Pharmacological interventions beyond “big four“ in HFrEF. What is new on horizon?

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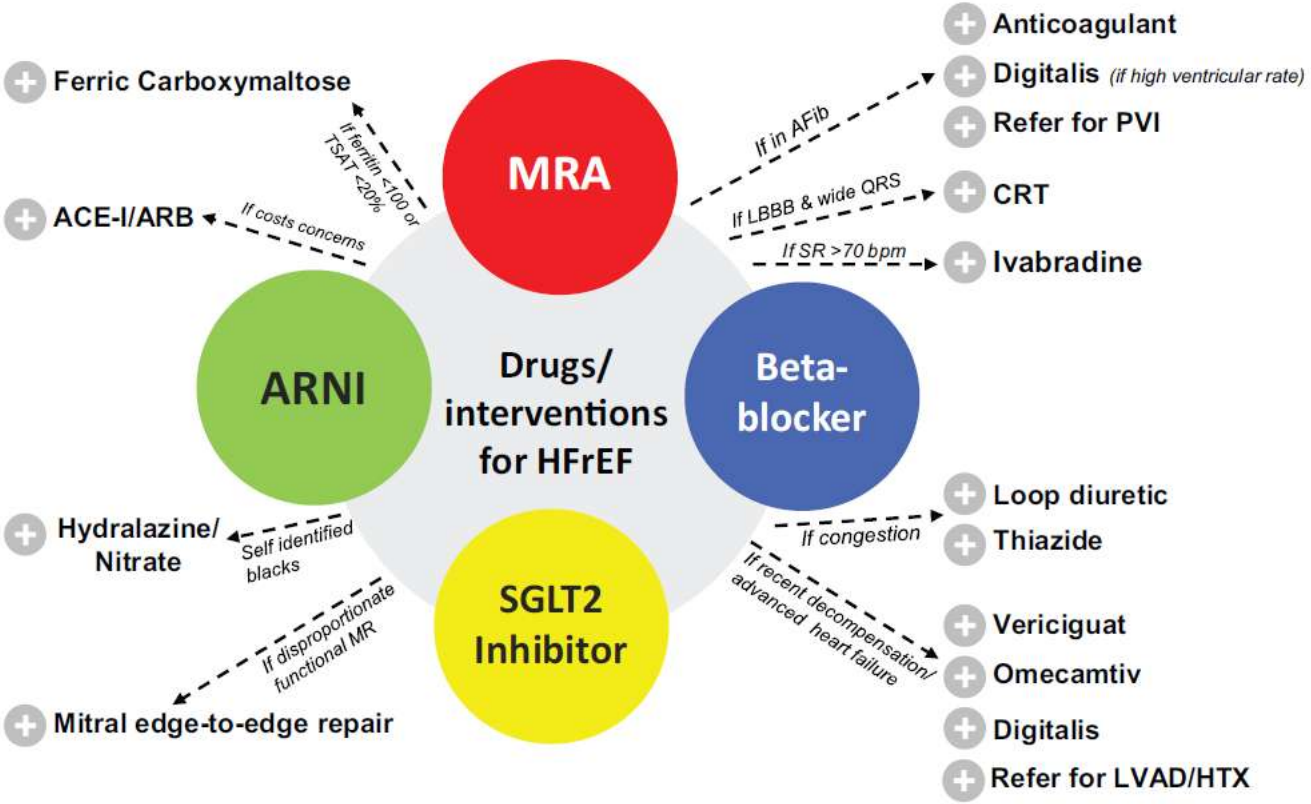
Declaration of interest

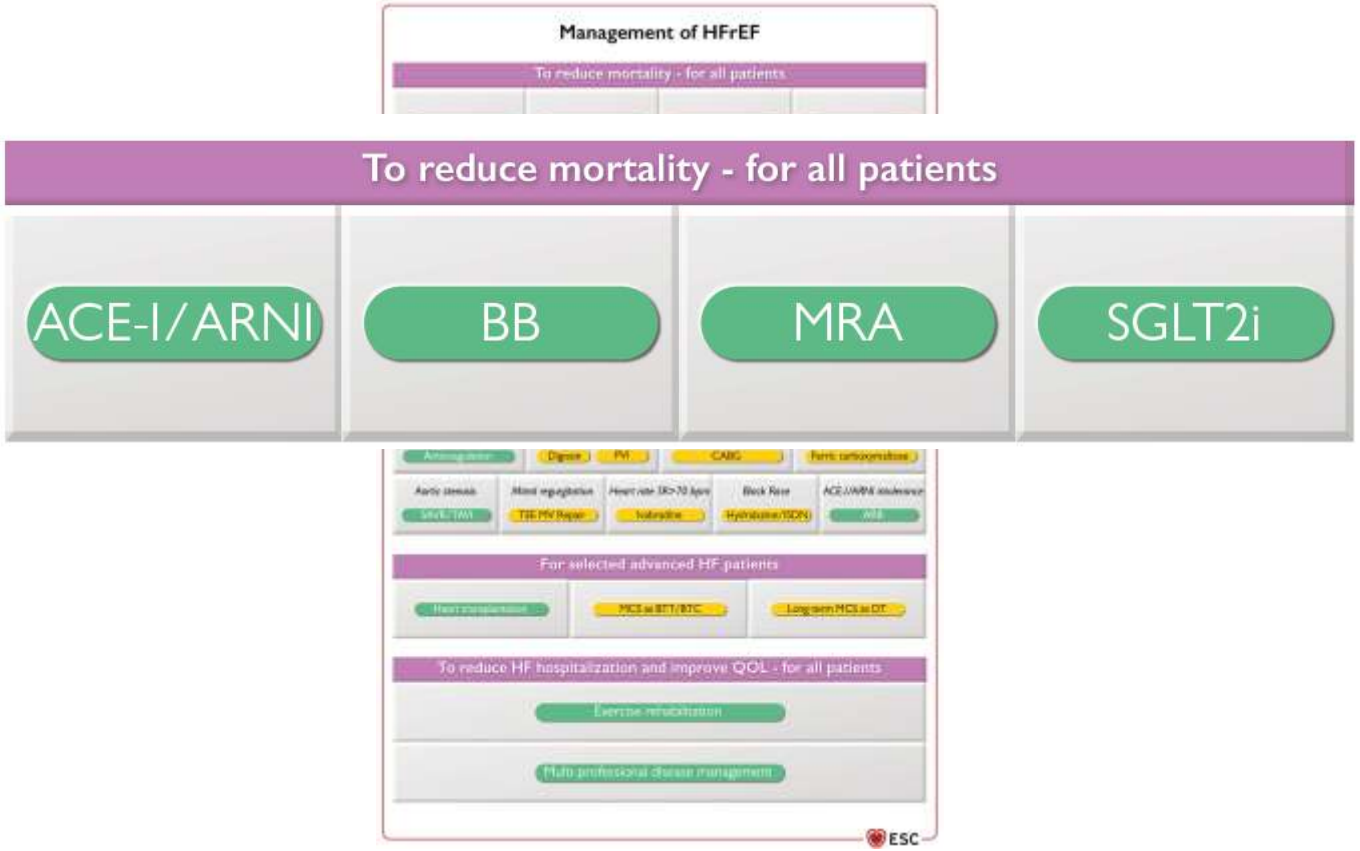
- National leader of the RCTs VICTORIA, EMPACT-MI
- Speaker bureau: Abbott, AstraZeneca, Bayer, Berlin Chemie-Menarini, Boehringer Ingelheim, Gedeon Richter, Merck, Novartis, Sanofi, Servier

