

Treatment to Improve Cardiometabolic Disease Outcomes: A Focus on HFpEF and Metabolic Dysfunction-Associated Steatohepatitis

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Disclosure

Advisory Board: AbbVie; Boehringer Ingelheim; Corcept; Eli Lilly; Fractyl Health; Gan & Lee; Genentech/Roche; Graviton Bioscience; i2o Therapeutics; Keros Therapeutics; Madrigal; MetSera; Neurocrine; Novo Nordisk; Pfizer; Regeneron; Terns Pharmaceuticals; Zealand

Data Monitoring Committee: Boehringer Ingelheim; Eli Lilly

Research Grant: Eli Lilly; Genentech/Roche; Kaleira; Novo Nordisk; Terns Pharmaceuticals; Viking Therapeutics; Zealand



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The AACE/EASO Medical Diagnostic Term for the Disease of Obesity Entrain's Complication Centric Care

Adiposity-Based Chronic Disease

Abnormalities in Adipose Tissue

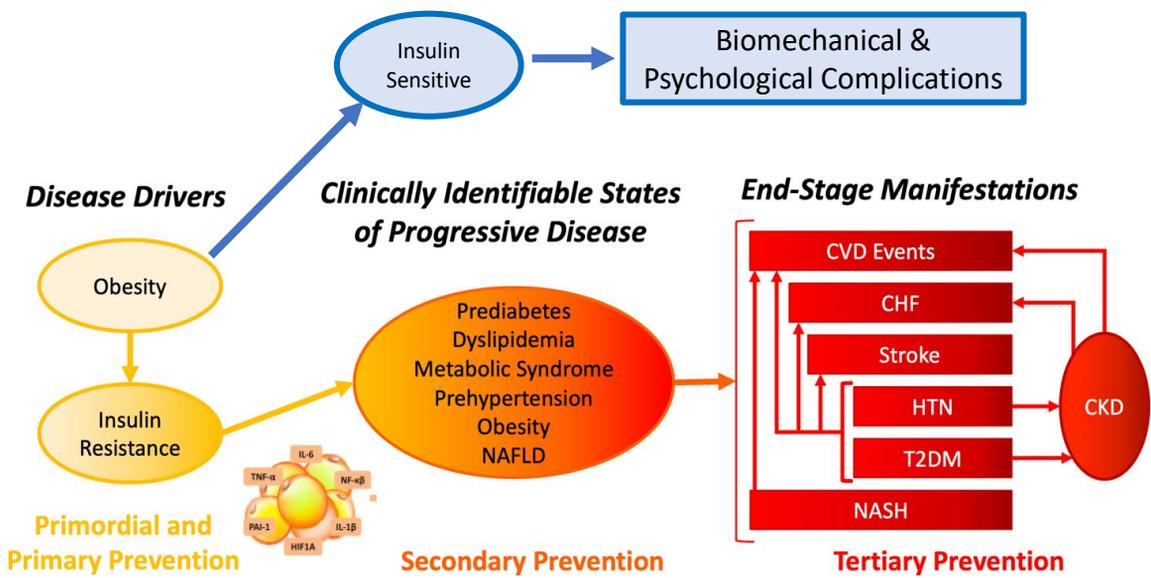
- Mass
- Distribution
- Function

Lifelong disease with complications that impair health and confer morbidity & mortality

Mechanick J, Hurley D, and Garvey WT. Endocrine Practice, 23(3):372-378, 2017
 Frühbeck G et al. Obes Facts 2019;12:131-6;

3

The Progression of Cardiometabolic Disease



Garvey WT

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Harmonization of Obesity Clinical Guidelines Around a Complication-Centric Approach to Obesity Care

2020 - Canada

Obesity in adults: a clinical practice guideline. CMAJ. 2020;192(31):E875-E891

2023 - OMA

Obesity Algorithm eBook, presented by the Obesity Medicine Association. 2023. <https://obesitymedicine.org/obesity-algorithm/>

2016 – AACE

AACE/ACE Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity. Endo Prac 2016;22(Suppl 3):1-203

2022 - India

ESI Clinical Practice Guidelines for the Evaluation and Management of Obesity In India. Indian J Endocr Metab 2022;26:295-318

2020 - World Obesity Gulf and

Lebanon Regional Recommendations

<https://www.worldobesity.org/resources/resource-library/gulf-lebanon-regional-recommendations>

2015 – EASO

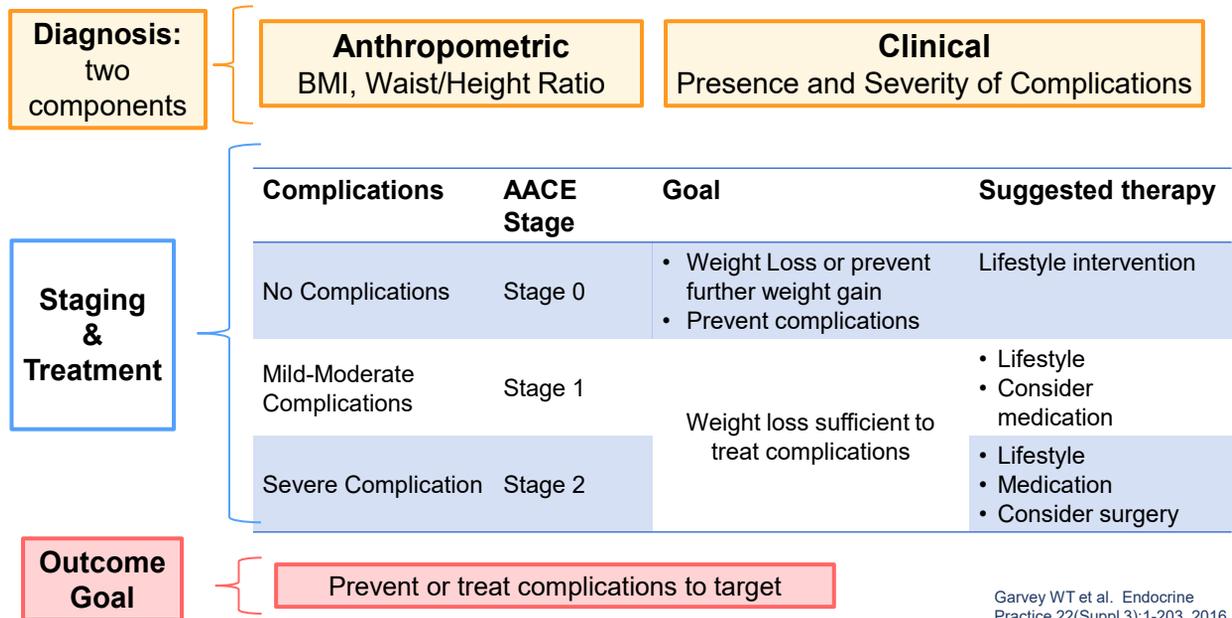
European Guidelines for Obesity Management in Adults. Obes Facts 2015;8:402-424

2022 - Australia

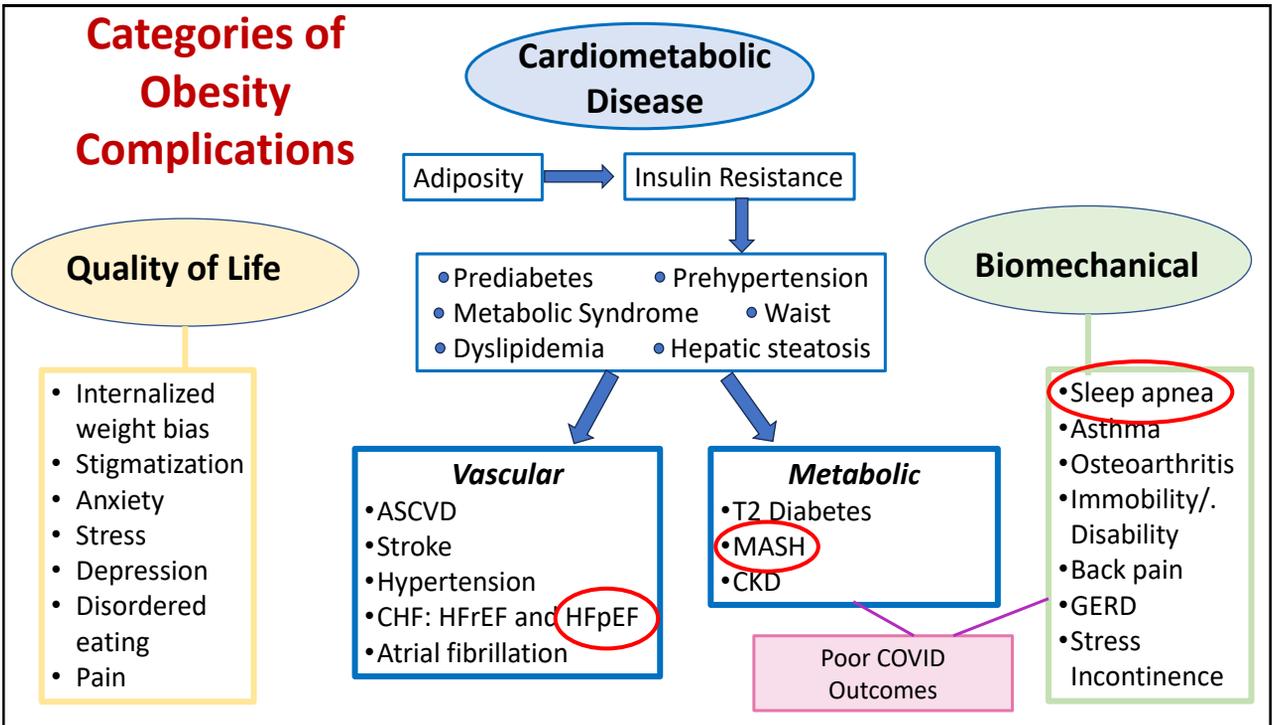
The Australian Obesity Management Algorithm: A simple tool to guide the management of obesity in primary care. Obes Res Clin Prac. 2022;16:353-363

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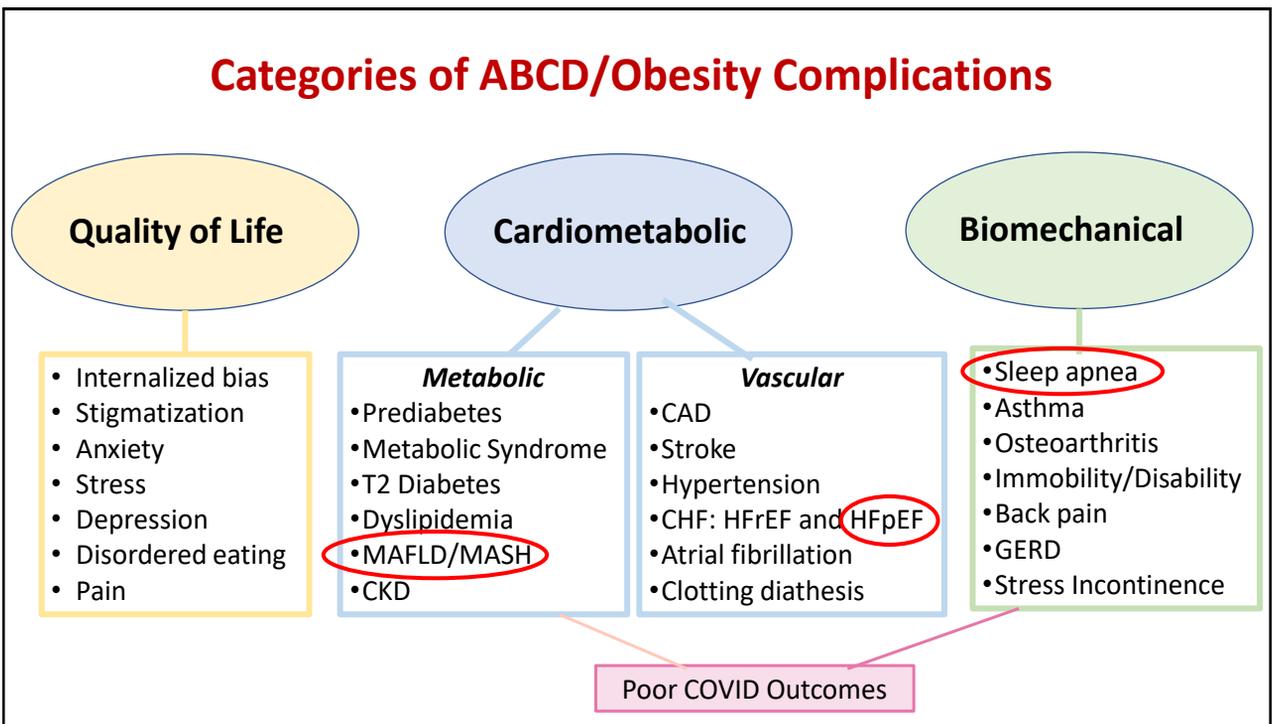
Basic Principles of the AACE Obesity Guidelines



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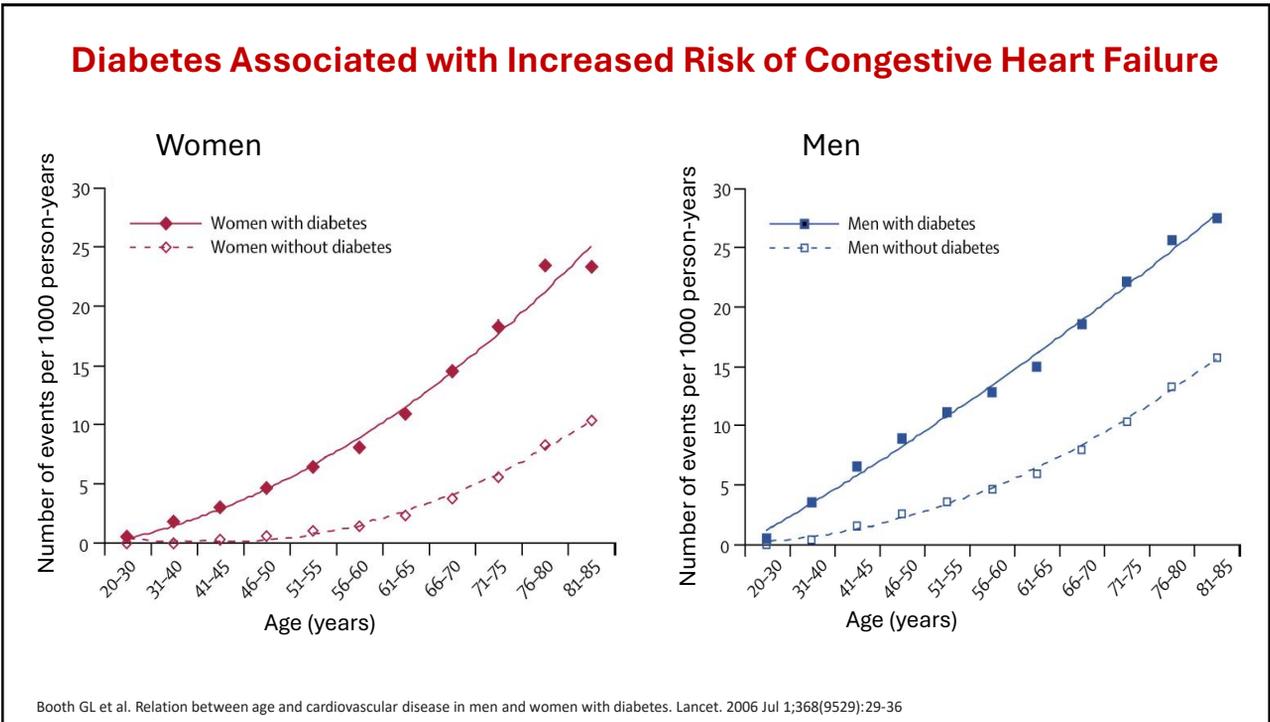


