SUPPLEMENTAL MATERIAL

Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses from the FIGARO-DKD Trial

Supplemental Methods

Criteria for Heart Failure Hospitalization Events and New-Onset Heart Failure

Hospitalization for Heart Failure

Hospitalization for heart failure (HHF) events reported by the investigator were evaluated by the independent cardiologist clinical event committee and were defined as events that meet ALL of the following criteria:

1. Patient was admitted to the hospital for ≥24 hours (or a change in calendar date if hospital admissions and discharge times are unavailable) with a primary diagnosis of heart failure (HF)
2. The patient exhibited documented new or worsening symptoms due to HF on presentation, including at least one of the following:
    a) Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea),
    b) Reduced tolerance to exercise,
    c) Fatigue, or
    d) Other symptoms of worsened end-organ perfusion or volume overload due to HF
3. The patient had objective evidence of worsening HF (consisting of ≥2 physical examination findings, OR 1 physical examination and ≥1 laboratory criterion), as indicated by:
    a) Physical examination findings of:
        i. Peripheral edema
        ii. Increasing abdominal distention or ascites
        iii. Pulmonary rales or crackles or crepitations
        iv. Increased jugular venous pressure and/or hepatojugular reflux
        v. Ventricular gallop
        vi. Clinically significant or rapid weight gain related to fluid retention
    b) Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
        i. B-type natriuretic peptide/N-terminal pro–B-type natriuretic peptide or mid-regional pro-atrial natriuretic peptide increase with decompensation of HF
        ii. Pulmonary congestion (indicated by radiological evidence)

iii. Clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output (indicated by non-invasive or invasive diagnostic evidence)

4. The patient received initiation or intensification of treatment specifically for HF, including at least 1 of the following:
    a) Intravenous diuretic, inotrope, or vasodilator therapy
    b) Mechanical or surgical intervention that includes mechanical circulatory support (e.g. intra-aortic balloon pump, ventricular assist device) and mechanical fluid removal (e.g. ultrafiltration, hemofiltration, dialysis)

New-Onset of Heart Failure

The following definition was used by the independent cardiologist clinical event committee to determine if cases referred by the investigators as HF met criteria for new onset of HF.

New onset of HF was defined as an event that meets ALL of the following criteria:

1. The patient does not have a prior history of HF documented
2. The patient must meet criteria 1 to 3 above for HHF
3. The patient received initiation of treatment specifically for HF as indicated in criterion 4 above, with the difference that the route of administration could be oral and/or intravenous

Additional Outcomes Analyzed

The composite cardiovascular outcome (defined as time to onset of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or HHF) was analyzed in the full analysis set.

Supplemental Results

Effect of Finerenone on Cardiovascular Outcomes by History of Heart Failure

In the total study population, finerenone significantly lowered the composite outcome of time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or HHF compared with placebo (**Supplemental Figure III**), whereby the incidence occurred in 12.4% versus 14.2% patients, respectively (hazard ratio, 0.87 [95% CI, 0.76–0.98]; *P*=0.03).[15] Patients with a history of HF had a higher risk of composite cardiovascular outcome (as indicated by the placebo incidence of 10.55 per 100 patient-years in patients with a history of HF versus 4.03

per 100 patient-years in patients without a history of HF). The effect of finerenone to reduce the risk of the composite cardiovascular outcome was not modified in patients with and without a history of HF (hazard ratio, 0.84 [95% CI, 0.60–1.19]; and hazard ratio, 0.88 [95% CI, 0.77–1.01], respectively).