Heart failure drug treatment: the “fantastic four”



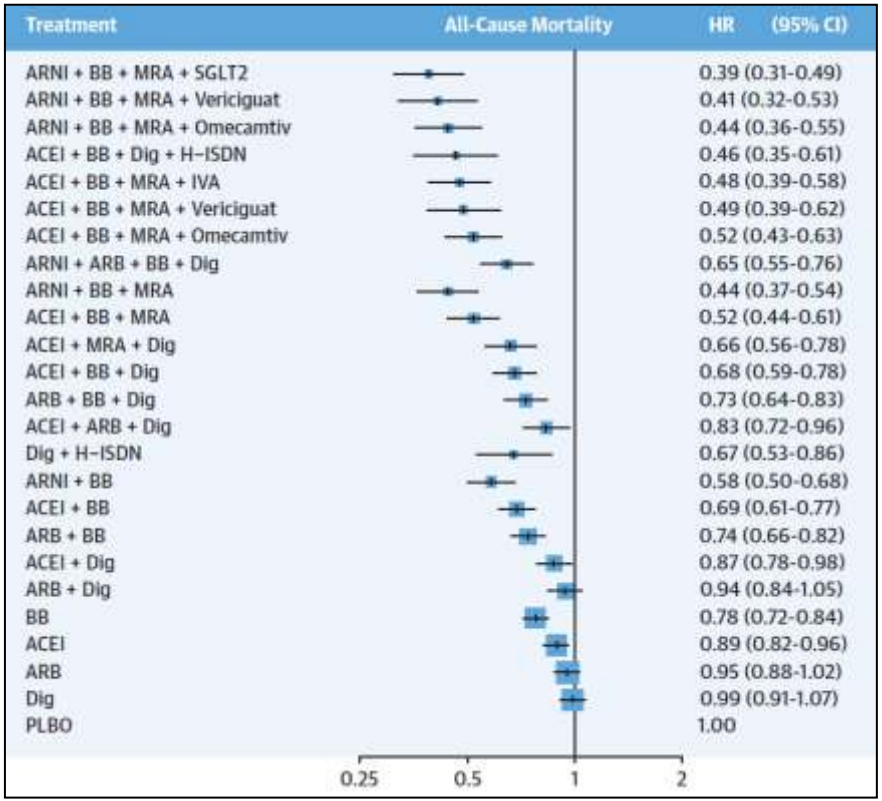
Bauersachs J. Eur Heart J. 2021 Feb 11;42(6):681-683.

Phenotypic approach to the management of HFrEF

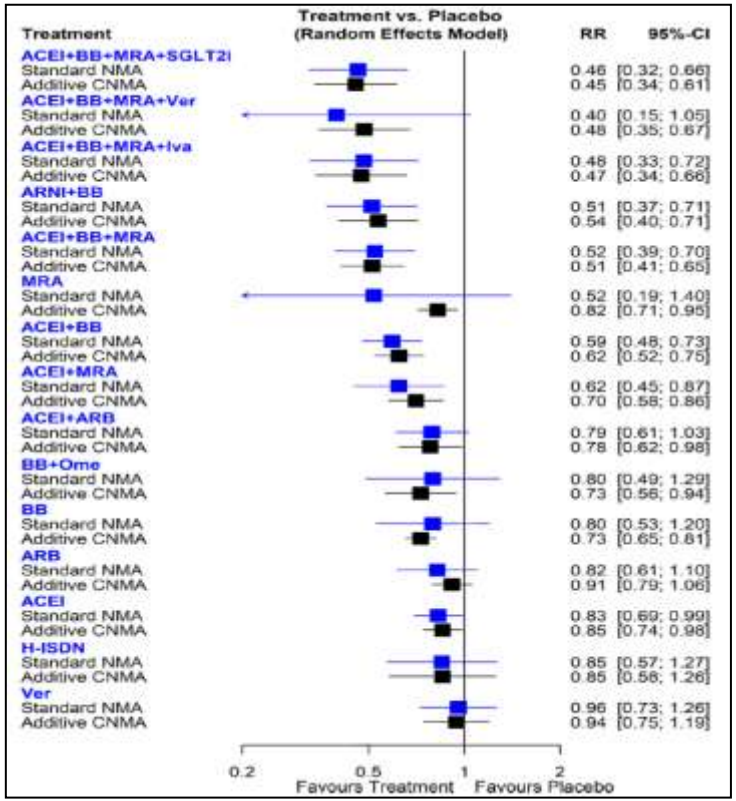


Gardner RS, 2021, Aug 27, ESC Congress 2021, Session type: New ESC Guidelines

The most effective combination of pharmacological therapy for HFrEF: systematic reviews and network meta-analyses

