

Vest AR, Price LL, Chanda A, Sweigart BA, Chery J, Lawrence M, Parsly L, Gulati G, Kiernan MS, Upshaw JN, Kawabori M, Couper GS and Saltzman E. Cardiac Cachexia in Left Ventricular Assist Device Recipients and the Implications of Weight Gain Early After Implantation. J Am Heart Assoc. 2023;e029086.

Skeletal Muscle Mass Recovery Early After LVAD Implantation in Patients with Advanced HFrEF

Prevalence of skeletal muscle wasting at LVAD implantation

52% sarcopenia

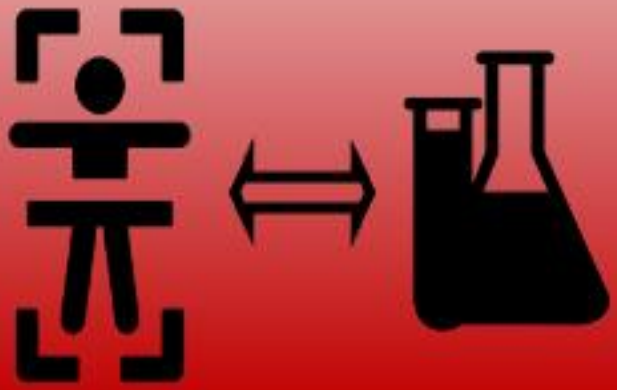
(percent of LVAD recipients meeting DXA criteria)

Change in fat free mass over the first 3 months of LVAD support

2.3 kg increase (CI 1.0, 3.5)

(mean change in fat free mass over first 3 months)

Agreement between DXA and deuterium fat free mass



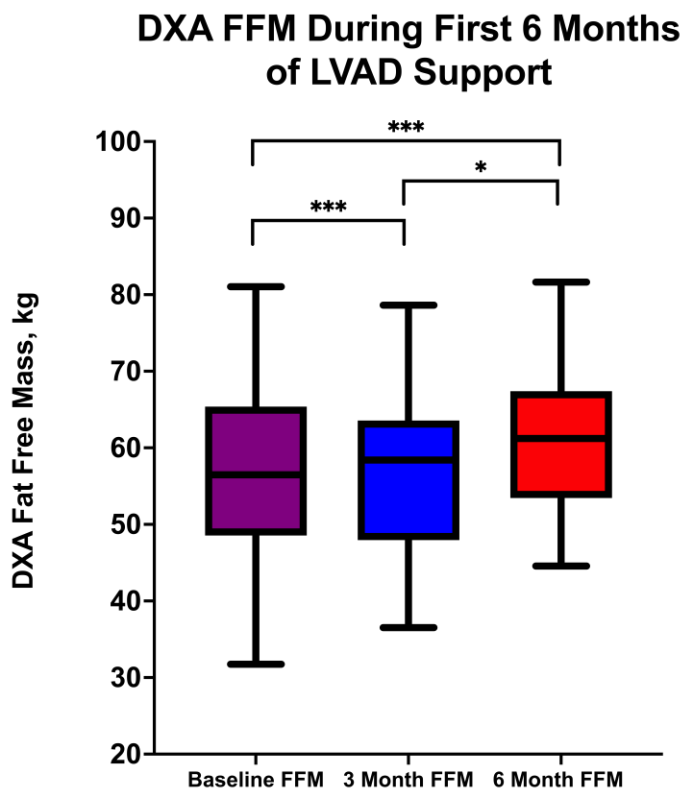
r=0.94, p<0.0001

(correlation for DXA vs deuterium fat free mass)

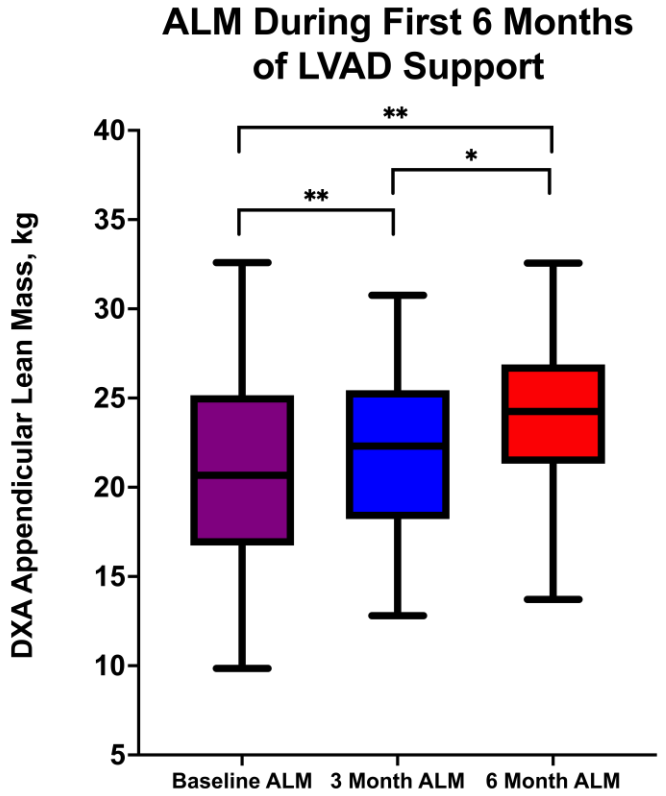
Vest AR et al. Skeletal Muscle Mass Recovery Early After Left Ventricular Assist Device Implantation in Patients with Advanced Systolic Heart Failure. Circ Heart Fail. 2022:101161CIRCHEARTFAILURE121009012.

Funded by an American Heart Association Scientist Development Grant

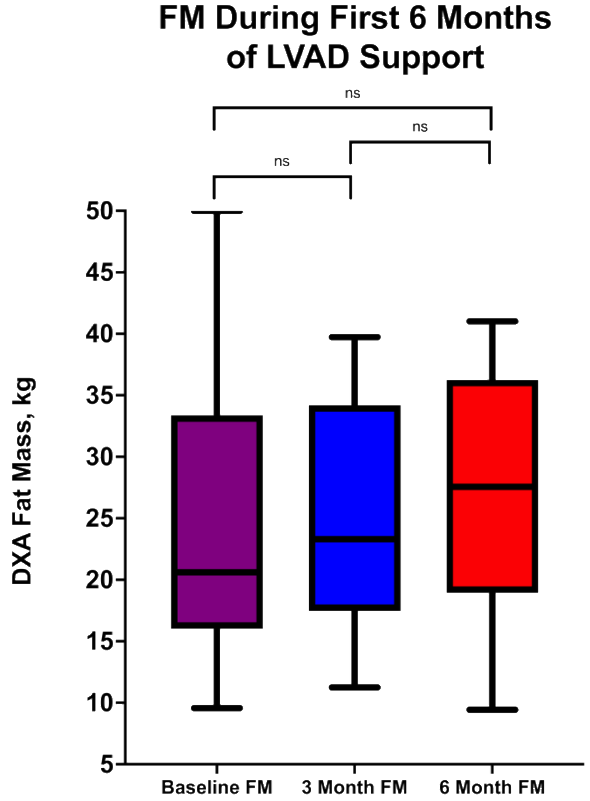
Skeletal Muscle Mass Recovery Early After LVAD Implantation in Patients with Advanced HFrEF