Supplemental Tables

Supplemental Table I. Patient Baseline Characteristics by History of HF at Baseline (Split by Treatment Arm)

Characteristic	With history of HF		Without history of HF	
	Finerenone (n=290)	Placebo (n=281)	Finerenone (n=3396)	Placebo (n=3385)
Age, y	64.89 (8.95)	66.32 (8.75)	64.06 (9.73)	63.95 (10.08)
Male sex	182 (62.8%)	168 (59.8%)	2346 (69.1%)	2409 (71.2%)
Race				
White	263 (90.7%)	239 (85.1%)	2409 (70.9%)	2366 (69.9%)
Black/African American	15 (5.2%)	11 (3.9%)	98 (2.9%)	134 (4.0%)
Asian	10 (3.4%)	18 (6.4%)	705 (20.8%)	721 (21.3%)
Systolic blood pressure, mm Hg	135.71 (13.58)	134.97 (13.88)	135.82 (14.00)	135.76 (14.07)
Diastolic blood pressure, mm Hg	77.58 (9.71)	75.95 (10.46)	76.67 (9.53)	76.87 (9.47)
BMI, kg/m^2	33.26 (6.42) [289/290]	32.36 (5.88) [281/281]	31.31 (5.98) [3386/3396]	31.32 (5.93) [3378/3385]
Duration of diabetes, y	15.11 (9.60) [290/290]	15.10±8.89 [281/281]	14.48 (8.50) [3392/3396]	14.39 (8.40) [3382/3385]
HbA1c, %	8.04 (1.48) [289/290[	7.91 (1.33) [279/281]	7.72 (1.38) [3392/3396]	7.67 (1.35) [3381/3385]
Serum potassium, mEq/L, mean ± SD (n/N)	4.42 (0.50) [290/290]	4.38 (0.45) [280/281]	4.32 (0.42) [3396/3396]	4.33 (0.43) [3384/3385]
eGFR, mL/min/1.73 m^2	63.97 (21.39) [290/290]	62.80 (22.00) [280/281]	67.93 (21.64) [3396/3396]	68.42 (21.66) [3385/3385]
eGFR, mL/min/1.73 m^2				

<25	3 (1.0%)	2 (0.7%)	12 (0.4%)	10 (0.3%)
25 to <45	62 (21.4%)	69 (24.6%)	579 (17.0%)	541 (16.0%)
45 to <60	67 (23.1%)	70 (24.9%)	678 (20.0%)	719 (21.2%)
≥60	158 (54.5%)	139 (49.5%)	2127 (62.6%)	2115 (62.5%)
UACR, mg/g	274.58 (110.69–745.03)	246.16 (84.95–729.24)	304.24 (105.06–749.24)	321.50 (113.28–731.01)
UACR, mg/g				
<30	12 (4.1%)	11 (3.9%)	97 (2.9%)	87 (2.6%)
30 to <300	138 (47.6%)	145 (51.6%)	1588 (46.8%)	1543 (45.6%)
≥300	140 (48.3%)	125 (44.5%)	1711 (50.4%)	1753 (51.8%)
Mean waist–hip ratio	1.01(0.16) [289/290]	1.00 (0.13) [280/281]	1.00 (0.10) [3379/3396]	1.00 (0.11) [3372/3385]
Waist circumference, cm	110.64 (15.26) [290/290]	109.50 (14.78) [280/281]	107.02 (15.21) [3384/3396]	106.97 (14.80) [3377/3385]
hs-CRP, mg/L	6.03 (7.88) [290/290]	4.81 (8.67) [281/281]	4.97 (11.74) [3396/3396]	4.66 (9.29) [3382/3385]
Heart rate, bpm	71.85 (10.70)	71.54 (10.97)	74. 05 (11.38)	73.72±11.58
History of cardiovascular disease	197 (67.9%)	195 (69.4%)	1479 (43.6%)	1459 (43.1%)
Coronary artery disease	156 (53.8%)	166 (59.1%)	992 (29.2%)	981 (29.0%)
Atrial fibrillation	60 (20.7%)	53 (18.9%)	248 (7.3%)	250 (7.4%)
Hypertension	270 (93.1%)	247 (87.9%)	3166 (93.2%)	3151 (93.1%)
Current smoker	38 (13.1%)	40 (14.2%)	613 (18.1%)	596 (17.6%)
Medication use at baseline				
ACE inhibitors	152 (52.4%)	145 (51.6%)	1424 (41.9%)	1416 (41.8%)
ARBs	137 (47.2%)	136 (48.4%)	1971 (58.0%)	1968 (58.1%)
Beta blocker	204 (70.3%)	202 (71.9%)	1570 (46.2%)	1560 (46.1%)
Diuretics	180 (62.1%)	183 (65.1%)	1568 (46.2%)	1565 (46.2%)