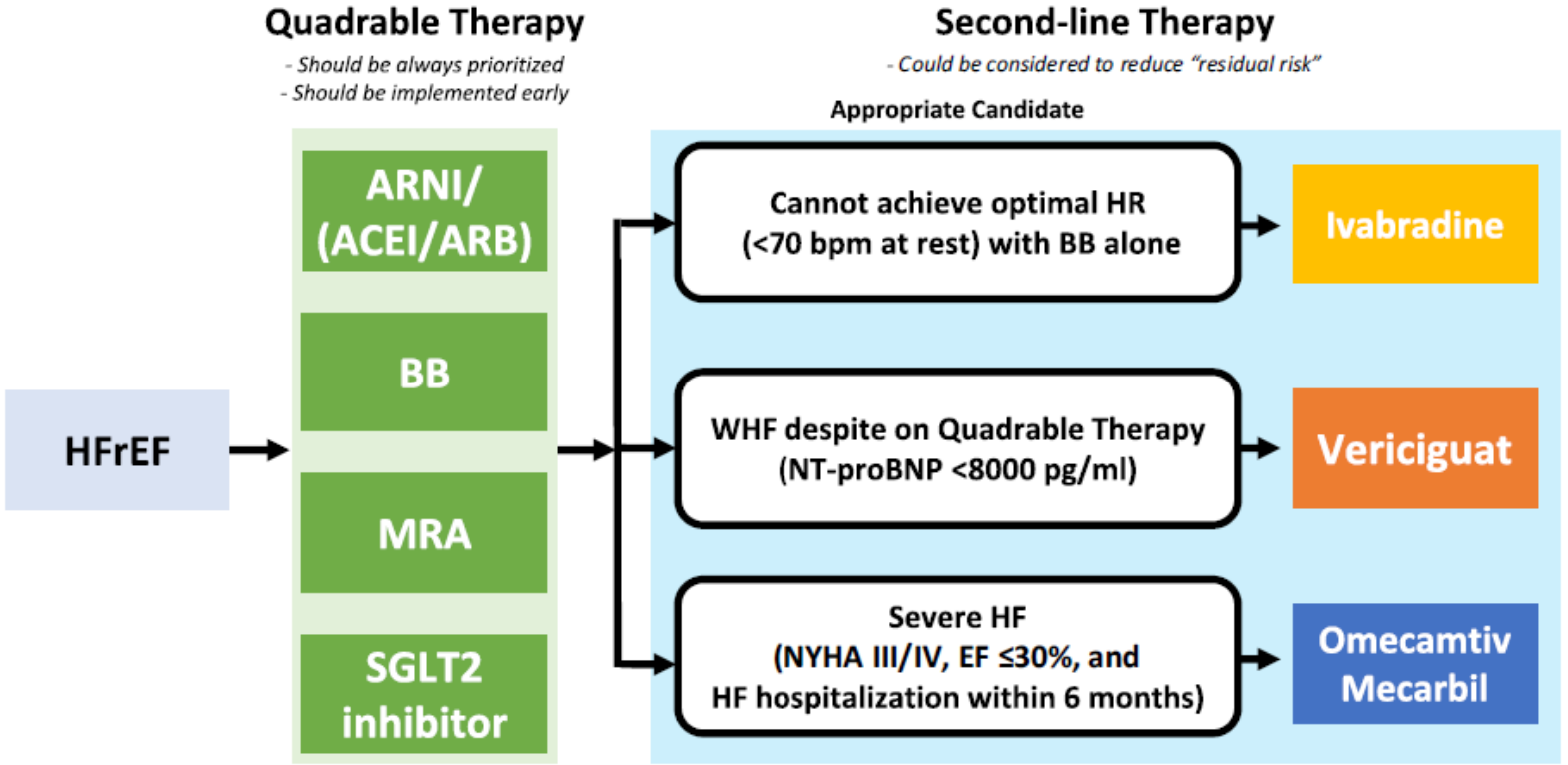


Tromp J, et al. J Am Coll Cardiol HF. 2022;10(2):73–84



Tang H, et al. BMC Cardiovasc Disord. 2024 Nov 23;24(1):666

Beyond Quadruple Therapy: The Potential Role of Ivabradine, Vericiguat, and Omecamtiv Mecarbil



Shoji S, Mentz RJ. Review Heart Fail Rev. 2024 Sep;29(5):949-955.

Comparison of population severity, background therapy and outcomes in recent trials of HFrEF

	PARADIGM-HF	DAPA-HF	SHIFT	VICTORIA	GALACTIC-HF
Medications	ARNI	SGLT2i	Ivabradine	Vericiguat	Omecamtiv Mecarbil
Severity of population					
HF hospitalization within 6 months	31%	16%	Not available	84%	76%
NYHA III or IV	25%	32%	52%	41%	47%
Median NT-proBNP (pg/mL)	1608	1437	Not available	2816	1977
Annualized rate of the primary composite outcome	21.8%	16.3%	Not available	33.6%	24.2%
Background therapy					
ACEI/ARB/ARNI	100%	94%	92%	88%	87%
ARNI	-	11%	Not available	15%	19%
BB	93%	96%	90%	93%	94%
MRA	56%	71%	60%	70%	78%
SGLT2i	Unknown	Unknown	Unknown	Unknown	3%
Outcomes (hazard ratio)					
CV death/ HF hospitalization	0.80 (0.73–0.87)	0.75 (0.65–0.85)	0.82 (0.75–0.90)	0.90 (0.82–0.98)	0.92 (0.86–0.99)[a]
CV death	0.80 (0.71–0.89)	0.82 (0.69–0.98)	0.91 (0.80–1.03)	0.93 (0.81–1.06)	1.01 (0.92–1.11)
HF hospitalization	0.79 (0.71–0.89)	0.70 (0.59–0.83)	0.74 (0.66–0.83)	0.90 (0.81–1.00)	0.95 (0.87–1.03)[a]
Efficacy	Strong	Strong	Modest	Modest	Modest to small
Reduced mortality?	Yes	Yes	No	No	No
Guideline recommendations	I	I	IIa	IIb	No recommendation

Shoji S, Mentz RJ. Review Heart Fail Rev. 2024 Sep;29(5):949-955.

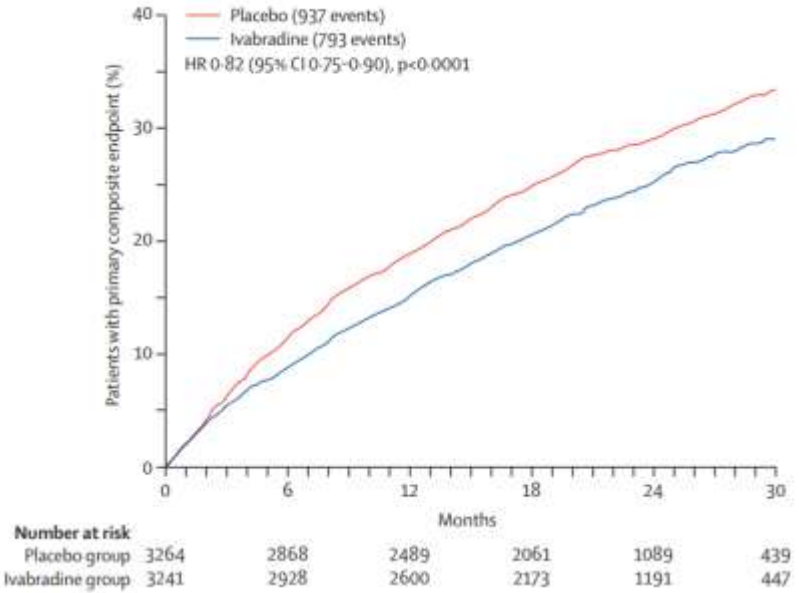
Other pharmacological treatments indicated in selected patients with HFrEF

Recommendations	Class	Level
I_f-channel inhibitor		
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/(or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA.	IIa	C

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Why Ivabradine retains a class IIa rather than a class I recommendation?

