



The future in heart failure

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The future in heart failure: focus on medical therapies

Adriaan Voors

28 november 2023



Disclosures

Potentiële belangenverstrengeling	
Voor presentatie mogelijk relevante relaties:	
Sponsoring of onderzoeksgeld	Roche Diagnostics, NovoNordisk
Honorarium of andere (financiële) vergoeding	AnaCardio, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Bayer AG, Cytokinetics, Corteria, Eli Lilly, Moderna, Merck, Novartis, NovoNordisk, Roche Diagnostics
Aandeelhouder	n.v.t.
Andere relatie, namelijk ...	n.v.t.

Promising late phase therapies

HFrEF

- Digoxin (DECISION)
- Vericiguat (VICTOR)

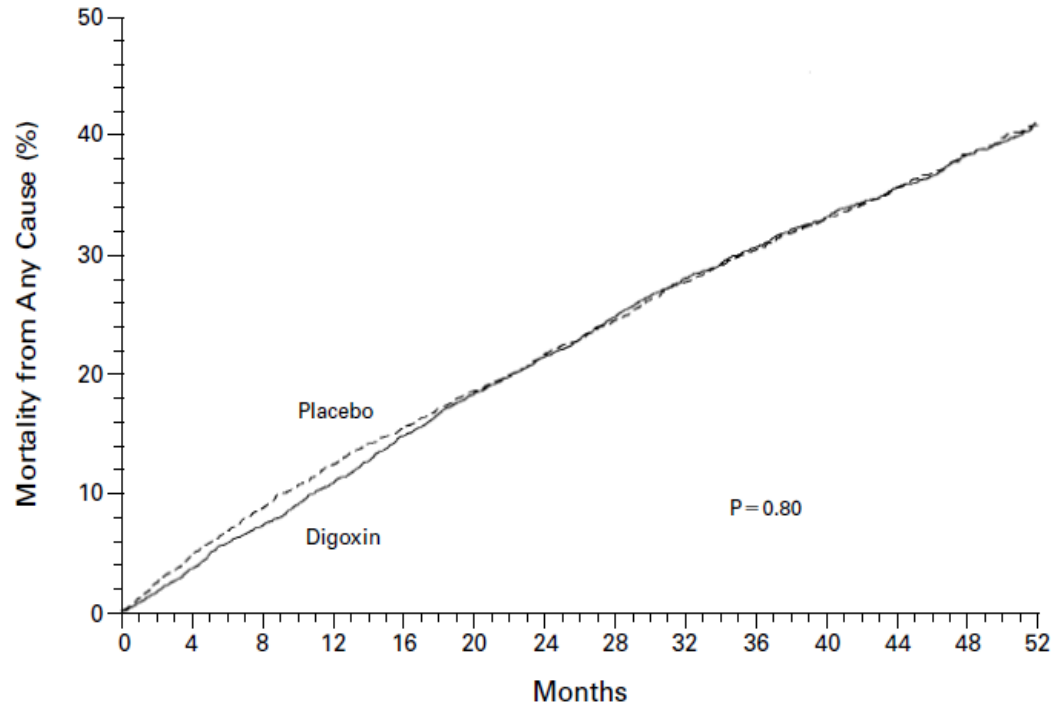
ATTR Cardiomyopathy

- ATTR-therapies

HFpEF

- Semaglutide (STEP-HFpEF)
- Ziltivekimab (HERMES)
- Finerenone (FINE-ARTS)

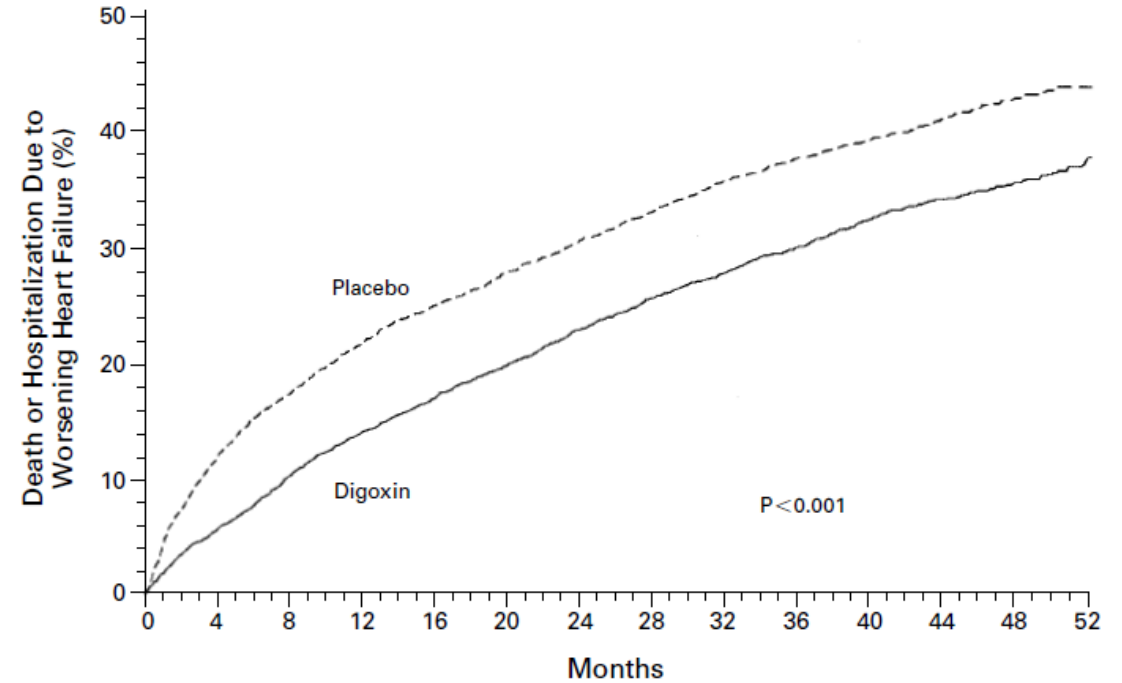
Digoxin did not reduce overall mortality, but it reduced the rate of hospitalization both overall and for worsening heart failure



NO. OF PATIENTS AT RISK

	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 1. Mortality in the Digoxin and Placebo Groups.



