The future in heart failure

Prof. dr. Adriaan Voors

The future in heart failure: focus on medical therapies

Adriaan Voors

28 november 2023

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cardiology
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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.

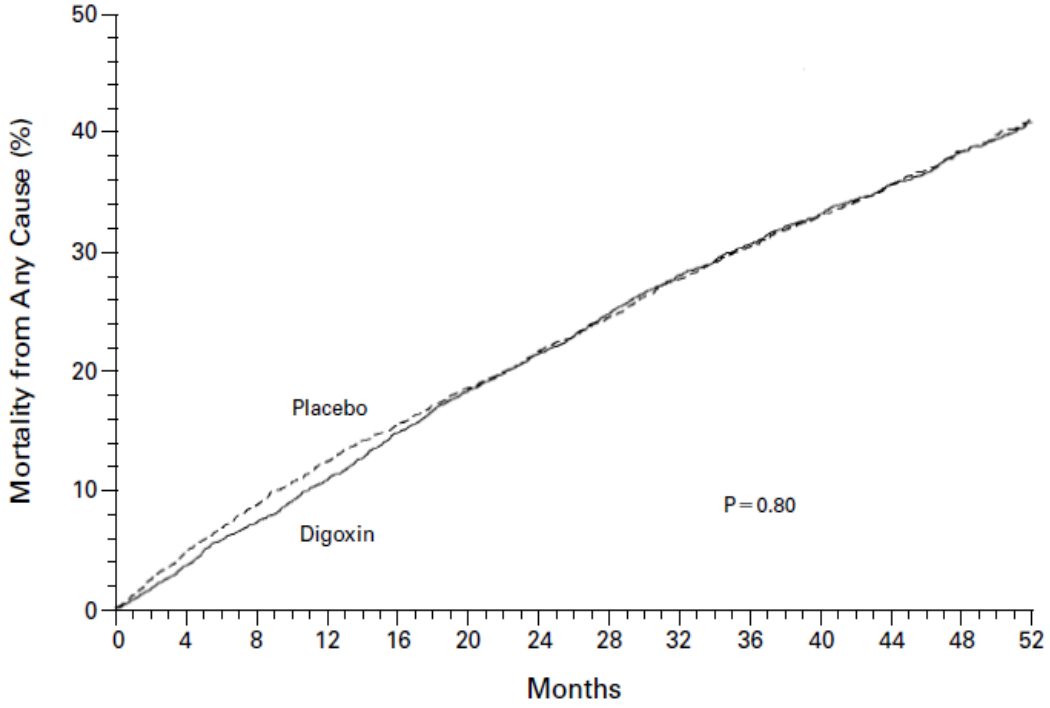
Promising late phase therapies

HFrEF
- Digoxin (DECISION)
- Vericiguat (VICTOR)

ATTR Cardiomyopahy
- ATTR-therapies

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

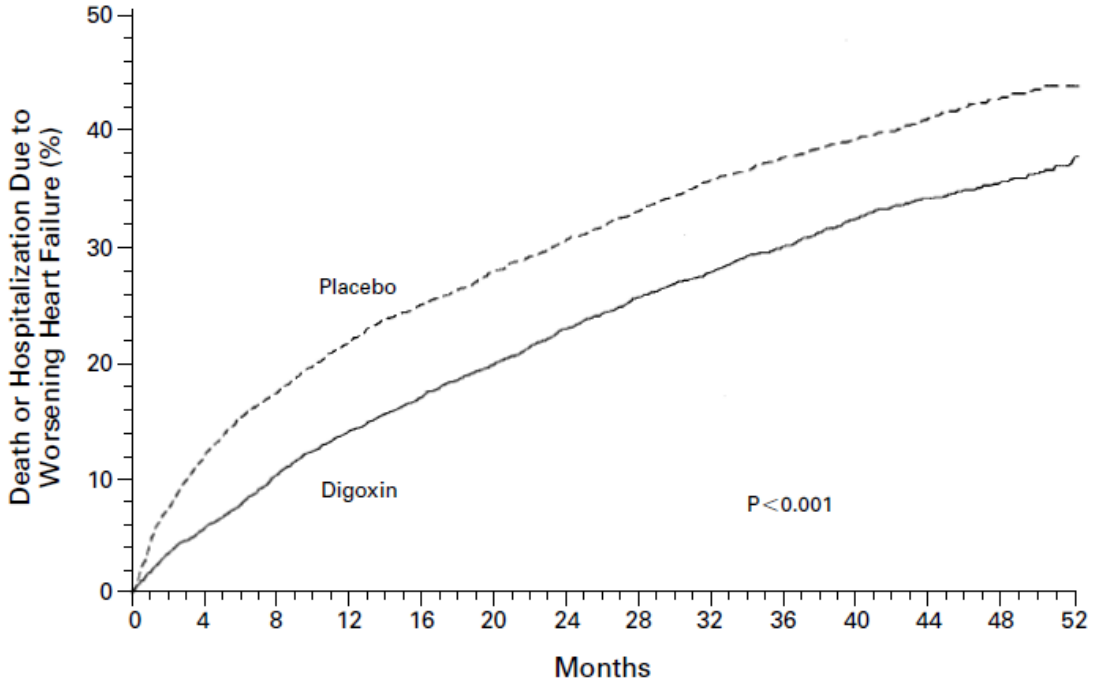
Digoxin did not reduce overall mortality, but it reduced the rate of hospitalization both overall and for worsening heart failure



No. of Patients at Risk

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.



