Finerenone in Patients with a Recent Worsening Heart Failure Event: The FINEARTS-HF Trial

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on behalf of the FINEARTS-HF Investigators

FINEARTS-HF

FINerenone trial to investigate **E**fficacy and s**A**fety superio**R** to placebo in pa**T**ient**S** with **H**eart **F**ailure

Declaration of Interest

- **Dr. Desai has received research grants from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer and has consulted for Abbott, Alnylam, AstraZeneca, Avidity Biopharma, Axon Therapeutics, Bayer, Biofourmis, Boston Scientific, Endotronix, GlaxoSmithKline, Medpace, Medtronic, Merck, New Amsterdam, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, scPharmaceuticals, Veristat, Verily, Zydus**

- **The FINEARTS-HF Trial was sponsored by Bayer**

Rationale

- **Patients with HF and a recent worsening heart failure (WHF) event are known to be at high risk for recurrent hospitalization and death, regardless of EF**
- **In FINEARTS-HF, treatment with the nonsteroidal MRA finerenone reduced the risk CV death and total WHF events in patients with HFmrEF/HFpEF**
- **Hospitalized HF patients and those with recent WHF events were eligible for enrollment in FINEARTS-HF, and the proportion of those** without **a recent WHF event was prospectively capped at ~50%**
- **In a prespecified analysis, we examined the safety and efficacy of finerenone in relationship to the recency of a WHF event**

Solomon SD, McMurray JJV, Vaduganathan M, et al N Engl J Med. 2024 Sep 1. doi: 10.1056/NEJMoa2407107. Online ahead of print.

FINEARTS-HF Study Design

Randomized, double-blind, placebo-controlled trial testing the hypothesis that finerenone would reduce cardiovascular death and total worsening heart failure events in patients with heart failure and mildly reduced or preserved ejection fraction

Key Inclusion Criteria

- **Symptomatic HF (NYHA class II-V) with LVEF ≥ 40%**
- **Hospitalized, recently hospitalized, or ambulatory**
- **Elevated natriuretic peptide levels**
- **Structural heart disease (LA Enlargement or LVH)**
- **Diuretics in the 30d prior to randomization**

Key Exclusion Criteria

- **Potassium > 5.0 mmol/L; eGFR <25 mL/min/1.73 m²**
- **MRA use 30d prior to randomization**
- **History of peripartum, chemotherapy induced, or infiltrative cardiomyopathy (e.g., amyloidosis)**
- **Alternative causes of signs or symptoms**

1:1 Randomization

Finerenone 10, 20 or 20, 40 mg *dosing based on eGFR: ≤60 max dose 20 mg, >60, max dose 40 mg*

N = 6,001 validly randomized

Uptitrate to maximally tolerated dose if K+<5.0mmol/L and eGFR decrease <30%

Matching Placebo

Visits: Month 1, then 3-monthly for first 12 months, 4-monthly visits thereafter with telephone contact in between

Study Endpoints

Primary Endpoint

- CV death and total HF events (hospitalizations/urgent visits)

Secondary Endpoints

- Total HF events
- KCCQ-TSS at 6,9, and 12 months
- NYHA class at 12 months
- Renal composite endpoint
- All-cause mortality

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Methods

- Patients grouped into categories according to time from most recent WHF to randomization (during or within 7 days of WHF, between 7 days and 3 months, or > 3 months or without WHF)
- Risk of primary composite outcome (CV death and total WHF events) and treatment effect of finerenone vs. placebo according to time from WHF evaluated in semiparametric proportional-rates models (LWYY) using an interaction term
- Risk of key secondary outcomes including time to first occurrence of CV death or HF hospitalization, overall mortality, and composite renal events analysed in Cox proportional hazards models
- Odds Ratios according to treatment assignment and time from WHF for adverse events including drug discontinuation, occurrence of hyperkalemia, hypokalemia, hypotension, rise in creatinine examined in logistic regression models with an interaction term

FINEARTS-HF: Baseline Characteristics by Time from WHF

Characteristic		Time from WHF to Randomization <= 7 days (n=1219)	7 days–3 months (n=2028)	> 3 months or no prior WHF (n=2754)	P value for trend
Age, years		72.2 ± 9.7	71.3 ± 10.3	72.4 ± 9.1	0.11
Women (%)		583 (47.8%)	936 (46.2%)	1213 (44.0%)	0.021
Race (%)	White/Asian	91/6	70/25	81/15	0.13
	Black/other	0.6/2.6	1.7/3.7	1.7/2.7	
History (%)	Type 2 diabetes	42	41	40	0.25
	Hypertension	92	87	89	0.08
	Myocardial infarction	22	22	30	<0.001
	HF hospitalization	87	83	32	<0.001
Atrial fibrillation on baseline ECG (%)		44	39	35	<0.001
Body mass index, kg/m^2		30.5 ± 6.2	29.4 ± 6.3	30.1 ± 5.9	0.68
Systolic blood pressure, mmHg		127 ± 14	129 ± 16	131 ± 15	<0.001
eGFR, mL/min/1.73 m^2		60 ± 20	63 ± 20	62 ± 19	0.05
LVEF, %		52 ± 8	52 ± 7	54 ± 8	<0.001
NT-proBNP, pg/mL		1168 [474 ,2451]	1119 [473, 2113]	952 [426, 1718]	<0.001
NYHA class (%) II vs. III/IV		51/49	72/28	75/25	<0.001