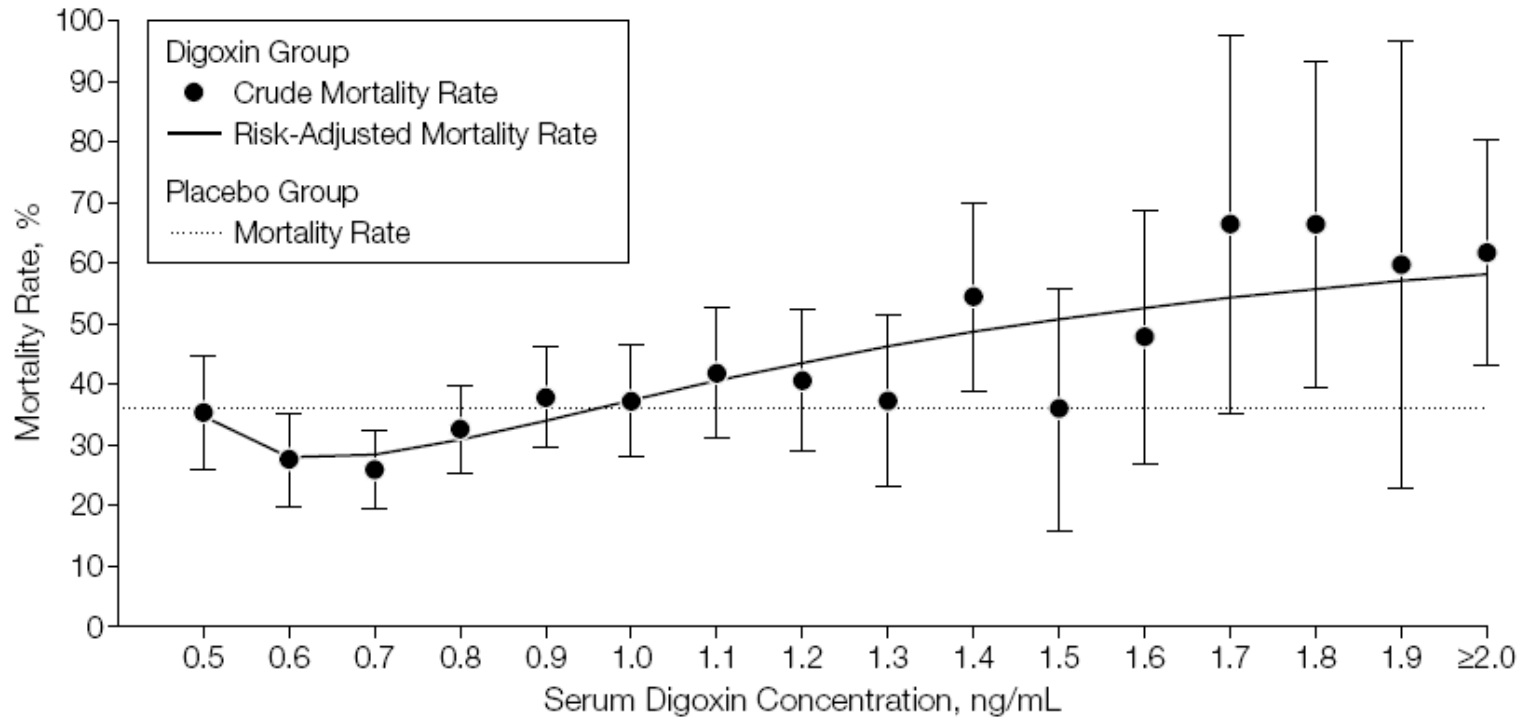
NO. OF PATIENTS AT RISK

	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	3403	2915	2674	2473	2328	2197	2071	1954	1659	1397	1111	859	546	250
Digoxin	3397	3120	2888	2696	2544	2392	2241	2115	1825	1521	1188	916	578	255

Figure 3. Incidence of Death or Hospitalization Due to Worsening Heart Failure in the Digoxin and Placebo Groups.

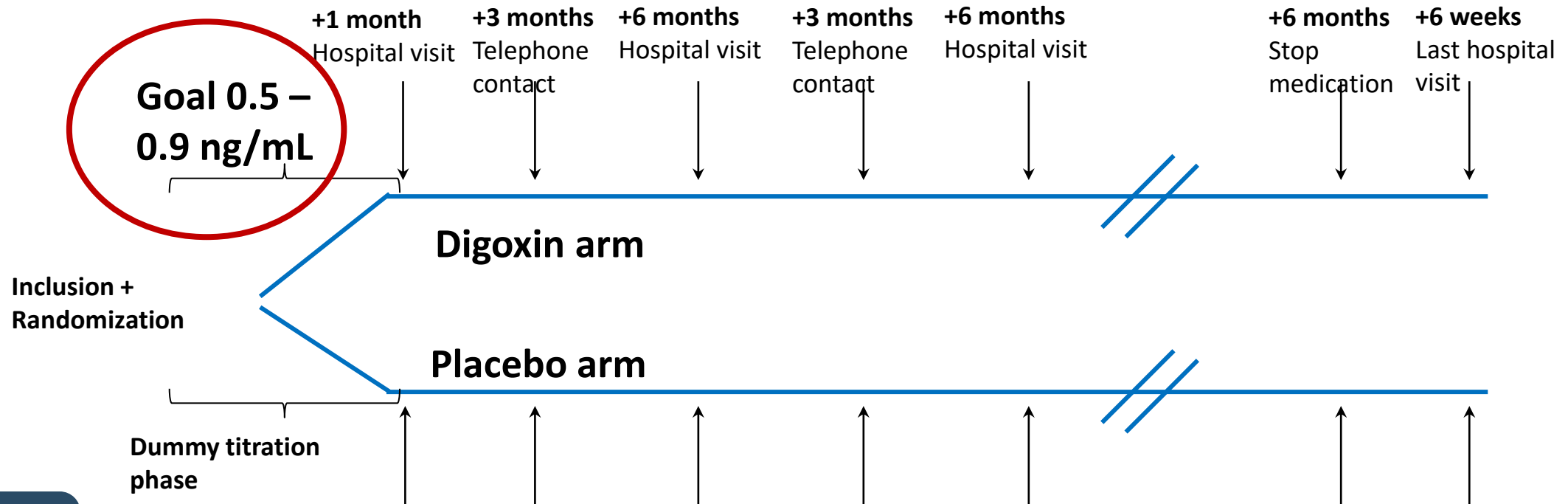
Lower mortality with digoxin when serum digoxin concentration was 0.5-0.8 pg/mL

Figure 3. All-Cause Mortality Rates by Serum Digoxin Concentration Groups



Study Design

- Randomized, placebo – controlled, double-blind multicenter phase 3 trial in Chronic HF NYHA II-IV, LVEF<50%, NT-proBNP >600 pg/mL
- DECISION is an event-driven trial powered to detect a 22% reduction in the primary composite of (repeated) HF hospitalizations or cardiovascular death



