

INSUFFICIENZA CARDIACA: HOT NEWS

Scompenso cardiaco a FE preservata: i nuovi "pilastri" della terapia medica

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Il sottoscritto PULIGNANO GIOVANNI
in qualità di relatore

ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5.
del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara
di aver avuto rapporti di finanziamento
Boheringher, Astra Zeneca, Pfizer, Novartis, Bayer, Menarini

- Lo scompenso cardiaco a frazione di eiezione preservata (HFpEF) è una delle sfide cliniche più significative e complesse nella cardiologia moderna.
- A differenza dello scompenso cardiaco a FE ridotta (HFrEF), per il quale da alcuni decenni sono disponibili terapie che riducono significativamente la mortalità e la morbidità, la gestione dell'HFpEF è stata a lungo un'area di incertezza terapeutica.
- La sua eterogeneità e la complessa fisiopatologia richiedono un approccio diagnostico e terapeutico che va oltre i paradigmi tradizionali.

HF reduced EF



HF preserved EF



Heart Failure With Preserved Ejection Fraction

Treat Now by Treating Comorbidities

Sanjiv J. Shah, MD

Mihai Gheorghiade, MD

JAMA, July 23/30, 2008—Vol 300, No. 4

the care of these patients should be redirected toward screening and treatment of important comorbidities such as hypertension, CAD, atrial fibrillation, diabetes, and chronic kidney disease

Do patients with suspected heart failure and preserved left ventricular systolic function suffer from “diastolic heart failure” or from misdiagnosis?

A prospective descriptive study

Lynn Caruana, Mark C Petrie, Andrew P Davie, John J V McMurray

Conclusions For most patients with a diagnosis of heart failure but preserved left ventricular systolic function there is an alternative explanation for their symptoms—for example, obesity, lung disease, and myocardial ischaemia—and the diagnosis of diastolic heart failure is rarely needed. These alternative diagnoses should be rigorously sought and managed accordingly.

Can Brain Natriuretic Peptide Be Used to Guide the Management of Patients With Heart Failure and a Preserved Ejection Fraction?

The Wrong Way to Identify New Treatments for a Nonexistent Disease

Milton Packer, MD

*Left ventricular filling pressures in patients with HFPEF are elevated not because the left ventricle cannot fill, but because it is **overfilled**, most likely as a result of the **interplay of numerous comorbid conditions** that can affect the level and distribution of circulating blood volume and ventricular-vascular coupling.*

Circ Heart Fail. 2011;4:538-540



ESC

European Society of Cardiology
European Heart Journal (2019) 40, 3277–3280
doi:10.1093/eurheartj/ehz756

ISSUE @ A GLANCE

Heart failure with preserved ejection fraction: towards an understanding of an **enigma**



Thomas F. Lüscher^{1,2,3}

Developing Therapies for Heart Failure With Preserved Ejection Fraction

Considering its prevalence and outcomes, future projections, and lack of effective therapies, HFpEF represents the single largest unmet need in cardiovascular medicine.

Javed Butler,

JACC: Heart Failure

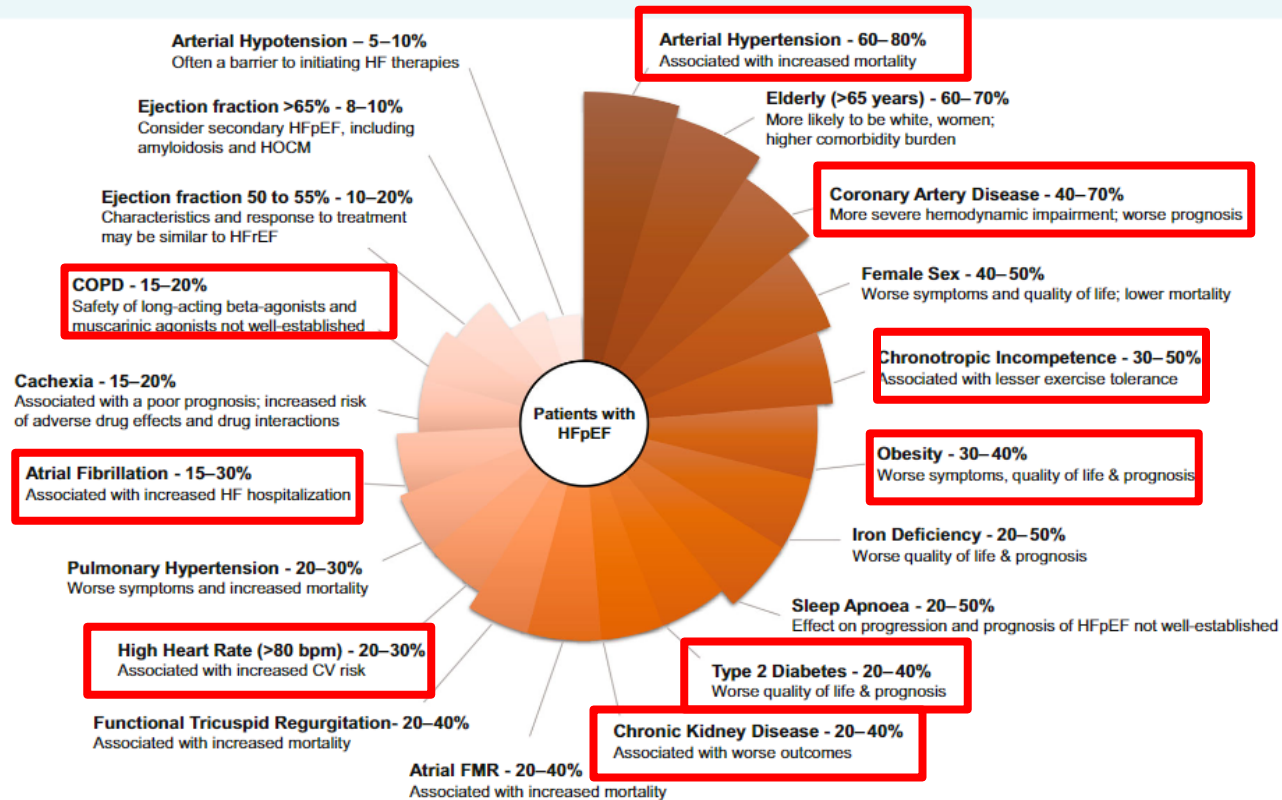
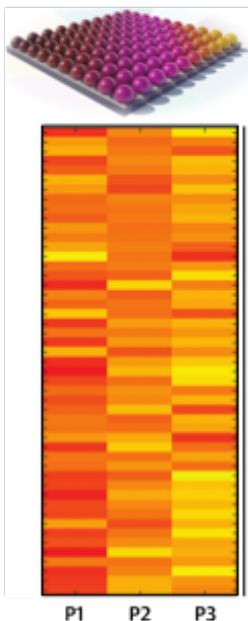


Figure 1 The estimated prevalence of important phenotypes of primary heart failure with preserved ejection fraction (HFpEF). COPD, chronic obstructive pulmonary disease; CV, cardiovascular; FMR, functional mitral regurgitation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy.

Clinical Phenogroups in HFpEF

Detailed Phenotypes, Prognosis, and Response to Spironolactone

- P1**
- Normal LV geometry
 - Low arterial stiffness
 - Low natriuretic peptides
 - Markers of COPD (not genuine HFpEF?)
 - Low event rate
 - Preferentially enrolled in Russia/Georgia
- P2**
- Concentric remodeling
 - Very stiff arteries
 - LA enlargement and AF
 - High natriuretic peptides
 - Innate immunity activation
 - High risk of primary endpoint
- P3**
- Obesity/Diabetes
 - Inflammation (TNF- α)
 - Abnormal metabolism, liver and renal injury/dysfunction
 - High renin
 - Highest risk of primary endpoint
 - Preferential response to spironolactone



Cluster analysis of 8 clinical variables in all participants in TOPCAT (n3,445)

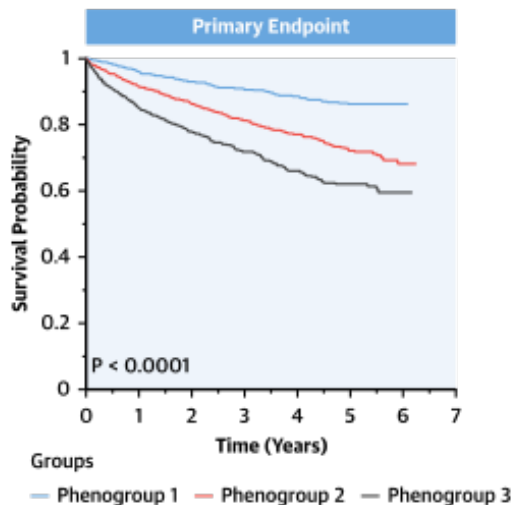
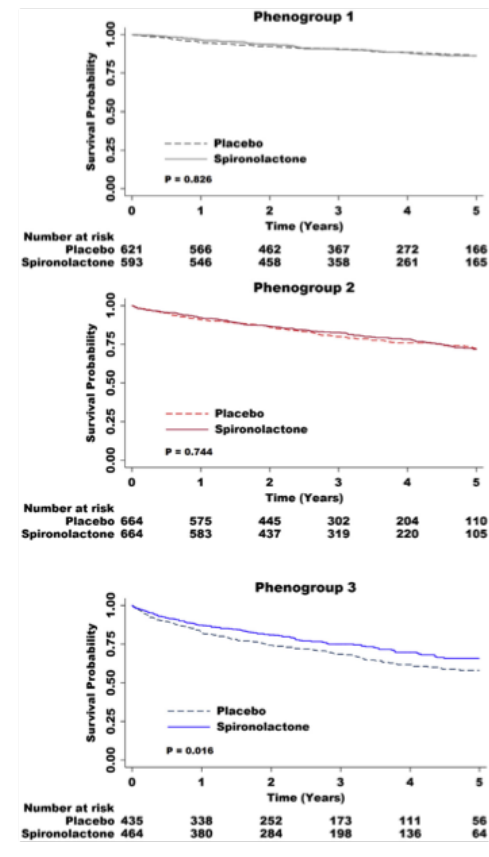


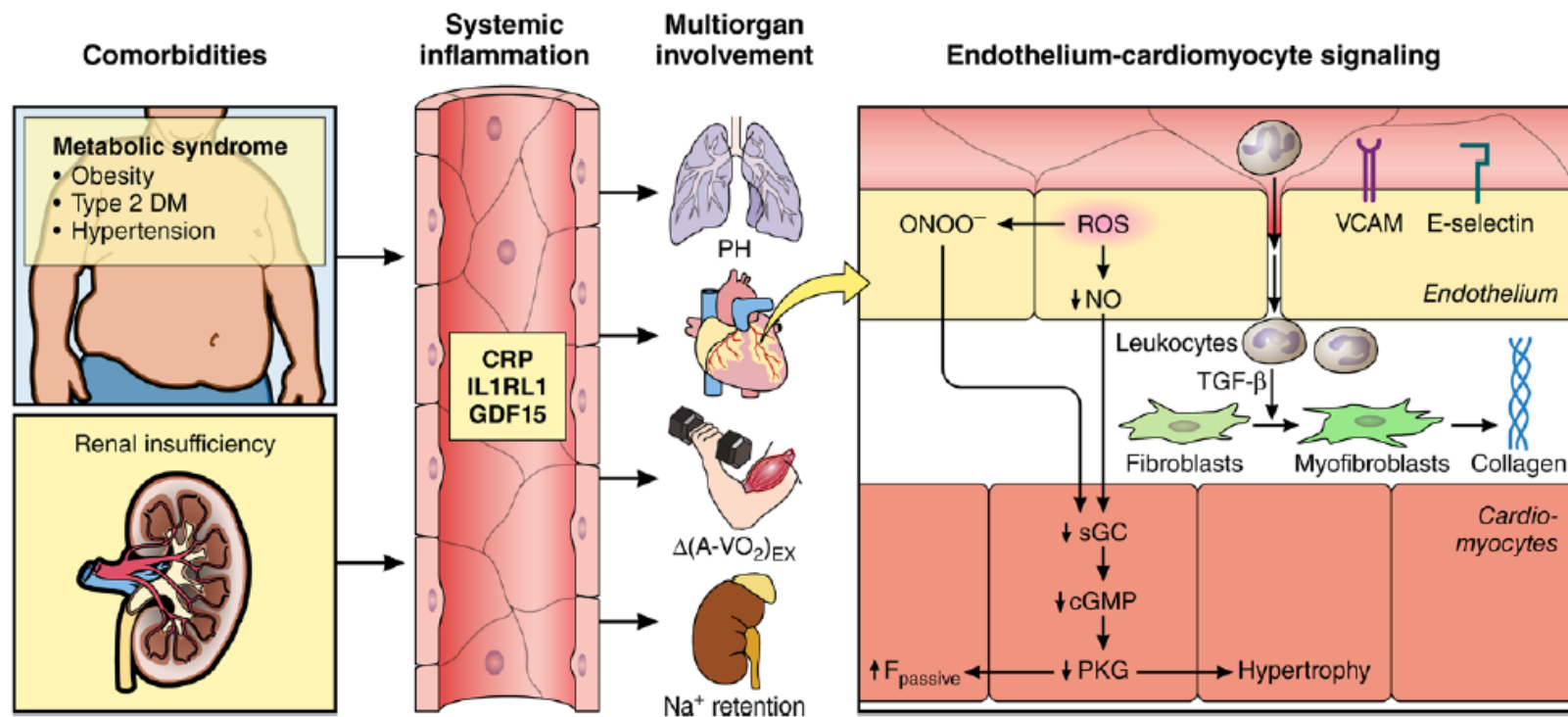
FIGURE 4 Kaplan-Meier Curves for the Primary Outcome by Spironolactone Treatment Status, Stratified by Clinical Phenogroup



