Glp-1RA e disfunzione ventricolare nel diabete e nell'obesità: una nuova frontiera nella cura dello scompenso?

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Disclosures

- I declare financial interest for **consultancy** with:

Novartis, Merck, Bayer, Vifor Pharma, Abbott, Boehringer Ingelheim, Astra-Zeneca, Bioventrix, Servier, **Novo Nordisk**, **Lilly**, Cardurion, AnaCardio, Occlutech

Is the phenotyping approach still valid after EMPEROR Preserved, DELIVER and FINEARTS ?

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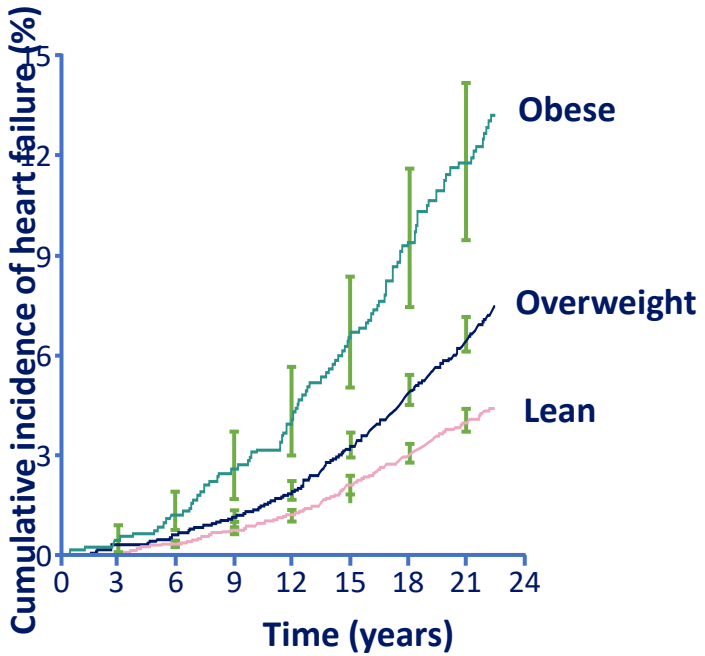
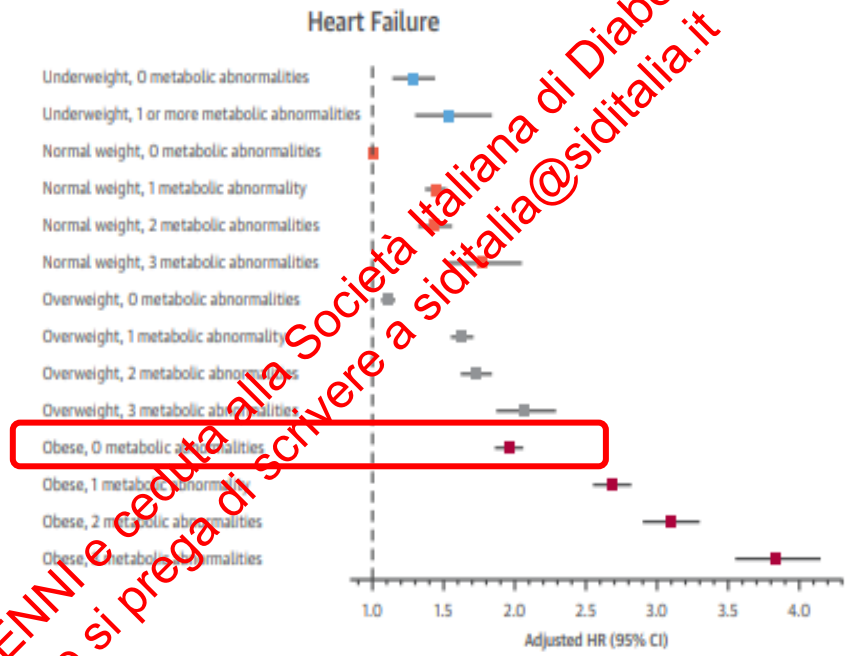
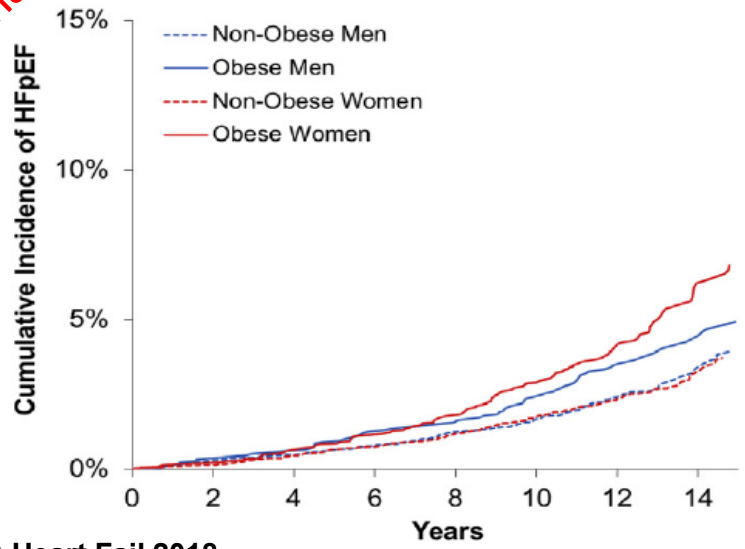
Obesity and incidence of HFpEF



Association of Obesity-Related Traits With HF Subtypes in Sex-Pooled Analyses		
		Multivariable-adjusted
Predictor	Outcome	HR (95% CI)*
BMI	Incident HFpEF	1.34 (1.24; 1.45)
	Incident HFrEF	1.18 (1.10; 1.27)
Waist circumference	Incident HFpEF	1.32 (1.22; 1.44)
	Incident HFrEF	1.19 (1.10; 1.29)



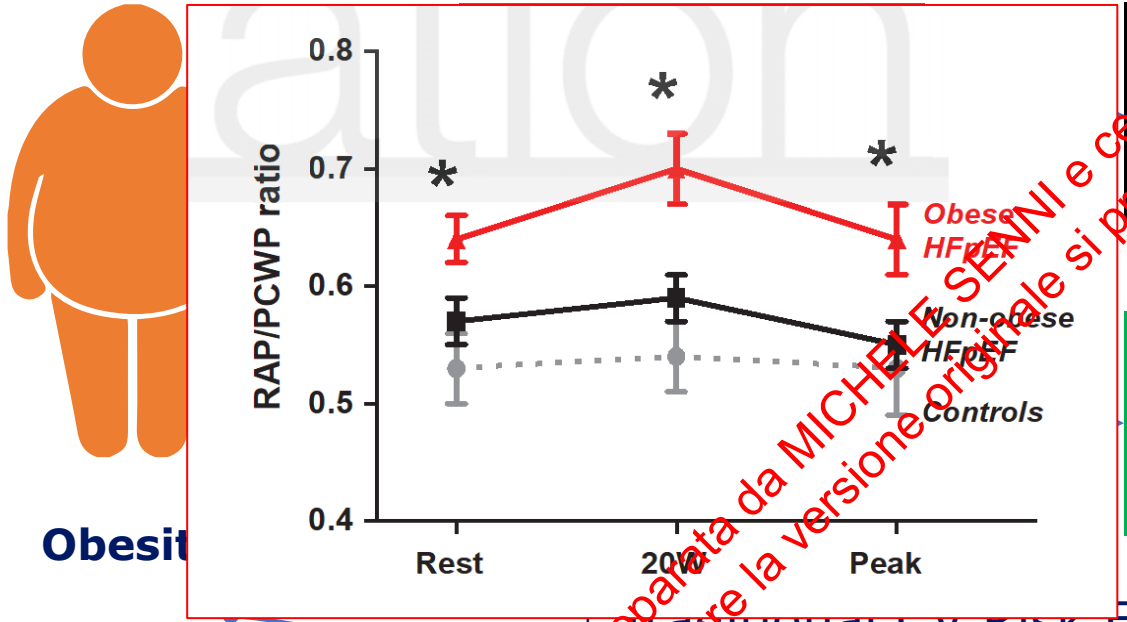
Caleyachetti R et al. JACC 2017

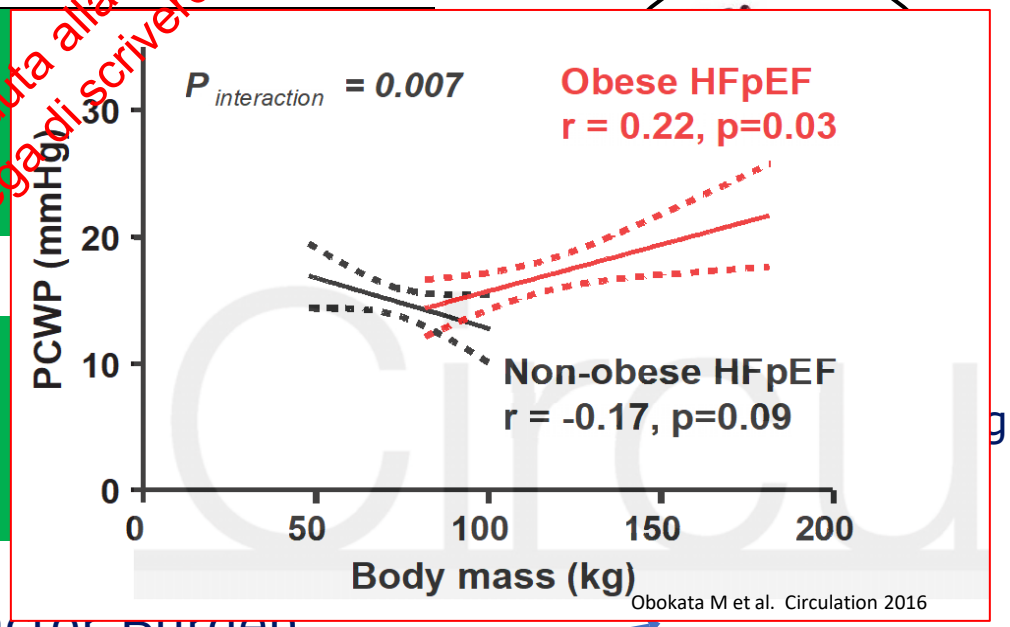


Savji N et al. JACC Heart Fail 2018

Mechanisms through which obesity may contribute to development of HFpEF

↓ Chest Wall Compliance





Obokata M et al. Circulation 2016

Obesit

↑ Additional CV Risk Factor Burden

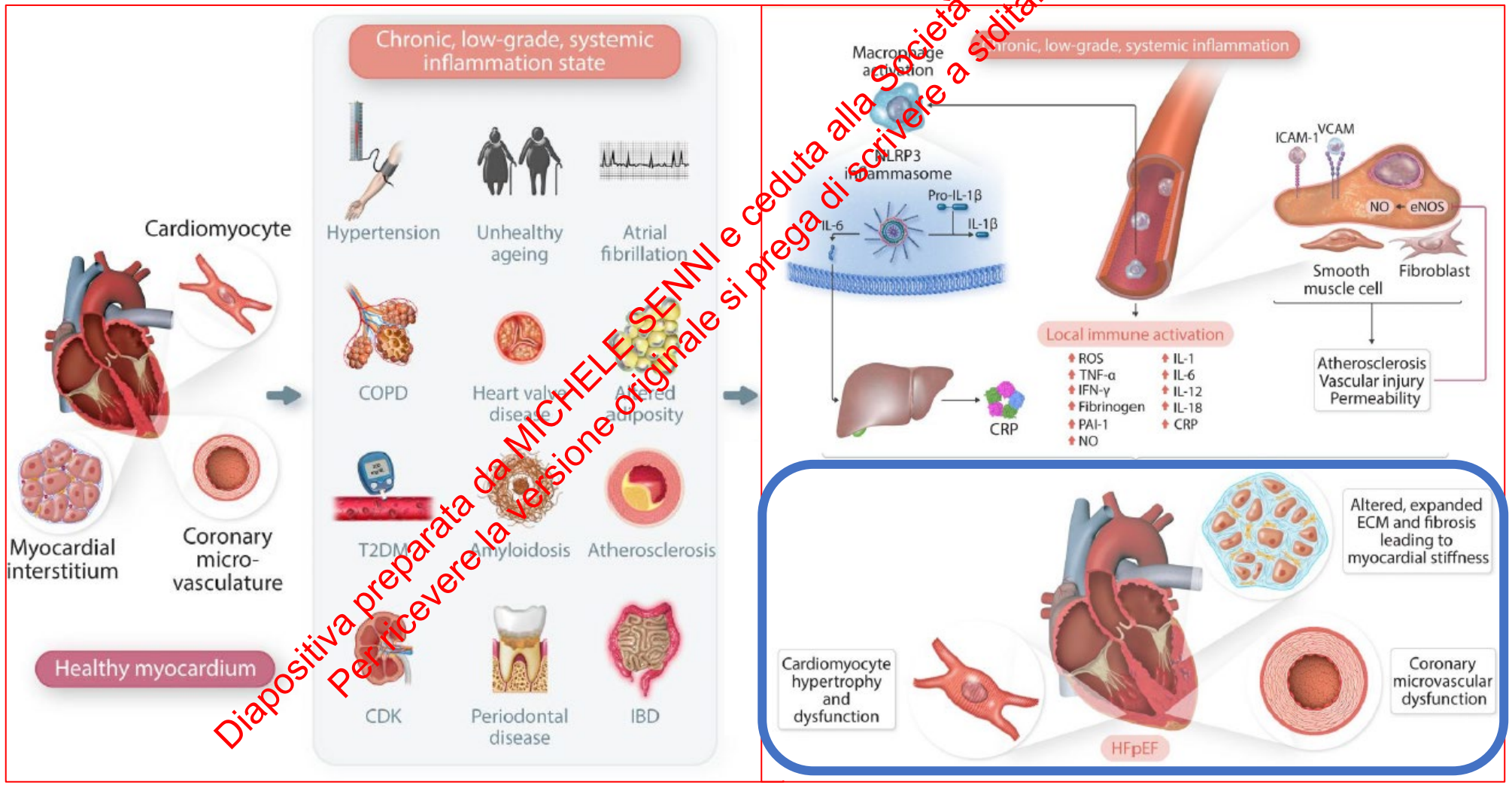
Modified from: Pandey et al. *J AM Coll Cardiol HF* 2018