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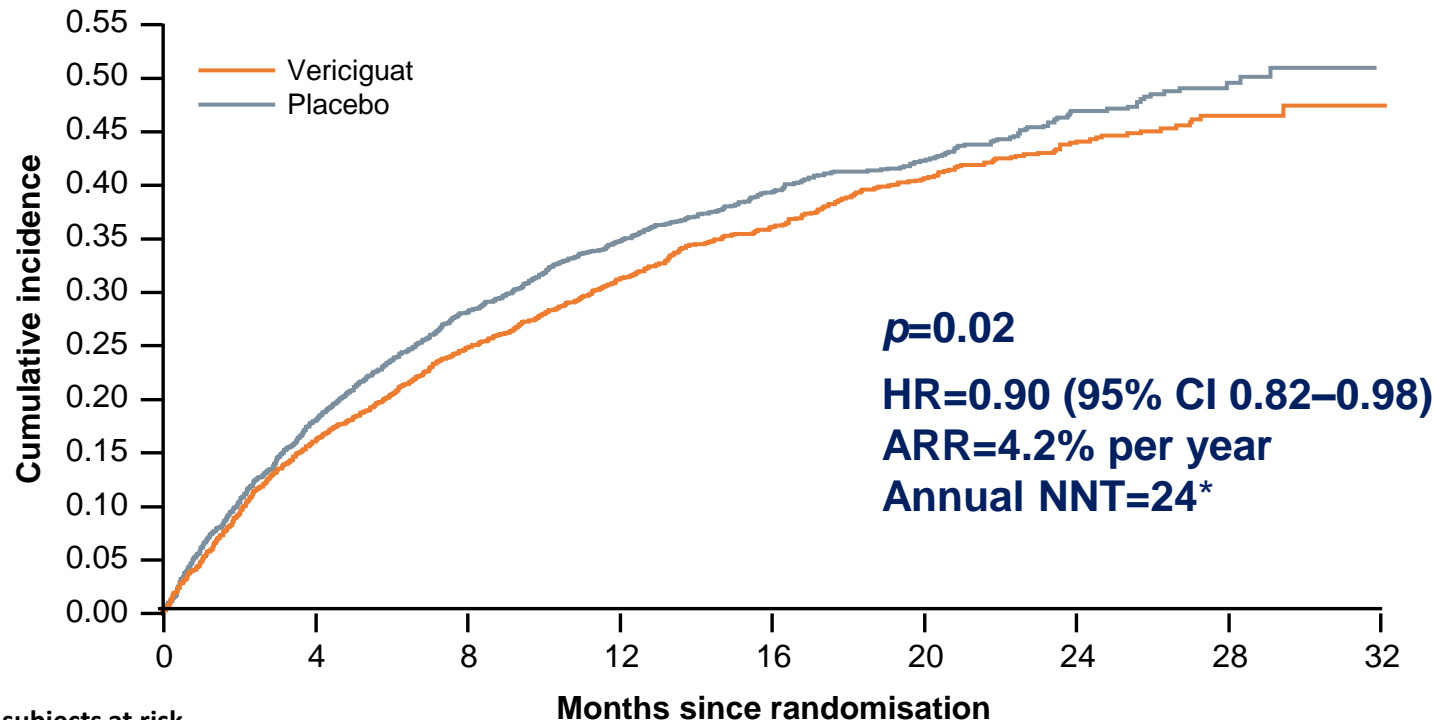
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VICTORIA: Primary Endpoint

Time to CV death or first HF hospitalisation

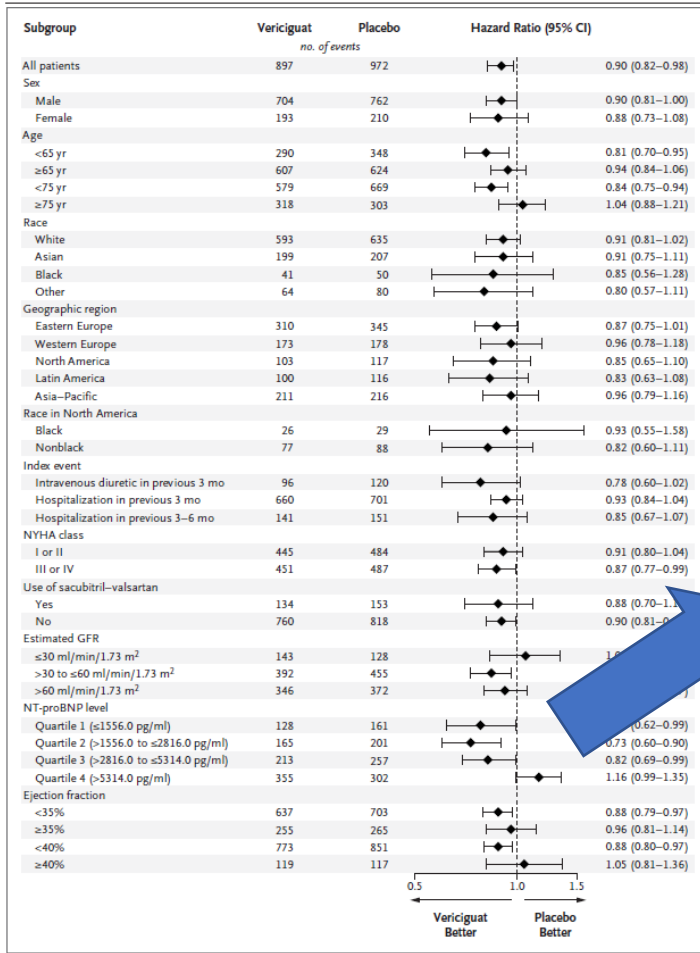


- N=5050 patients with recent WHF, NYHA 2-4 and LVEF<45%
- Median treatment duration for primary endpoint: 10.8 months
- Annual event rates for vericiguat and placebo per 100 patient-years were 33.6% and 37.8%

Number of subjects at risk

	0	4	8	12	16	20	24	28	32
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

VICTORIA – Subgroup analysis (ITT)



Significant treatment interaction with NTproBNP quartiles:

Largest benefit in Q1-Q3

NT-proBNP level

NT-proBNP level	Vericiguat	Placebo	Hazard Ratio (95% CI)
Quartile 1 (≤1556.0 pg/ml)	128	161	0.78 (0.62–0.99)
Quartile 2 (>1556.0 to ≤2816.0 pg/ml)	165	201	0.73 (0.60–0.90)
Quartile 3 (>2816.0 to ≤5314.0 pg/ml)	213	257	0.82 (0.69–0.99)
Quartile 4 (>5314.0 pg/ml)	355	302	1.16 (0.99–1.35)

Category	VICTORIA	VICTOR
Size	5050	6000
LV ejection fraction (EF)	EF < 45%	EF ≤ 40%
NT-proBNP <ul style="list-style-type: none"> • Entry criteria • Upper limit 	<ul style="list-style-type: none"> • NT-proBNP ≥ 1000 pg/mL (in SR); ≥ 1600 pg/mL (in AF) • No upper limit 	<ul style="list-style-type: none"> • NT-proBNP ≥ 600 pg/mL ≥ 900 pg/mL for those in Afib) • Upper limit of 6000 pg/mL
Time since index event to enrollment	HF hosp within 6 mos or IV diuretic use within 3 mos	No HFH event 6 mos prior to rand; no IV diuretic past 3 mos
Titration	2.5 → 5 mg → 10 mg at 2-week intervals as tolerated	Same as VICTORIA
eGFR	eGFR ≥ 15 ml/min/1.73m ² and not on chronic dialysis	Same as VICTORIA
Primary endpoint	Time to HF hospitalization or CV death	Same as VICTORIA
Median follow-up	10.8 months	22.5 mos planned
# of sites	616	Targeting 490