Mean	56.4	57.7	62.3
Std. Deviation	11.7	11.2	10.9
Number of values	27	23	17



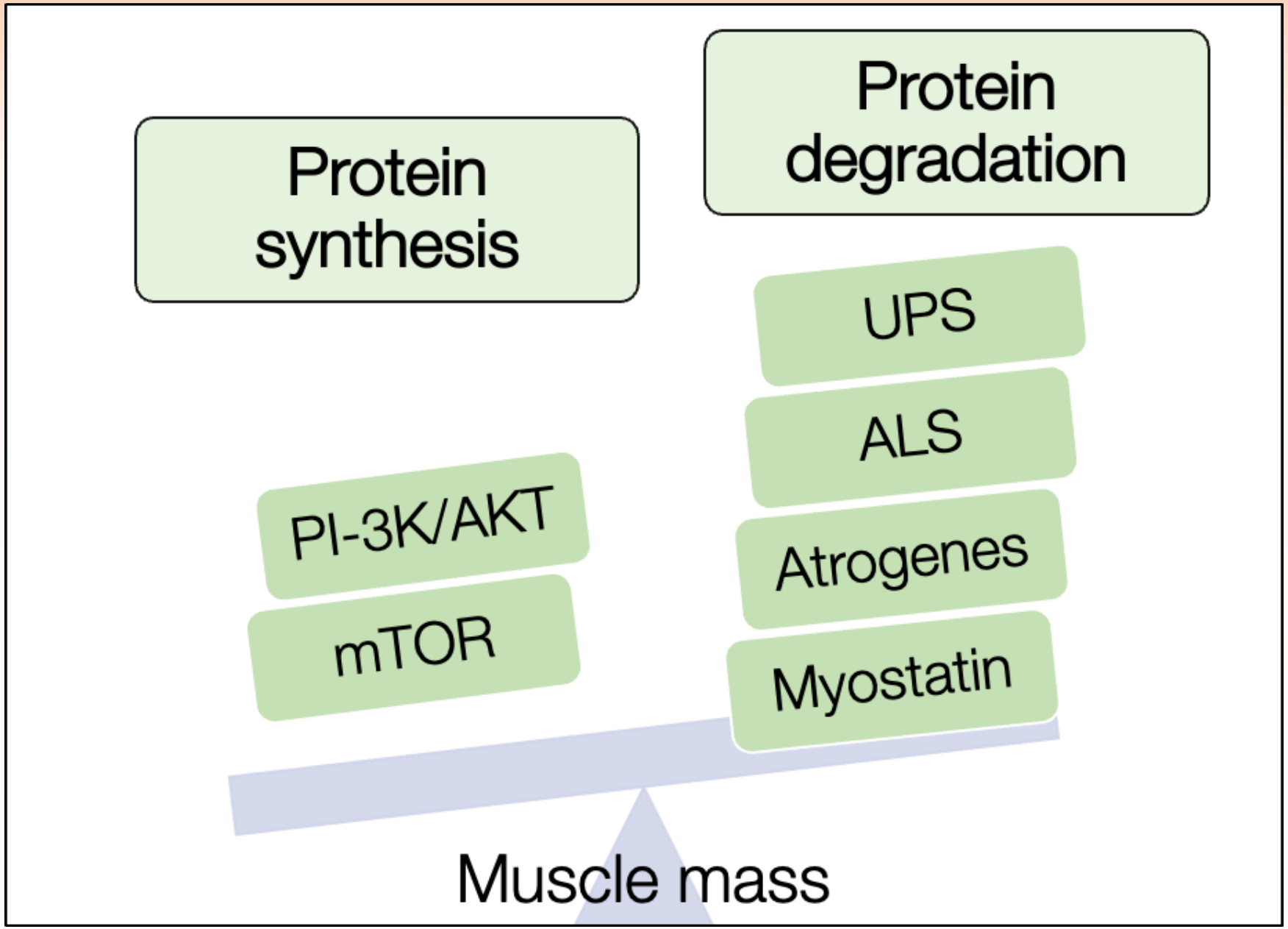
Mean	21.0	22.0	24.1
Std. Deviation	5.26	4.77	4.57
Number of values	27	23	17

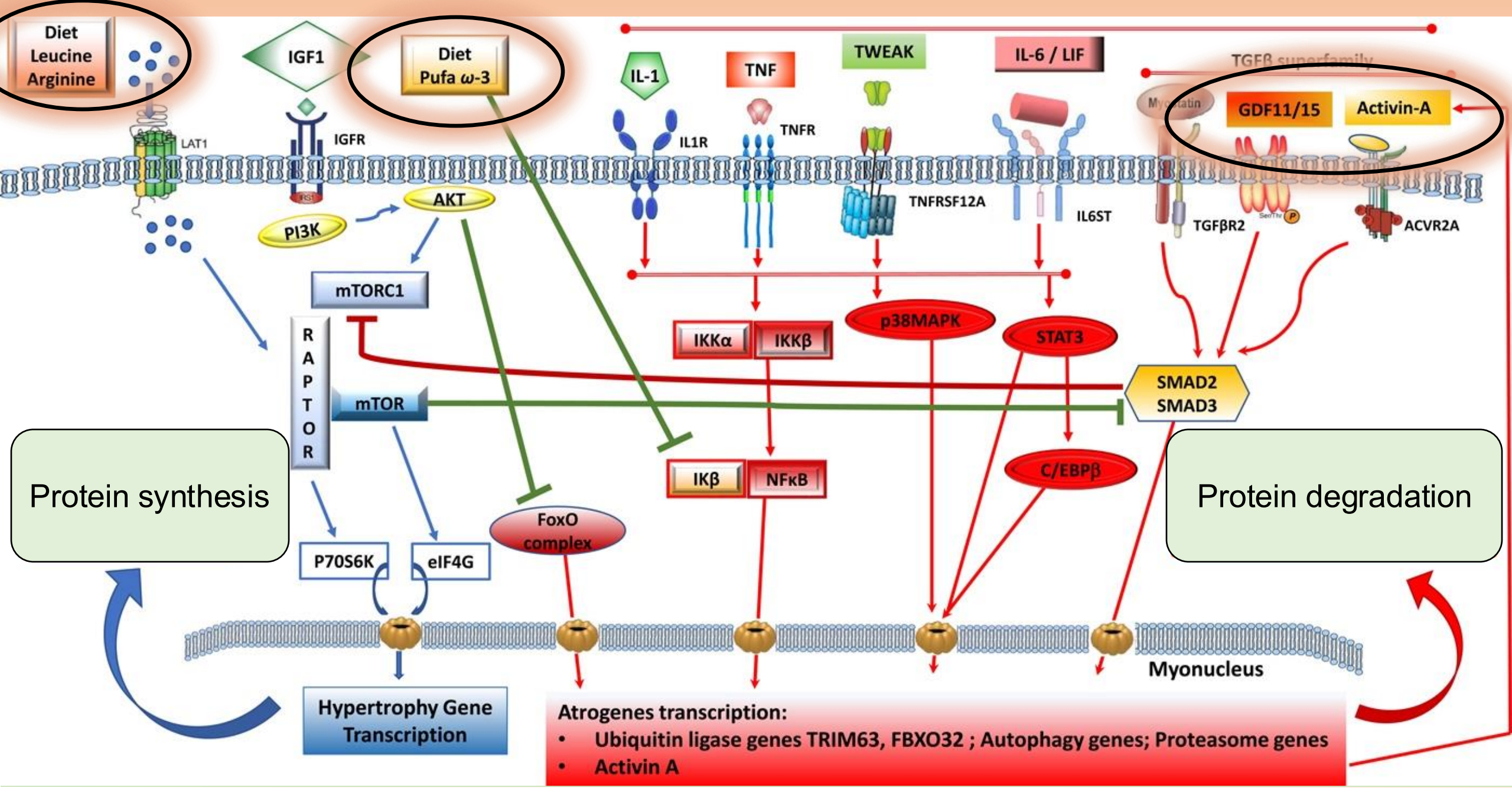


Mean	24.4	25.1	27.8
Std. Deviation	10.6	9.16	9.81
Number of values	27	23	17

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.

