Efficacy and Safety of Finerenone in Type 2 Diabetes: A Pooled Analysis of Trials of Heart Failure and Chronic Kidney Disease – FINE-HEART

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Disclosures

- **Presenter Disclosure**: Speakers Fees –AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals, Intas pharma; Advisory Board – AstraZeneca, Boehringer Ingelheim, Novartis; Research Funding – AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, Roche Diagnostics; My employer, the University of Glasgow, has been remunerated for my time working on clinical trials by AstraZeneca, Novartis, NovoNordisk and Bayer AG

FINE-HEART: Background & introduction

- The increasing overlap between type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD) and heart failure (HF) is well recognised
- Recently treatment SGLT2 inhibitors have been shown to benefit each of these growing populations alone, and, when found together
- Another common pathway in the pathogenesis of these conditions is mineralocorticoid receptor activation
- Finerenone, a non-steroidal mineralocorticoid receptor antagonist (MRA), has been shown to reduce the risk of cardiovascular events and kidney failure in patients with T2DM and CKD and more recently in patients with HF with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) without T2DM and CKD
- We evaluated the efficacy and safety of finerenone versus placebo on cardiovascular-kidney outcomes in participants with T2DM according to baseline glycemic control and background glucose-lowering therapy (GLT)

Design of FINE-HEART Umbrella Program

FINEHEART

(n=18,991 Participants)

Prospectively Registered:
PROSPERO CRD42024570467

Prespecified in Dedicated Statistical Analysis Plans

FINEARTS-HF

FIDELIO-DKD

FIGARO-DKD

Pooling data in the FINE-HEART program increased precision to robustly assess the efficacy and safety of the non-steroidal MRA finerenone on important cardio-kidney outcomes and is enriched for participants with a high burden of CKM multimorbidity.

Vaduganathan M et al. *Nat Med* (2024). https://doi.org/10.1038/s41591-024-03264-4

Study design of the included trials

	FINEARTS-HF	FIDELIO-DKD and FIGARO-DKD
Validly Randomized	6,001	12,990
Countries	37	48
Patient population	HFmrEF or HFpEF	CKD and T2D
Inclusion criteria	• Adults (≥40 years) • Symptomatic HF • LVEF ≥40% • Elevation natriuretic peptides • Structural heart disease • Recent diuretic use	• Adults (≥18 years old) • T2D • UACR ≥ 30 mg/g • Maximally tolerated RASi
Exclusion criteria	Potassium ≥5.0 mmol/L	Potassium ≥4.8 mmol/L
Dosage and titration	eGFR ≤60: 10 up to 20 mg eGFR >60: 20 up to 40 mg (potentially down to 10 mg)	eGFR <60: 10 up to 20 mg eGFR ≥60: 20 mg (potentially down to 10 mg)
Study duration	2.6 years	2.6 years (FIDELIO-DKD) 3.4 years (FIGARO-DKD)

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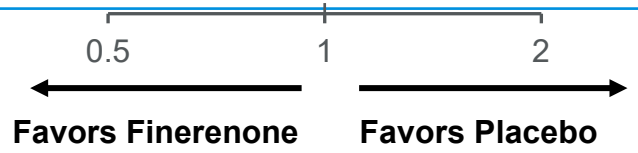
FINE-HEART: Pre-specified Efficacy Endpoints

Outcome	HR (95% CI)	P-value
Primary Endpoint		
CV death (excluding undetermined death)	0.89 (0.78–1.01)	0.076
Prespecified sensitivity analysis: CV death (including undetermined death)	0.88 (0.79–0.98)	0.025
Secondary Endpoints		
Kidney Composite Endpoint	0.80 (0.72–0.90)	<0.001
HF Hospitalization	0.83 (0.75–0.92)	<0.001
CV Death or HF Hospitalization	0.85 (0.78–0.93)	<0.001
New-onset Atrial Fibrillation	0.83 (0.71–0.97)	0.018
Major Adverse Cardiovascular Events	0.91 (0.85–0.98)	0.010
All-cause Death	0.91 (0.84–0.99)	0.027
All-cause Hospitalization	0.95 (0.91–0.99)	0.025
All-cause Death or All-cause Hospitalization	0.94 (0.91–0.98)	0.007



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FINE-HEART: Methods

- Individual patient level data from all three trials were combined
- Patients with T2DM (as defined by investigator report) were included in this analysis
- Subgroups were defined according to baseline glycated hemoglobin (HbA1c) category
  - ≤6.9%
  - ≥7.0 to ≤8.0%
  - ≥8.1%
- Glucose lowering therapy (GLT) regimens were defined according to the following categories:
  - insulin monotherapy
  - insulin plus metformin
  - metformin monotherapy
  - metformin plus sulfonylurea
  - other (any regimen used by <1000 patients)
- Additional groups by SGLT2 inhibitor or GLP-1RA use as well as number of GLT at baseline (0-1, 2, or ≥3)
- Safety according to baseline HbA1c