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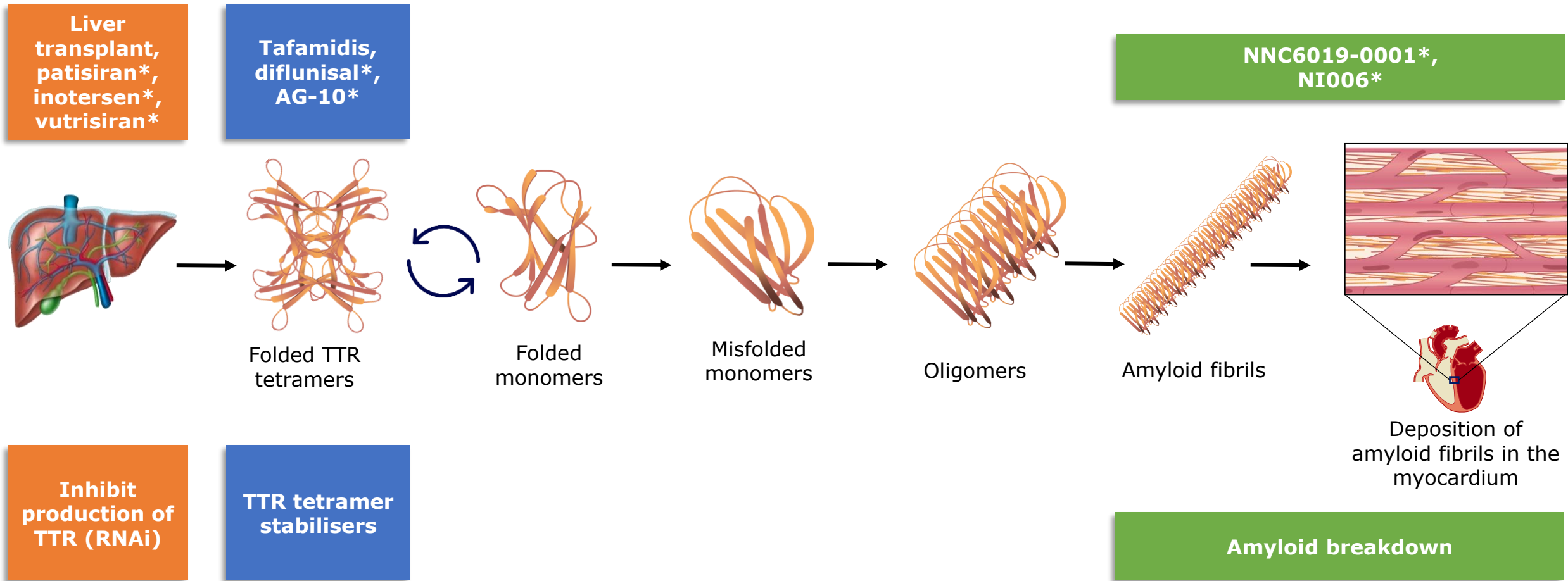
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Treatment of ATTR-CM



Ongoing clinical trials on ATTR-CM

Suppression of TTR synthesis

CARDIO-TTRansform (Eplontersen [TR-LRx])

NTLA-2001

HELIOS-B (vutrisiran)

APOLLO-B (patisiran)

Phase 1

Phase 2

Phase 3

TTR stabilisation

ATTRibute-CM (acoramidis)

Amyloid depletion

Doxy/TUDCA

NI006

NNC6019-0001

2016

2017

2018

2019

2020

2021

2022

2023

2024

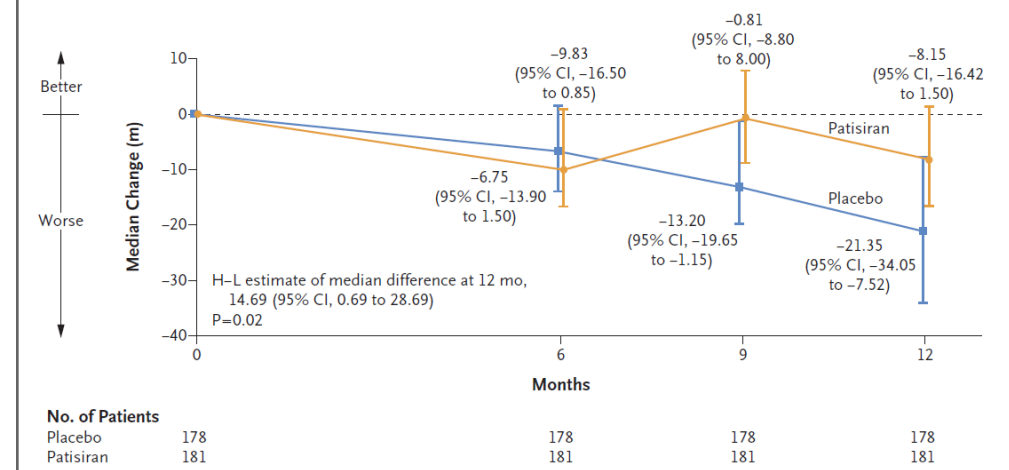
2025

2026

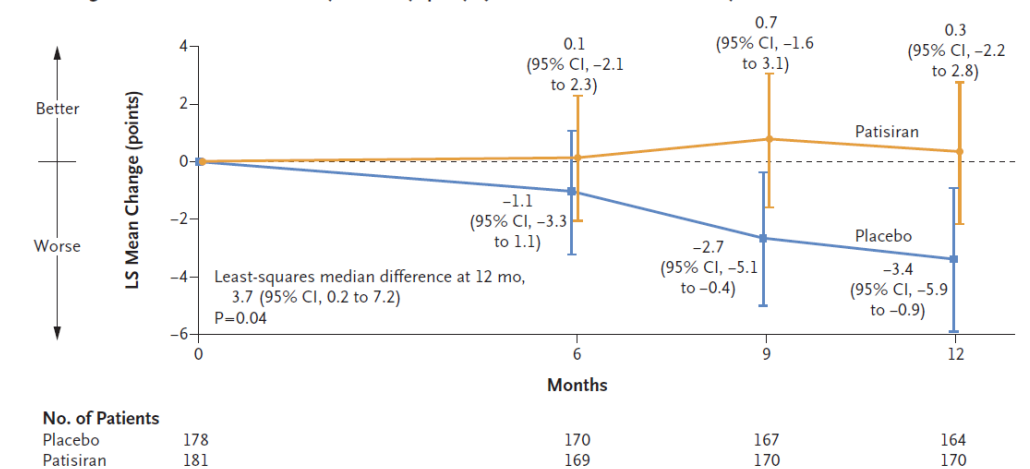
Patisiran Treatment in Patients with Transthyretin Cardiac Amyloidosis

- Phase 3, double-blind, randomized trial
- 360 patients with hereditary or wild-type ATTR cardiac amyloidosis
- Randomization to patisiran (0.3 mg per kilogram of body weight) or placebo once every 3 weeks for 12 months.

A Change from Baseline in 6-Minute Walk Test



B Change from Baseline in Kansas City Cardiomyopathy Questionnaire—Overall Summary



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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

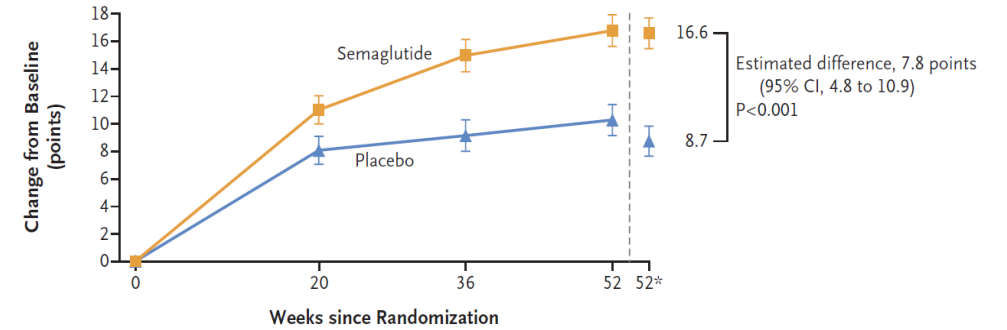
SEPTEMBER 21, 2023

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

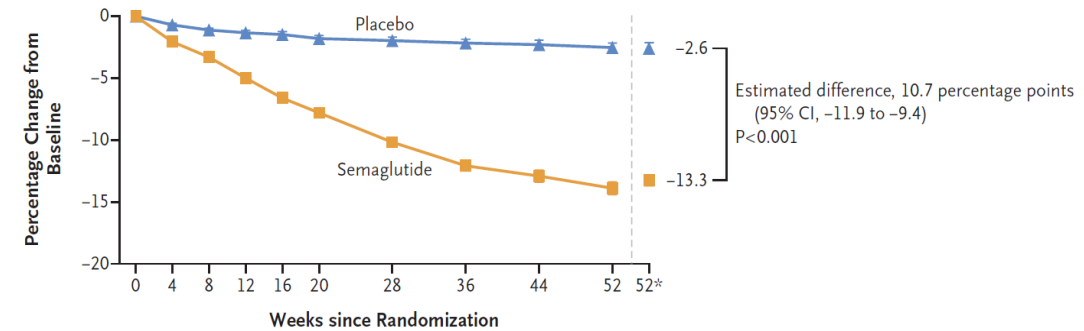
- Phase 2b, double-blind, randomized trial
- 529 patients with HFpEF and BMI >30
- Randomization to once-weekly semaglutide (2.4 mg) or placebo for 52 weeks