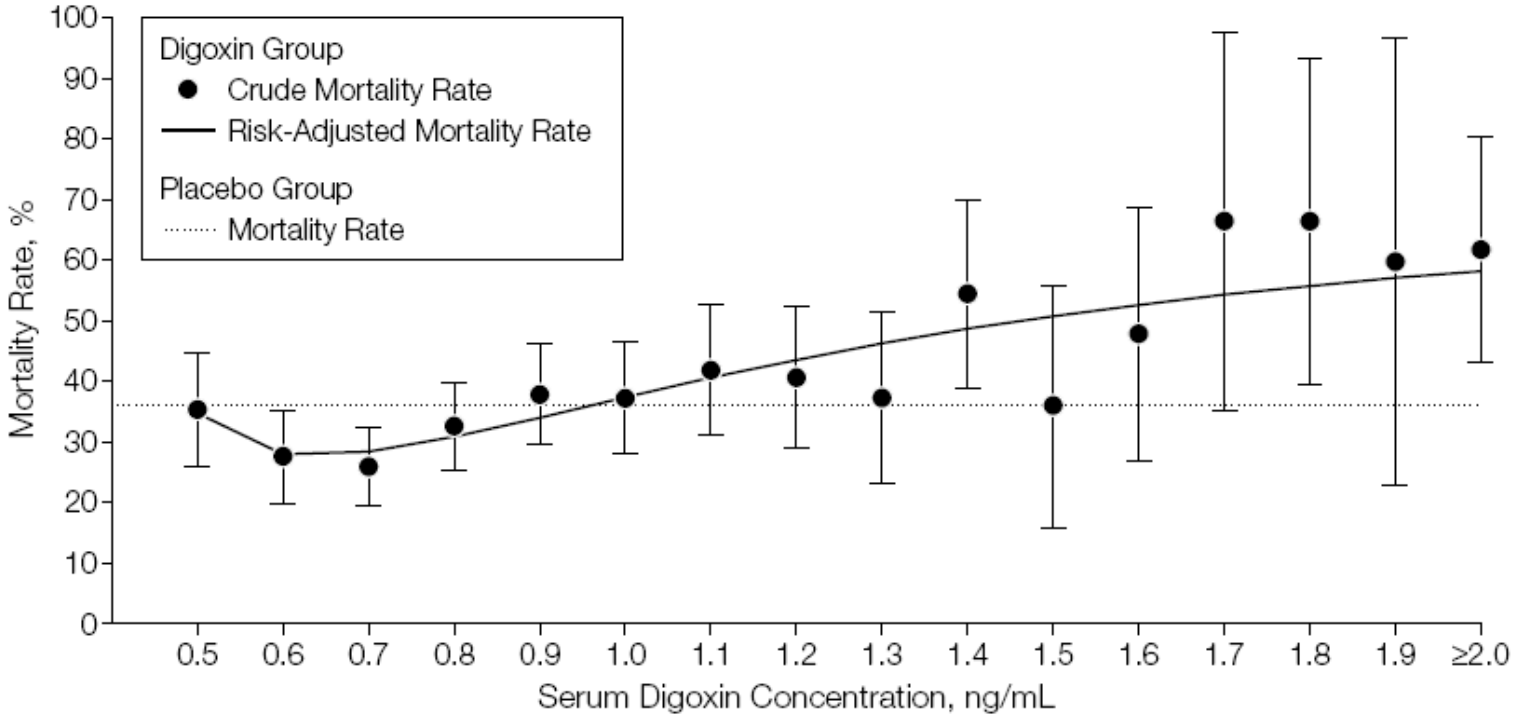
No. of Patients at Risk

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



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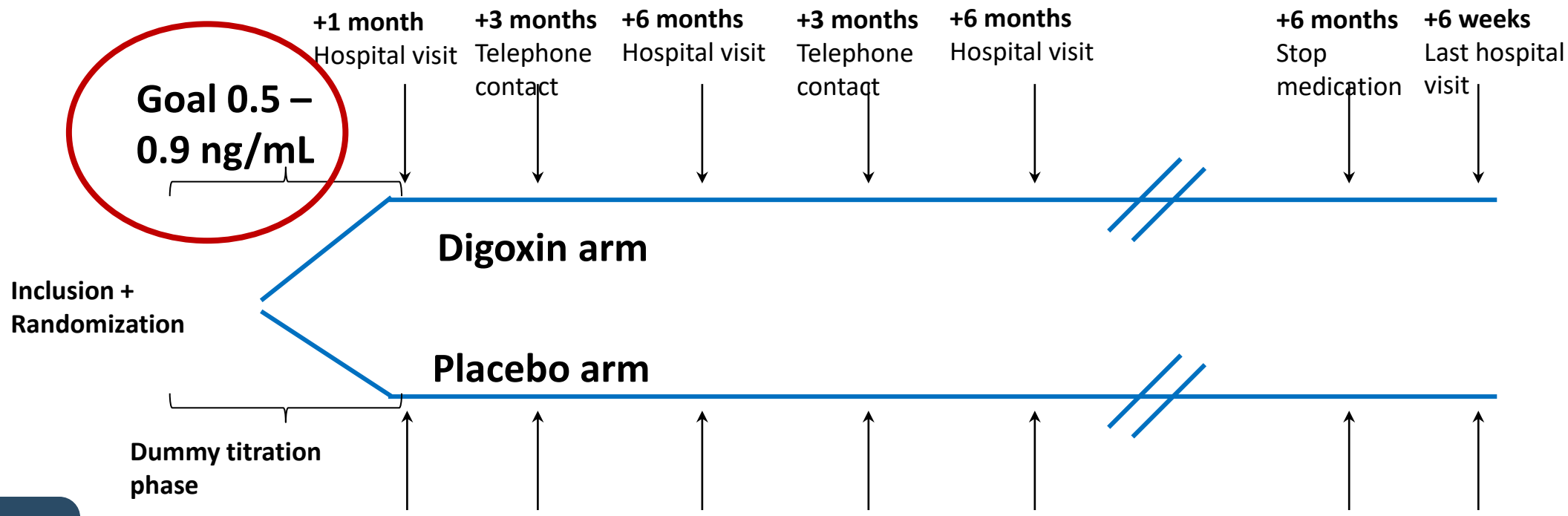
Rathore et al. JAMA 2003

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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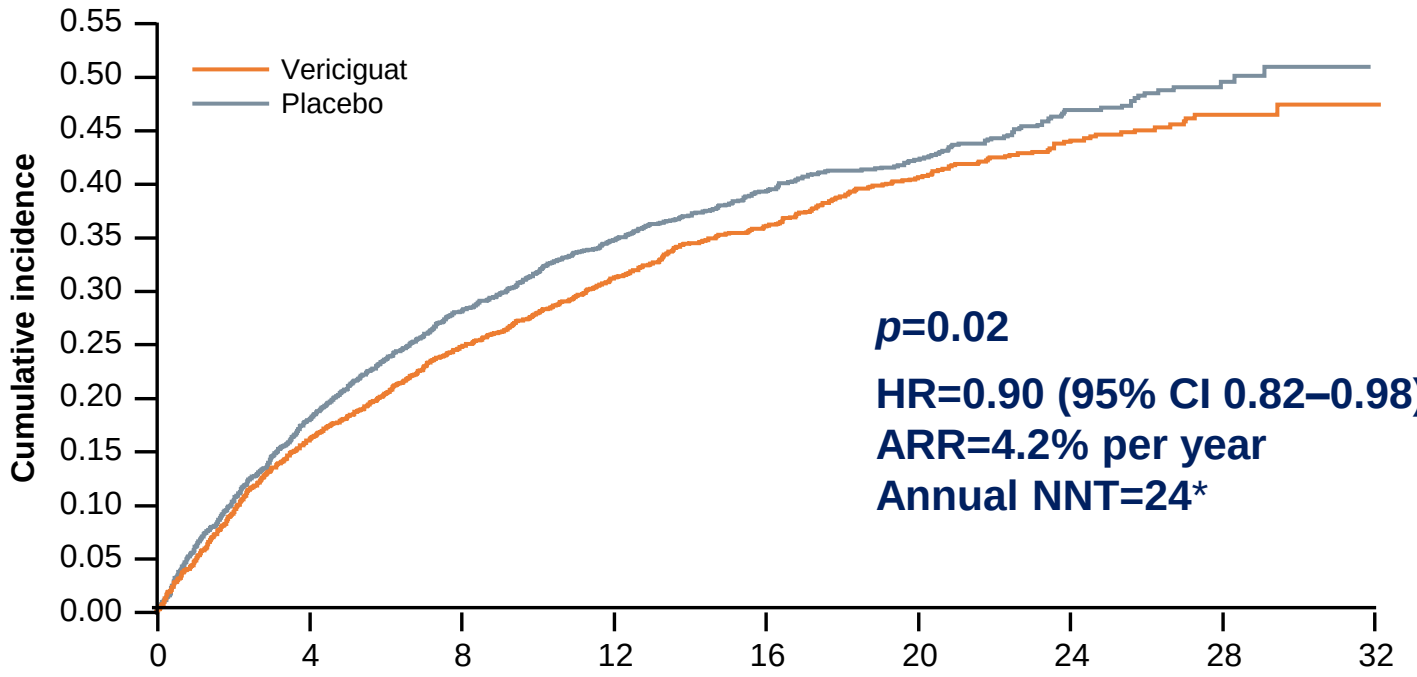
VICTORIA: Primary Endpoint

Time to CV death or first HF hospitalisation



Number of subjects at risk									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