FINE-HEART: Baseline characteristics by HbA1c

		Baseline HbA_{1c} Category		
	Overall (n=15365)	≤6.9% (n=5564)	≥7.0% to ≤8.0% (n=4780)	≥8.1% (n=5021)
Age, y	65.8 ± 9.8	67.4 ± 9.8	66.2 ± 9.6	63.7 ± 9.6
Female	4938 (32%)	1662 (30%)	1410 (30%)	1866 (37%)
Race				
Asian	3237 (21%)	1254 (23%)	1088 (23%)	895 (18%)
Black	559 (4%)	163 (3%)	179 (4%)	217 (4%)
Other	801 (5%)	226 (4%)	237 (5%)	338 (7%)
White	10768 (70%)	3921 (71%)	3276 (69%)	3571 (71%)
Region				
Asia	3013 (20%)	1178 (21%)	1008 (21%)	827 (17%)
Eastern Europe	4336 (28%)	1618 (29%)	1192 (25%)	1526 (30%)
Latin America	1698 (11%)	477 (9%)	480 (10%)	741 (15%)
North America	2268 (15%)	782 (14%)	719 (15%)	767 (15%)
Western Europe, Oceania and Others	4050 (26%)	1509 (27%)	1381 (29%)	1160 (23%)

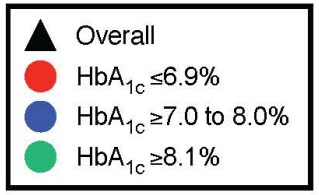
FINE-HEART: Baseline characteristics by HbA1c

		Baseline HbA_{1c} Category		
	Overall (n=15365)	**≤6.9%** (n=5564)	**≥7.0% to ≤8.0%** (n=4780)	**≥8.1%** (n=5021)
Baseline body mass index, kg/m²	31.3 ± 6.0	30.6 ± 6.0	31.1 ± 5.9	32.2 ± 6.1
Baseline systolic blood pressure, mm Hg	135.8 ± 14.5	134.6 ± 14.5	136.2 ± 14.8	136.6 ± 14.2
Baseline potassium, mmol/L	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.4	4.4 ± 0.5
Baseline HbA_{1c}, %	7.6 ± 1.4	6.3 ± 0.5	7.5 ± 0.3	9.2 ± 1.0
Baseline eGFR, mL/min/1.73 m²	57.9 ± 21.5	56.6 ± 20.4	57.3 ± 21.2	60.0 ± 22.6
eGFR category, mL/min/1.73 m²				
<25	183 (1%)	60 (1%)	66 (1%)	57 (1%)
25 to <45	4844 (32%)	1820 (33%)	1552 (33%)	1472 (29%)
45 to <60	4050 (26%)	1530 (28%)	1267 (27%)	1253 (25%)
≥60	6288 (41%)	2154 (39%)	1895 (40%)	2239 (45%)
Baseline UACR, mg/g	423 [114, 1030]	340 [75, 884]	426 [125, 1033]	515 [174, 1176]
Baseline UACR category, mg/g				
<30	1344 (9%)	742 (13%)	332 (7%)	270 (5%)
30 to <300	4895 (32%)	1867 (34%)	1579 (33%)	1449 (29%)
≥300	9054 (59%)	2920 (53%)	2855 (60%)	3279 (66%)

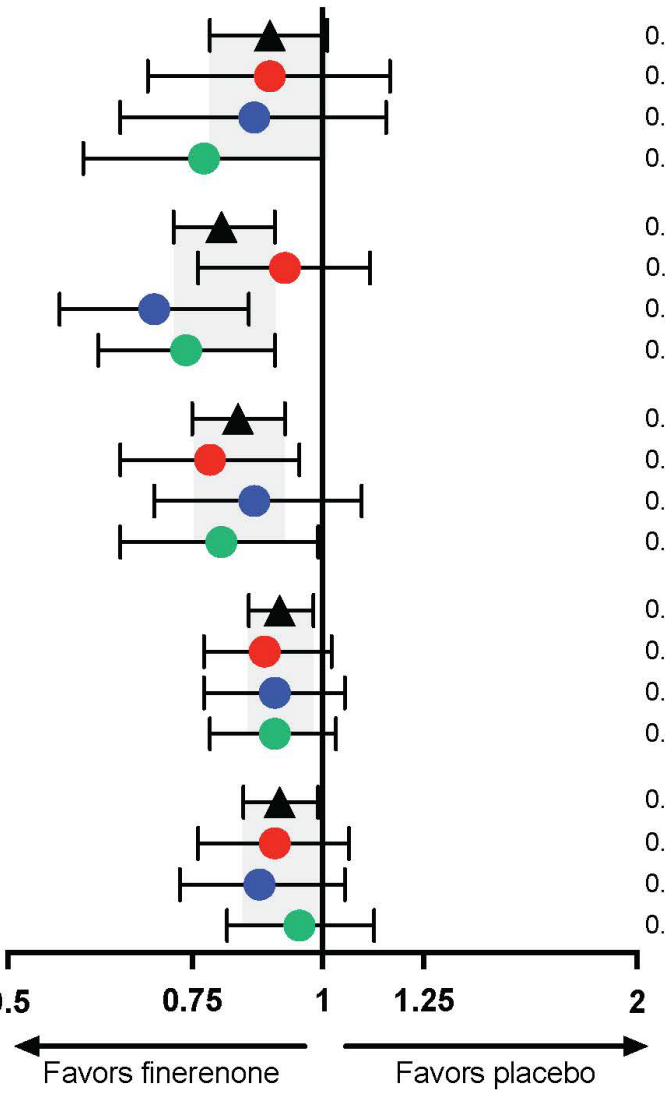
FINE-HEART: Baseline characteristics by HbA1c