A Change in KCCQ-CSS



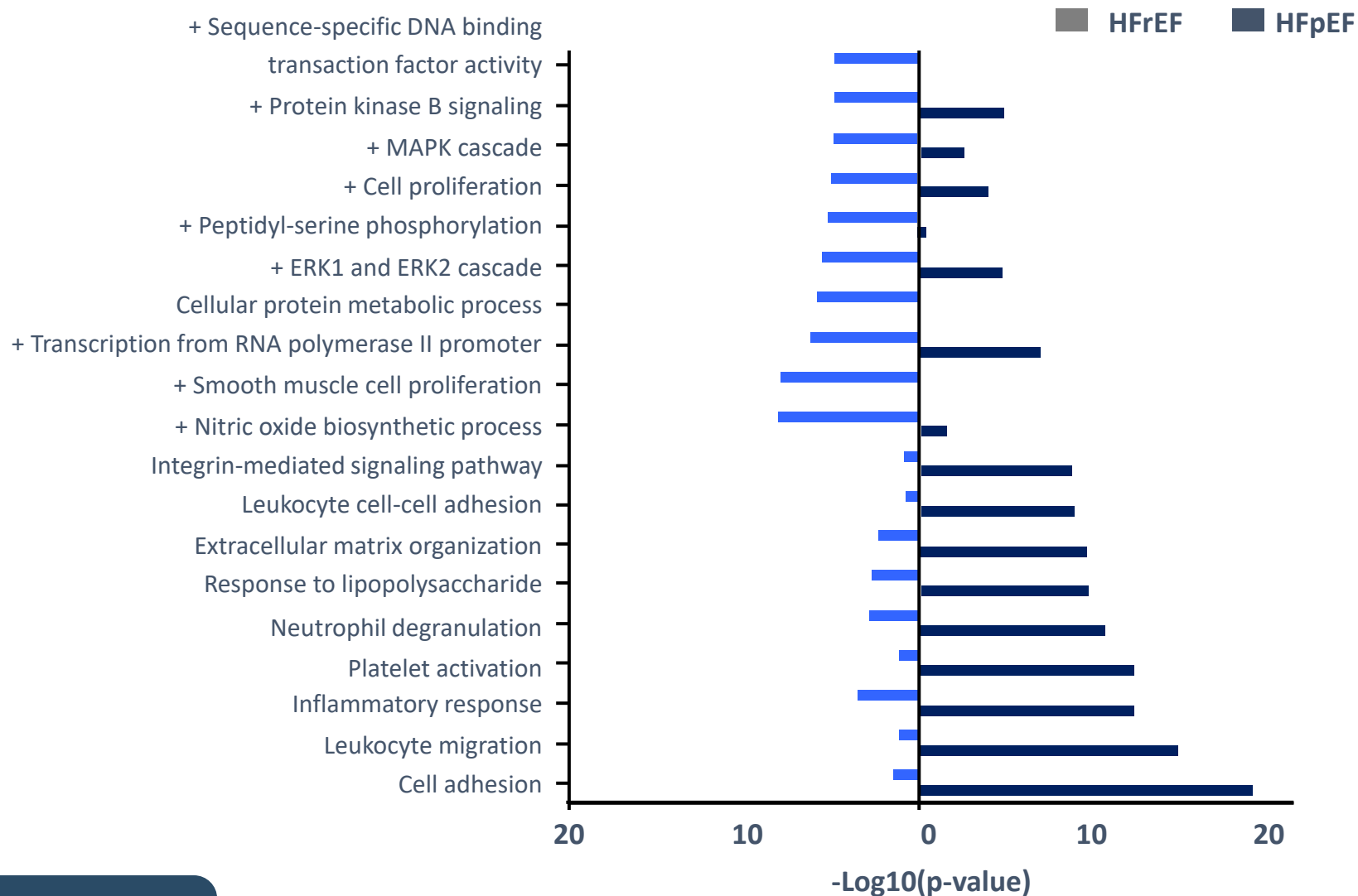
No. of Participants	0	20	36	52	52*
Semaglutide	263	249	225	243	263
Placebo	266	242	217	237	266

B Change in Body Weight



No. of Participants	0	4	8	12	16	20	28	36	44	52	52*
Semaglutide	263	255	254	250	246	252	239	243	240	246	263
Placebo	266	259	249	250	243	246	243	239	233	242	266