Loop diuretics	111 (38.3%)	109 (38.8%)	485 (14.3%)	479 (14.2%)
Thiazide diuretics	41 (14.1%)	49 (17.4%)	868 (25.6%)	839 (24.8%)
Statins	200 (69.0%)	214 (76.2%)	2352 (69.3%)	2418 (71.4%)
Potassium supplements	13 (4.5%)	15 (5.3%)	98 (2.9%)	89 (2.6%)
Potassium-lowering agents	2 (0.7%)	0	22 (0.6%)	22 (0.6%)
Glucose-lowering therapies	279 (96.2%)	275 (97.9%)	3328 (98.0%)	3314 (97.9%)
Insulin and analogues	185 (63.8%)	178 (63.3%)	1838 (54.1%)	1792 (52.9%)
Metformin	174 (60.0%)	164 (58.4%)	2387 (70.3%)	2342 (69.2%)
Sulfonylureas	85 (29.3%)	76 (27.0%)	952 (28.0%)	949 (28.0%)
DPP-4is	48 (16.6%)	49 (17.4%)	848 (25.0%)	811 (24.0%)
GLP-1RAs	17 (5.9%)	7 (2.5%)	291 (8.6%)	235 (6.9%)
SGLT-2is	18 (6.2%)	14 (5.0%)	296 (8.7%)	290 (8.6%)

Data are mean (SD), mean (SD) [n/N], median (±IQR), or n (%).

Medical history of HF was determined by the investigator.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; and UACR, urine albumin-to-creatinine ratio.

Supplemental Table II. Summary of HF-Associated Outcomes

HHF outcomes	Finerenone		Placebo		HR*/RR# (95% CI)	*P*-value
	n/N (%)	n/100 PY	n/N (%)	n/100 PY		
In patients without a history of HF						
First HHF	65/3396 (1.9%)	0.57	95/3385 (2.8%)	0.84	0.68 (0.50–0.93)	0.0162
In the overall population						
CV death and first HHF	290/3686 (7.9%)	2.38	351/3666 (9.6%)	2.92	0.82 (0.70–0.95)	0.0105
HF-related death and first HHF	120/3686 (3.3%)	0.99	173/3666 (4.7%)	1.44	0.68 (0.54–0.86)	0.0013
First HHF	117/3686 (3.2%)	0.96	163/3666 (4.5%)	1.36	0.71 (0.56–0.90)	0.0043
CV death or total HHF	NA	3.04	NA	3.84	0.79 (0.66–0.95)	0.0131
HF-related death and total HHF	NA	1.55	NA	2.21	0.70 (0.53–0.93)	0.0139
Total HHF	NA	1.47	NA	2.09	0.70 (0.52–0.94)	0.0177

CV indicates cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; NA, not applicable; PY, patient-years; and RR, rate ratio.

* For time-to-first event outcomes.

For time-to-total event outcomes (first and current events).