		Baseline HbA_{1c} Category		
	Overall (n=15365)	**≤6.9%** (n=5564)	**≥7.0% to ≤8.0%** (n=4780)	**≥8.1%** (n=5021)
Background medication use				
Diuretics	9058 (59%)	3395 (61%)	2775 (5%)	2888 (58%)
ACEi/ARB/ARNI	14902 (97%)	5336 (96%)	4657 (97%)	4909 (98%)
Aspirin	7276 (47%)	2415 (43%)	2316 (49%)	2545 (51%)
Statin	11175 (73%)	3958 (71%)	3569 (75%)	3648 (73%)
SGLT2i	1476 (10%)	462 (8%)	517 (11%)	497 (10%)
GLP-1RA	1101 (7%)	292 (5%)	399 (8%)	410 (8%)
Potassium lowering therapies	190 (1%)	73 (1%)	66 (1%)	51 (1%)

FINE-HEART: Efficacy by Baseline HbA1c categories

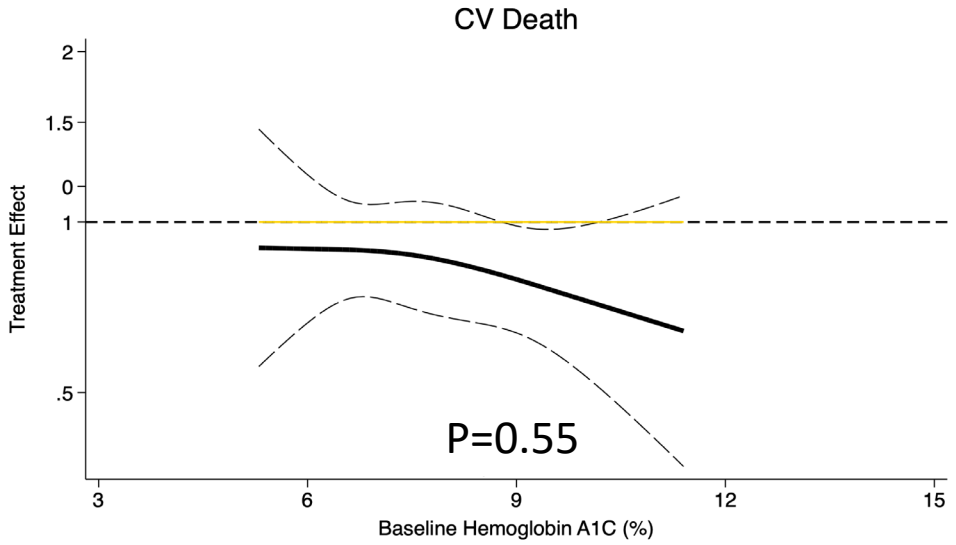


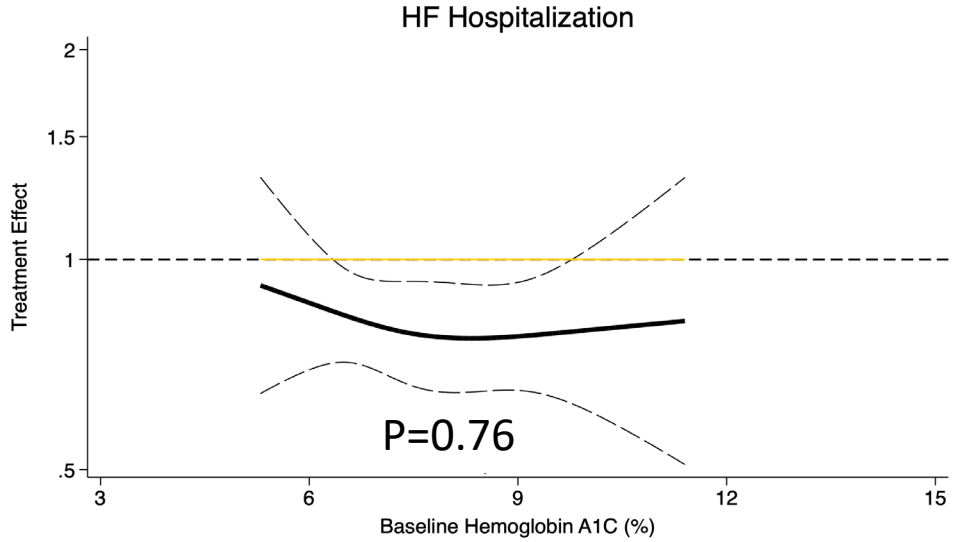
	Finerenone		Placebo		Hazard ratio (95% CI)	$P_{interaction}$
	# Patients with Event (%)	IR per 100 py	# Patients with Event (%)	IR per 100 py		
CV death*	421 (4.4)	1.5	471 (5.0)	1.7	0.89 (0.78-1.01)	0.75
	103 (3.8)	1.3	117 (4.1)	1.4	0.89 (0.68-1.16)	
	85 (3.6)	1.2	100 (4.2)	1.4	0.86 (0.64-1.15)	
	101 (4.0)	1.4	124 (5.0)	1.7	0.77 (0.59-1.00)	
Kidney composite endpoint	557 (5.9)	2.3	685 (7.2)	2.8	0.80 (0.72-0.90)	0.14
	202 (7.4)	2.8	226 (8.0)	3.0	0.92 (0.76-1.11)	
	148 (6.2)	2.3	206 (8.6)	3.2	0.69 (0.56-0.85)	