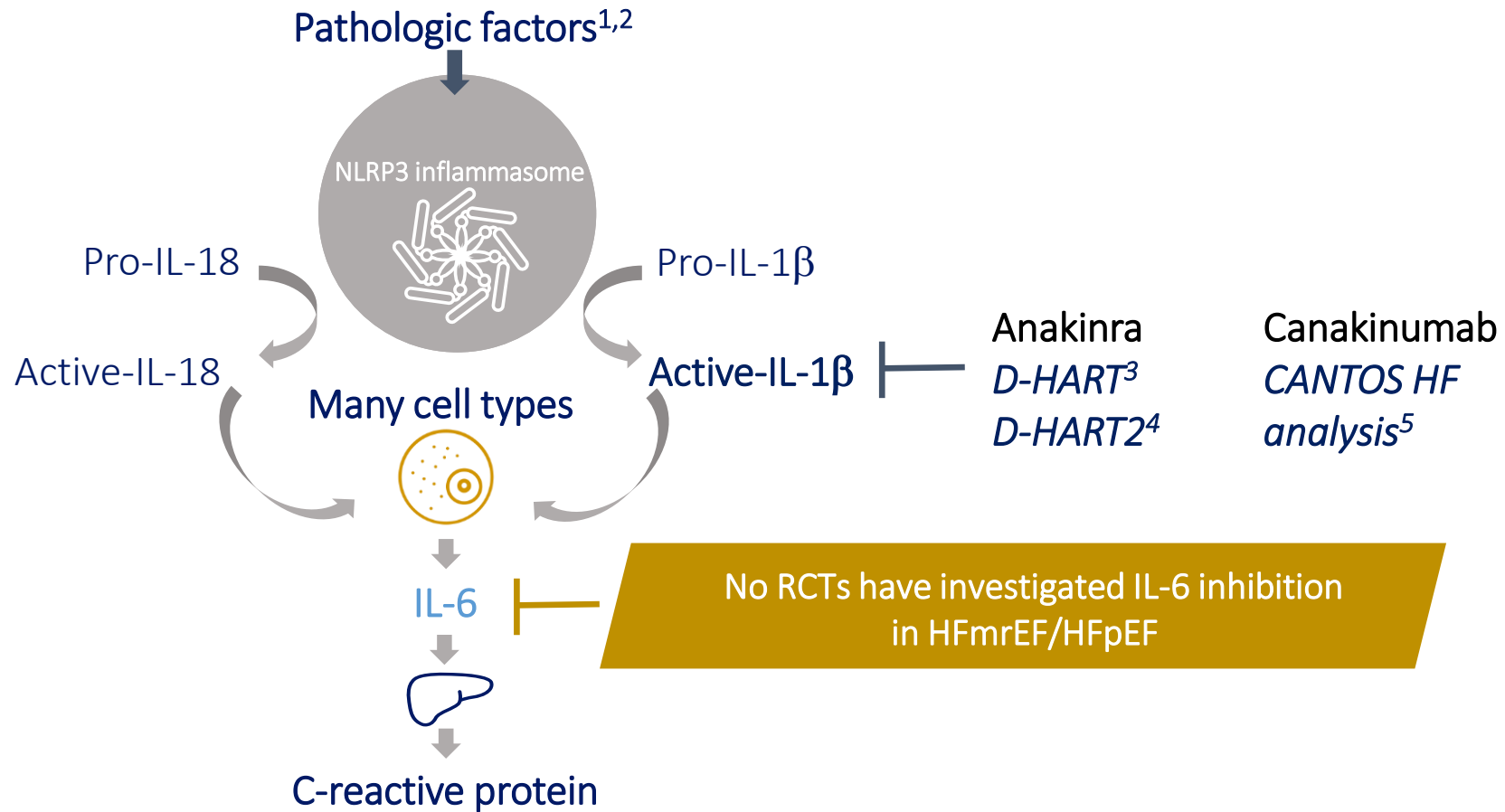
HFpEF is an inflammatory disease



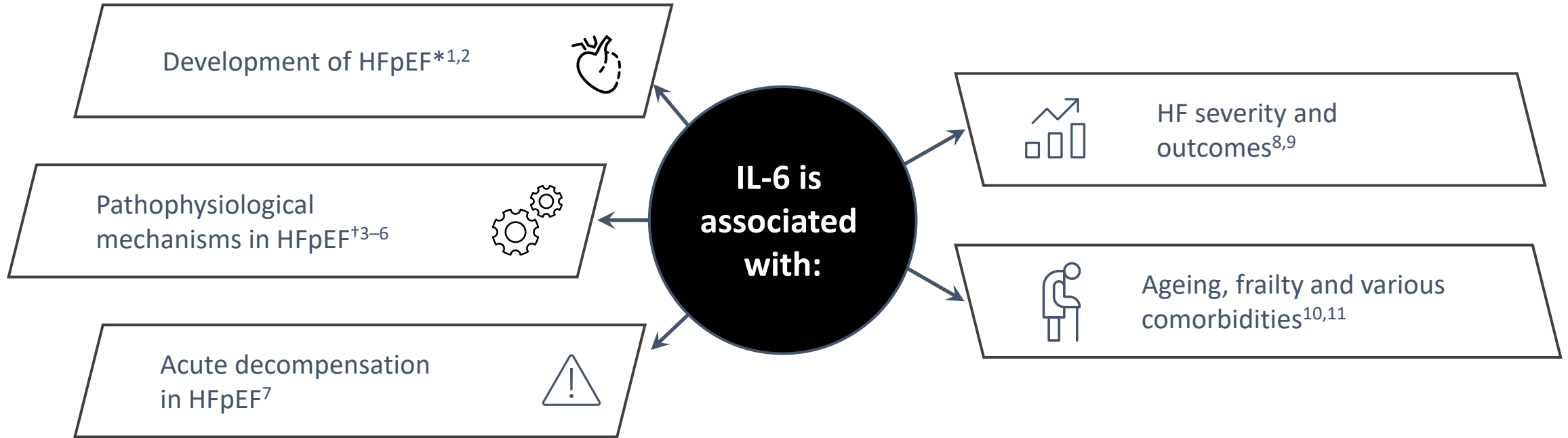
Biomarker profiles specific for **HFrEF** are related to **cellular proliferation and metabolism**

Biomarker profiles specific for **HFpEF** are related to **inflammation and endothelial function**

RCTs investigating the same inflammatory pathways



IL-6 in HFpEF

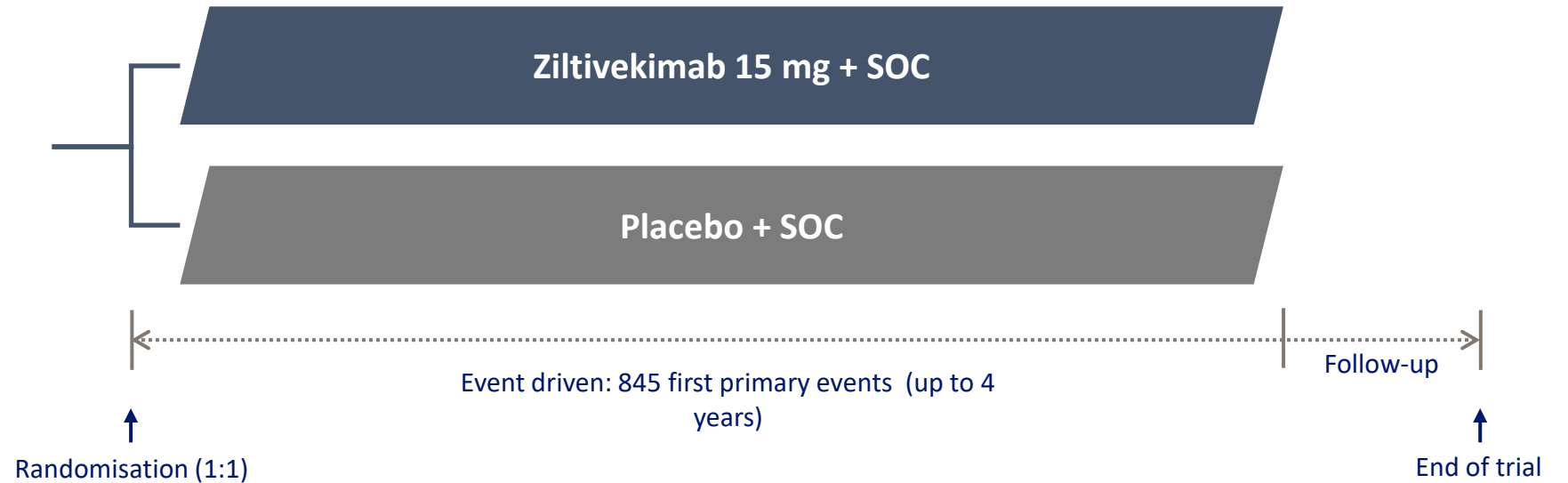


However, there are no data showing the causal role of IL-6 in HFmrEF/HFpEF

HERMES CVOT

5,600 patients

- Elevated hsCRP ≥ 2 mg/L
- NYHA II–IV
- LVEF >40 %
- Elevated NT-proBNP levels
- Echo signs of HFmrEF or HFpEF



Primary endpoint: Time to the first occurrence of CV death, HHF or urgent HF visit

Treatment recommendation with steroidal MRA is well established for HFrEF but less defined for HFpEF