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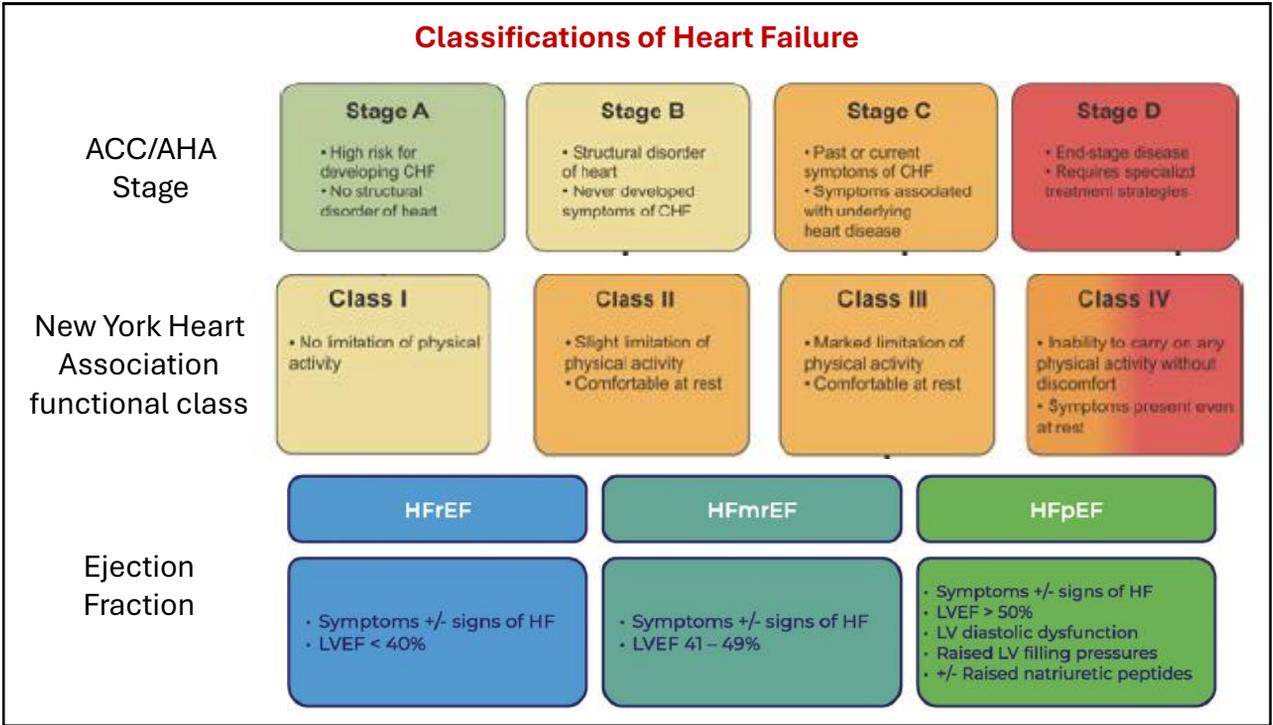
Congestive Heart Failure

Heart Failure with Preserved Ejection Fraction (HFpEF)

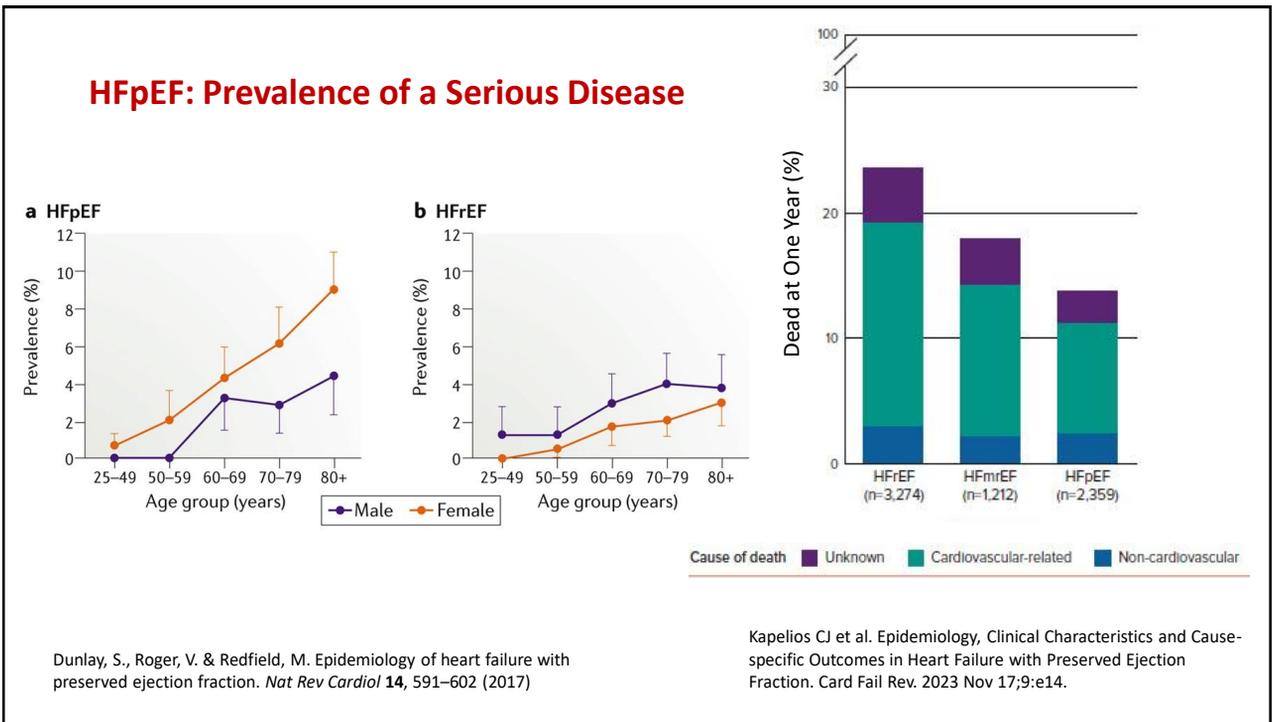
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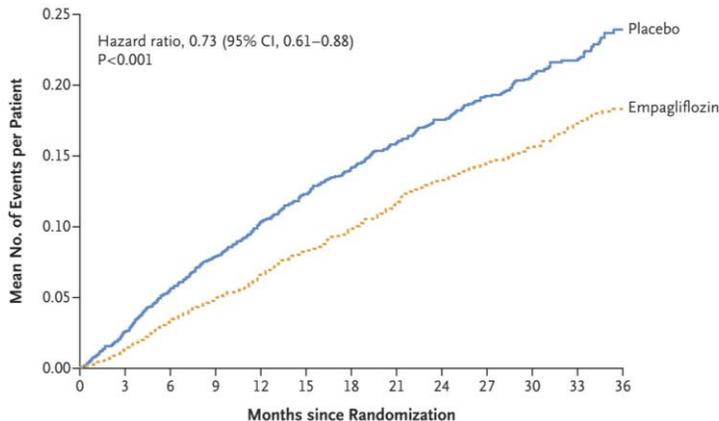
Recommended Pharmacologic Management of CHF in Diabetes

	ESC	AACE	AHA
Medications	<ul style="list-style-type: none"> • for HFrEF, HFmrEF, HFpEF SGLT2i (dapagliflozin, empagliflozin, sotagliflozin) • For HFpEF Early intensive treatment is ARNi or ACEi+ beta blocker, MRAs 	<ul style="list-style-type: none"> • for HFrEF, HFmrEF, HFpEF SGLT2i (dapagliflozin, empagliflozin, sotagliflozin) • For HFpEF in DM and stage B failure ACEi or ARBs and b-blockers 	<ul style="list-style-type: none"> • HFrEF: LVEF ≤ 40% • HFmrEF 41-49% ACEi or ARB or ARNi, SGLT2i, beta blocker, MRA, diuretics as needed • HFpEF: LVEF ≥ 50% SGLT2i

Heidenreich P et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. Circulation 2022;145(18):E895-E1032
 Marx N et al. Eur Heart J. 2023 Oct 14;44(39):4043-4140. Samson SL et al. Endocr Pract. 2023 May;29(5):305-340.

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Empagliflozin Reduces Hospitalizations for Heart Failure with Preserved Ejection Fraction



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

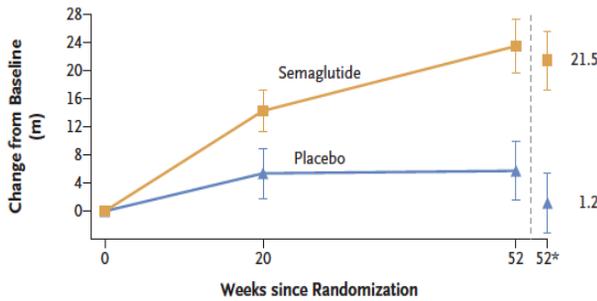
Anker SD,.....EMPEROR-Preserved Trial Investigators, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461

14

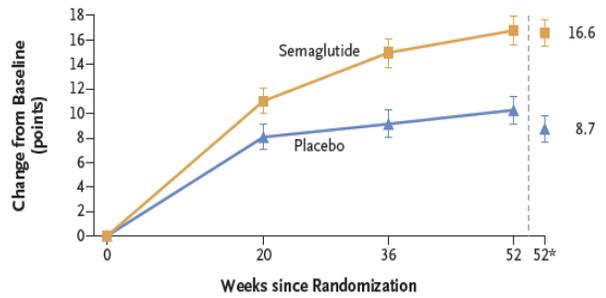
STEP HFpEF: Effects of Semaglutide 2.4 mg in Patients with Symptomatic HFpEF and Obesity

- 529 patients with obesity and T2D
- NY Class II-IV CHF symptoms

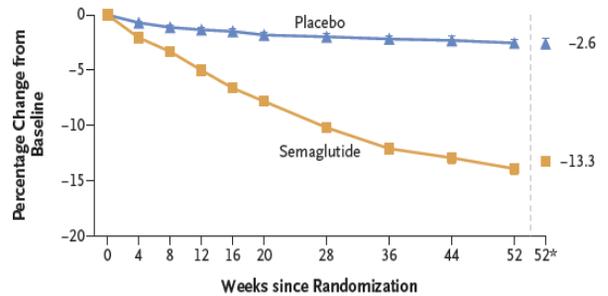
Change in 6-Minute Walk Distance



Change in KCCQ-CSS*



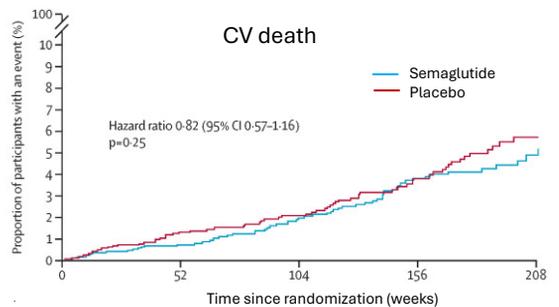
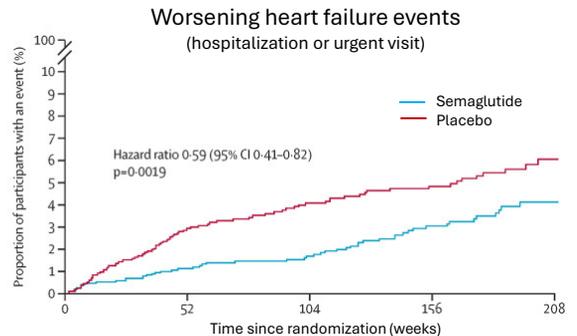
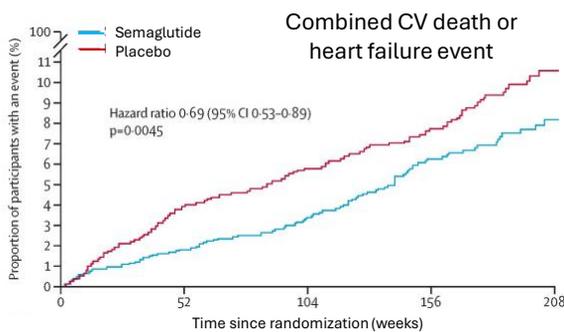
% Change in Body Weight



*Kansas City Cardiomyopathy Questionnaire
Kosiborod MN et al. NEJM. DOI: 10.1056/NEJM oa2306963. Epub Aug 25, 2023

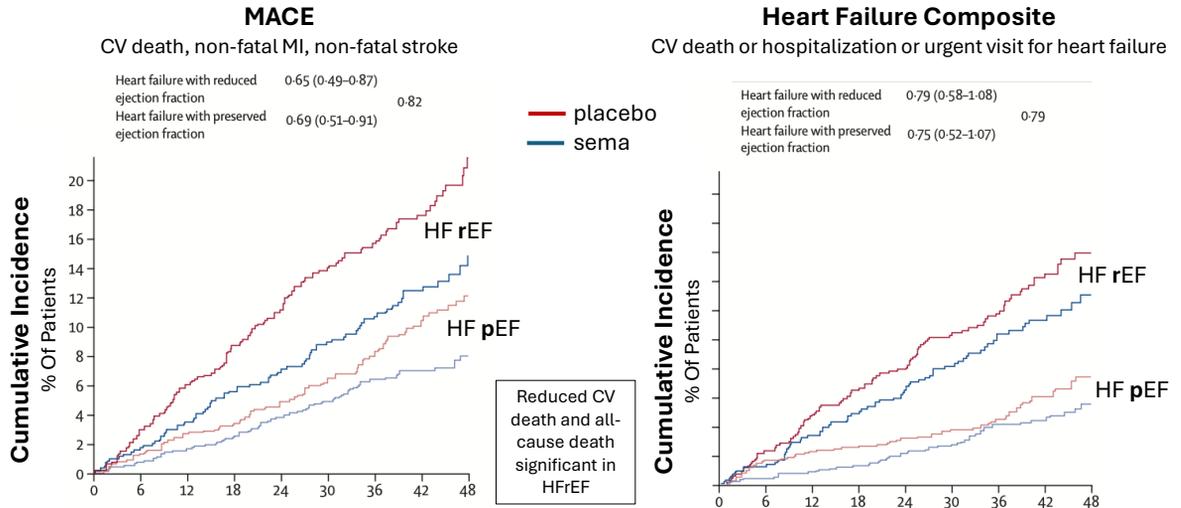
Semaglutide Improves Heart Failure

- 3743 patients with HFpEF from SELECT, FLOW, STEP-HFpEF, STEP-HFpEF DM
- Improvements in HFpEF and HFrEF
- Additive benefit to SGLT2i



Kosiborod MN et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. Lancet. 2024;404(10456):949-961.