	175 (6.9)	2.6	224 (9.1)	3.4	0.74 (0.61-0.90)	
HF hospitalization	705 (7.4)	2.7	839 (8.8)	3.2	0.83 (0.75-0.92)	0.80
	174 (6.3)	2.2	222 (7.9)	2.8	0.78 (0.64-0.95)	
	138 (5.8)	2.0	162 (6.8)	2.4	0.86 (0.69-1.09)	
	148 (5.8)	2.0	179 (7.2)	2.6	0.80 (0.64-0.99)	
MACE	1428 (15.0)	5.6	1554 (16.4)	6.2	0.91 (0.85-0.98)	0.99
	362 (13.2)	4.8	409 (14.5)	5.3	0.88 (0.77-1.02)	
	301 (12.6)	4.4	337 (14.1)	5.0	0.90 (0.77-1.05)	
	379 (14.9)	5.4	408 (16.5)	6.1	0.90 (0.78-1.03)	
All-cause death	1042 (11.0)	3.8	1136 (12.0)	4.2	0.91 (0.84-0.99)	0.76
	276 (10.1)	3.4	314 (11.1)	3.8	0.90 (0.76-1.06)	
	224 (9.4)	3.1	257 (10.8)	3.6	0.87 (0.73-1.05)	
	284 (11.1)	3.8	285 (11.5)	3.9	0.95 (0.81-1.12)	

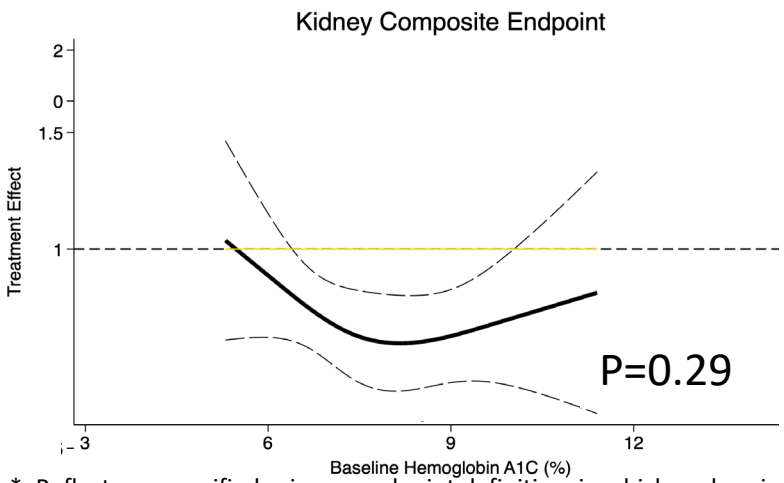


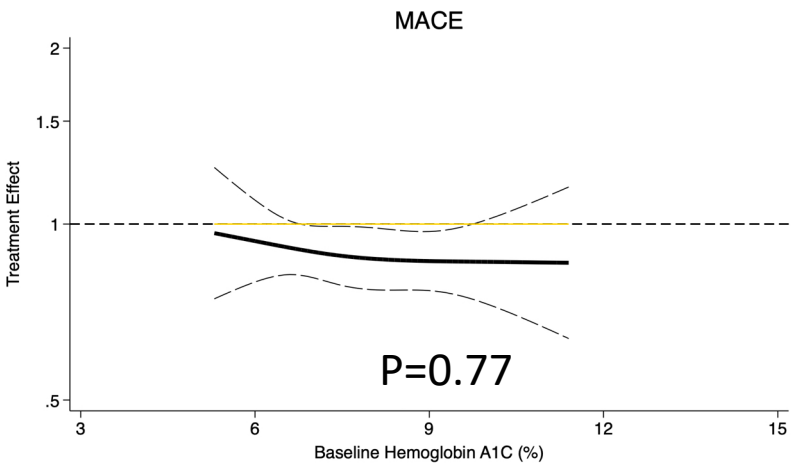
*: Reflects prespecified primary endpoint definition, in which undermined death was excluded.
MACE - composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization, or cardiovascular death
Kidney Outcome - sustained ≥50% decline in eGFR from baseline, sustained decrease in eGFR to <15 mL/min/1.73m2, end-stage kidney disease, and death due to kidney failure