ESC European Society of Cardiology
Cardiovascular Research (2022) 118, 3536–3555
https://doi.org/10.1093/cvr/cvac133

SPOTLIGHT REVIEW

Inflammatory pathways in heart failure with preserved left ventricular ejection fraction: implications for future interventions

Nicola Riccardo Pugliese [1†], Pierpaolo Pellicori [2†], Francesco Filidei[1], Nicolò De Biase[1], Pasquale Maffia [3,4,5], Tomasz J. Guzik[4,6], Stefano Masi[1], Stefano Taddei [1], and John G.F. Cleland[2]*



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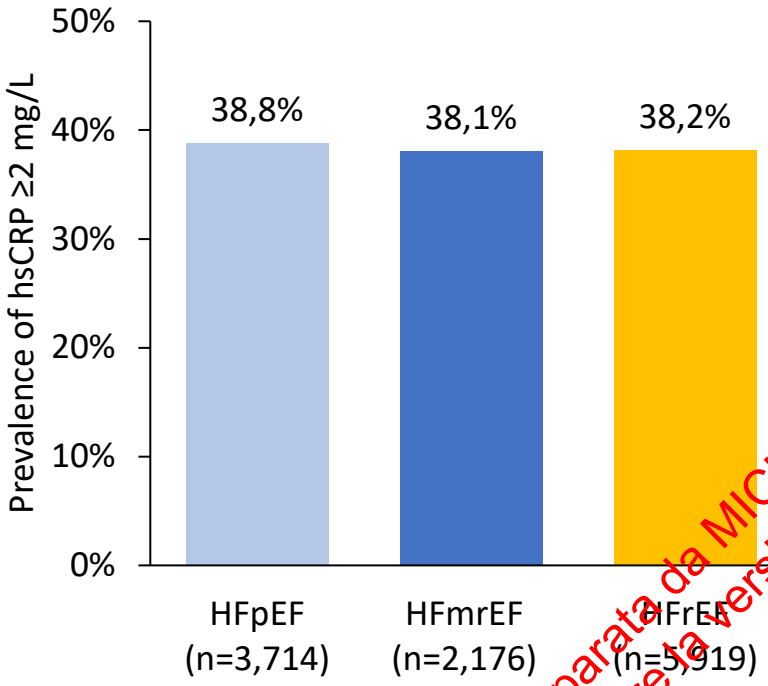
ESC European Society of Cardiology
European Journal of Heart Failure (2026) 00, 1–20
https://doi.org/10.1093/ejhf/xuag155

RESEARCH ARTICLE

Prevalence and predictors of high inflammatory risk in heart failure subtypes: findings from the global POSEIDON study

Carolyn S.P. Lam [1,2,*], Johanna Contreras[3], Raed Darwesh[4], Aguinaldo F. Freitas Junior[5], Søren Lund Kristensen[4], Koichiro Kuwahara[6], Andrew J. Ludman[7], Changsheng Ma [8], Nikolaus Marx [9], Jimmi Mathisen[4], Ann Marie Navar[10], Adam J. Nelson[11,12], Matteo Pirro[13], Hongye Ren[4], Shelley Zieroth[14], and Adriaan A. Voors [15,*]



Median hsCRP was similar across HF subtypes

HFpEF	**1.33**	[0.64–3.52] mg/L
HFmrEF	**1.26**	[0.59–3.24] mg/L
HFrEF	**1.28**	[0.59–3.29] mg/L

JACC: HEART FAILURE
VOL. 13, NO. 12, 2025

PUBLISHED BY ELSEVIER

COMMENTARIES

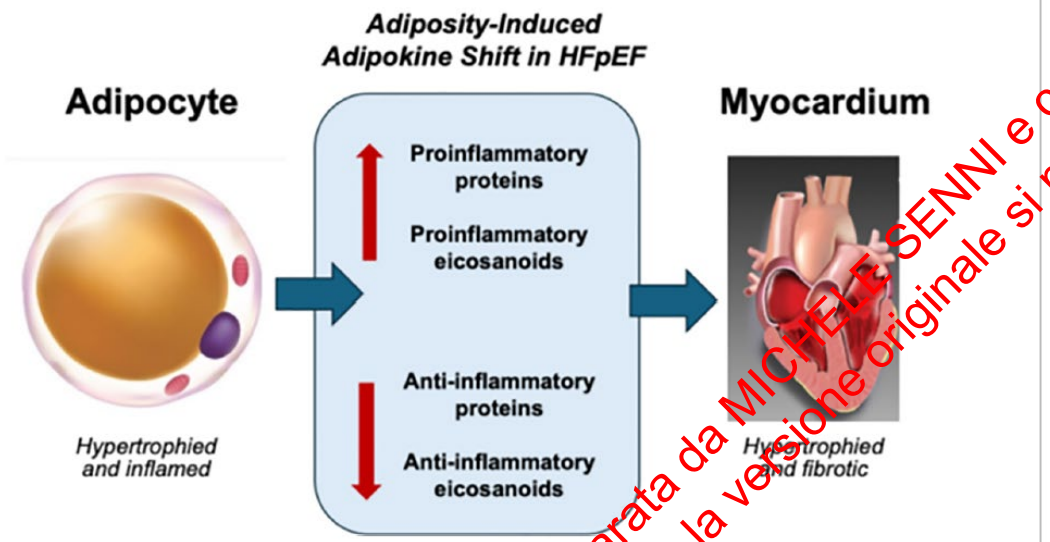
AU CONTRAIRE

What Causes Inflammation in Heart Failure With a Preserved Ejection Fraction?

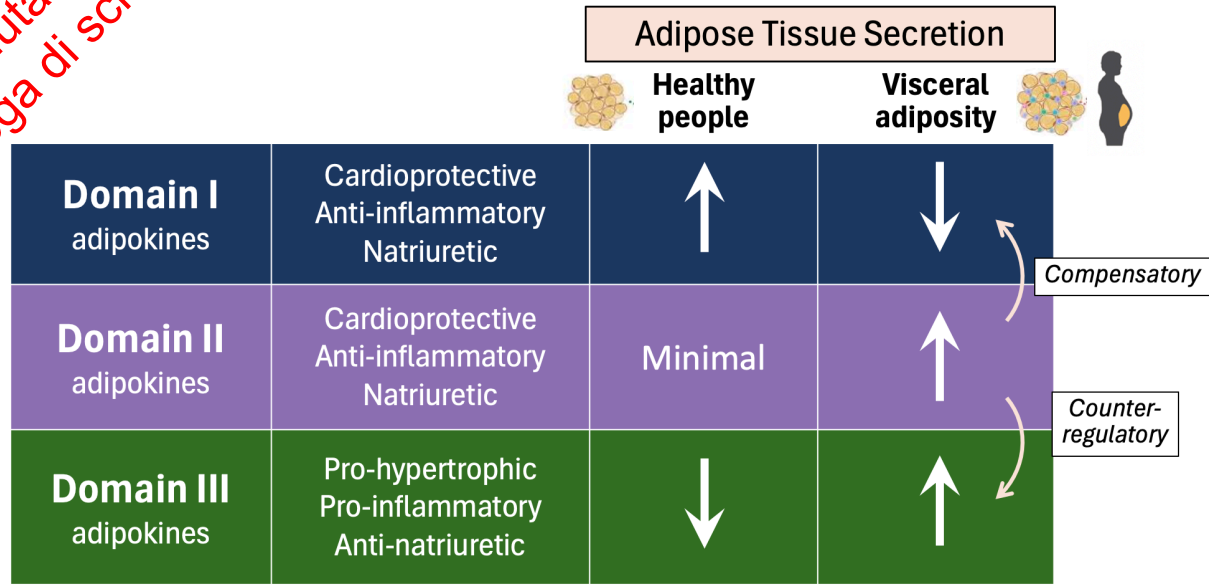
Potential Role of Eicosanoid Adipokines

Milton Packer, MD

FIGURE 1 Shift in the Balance of Protein and Eicosanoid Adipokines in HFpEF



Excess visceral adiposity leads to adipose tissue to enhance its secretion of proinflammatory adipokine proteins and eicosanoids and to diminish its secretion of anti-inflammatory adipokine proteins and eicosanoids. HFpEF = heart failure with a preserved ejection fraction.

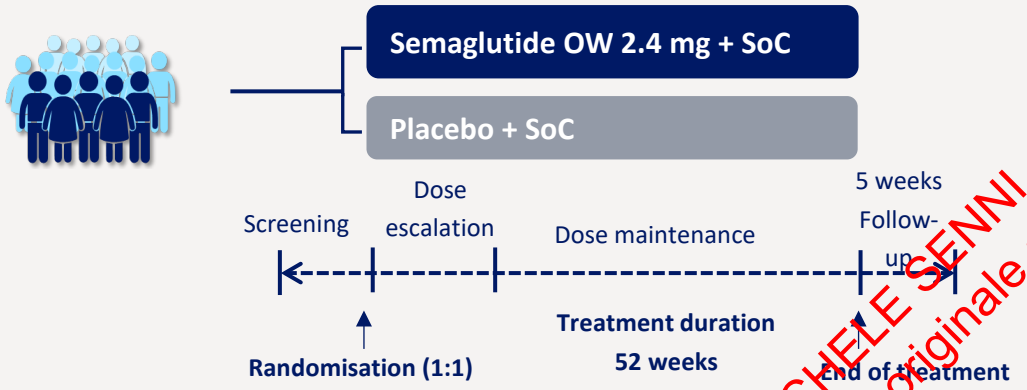


STEP-HFpEF and STEP-HFpEF DM trial design

STEP-HFpEF Trial Design[1,2]

N=529

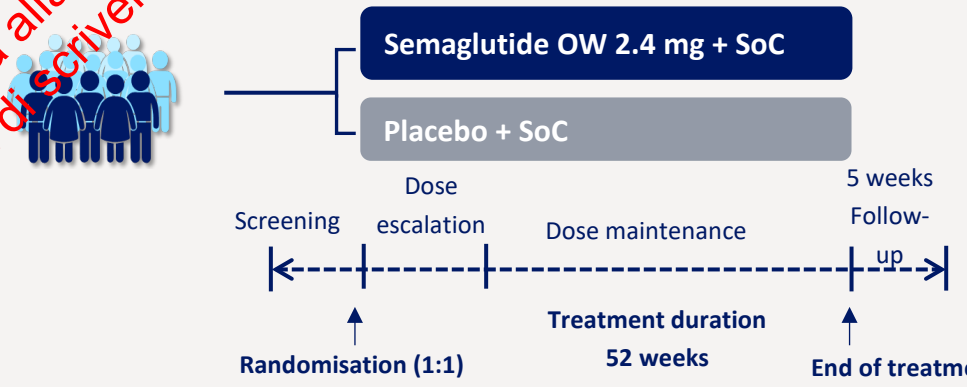
- NYHA II–IV
- Ejection fraction ≥45%
- BMI ≥30 kg/m²



STEP-HFpEF-DM Trial Design[3]