SELECT: Effects of Semaglutide on CVD Outcomes in Patients with HFpEF and HFrEF at Baseline



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

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The SUMMIT Trial: Tirzepatide Improves HFpEF Outcomes and Symptoms

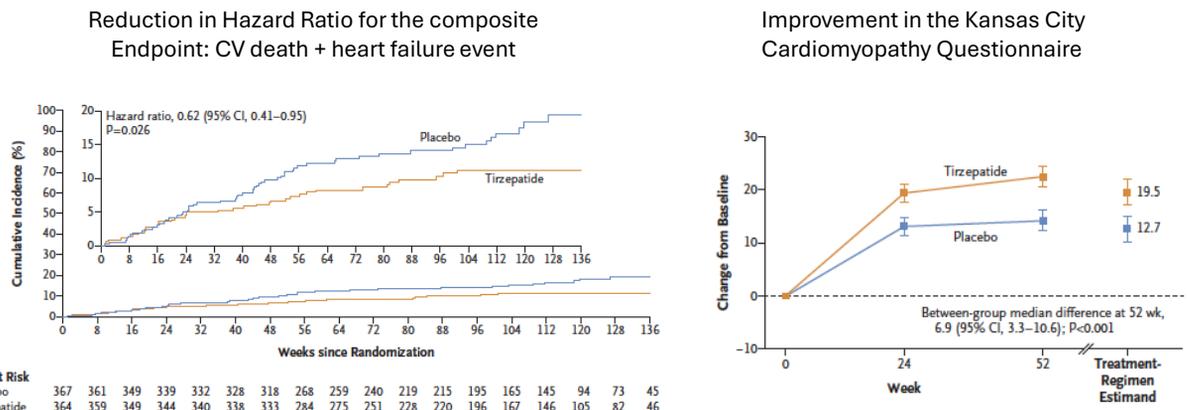


Figure 1. Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event.
 Shown is the cumulative incidence of death from cardiovascular causes or a worsening heart-failure event (the composite primary end point), assessed in a time-to-first-event analysis, among 364 patients who received tirzepatide and 367 patients who received placebo. The inset shows the same data on an expanded y axis.

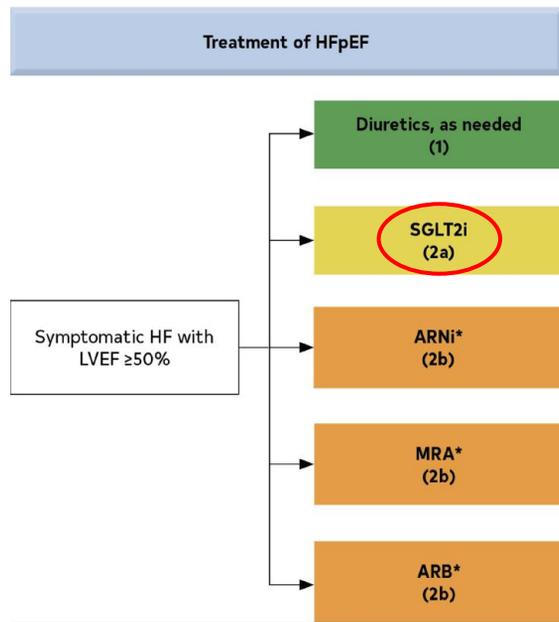
Packer M et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med.* 2025;392(5):427-437

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2022 AHA/ACC Recommendations for Treatment of HFpEF

Add:
Semaglutide 2.4 mg
Tirzepatide 15 mg

Heidenreich PA. 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. *Circulation*. 2022;145(18):e895-e1032



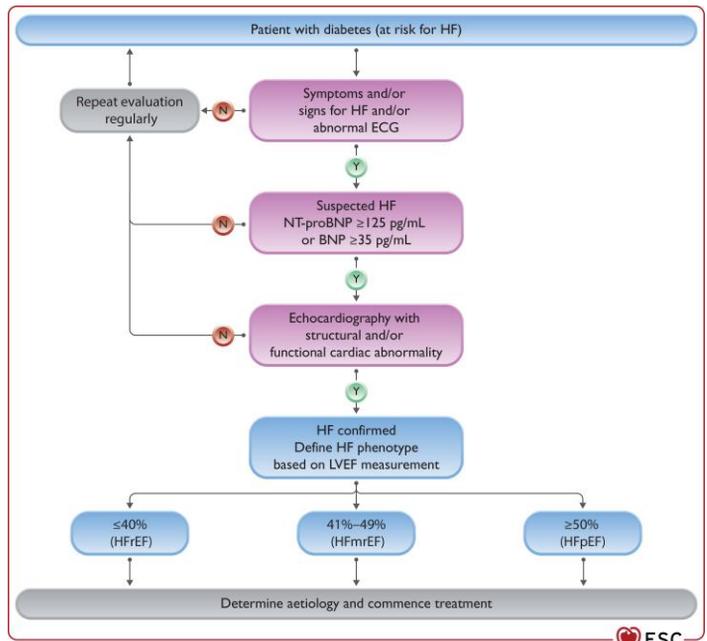
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ESC Diagnostic Algorithm for Heart Failure in Patients with Diabetes

Evaluation should also include: CXR, ECG, and blood tests including full blood count, urea, HbA1c, creatinine and electrolytes, thyroid function, lipids, and iron status (ferritin and TSAT).

Recommended options for **HFref**:
SGLT2i (dapa, empa, sota), ACE inhibitors, Sacubitril/valsartan, beta blockers, MRAs
Intensive strategy combines SGLT2i, ARNi/ACEi, beta blocker, and MRA

Recommended options for **HFpEF**:
SGLT2i (empa, dapa)
Diuretics if needed
BUT, what about obesity medications (i.e., sema)

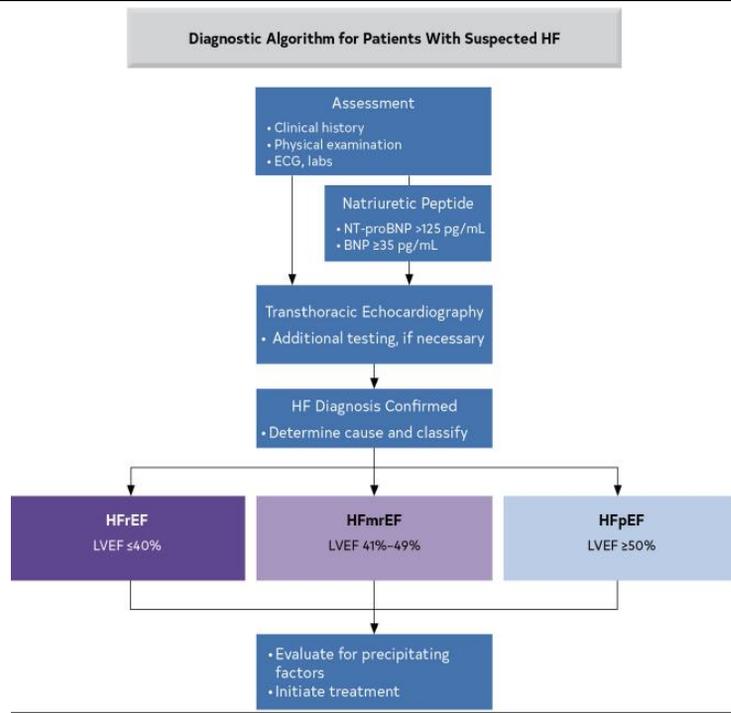


Eur Heart J, Volume 44, Issue 39, 14 October 2023, Pages 4043–4140, <https://doi.org/10.1093/eurheartj/ehad192>

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2022 AHA/ACC Algorithm for Diagnosis of Heart Failure

Heidenreich PA. 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.
Circulation. 2022;145(18):e895-
e1032



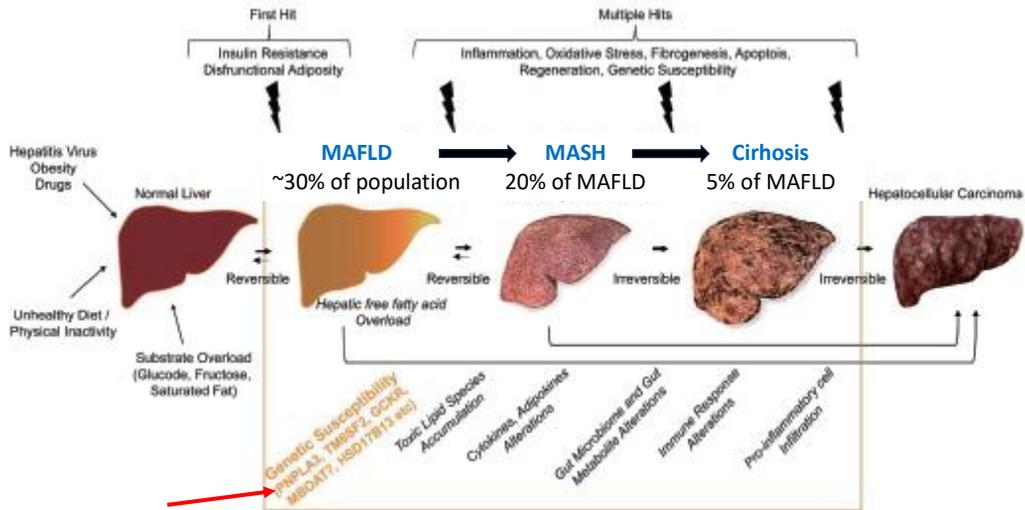
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Metabolic-Dysfunction Associated Fatty Liver Disease (MAFLD)

Metabolic-Dysfunction Associated Steatohepatitis (MASH)

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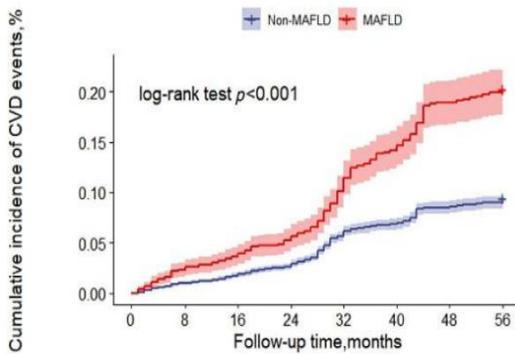
Progression of Metabolic-Dysfunction Associated Fatty Liver Disease



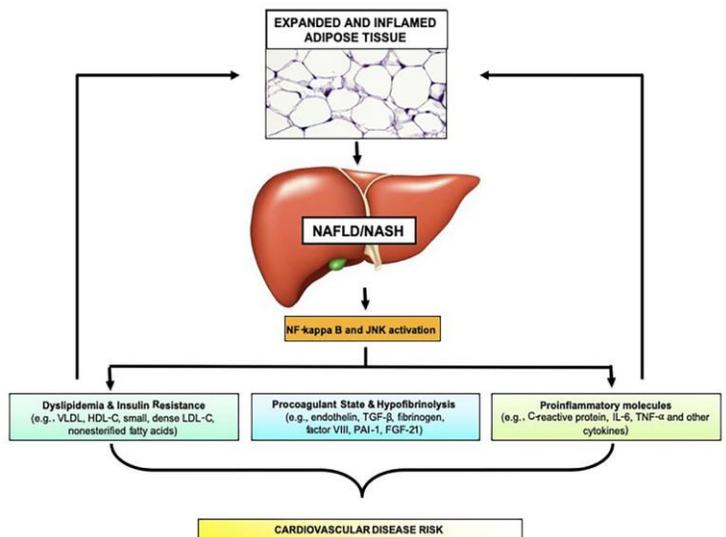
Mungamuri SK et al. Evolution of Non-alcoholic Fatty Liver Disease to Liver Cancer: Insights from Genome-wide Association Studies. *Gene Expr.* 2023;22(1):47-61

23

MAFLD and Cardiovascular Disease Risk



Guo Y et al. *Nutrients* 2022;14(12):2361



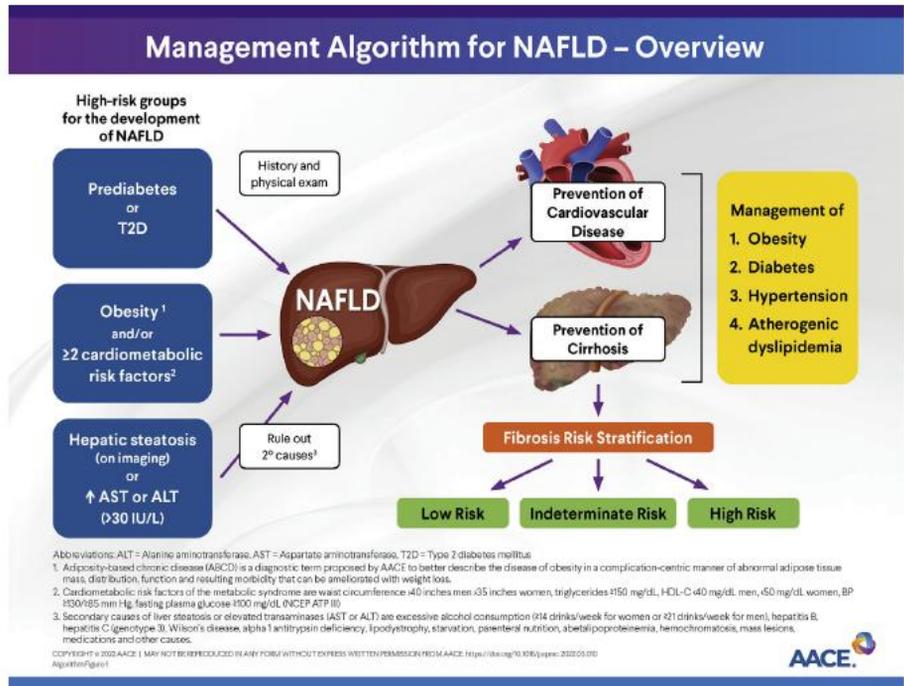
Przybyszewski EM et al. *Clin Liver Dis* 2021;17(1):19-22

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NAFLD and NASH Require Comprehensive Management of Cardiometabolic Disease

AACE/AASLD 2022 NAFLD Guidelines

Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JI, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract.* 2022 May;28(5):528-562.