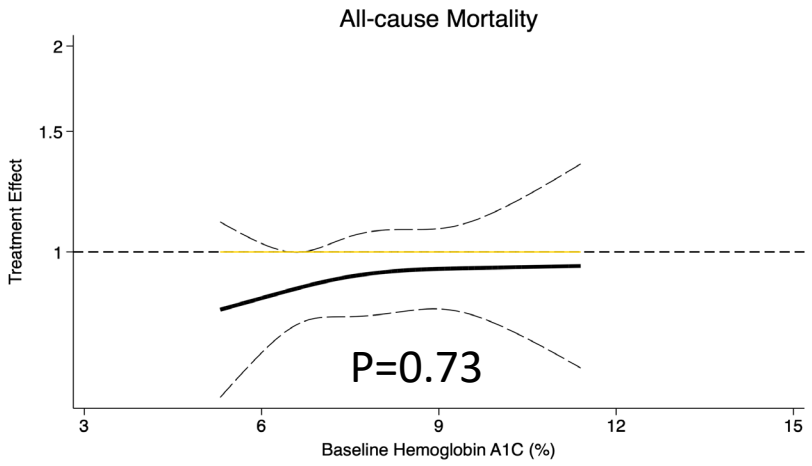
FINE-HEART: Efficacy by Baseline HbA1c (continuous)