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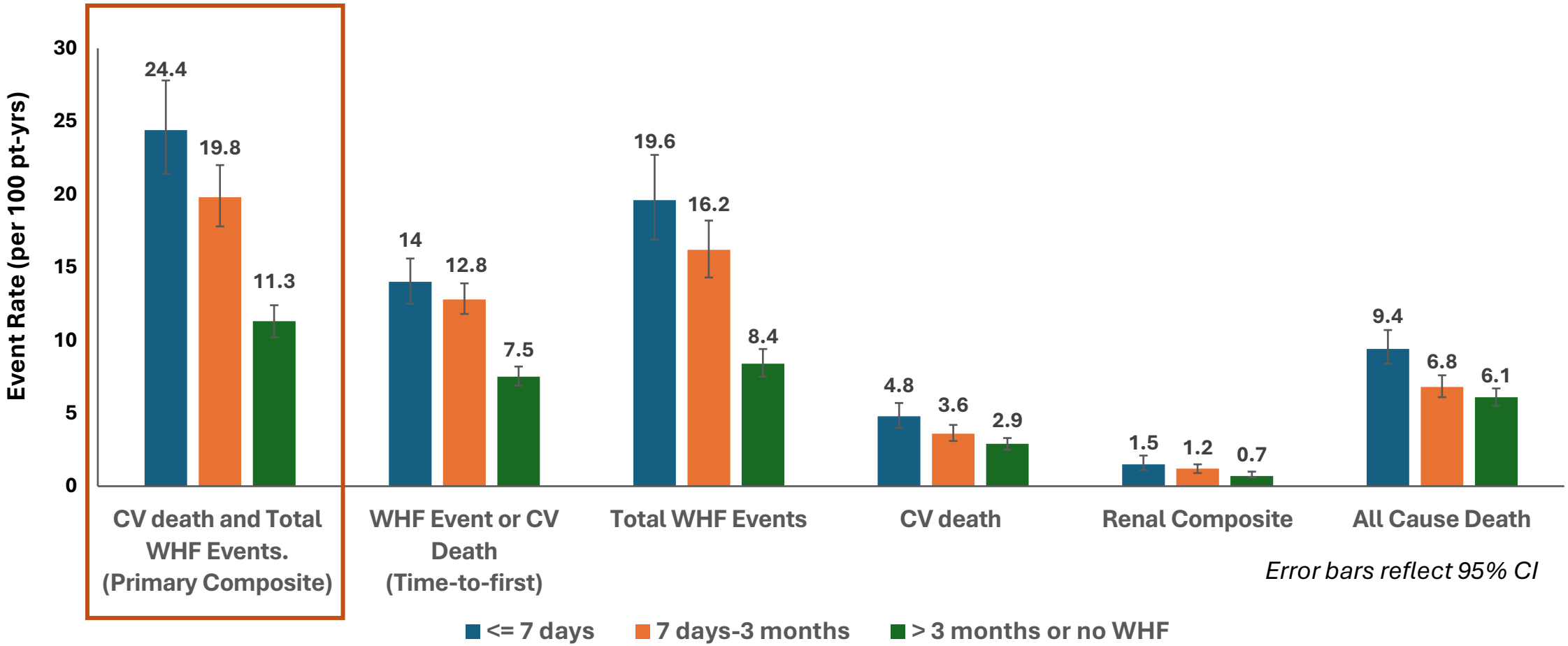
Clinical Event Rates According to Time from WHF to Randomization



Error bars reflect 95% CI

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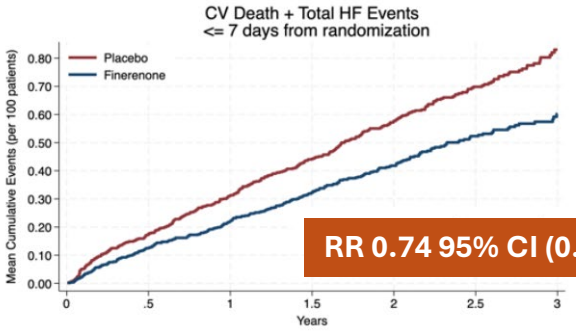
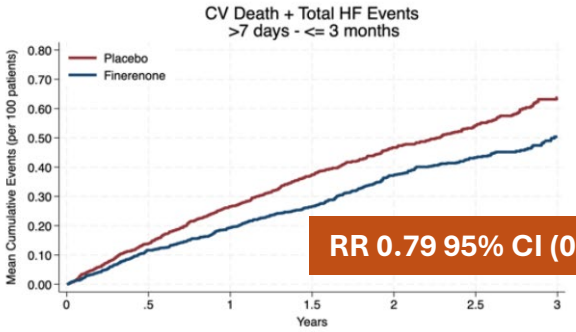
Treatment Effect of Finerenone According to Time from WHF to Randomization (Primary Composite)