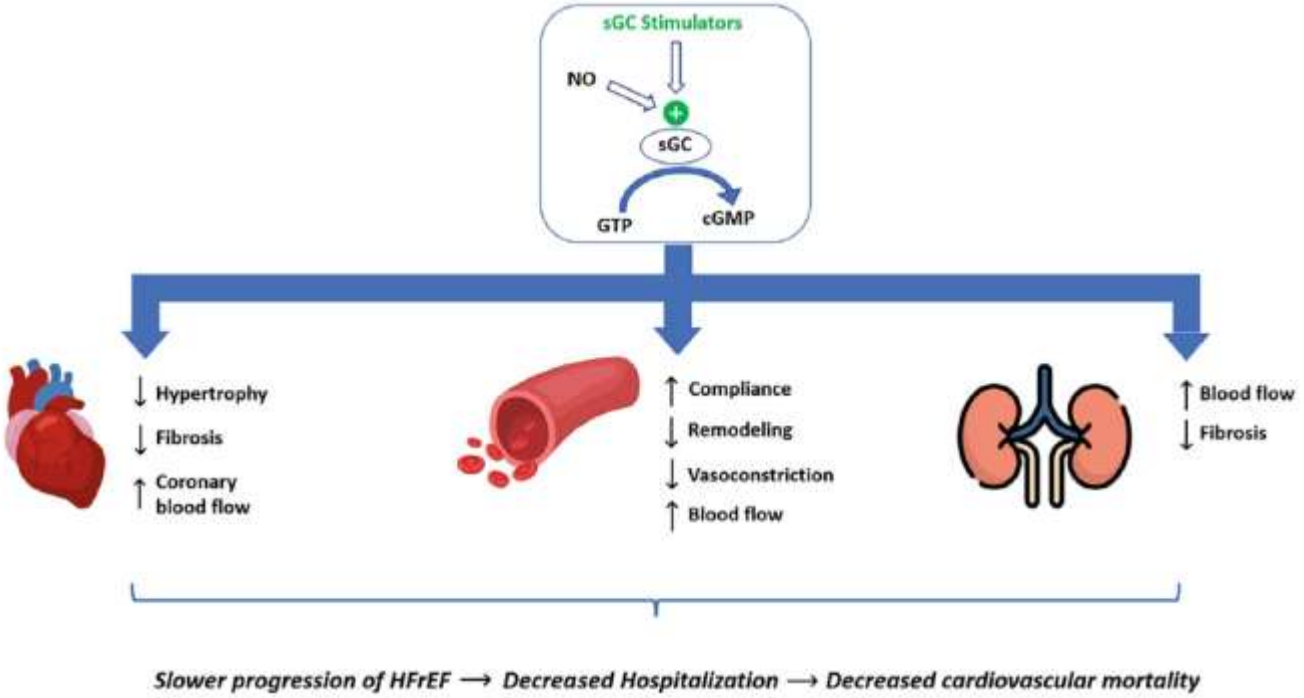
SHIFT trial



Swedberg K, et al. Lancet 376:875–885

- ivabradine is primarily beneficial for a specific subset of HFrEF patients (sinus rhythm, heart rate ≥ 70 beats per min);
- primary outcome of the composite of CV death and HF hospitalization was mainly driven by a reduction in HF hospitalization;
- only 25% of patients in SHIFT were on optimal doses of beta-blocker therapy;
- beta-blockers should always be prioritized and up-titrated to target doses as tolerated, rather than administering ivabradine as a first-line treatment.

Potential clinical benefits of soluble guanylate cyclase stimulators in patients with HFrEF



sGC, soluble guanylate cyclase stimulators; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide.

Butler J, et al. Eur J Heart Fail. 2022 Nov;24(11):2029-2036.

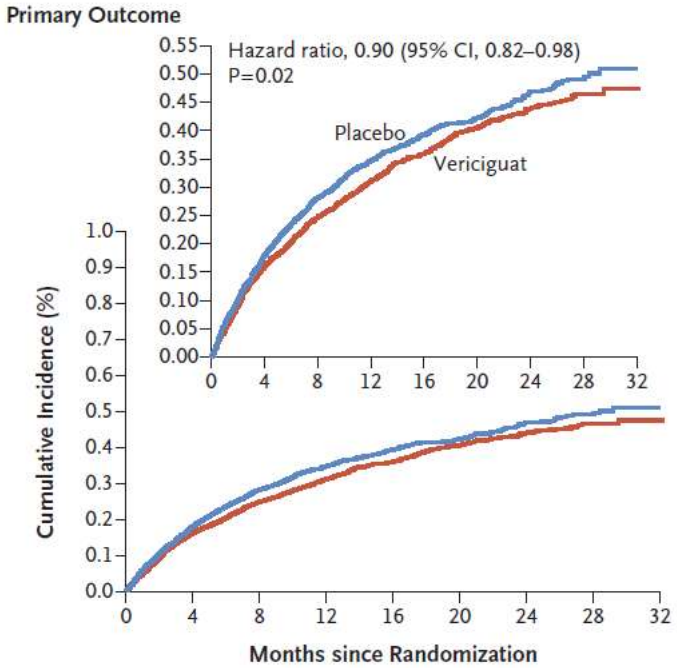
VICTORIA trial: vericiguat in patients with heart failure and reduced ejection fraction

Phase 3, randomized, double-blind, placebo-controlled trial

5050 patients with CHF (recent hospitalization or received iv. diuretic therapy), NYHA class II-IV, LVEF < 45%

Vericiguat (target dose, 10 mg once daily) vs. placebo, in addition to guideline-based medical therapy

Primary outcome: composite of death from cardiovascular causes or first hospitalization for heart failure



Armstrong PW, et al. N Engl J Med 2020;382:1883–1893.

VICTORIA trial: standard of care treatment

	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
ACE inhibitor or ARB, no./No. (%)	1847/2521 (73.3%)	1853/2519 (73.6%)	3700/5040 (73.4%)
Beta blocker, no./No. (%)	2349/2521 (93.2%)	2342/2519 (93.0%)	4691/5040 (93.1%)
MRA, no./No. (%)	1747/2521 (69.3%)	1798/2519 (71.4%)	3545/5040 (70.3%)
Angiotensin receptor–neprilysin inhibitor (Sacubitril/Valsartan), no./No. (%)	360/2521 (14.3%)	371/2519 (14.7%)	731/5040 (14.5%)
Triple therapy, no./No. (%)	1480/2521 (58.7%)	1529/2519 (60.7%)	3009/5040 (59.7%)
ICD, no./No. (%)	696/2521 (27.6%)	703/2519 (27.9%)	1399/5040 (27.8%)
Biventricular pacemaker, no./No. (%)	370/2521 (14.7%)	369/2519 (14.6%)	739/5040 (14.7%)

Armstrong PW, et al. N Engl J Med 2020;382:1883–1893.