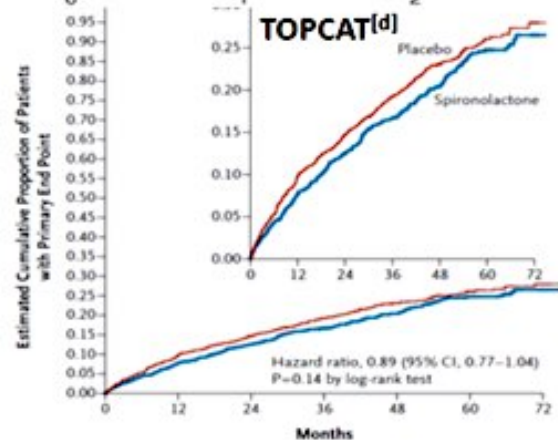
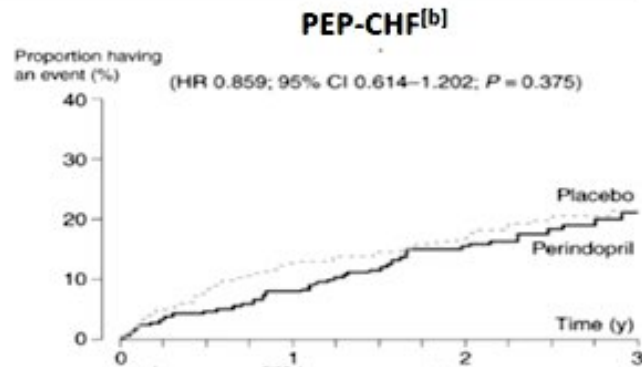
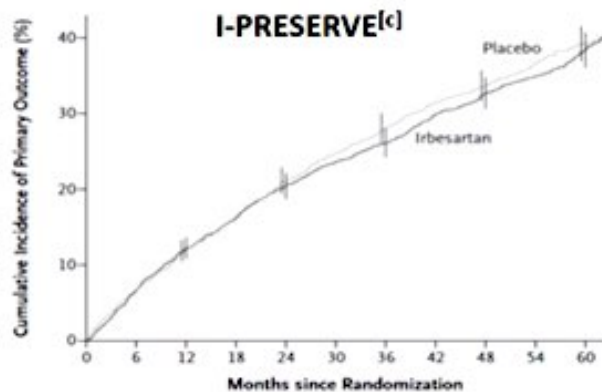
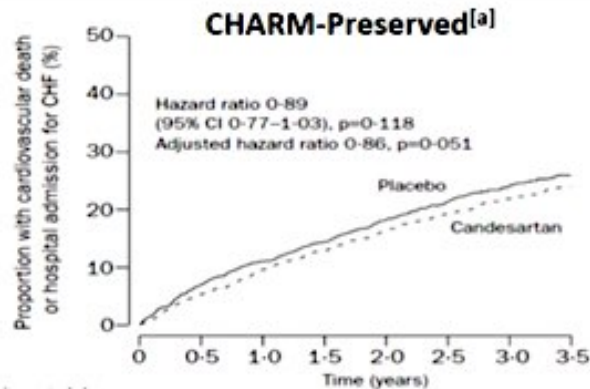
Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction

A Multiorgan Roadmap

Systemic and myocardial signaling in HFPEF.



Terapia HFpEF: Perchè questi trial hanno “fallito” ?

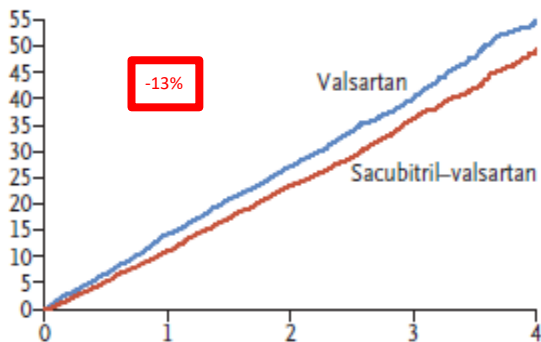


Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

Older (65-75 yrs) white woman with EF 45-57%?

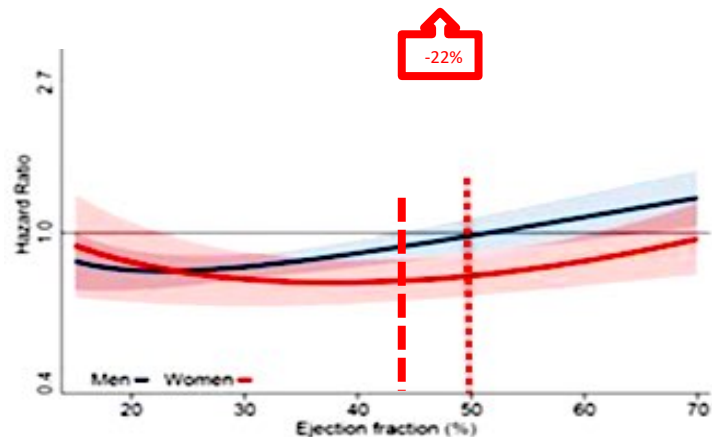
PARAGON-HF

Total Hospitalizations for Heart Failure and Death from Cardiovascular Causes



RR 0,87 [IC 95%, 0,75-1,01]; P=0,059

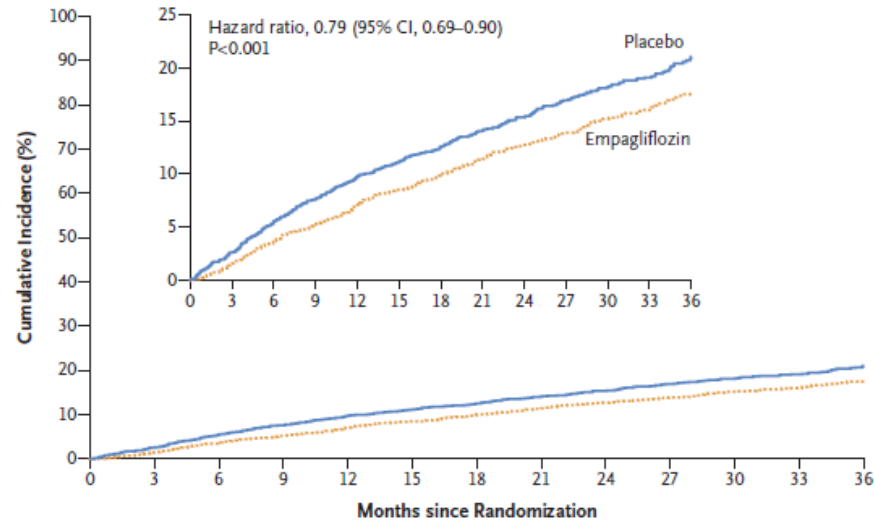
Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75–1.01)
Age		
<65 yr	276/825	0.99 (0.64–1.53)
≥65 yr	1627/3971	0.85 (0.73–0.99)
Age		
<75 yr	938/2597	0.82 (0.66–1.02)
≥75 yr	965/2199	0.92 (0.76–1.11)
Sex		
Male	980/2317	1.03 (0.83–1.23)
Female	923/2479	0.73 (0.59–0.90)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64–0.95)
>Median (57%)	855/2301	1.00 (0.81–1.23)



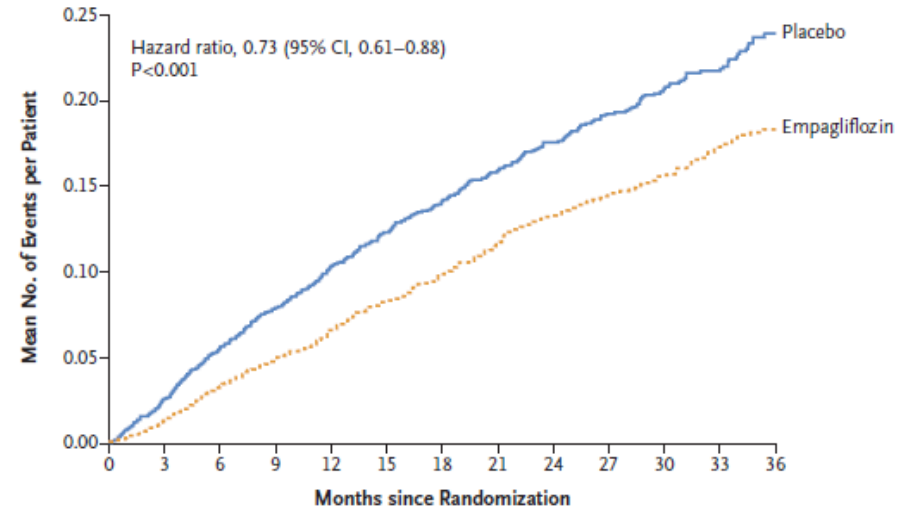
Empagliflozin in Heart Failure with a Preserved Ejection Fraction

EMPEROR-PRESERVED

Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure

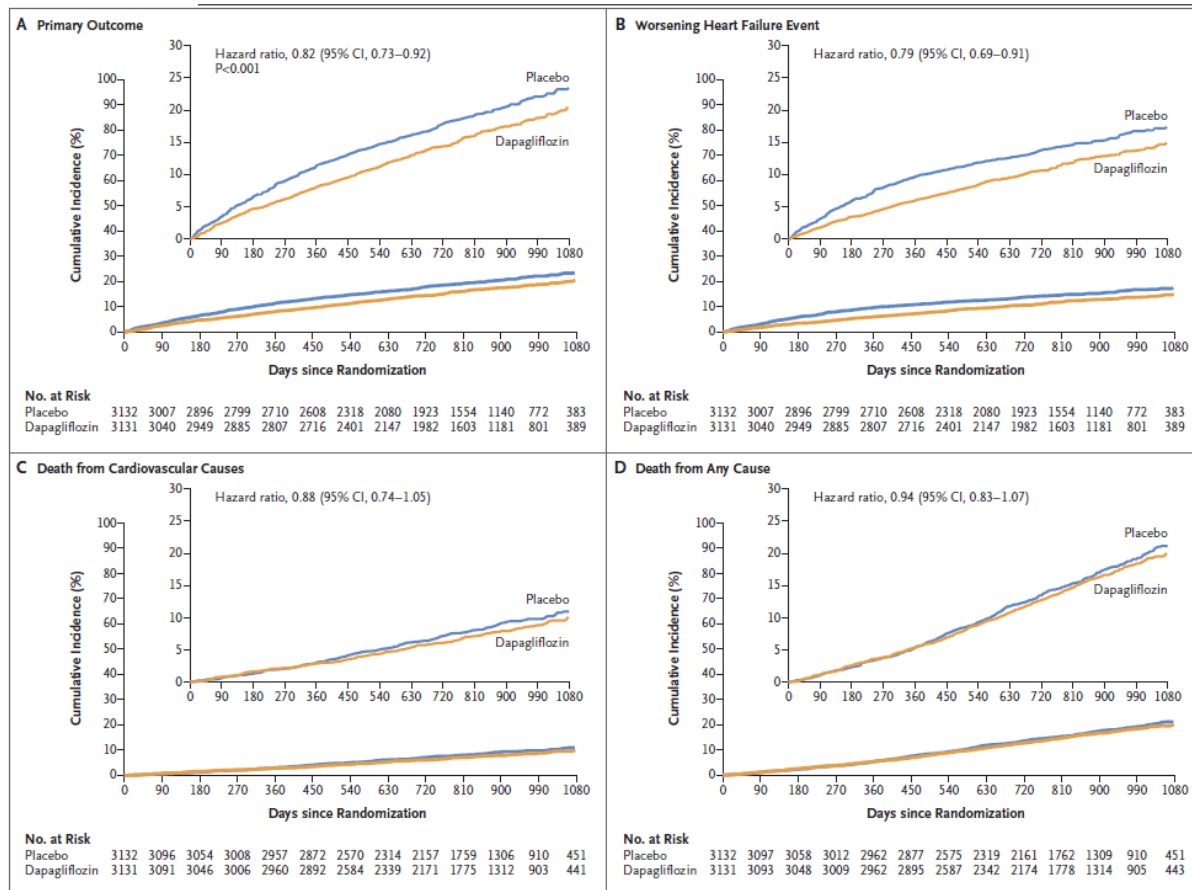


Hospitalizations for Heart Failure.