- 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%

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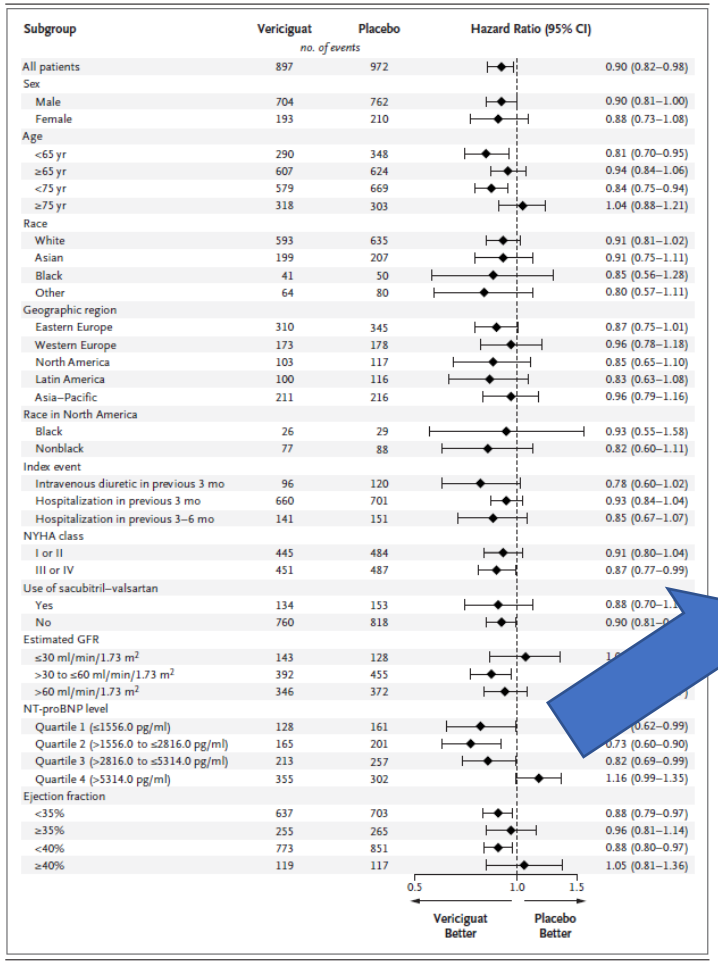
Armstrong PW,, et al. N Engl J Med. 2020;382:1883–1893

VICTORIA – Subgroup analysis (ITT)



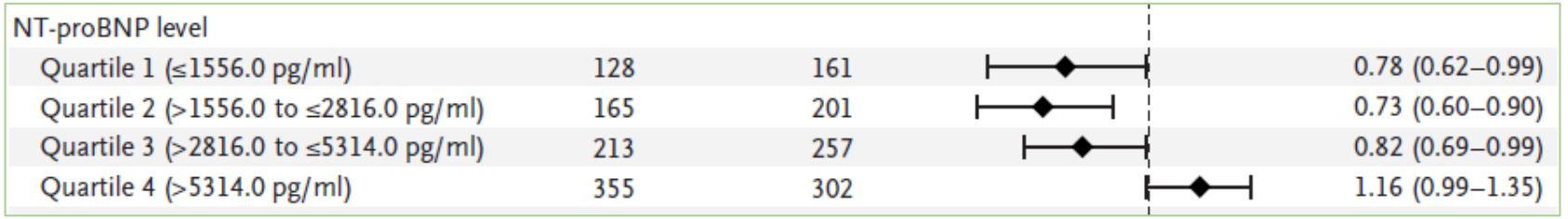
Subgroup	Vericiguat	Placebo	Hazard Ratio (95% CI)
	no. of events		
All patients	897	972	0.90 (0.82–0.98)
Sex			
Male	704	762	0.90 (0.81–1.00)
Female	193	210	0.88 (0.73–1.08)
Age			
<65 yr	290	348	0.81 (0.70–0.95)
≥65 yr	607	624	0.94 (0.84–1.06)
<75 yr	579	669	0.84 (0.75–0.94)
≥75 yr	318	303	1.04 (0.88–1.21)
Race			
White	593	635	0.91 (0.81–1.02)
Asian	199	207	0.91 (0.75–1.11)
Black	41	50	0.85 (0.56–1.28)
Other	64	80	0.80 (0.57–1.11)
Geographic region			
Eastern Europe	310	345	0.87 (0.75–1.01)
Western Europe	173	178	0.96 (0.78–1.18)
North America	103	117	0.85 (0.65–1.10)
Latin America	100	116	0.83 (0.63–1.08)
Asia–Pacific	211	216	0.96 (0.79–1.16)
Race in North America			
Black	26	29	0.93 (0.55–1.58)
Nonblack	77	88	0.82 (0.60–1.11)
Index event			
Intravenous diuretic in previous 3 mo	96	120	0.78 (0.60–1.02)
Hospitalization in previous 3 mo	660	701	0.93 (0.84–1.04)
Hospitalization in previous 3–6 mo	141	151	0.85 (0.67–1.07)
NYHA class			
I or II	445	484	0.91 (0.80–1.04)
III or IV	451	487	0.87 (0.77–0.99)
Use of sacubitril–valsartan			
Yes	134	153	0.88 (0.70–1.1
No	760	818	0.90 (0.81–0
Estimated GFR			
≤30 ml/min/1.73 m²	143	128	1.0
>30 to ≤60 ml/min/1.73 m²	392	455	
>60 ml/min/1.73 m²	346	372	
NT-proBNP level			
Quartile 1 (≤1556.0 pg/ml)	128	161	(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)
Ejection fraction			
<35%	637	703	0.88 (0.79–0.97)
≥35%	255	265	0.96 (0.81–1.14)
<40%	773	851	0.88 (0.80–0.97)
≥40%	119	117	1.05 (0.81–1.36)

0.5 1.0 1.5

Vericiguat Better | Placebo Better

Significant treatment interaction with NTproBNP quartiles:

Largest benefit in Q1-Q3



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Armstrong P. et al., N Engl J Med 2020;382:1883-1893

Category	VICTORIA	VICTOR
Size	5050	6000
LV ejection fraction (EF)	EF < 45%	EF ≤ 40%
NT-proBNP • Entry criteria • **Upper limit**	• NT-proBNP ≥ 1000 pg/mL (in SR); ≥ 1600 pg/mL (in AF) • **No upper limit**	• 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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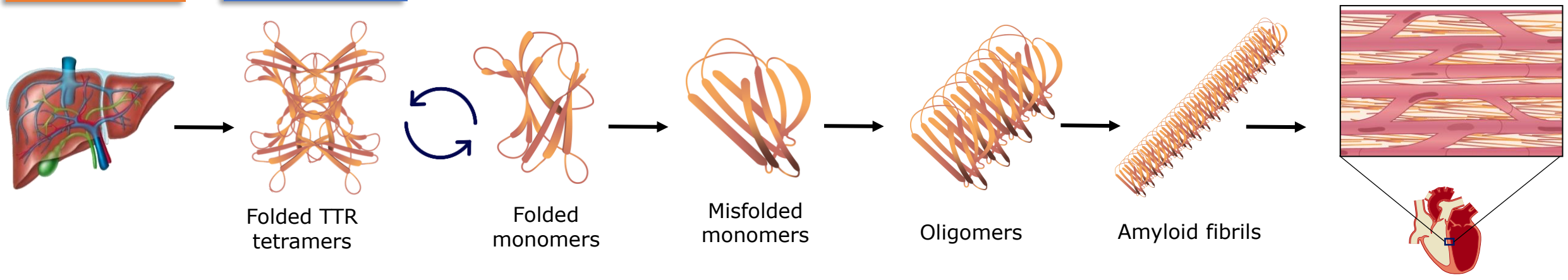
Treatment of ATTR-CM