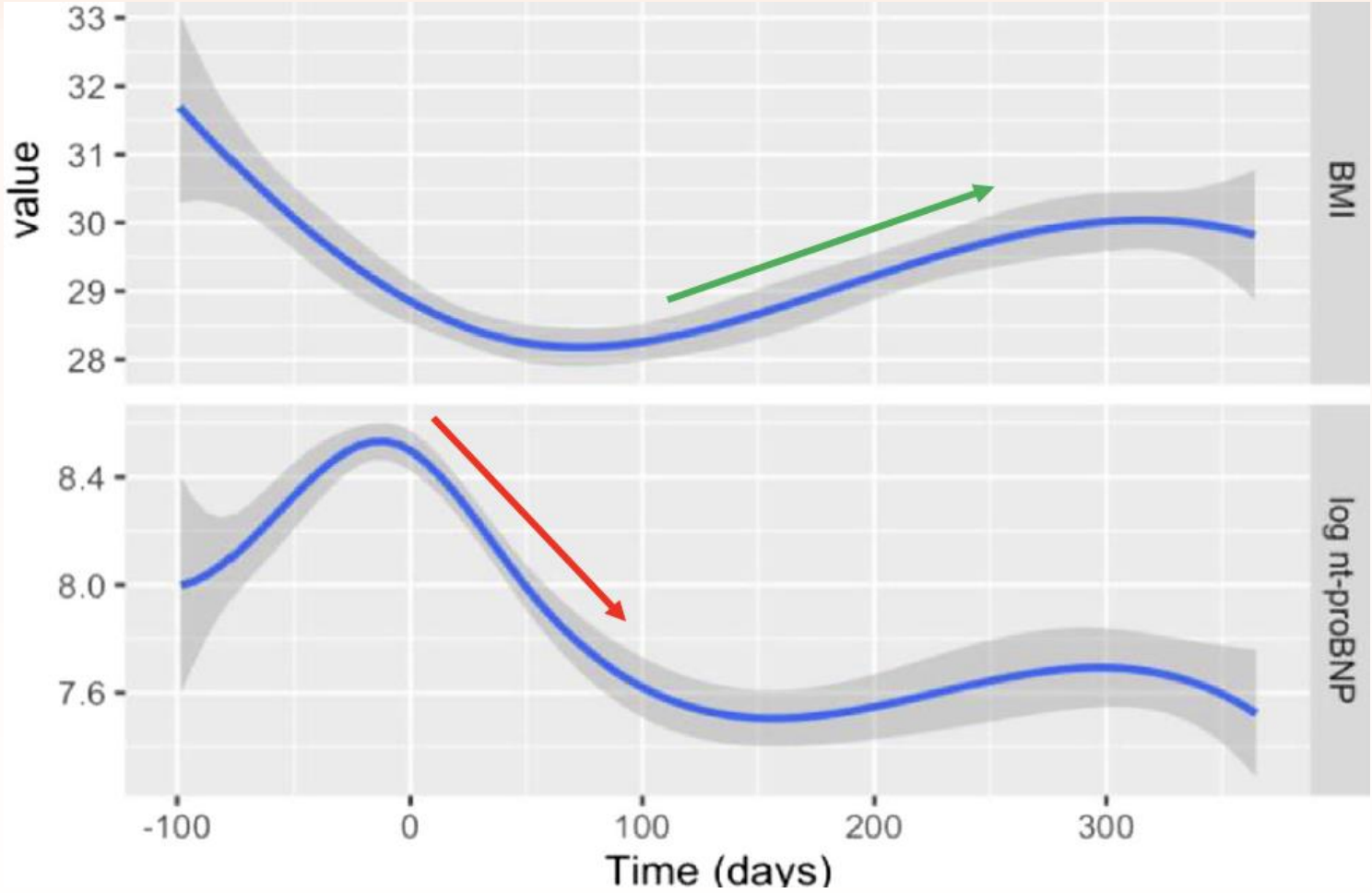
Funded by an American Heart Association Scientist Development Grant


Protein synthesis
Protein degradation
UPS
ALS
Atrogenes
Myostatin
PI-3K/AKT
mTOR
Muscle mass



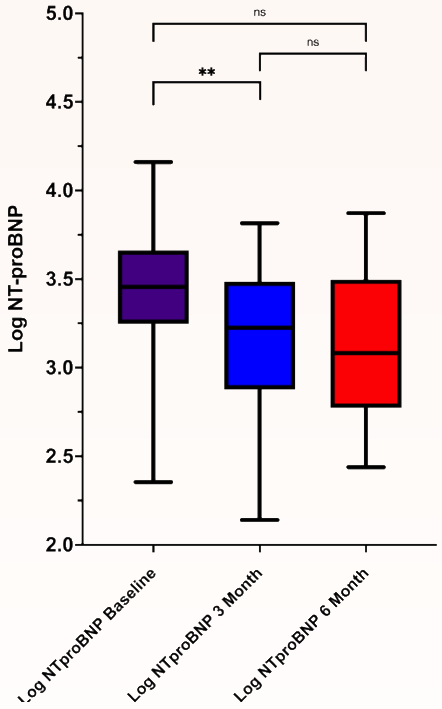
Schiessel DL and Baracos VE. Barriers to cancer nutrition therapy: excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. Proc Nutr Soc. 2018;77:394-402. doi:10.1017/S0029665118000186.

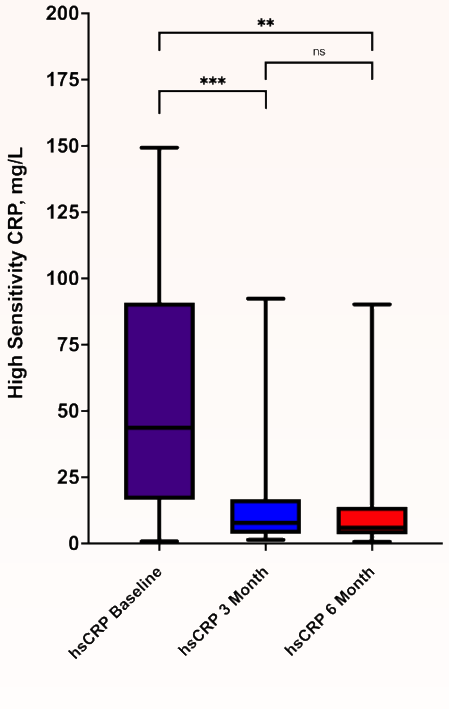
The Importance of NT-proBNP Recovery for BMI Recovery Post-LVAD Implantation

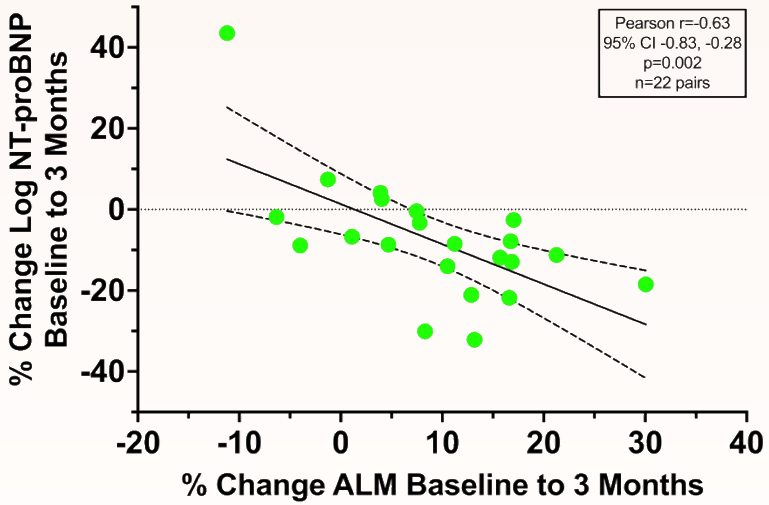


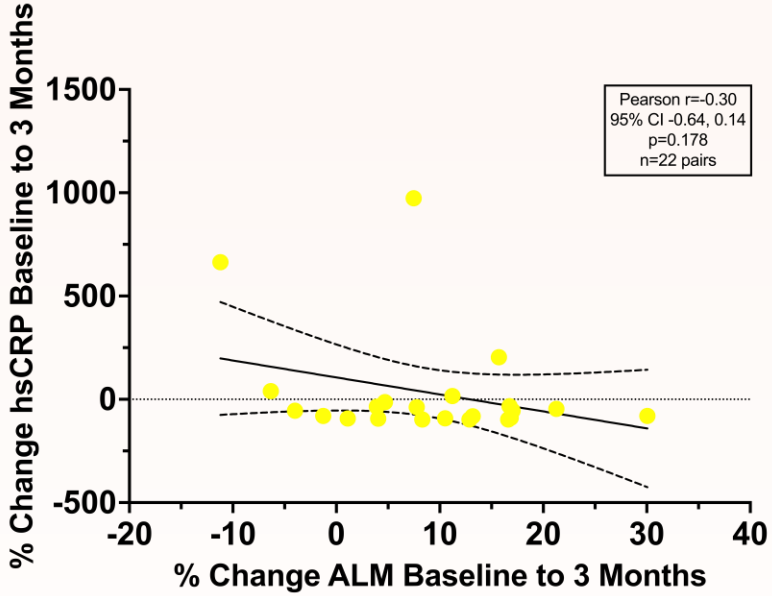
Schultz J, Vest AR, Masotti M, Hoeg A, Teigen LM, John R, Shaffer AW, Alexy T, Martin CM and Cogswell R. Body mass index and natriuretic peptides trends before and after left ventricular assist device. JCSM Rapid Communications. 2023;6:42-49.