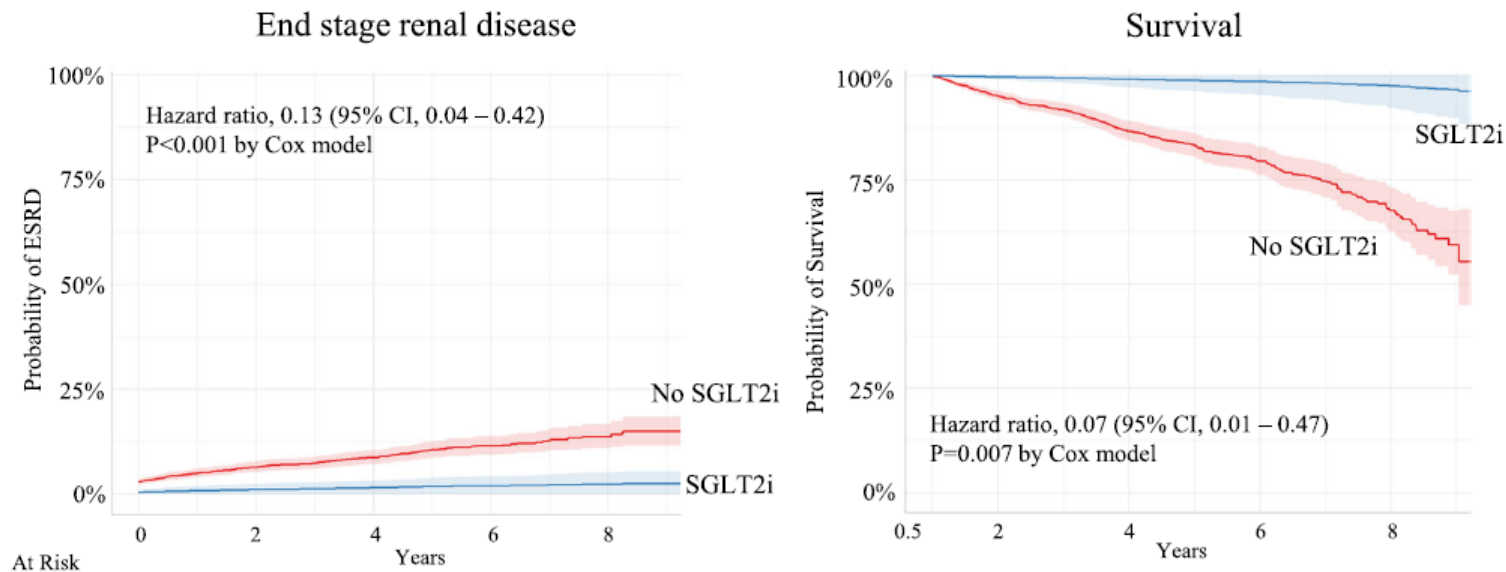
Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

DELIVER



Retrospective analysis of SGLT2 inhibitors in heart failure with preserved ejection fraction

Figure 3 Risk of end stage renal disease and all-cause mortality in heart failure with preserved ejection fraction patients prescribed SGLT2i after adjusting for age, sex, race, hypertension status, and diabetes status. Kaplan–Meier curves for mortality were also adjusted for chronic kidney disease status.



MRA non steroidei vs steroidei

- Blocco selettivo dell'attivazione patologica mediata da aldosterone e cortisolo
- Riduzione dell'infiammazione e della fibrosi a livello renale, cardiaco e vascolare

Steroidal Aldosterone antagonists



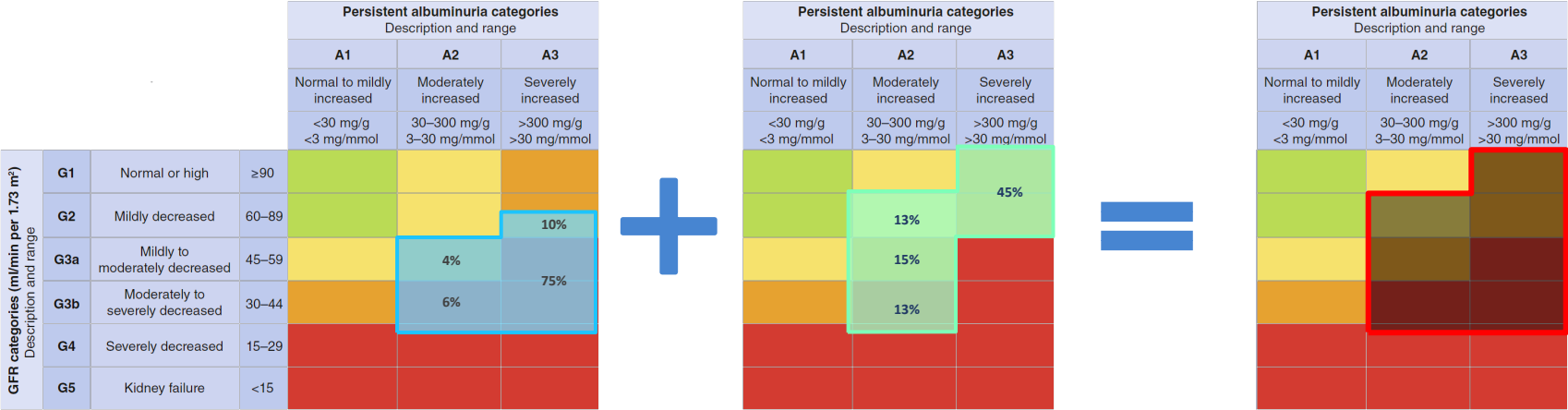
Structural properties	Flat (steroidal)	Flat (steroidal)
Potency to MR	High ^{4,10}	Moderate ^{1,4,10}
Selectivity to MR	Low ^{4,10}	Moderate ^{4,10}
Half-life	>20 hours*	4–6 hours*
Active metabolites	++	–
CNS penetration	Yes	Yes
Gynecomastia	Yes ⁴	Less than spironolactone ⁴
Hyperkalaemia	Yes ⁴	Yes ⁴
Tissue distribution	Kidney > heart (at least 6-fold) ^{6,10}	Kidney > heart (~3-fold) ^{6,10}

Finerenone



Bulky (nonsteroidal) ^{1,5}
High ^{1,2,10}
High ^{1,2,10}
2–3 hours#
–
No based on preclinical data ³
No signal in phase II studies ⁷⁻⁹
Moderately increased*, ⁷⁻⁹
Based on preclinical data and ARTS phase II programme
Balanced kidney : heart (1:1) ^{6,10}

FIDELITY Pooled Analysis



PRIMARY CV ENDPOINT
Time to CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF



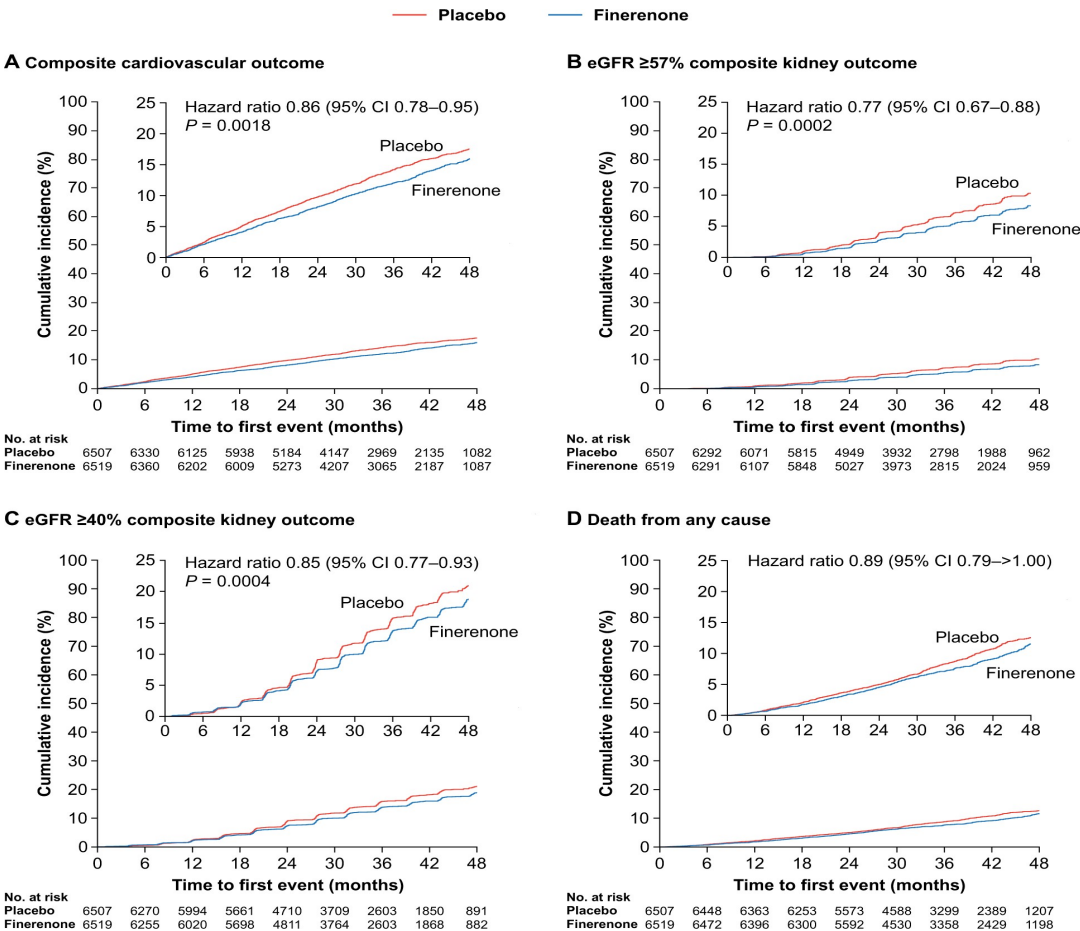
KEY SECONDARY KIDNEY ENDPOINT
Time to kidney failure (initiation of chronic dialysis for ≥90 days, kidney transplantation or sustained eGFR <15 ml/min/1.73 m²), **sustained ≥57% decrease in eGFR from baseline, or renal death**

**30≤UACR<300 mg/g and
25≤eGFR<90 mL/min/1.73m²**

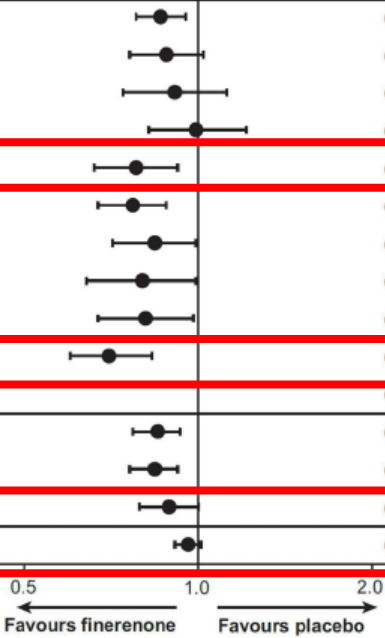
or

**300≤UACR≤5000 mg/g and
eGFR≥25 mL/min/1.73m²**

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis



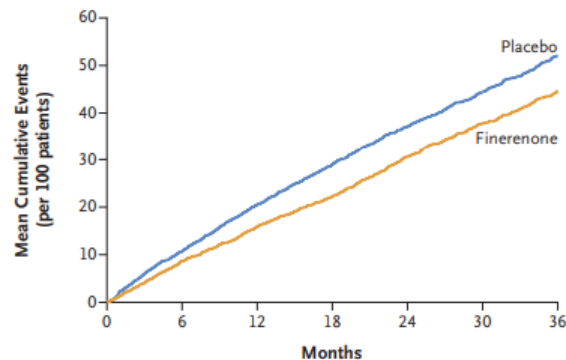
Il finerenone ha ridotto il rischio di esiti cardiovascolari e renali clinicamente importanti rispetto al placebo nell'intero spettro della malattia renale cronica nei pazienti con diabete di tipo 2.

Outcome	Finerenone (n = 6519)		Placebo (n = 6507)			Hazard ratio (95% CI)	P-value ^a
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years			
Composite cardiovascular outcome ^b	825 (12.7)	4.34	939 (14.4)	5.01		0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84		0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97		0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02		0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68		0.78 (0.66–0.92)	0.0030
eGFR ≥57% composite kidney outcome ^c	360 (5.5)	1.96	465 (7.1)	2.55		0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62		0.84 (0.71–0.99)	0.039
End-stage kidney disease ^d	151 (2.3)	0.76	188 (2.9)	0.96		0.80 (0.64–0.99)	0.040 ^e
Sustained decrease in eGFR to <15 mL/min/1.73 m ²	195 (3.0)	1.06	237 (3.6)	1.29		0.81 (0.67–0.98)	0.026 ^e
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03		0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02		0.53 (0.10–2.91)	0.46 ^e
eGFR ≥40% composite kidney outcome ^f	854 (13.1)	4.81	995 (15.3)	5.64		0.85 (0.77–0.93)	0.0004
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45		0.84 (0.76–0.92)	0.0002
Death from any cause	552 (8.5)	2.76	614 (9.4)	3.10		0.89 (0.79–1.00 ^g)	0.051 ^e
Hospitalization for any cause	2836 (43.5)	19.04	2926 (45.0)	19.91		0.96 (0.91–1.01)	0.087 ^e

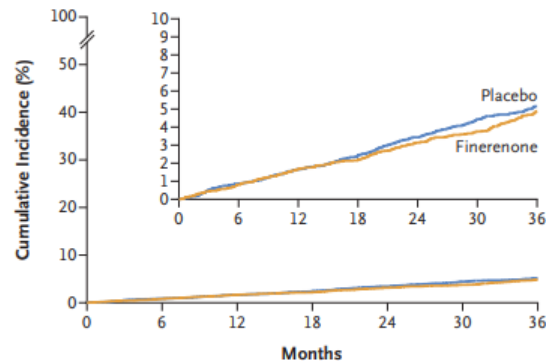
Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