N=616

- NYHA II–IV
- Ejection fraction ≥45%
- BMI ≥30 kg/m²
- T2D
- HbA_{1c} ≤10%

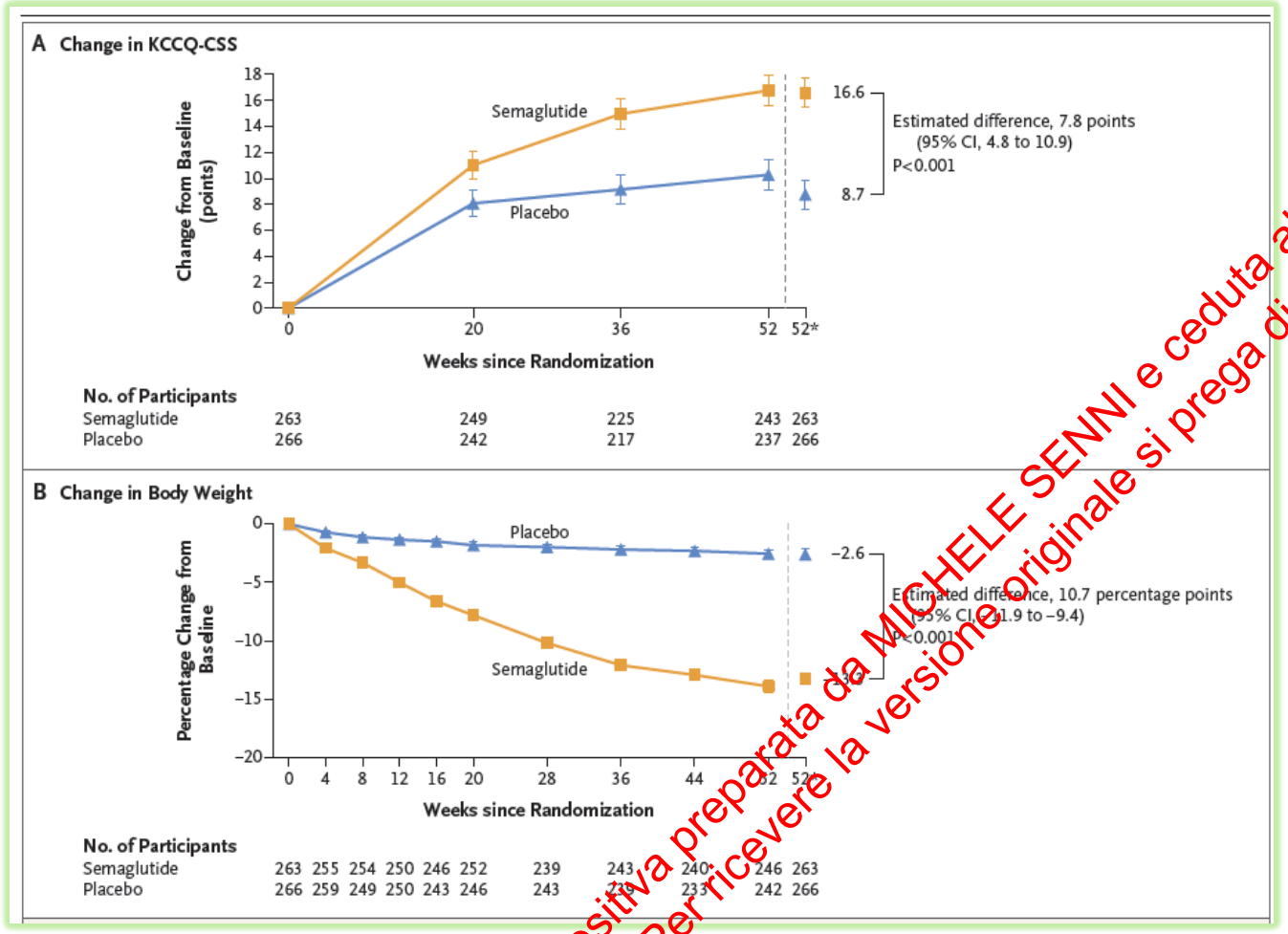


Trials Objective	Key Endpoints
To investigate the effects of semaglutide 2.4 mg s.c. once weekly on **physical function**, **symptoms** and **body weight** compared with placebo, both added to SoC, in people with the obesity phenotype of HFpEF with/without T2D	• **Dual primary endpoints:** KCCQ-CSS and body **weight** • **Confirmatory secondary endpoints:** 6MWD, hierarchical composite endpoint*, hs-CRP • **Key exploratory endpoints:** loop diuretic medication, NT-proBNP, NYHA class, time to first HF event (hospitalisation or urgent visit)

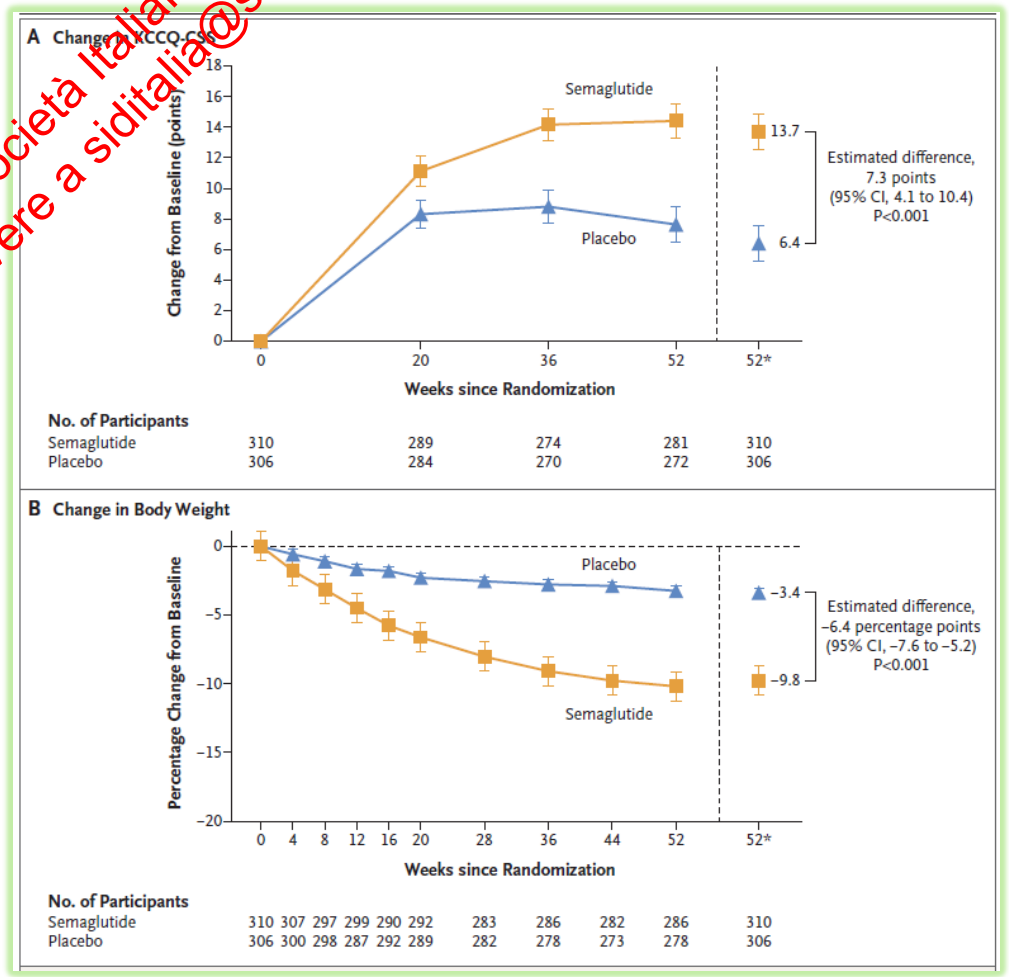
1. Kosiborod MN et al. JACC HF 2023;11(8_Part_1):1000–1010.

Primary endpoints: KCCQ-CSS and BW with semaglutide 2.4 mg vs placebo at week 52

STEP HFpEF



STEP HFpEF DM



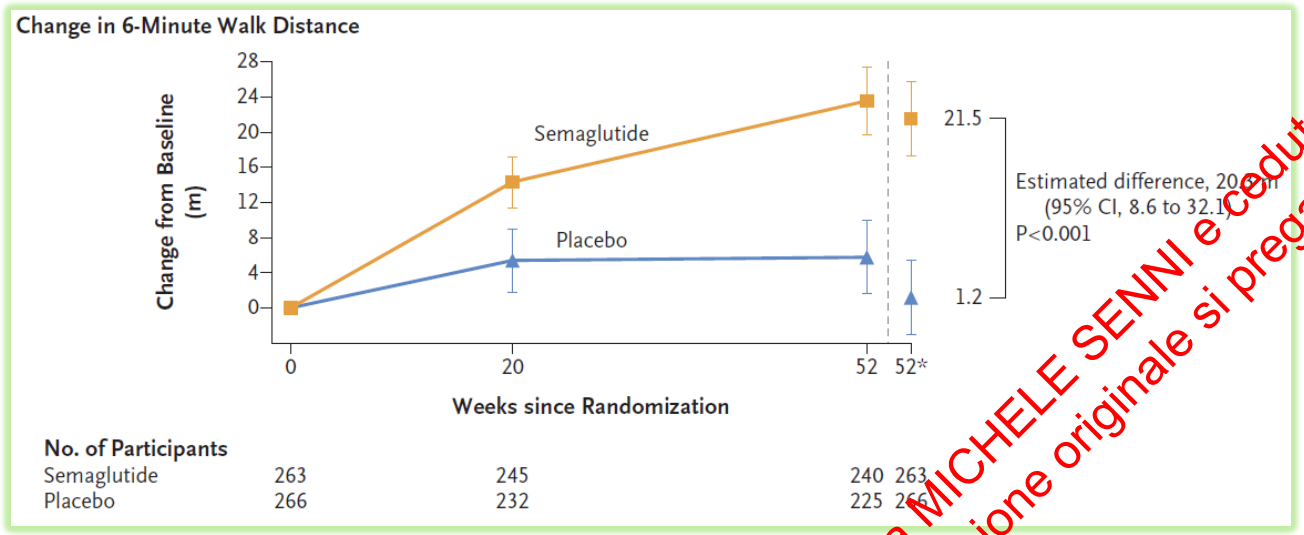
1. Kosiborod MN et al. JACC HF 2023;11(8_Part_1):1000–1010.

2. Kosiborod MN et al. N Engl J Med 2024;390(15):1394-1407

6MWD with semaglutide 2.4 mg vs placebo at week 52

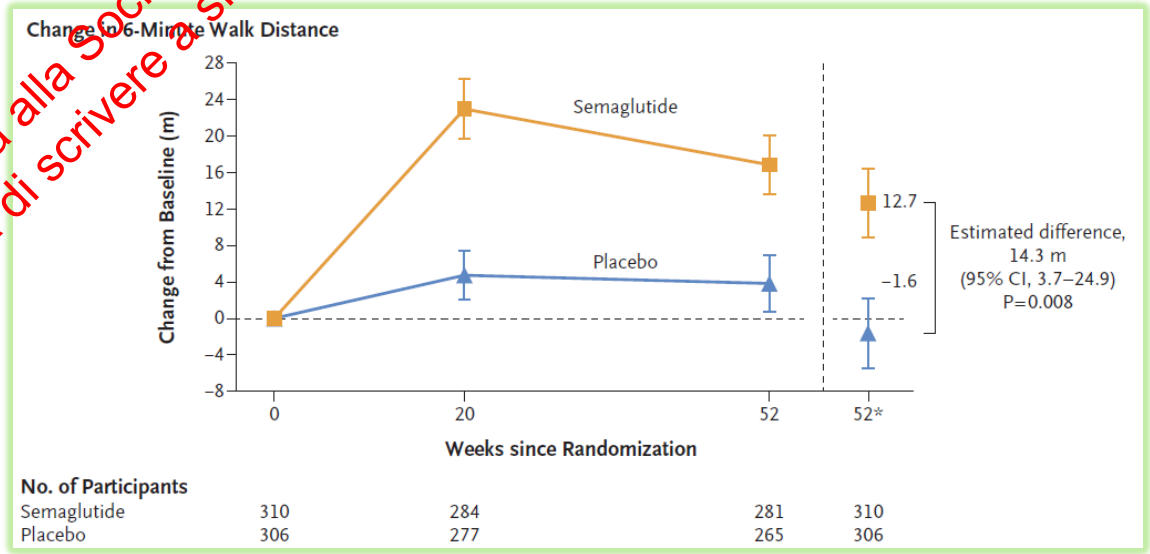
Confirmatory secondary endpoint

STEP HFpEF



1. Kosiborod MN et al. JACC HF 2023;11(8_Part_1):1000–1010.

STEP HFpEF DM



2. Kosiborod MN et al. N Engl J Med 2024;390(15):1394-1407

6MWD

320.0 m
(240.0; 389.0)

Baseline

6MWD (m)