MRAs recommendations

Treatment for HFrEF^{1,2}

Class I



Recommended for patients with HFrEF to reduce the risk of HHF and death



Recommended to reduce morbidity and mortality*

Treatment for HFmrEF^{1,2}

Class IIb



May be considered to reduce the risk of HHF and death



May be considered to reduce the risk of HHF and CV death, particularly among patients with LVEF on the lower end of the spectrum

Treatment for HFpEF²

Class IIb



May be considered in selected patients to reduce the risk of hospitalisation, particularly among patients with LVEF on the lower end of the spectrum

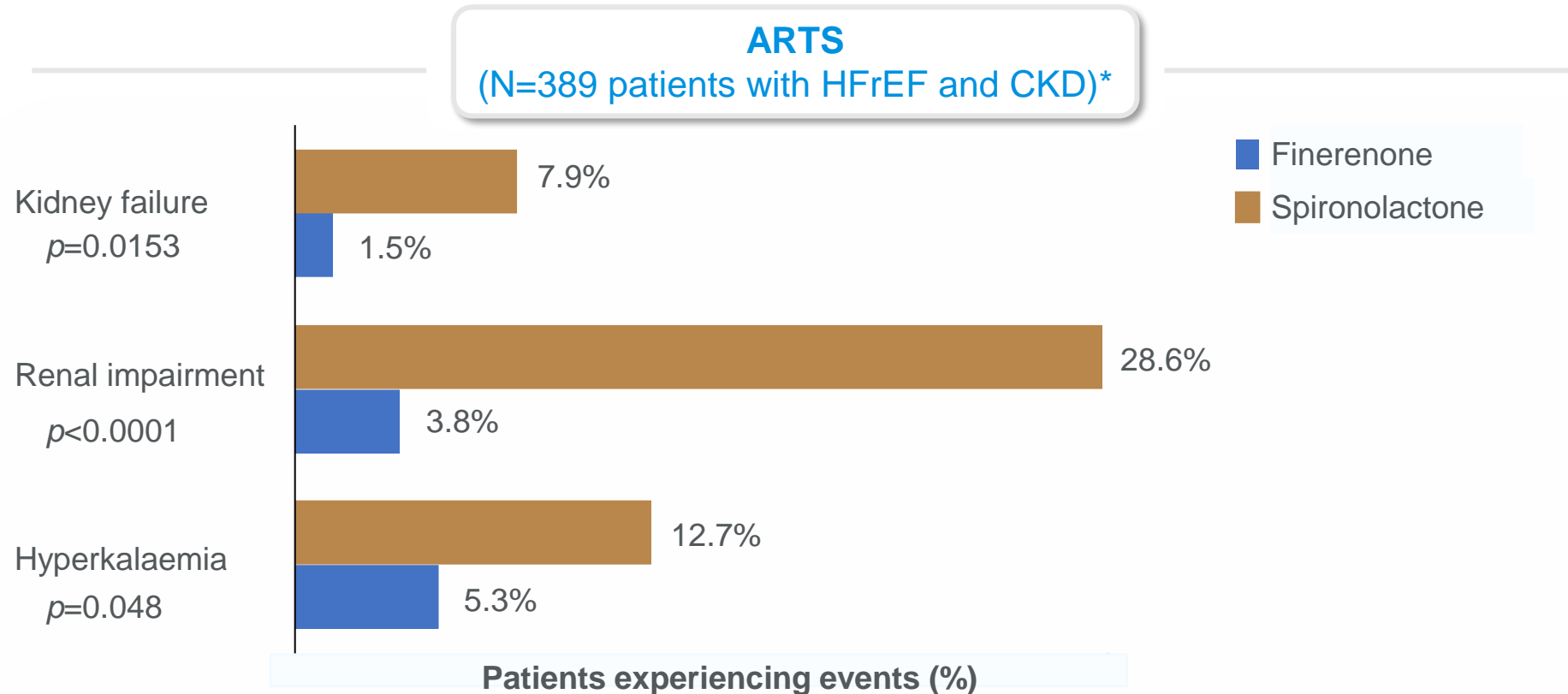


ESC guidelines:
Recommendations for chronic HF (2021)



AHA/ACC/HFSA guidelines:
Recommendations for chronic HF (2022)

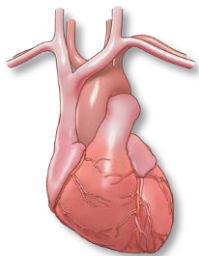
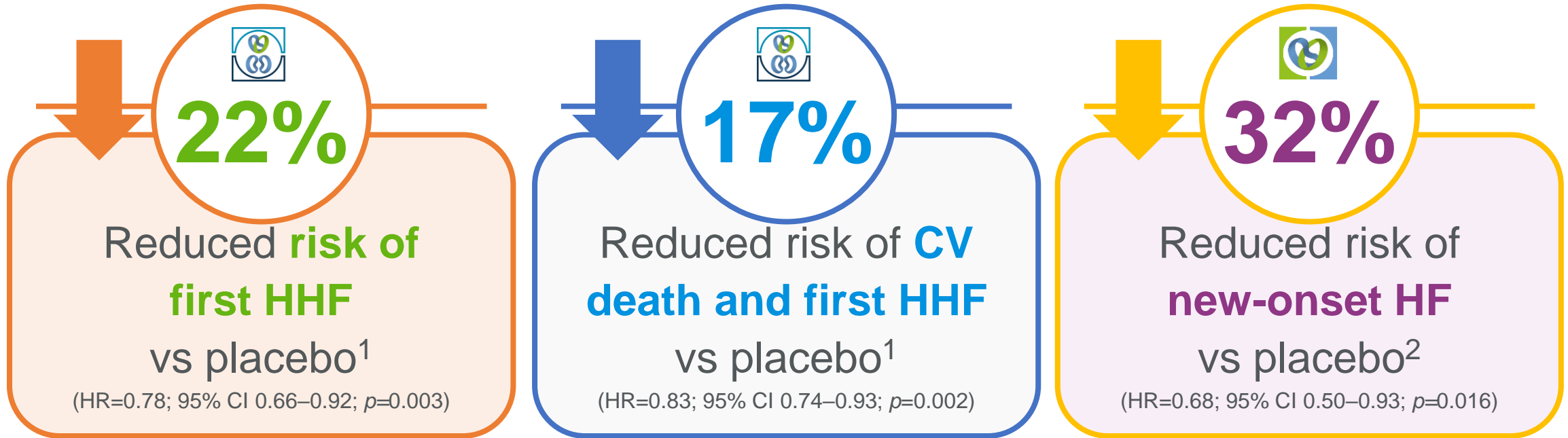
Finerenone was well tolerated, with fewer patients experiencing hyperkalaemia vs spironolactone¹



Worsening kidney failure and hyperkalaemia occurred less frequently in all groups of patients receiving finerenone compared with spironolactone



In FIDELITY (N=13,026), finerenone improved CV and HF outcomes versus placebo in patients with CKD and T2D



Finerenone reduced the incidence of **all-cause and CV mortality** (on-treatment analysis) vs placebo and **lowered the risk of sudden cardiac death** (intention-to-treat population)³