Supplemental Table III. Safety Outcomes by History of HF at Baseline

Treatment-emergent AEs	With history of HF		Without history of HF	
	Finerenone (n=289)	Placebo (n=281)	Finerenone (n=3394)	Placebo (n=3377)
Any AE	230 (79.6%)	241 (85.8%)	2904 (85.6%)	2888 (85.5%)
Any study drug-related AE	28 (9.7%)	32 (11.4%)	532 (15.7%)	381 (11.3%)
Any AE leading to discontinuation of study drug	8 (2.8%)	13 (4.6%)	199 (5.9%)	170 (5.0%)
Any SAE*	100 (34.6%)	89 (31.7%)	1058 (31.2%)	1126 (33.3%)
Any study drug-related SAE*	2 (0.7%)	1 (0.4%)	33 (1.0%)	26 (0.8%)
Any SAE* leading to discontinuation of study drug	3 (1.0%)	3 (1.1%)	67 (2.0%)	73 (2.2%)
AE with outcome death	6 (2.1%)	8 (2.8%)	73 (2.2%)	92 (2.7%)
Any hyperkalemia	24 (8.3%)	13 (4.6%)	372 (11.0%)	180 (5.3%)
Drug-related	9 (3.1%)	6 (2.1%)	231 (6.8%)	108 (3.2%)
Leading to hospitalization	2 (0.7%)	0	19 (0.6%)	2 (<0.1%)
Leading to permanent discontinuation of study drug	1 (0.3%)	2 (0.7%)	45 (1.3%)	11 (0.3%)
SAE*	2 (0.7%)	0	23 (0.7%)	4 (0.1%)
Leading to death	0	0	0	0

Treatment-emergent serum $[K^+]$				
>5.5 mmol/L	45/276 (16.3%)	23/272 (8.5%)	433/3341 (13.0%)	191/3323 (5.7%)
>6.0 mmol/L	6/282 (2.1%)	2/276 (0.7%)	79/3355 (2.4%)	40/3341 (1.2%)

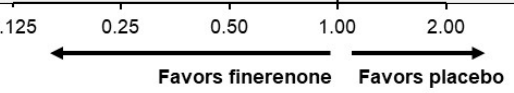
Data are n (%) or n/N (%).

AE indicates adverse event; HF, heart failure; $[K^+]$, potassium concentration; and SAE, serious adverse event.

* SAEs were defined as treatment-emergent events that: *(1)* resulted in death; *(2)* were life-threatening; *(3)* required inpatient hospitalization (or prolongation of existing hospitalization); *(4)* caused persistent or significant disability/incapacity; *(5)* were congenital abnormalities or birth defects; or *(6)* were judged by the investigator to be a serious or important medical event.

Supplemental Figures

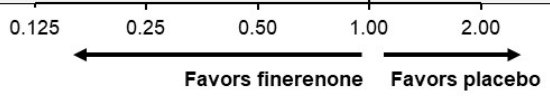
Subgroup	Finerenone		Placebo		Hazard ratio (95% CI)	Interaction *P*-value
	n/N (%)	n/100 PY	n/N (%)	n/100 PY		
Sex						
Male	72/2528	0.9	129/2577	1.5	0.55(0.41–0.74)	0.02
Female	48/1158	1.3	44/1089	1.3	0.99 (0.65–1.49)	
Age, years						
<65	49/1753	0.9	67/1757	1.2	0.72 (0.50–1.05)	0.72
≥65	71/1933	1.1	106/1909	1.7	0.66 (0.49–0.90)	
Duration of diabetes, years						
<13.3 (median)	42/1870	0.7	67/1802	1.1	0.61 (0.41–0.89)	0.41
≥13.3 (median)	78/1812	1.3	106/1861	1.8	0.75 (0.56–1.00)	
BMI, kg/m^2						
<30	46/1628	0.9	61/1649	1.1	0.76 (0.52–1.12)	0.51
≥30	74/2047	1.1	112/2010	1.7	0.64 (0.48–0.87)	
History of CV disease						
Yes	76/1676	1.5	120/1654	2.4	0.62 (0.47–0.83)	0.28
No	44/2010	0.6	53/2012	0.8	0.82 (0.55–1.22)	
Baseline diuretic use						
Yes	79/1748	1.4	125/1748	2.2	0.64 (0.48–0.85)	0.34
No	41/1938	0.6	48/1918	0.8	0.83 (0.54–1.26)	
Baseline insulin use						
Yes	78/2023	1.2	126/1970	2.0	0.60 (0.45–0.80)	0.13
No	42/1663	0.8	47/1696	0.8	0.90 (0.59–1.37)	
Baseline SGLT-2i use						
Yes	6/314	0.6	14/304	1.5	0.34 (0.13–0.92)	0.21
No	114/3372	1.0	159/3362	1.4	0.71 (0.56–0.91)	
Baseline GLP-1RA use						
Yes	6/308	0.6	10/242	1.2	0.46 (0.16–1.31)	0.39
No	114/3378	1.0	163/3424	1.5	0.70 (0.55–0.90)	



Supplemental Figure I. Time to HF-related death or first HHF in key prespecified and post hoc subgroups.