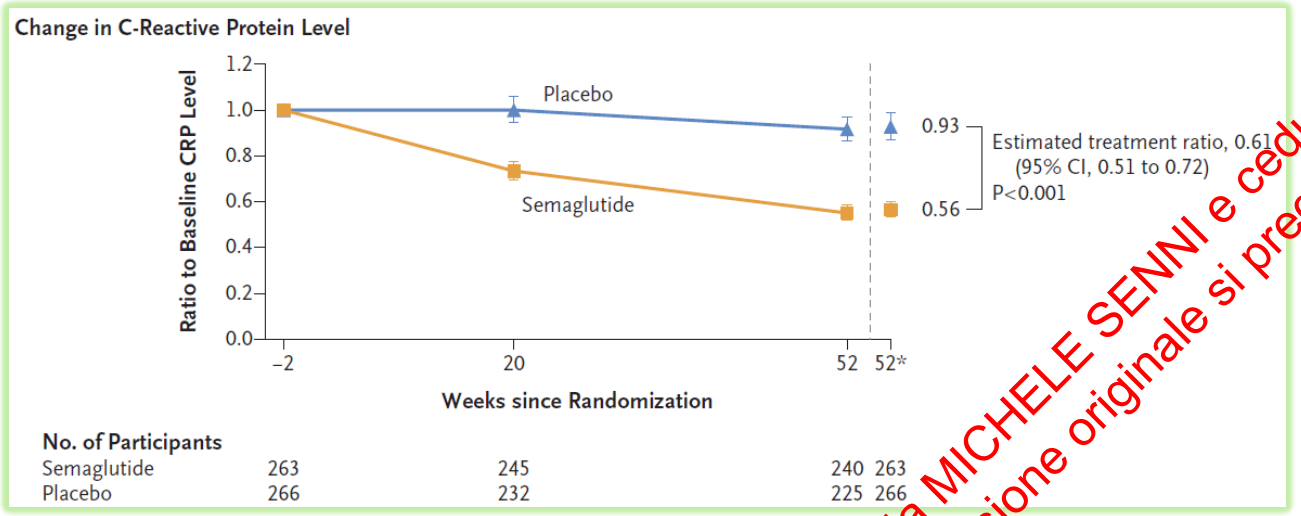
280.0 (205.1–357.6)
280.0 (200.0–345.0)

**Estimated mean changes from baseline to week 52 based on analysis of covariance (ANCOVA) and an imputation approach for missing data. In the left figure, error bars are ± standard error of the mean. Numbers shown in the lower panel are numbers of patients contributing to the mean*

hs-CRP levels with semaglutide vs placebo

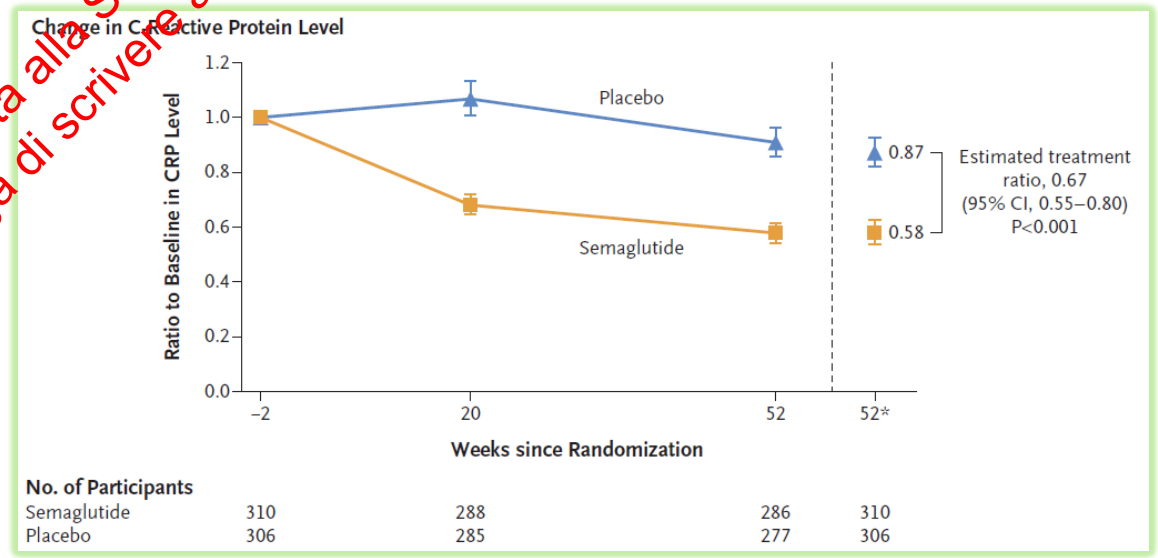
Confirmatory secondary endpoint

STEP HFpEF[1]



1. Kosiborod MN et al. JACC HF 2023;11(8_Part_1):1000–1010.

STEP HFpEF DM[2]



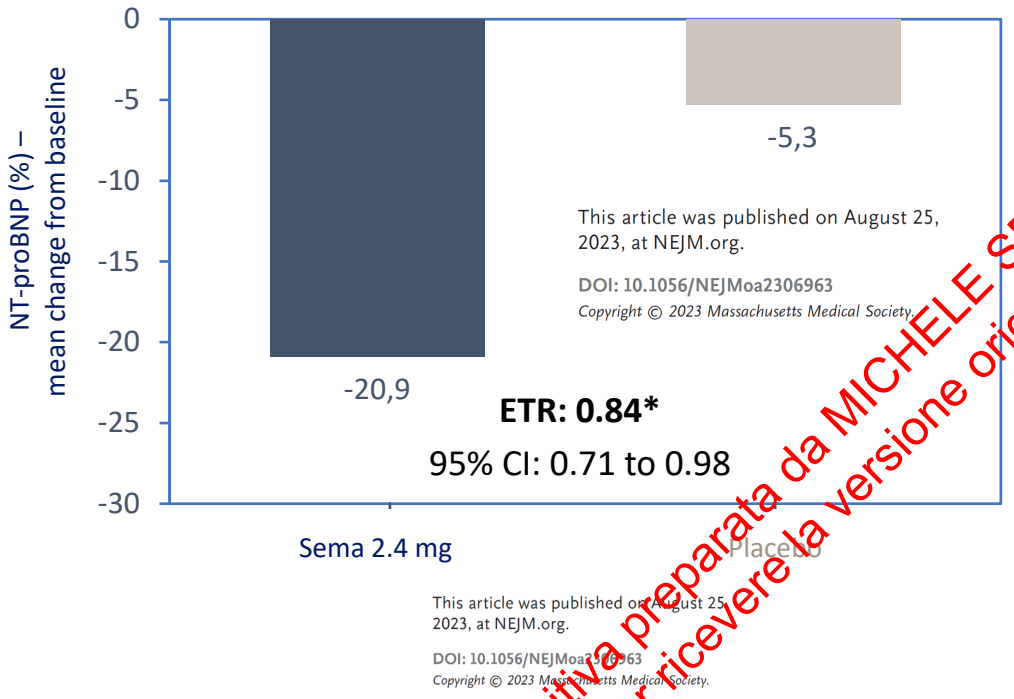
2. Kosiborod MN et al. N Engl J Med 2024;390(15):1394-1407

NT-proBNP levels with semaglutide vs placebo

Exploratory endpoints

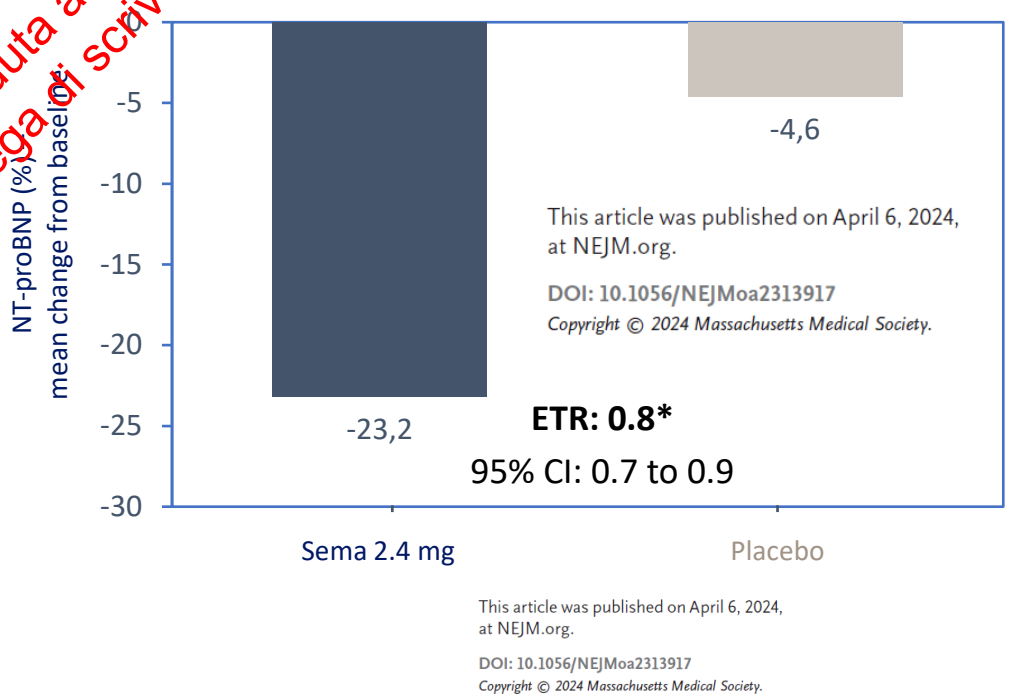
STEP HFpEF[1]

Treatment policy estimand (week 52)



STEP HFpEF DM[2]

Treatment policy estimand (week 52)



1. Kosiborod MN, et al. N Engl J Med. 2023;389(12):1069-1084. 2. Kosiborod MN, et al. N Engl J Med. 2024;390(15):1394-1407.

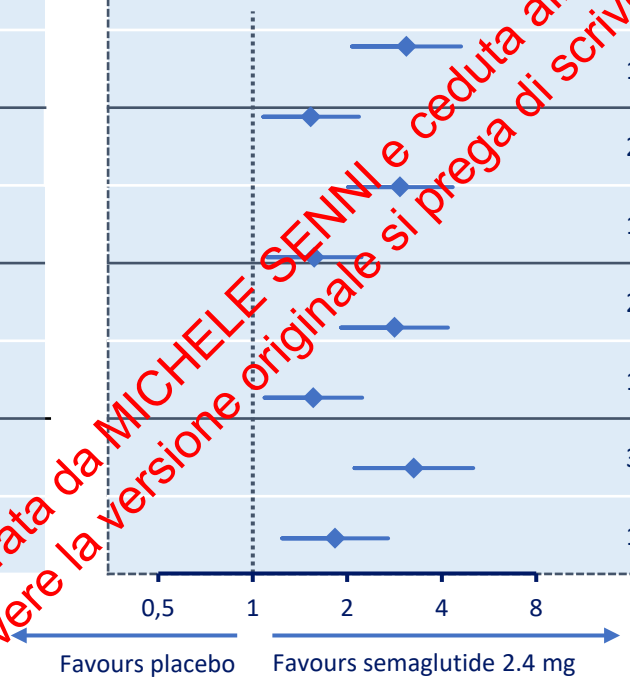
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2024

Atrial Fibrillation and Semaglutide Effects in Obesity-Related Heart Failure With Preserved Ejection Fraction

STEP-HFpEF Program

KCCQ-CSS responder analysis

Improvement		Odds ratio (95% CI)	*p*-value
≥5 points	Any AF (n=518)*	3.09 (2.07; 4.61)	0.0094
	No AF (n=627)	1.53 (1.08; 2.18)	
≥10 points	Any AF (n=518)*	2.95 (2.01; 4.34)	0.0155
	No AF (n=627)	1.57 (1.11; 2.22)	
≥15 points	Any AF (n=518)*	2.83 (1.91; 4.19)	0.0262
	No AF (n=627)	1.56 (1.09; 2.23)	
≥20 points	Any AF (n=518)*	3.26 (2.11; 5.04)	0.0489
	No AF (n=627)	1.83 (1.24; 2.70)	