FINEARTS-HF

A Total Worsening Heart Failure Events and Death from Cardiovascular Causes



C Death from Cardiovascular Causes



Finerenone 10-20/ 20- 40 vs placebo
(se GFR >>60 ml/min)

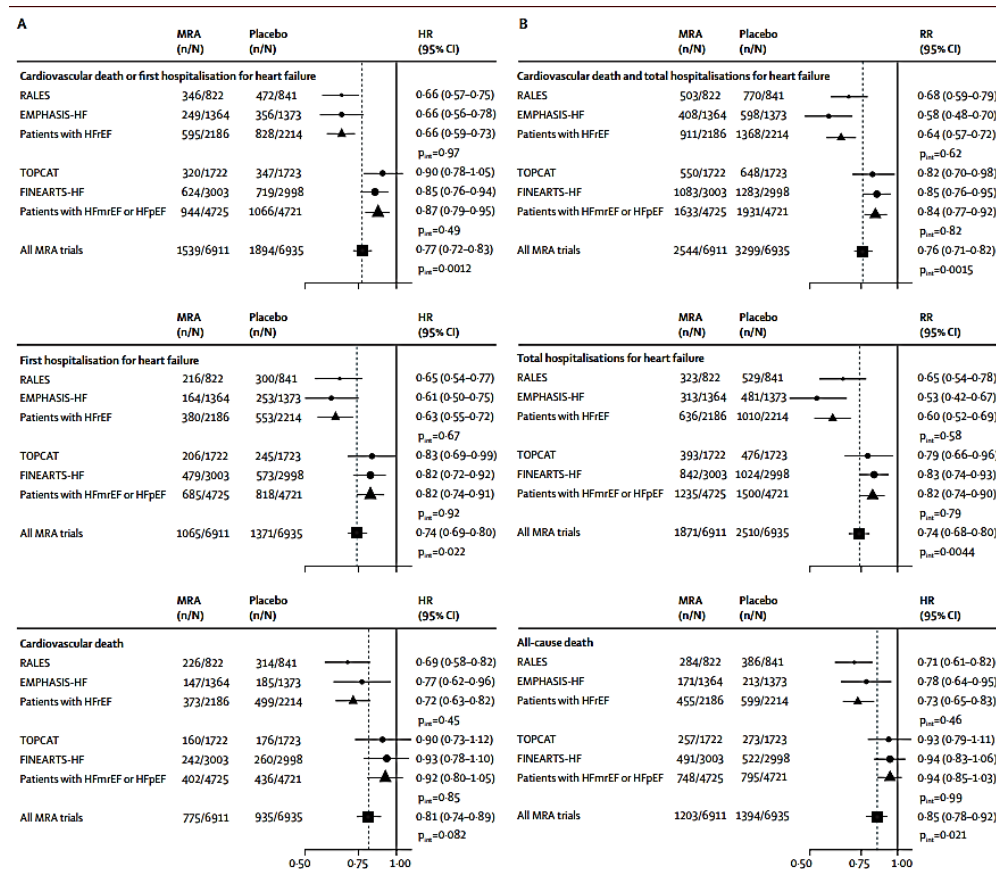
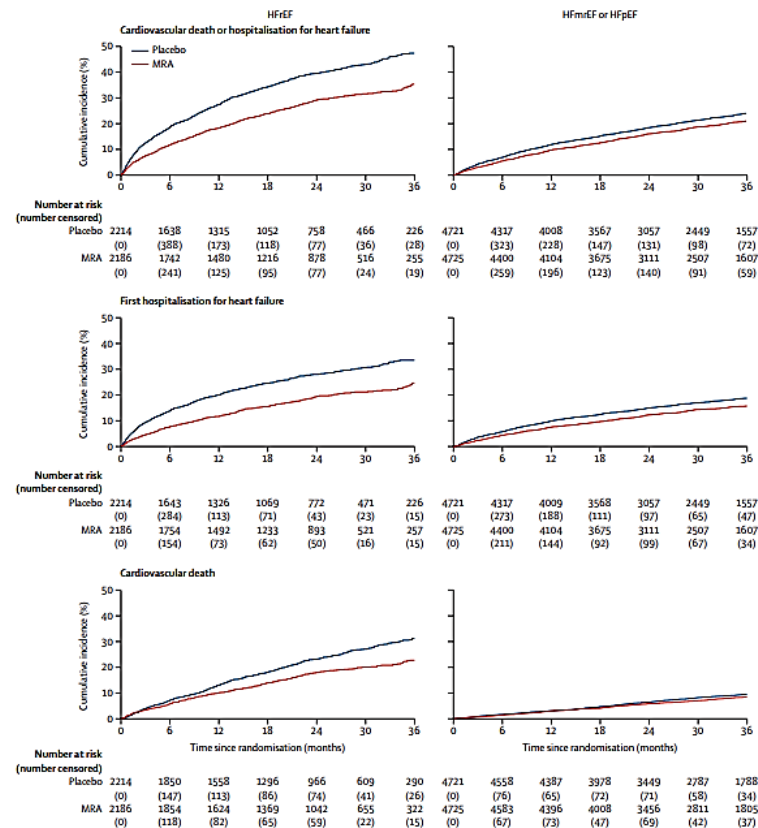
Nei pazienti con HF FE lievemente ridotta o preservata, il finerenone ha determinato una riduzione dell'end-point primario (eventi WHF totali e decessi per cause CV) rispetto al placebo

- Riduzione del 16% (RR 0.84, IC95% 0.74-0.95, $p=0.007$)
- Eventi HF totali ridotti del 18% (RR 0.82, $p=0.006$)
- Ospedalizzazioni HF ridotte del 14% (HR 0.86, $p=0.02$)

Subgroup	Finerenone no. of events	Placebo no. of events	Rate Ratio (95% CI)
Age			
≤73 yr	468	623	0.76 (0.63–0.92)
>73 yr	615	660	0.92 (0.77–1.09)
Sex			
Male	632	691	0.88 (0.74–1.04)
Female	451	592	0.78 (0.65–0.95)
Race			
Asian	211	218	0.96 (0.72–1.29)
Black	29	22	0.98 (0.37–2.62)
Other	34	57	0.60 (0.26–1.42)
White	809	986	0.82 (0.71–0.95)
Geographic region			
Asia	211	218	0.95 (0.71–1.27)
Eastern Europe	322	389	0.83 (0.67–1.03)
Latin America	106	163	0.65 (0.43–0.98)
North America	122	118	0.98 (0.67–1.45)
Western Europe, Oceania, or other	322	395	0.82 (0.64–1.06)
NYHA functional class			
II	646	741	0.86 (0.73–1.02)
Left ventricular ejection fraction			
<60%	877	1061	0.82 (0.71–0.94)
≥60%	206	222	0.94 (0.70–1.26)
NT-pro-BNP level at baseline			
≤1041 pg/ml	266	342	0.78 (0.62–0.99)
>1041 pg/ml	782	918	0.83 (0.71–0.96)
Time since heart failure event at randomization			
≤7 days	270	372	0.74 (0.57–0.95)
>7 days to 3 mo	404	492	0.79 (0.64–0.97)
>3 mo or no index event	409	419	0.99 (0.81–1.21)
ACEI, ARB, or ARNI use at baseline			
No	288	332	0.85 (0.66–1.11)
Yes	795	951	0.83 (0.72–0.96)
SGLT2 inhibitor use at baseline			
No	907	1049	0.85 (0.74–0.98)
Yes	176	234	0.83 (0.60–1.16)
Atrial fibrillation at baseline			
Yes	521	621	0.80 (0.66–0.97)
No	562	660	0.85 (0.73–1.01)
Diabetes mellitus at baseline			
Yes	524	638	0.83 (0.69–1.00)
No	559	645	0.85 (0.71–1.01)
Body-mass index			
<30	586	648	0.88 (0.74–1.05)
≥30	486	632	0.79 (0.66–0.95)
eGFR at baseline			
<60 ml/min/1.73 m ²	727	796	0.91 (0.78–1.07)
≥60 ml/min/1.73 m ²	356	487	0.72 (0.59–0.88)
Serum potassium level at baseline			
≤4.5 mmol/liter	714	875	0.81 (0.69–0.95)
>4.5 mmol/liter	369	408	0.91 (0.74–1.11)
Systolic blood pressure at baseline			
≤130 mm Hg	608	740	0.85 (0.72–1.01)
>130 mm Hg	475	543	0.84 (0.69–1.02)
Urinary albumin:creatinine ratio at baseline			
<30 mg/g	429	518	0.81 (0.67–0.97)
≥30 mg/g	601	705	0.88 (0.74–1.05)

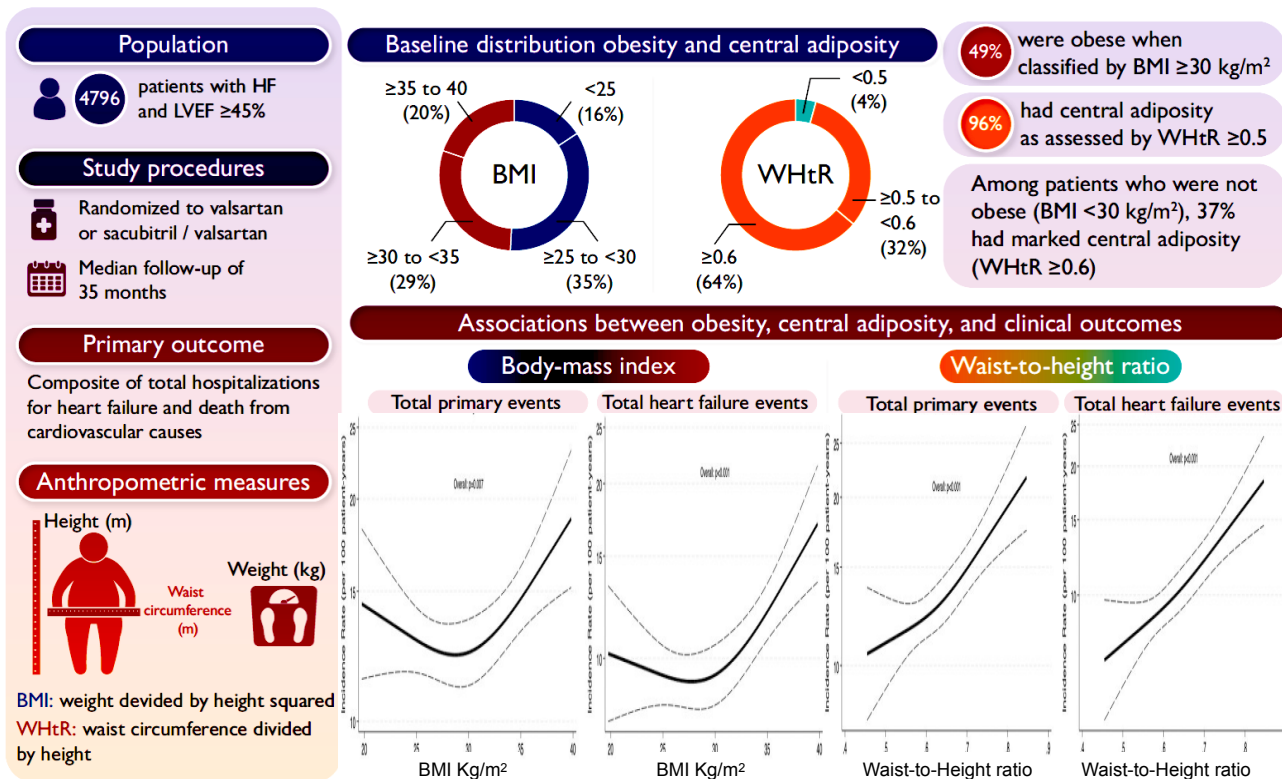
Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis

RALES, EMPHASIS-HF, TOPCAT FINEARTS-HF



Near-universal prevalence of central adiposity in HFpEF:

the PARAGON-HF trial

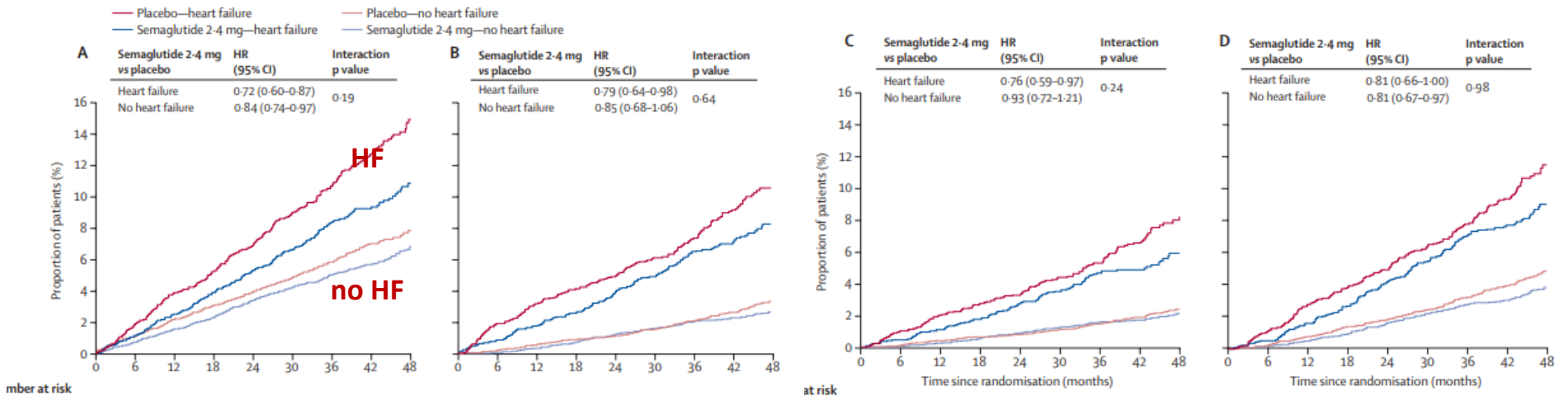


In **PARAGON-HF**, in contrast with BMI, **nearly every patient with HFpEF had central adiposity** (as assessed by WHtR), and the risks of adverse HF events were more robustly related to WHtR