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



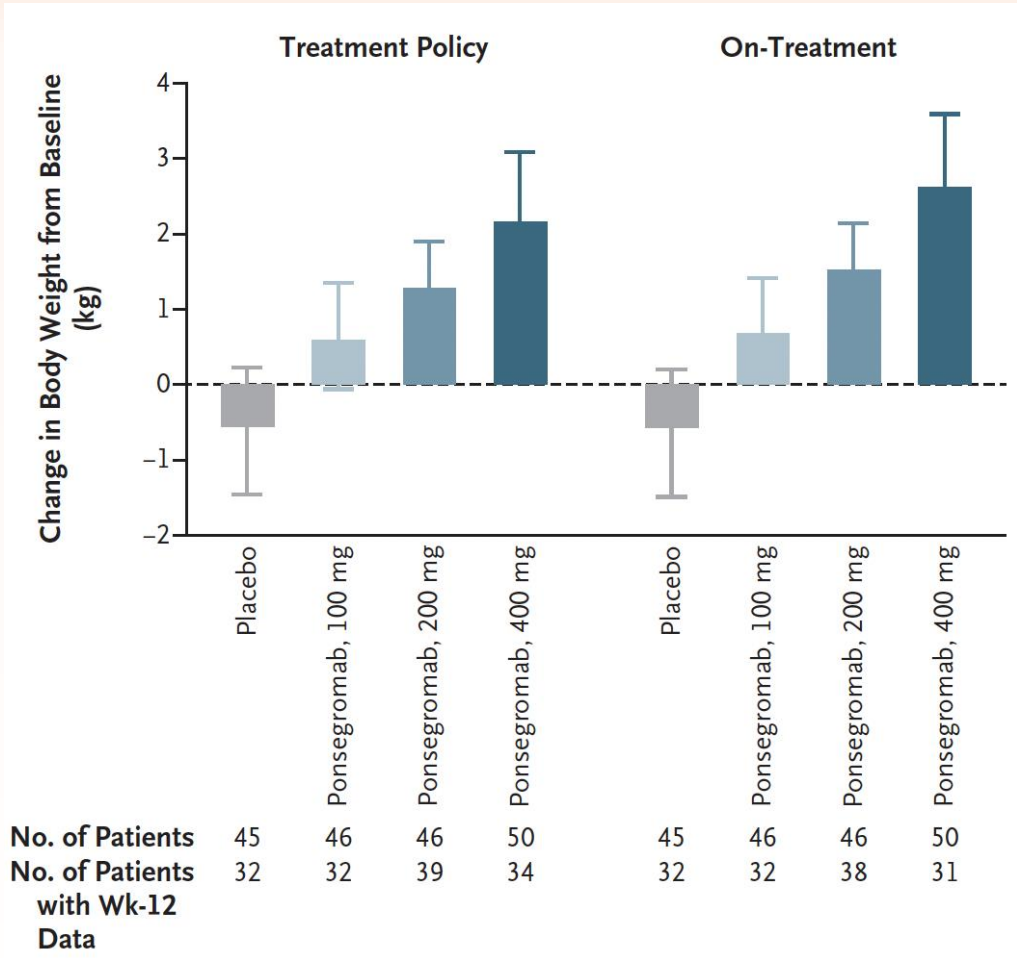




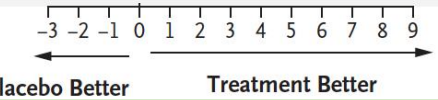


Celkupa D, Sweigart BA, Chery J, Coston A, Telfer L, Lawrence M, Kiernan MS, Couper GS, Kawabori M, LeBrasseur N, Saltzman E and Vest AR. Evaluation of potential mechanisms for skeletal muscle mass recovery early after left ventricular assist device implantation. *JHLT Open*. 2025;9:100338.