Liver transplant, patisiran*, inotersen*, vutrisiran*

Tafamidis, diflunisal*, AG-10*

NNC6019-0001*, NI006*



Inhibit production of TTR (RNAi)

TTR tetramer stabilisers

Amyloid breakdown

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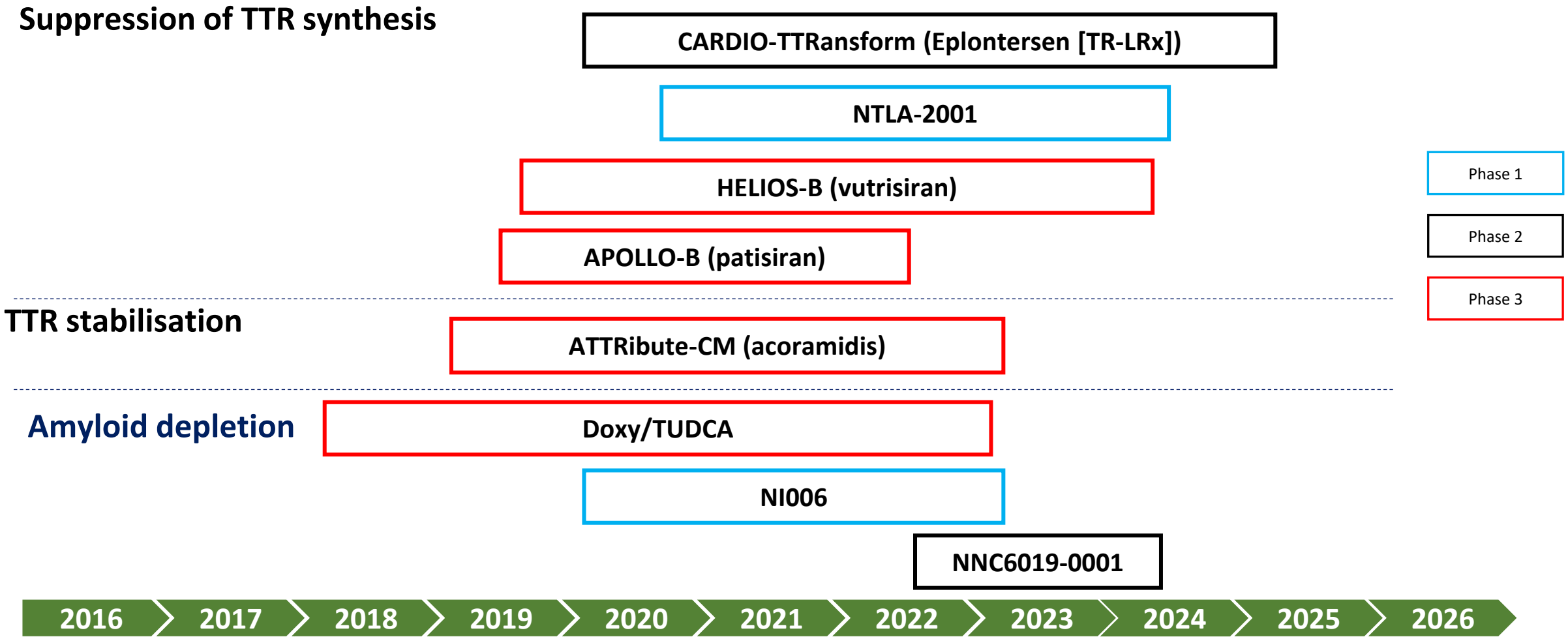
ATTR-CM, transthyretin amyloid cardiomyopathy; RNAi, ribonucleic acid interference; TTR, transthyretin

Garcia-Pavia P et al. *Eur Heart J* 2021;42:1554–1568

Ongoing clinical trials on ATTR-CM



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The estimated trial length is based on the estimated primary completion date (EPCD) with possible reporting of primary endpoint results, accessed on ClinicalTrials.gov on 23 November 2022: CARDIO-TTRansform EPCD June 2025; NTLA-2001 EPCD August 2024; HELIOS-B EPCD June 2024; APOLLO-B EPCD June 2022; ATTRibute-CM (Part B) EPCD April 2023; Doxy/TUDCA EPCD January 2023; NI006 EPCD February 2023; NNC6019-0001 EPCD May 2024

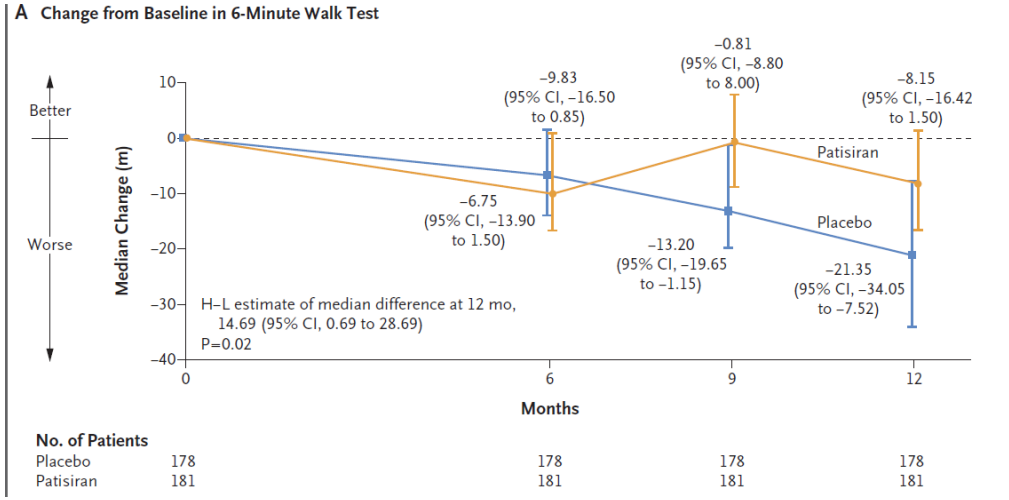
ATTR-CM, transthyretin amyloid cardiomyopathy; Doxy/TUDCA, doxycycline and tauroursodeoxycholic acid; EPCD, estimated primary completion date; TTR, transthyretin

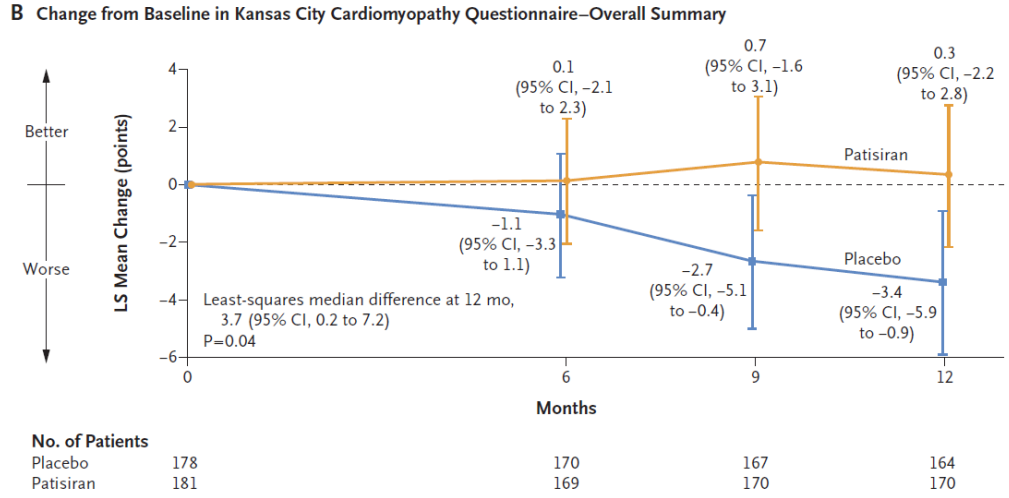
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 26, 2023 VOL. 389 NO. 17

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.