Other pharmacological treatments indicated in selected patients with HFrEF

Recommendations	Class	Level
Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	IIb	B
Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III/IV despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

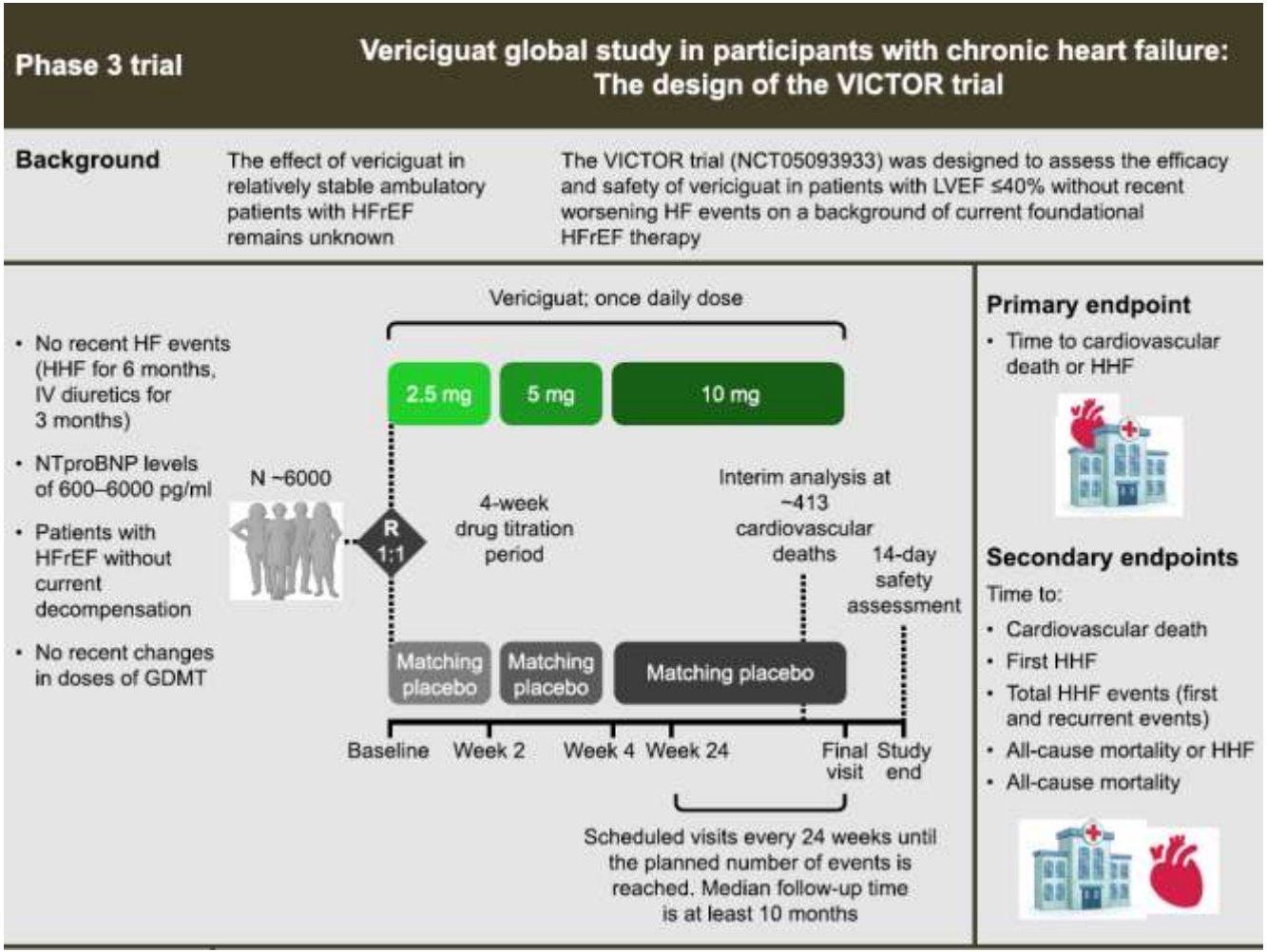
VICTOR is the first large event-driven HFrEF trial performed in the contemporary era of quadruple foundational guideline-directed medical therapy

Vericiguat Global Study in Participants with Chronic Heart Failure: Design of the VICTOR trial

Yogesh N.V. Reddy[1], Javed Butler[2,3]*, Kevin J. Anstrom[4], Robert O. Blaustein[5], Marc P. Bonaca[6], Stefano Corda[7], Justin A. Ezekowitz[8], Carolyn S.P. Lam[9], Eldrin F. Lewis[10], JoAnn Lindenfeld[11], Ciaran J. McMullan[5], Robert J. Mentz[12], Christopher O'Connor[13], Mahesh Patel[5], Piotr Ponikowski[14], Giuseppe M.C. Rosano[15], Clara I. Saldarriaga[16], Michele Senni[17], James Udelson[18], Adriaan A. Voors[19], and Faiez Zannad[20]*

Reddy YNV, et al. Eur J Heart Fail. 2024 Oct 30. doi: 10.1002/ejhf.3501. Online ahead of print.

VICTOR is the first large event-driven HFrEF trial performed in the contemporary era of quadruple foundational guideline-directed medical therapy, in a compensated ambulatory HF population



Reddy YNV, et al. Eur J Heart Fail. 2024 Oct 30. doi: 10.1002/ejhf.3501. Online ahead of print.

National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov

Active, not recruiting

A Study of Vericiguat (MK-1242) in Participants With Chronic Heart Failure With Reduced Ejection Fraction (HFrEF) (MK-1242-035) (VICTOR)

ClinicalTrials.gov ID NCT05093933

Sponsor Merck Sharp & Dohme LLC

Information provided by Merck Sharp & Dohme LLC (Responsible Party)

Last Update Posted 2024-11-18

Study Start (Actual)

2021-11-02

Primary Completion (Estimated)

2025-03-31

Study Completion (Estimated)

2025-06-15

Enrollment (Estimated)