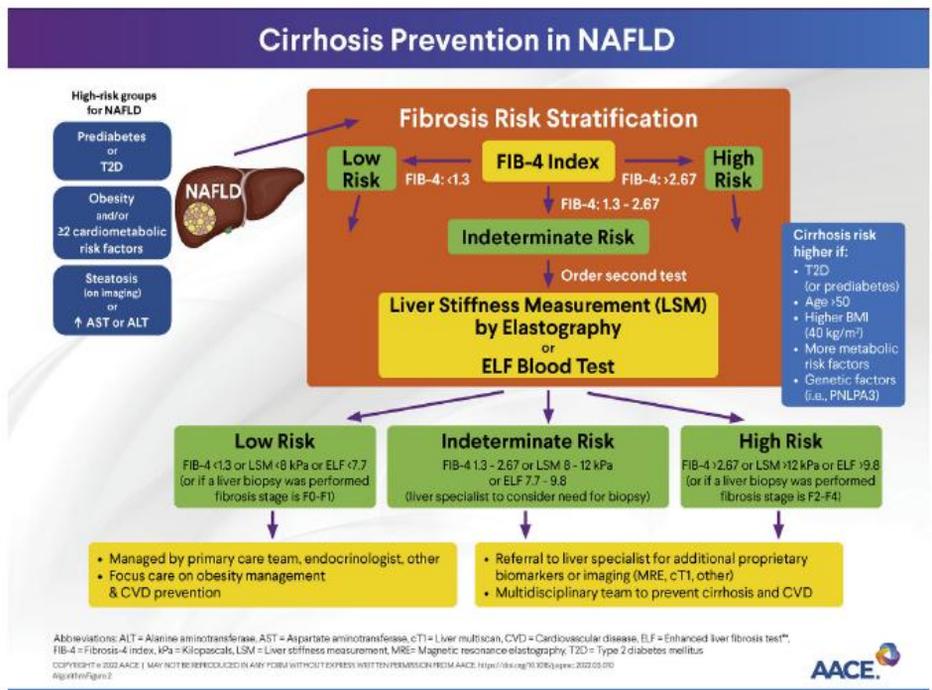


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Fibrosis Risk Stratification in NAFLD

AACE/AASLD 2022 NAFLD Guidelines

Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JI, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract.* 2022 May;28(5):528-562.



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Clinical Evaluation of MASH - Biochemical

Fibrosis -4 (Fib 4) Test

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = \text{Yellow pill}$$

Enhanced Liver Fibrosis Test (ELF)

ELF measures specific biomarkers related to liver fibrosis, including:

- hyaluronic acid (HA),
- procollagen III amino-terminal peptide (PIIINP),
- tissue inhibitor of matrix metalloproteinase 1 (TIMP-1)

<https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4>
 Are VS et al. Clin Gastroenterol Hepatol. 2021;19(6):1292-1293.e3

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Clinical Evaluation of MASH - Fibroscan

FibroScan is a non-invasive ultrasound test that measures:

- (i) liver stiffness due to fibrosis and
- (ii) amount of steatosis as the Capillary Attenuation Profile (CAP) Score

Capillary Attenuation Profile (CAP) Score:

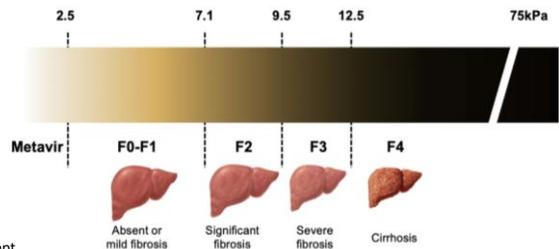
This score measures the amount of fat in the liver in units of decibels per meter (dB/m)

CAP Score	Steatosis Grade	Live fat content
238-260 dB/m	S1	11% to 33%
260-290 dB/m	S2	34% to 66%
290-400 dB/m	S3	> 67%

Liver Stiffness

Measured in kilopascals (kPa)

2 to 7 kPa	F0 to F1	Normal.
7.5 to 10 kPa	F2	Moderate scarring
10 to 14 kPa	F3	Severe scarring.
> 14 kPa	F4	Cirrhosis.



Kim HN et al. Evaluation and Staging of Liver Fibrosis. Hepatitis C Online. <https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-staging/core-concept>

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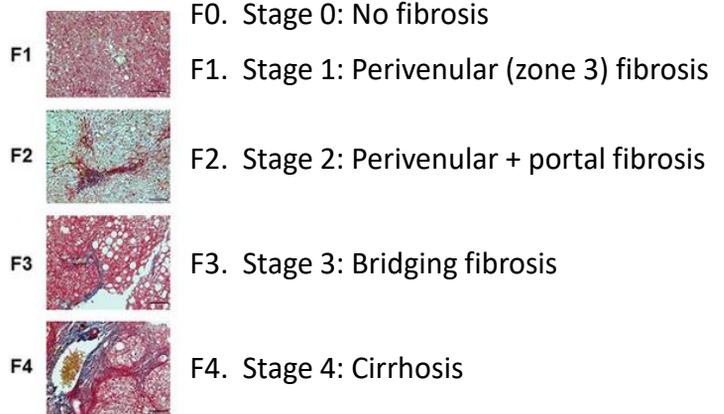
Histological Criteria for MASH

NAFLD Activity Score (NAS)

The NAS can range from 0 to 8 and is calculated by the sum of scores of:

- steatosis (0-3),
- lobular inflammation (0-3)
- hepatocyte ballooning (0-2)
- NAS score of ≥ 5 correlated with a diagnosis of "definite NASH".

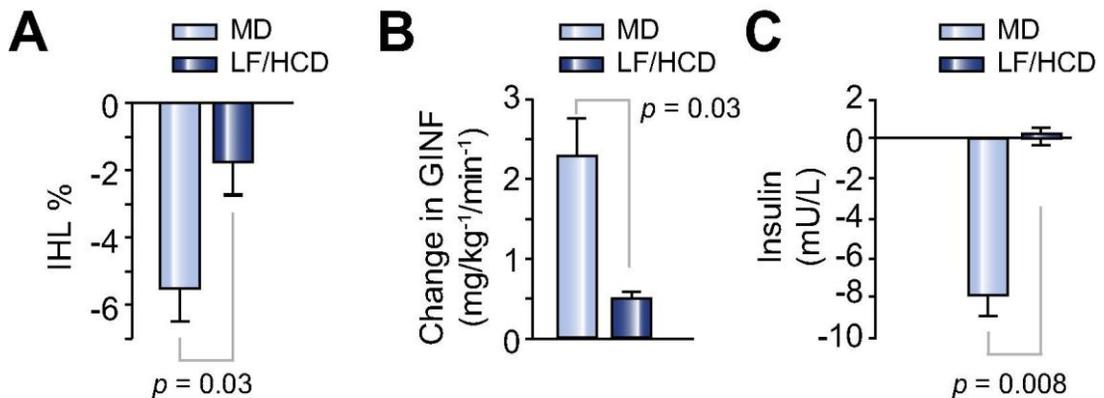
Fibrosis Score



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Mediterranean Diet Reduces Intrahepatocellular Lipid

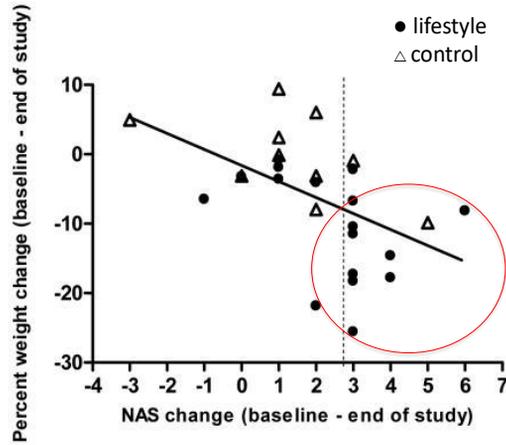
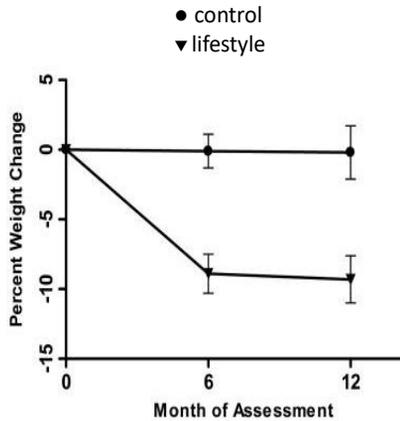
Twelve non-diabetic subjects (6 Females/6 Males) with biopsy-proven NAFLD were recruited for a randomised, cross-over 6-week dietary intervention study



Ryan MC et al. J Hepatol. 2013 Jul;59(1):138-43

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Randomized Controlled Trial Assessing Lifestyle-Induced Weight Loss on NAFLD Histology



Promrat K et al, Hepatology 51:121-129, 2010

NASH Activity Score: steatosis, lobular inflammation, hepatocyte ballooning. Improvement = change in 3 points

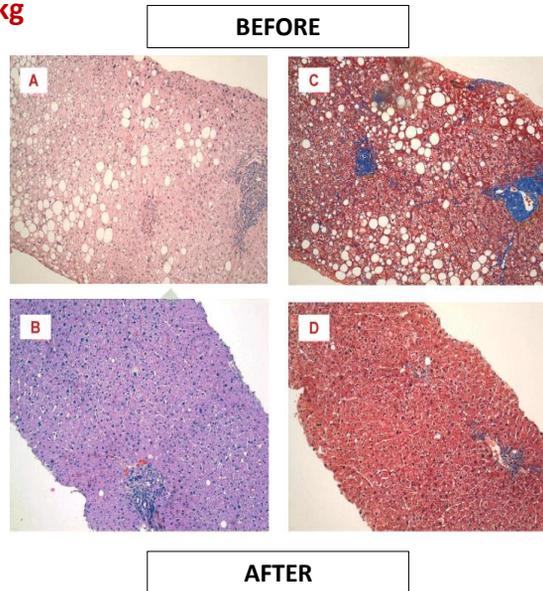
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Gastric Bypass Surgery and NAFLD

18 Months After Roux-en-Y, Weight Loss 50 kg

Histological Finding	Prevalence Before	Prevalence After
Steatosis	89.7%	2.9%
Hepatocellular Ballooning	58.9%	0%
Centrilobular Fibrosis	50%	25%

Note: no improvements in portal tract inflammation and fibrosis

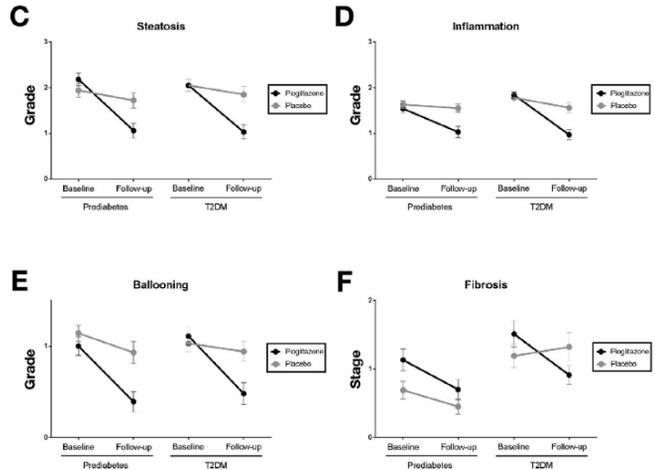
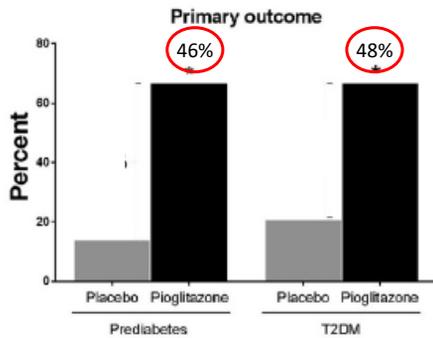


Liu X et al, Obesity Surgery 17:486-492, 2007

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Pioglitazone Improves NAS Histology Score in Both Prediabetes and T2D

- 49 with prediabetes
- 52 with T2D
- 18 month study
- Note: improvement in fibrosis not significant

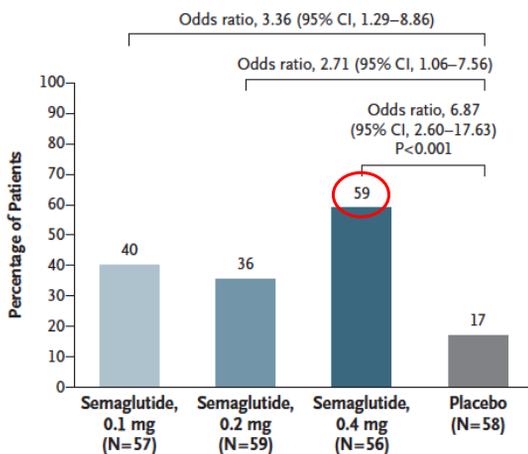


Bril F et al. Response to Pioglitazone in Patients With Nonalcoholic Steatohepatitis With vs Without Type 2 Diabetes. *Clinical Gastroenterology and Hepatology*. 2018;16(4):558-566.e2

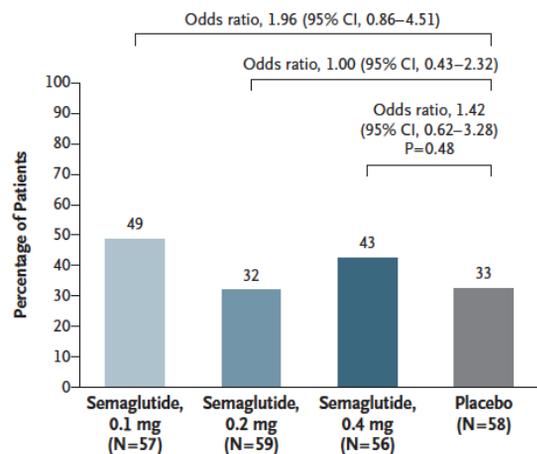
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Phase 2 RCT: Effects of High-Dose Semaglutide in Patients with NASH

A Resolution of NASH with No Worsening of Liver Fibrosis (primary end point)



B Improvement in Liver Fibrosis Stage with No Worsening of NASH (confirmatory secondary end point)

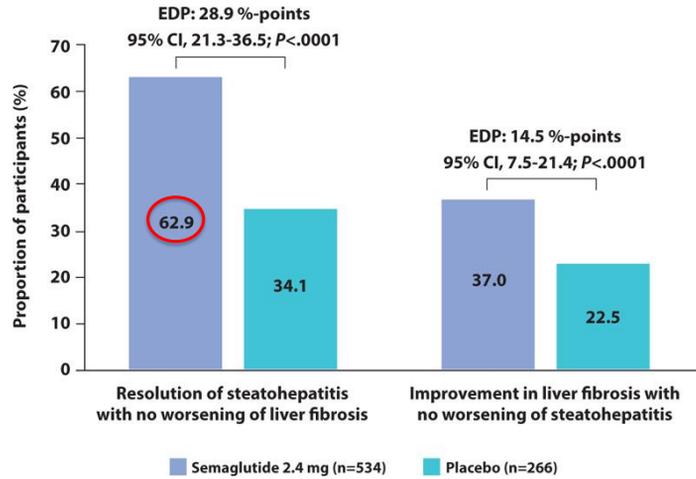


Resolution NASH = no inflammation or ballooning; change in fibrosis = change in one or more F1 to F4 fibrosis stage by week 72
 Newsome PN et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *NEJM* 2021;384(12):1113-1124.