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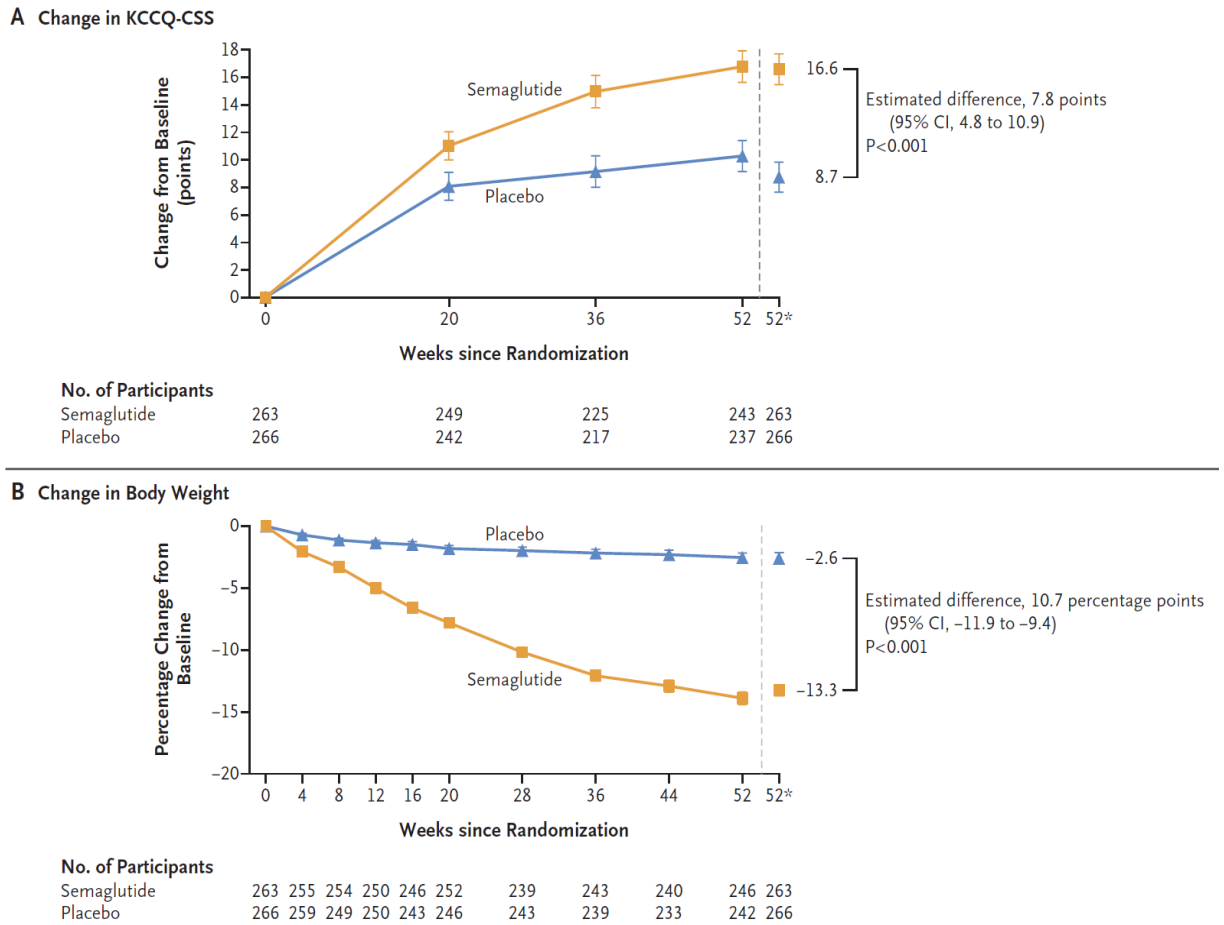
The NEW ENGLAND JOURNAL of MEDICINE

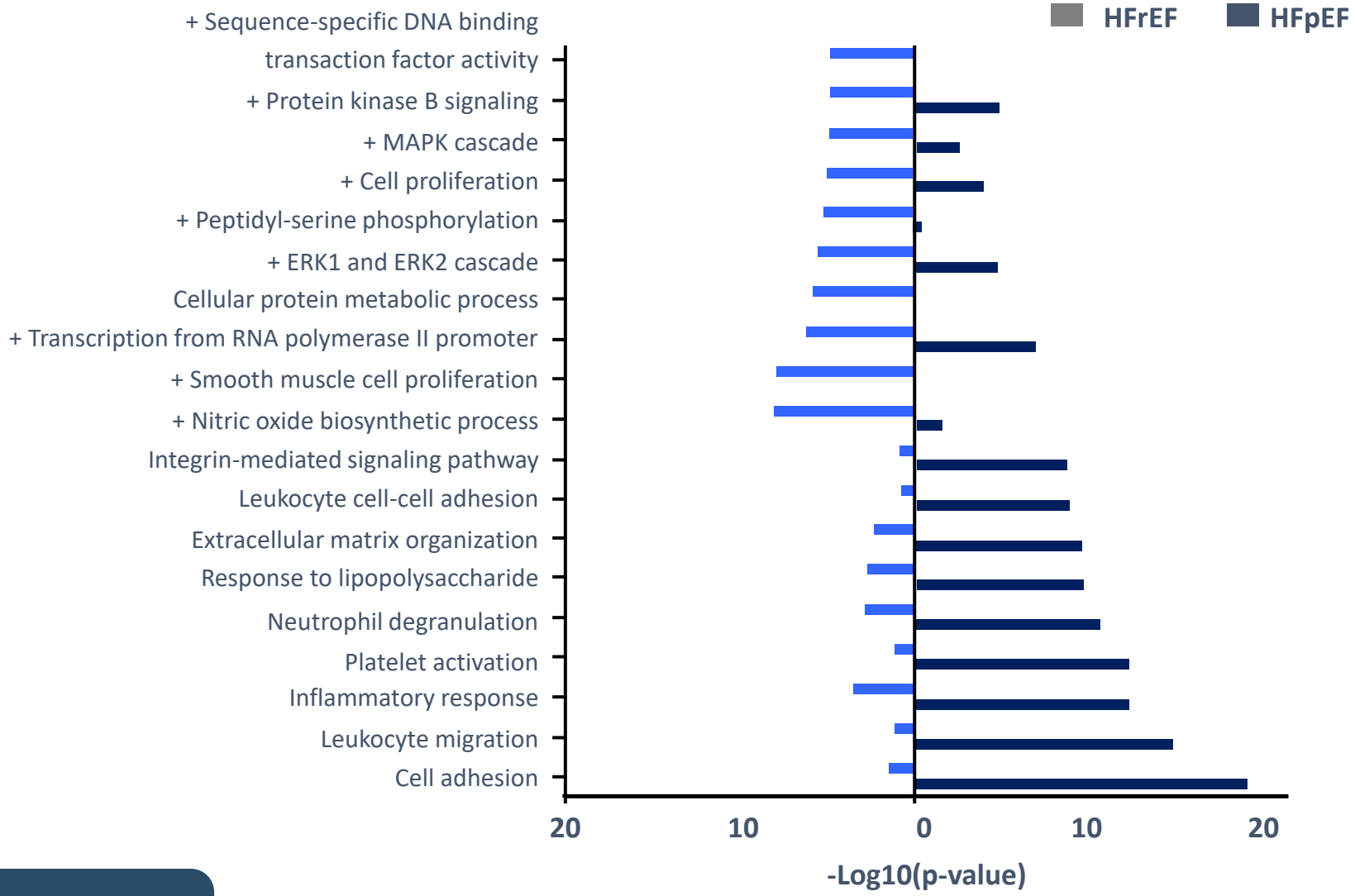
ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