6000

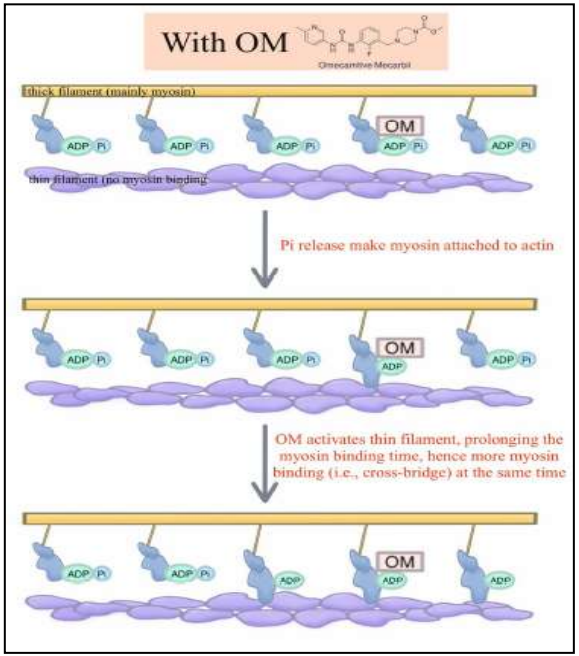
Study Type

Interventional

Phase

Phase 3

Omecamtiv Mecarbil



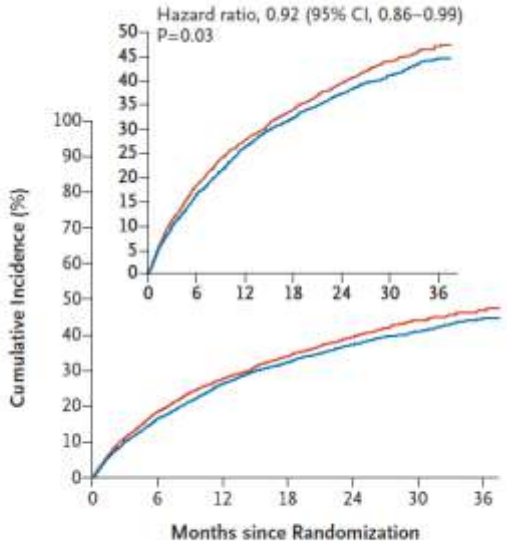
Clinical trial	Results published	Trial design	Endpoints	Primary findings
ATOMIC-HF	PMID: 27012405	Phase IIb, double-blind, placebo-controlled, randomized	Primary: effect on dyspnea of 48 h of intravenous OM administration	Primary endpoint: missed
			Secondary: safety and tolerability of the 3 dose levels of OM	Secondary endpoint: met
COSMIC-HF	PMID: 27914656	Phase II, double-blind, placebo-controlled, randomized	Primary: safety, tolerability, and pharmacokinetics of the oral dosage of OM	Primary endpoint: met
			Secondary: change from baseline in systolic ejection time, stroke volume, left ventricular end-systolic and end-diastolic diameters, heart rate, and the level of NT-proBNP	Secondary endpoint: met
GALACTIC-HF	PMID: 33185990	Phase III, double-blind, placebo-controlled, randomized	Primary: time to cardiovascular death or first heart failure event	Primary endpoint: met
			Secondary: time to CV death, patient reported outcomes measured by Kansas City Cardiomyopathy Questionnaire, time to first heart failure hospitalization and time to all-cause death	Secondary endpoint: missed
METEORIC-HF	PMID: 35852527	Phase III, double-blind, placebo-controlled, randomized	Primary: change in peak oxygen uptake on cardiopulmonary exercise testing	Primary endpoint: missed
			Secondary: alterations in peak exercise workload, ventilatory efficiency, and average daily activity units	Secondary endpoint: missed

Zhou S, et al. Omecamtiv Mecarbil in the treatment of heart failure: the past, the present, and the future. Front Cardiovasc Med. 2024 Mar 19:11:1337154.

GALACTIC-HF trial

Omecamtiv mecarbil vs. placebo in 8256 patients with HFrEF (LVEF ≤ 35%) receiving background GDMT during a median follow-up of 21.8 months

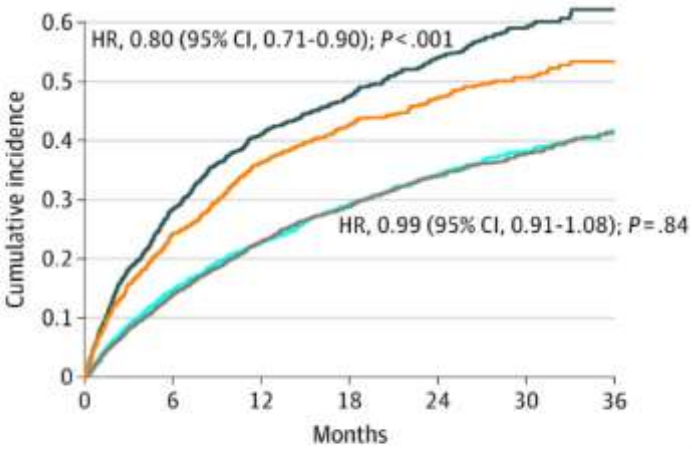
CV death or HF event



No. at Risk							
Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

Teerlink JR, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med 2021; 384:105–116

CV death or HF event



No. at risk							
No severe HF with placebo	2960	2492	2228	1602	1003	479	97
Severe HF with placebo	1152	808	650	464	290	119	13
No severe HF with OM	3014	2565	2271	1651	1051	516	96
Severe HF with OM	1106	814	671	480	320	137	31

Felker GM, et al. Assessment of omecamtiv mecarbil for the treatment of patients with severe heart failure: a post hoc analysis of data from the GALACTIC-HF randomized clinical trial. JAMA Cardiol 2022; 7:26–34.

Simple algorithm for considering omecamtiv mecarbil

- Possible role of omecamtiv mecarbil is in patients with severe HF (NYHA class III to IV, LVEF ≤ 30%, and HF hospitalization within 6 months) when current GDMT options are limited.

- Given the modest effect of omecamtiv mecarbil in the entire cohort and the benefit observed in the severe HF population coming from subgroup analyses, the present suggestion regarding omecamtiv mecarbil should be viewed as hypothesis-generating.

- Omecamtiv mecarbil is not approved for use in the Unites States, and the Food and Drug Administration requires an additional clinical trial to establish substantial evidence.

Ongoing randomized controlled trials in HFrEF

Study ID (date published)	Study design; follow-up	Population	Sample size	Number (%) with low LVEF	Intervention	Endpoints	Safety Data
COLICA (June 2024 – ongoing)	RCT, parallel, DB (1:1, phase III); 2m	Adult patients regardless of LVEF admitted with clinical signs of ADHF	278	NR	Colchicine vs placebo	Will record changes in NT-proBNP levels, HF events, PRO, biomarker levels	Will record adverse events, gastrointestinal and hematological disorders, infection, renal and hepatic function
CORTAHF (June 2024 – ongoing)	RCT, parallel, OL (1:1, phase: NR); 3m	Adult patients regardless of LVEF admitted with 12 h of clinical signs of ADHF	100	NR	Prednisolone vs usual care	Will record changes in CRP levels, HF events, HHF and mortality rates	Will record adverse events
NCT05420012 (May 2023 – ongoing)	RCT, parallel, DB (1:1, phase IV); 3m	Adult patients with LVEF ≤ 45% or NYHA class II/III	24	100%	Vericiguat vs placebo	Flow-mediated vasodilation, inflammatory biomarkers and PRO	NR
NCT05658458 (December 2022 – ongoing)	Single group assignment, OL (phase IV), 12m	Adult patients with LVEF ≤ 45% or NYHA class II-IV	200	100%	Effectiveness and safety of vericiguat	HHF and mortality rates	Will record adverse events
VINDICATE2 (March 2016 – ongoing)	RCT, parallel, DB (1:1, phase III); 24m	Adult patients with LVEF <50%	1278	NR	Vitamin D3 vs placebo	HHF and mortality rates, cost effectiveness and PRO	Will record adverse events

Ismail Z, et al. Advances in pharmacotherapy for heart failure and reduced ejection fraction: what's new in 2024? Expert Opin Pharmacother. 2024 Oct;25(14):1887-1902.