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Phase 3 ESSENCE Trial: Semaglutide Improves MASH Histology

- 1197 patients with F2-F3 MASH
- 72 week interim analysis of 240 week study



Combined resolution of steatohepatitis and improvement in liver fibrosis was reported in 32.7% of the patients in the semaglutide group and in 16.1% of those in the placebo group (difference, 16.5 percentage points; 95% CI, 10.2 to 22.8; P<0.001)



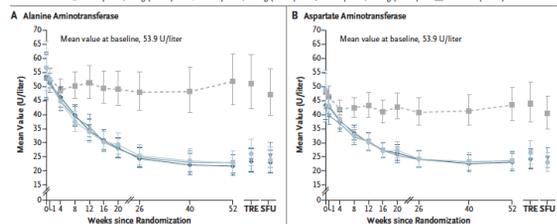
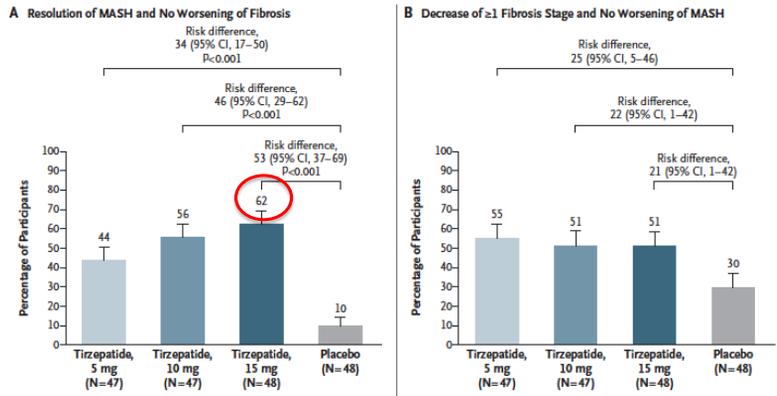
Mean change in body weight was -10.5% with semaglutide and -2.0% with placebo (difference, -8.5 percentage points; 95% CI, -9.6 to -7.4; P<0.001)

Sanyal AJ et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025 Apr 30.
doi: 10.1056/NEJMoa2413258

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SYNERGY-NASH Study: Tirzepatide Improves MASH Histology

- Tirzepatide is a GLP-1/GIP dual agonist
- Phase 2 study
- 190 patients with F2-F3 MASH histology
- 52 week study



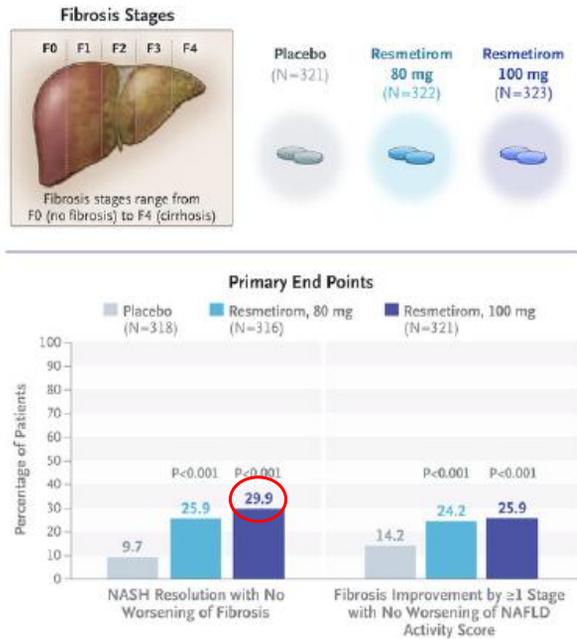
Loomba R et al. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. The New England Journal of Medicine. 2024;391(4):299-310

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Resmetiron, a Thyroid Hormone Beta Receptor Agonist, First Medication Approved for Treatment of NASH on March 14, 2024

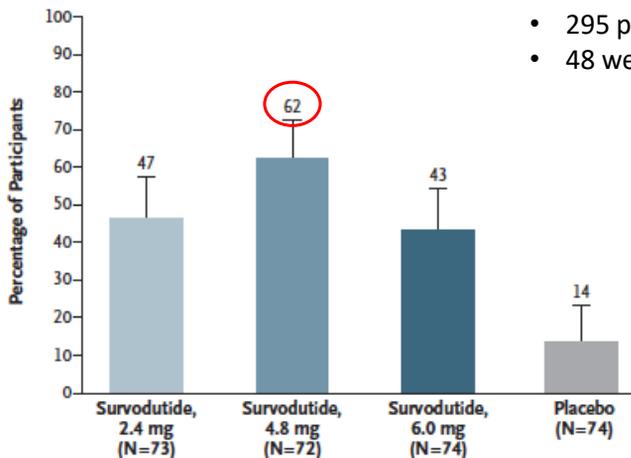
Resmetiron works to reduce liver fat by stimulating fatty acid degradation and oxidation.

Harrison SA et al...and MAESTRO-NASH Investigators. A Phase 3, Randomized, Controlled Trial of Resmetiron in NASH with Liver Fibrosis. N Engl J Med. 2024 Feb 8;390(6):497-509.



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Phase 2: Efficacy of Survodutide in MASH



- Survodutide is a GLP-1/Glucagon dual agonist
- 295 patients with with F1-F3 fibrosis on biopsy
- 48 week study

Improvement in fibrosis

- 34% in the survodutide 2.4 mg group,
- 36% in the survodutide 4.8-mg group
- 34% in the Survodutide 6.0 mg group,
- 22% in the placebo group

Sanyal AJ et al. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. N Engl J Med. 2024;391(4):311-319.

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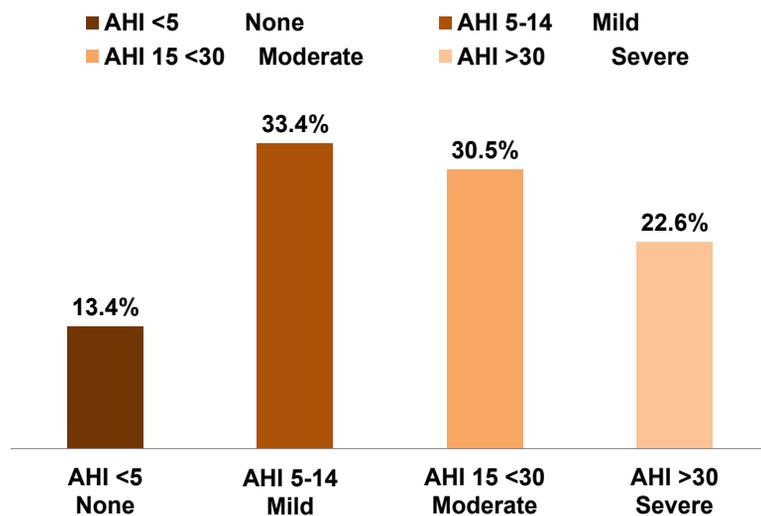
Obstructive Sleep Apnea

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The Sleep AHEAD Study: Presence and Severity of Sleep Apnea in Patients with Obesity and T2DM

Mean BMI = 36.7
Mean HbA1c = 7.2%

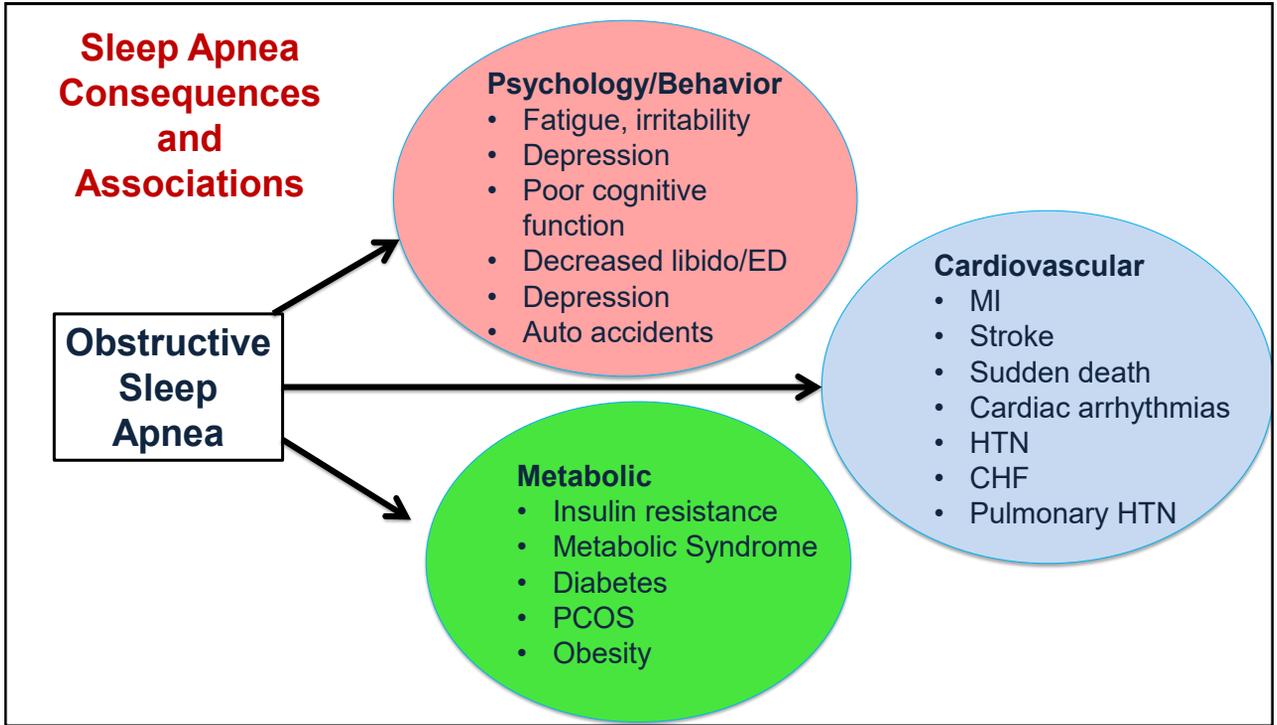
86.6%
patients have
sleep apnea



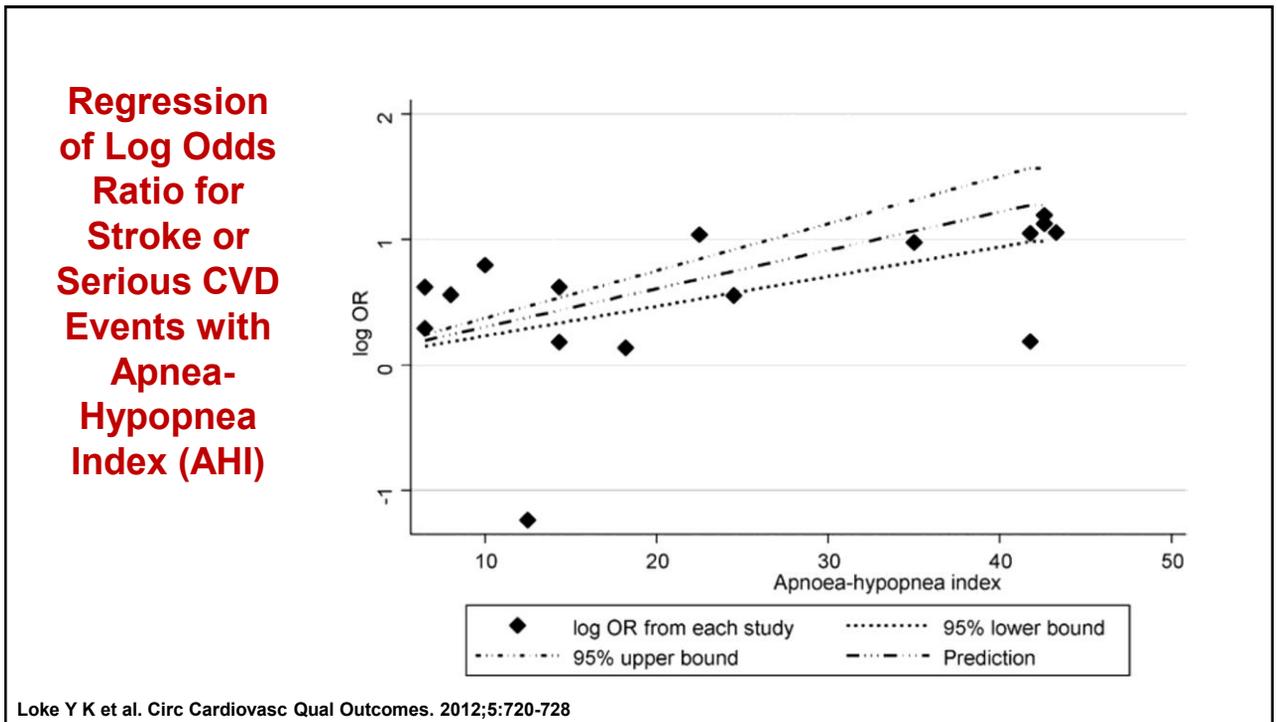
Foster GD, et al. *Diabetes Care*. 2009;32(6):1017-1019.