<=7 days



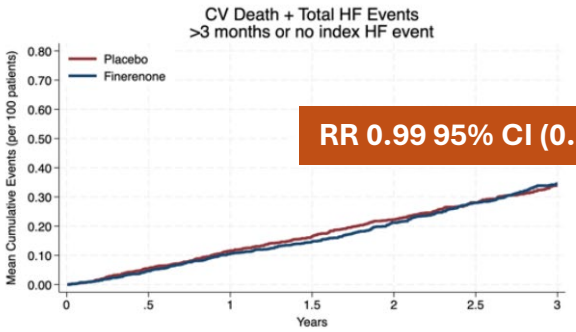
RR 0.74 95% CI (0.57,0.95)

7 days-3 mos



RR 0.79 95% CI (0.64,0.98)

> 3 mos or no WHF



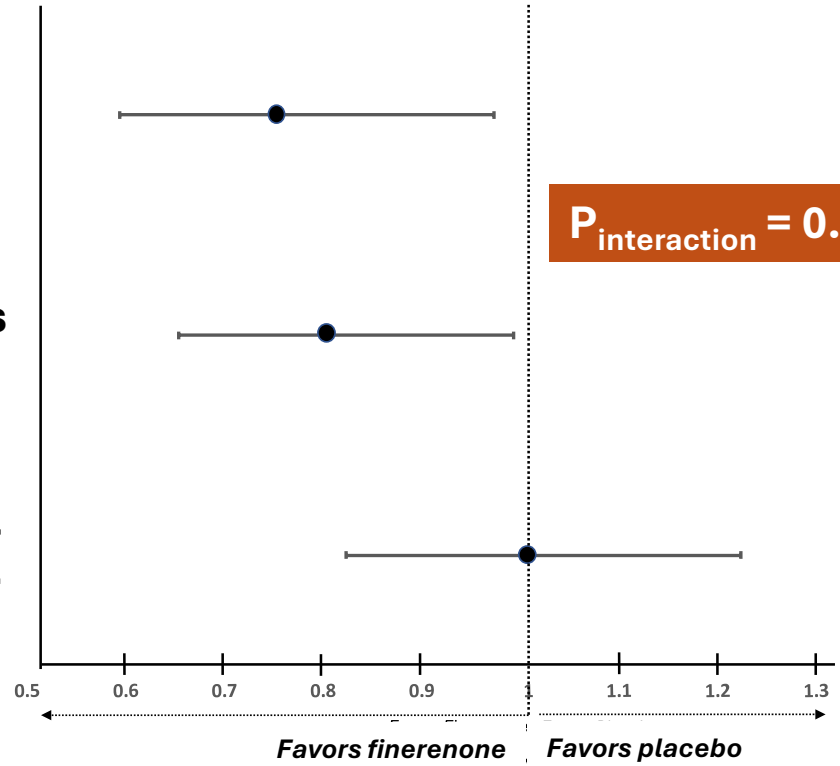
RR 0.99 95% CI (0.81,1.21)

<=7 days

7 days-3 mos

> 3 mos or no WHF

$P_{interaction} = 0.07$



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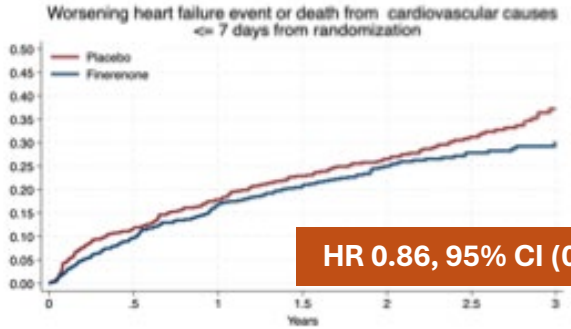
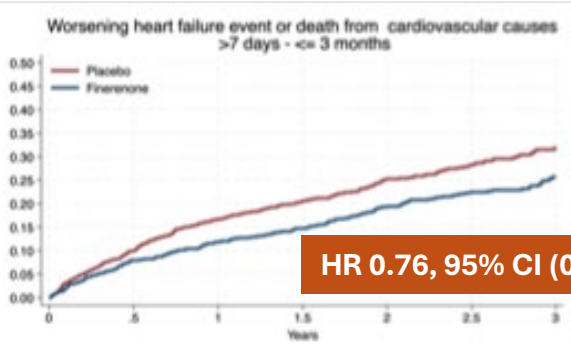
Treatment Effect of Finerenone According to Time from WHF to Randomization (Time to First)

<=7 days



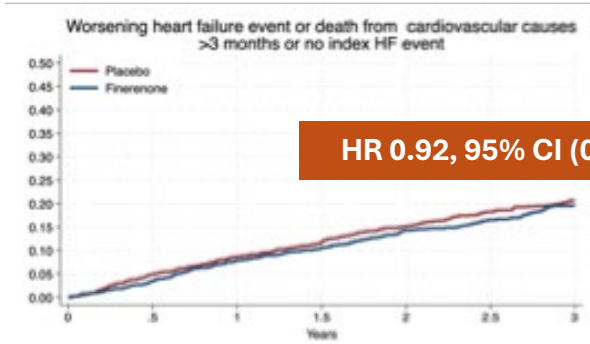
HR 0.86, 95% CI (0.69, 1.06)