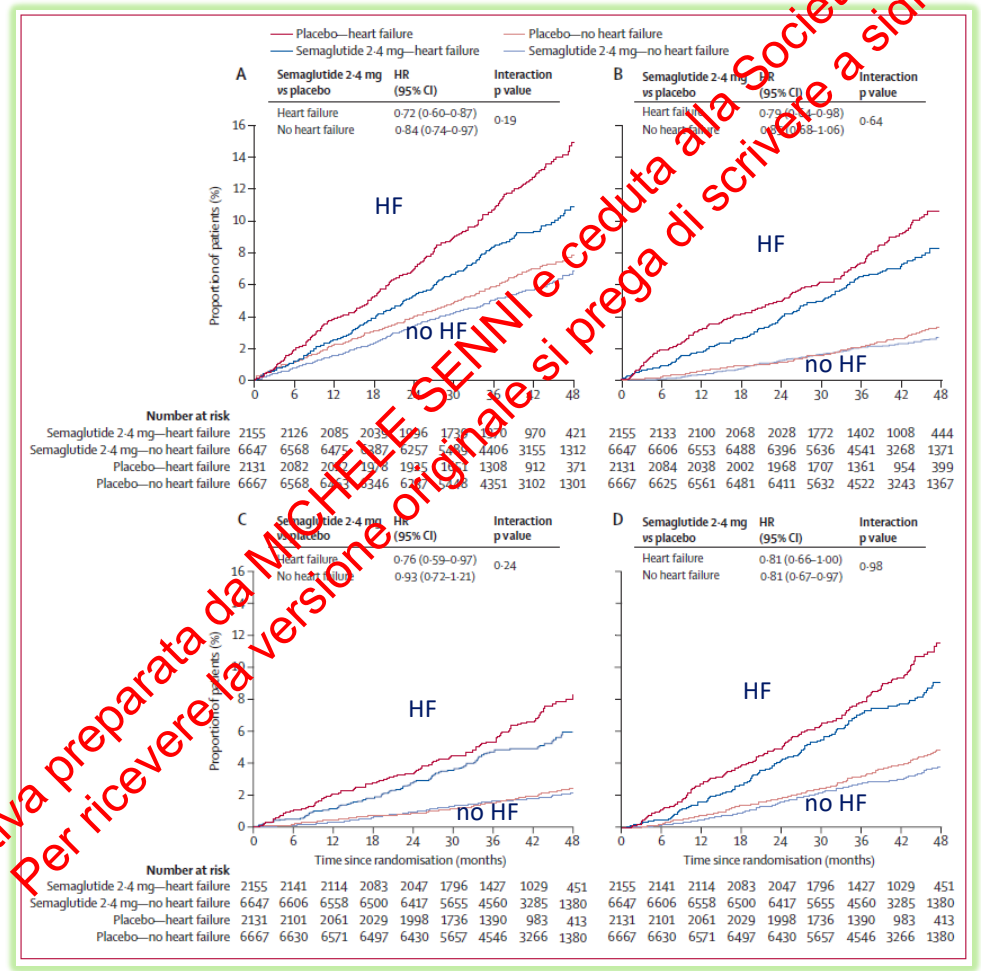
Verma S et al. J Am Coll Cardiol. 2024

SELECT: outcomes in obese patients with HF and HFrEF & HFpEF history

Pre-specified analysis

MACE (A), HF composite (B), CV death (C), All-cause death (D)

by **HF hystory**

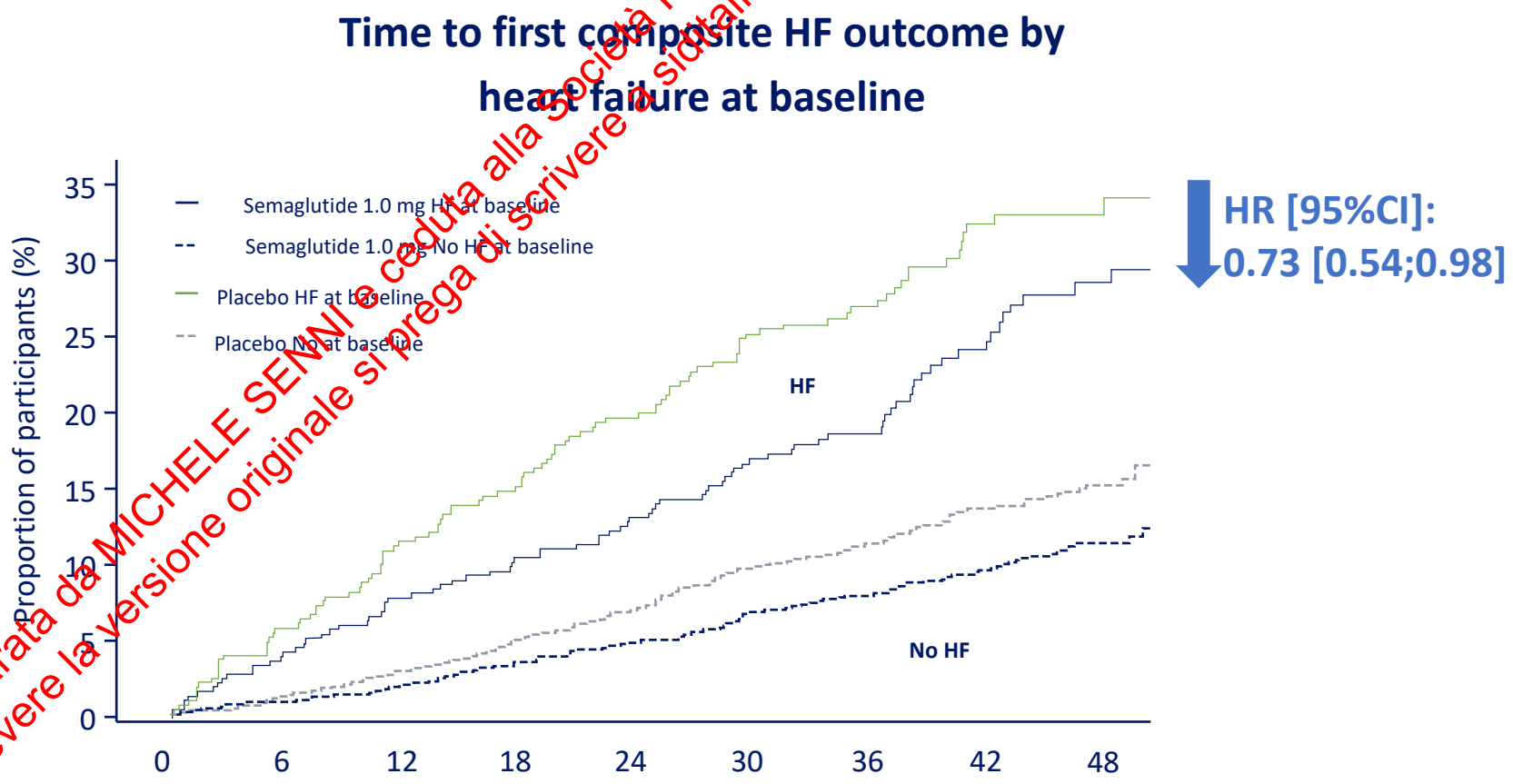


Deanfield J, et al. Lancet. 2024;404(10454):773–786.

FLOW trial: composite heart failure outcome in people with heart failure at baseline

FLOW
Adults with T2D and CKD

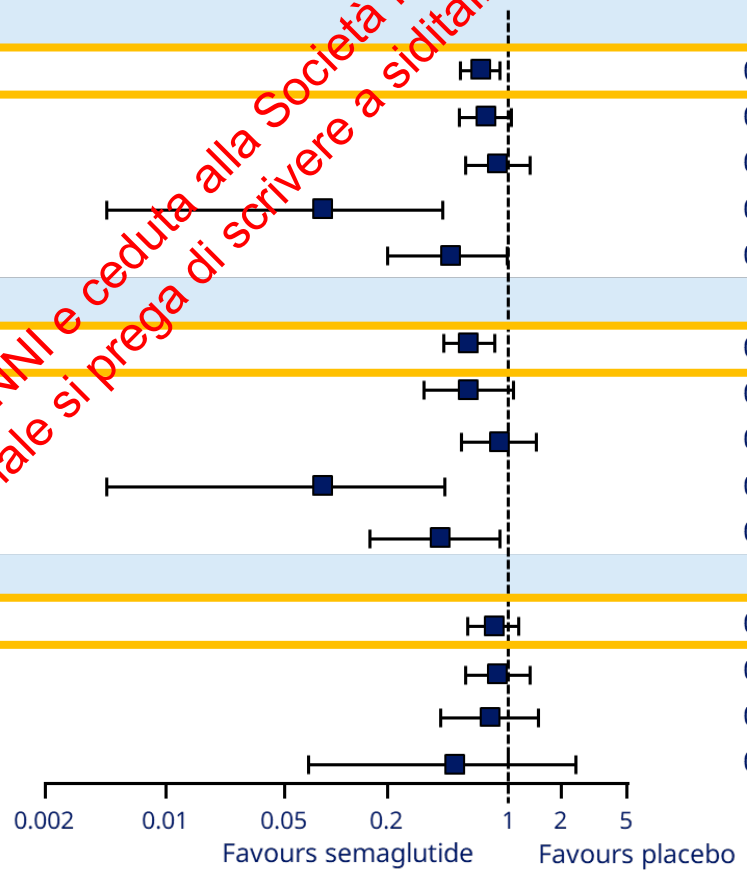
Composite heart failure outcome
HR [95%CI]: 0.73 [0.62;0.87]



Perkovic V, et al. N Engl J Med. 2024;391:109-21

Pooled analysis: CV outcomes overall and by trial (STEP-HFpEF trials, SELECT, FLOW)

	Number of events/analysed participants: semaglutide	Number of events/analysed participants: placebo	Incidence rate (semaglutide: placebo)	HR (95% CI)	p value
Composite of CV death or HF events					
OVERALL	103/1,914	138/1,829	2.1; 3.0	0.69 (0.53, 0.89)	0.0045
SELECT	53/1,174	66/1,099	1.4; 1.8	0.75 (0.52, 1.07)	
FLOW	40/167	40/158	8.1; 9.2	0.87 (0.56, 1.36)	
STEP-HFpEF	1/263	12/266	0.3; 4.2	0.08 (0.00, 0.42)	
STEP-HFpEF DM	9/310	20/306	2.7; 6.2	0.46 (0.20, 0.98)	
HF events					
OVERALL	54/1,914	86/1,829	1.1; 1.8	0.59 (0.41, 0.82)	0.0019
SELECT	17/1,174	27/1,099	0.4; 0.7	0.58 (0.31, 1.06)	
FLOW	29/167	29/158	5.9; 8.7	0.88 (0.53, 1.48)	
STEP-HFpEF	1/263	12/266	0.3; 4.2	0.08 (0.00, 0.42)	
STEP-HFpEF DM	7/310	18/306	2.1; 5.5	0.40 (0.15, 0.92)	
CV deaths*					
OVERALL	59/1,914	67/1,829	1.2; 1.4	0.82 (0.57, 1.16)	0.25
SELECT	40/1,174	43/1,099	1.0; 1.2	0.87 (0.56, 1.34)	
FLOW	17/167	19/158	3.2; 4.0	0.78 (0.40, 1.51)	
STEP-HFpEF DM	2/310	4/306	0.6; 1.2	0.49 (0.07, 2.53)	