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



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**

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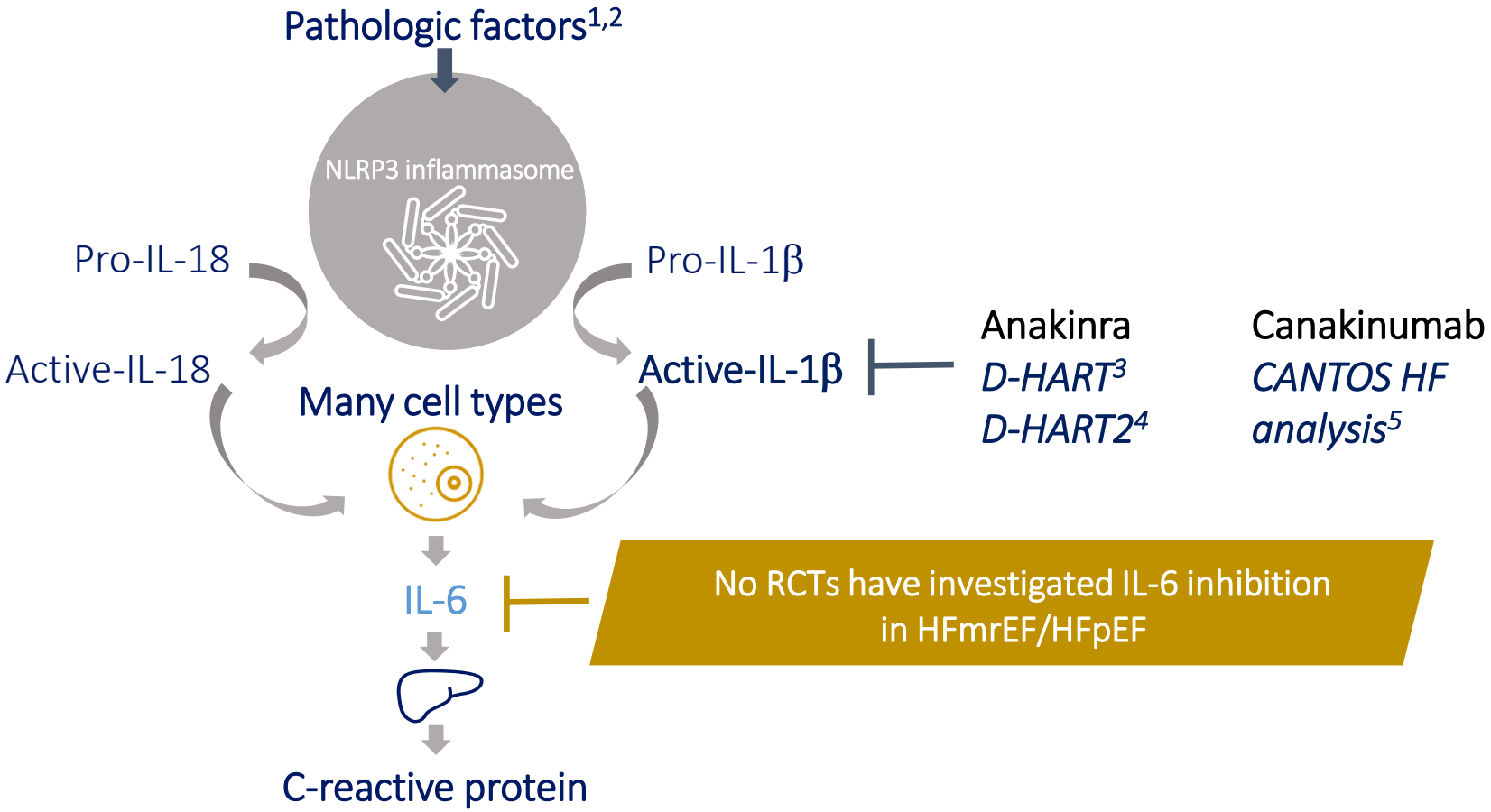
Tromp J, et al. J Am Coll Cardiol 2018;72(10):1081-1090

RCTs investigating the same inflammatory pathways



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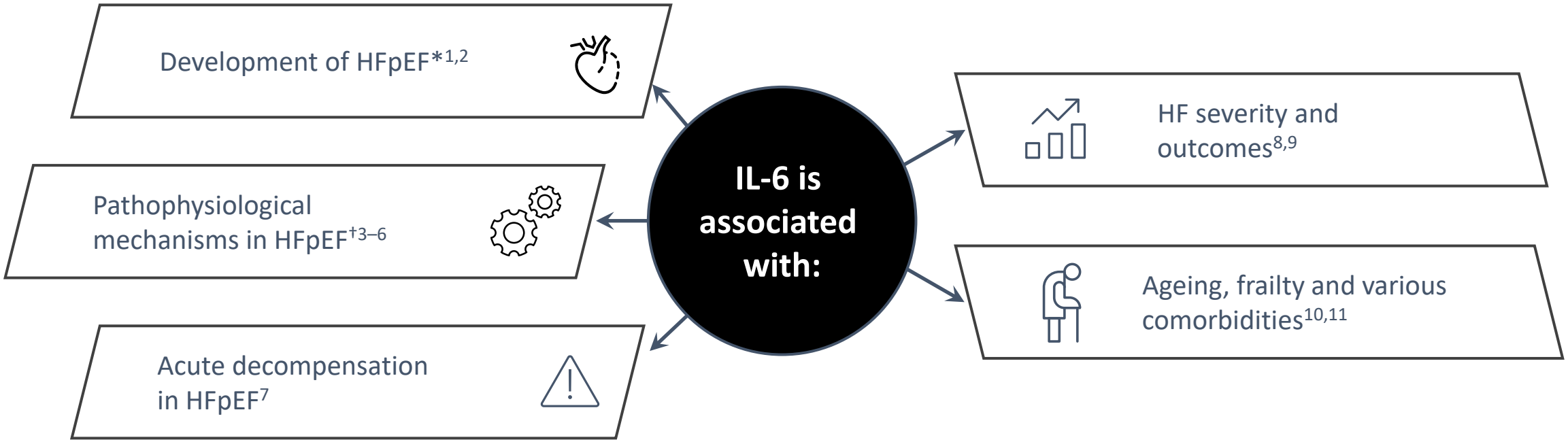
HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IL-18, interleukin-18; IL-1β; interleukin-1β; IL-1R, interleukin-1 receptor; IL-6, interleukin 6; NLRP3, NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3; RCT, randomised controlled trial

1. Ridker PM et al. Circ Res 2016;118:145–156 (Figure adapted); 2. Wu J et al. Front Physiol 2021;12:709703; 3. Van Tassell BW et al. Am J Cardiol 2014;113(2):321–327; 4. Van Tassell BW et al. Am J Cardiol 2018;11:e005036; 5. Everett BM et al. Circulation 2019;139:1289–1299