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

- Age ≥45 years
- BMI ≥27 kg/m²
- Prior MI or Stroke or PAD with claudication and ankle-brachial index <0.85 prior revascularization, or amputation

MACE (A), heart failure composite (B), cardiovascular death (C), and all-cause death (D)

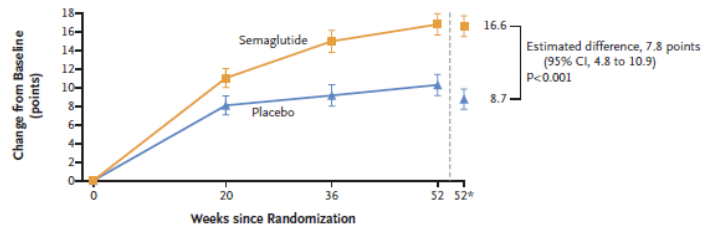


In patients with atherosclerotic cardiovascular disease and overweight or obesity, treatment with semaglutide 2.4 mg reduced MACE and composite heart failure endpoints compared with placebo in those with and without clinical heart failure, regardless of heart failure subtype

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

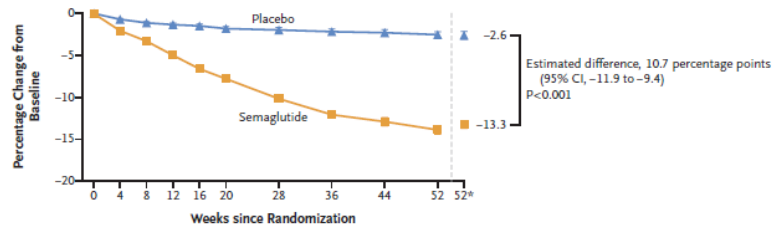
STEP-HFpEF: n=529; LVEF≥45%; NYHA II-IV; elevated NP; **BMI>30 kg/m²**, Semaglutide (up to 2.4 mg)

A Change in KCCQ-CSS



No. of Participants				
Semaglutide	263	249	225	243
Placebo	266	242	217	237

B Change in Body Weight

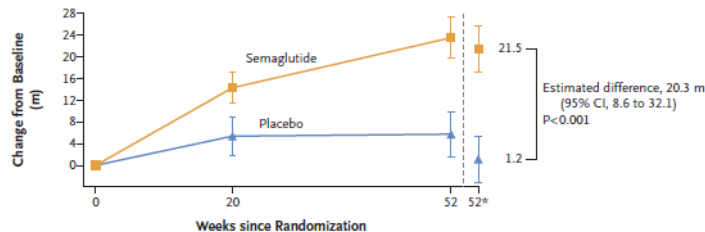


No. of Participants									
Semaglutide	263	255	254	250	246	252	239	243	240
Placebo	266	259	249	250	243	246	243	239	233

In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo

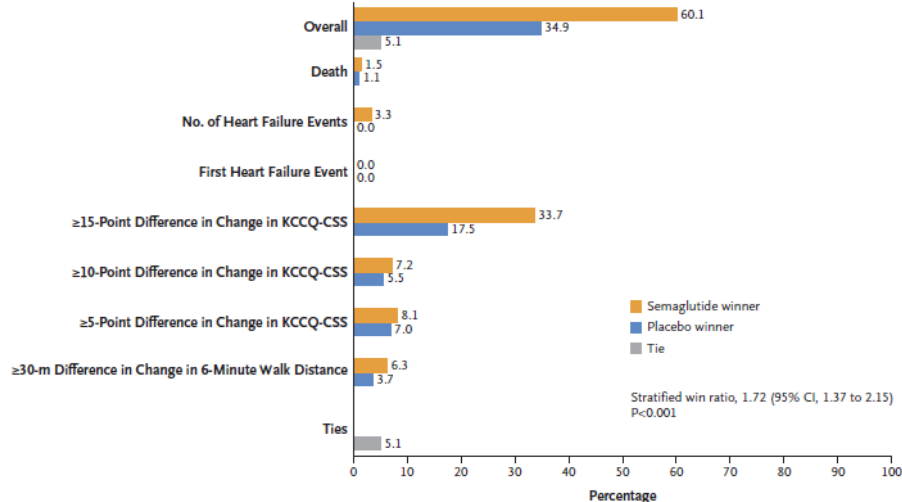
STEP-HFpEF

A Change in 6-Minute Walk Distance



No. of Participants			
Semaglutide	263	245	240
Placebo	266	232	225

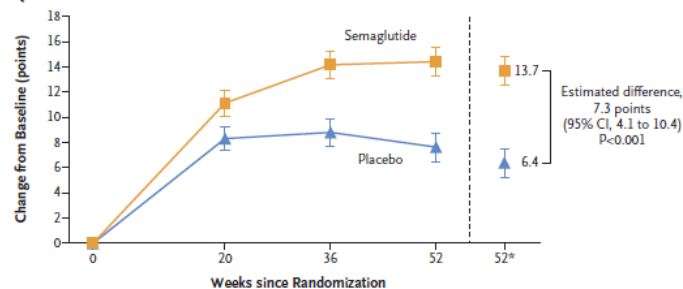
B Stratified Win Ratio for Hierarchical Composite End Point



Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

STEP-HFpEF – DM

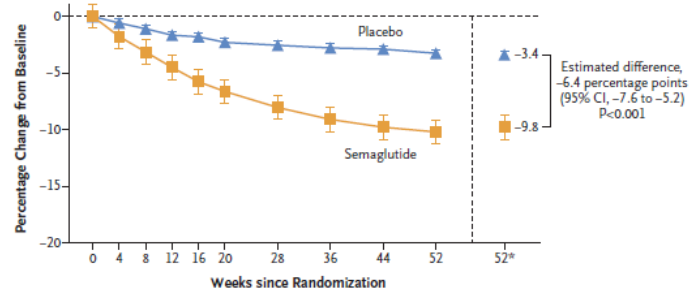
A Change in KCCQ-CSS



No. of Participants
Semaglutide
Placebo

310	289	274	281	310
306	284	270	272	306

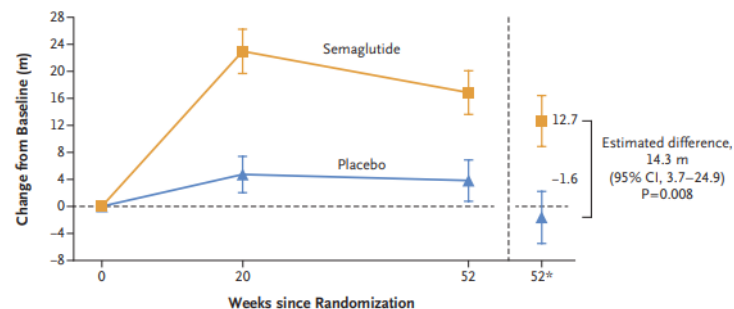
B Change in Body Weight



No. of Participants
Semaglutide
Placebo

310	307	297	299	290	292	283	286	282	286	282	286	310
306	300	298	287	292	289	282	278	273	278	278	278	306

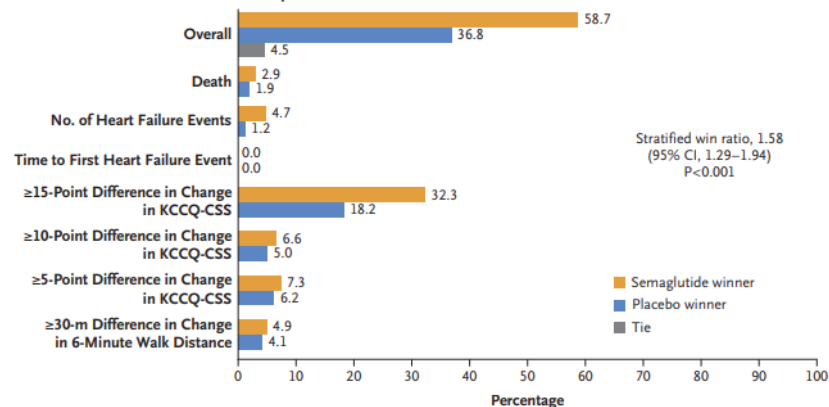
A Change in 6-Minute Walk Distance



No. of Participants
Semaglutide
Placebo

310	284	281	310
306	277	265	306

B Stratified Win Ratio for Hierarchical Composite End Point



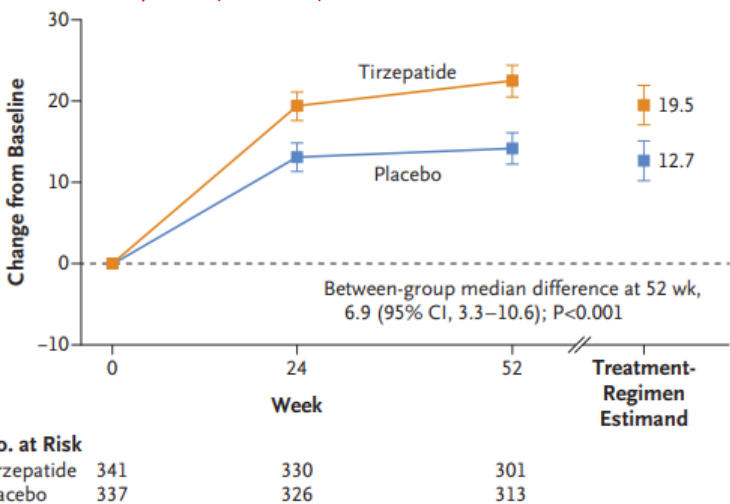
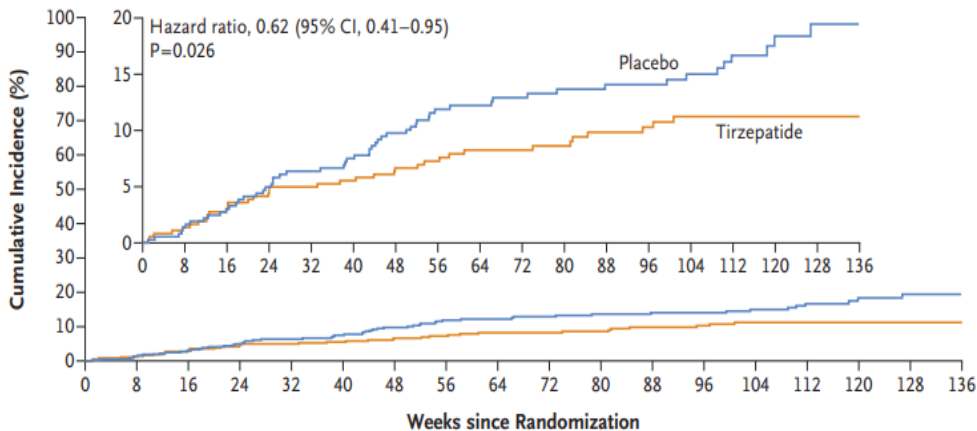
Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

SUMMIT Trials

731 patients with HF, EF at least 50%, BMI at least 30 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo

Change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS).

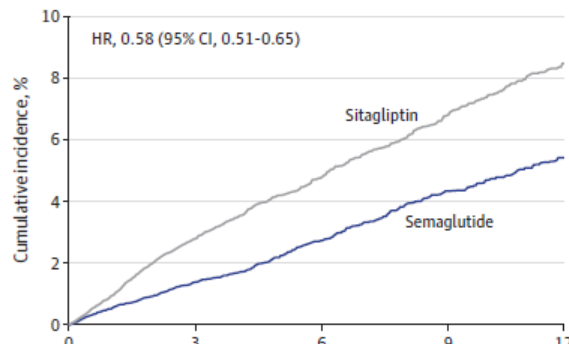
Death from Cardiovascular Causes or a Worsening Heart-Failure Event.



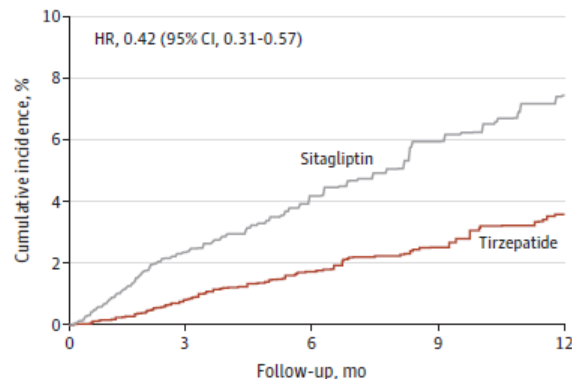
Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity.