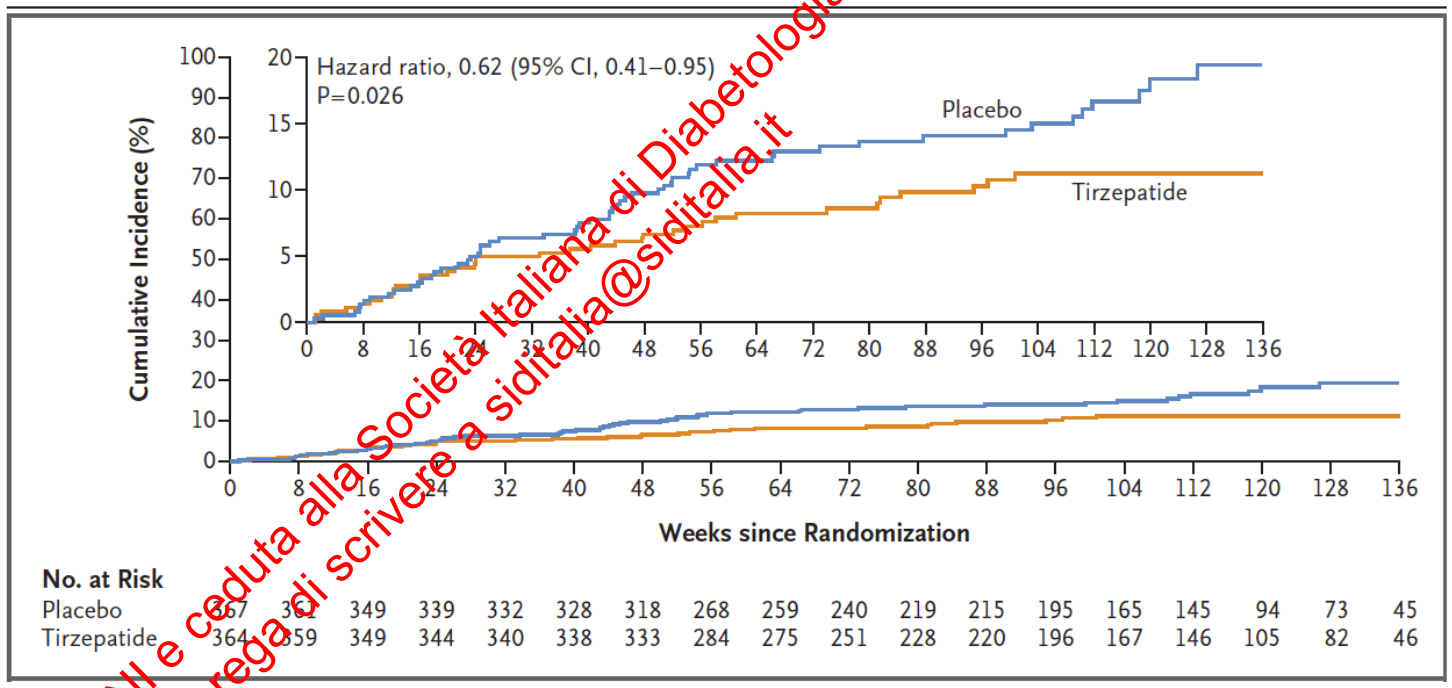
Kosiborod MN, et al. Lancet. 2024

The NEW ENGLAND JOURNAL of MEDICINE

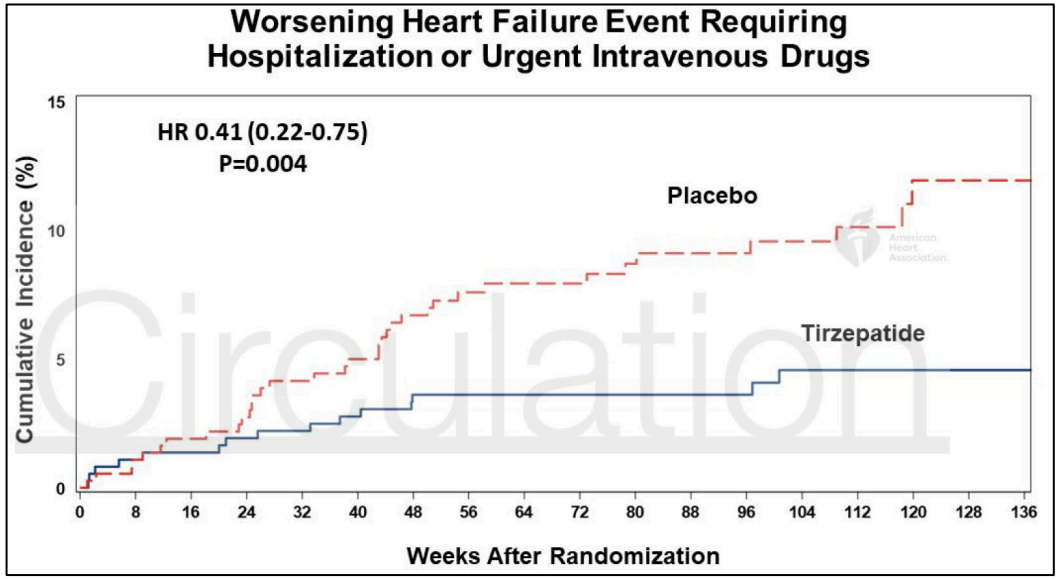
ORIGINAL ARTICLE

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

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



ducted any efficacy analyses. After a formal amendment and discussions with the FDA, the two primary end points of the trial were designated as a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event, assessed in a time-to-first-event analysis



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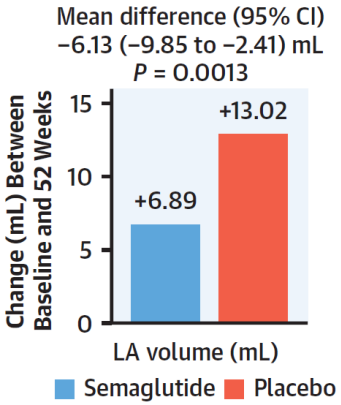
VOL. ■, NO. ■, 2024

Effect of Semaglutide on Cardiac Structure and Function in Patients With Obesity-Related Heart Failure

Treatment Effects of Semaglutide on LA Volume and Other Parameters



Benefits of semaglutide on LA remodeling were consistent irrespective of age, sex, BMI, NT-proBNP, hsCRP, diabetes status, AF status, LVEF, and background pharmacotherapy

Semaglutide also improved E wave velocity, E/A ratio, E/e' average, and

ABLE 3 Treatment Effects of Semaglutide vs Placebo on Echocardiography Parameters from Baseline to Week 52 in the STEP-HFpEF Program

	Semaglutide (2.4 mg) (n = 253)			Placebo (n = 238)			Treatment Effect at 52 Weeks (Semaglutide vs Placebo)	
	n	Baseline	Estimated Mean Change	n	Baseline	Estimated Mean Change	LS Mean Difference (95% CI)	*P* Value
V size and systolic function								
LVEDV, mL	176	75.46 ± 29.96	+9.81	160	72.96 ± 26.56	+13.75	−3.94 (−9.98 to 2.10)	0.20
LVESV, mL	176	31.72 ± 16.07	+5.57	160	30.98 ± 15.69	+6.89	−1.32 (−5.00 to 2.36)	0.48
LV mass, g	187	206.5 ± 64.48	−5.82	176	200.1 ± 73.88	−0.42	−5.40 (−14.47 to 3.68)	0.24
LVEF, %	176	58.98 ± 7.64	−1.22	160	58.90 ± 7.78	−0.91	−0.31 (−1.79 to 1.17)	0.68
Stroke volume, mL	176	43.75 ± 15.99	+4.42	161	42.11 ± 13.55	+6.70	−2.28 (−5.32 to 0.76)	0.14
TDI septal S', cm/s	187	6.29 ± 1.69	−0.16	177	6.08 ± 1.45	−0.39	+0.25 (0.00 to 0.49)	0.046
GLS, %	191	−14.7 ± 3.79	−0.73	183	−14.1 ± 3.48	+0.10	+0.03 (−0.62 to 0.68)	0.94
LV diastolic function								
E/A ratio	128	1.08 ± 0.53	−0.11	106	1.14 ± 0.53	+0.02	−0.14 (−0.24 to −0.04)	0.0075
E-wave, cm/s	198	84.41 ± 26.40	−6.30	182	86.62 ± 28.21	−0.67	−5.63 (−9.42 to −1.84)	0.0037
A-wave, cm/s	129	77.84 ± 24.49	−0.12	109	76.85 ± 24.35	−0.15	+0.04 (−3.63 to 3.70)	0.98
e' lateral, cm/s	185	6.84 ± 2.32	−0.36	168	6.60 ± 2.00	−0.32	−0.04 (−0.51 to 0.42)	0.86
e' septal, cm/s	184	12.30 ± 5.03	−0.36	172	12.48 ± 5.15	−0.35	−0.02 (−0.35 to 0.32)	0.92
							60 to 0.01)	0.05
							24 to −0.04)	0.0089
							35 to −2.41)	0.0013
							83 to 2.40)	0.34
a' lateral, cm/s	120	9.03 ± 2.90	+0.46	99	8.73 ± 2.92	−0.35	+0.81 (0.21 to 1.42)	0.0086
a' septal, cm/s	120	7.81 ± 2.56	+0.39	104	7.46 ± 2.33	−0.40	+0.79 (0.40 to 1.17)	<0.0001
RV function and pulmonary pressure								
RVSP, mm Hg	84	25.55 ± 8.94	−1.42	72	25.92 ± 8.38	+0.37	−1.80 (−4.28 to 0.69)	0.16
TAPSE, cm	173	2.05 ± 0.49	−0.06	161	1.99 ± 0.44	−0.03	−0.03 (−0.12 to 0.05)	0.43
S', cm/s	166	11.26 ± 3.35	−0.46	140	10.59 ± 2.63	−0.37	−0.09 (−0.57 to 0.39)	0.71
RV FAC, %	64	46.33 ± 9.24	+1.10	63	47.35 ± 7.39	−0.54	+1.64 (−0.87 to 4.15)	0.20
RVEDA, cm^2	67	20.50 ± 6.17	+0.65	64	18.91 ± 5.62	+2.64	−1.99 (−3.60 to −0.38)	0.016
RVESA, cm^2	64	11.28 ± 4.49	+0.09	63	10.13 ± 3.79	+1.51	−1.41 (−2.42 to −0.40)	0.0064

Baseline values reported as mean ± SD. Treatment effects of semaglutide versus placebo compared via analysis of covariance, stratified by body mass index (<35 and ≥35 kg/m^2) and including terms for randomized treatment and baseline value of the parameter. Values log-transformed prior to analysis, with results reported in table reflective of back-transformation. For each parameter, missing values were noted for some of the study participants; n refers to the number of participants contributing to the analysis (available data for echocardiography parameters and covariates). [a]Prespecified primary endpoint.

LS = least squares; other abbreviations as in Tables 1 and 2.

Disease-modifying therapy

Solomon SD, et al. J Am Coll Cardiol. 2024:S0735-1097(24)08192-0. doi: 10.1016/j.jacc.2024.08.021.

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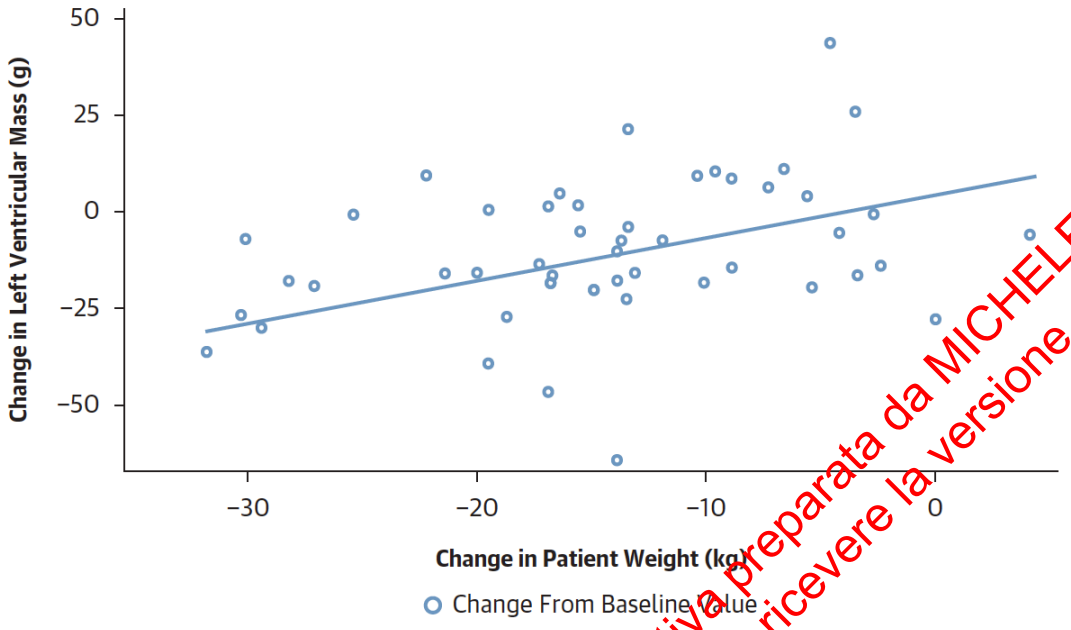
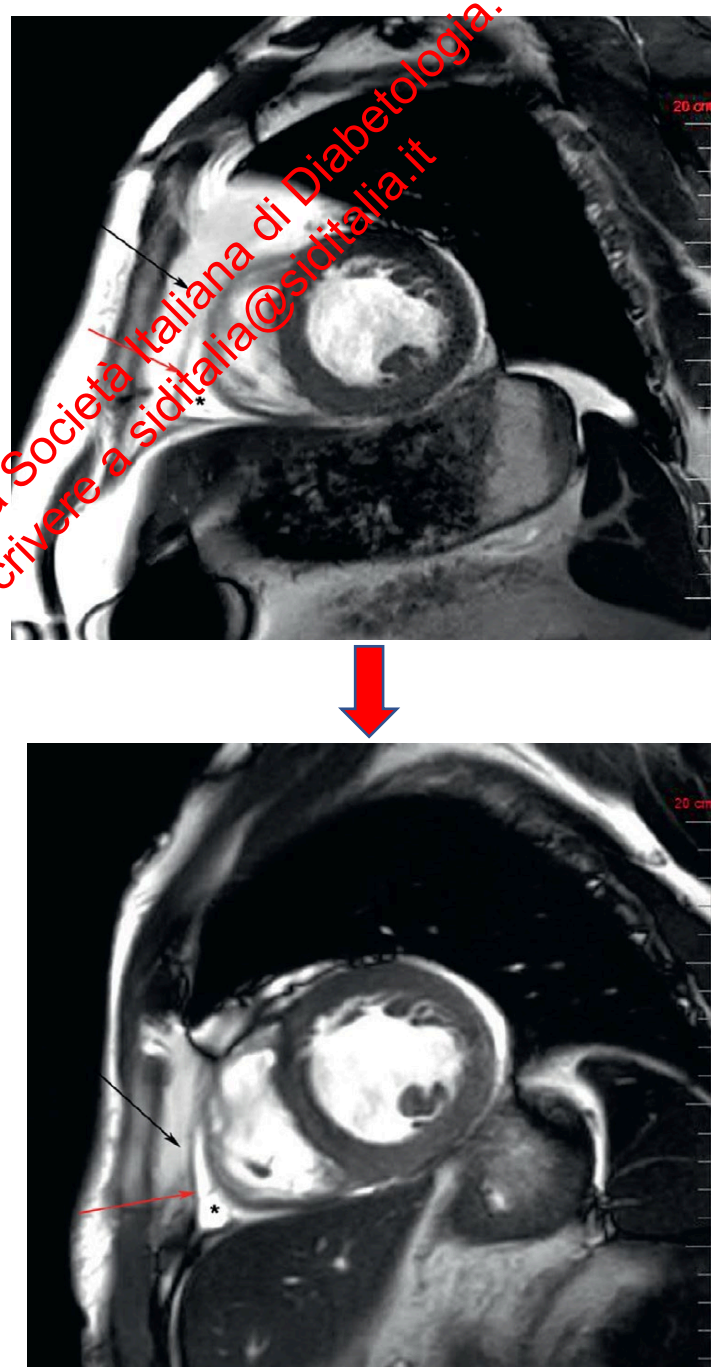
Tirzepatide Reduces LV Mass and Paracardiac Adipose Tissue in Obesity-Related Heart Failure