7 days-3 mos

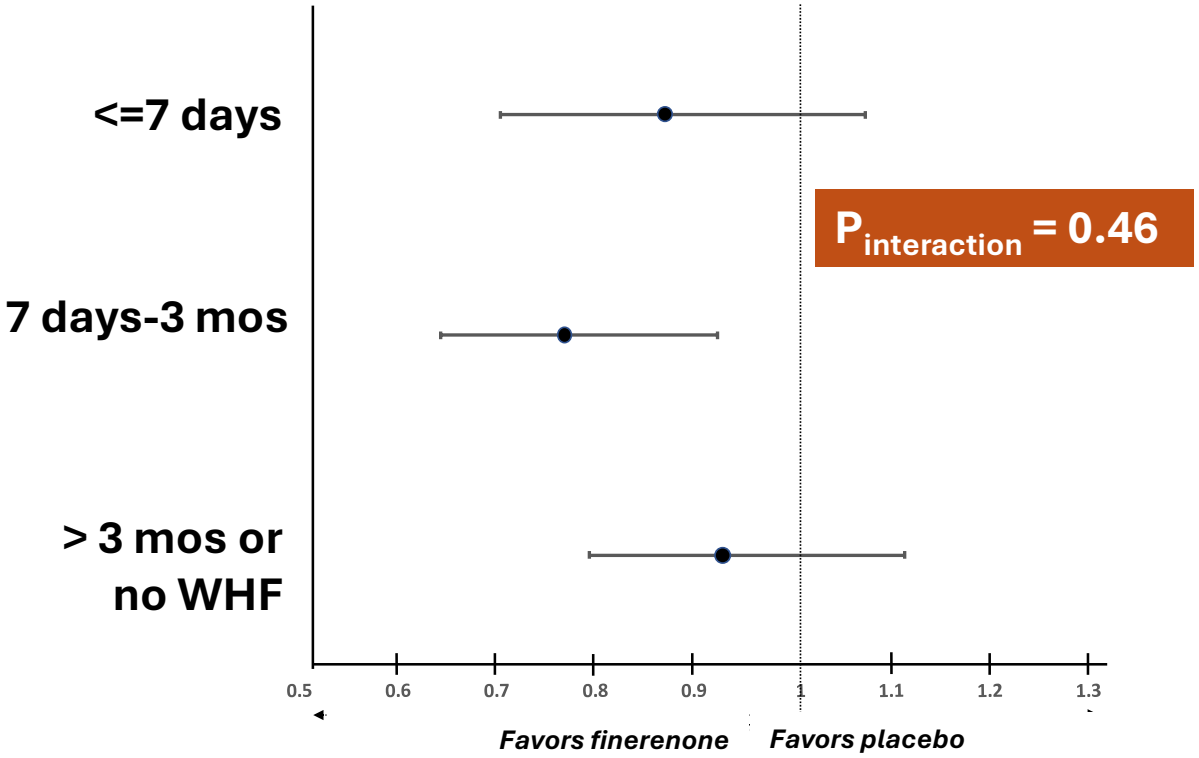


HR 0.76, 95% CI (0.63, 0.91

> 3 mos or no WHF



HR 0.92, 95% CI (0.78, 1.21)