Semaglutide and Tirzepatide in Patients With Heart Failure With Preserved Ejection Fraction

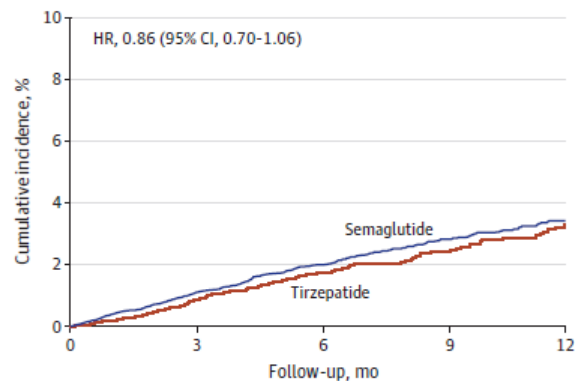
A Semaglutide vs sitagliptin



B Tirzepatide vs sitagliptin

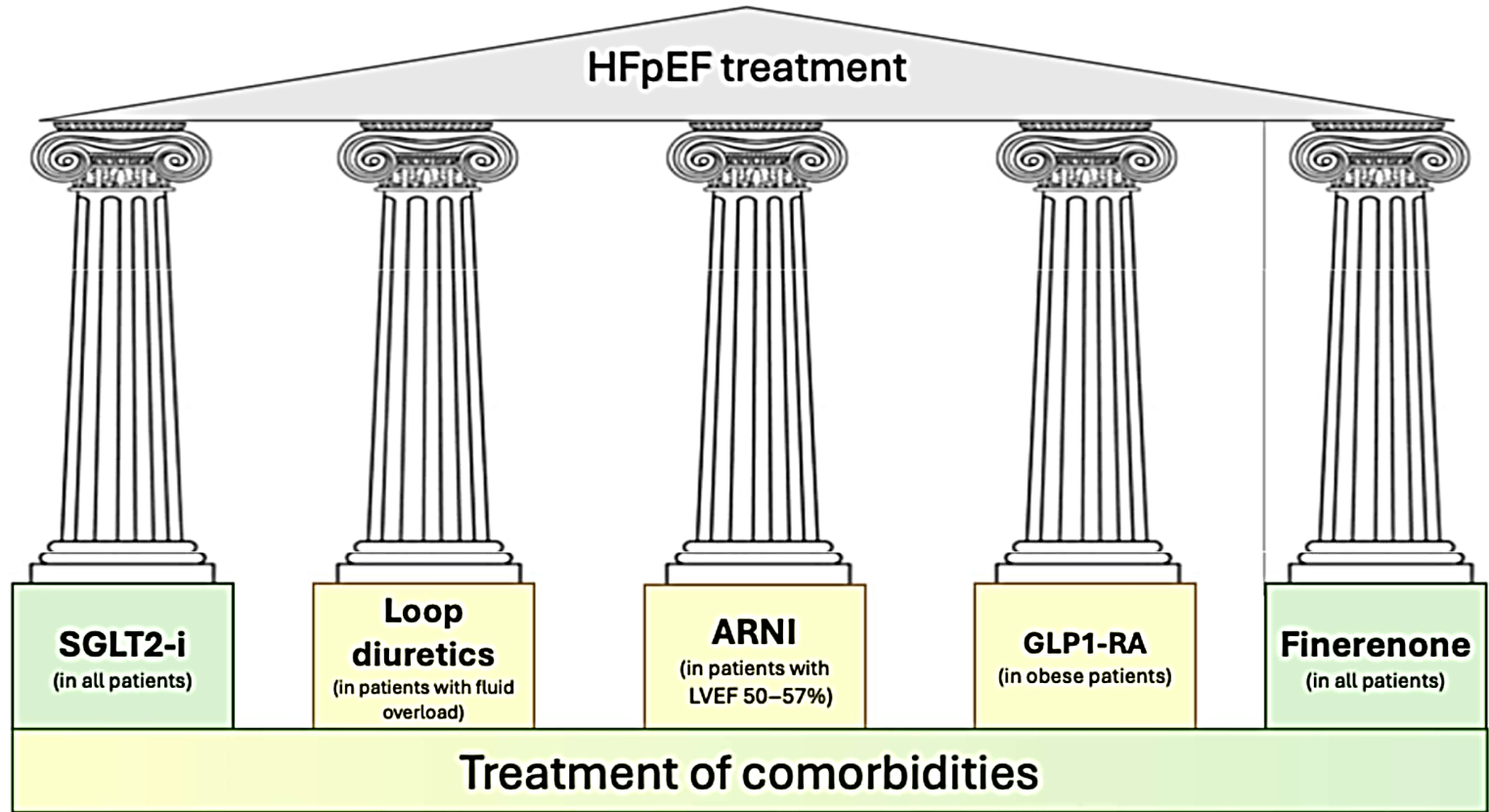


C Tirzepatide vs semaglutide



Clinical Practice
3US claims data
sources: Medicare
Parts A, B, and D (2018 through
2020), Optum Clinformatics
Data Mart (2018 through
November 2024),
and Merative MarketScan (2018
through 2022).
STEP-HFpEF DM and SUMMIT
CRITERIA

In patients with cardiometabolic HFpEF, semaglutide and tirzepatide showed **more than 40% risk reduction** for the composite of hospitalization for heart failure or all-cause mortality compared with a placebo proxy. Tirzepatide showed no meaningful benefit over semaglutide.

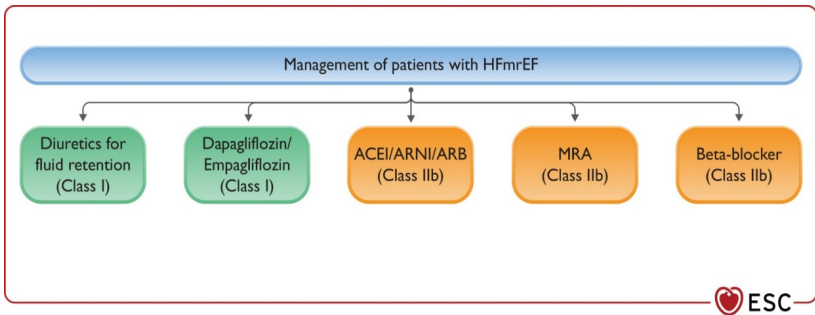


Management of patients with heart failure with mildly reduced ejection fraction.

Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class ^a	Level ^b
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death. ^{c 6,8}	I	A

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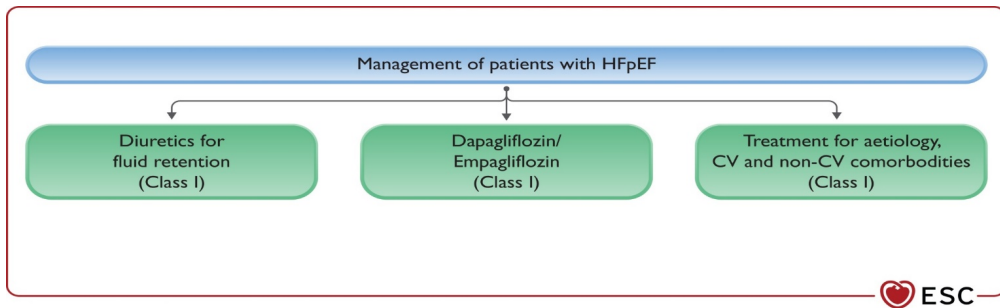


Management of patients with heart failure with preserved ejection fraction.

Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

Recommendation	Class ^a	Level ^b
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death. ^{c 6,8}	I	A

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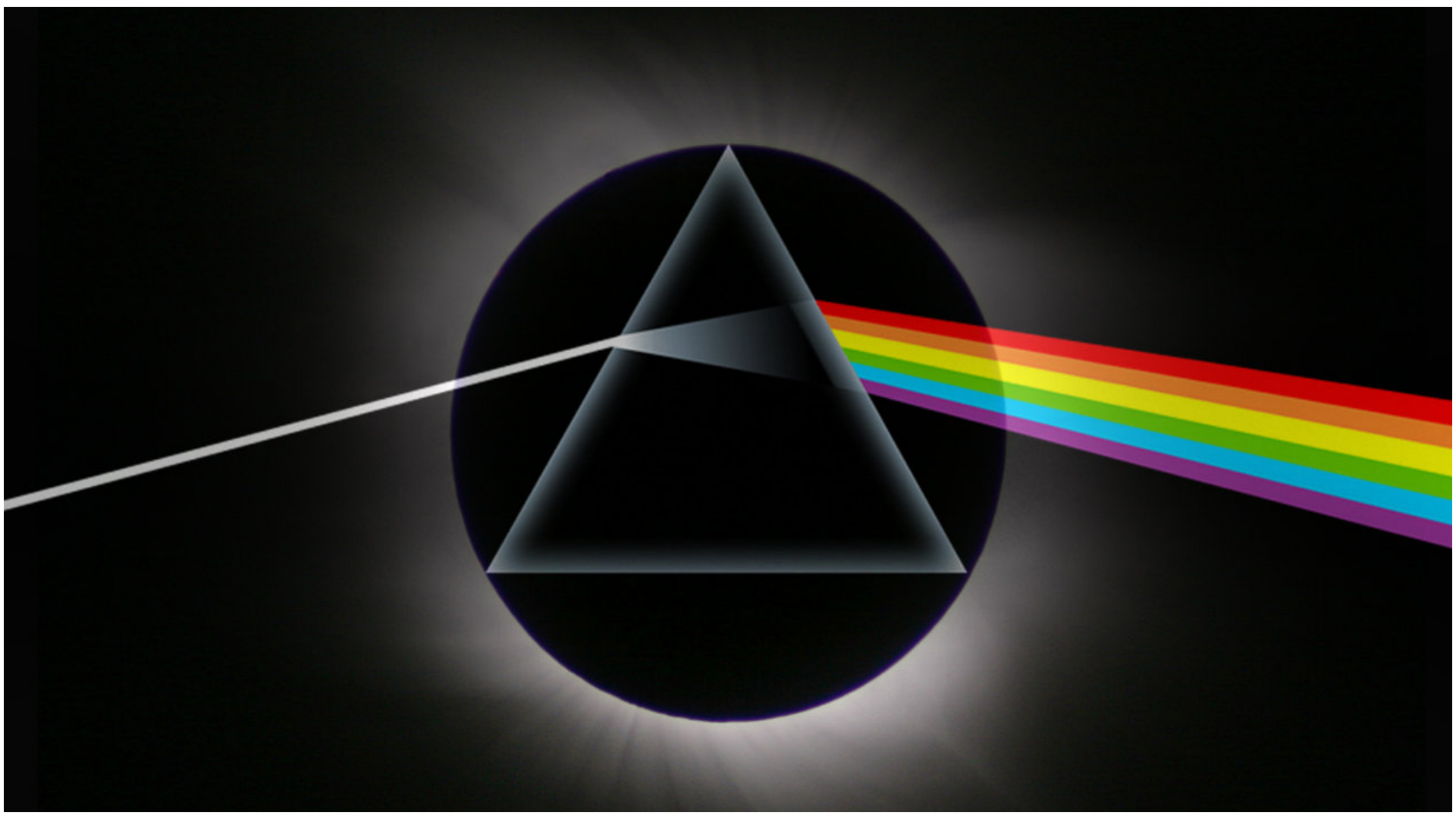


Recommendations	Class ^a	Level ^b
In patients with T2DM and CKD, ^c SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death. ³⁵	I	A
In patients with T2DM and CKD, ^c finerenone is recommended to reduce the risk of HF hospitalization. ^{10,11,34,40}	I	A

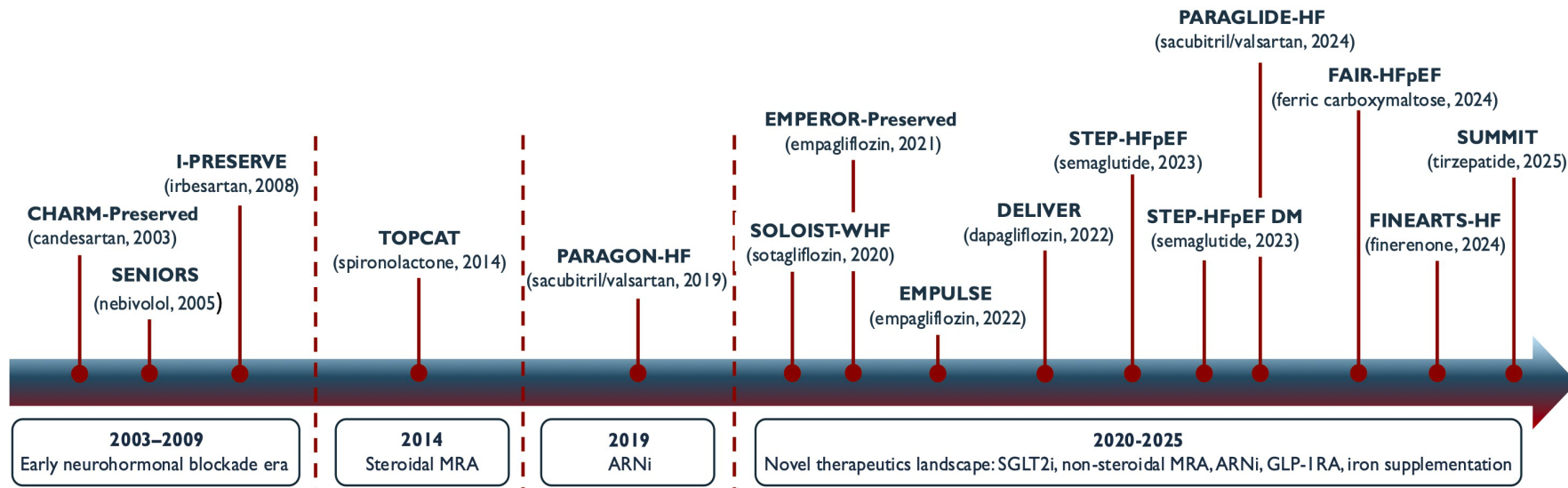
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Conclusioni

- L'HFpEF rappresenta circa il 50% dei casi di scompenso cardiaco, con elevata mortalità e morbidità.
- L'HFpEF è una sindrome clinica eterogenea, influenzata nel suo sviluppo e progressione da numerose comorbidità.
- La disfunzione del ventricolo sinistro può essere una manifestazione di varie combinazioni di condizioni cardiache, vascolari, metaboliche, polmonari, renali e legate all'invecchiamento.
- Pertanto, oltre al trattamento con Diuretici, SGLT2i, Finerenone (e GLP1-RA negli obesi), il metodo più efficace per migliorare la prognosi può essere una terapia su misura per il profilo clinico di ciascun paziente.
- Un approccio basato su algoritmi per identificare i fenotipi HFpEF più comuni e identificare la strategia di trattamento deve tenere conto della complessità delle molteplici comorbidità .