SUMMIT CMR Substudy

Christopher M. Kramer, MD,[a] Barry A. Borlaug, MD,[b] Michael R. Zile, MD,[c] Dustin Ruff, PHD,[d] Joseph M. DiMaria, BA,[a] Venu Menon, MD,[e] Yang Ou, PHD,[d] Angela M. Zarante, MD,[f] Karla C. Hurt, BSN, MBA,[d] Masahiro Murakami, MD,[d] Milton Packer, MD,[g,h] the SUMMIT Trial Study Group

Relationship Between Change in Body Weight and LV Mass Over 52 Weeks in the Treated Group

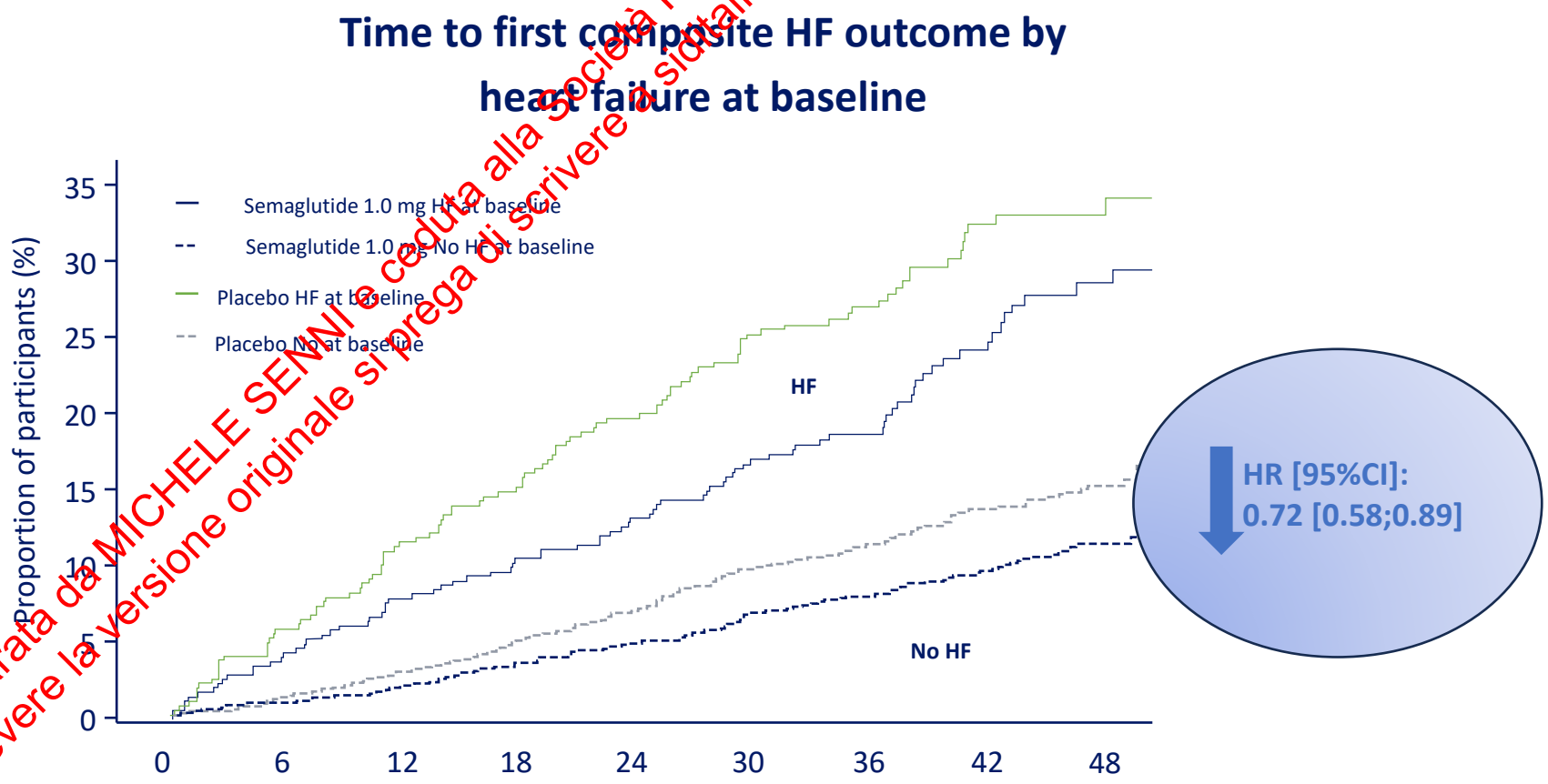




FLOW trial: composite heart failure outcome in people with heart failure at baseline

FLOW
Adults with T2D and CKD

Composite heart failure outcome
HR [95%CI]: 0.73 [0.62;0.87]



Perkovic V, et al. N Engl J Med. 2024;391:109-21

Obesity Reviews

WILEY | WORLD OBESITY

REVIEW OPEN ACCESS

GLP-1 Receptor Agonists for the Prevention of New-Onset Heart Failure: A Systematic Review and Meta-Analysis of Placebo-Controlled Randomized Clinical Trials

João Sérgio Neves[1,2] | Carolina B. Lobato[3,4] | Ana Rita Leite[1,2] | Catarina Vale[1,5] | Francisco Vasques-Nóvoa[1,5] | Francisca Saraiva[1] | Adelino Leite-Moreira[1,6] | Jens J. Holst[4] | João Pedro Ferreira[1,7]

New-Onset Heart Failure

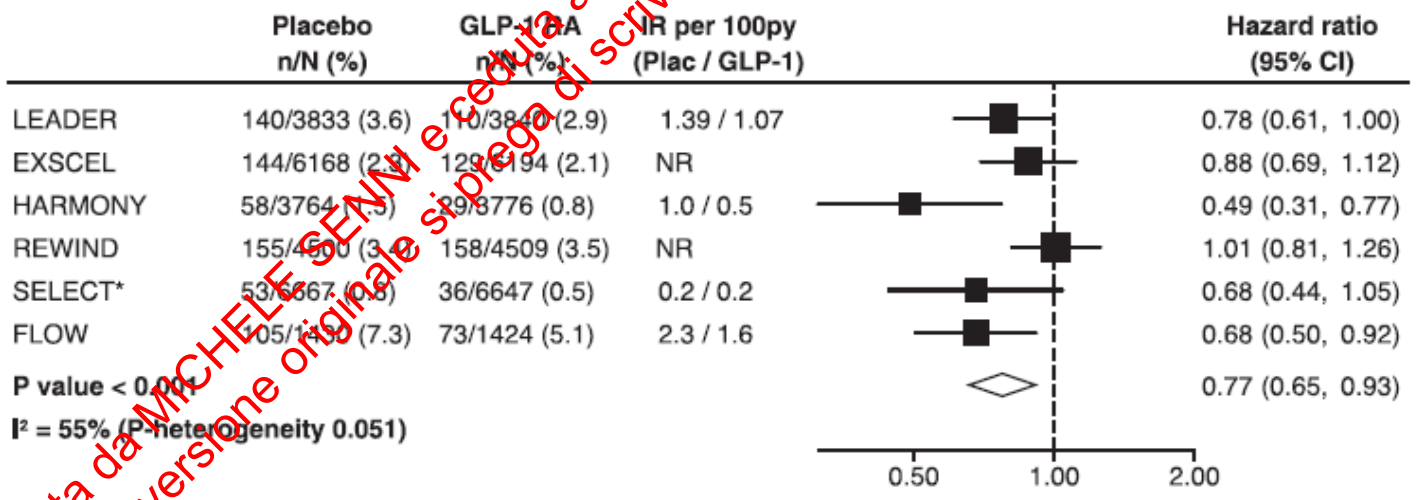


FIGURE 2 | Effects of GLP-1 RA versus placebo on heart failure events (A) or composite outcome of heart failure events or cardiovascular death (B) in patients without heart failure. Abbreviations: EXSCEL, Exenatide Study of Cardiovascular Event Lowering; FLOW, Research Study To See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease; HARMONY, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; IR, incidence rate; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SELECT, Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity.

Neves JS et al. Obesity review 2025

RCTs with GLP1a in HFrEF

LIVE Trial

European Journal of Heart Failure (2017) 19, 69–77
doi:10.1002/ejhf.657

RESEARCH ARTICLE

Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)—a multicentre, double-blind, randomised, placebo-controlled trial

Anders Jorsal[1,2]*, Caroline Kistorp[3,4], Pernille Holmager[3], Rasmus Stilling Tougaard[1,2], Roni Nielsen[1,2], Anja Hänselmann[5], Brian Nilsson[6], Jacob Eifer Møller[5], Jakob Hjort[2], Jon Rasmussen[3,4], Trine Welløv Boesgaard[7], Morten Schou[4,8], Lars Videbæk[5], Ida Gustafsson[6], Allan Flyvbjerg[2,9,10], Henrik Wiggers[1,2], and Lise Tarnow[7,9,11]

Jorsal A et al. EJHF 2016

FIGHT Trial

JAMA | Original Investigation

Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction
A Randomized Clinical Trial

Kenneth B. Margulies, MD; Adrian F. Hernandez, MD, MHS; Margaret M. Redfield, MD; Michael M. Givertz, MD; Guilherme H. Oliveira, MD; Robert Cole, MD; Douglas L. Mann, MD; David J. Whellan, MD, MHS; Michael S. Kiernan, MD, MS; G. Michael Felker, MD, MHS; Steven E. McNulty, MS; Kevin J. Anstrom, PhD; Monica R. Shah, MD, MSH; Eugene Braunwald, MD; Thomas P. Cappola, MD, ScM; for the NHLBI Heart Failure Clinical Research Network