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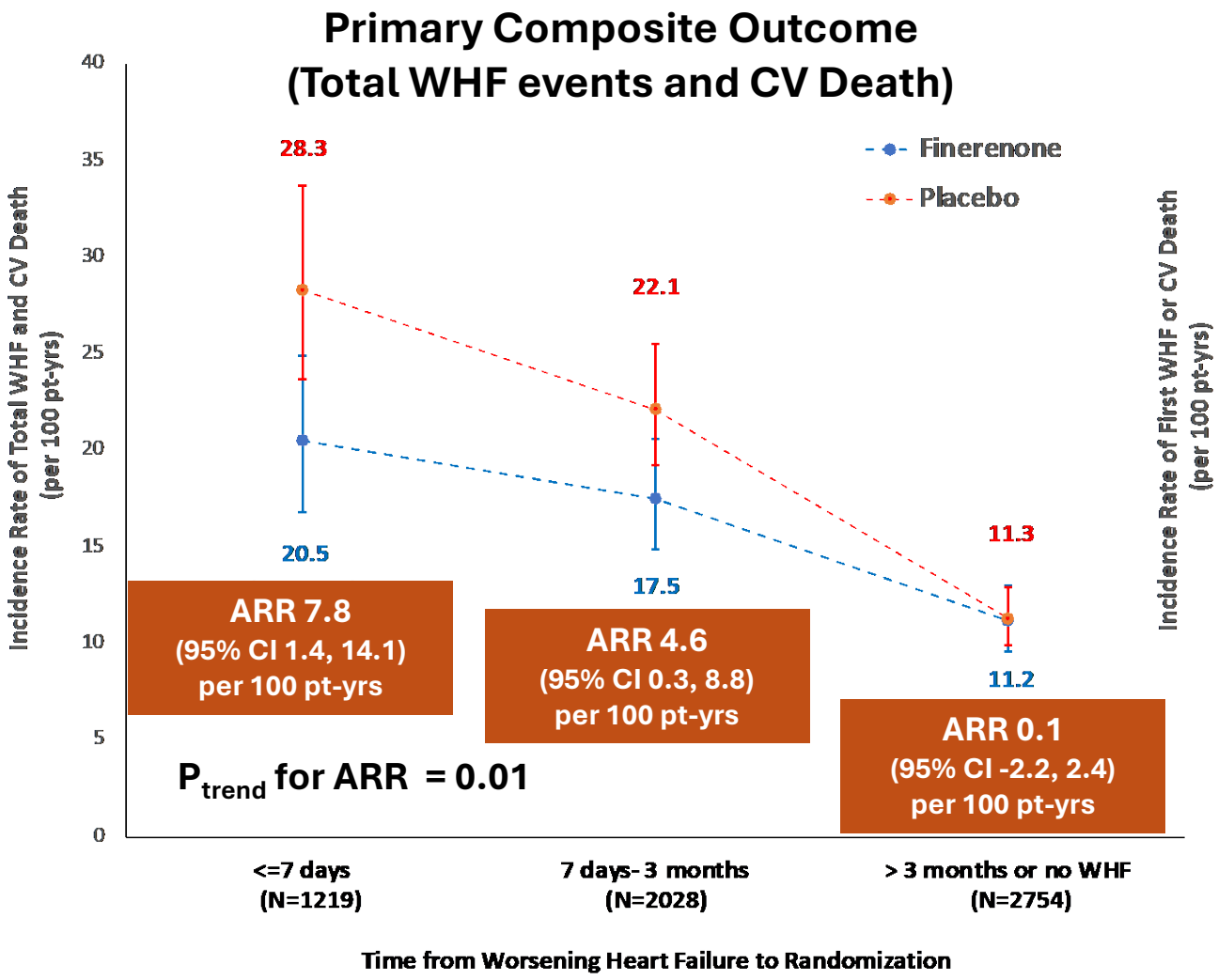
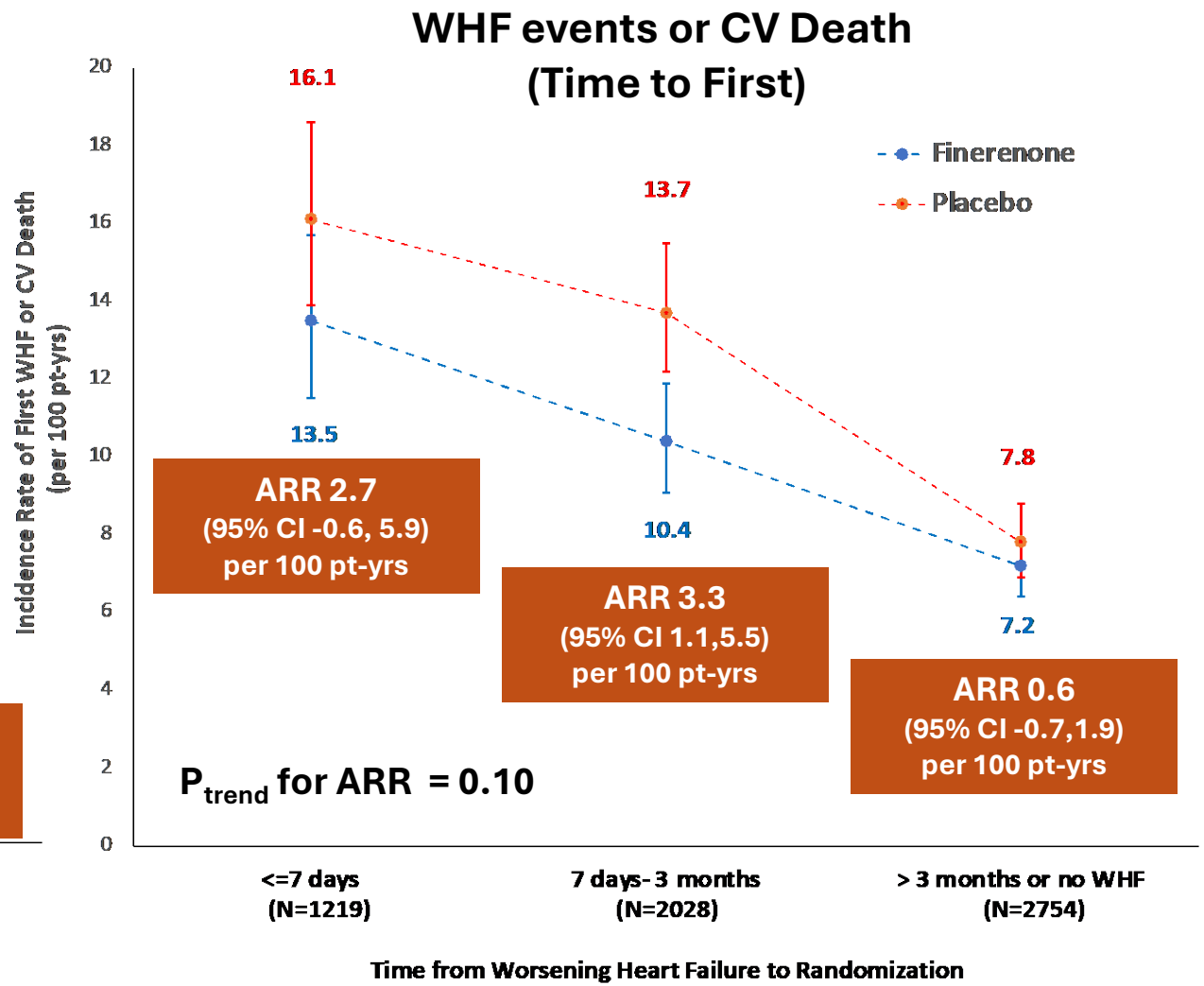
Absolute Risk Reductions with Finerenone According to time from WHF to Randomization