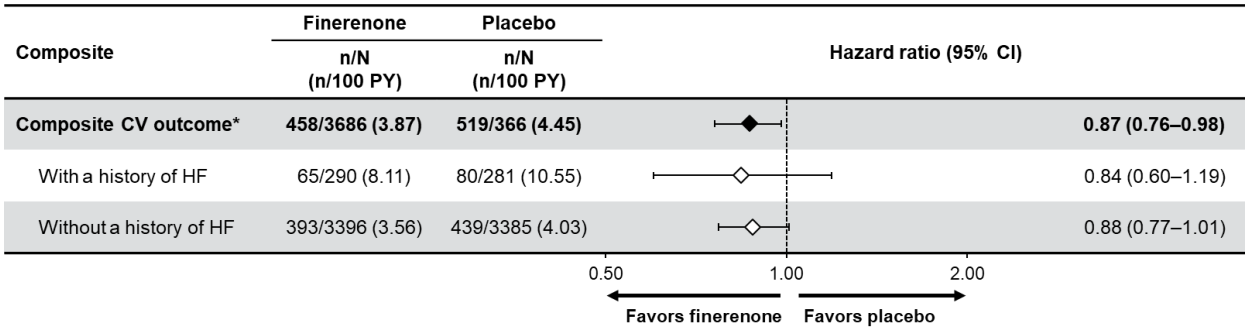
BMI indicates body mass index; CI confidence interval; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HHF, hospitalization for heart failure; PY, patient-years; and SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

Subgroup	Finerenone		Placebo		Hazard ratio (95% CI)	Interaction *P*-value
	n/N (%)	n/100 PY	n/N (%)	n/100 PY		
Sex						
Male	70/2528	0.8	124/2577	1.5	0.56 (0.42–0.75)	0.01
Female	47/1158	1.3	39/1970	1.1	1.07 (0.70–1.65)	
Age, years						
<65	48/1753	0.8	66/1757	1.2	0.72 (0.49–1.05)	0.92
≥65	69/1933	1.1	97/1909	1.6	0.70 (0.52–0.96)	
Duration of diabetes, years						
<13.3 (median)	40/1870	0.6	63/1802	1.1	0.61 (0.41–0.91)	0.34
≥13.3 (median)	77/1812	1.3	100/1861	1.7	0.78 (0.58–1.05)	
BMI, kg/m^2						
<30	45/1628	0.8	57/1649	1.0	0.80 (0.54–1.18)	0.49
≥30	72/2047	1.1	106/2010	1.6	0.67 (0.49–0.90)	
History of CV disease						
Yes	75/1676	1.5	113/1654	2.3	0.66 (0.49–0.88)	0.36
No	42/2010	0.6	50/2012	0.7	0.83 (0.55–1.25)	
Baseline diuretic use						
Yes	76/1748	1.3	119/1748	2.1	0.65 (0.48–0.86)	0.22
No	41/1938	0.6	44/1918	0.7	0.90 (0.59–1.38	
Baseline insulin use						
Yes	77/2023	1.2	118/1970	1.9	0.63 (0.47–0.84)	0.20
No	40/1663	0.7	45/1696	0.8	0.90 (0.59–1.38)	
Baseline SGLT-2i use						
Yes	6/314	0.6	14/304	1.5	0.34 (0.13–0.92)	0.20
No	111/3372	1.0	149/3362	1.4	0.74 (0.58–0.94)	
Baseline GLP-1RA use						
Yes	6/308	0.6	10/242	1.2	0.46 (0.16–1.31)	0.37
No	111/3378	1.0	153/3424	1.4	0.73 (0.57–0.93)	