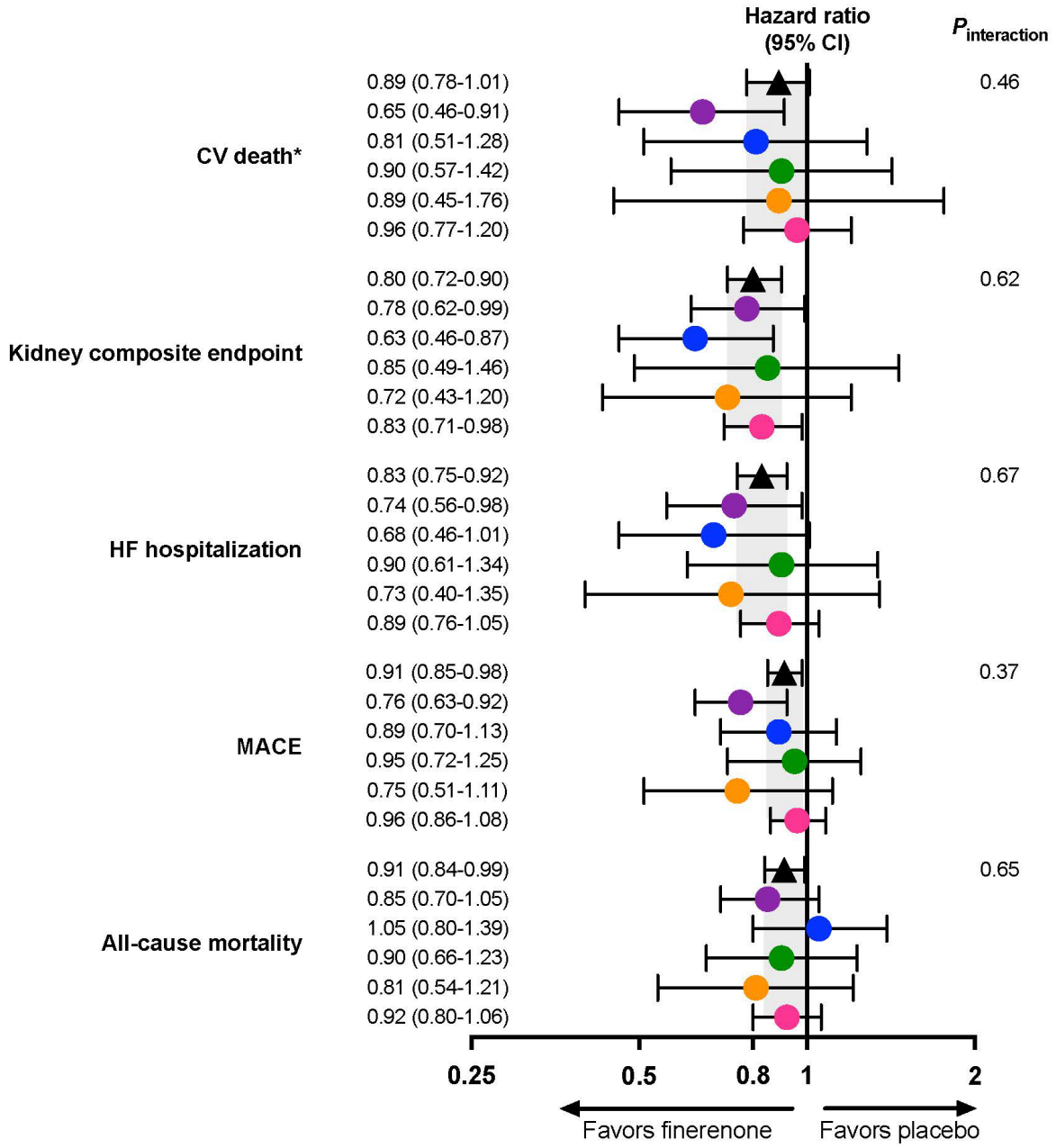


*: Reflects prespecified primary endpoint definition, in which undermined death was excluded.

MACE - composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization, or cardiovascular death

Kidney Outcome - sustained ≥50% decline in eGFR from baseline, sustained decrease in eGFR to <15 mL/min/1.73m2, end-stage kidney disease, and death due to kidney failure

FINE-HEART: Baseline Diabetes Therapy Regimen

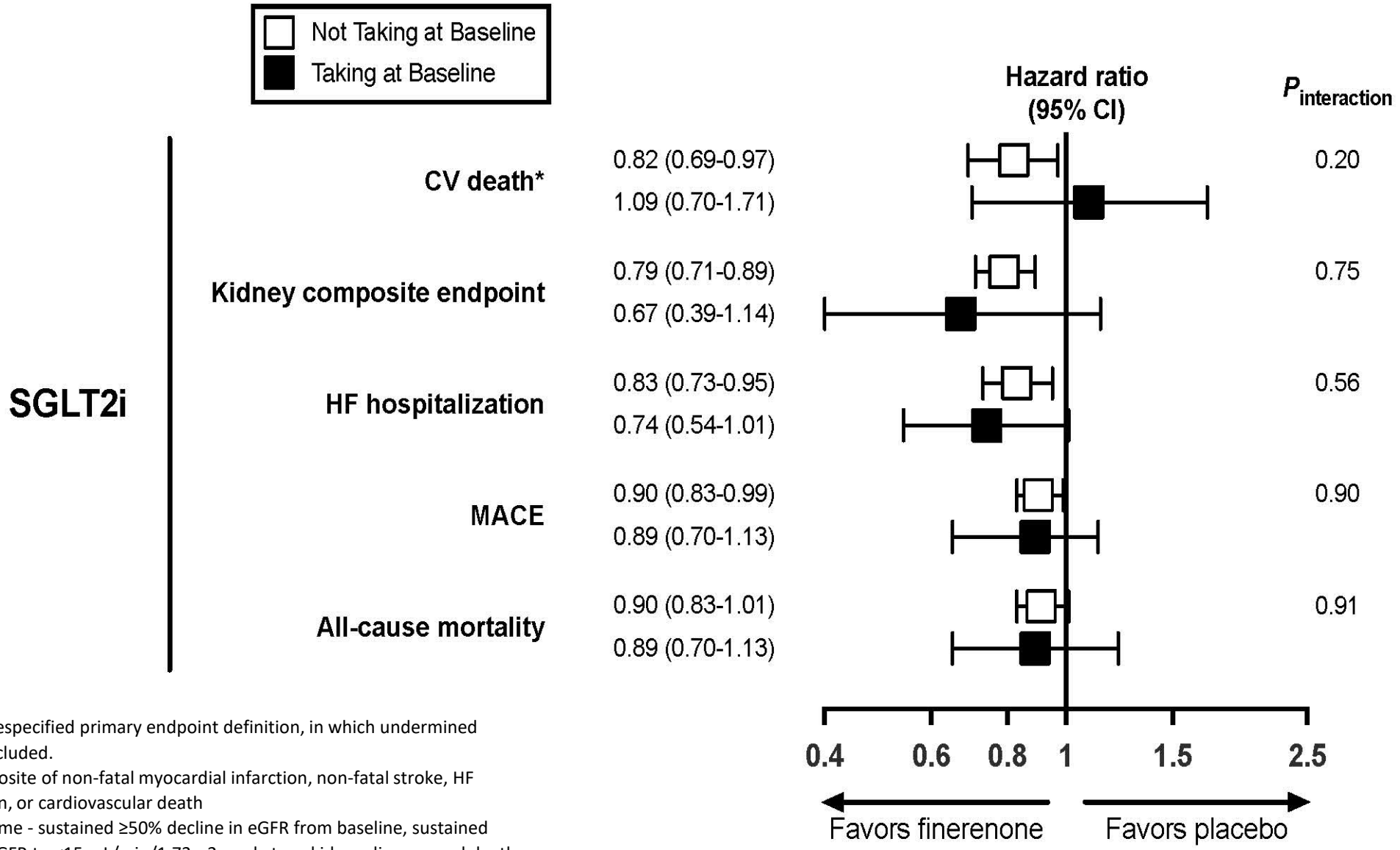


*: Reflects prespecified primary endpoint definition, in which undermined death was excluded.
MACE - composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization, or cardiovascular death
Kidney Outcome - sustained ≥50% decline in eGFR from baseline, sustained decrease in eGFR to <15 mL/min/1.73m2, end-stage kidney disease, and death due to kidney failure