HFpEF Therapy: Unmet needs and future directions



Future directions

REDEFINE-HF – finerenone in hospitalised HFpEF/HFmrEF

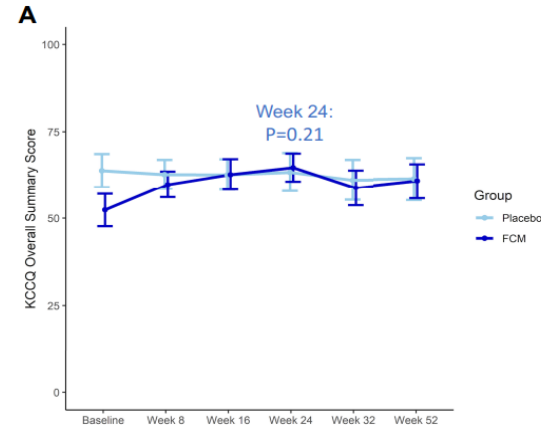
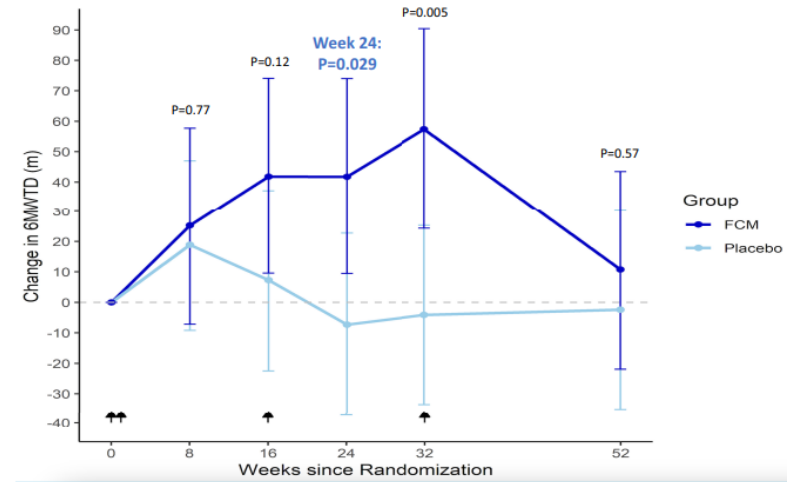
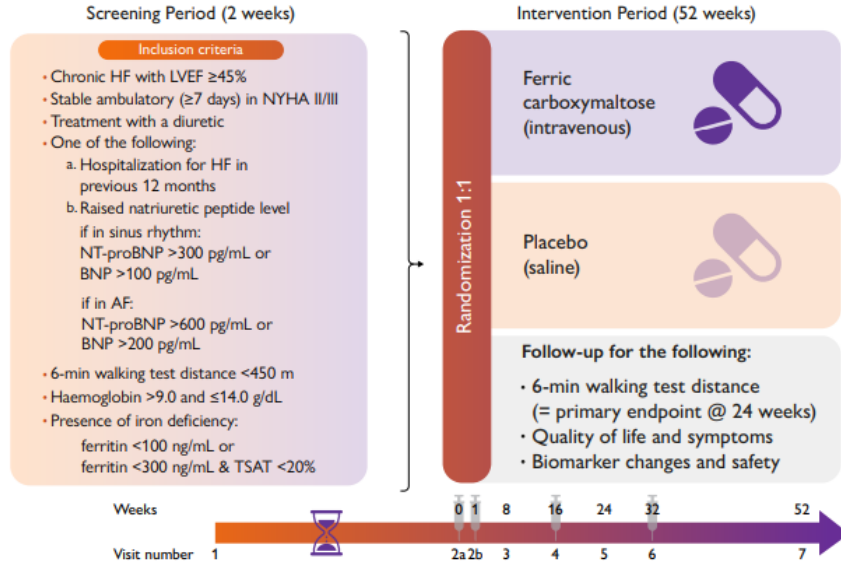
CONFIRMATION-HF – finerenone + dapagliflozin

BalanceD-HF – balcinrenone + dapagliflozin

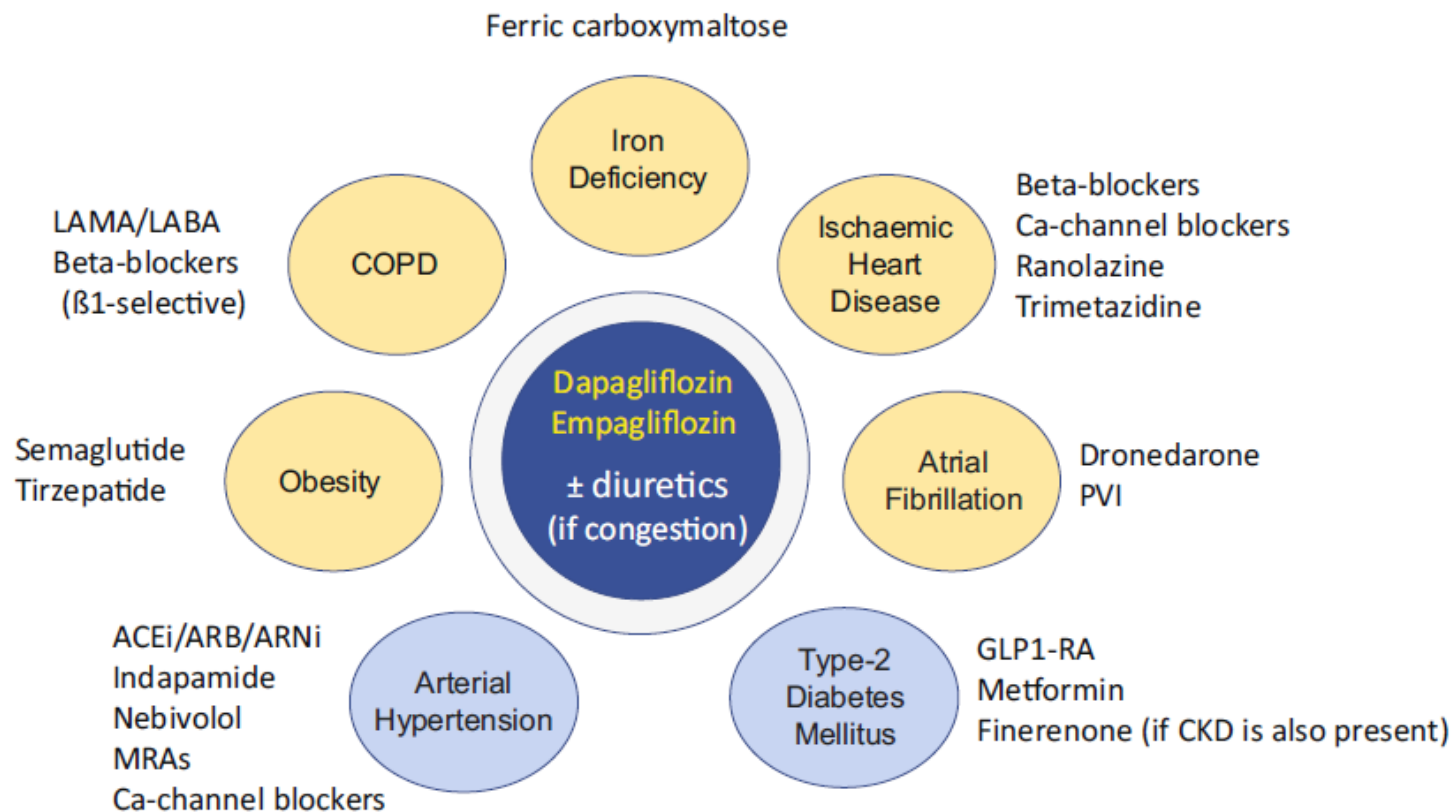
SPIRIT-HF – spironolactone vs placebo in HFpEF/HFmrEF

SPIRIT-HFpEF – registry-based RCT of spironolactone / eplerenone in HFpEF/HFmrEF

Ferric carboxymaltose and exercise capacity in heart failure with preserved ejection fraction and iron deficiency: the FAIR-HFpEF trial



Verso una terapia “di precisione” nel HFpEF?

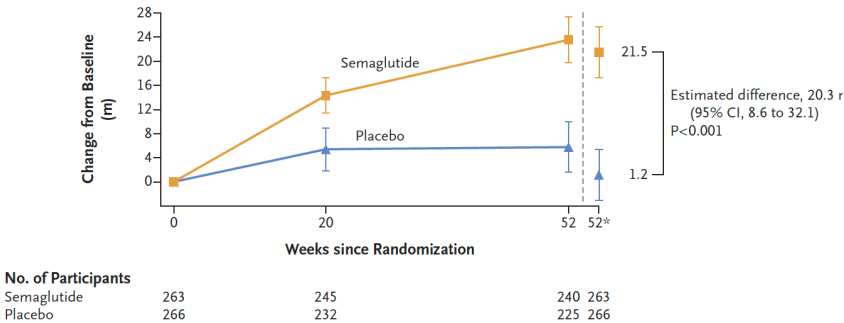


Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

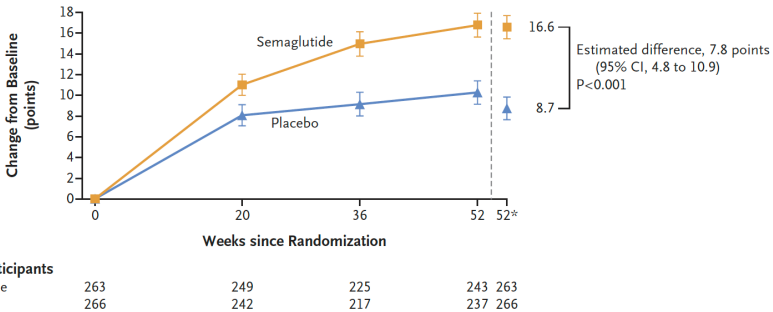
HFpEF and obesity: target therapy

STEP-HFpEF: n=529; LVEF≥45%;
NYHA II-IV; elevated NP; **BMI>30 kg/m2**
Semaglutide (up to 2.4 mg)

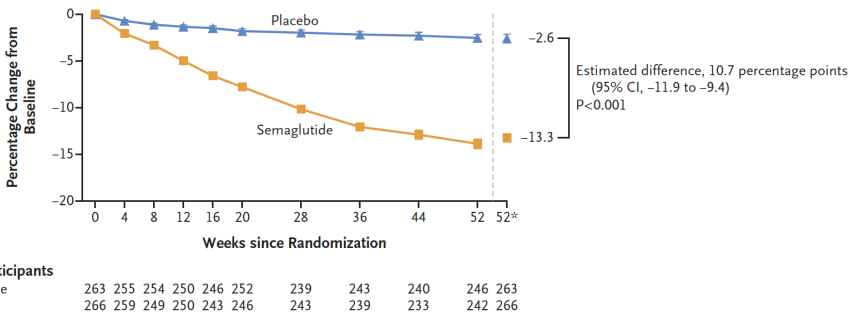
A Change in 6-Minute Walk Distance



A Change in KCCQ-CSS



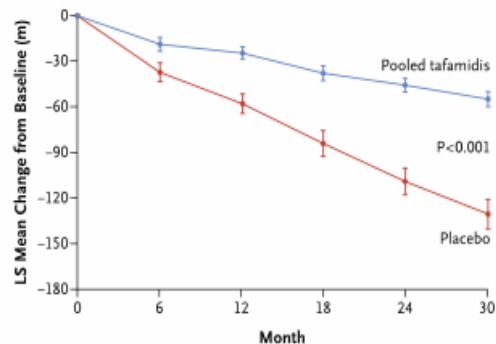
B Change in Body Weight



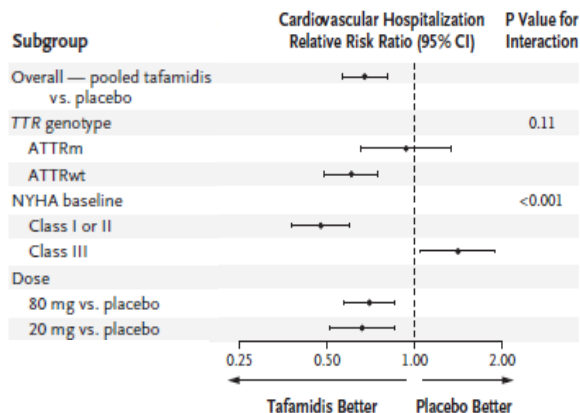
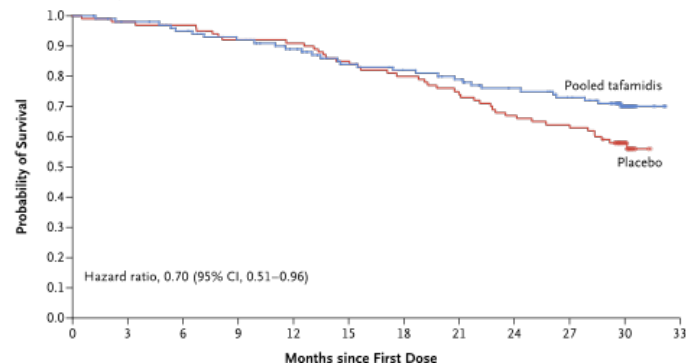
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