GDF-15 Inhibitor Ponsegromab in Cancer Cachexia

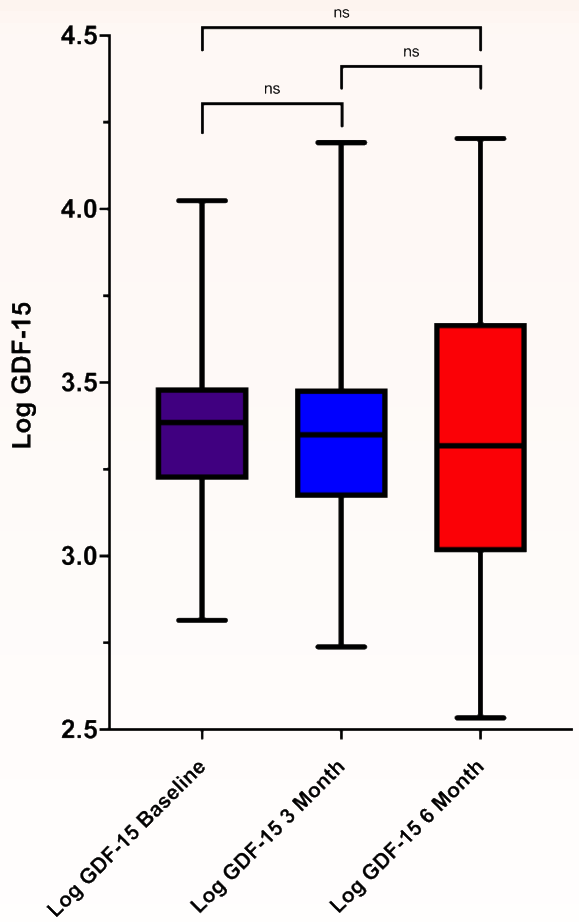


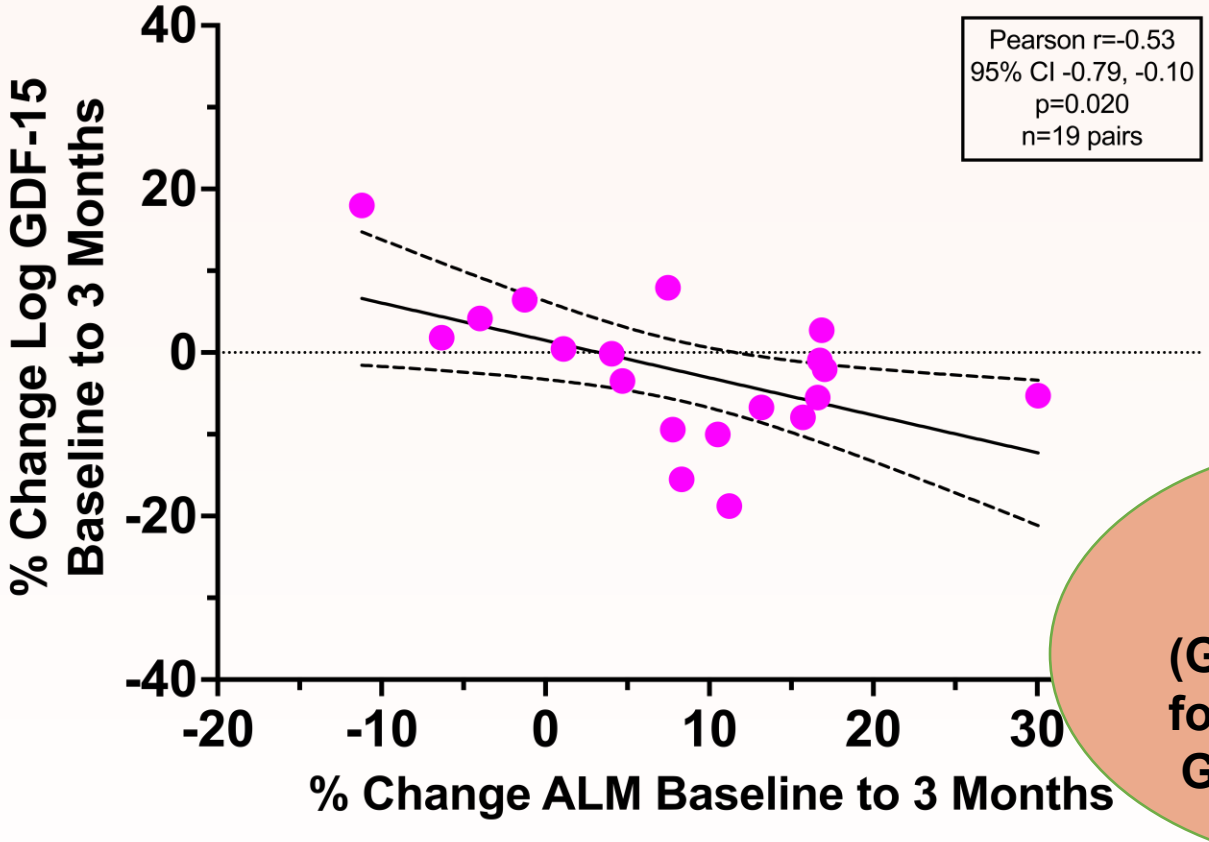
Subgroup	Placebo	Treatment	(95% credible interval)
	no. of patients		*kg*
All patients	32	34	3.03 (1.70 to 4.36)
Cancer type			
Colorectal cancer	12	9	4.94 (2.75 to 7.17)
Non–small-cell lung cancer	12	15	1.77 (−0.34 to 3.86)
Pancreatic cancer	8	10	2.52 (−0.12 to 4.96)
Serum GDF-15 at screening			
First quartile (<2366 pg/ml)	7	10	2.79 (0.22 to 5.29)
Second quartile (2366 to <3903 pg/ml)	10	8	1.91 (−0.49 to 4.40)
Third quartile (3903 to <7677 pg/ml)	8	7	5.64 (2.90 to 8.41)
Fourth quartile (≥7677 pg/ml)	7	9	2.63 (−0.18 to 5.42)
Platinum-based chemotherapy			
Yes	12	14	2.19 (0.08 to 4.27)
No	20	20	3.70 (2.09 to 5.39)
BMI at randomization			
<20	21	11	3.19 (1.16 to 5.18)
≥20	11	23	3.34 (1.40 to 5.30)
BMI-adjusted weight loss category			
1, 2, or 3	11	21	1.24 (−0.71 to 3.20)
4	21	13	5.20 (3.45 to 6.97)
CRP:albumin ratio			
Low (<0.189)	10	15	2.50 (0.35 to 4.72)
High (≥0.189)	12	14	3.07 (0.86 to 5.22)
Modified Glasgow Prognostic Score			
0	14	15	1.92 (−0.06 to 3.82)
1 or 2	8	14	3.85 (1.47 to 6.27)



Groarke JD, Crawford J, Collins SM, Lubaczewski S, Roeland EJ, Naito T, Hendifar AE, Fallon M, Takayama K, Asmis T, Dunne RF, Karahanoglu I, Northcott CA, Harrington MA, Rossulek M, Qiu R and Saxena AR. Ponsegromab for the Treatment of Cancer Cachexia. *N Engl J Med*. 2024;doi:10.1056/NEJMoa2409515.

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





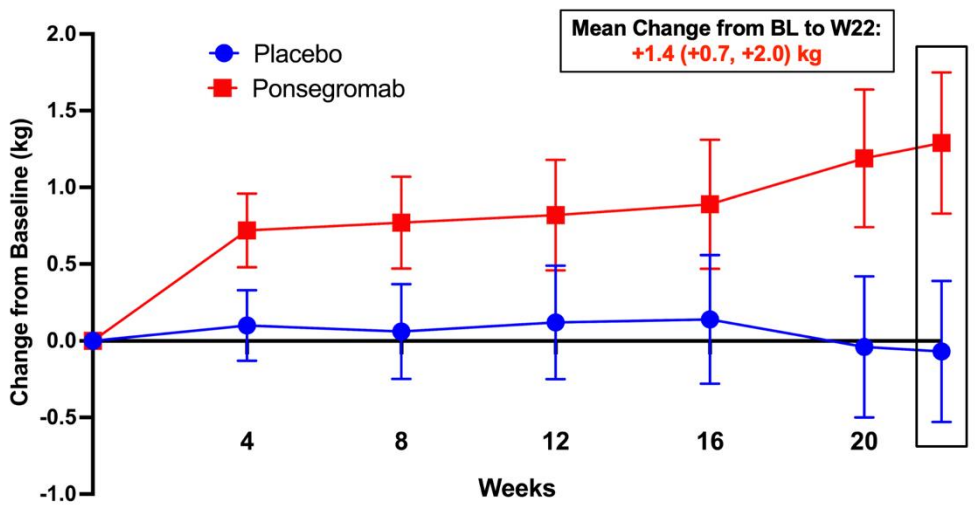
Example: Ponsegromab (GDF-15 inhibitor) for heart failure in GARDEN TIMI 74

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.