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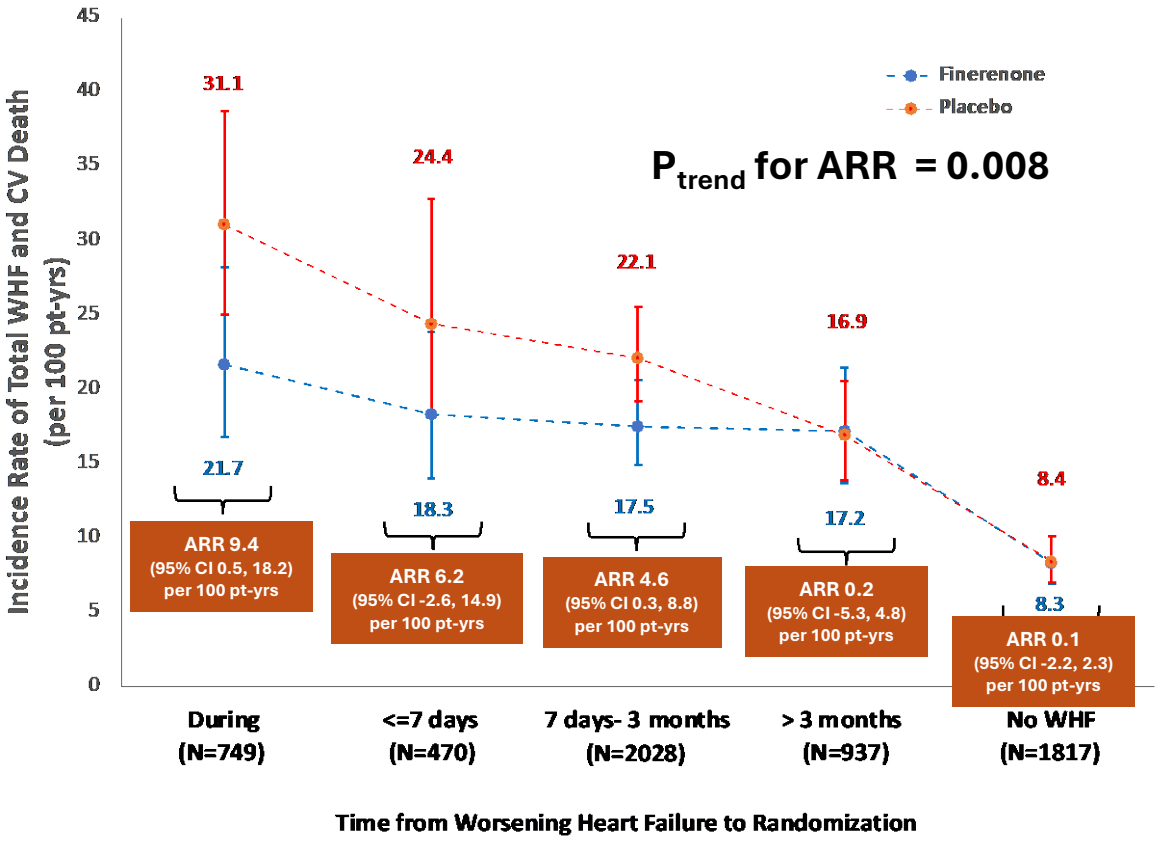
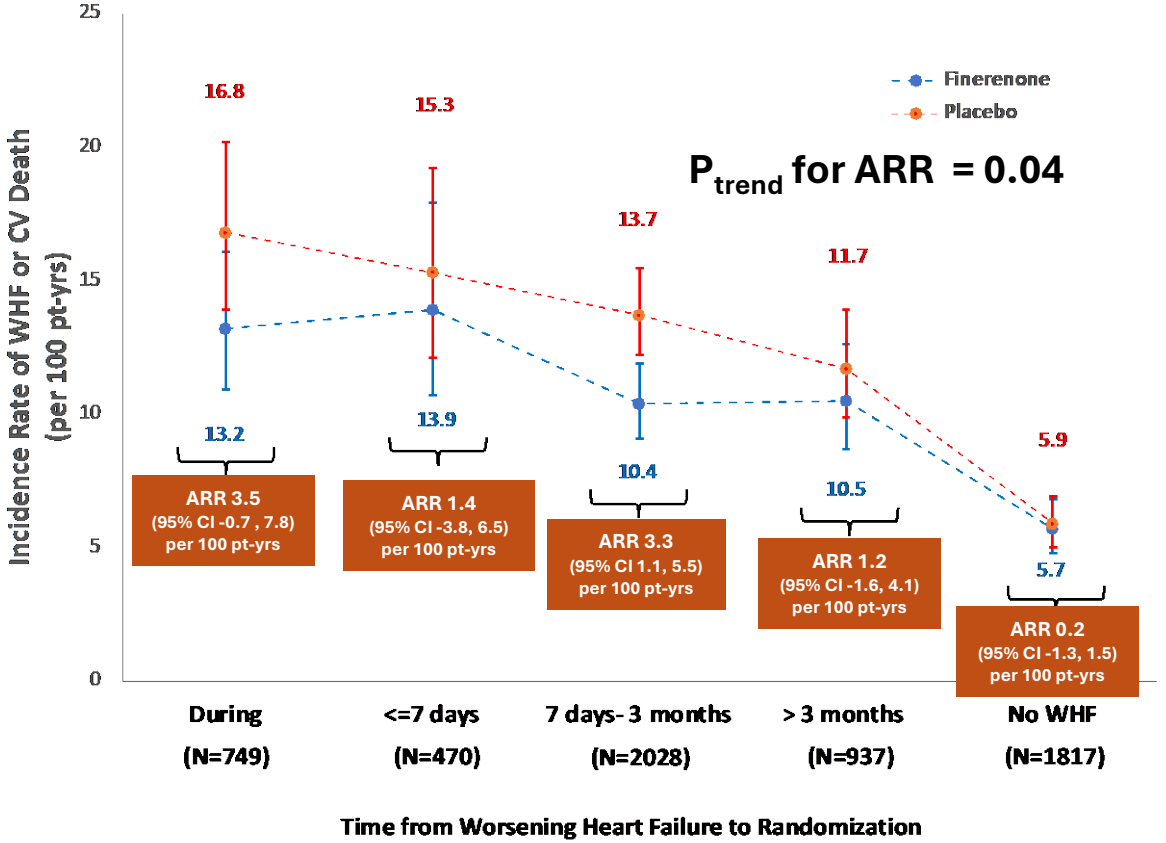
Absolute Risk Reductions with Finerenone According to time from WHF to Randomization (5-category)