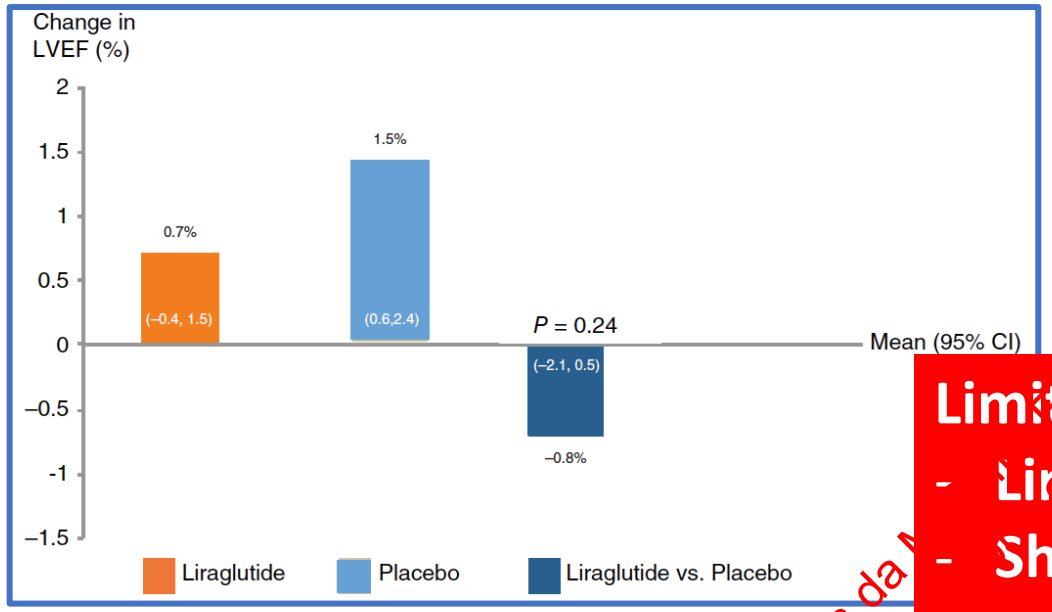
Mergulies KB et al. JAMA 2016

LIVE Trial

Liraglutide vs placebo
241 chronic HF
Four Danish Centres

LVEF ≤45%
NYHA I-III
BMI 29 kg/m²
DM 30%

Follow-up 24 mo



	Liraglutide (*n* = 122)	Placebo (*n* = 119)	Delta estimates (95% CI)	*P*-value
Change in echocardiographic data				
Systolic function				
LVEF, %	0.7 (5.4)	1.5 (5.0)*	−0.8 (−2.1, 0.5)	0.24
Global longitudinal strain, %	0.6 (2.2)*	0.1 (1.8)	0.5 (−0.1, 1.1)	0.13
s′max, cm/s	−0.03 (1.2)	0.17 (1.8)	−0.2 (−0.6, 0.2)	0.28
LVESV, mL	2.3 (17)	−0.3 (9)	2.6 (−1.2, 6.4)	0.19
LVEDV, mL	3.4 (25)	0.0 (15)	3.4 (−2.3, 9.2)	0.24
Diastolic function				
E-wave, cm/s	−4.5 (17)*	−0.3 (14)	−4.2 (−8.5, 0.1)	0.056
A-wave, cm/s	2.5 (25)	0.3 (16)	2.2 (−3.7, 8.1)	0.46
E-deceleration, ms	−12.4 (44)*	2.4 (36)	−10.0 (−21.2, 1.2)	0.08
IVRT, ms	−0.2 (11)	−8.1 (45)	7.9 (−9.7, 25.5)	0.37
Atrial volume, mL	−5.0 (18)*	3.7 (18)	−8.7 (−14.2, −3.2)	0.002
e′ (average), cm/s	0.01 (1.4)	−0.05 (1.6)	0.1 (−0.4, 0.5)	0.81
E/e′ ratio	−0.7 (4.6)	0.7 (4.3)	−1.4 (−2.7, −0.1)	0.03
Change in clinical and laboratory data				
6MWT, m, median (IQR)	28 (65)*	3 (89)	24 (2, 47)	0.04
MLHFQ, grade	−2.7 (12)	−1.1 (15)	−1.6 (−5.3, 2.0)	0.39
Systolic BP, mmHg	−4 (12)*	−2 (16)	−2 (−6, 3)	0.45
	−1 (10)	−1 (9)	−0.2 (−3, 2)	0.89
	6 (9)*	−1 (8)	7 (5, 9)	<0.0001
	−0.7 (1.0)	0.1 (1.1)	−0.8 (−1.1, −0.4)	<0.0001
	−0.3 (0.6)* −2.9 (6.2)*	0.1 (0.5)* 1.5 (5.3)	−0.4 (−0.5, −0.3) −4.4 (−6, −3)	<0.0001

Limitations
- **Limited population**
- **Short follow-up**
- **Not obese patients**

	Liraglutide *n* (%)	Placebo *n* (%)
Death due to ventricular tachycardia	1	0
Ventricular tachycardia	3	1
Atrial fibrillation (DC-converted)	4	2
Acute coronary syndrome	3	0
Worsening of CHF	1	0
Subtotal	12 (10)*	3 (3)

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Jorsal A et al. EJHF 2016

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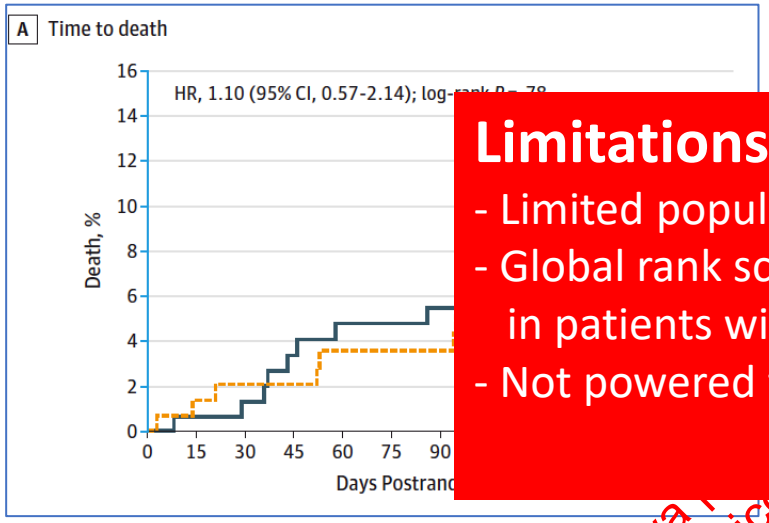
FIGHT Trial

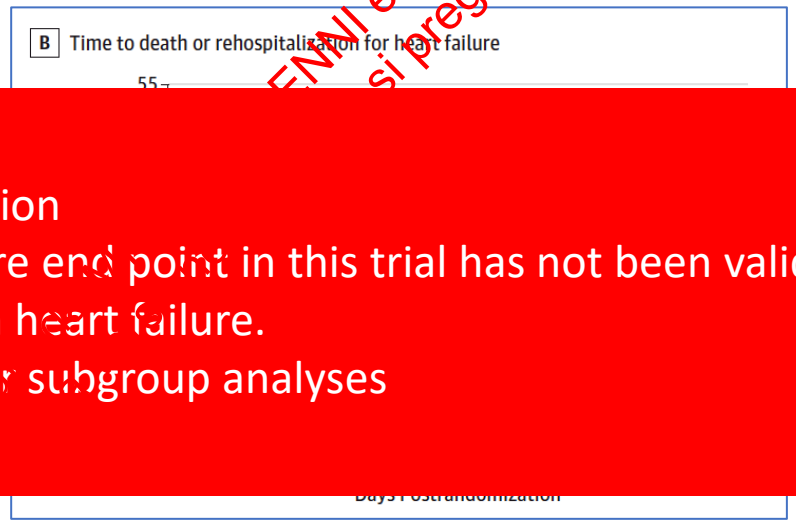
Liraglutide vs placebo
300 Advanced HF

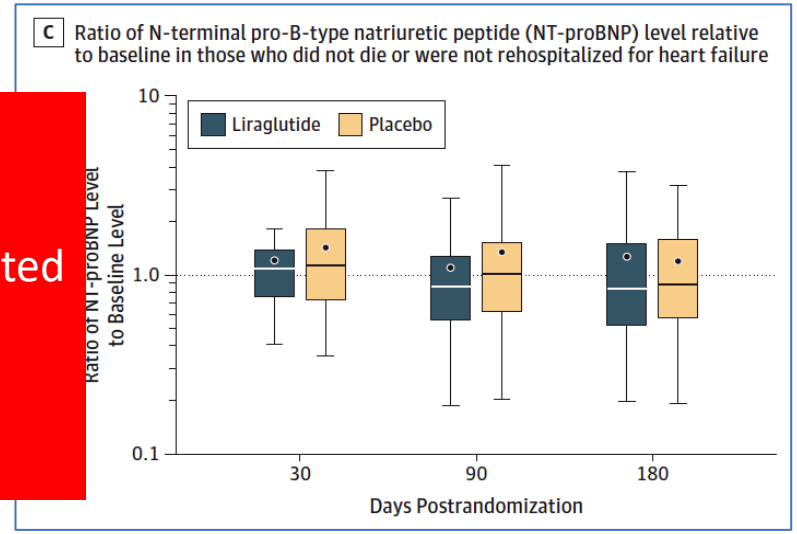
LVEF ≤40%
recent (within 14 days) HFH
preadmission at least 40mg of furosemide

BMI 32 kg/m²
F-up 6 mo

	Liraglutide (n = 154)	Placebo (n = 146)	Treatment Effect (95% CI)[a]	*P* Value
Primary End Point				
Mean global rank score[b]	146	156		.31[c]







Limitations

- Limited population
- Global rank score end point in this trial has not been validated in patients with heart failure.
- Not powered for subgroup analyses

Mergulies KB et al. JAMA 2016

Cardiovascular-Renal-Metabolic Syndrome (CKM)

Excess or dysfunctional adiposity (BMI >25, visceral obesity, IGT)

CV Risk Factors Metabolic Disorders (Hypertension, Dyslipidemia, T2DM)

CKD

Cardiovascolar Disease *(FA, HF, ASCVD, stroke, PAD)*

Drug treatments...

- **GLP-1-RA**: semaglutide per os, semaglutide s.c., liraglutide
- **GIP / GLP-1 RA**: tirzepatide
- Other: orlistat, fentermina/topiramato, naltrexone/bupropione

↓ Weight
No benefits on outcomes

…with cardiovascular outcome data

CVOT

- **SELECT** (semaglutide 2.4 mg s.c.): ↓ 20% MACE
  [BMI > 27kg/m2, known disease CV, T2DM -]

HFpEF (BMI >30)

- **STEP-HFpEF** e **STEP-HFpEF DM** (semaglutide 2.4 mg s.c.): ↑ KCCQ-CCS, ↑ 6MWD, ↓ weight, ↓ PCR
- **pooled analysis** STEP-HFpEF e STEP-HFpEF DM: ↓ HF and combined endpoint HF/morte CV
- **SUMMIT** (tirzepatide max 15 mg s.c.): ↓ combined endpoint HF/morte CV, ↑ KCCQ-CSS

HFmrEF / HFpEF

- **post-hoc analysis** SELECT, STEP-HFpEF, STEP-HFpEF DM e FLOW (semaglutide s.c.): ↓ HF e endpoint combinato HF/morte CV

Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial

John Deanfield, Subodh Verma, Benjamin M Scirica, Steven E Kahn, Scott S Emerson, Donna Ryan, Ildiko Lingvay, Helen M Colhoun, Jorge Plutzky, Mikhail N Kosiborod, G Kees Hovingh, Søren Hardt-Lindberg, Ofir Frenkel, Peter E Weeke, Søren Rasmussen, Assen Goudev, Chim C Lang, Miguel Urina-Triana, Mikko Pietilä, A Michael Lincoff, for the SELECT Trial Investigators

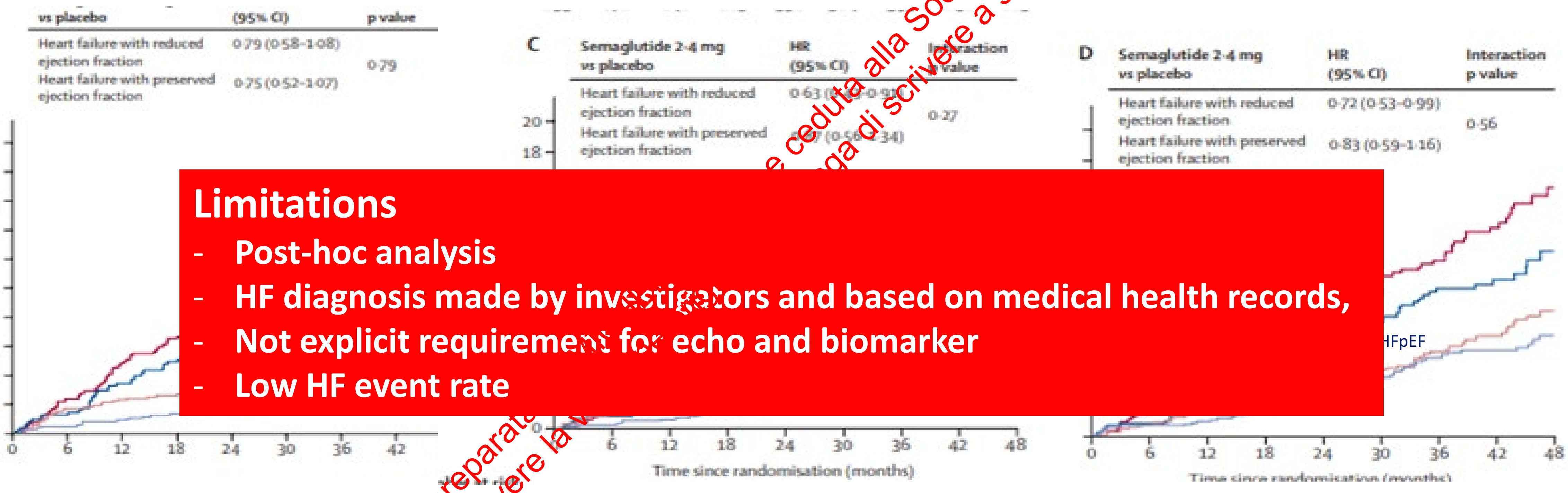
Semaglutide sc 2.4 BMI >27 kg/m² CVD (MI, Stroke, PAD) No DM	4,286 (24.3%) chronic HF	Hf subtypes HFpEF 53% HFrEF 31% Unclassified 16%	Follow-up 40 mo

SELECT:
Pre-specified outcome analysis by HF subtype

HF composite

CV death

All-cause death



Limitations

- Post-hoc analysis
- HF diagnosis made by investigators and based on medical health records,
- Not explicit requirement for echo and biomarker
- Low HF event rate

Deanfield J, et al. Lancet. 2024;404(10454):773–786.

The cumulative incidence rate is calculated using the Aalen–Johansen method. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events.

CONCLUSIONS

The use of GLP-1a in obese patients with HFpEF seems to have encouraging results, however we need CVOT trials.

In obese HFrEF patients we need dedicated and adequately powered trials to address this issue.