AHI=apnea-hypopnea index

40



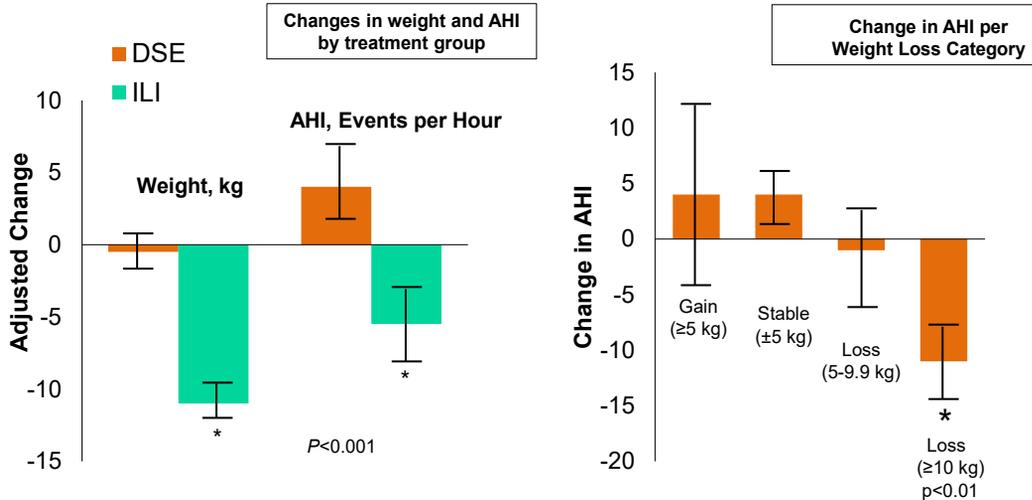
41



Loke Y K et al. Circ Cardiovasc Qual Outcomes. 2012;5:720-728

42

Effect of Lifestyle-Medicated Weight Loss on Sleep Apnea in Sleep AHEAD



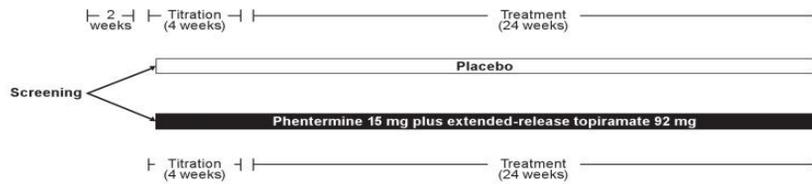
Foster GD, et al. *Arch Intern Med.* 2009;169(17):1619-1626.

ILI=Intensive lifestyle intervention
 DSE=Diabetes support and education
 AHI=apnea-hypopnea index

43

Effects of Phentermine/Topiramate ER-Induced Weight Loss in Patients with Sleep Apnea

RCT: all treated with lifestyle and then randomized to placebo or drug

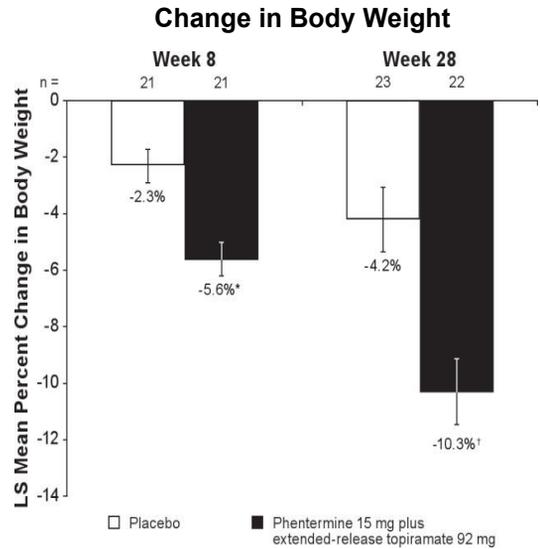
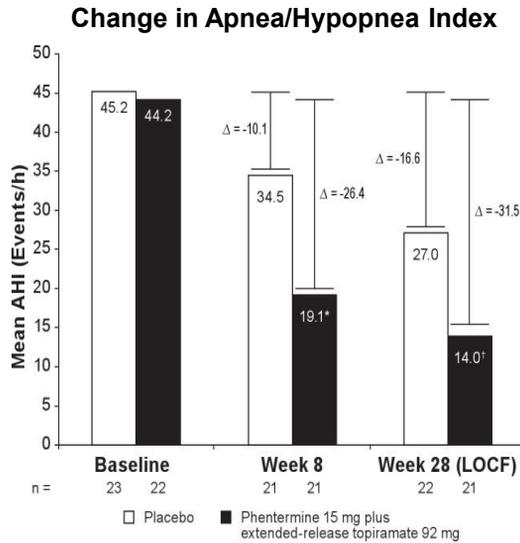


Parameter	Placebo (n = 23)	Phentermine 15 mg plus Extended-Release Topiramate 92 mg (n = 22)
AHI, events/h (SD)	45.2 (34.25)	44.2 (22.40)
RDI, events/h (SD)	60.7 (31.78)	58.8 (21.24)
Mean overnight oxygen saturation, % (SD)	93.9 (2.39)	93.4 (1.99)
Minimum overnight oxygen saturation, % (SD)	76.3 (13.88)	77.1 (13.59)
Arousal index, arousals/h (SD)	63.5 (30.49)	61.5 (20.27)
Apnea index, events/h (SD)	16.1 (24.23)	9.4 (15.95)
Hypopnea index, events/h (SD)	29.1 (18.78)	34.8 (18.76)

Winslow DH et al, *Sleep* 35:1529-1539, 2012

44

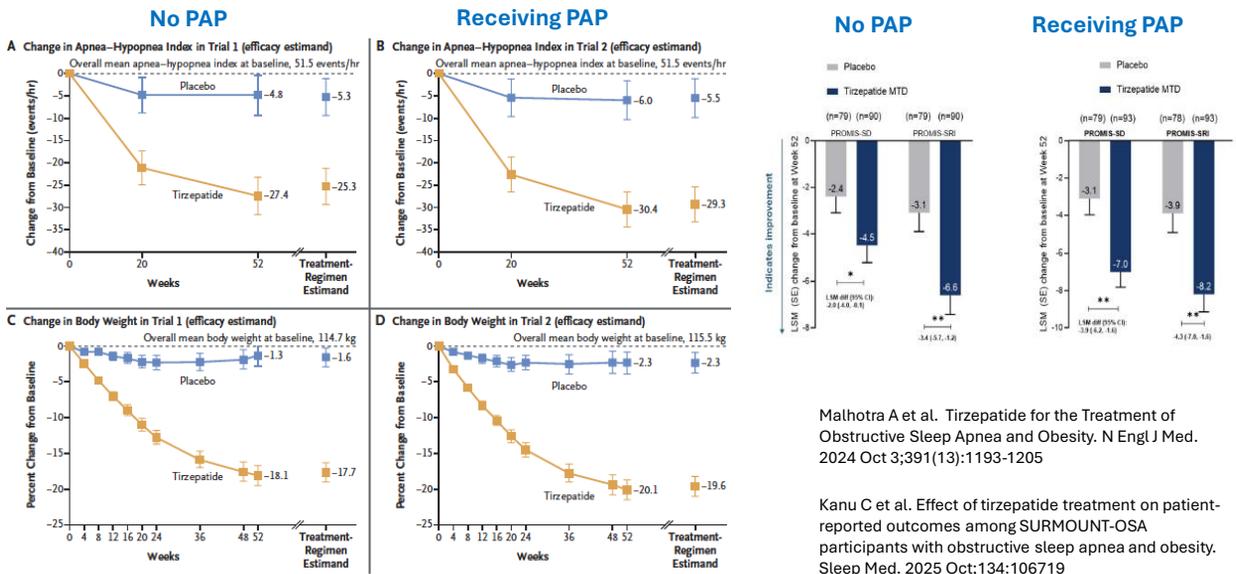
Improvements in Sleep Apnea with Phentermine/Topiramate ER Therapy



Winslow DH et al. *Sleep*, 35:1529, 2012

45

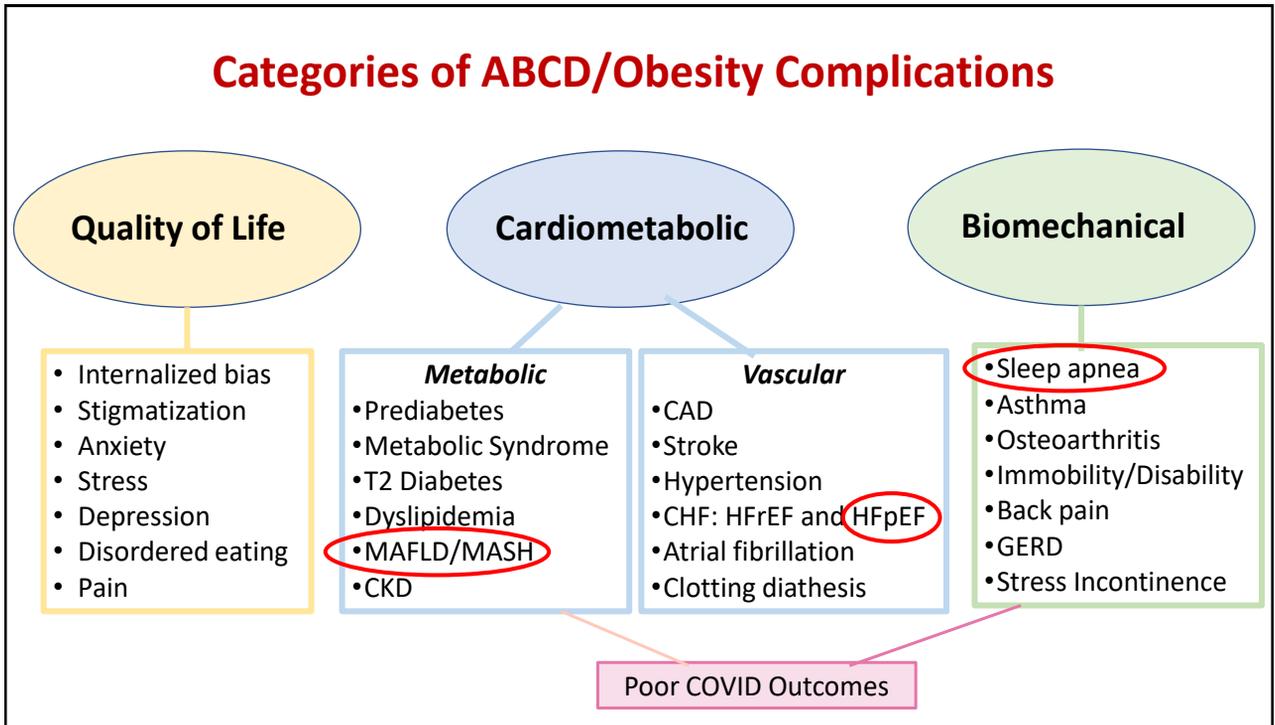
Tirzepatide Improves Obstructive Sleep Apnea: SURMOUNT-OSA Trial



Mathotra A et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *N Engl J Med*. 2024 Oct 3;391(13):1193-1205

Kanu C et al. Effect of tirzepatide treatment on patient-reported outcomes among SURMOUNT-OSA participants with obstructive sleep apnea and obesity. *Sleep Med*. 2025 Oct;134:106719

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47

TM Is a 57-Year-Old Asian Woman seeks Assistance with Weight Loss

- **Weight History:** ▪ slow weight gain throughout adulthood; failed multiple diet plans with weight regain; ▪ busy Mom and receptionist; ends up eating fast foods due to time constraints
- **Medical:** Hypertension for 5 years on HCTZ 25 mg/day
- **ROS:** complains of knee pain that limits her walking program; noted increasing SOB with less exertion over the past 4 months
- **Family history:** T2D and CAD in father, T2D in sister age 60



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Exam and Laboratory Data

Physical Exam: 5' 4"; 216 lbs; BMI 37 kg/m²; waist 94 cm
BP 140/84;
heart & lungs normal, trace edema both ankles

Labs

Fasting glucose 121 mg/dL; HbA1c 6.3%;
Triglycerides 178; HDLc 38; LDL 105; non-HDL 138
LFTs WNL; TSH WNL; eGFR 78; no albuminuria
ECG unremarkable;
Knee films show narrowing of joint space bilaterally

Assessment

1. Adiposity Based Chronic Disease
2. Anthropometric: Class II Obesity
3. Clinical: Multiple Weight Related Complications, Stage TBD
4. Hypertension - One Medication with BP Not at Target
5. Osteoarthritis Bilateral Knees - Symptomatic
6. Increasing SOB - Causation Not Established
7. Prediabetes
8. Metabolic Syndrome with Dyslipidemia

Which of the Following Assessments Is Potentially the Most Harmful in the Short Term and Warrants More Pressing Evaluation?

- A. Excess adiposity
- B. Shortness of breath
- C. Prediabetes
- D. Hypertension
- E. Osteoarthritis



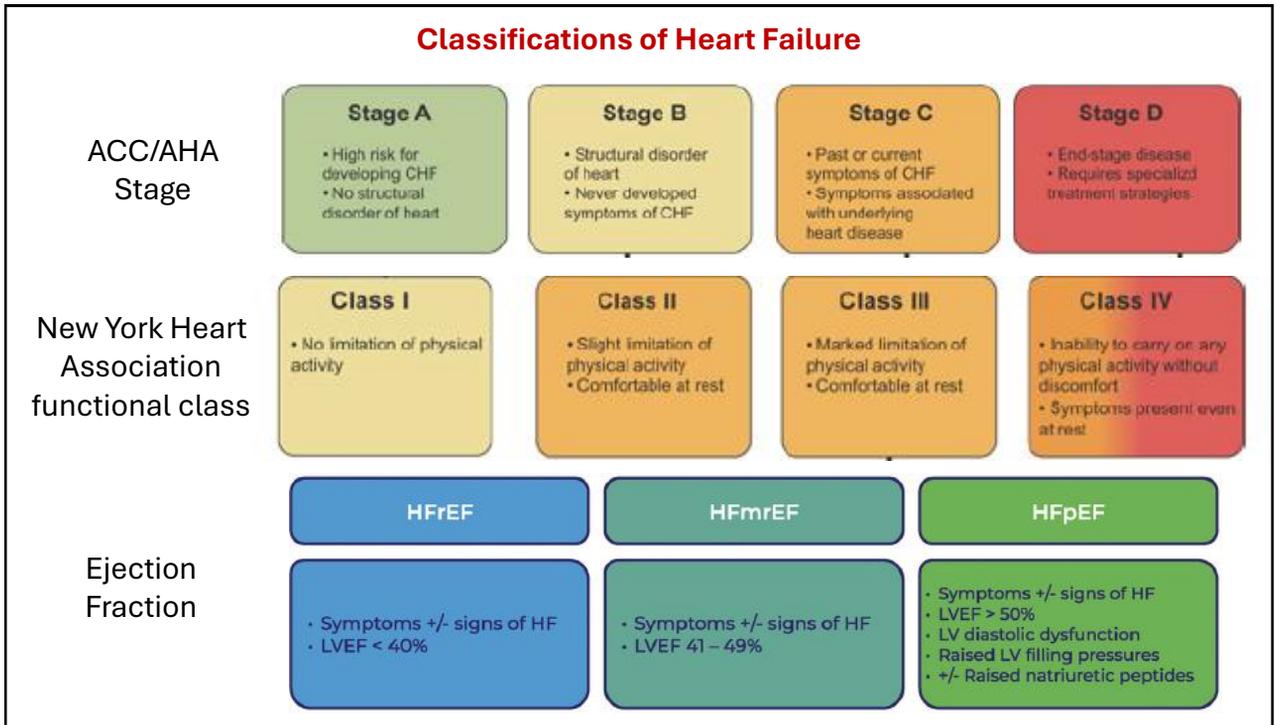
51

Which of the Following Is the Worst Choice in the Differential Diagnosis of the SOB?