ATTR-ACT

A Change from Baseline in 6-Minute Walk Test



B Analysis of All-Cause Mortality

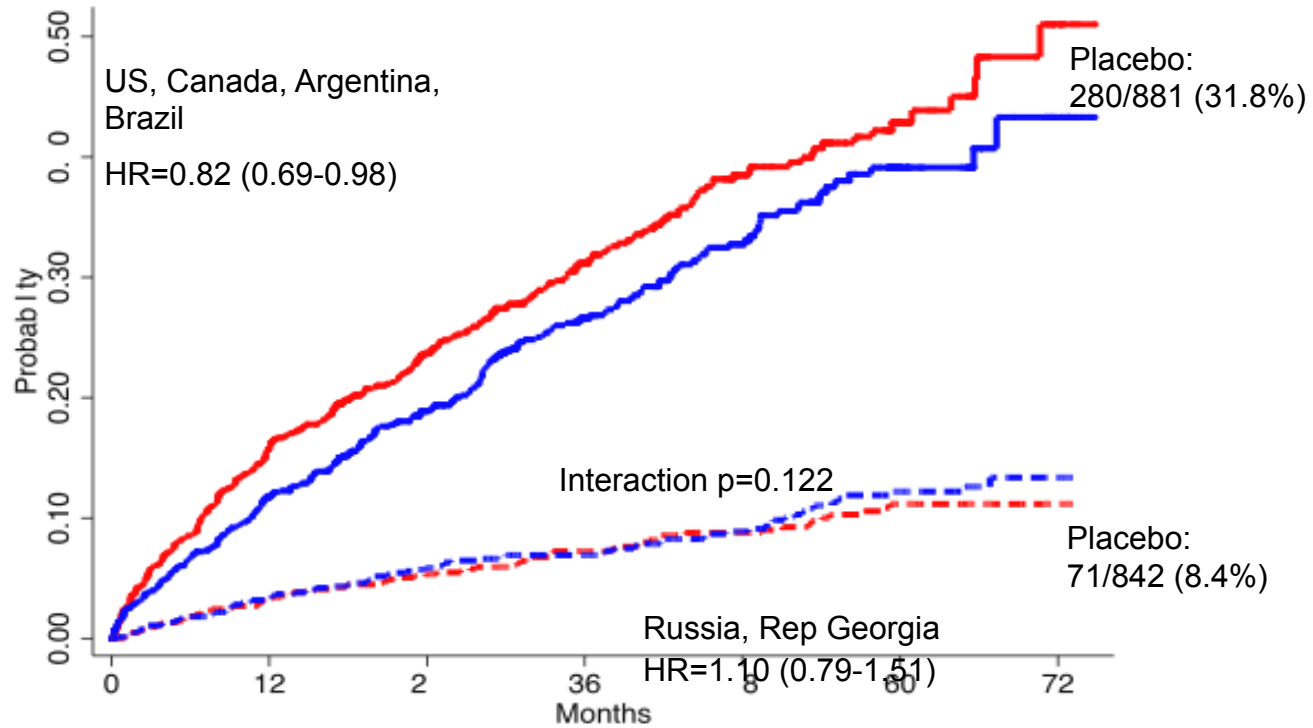


ATTR-ACT: the «three first times» trial

- The first time a medical treatment has been shown to reduce mortality and morbidity in TTR-related CA
- The first time a medical treatment has been shown to reduce mortality and HF hospitalisation in HFpEF.
- The first time a HF drug is effective on a hard endpoint by acting centrally (on the myocardium), rather than peripherally or by neurohormonal modulation (ACE-inhibitors, ARBs, Sacubitril, beta-blockers, diuretics, Ivabradine).

Spironolactone for Heart Failure with Preserved Ejection Fraction

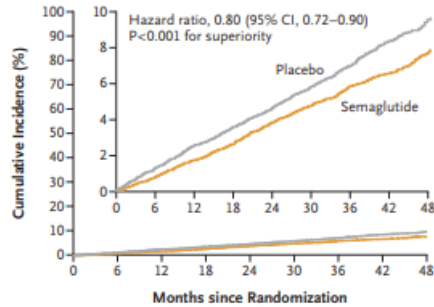
Exploratory (post-hoc): Placebo vs. Spiro by region



Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

SELECT

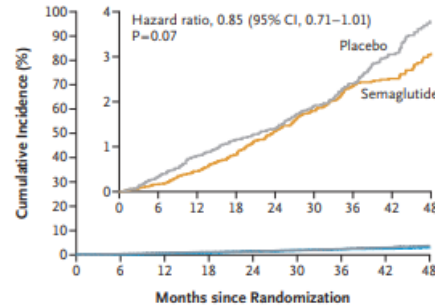
A Primary Cardiovascular Composite End Point



No. at Risk

Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

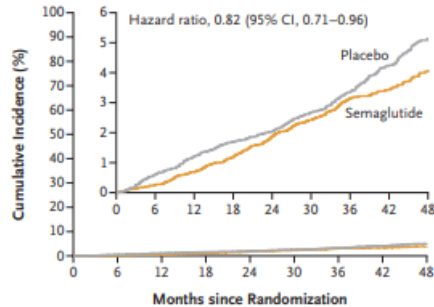
B Death from Cardiovascular Causes



No. at Risk

Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

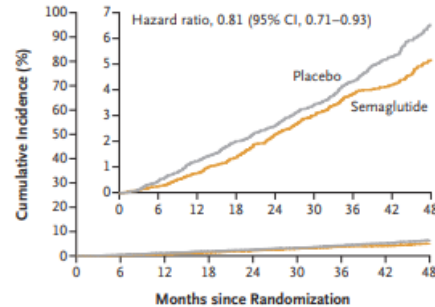
C Heart Failure Composite End Point



No. at Risk

Placebo	8801	8711	8601	8485	8381	7341	5885	4198	1766
Semaglutide	8803	8740	8654	8557	8425	7409	5944	4277	1816

D Death from Any Cause



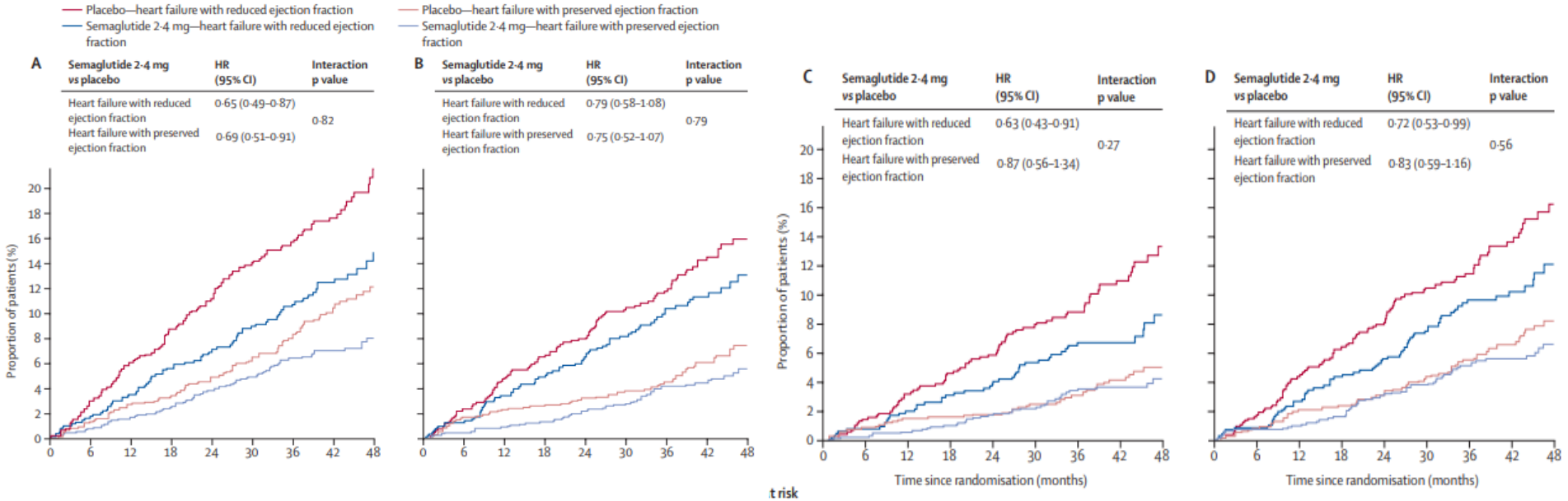
No. at Risk

Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

In patients with preexisting cardiovascular disease and overweight or obesity but **without diabetes**, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months.

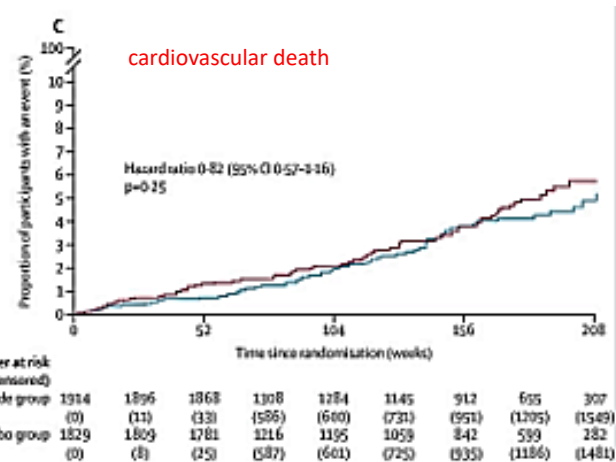
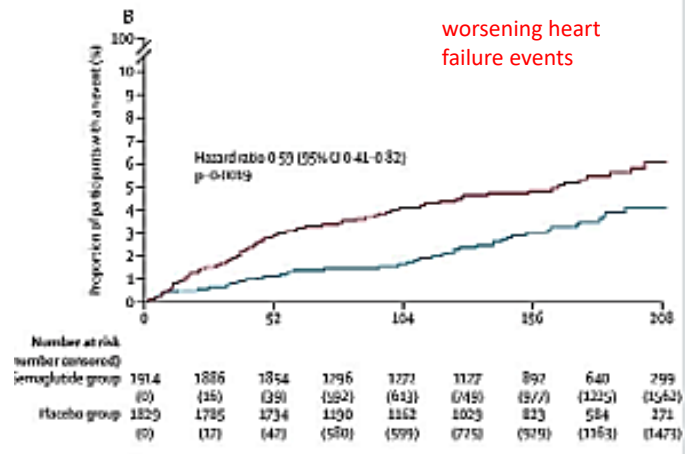
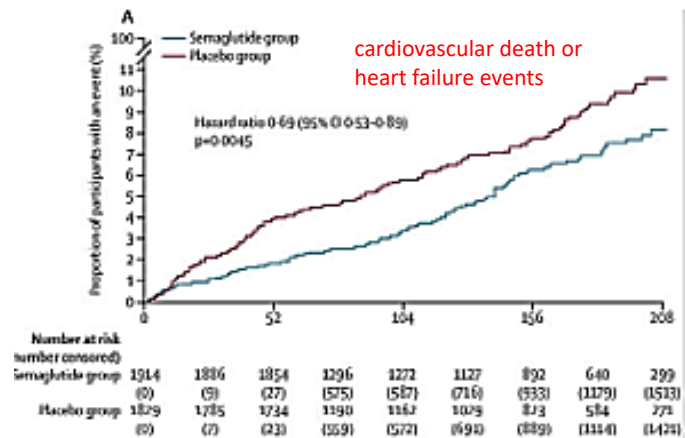
Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial

risk of MACE (A), heart failure composite (B), cardiovascular death (C), and all-cause death (D)



In patients with atherosclerotic cardiovascular disease and overweight or obesity, treatment with semaglutide 2·4 mg reduced MACE and composite heart failure endpoints compared with placebo in those with and without clinical heart failure, regardless of heart failure subtype

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



In patients with HFpEF, semaglutide reduced the risk of the combined endpoint of cardiovascular death or worsening heart failure events, and worsening heart failure events alone, whereas its effect on cardiovascular death alone was not significant.

CME

Developing Therapies for Heart Failure With Preserved Ejection Fraction

Current State and Future Directions

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Considering its prevalence and outcomes, future projections, and lack of effective therapies, HFpEF represents the single largest unmet need in cardiovascular medicine.