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

Garden TIMI 74

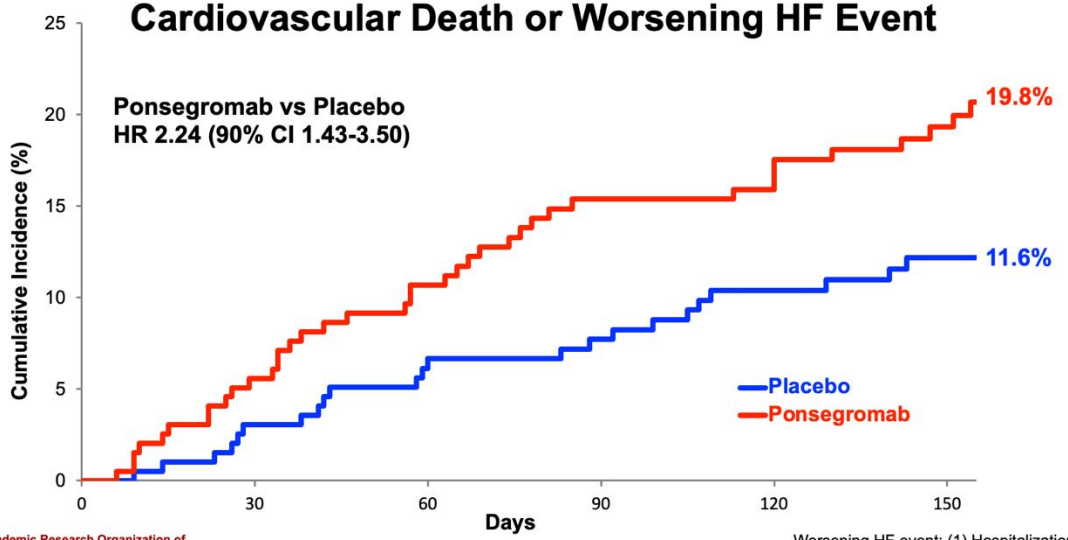
Body Weight



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

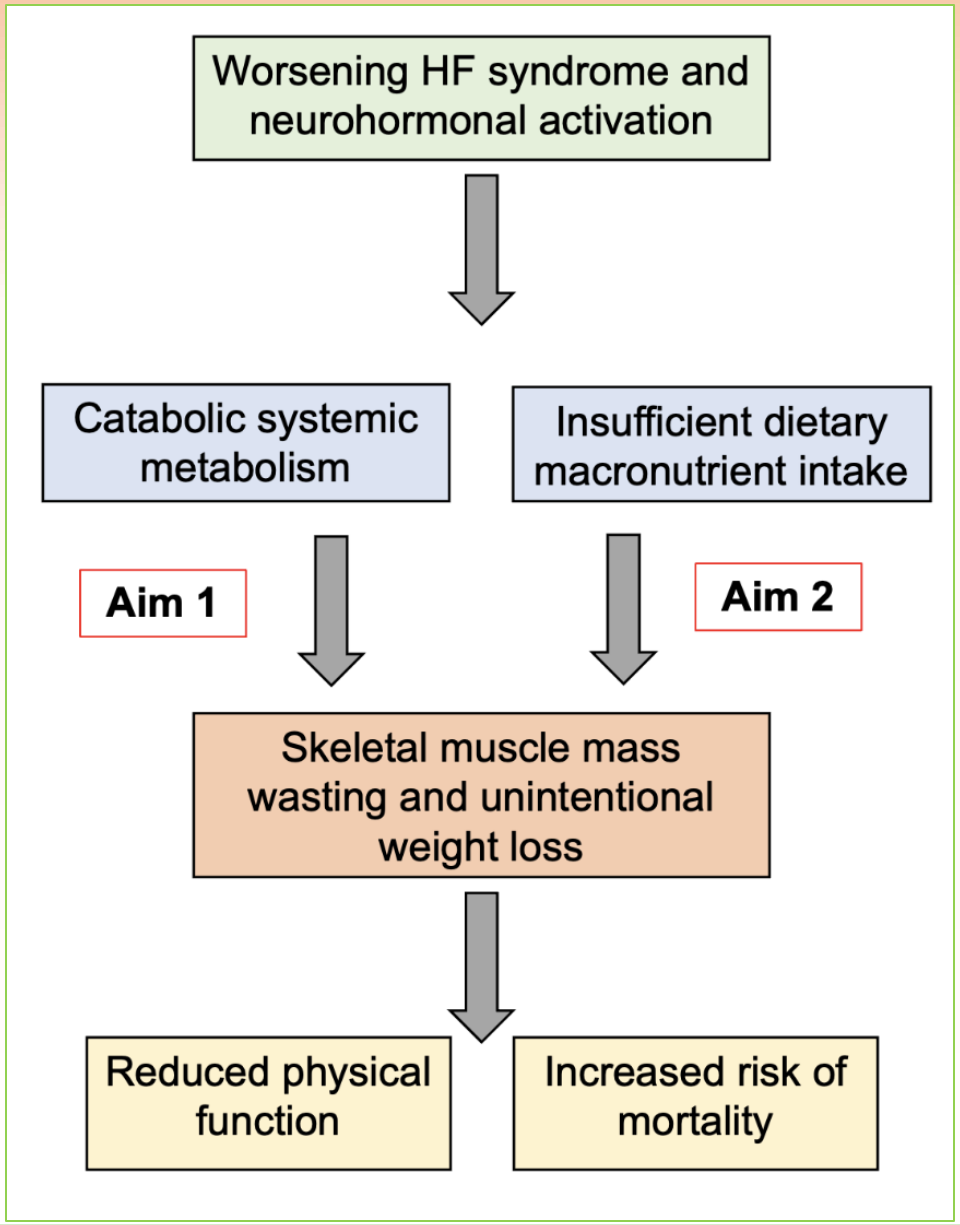
Clinical Composite Outcome



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

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



ASTRID-HF OVERVIEW

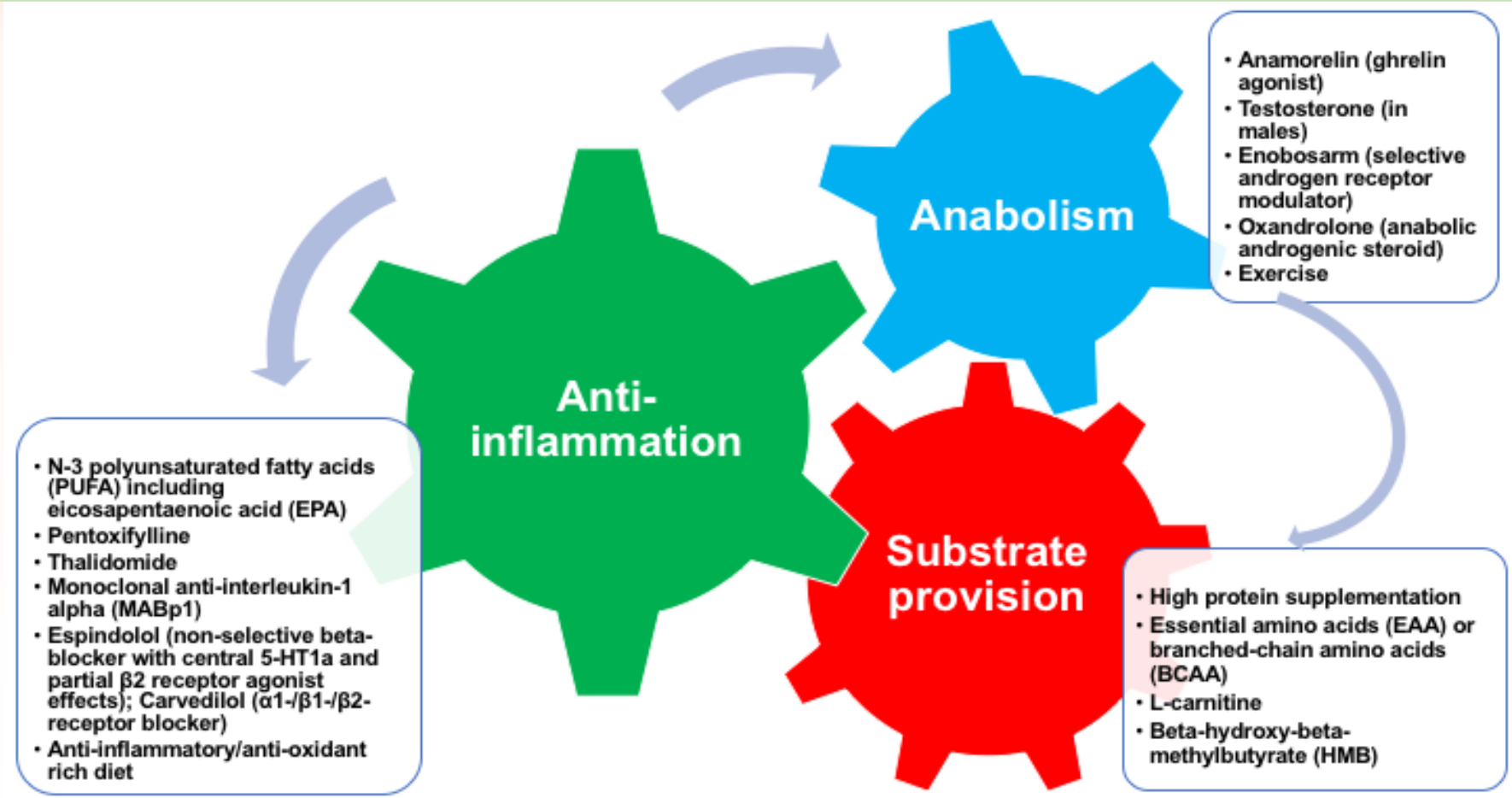
Muscle wasting and weakened physical function in patients with HFrEF	Prospective randomized controlled trial	Comparing changes in DXA appendicular lean mass (ALM) baseline to 6 months	Randomized between 3 groups of 0 vs 9 vs 30 g/day oral protein supplementation (Ensure®)	Sample size 120 with 40 participants per group, stratified by sex and baseline NT-proBNP