Primary Composite Outcome (Total WHF events and CV Death)



WHF events or CV Death (Time to First)



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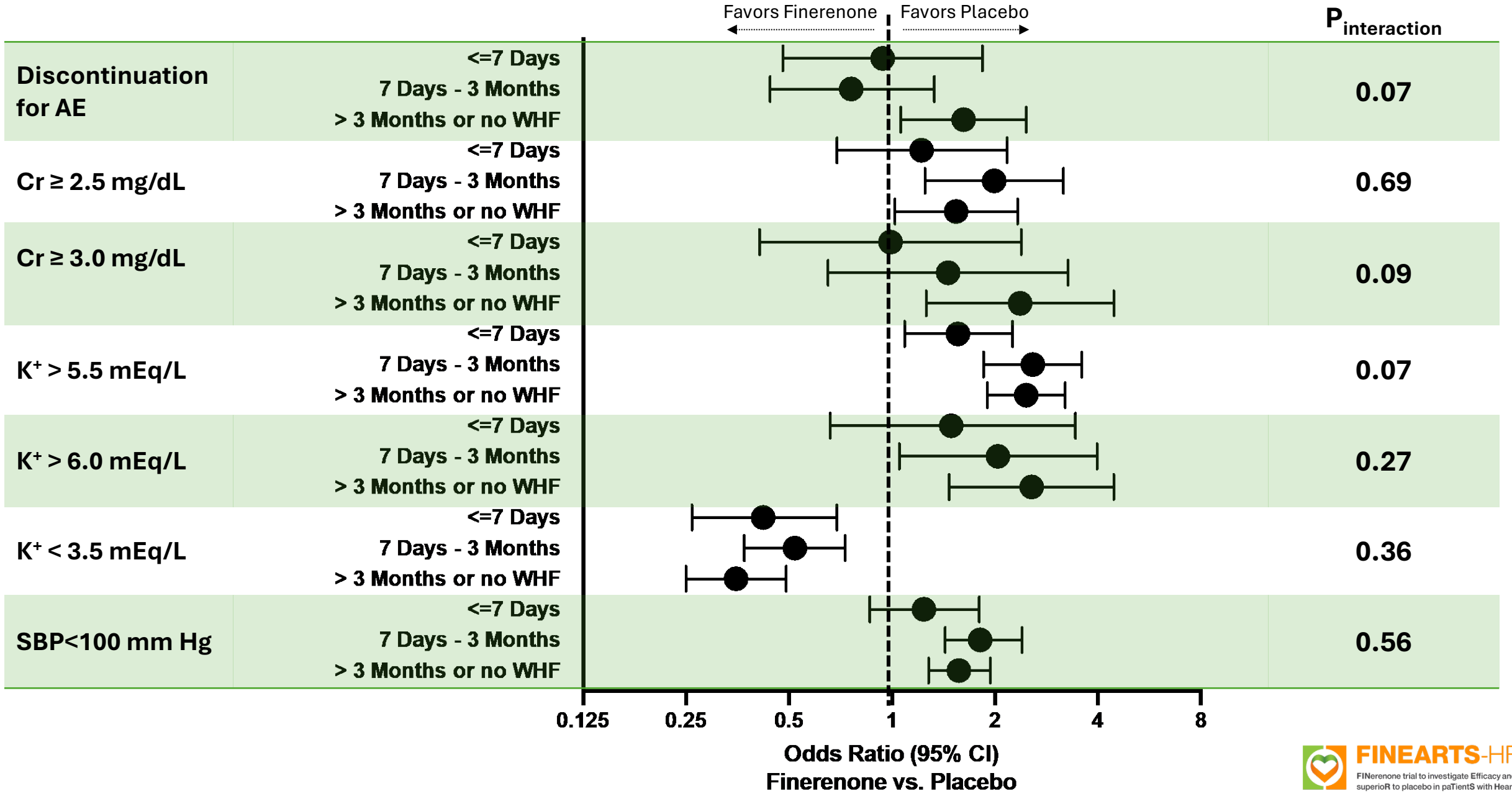
Risk of Adverse Events by Time from WHF to Randomization