IL-6 in HFpEF



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

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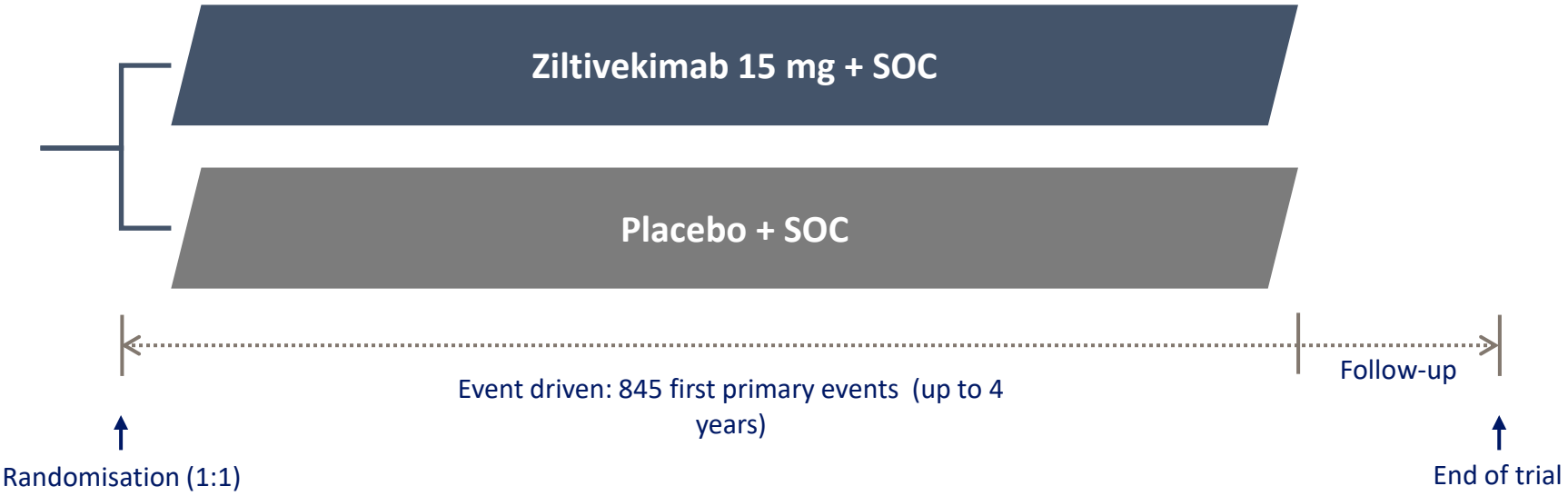
*There is no consistency for classification of HFpEF based on LVEF in previous research and HFpEF was defined as LVEF >40%, LVEF >45% or LVEF >50% in these different studies; †LV hypertrophy, cardiac remodelling and myocardial fibrosis
HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IL-6, interleukin-6; LV, left ventricular; LVEF, left ventricular ejection fraction

1. Kalogeropoulos A et al. J Am Coll Cardiol 2010;55:2129–2137; 2. Chia YC et al. J Am Heart Assoc 2021;10:e018549; 3. Meléndez GC et al. Hypertension 2010;56:225–231; 4. Hirota H et al. Proc Natl Acad Sci 1995;92:4862–4866; 5. Zhao L et al. Circ Res 2016;118:1918–1929; 6. Savvatis K et al. Basic Res Cardiol 2014;109–449; 7. Abernethy A et al. J Am Heart Assoc 2018;7:e007385; 8. Fontes JA et al. Cytokine 2015;74:62–68; 9. Markousis-Mavrogenis G et al. Eur J Heart Fail 2019;21:965–973; 10. Povar-Echeverría M et al. J Clin Med 2021;10:504; 11. Gómez-Rubio P et al. Diagnostics (Basel). 2022;12:117

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

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CV, cardiovascular; CVOT, cardiovascular outcome trial; HF, heart failure; HFF, hospitalisation for heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SOC, standard of care

Novo Nordisk A/S. NCT05636176. Available at: https://clinicaltrials.gov/ct2/show/NCT05636176 (accessed February 2023)

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 HFpEF[2]

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)

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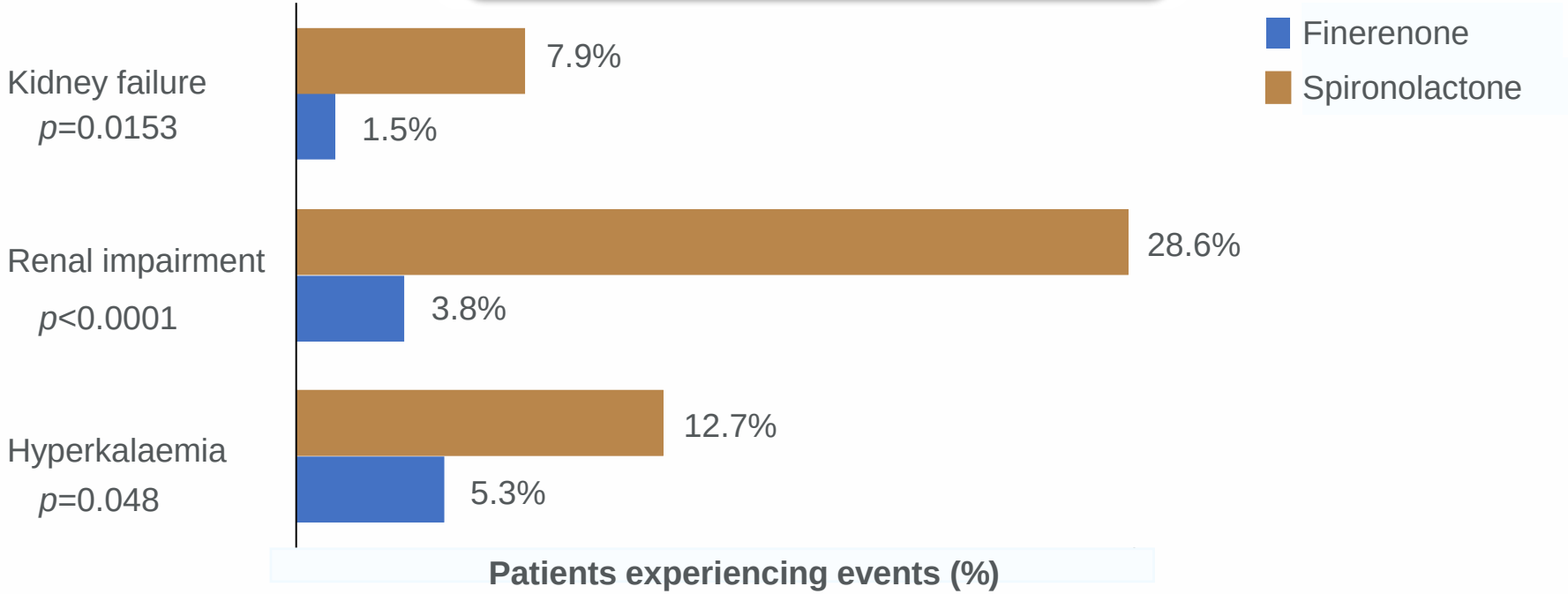
*If eGFR >30 ml/min/1.73 m^2 and serum [K^+] <5.0 mmol/l

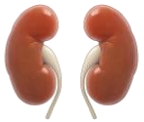
ACC, American College of Cardiology; AHA, American Heart Association; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America;

[K^+], potassium concentration 1. McDonagh TA, *et al. Eur Heart J* 2021;42:3599–3726; 2. Heidenreich PA, *et al. Circulation* 2022;145:e895–e1032

Finerenone was well tolerated, with fewer patients experiencing hyperkalaemia vs spironolactone[1]

ARTS
(N=389 patients with HFrEF and CKD)*





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

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Finerenone is indicated for the treatment of CKD (with albuminuria) associated with T2D in adults.[2] For prescribing information please refer to the SmPC of the product applicable in your country.