SCAN ME

ClinicalTrials.gov Identifier: NCT05627440

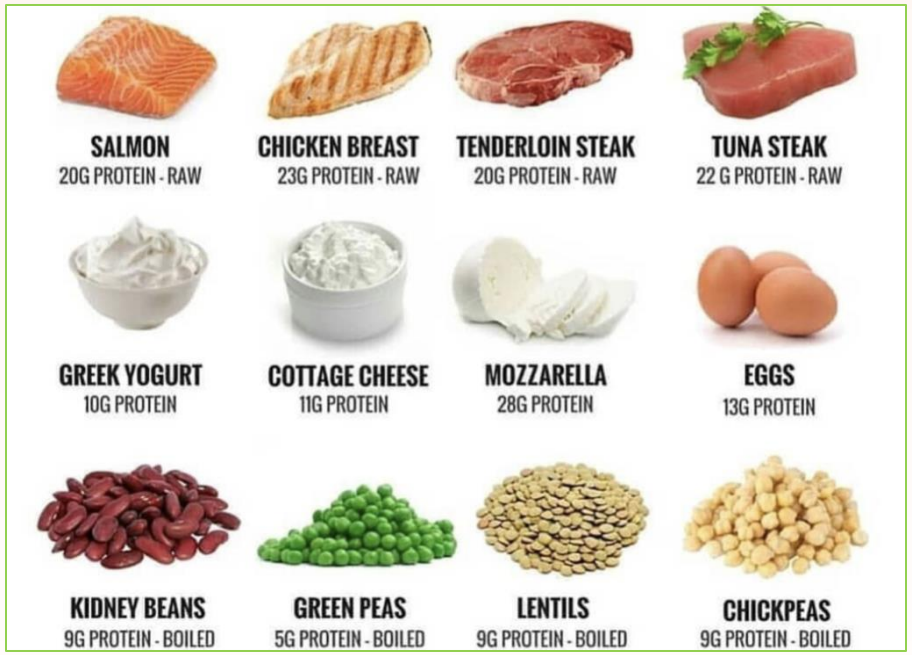
Funded by NHLBI R01HL167113

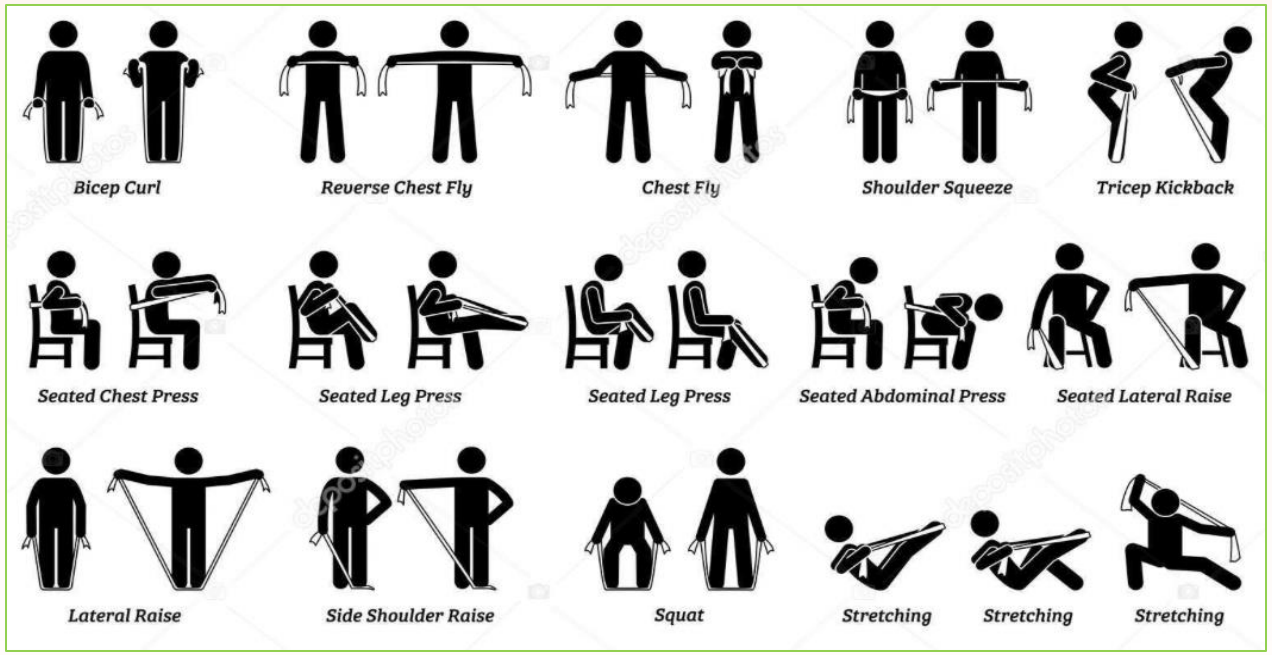
Framework for Potential Therapies for Cardiac Cachexia Reveral



Vest, A et al. Nutrition, Obesity and Cachexia in Patients with Heart Failure: A Consensus Statement from the HFSA Scientific Statements Committee. *J Card Fail* 2019;25(5):380-400.

Lean Mass Sparing Recommendations During AOM Therapy, Pending Further Study





1-1.2 g/kg/day dietary **protein**

Resistance **exercises** at least 2 days/wk

Research Tools: Whole Body DXA Imaging

- EWGSOP2 2018 criteria give sex-specific appendicular lean mass (ALM) thresholds:

  ALM: men < 20 kg, women < 15 kg/m^2

  ALM/(height)^2: men < 7.0 kg/m^2, women < 6.0 kg/m^2

- Also grip strength, SPPB, chair stand, gait speed
- *Limitations:* ALM requires dual energy X-ray absorptiometry (DXA); not validated with significant edema; not portable readily available

Body Composition Results

Region	Fat Mass (g)	Lean + BMC (g)	Total Mass (g)	% Fat	%Fat Percentile YN	AM
L Arm	984	2066	3050	32.3	20	5
R Arm	1094	2123	3217	34.0	28	8
Trunk	6750	20123	26874	25.1	20	4
L Leg	2354	7055	9409	25.0	1	1
R Leg	2525	7258	9783	25.8	1	1
Subtotal	13707	38625	52333	26.2	7	1
Head	886	3091	3978	22.3		
Total	**14593**	**41717**	**56310**	**25.9**	**7**	**1**
Android (A)	1119	2853	3972	28.2		
Gynoid (G)	2626	6327	8953	29.3		

Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M, Writing Group for the European Working Group on Sarcopenia in Older P and the Extended Group for E. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* 2019;48:16-31.

Research Tools: Short Physical Performance Battery (SPPB)

SCORING:

A. Side-by-side-stand
Held for 10 sec ❒ 1 point
Not held for 10 sec ❒ 0 points
Not attempted ❒ 0 points
If 0 points, end Balance Tests

Number of seconds held if less than 10 sec: ___.__ __sec

If participant did not attempt test or failed, circle why:
Tried but unable 1
Participant could not hold position unassisted 2
Not attempted, you felt unsafe 3
Not attempted, participant felt unsafe 4
Participant unable to understand instructions 5
Other (specify) _____ 6
Participant refused 7

B. Semi-Tandem Stand
Held for 10 sec ❒ 1 point
Not held for 10 sec ❒ 0 points
Not attempted ❒ 0 points *(circle reason above)*
If 0 points, end Balance Tests

Number of seconds held if less than 10 sec: ___.__ __sec

C. Tandem Stand
Held for 10 sec ❒ 2 points
Held for 3 to 9.99 sec ❒ 1 point
Held for < than 3 sec ❒ 0 points
Not attempted ❒ 0 points (circle reason above)

Number of seconds held if less than 10 sec: ___.__ __sec

D. Total Balance Tests score_____(sum points)

Max score 12
Abnormal ≤8

Comments: _____

GAIT SPEED TEST SCORING:

Length of walk test course: Four meters ❒ Three meters ❒

A. Time for First Gait Speed Test (sec)
1. Time for 3 or 4 meters __ __.__ __sec
2. If participant did not attempt test or failed, circle why:
Tried but unable 1
Participant could not walk unassisted 2
Not attempted, you felt unsafe 3
Not attempted, participant felt unsafe 4
Participant unable to understand instructions 5
Other (Specify) _____ 6
Participant refused 7
Complete score sheet and go to chair stand test

3. Aids for first walk.....None ❒ Cane ❒ Other ❒

Comments:_____

B. Time for Second Gait Speed Test (sec)
1. Time for 3 or 4 meters __ __.__ __ sec
2. If participant did not attempt test or failed, circle why:
Tried but unable 1
Participant could not walk unassisted 2
Not attempted, you felt unsafe 3
Not attempted, participant felt unsafe 4
Participant unable to understand instructions 5
Other (Specify) 6
Participant refused 7

3. Aids for second walk..... None ❒ Cane ❒ Other ❒

What is the time for the faster of the two walks?
Record the shorter of the two times __ __.__ __ sec
[If only 1 walk done, record that time] __ __.__ __ sec

If the participant was unable to do the walk: ❒ **0 points**

For 4-Meter Walk:
If time is more than 8.70 sec: ❒ **1 point**
If time is 6.21 to 8.70 sec: ❒ **2 points**
If time is 4.82 to 6.20 sec: ❒ **3 points**
If time is less than 4.82 sec: ❒ **4 points**

For 3-Meter Walk:
If time is more than 6.52 sec: ❒ **1 point**
If time is 4.66 to 6.52 sec: ❒ **2 points**
If time is 3.62 to 4.65 sec: ❒ **3 points**
If time is less than 3.62 sec: ❒ **4 points**

SCORING
Single Chair Stand Test

	YES	NO
A. Safe to stand without help	❒	❒

B. Results:
Participant stood without using arms ❒ → Go to Repeated Chair Stand Test
Participant used arms to stand ❒ → End test; score as 0 points
Test not completed ❒ → End test; score as 0 points