FINE-HEART: Number of Baseline Diabetes Therapies

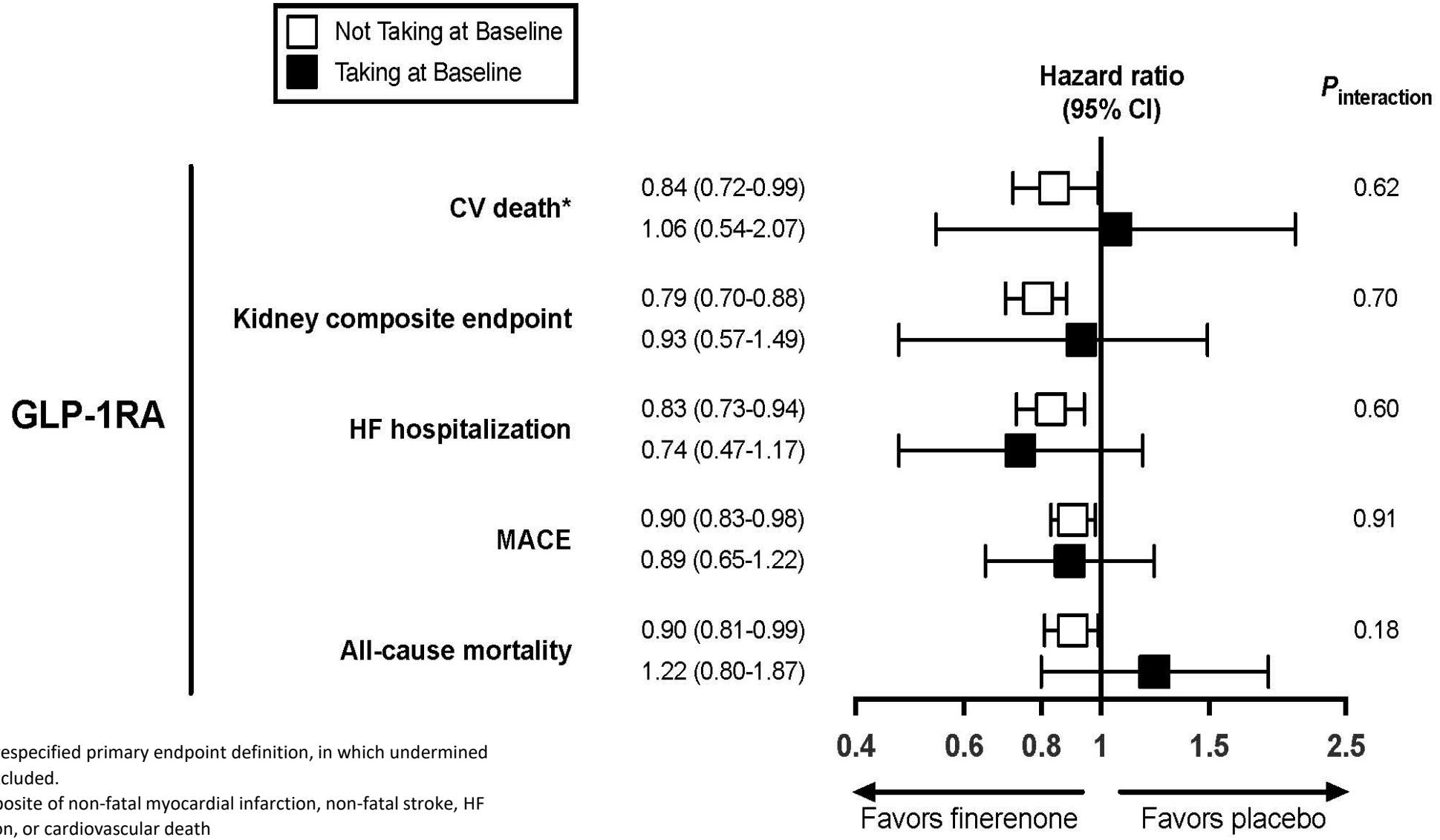
*: Reflects prespecified primary endpoint definition, in which undermined death was excluded.
MACE - composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization, or cardiovascular death
Kidney Outcome - sustained ≥50% decline in eGFR from baseline, sustained decrease in eGFR to <15 mL/min/1.73m2, end-stage kidney disease, and death due to kidney failure