*Post hoc analysis in pooled dosing groups

1. Pitt B, *et al. Eur Heart J* 2013;34:2453–2463;2. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 03 July 2023]

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

22%

Reduced **risk of first HHF** vs placebo[1]

(HR=0.78; 95% CI 0.66–0.92; *p*=0.003)

17%

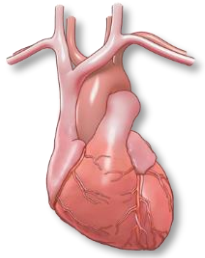
Reduced risk of **CV death and first HHF** vs placebo[1]

(HR=0.83; 95% CI 0.74–0.93; *p*=0.002)

32%

Reduced risk of **new-onset HF** vs placebo[2]

(HR=0.68; 95% CI 0.50–0.93; *p*=0.016)



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]

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Finerenone is indicated for the treatment of CKD (with albuminuria) associated with T2D in adults.[4]
For prescribing information please refer to the SmPC of the product applicable in your country.

1. Filippatos G, *et al. JACC HF* 2022;10:860–870; 2. Filippatos G, *et al. Circulation* 2022;145:437–447; 3. Filippatos G, *et al. Eur Heart J Cardiovasc Pharmacother* 2023;9:183–191; 4. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 03 July 2023]

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

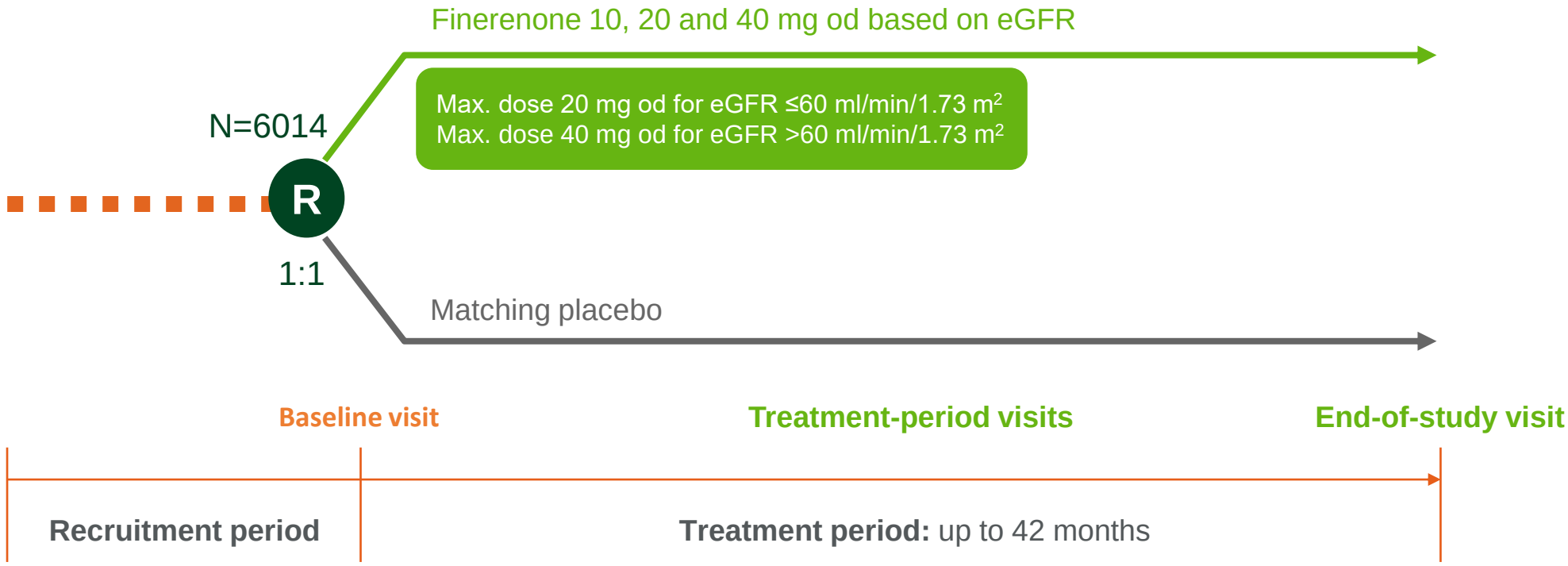
FINEARTS-HF

FINEARTS-HF

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

Study start: **Sept 2020**

Estimated study completion: **Sept 2024**



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Finerenone is indicated for the treatment of CKD (with albuminuria) associated with T2D in adults.[3] For prescribing information please refer to the SmPC of the product applicable in your country.

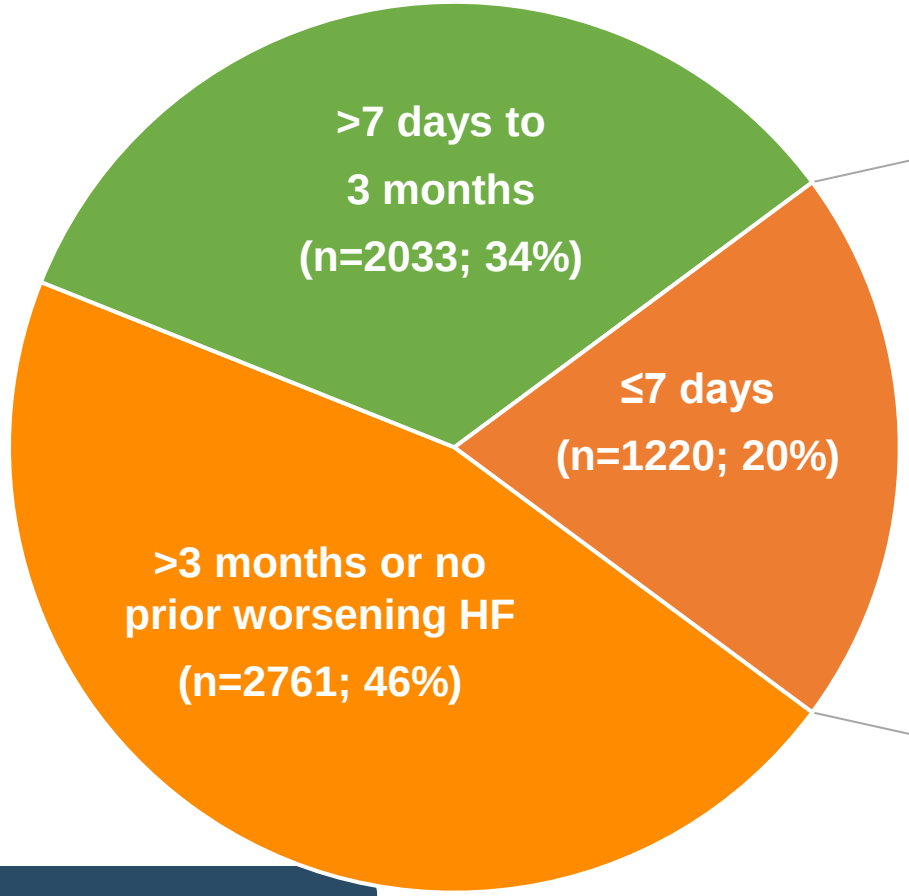
od, once daily; R, randomisation

1. Bayer . https://clinicaltrials.gov/ct2/show/NCT04435626 [accessed 06 June 2023]; 2. Bayer. Data on file; 3. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 03 July 2023]

FINEARTS-HF includes a large patient population with a recent worsening HF event[1]

FINEARTS-HF

Enrolment timing relative to most recent worsening HF event



Enrolment setting

HHF
(n=652; 53%)

Urgent HF (n=96; 8%)

Ambulatory care
(n=472; 39%)

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

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Finerenone is indicated for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults.[2] For prescribing information please refer to the SmPC of the product applicable in your country. Finerenone is not indicated for the treatment of heart failure.

1. Bayer. Data on file; Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 03 July 2023]

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?