C. If participant did not attempt test or failed, circle why:
Tried but unable 1
Participant could not stand unassisted 2
Not attempted, you felt unsafe 3
Not attempted, participant felt unsafe 4
Participant unable to understand instructions 5
Other (Specify) _____ 6
Participant refused 7

Repeated Chair Stand Test

	YES	NO
A. Safe to stand five times	❒	❒

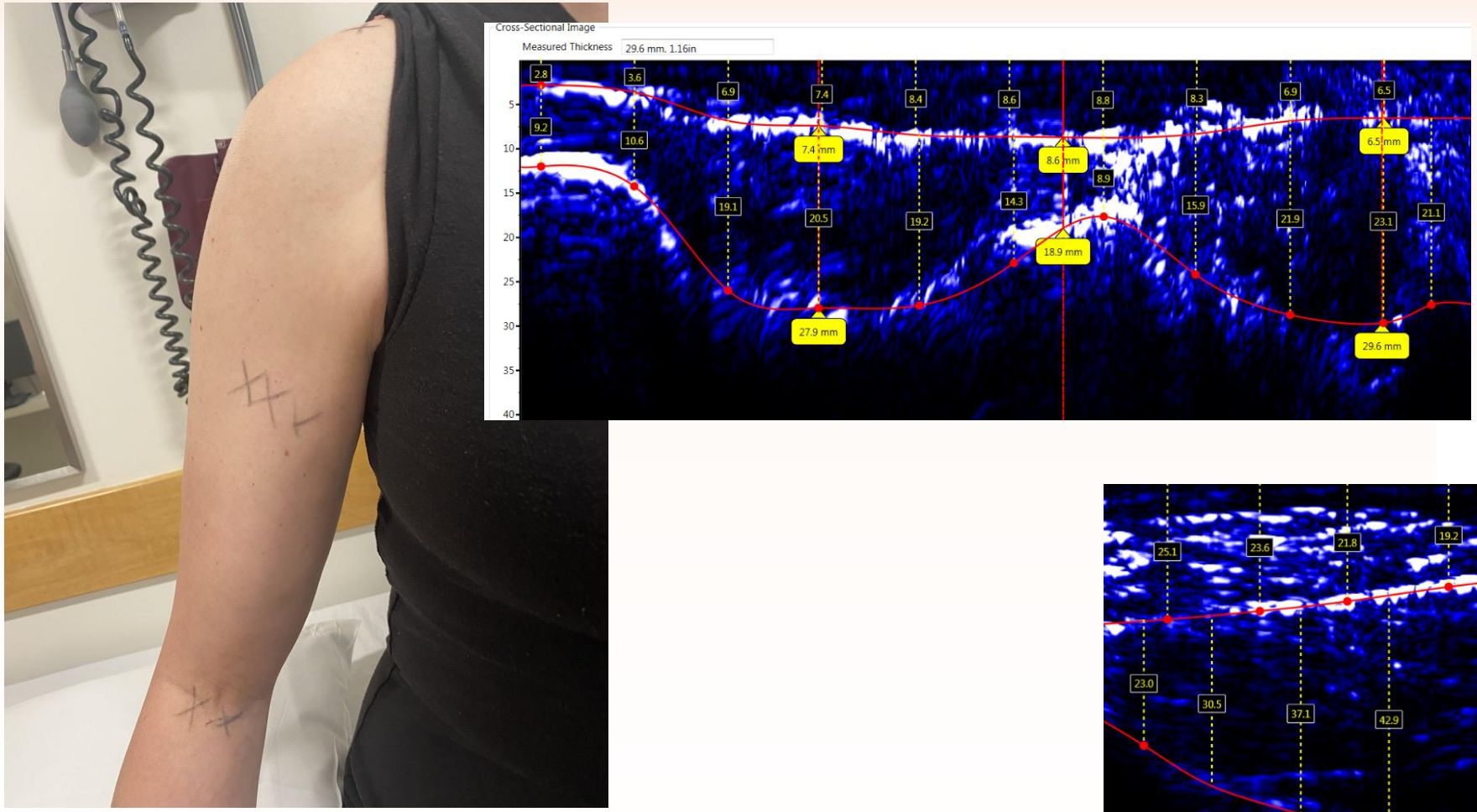
B. If five stands done successfully, record time in seconds.
Time to complete five stands __ __.__ __ sec

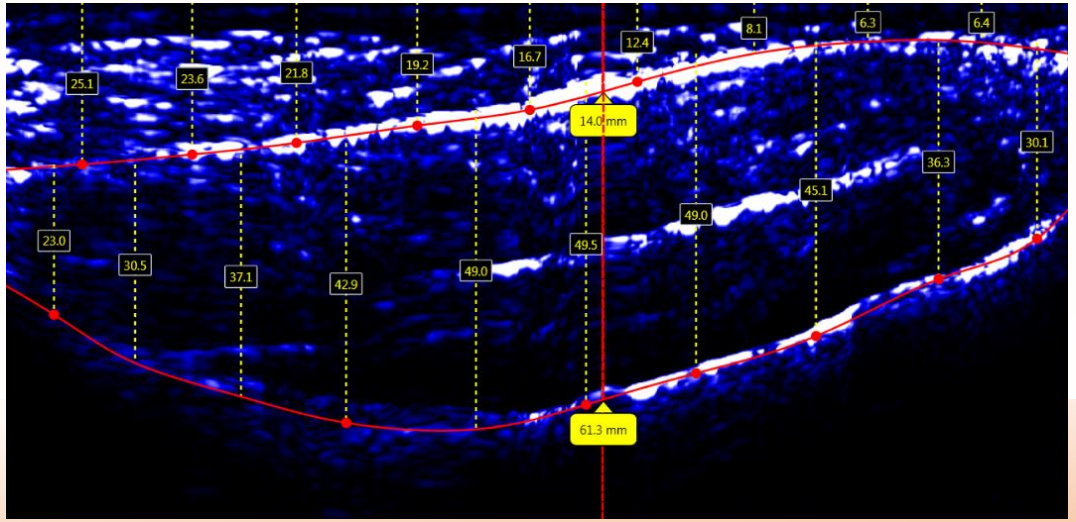
C. If participant did not attempt test or failed, circle why:
Tried but unable 1
Participant could not stand unassisted 2
Not attempted, you felt unsafe 3
Not attempted, participant felt unsafe 4
Participant unable to understand instructions 5
Other (Specify) 6
Participant refused 7

Scoring the Repeated Chair Test
Participant unable to complete 5 chair stands or completes stands in >60 sec: ❒ 0 points
If chair stand time is 16.70 sec or more: ❒ 1 points
If chair stand time is 13.70 to 16.69 sec: ❒ 2 points
If chair stand time is 11.20 to 13.69 sec: ❒ 3 points
If chair stand time is 11.19 sec or less: ❒ 4 points

Fielding RA, Guralnik JM, King AC, Pahor M, McDermott MM, Tudor-Locke C, Manini TM, Glynn NW, Marsh AP, Axtell RS, Hsu FC, Rejeski WJ and group Ls. Dose Of Physical Activity, Physical Functioning And Disability Risk In Mobility-limited Older Adults: Results From The LIFE Study Randomized Trial. PLoS One. 2017;12:e0182155.

Current Research: Skeletal Muscle Ultrasound





Lateral thigh skeletal muscle ultrasound

Practical Advice: Muscle Strength Assessment in Clinic

Pick one of the following clinic screening tools:

- ❑ **5 sit-to-stands >15 seconds to complete**
  - No equipment, could be limited by dizziness
  - Just try one!
- ❑ **Handgrip strength <27 kg men or <16 kg women**
  - Quick, portable, but does require equipment
- ❑ **4-meter walk takes >5 seconds**
  - Equates to gait speed ≤0.8 m/sec
  - Quick but does require some planning, a stopwatch

Cruz-Jentoft AJ, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* 2019;48:16-31.
Video Credit: Physical Therapy at University of Pittsburg

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:*
  - RCT of protein supplementation in advanced HFrEF: *ASTRID-HF*
  - Skeletal muscle US for bedside assessment of wasting
  - Dietary protein and resistance exercises for prevention of GLP-1RA wasting