Not yet recruiting

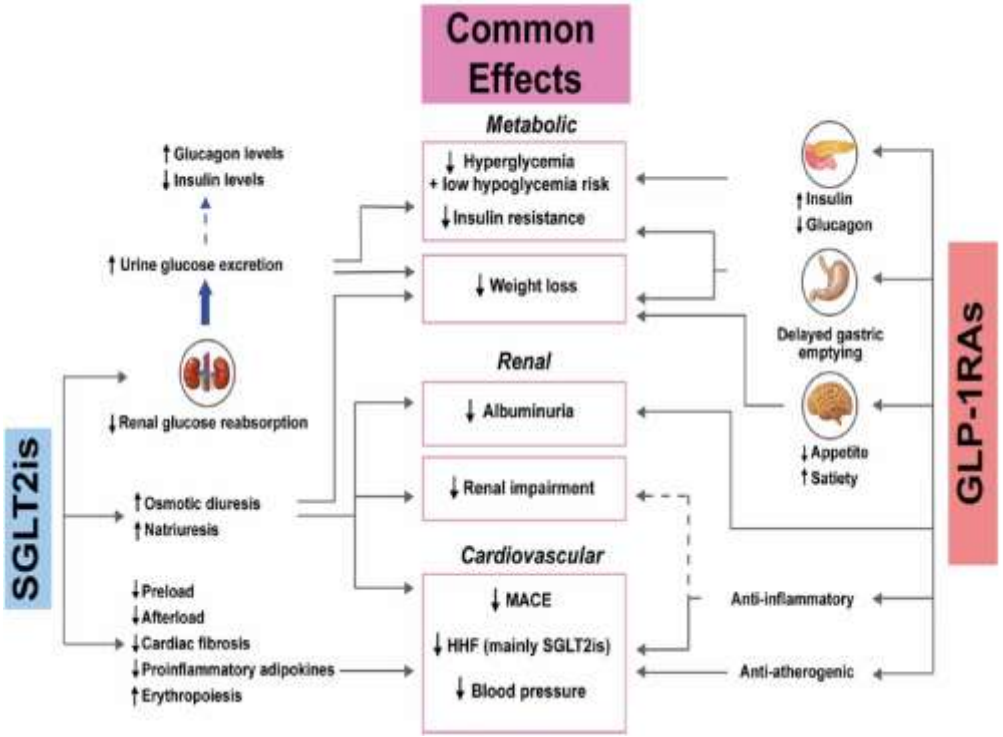
A Study to Evaluate Finerenone on Clinical Efficacy and Safety in Patients With Heart Failure Who Are Intolerant or Not Eligible for Treatment With Steroidal Mineralocorticoid Receptor Antagonists (FINALITY-HF)

ClinicalTrials.gov ID NCT06033950

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Time to first occurrence of cardiovascular (CV) death or HF event.	- Time to first CV death or HF event with finerenone compared to placebo.	Ongoing, up to ~30 months
Number of serious adverse events	- Serious adverse events (excluding efficacy endpoints) with finerenone compared to placebo.	Ongoing, up to ~30 months
Number of adverse events leading to discontinuation of study drug.	- Number of adverse events leading to discontinuation of investigational product with finerenone compared to placebo.	Ongoing, up to ~30 months

Combining glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes mellitus



Patient profile with anticipated benefit from GLP-1RA + SGLT2i combination

Patients with ASCVD or MRF* for ASCVD without HFrEF**

Patients not reaching treatment goals:
- HbA1c above individualized target
- Overweight/obesity
- High blood pressure

Patients with CKD in case of:
- Persistent albuminuria with SGLT2is
- Uncontrolled metabolic risks with SGLT2is

Gourdy P, et al. Cardiovasc Diabetol. 2023 Apr 1;22(1):79.

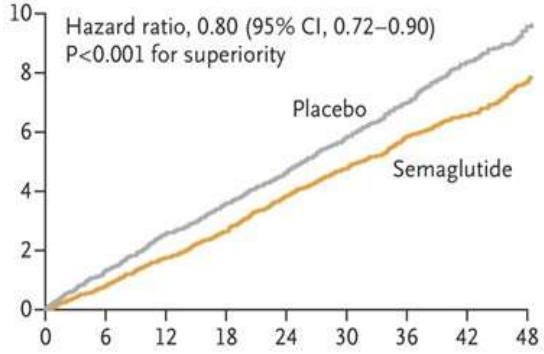
SELECT Trial

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

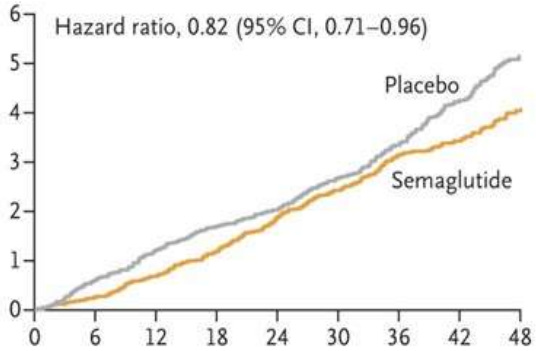
Multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial

**17,604 patients with CVD, BMI ≥27 kg/m2 (mean BMI 33.3±5.0) with no history of diabetes;
once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo, mean duration of follow-up 39.8±9.4 months**

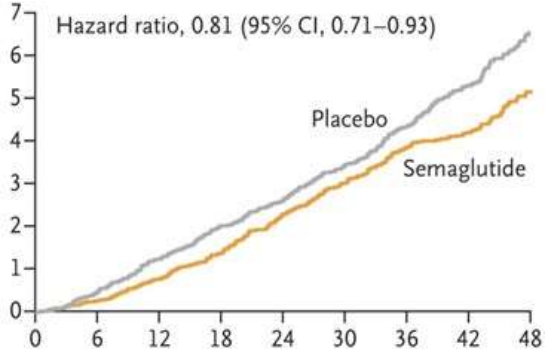
Primary Cardiovascular Composite Endpoint