FINE-HEART: Baseline SGLT2 inhibitor use



*: Reflects prespecified primary endpoint definition, in which undermined death was excluded.
MACE - composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization, or cardiovascular death
Kidney Outcome - sustained ≥50% decline in eGFR from baseline, sustained decrease in eGFR to <15 mL/min/1.73m2, end-stage kidney disease, and death due to kidney failure

FINE-HEART: Baseline GLP-1RA use



*: Reflects prespecified primary endpoint definition, in which undermined death was excluded.
MACE - composite of non-fatal myocardial infarction, non-fatal stroke, HF hospitalization, or cardiovascular death
Kidney Outcome - sustained ≥50% decline in eGFR from baseline, sustained decrease in eGFR to <15 mL/min/1.73m2, end-stage kidney disease, and death due to kidney failure

FINE-HEART: Safety by baseline HbA1c – Kidney and blood pressure outcomes

	Baseline HbA_{1c} Category					
	≤6.9%		≥7.0% to ≤8.0%		≥8.1%	
	Finerenone (n=2739)	Placebo (n=2816)	Finerenone (n=2388)	Placebo (n=2385)	Finerenone (n=2545)	Placebo (n=2462)
Acute kidney injury[b]	94 (3.4 %)	96 (3.4 %)	90 (3.8 %)	101 (4.2 %)	107 (4.2 %)	91 (3.7 %)
Acute kidney injury leading to treatment discontinuation	5 (0.2 %)	5 (0.2 %)	4 (0.2 %)	3 (0.1 %)	5 (0.2 %)	4 (0.2 %)
Acute kidney injury leading to hospitalization	41 (1.5 %)	42 (1.5 %)	29 (1.2 %)	41 (1.7 %)	51 (2.0 %)	26 (1.1 %)
Any systolic blood pressure <100 mm Hg	286 (10.6%)	147 (5.3 %)	199 (8.4 %)	136 (5.8 %)	205 (8.1 %)	133 (5.5 %)
Gynecomastia	2 (0.1 %)	1 (0.0 %)	6 (0.3 %)	9 (0.4 %)	4 (0.2 %)	6 (0.2 %)

[b]: Based on investigator-reported adverse events

1 patient with baseline HbA_{1c} ≥8.1% who was randomized to placebo but who actually received finerenone. There were no instances of death due to hyperkalemia.

FINE-HEART: Safety by baseline HbA1c - Potassium

	Baseline HbA_{1c} Category					
	≤6.9%		≥7.0% to ≤8.0%		≥8.1%	
	Finerenone (n=2739)	Placebo (n=2816)	Finerenone (n=2388)	Placebo (n=2385)	Finerenone (n=2545)	Placebo (n=2462)
Any potassium >5.5 mmol/L[a]	468 (17.3%)	187 (6.7 %)	407 (17.3%)	190 (8.1 %)	454 (18.1%)	230 (9.5 %)
Any potassium >6.0 mmol/L[a]	103 (3.8 %)	32 (1.2 %)	76 (3.2 %)	33 (1.4 %)	92 (3.7 %)	44 (1.8 %)
Any potassium <3.5 mmol/L[a]	129 (4.8 %)	303 (10.9%)	107 (4.5 %)	238 (10.1%)	121 (4.8 %)	224 (9.2 %)
Hyperkalemia[b]	382 (13.9%)	193 (6.9 %)	334 (14.0%)	162 (6.8 %)	357 (14.0%)	177 (7.2 %)
Hyperkalemia leading to treatment discontinuation[b]	48 (1.8 %)	18 (0.6 %)	27 (1.1 %)	13 (0.5 %)	43 (1.7 %)	10 (0.4 %)
Hyperkalemia leading to hospitalization[b]	30 (1.1 %)	4 (0.1 %)	16 (0.7 %)	4 (0.2 %)	24 (0.9 %)	8 (0.3 %)

[a]: Based on central laboratory measurements of potassium levels, [b]: Based on investigator-reported adverse events

1 patient with baseline HbA_{1c} ≥8.1% who was randomized to placebo but who actually received finerenone. There were no instances of death due to hyperkalemia.

FINE-HEART: Summary and conclusions

- In the FINE-HEART trials, including participants with investigator-reported T2DM and either CKD or HFmrEF/HFpEF, finerenone reduced kidney disease progression, HF hospitalisation, major adverse cardiovascular events, and all-cause mortality in patients with T2D
- The benefits were consistent across baseline HbA1c levels, number and categories of baseline glucose lowering therapies and regardless of SGLT2 inhibitor or GLP-1RA use
- Hyperkalaemia was more common, and hypokalaemia less common, in those randomised to finerenone (compared to placebo) but this was not different in any of the subgroups above
- Finerenone reduces the risk of a broad range of outcomes in patients with type 2 diabetes mellitus who also have chronic kidney disease or HFmrEF/HFpEF