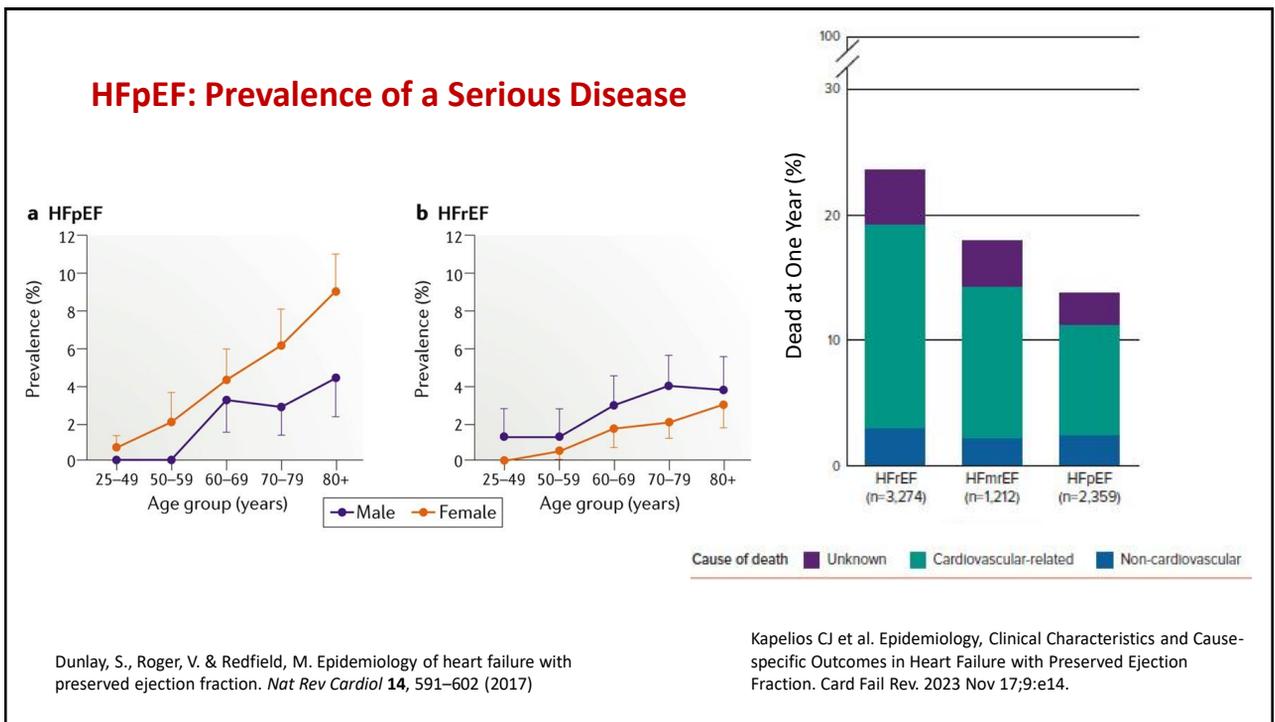
- A. Obstructive sleep apnea
- B. HFpEF
- C. HFrEF
- D. Multiple pulmonary emboli
- E. Just part of having obesity
- F. Intermittent atrial fibrillation



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TM complains of SOB increasing over 4 months. She gets SOB walking one block. Trace edema noted. No atrial fibrillation on ECG, lungs clear, CXR normal
What Is a Reasonable Next Step for Evaluation?

- A. Get arterial blood gases
- B. Obtain pulmonary function tests
- C. Get NT-proBNP level
- D. Obtain pulmonary function tests
- E. Cardiac ultrasound
- F. Order exercise stress test
- G. Pulmonary V/Q scan

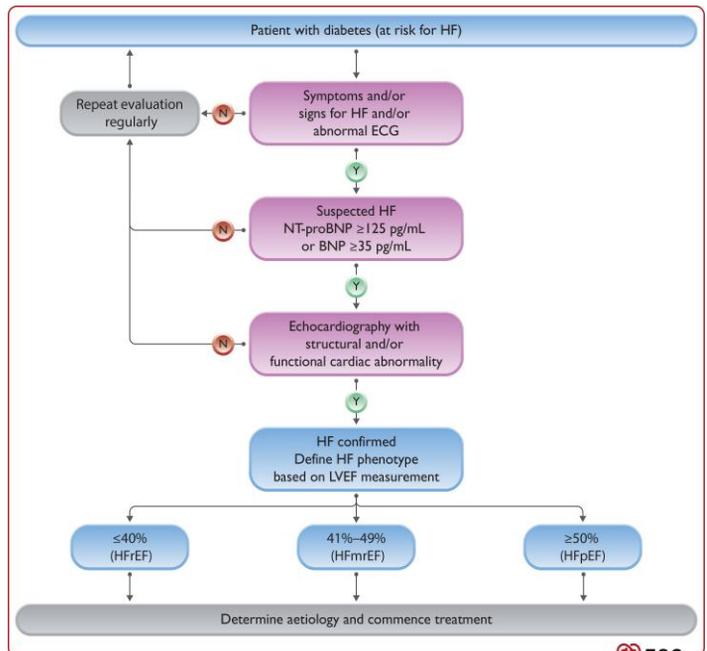


ESC Diagnostic Algorithm for Heart Failure in Patients with Diabetes

Evaluation should also include: CXR, ECG, and blood tests including full blood count, urea, HbA1c, creatinine and electrolytes, thyroid function, lipids, and iron status (ferritin and TSAT).

Recommended options for **HF_rEF**:
 SGLT2i (dapa, empa, sota), ACE inhibitors
 Sacubitril/valsartan, beta blockers, MRAs
 Intensive strategy combines SGLT2i, ARNi/ACEi, beta blocker, and MRA

Recommended options for **HF_pEF**:
 SGLT2i (empa, dapa)
 Diuretics if needed
 BUT, what about obesity medications (i.e., sema)

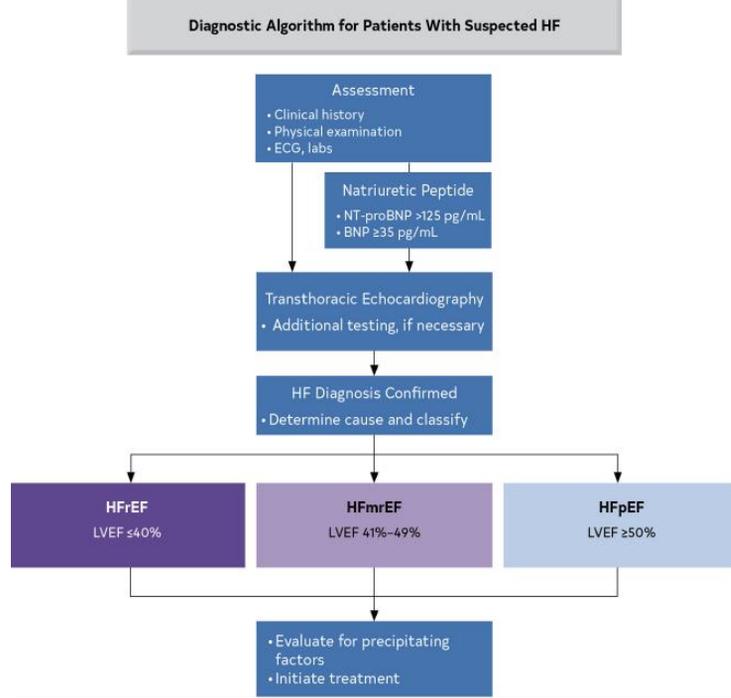


Eur Heart J, Volume 44, Issue 39, 14 October 2023, Pages 4043–4140, <https://doi.org/10.1093/eurheartj/ehad192>



2022 AHA/ACC Algorithm for Diagnosis of Heart Failure

Heidenreich PA. 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.
Circulation. 2022;145(18):e895-
e1032



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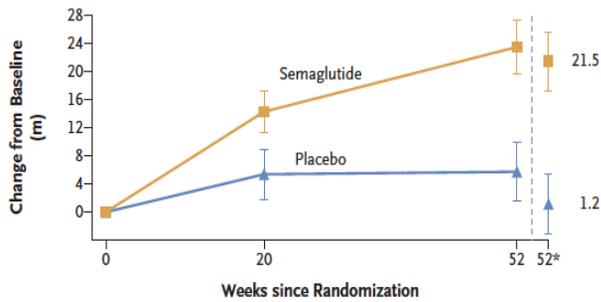
For Which Medications Approved for Obesity Is There Evidence for Improvement in HFpEF? (Check All that Are Correct)

- A. Tirzepatide
- B. SGLT1 inhibitors
- C. Finerenone
- D. Semaglutide
- E. ACEi and ARBs
- F. Beta Blockers

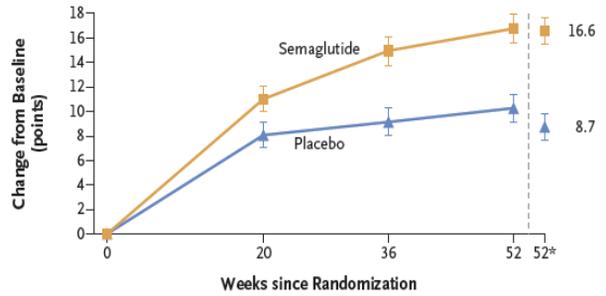
58

STEP HFpEF: Effects of Semaglutide 2.4 mg in Patients with Symptomatic HFpEF and Obesity

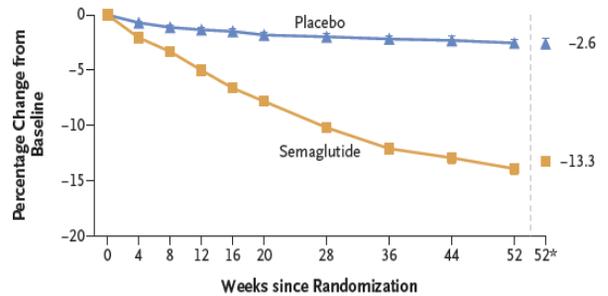
Change in 6-Minute Walk Distance



Change in KCCQ-CSS*



% Change in Body Weight

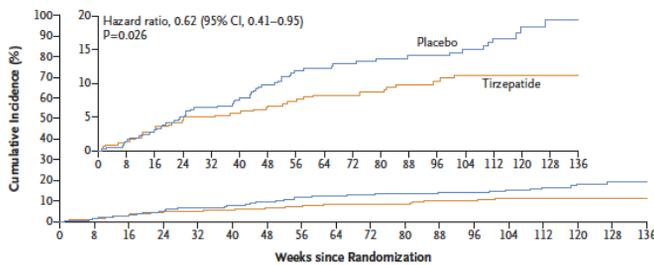


*Kansas City Cardiomyopathy Questionnaire
Kosiborod MN et al. NEJM. DOI: 10.1056/NEJM oa2306963. Epub Aug 25, 2023

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The SUMMIT Trial: Tirzepatide Improves HFpEF Outcomes and Symptoms

Reduction in Hazard Ratio for the composite Endpoint: CV death + heart failure event



No. at Risk	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

Improvement in the Kansas City Cardiomyopathy Questionnaire

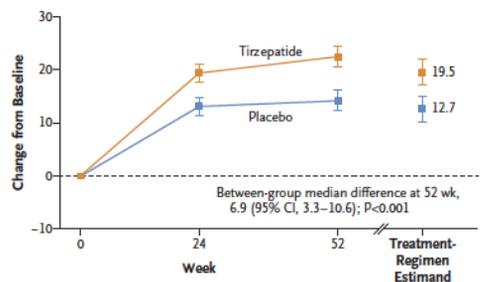


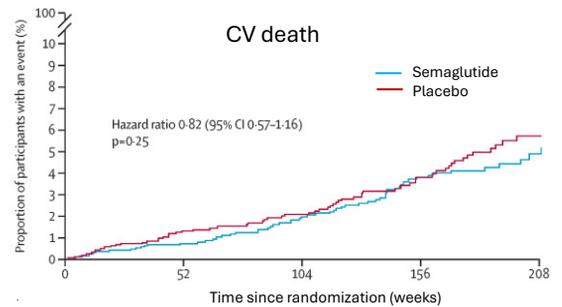
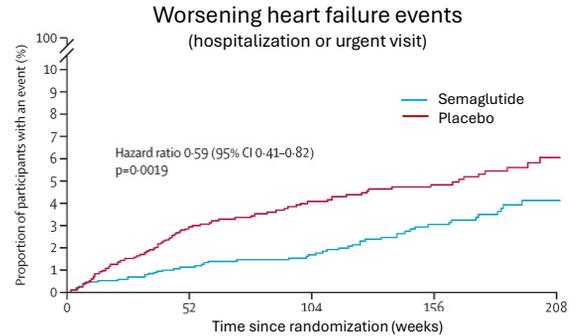
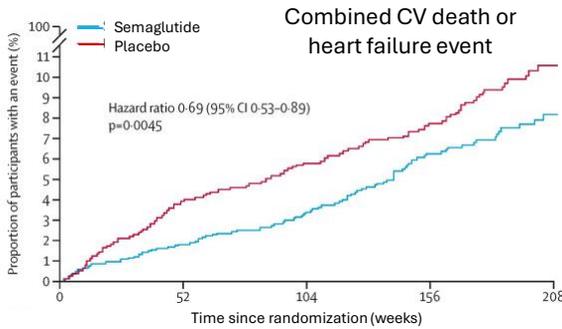
Figure 1. Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event.
Shown is the cumulative incidence of death from cardiovascular causes or a worsening heart-failure event (the composite primary end point), assessed in a time-to-first-event analysis, among 364 patients who received tirzepatide and 367 patients who received placebo. The inset shows the same data on an expanded y axis.

Packer M et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2025;392(5):427-437

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Semaglutide Improves Heart Failure

- 3743 patients with HFpEF from SELECT, FLOW, STEP-HFpEF, STEP-HFpEF DM
- Improvements in HFpEF and HFrEF
- Additive benefit to SGLT2i



Kosiborod MN et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. *Lancet*. 2024;404(10456):949-961.