Heart Failure Composite End Point



Death from Any Cause

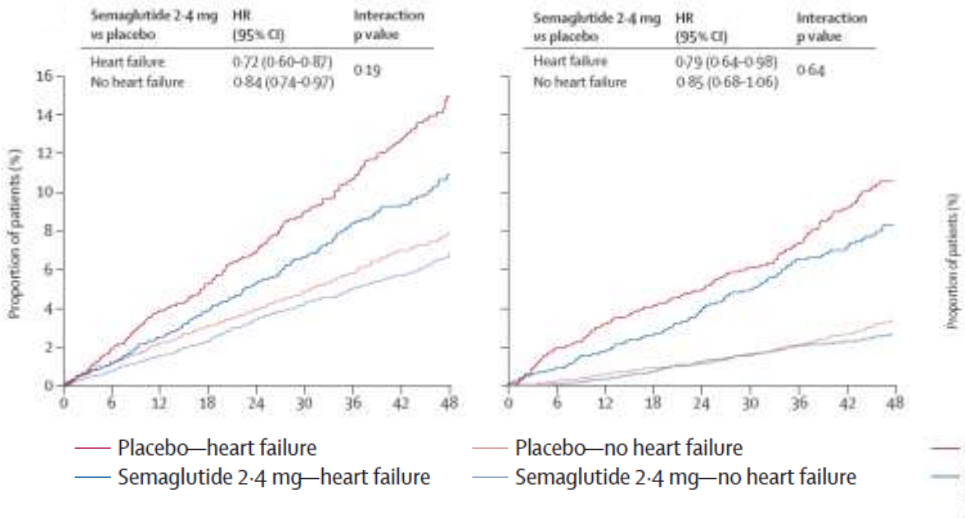


Lincoff AM, et al. N Engl J Med. 2023 Dec 14;389(24):2221-2232.

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

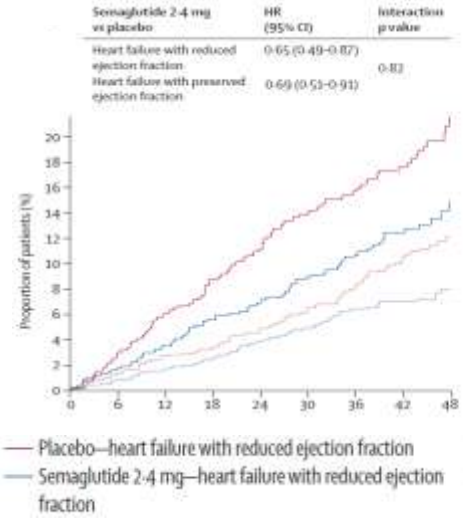
4286 (24.3%) of 17604 patients had a history of investigator-defined heart failure at enrollment:
HFpEF – 2273 (53.0%) of 4286 patients; HFrEF – 1347 (31.4%); Unclassified – 666 (15.5%).

MACE

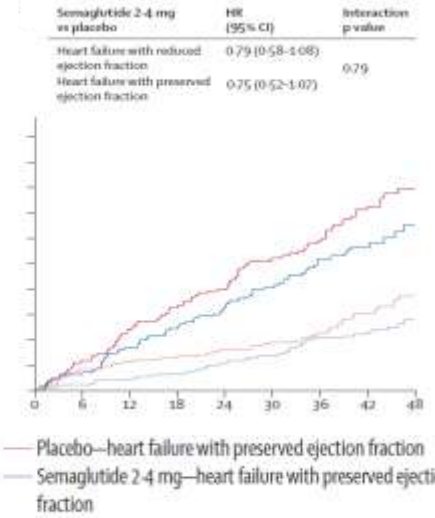


Composite HF outcome

MACE

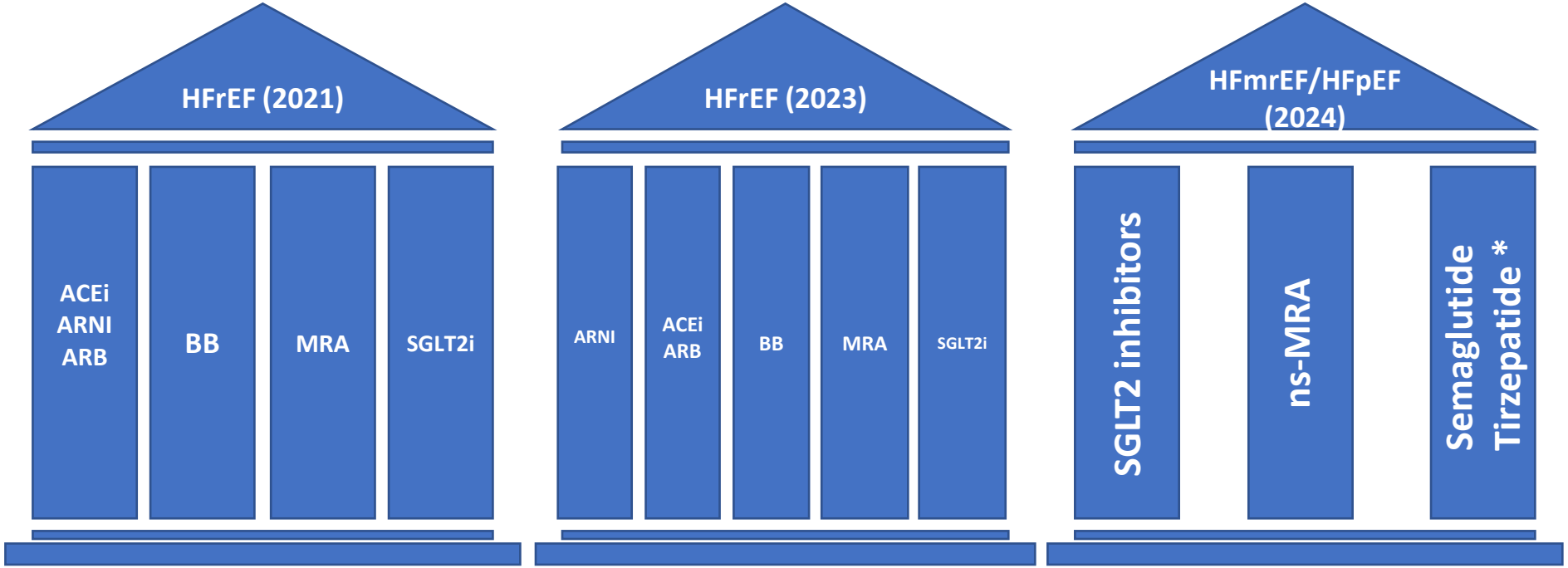


Composite HF outcome



Deanfield J, et al. Lancet. 2024 Aug 24;404(10454):773-786

How many pillars for heart failure treatment?



* In patients with obesity

Lake Elton, Volgograd Region, Russia