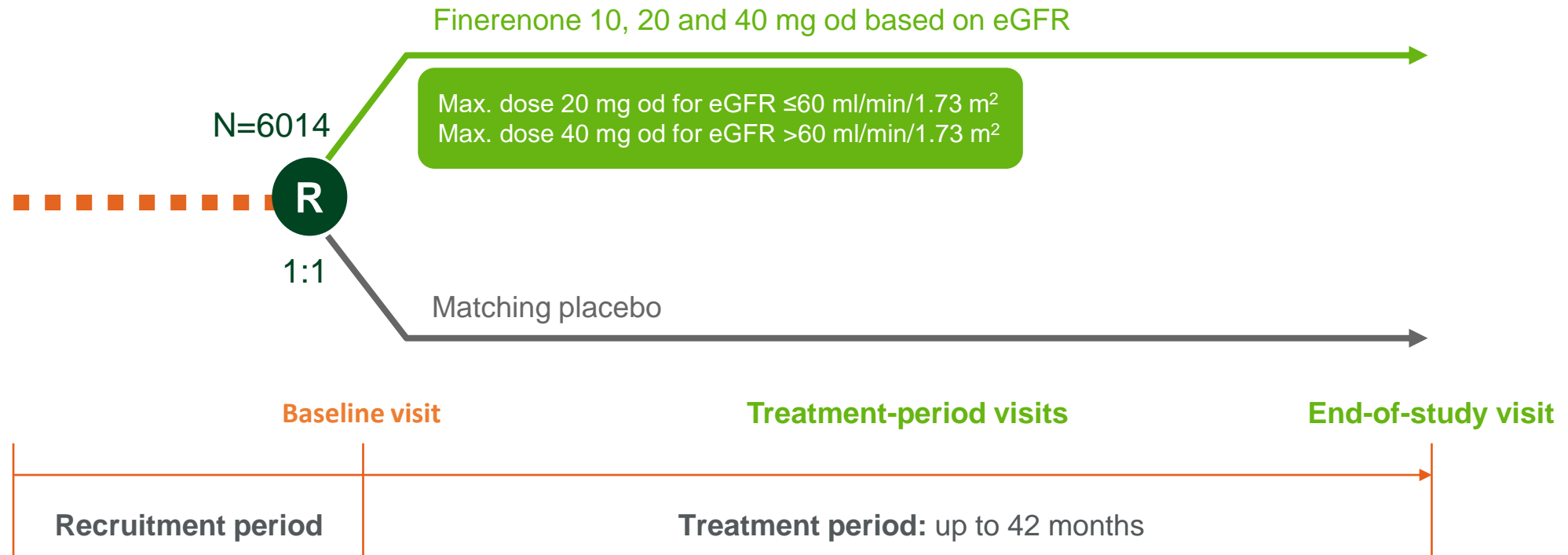
FINEARTS-HF evaluates the efficacy and safety of finerenone in patients with HF



To evaluate the efficacy and safety of **finerenone** on morbidity and mortality in patients with **symptomatic HF** (NYHA class II–IV and LVEF $\geq 40\%$)

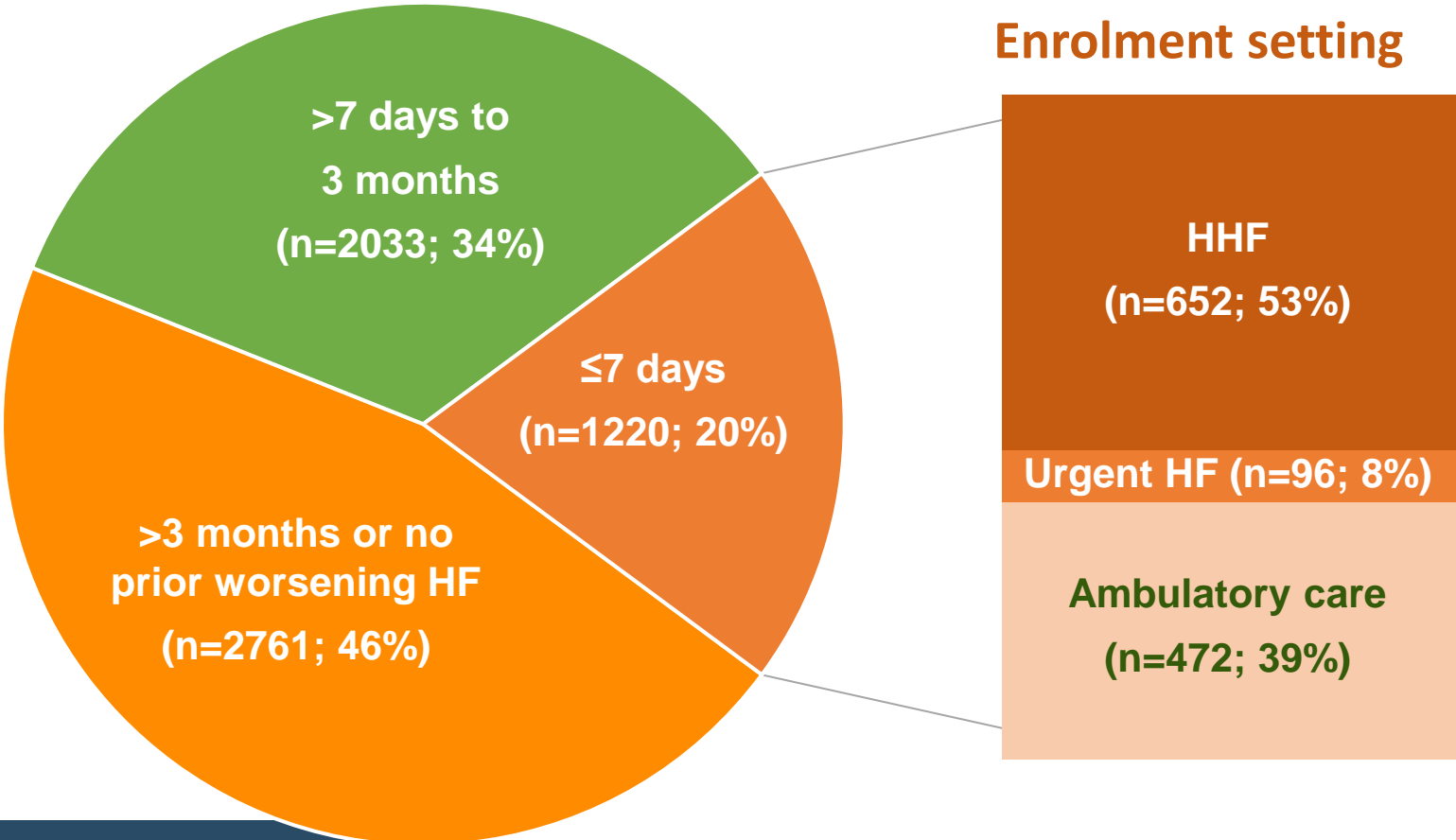

Study start: **Sept 2020**

Estimated study completion: **Sept 2024**



FINEARTS-HF includes a large patient population with a recent worsening HF event¹

Enrolment timing relative to most recent worsening HF event

Among the patients in FINEARTS-HF, 20% were enrolled within 7 days and >50% within 3 months of a worsening HF event

The Future of Drugs in Heart Failure

Conclusions:

- Despite major improvements still residual mortality and morbidity in HFrEF
- As of yet only one proven therapy for HFpEF and no proven therapies for acute heart failure
- A tremendous number of drugs in various stages of development

Current Trends in trial design:

- Trend towards more personalized therapies?
- Trend towards “irrespective of LVEF”?
- Trend towards chronic HF drugs to be tested in acute HF?