61

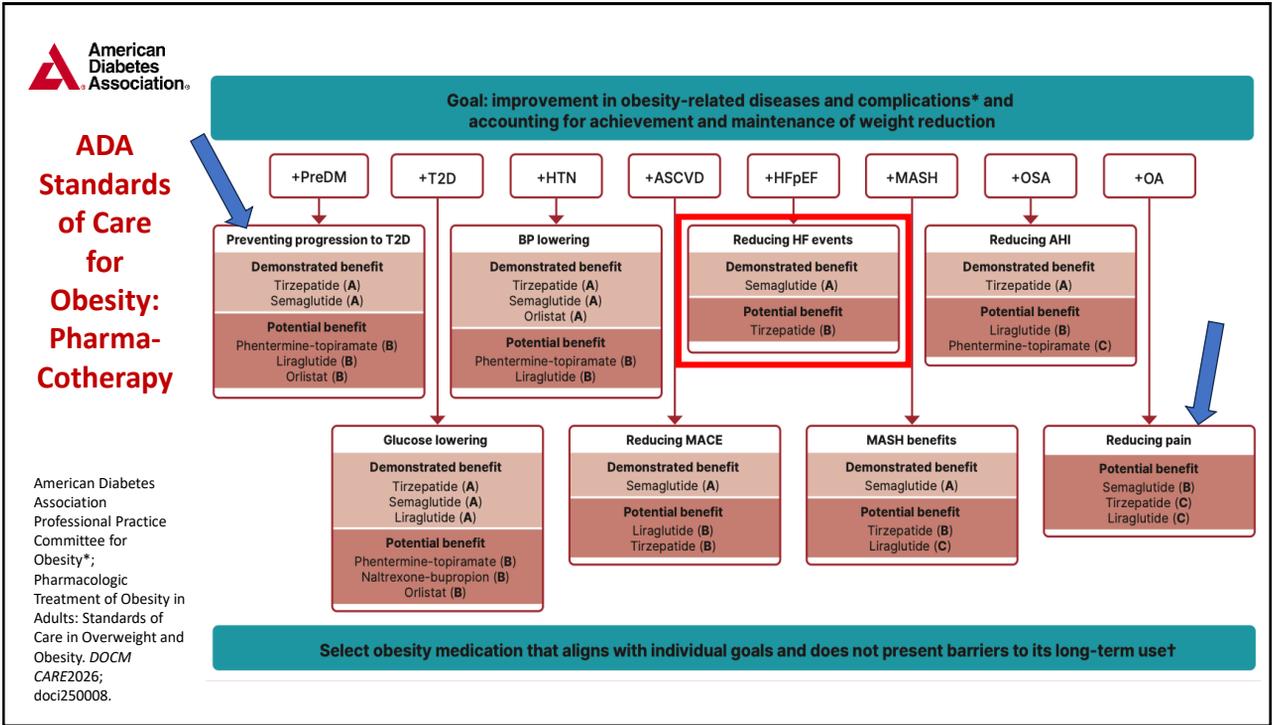
Recommended Pharmacologic Management of CHF in Diabetes

	ESC	AACE	AHA
Medications	<ul style="list-style-type: none"> • for HFrEF, HFmrEF, HFpEF SGLT2i (dapagliflozin, empagliflozin, sotagliflozin) • For HFrEF Early intensive treatment is ARNi or ACEi+ beta blocker, MRAs 	<ul style="list-style-type: none"> • for HFrEF, HFmrEF, HFpEF SGLT2i (dapagliflozin, empagliflozin, sotagliflozin) • For HFrEF in DM and stage B failure ACEi or ARBs and b-blockers are recommended to reduce the risk for symptomatic stage C 	<ul style="list-style-type: none"> • HFrEF: LVEF ≤ 40% ACEi or ARB or ARNi, SGLT2i, beta blocker, MRA, diuretics as needed • HFmrEF: LVEF 41-49% ACEi or ARB or ARNi, SGLT2i, beta blocker, MRA, diuretics as needed • HFpEF: LVEF ≥ 50% SGLT2i

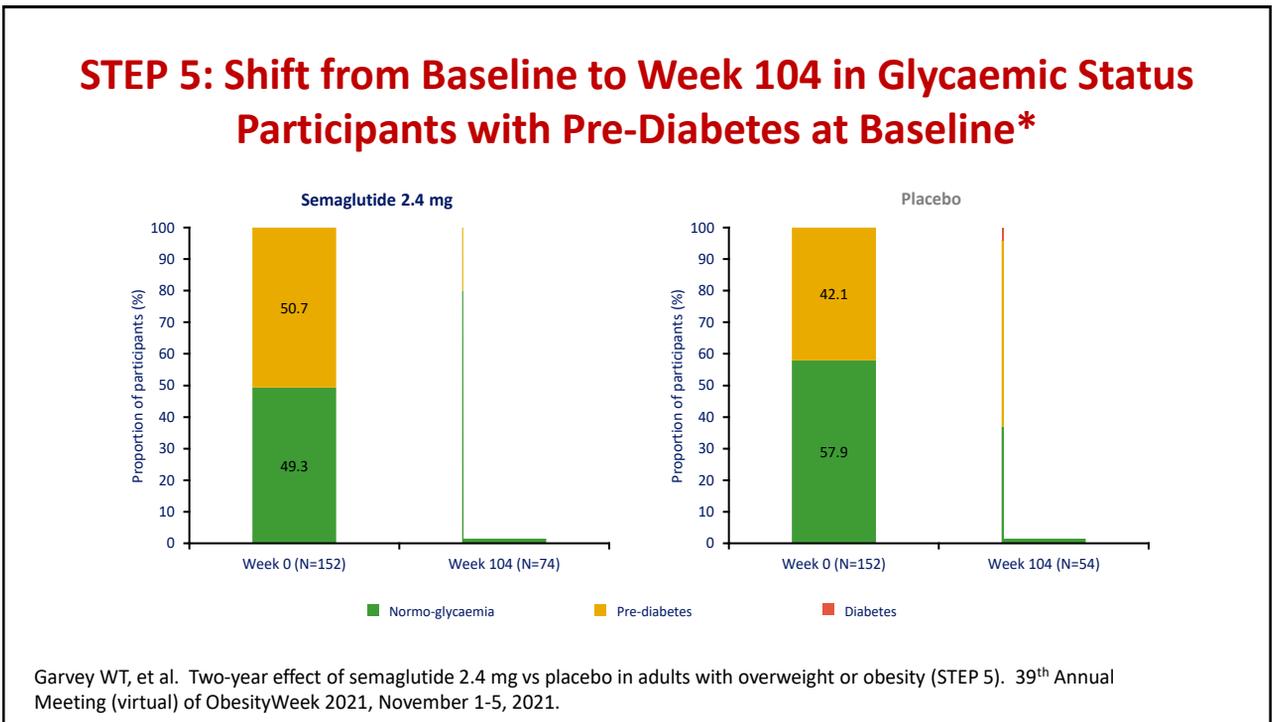
But what about GLP-1 agonist mediations ?

Heidenreich P et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation* 2022;145(18):E895-E1032
 Marx N et al. *Eur Heart J*. 2023 Oct 14;44(39):4043-4140. Samson SL et al. *Endocr Pract*. 2023 May;29(5):305-340.

62

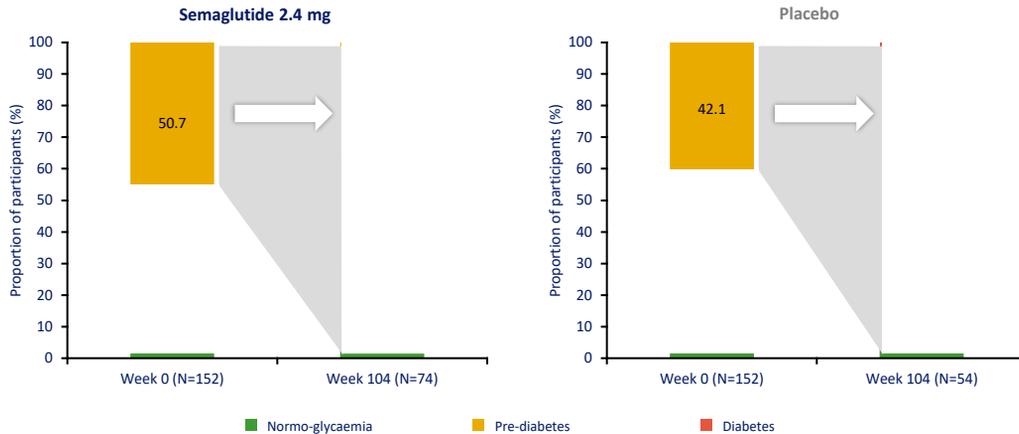


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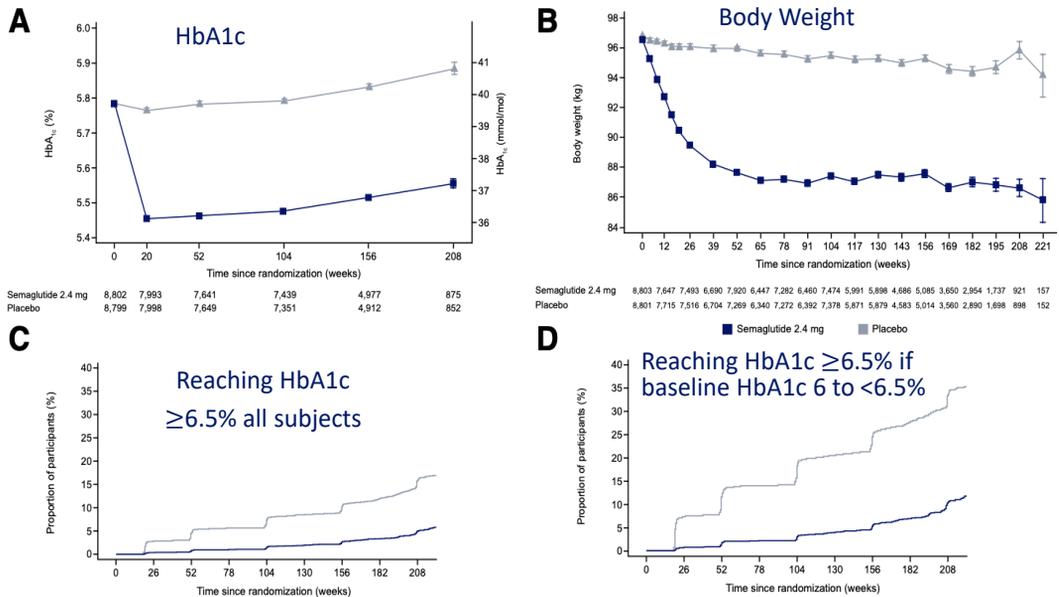
STEP 5: Shift from Baseline to Week 104 in Glycaemic Status Participants with Pre-Diabetes at Baseline*



Garvey WT, et al. Two-year effect of semaglutide 2.4 mg vs placebo in adults with overweight or obesity (STEP 5). 39th Annual Meeting (virtual) of ObesityWeek 2021, November 1-5, 2021.

65

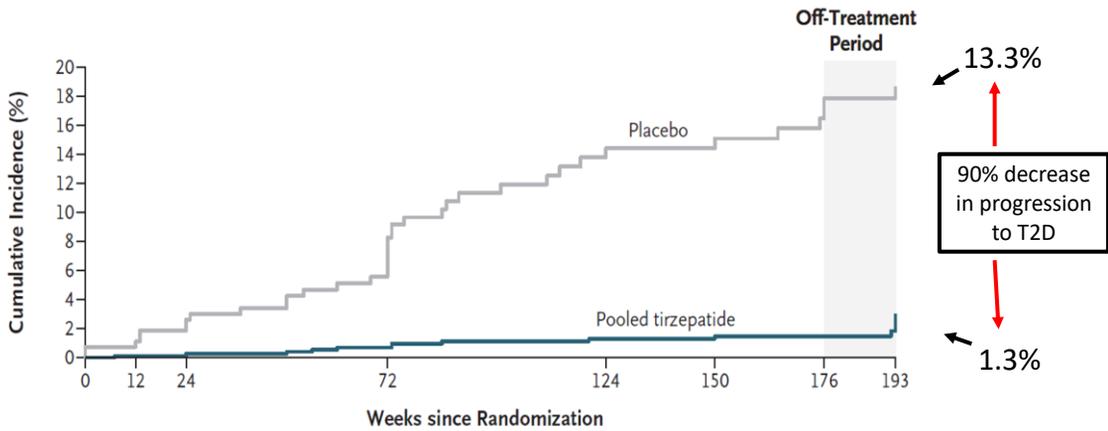
Semaglutide Prevents Progression to Diabetes in the SELECT Trial



Steven E. Kahn SE et al. Effect of Semaglutide on Regression and Progression of Glycemia in People With Overweight or Obesity but Without Diabetes in the SELECT Trial. *Diabetes Care* 25 July 2024; 47 (8): 1350–1359

66

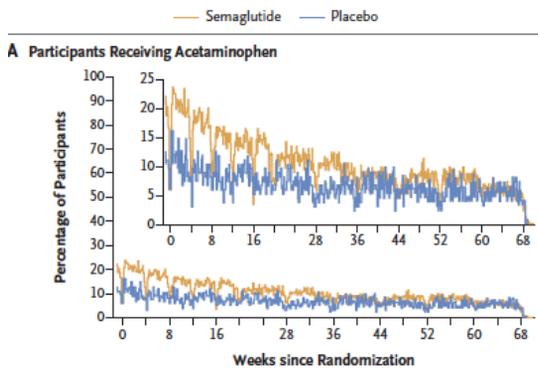
SURMOUNT-1 T2D Prevention Study Cumulative Incidence of T2D During the Course of the Trial



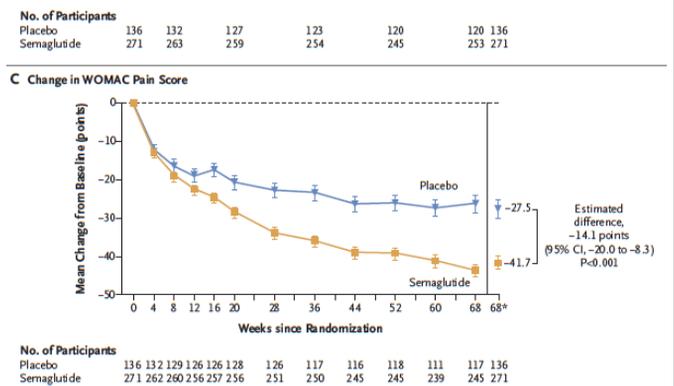
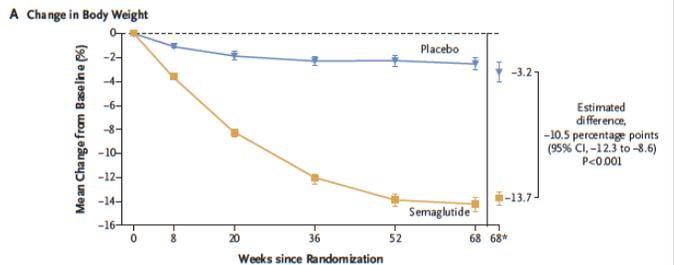
Jastreboff AM, le Roux CW, Stefanski A, et al. N Engl J Med. 2025;392:958-971

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STEP-OA Trial: Semaglutide Improves Symptoms of Osteoarthritis and Reduces Need for Pain Medications



Bliddal H et al. Once Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. NEJM. 2024; 391(17):1573-1583



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Second Generation Obesity Medications Treat Cardiometabolic Disease