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Conclusions

- **HFmrEF/HFpEF Patients with recent WHF (hospitalized or ambulatory) were at higher risk for subsequent overall mortality, CV death and HF events**
- **Although reduction in the** relative **risk of total (first and recurrent) WHF events and CV death appeared to be larger with finerenone for those in close proximity to WHF, no formal treatment interaction was seen and the trend was less pronounced in a time-to-first event analysis**
- **A trend to greater** absolute **risk reduction with finerenone seen in those with recent WHF**
- **Finerenone similarly increased risk of hypotension, hyperkalemia, and worsening renal function and lowered risk of hypokalemia in those with and without recent WHF**
- **These data support a favorable balance of safety and efficacy of finerenone in patients with HFmrEF/HFpEF and a recent WHF event**

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

Finerenone in Patients With a Recent Worsening Heart Failure Event

The FINEARTS-HF Trial

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ABSTRACT

BACKGROUND Patients with heart failure (HF) and a recent worsening heart failure (WHF) event are known to be at high risk of recurrent hospitalization and death, regardless of ejection fraction.

OBJECTIVES This study examined the efficacy and safety of the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone in relation to the recency of a WHF event.

METHODS FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure) was a randomized, double-blind, placebo-controlled trial of finerenone in patients with HF and left ventricular ejection fraction ≥40%. In this prespecified analysis, we assessed the risk of cardiovascular (CV) events and response to finerenone vs placebo in relation to the time from WHF to randomization (during or within 7 days, 7 days to 3 months, >3 months, or no prior WHF). The primary outcome was a composite of total (first and recurrent) WHF events and CV death, analyzed using a proportional rates method.

RESULTS Of 6,001 patients validly randomized to finerenone or placebo, 1,219 (20.3%) were enrolled during (749 [12.5%]) or within 7 days (470 [7.8%]), 2,028 (33.8%) between 7 days and 3 months, and 937 (15.6%) >3 months from a WHF event; 1,817 (30.3%) had no prior history of WHF. Rates of the primary composite outcome varied inversely with time since WHF, with >2-fold higher risk in those enrolled during or within 7 days of WHF compared with those enrolled >3 months from WHF or without prior WHF (risk ratio [RR]: 2.13; 95% CI: 1.82-2.55). Compared to placebo, finerenone appeared to lower the risk of the primary composite to a greater extent in those enrolled within 7 days of WHF (RR: 0.74; 95% CI: 0.57-0.95) or between 7 days and 3 months of WHF (RR: 0.79; 95% CI: 0.64-0.97) than in those >3 months from WHF or without prior WHF (RR: 0.99; 95% CI: 0.81-1.21); however, no definitive treatment-by-time interaction could be confirmed ($P = 0.07$). Greater absolute risk reductions with finerenone were accordingly seen in those with recent WHF ($P_{trend} = 0.011$). The risk of adverse events including hyperkalemia and worsening renal function among patients assigned to finerenone was not increased in those with recent WHF.

CONCLUSIONS Compared with those without recent WHF, patients with HF and mildly reduced or preserved ejection fraction who have experienced a recent WHF event are at higher risk for recurrent HF events and CV death; a possible signal of enhanced absolute treatment benefit with finerenone in this population requires further confirmation in future studies. (Study to Evaluate the Efficacy [Effect on Disease] and Safety of Finerenone on Morbidity [Events Indicating Disease Worsening] & Mortality [Death Rate] in Participants With Heart Failure and Left Ventricular Ejection Fraction [Proportion of Blood Expelled Per Heart Stroke] Greater or Equal to 40% [FINEARTS-HF], NCT04435626; A study to gather information on the influence of study drug finerenone on the number of deaths and hospitalizations in participants with heart failure EudraCT 2020-000306-29) (JACC. 2024;■:■-■)

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2024.09.004

Simultaneously published in *JACC*

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