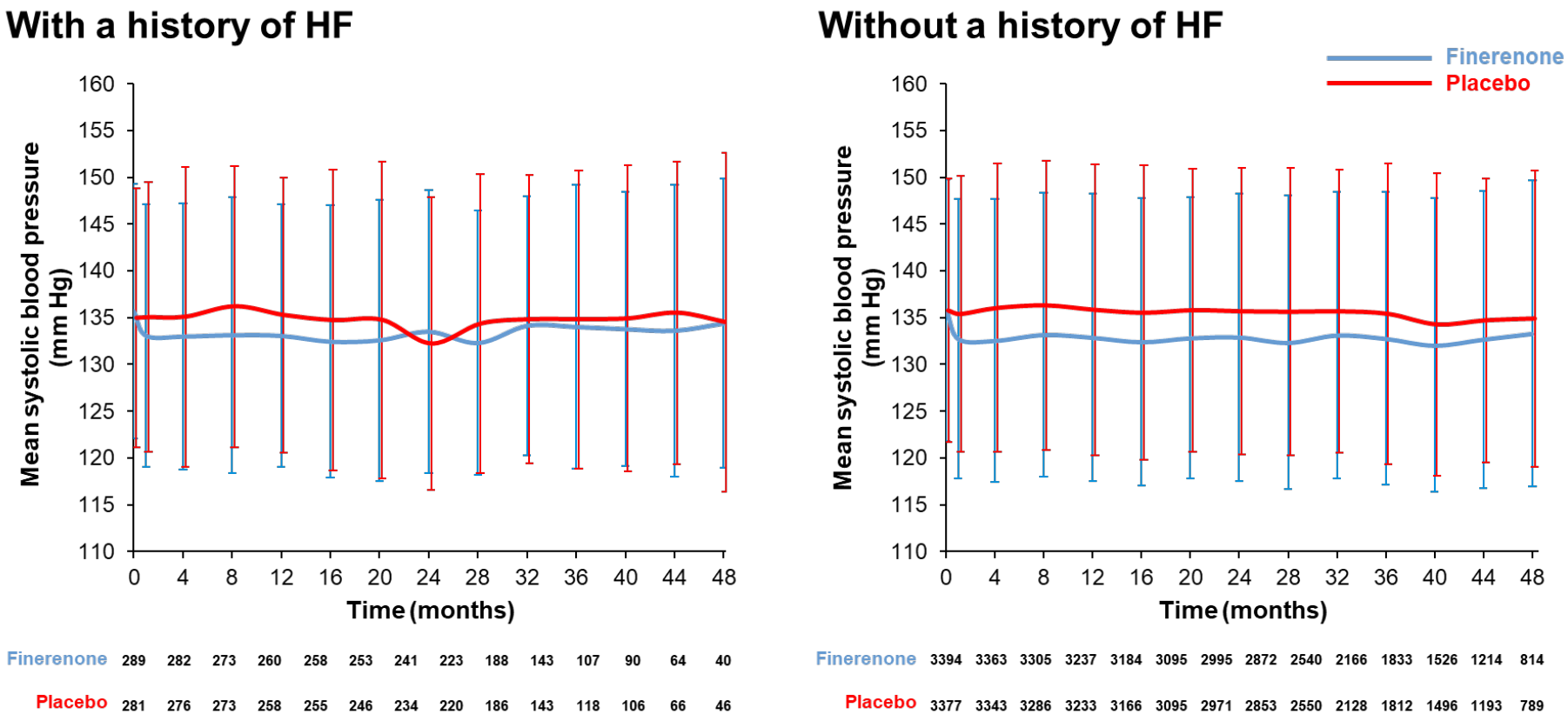
Supplemental Figure II. Time to first HHF in key prespecified and post hoc subgroups.

BMI indicates body mass index; CI confidence interval; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HHF, hospitalization for heart failure; PY, patient-years; and SGLT-2i, sodium-glucose co-transporter-2 inhibitor.



Supplemental Figure III. Composite cardiovascular outcome by history of HF.

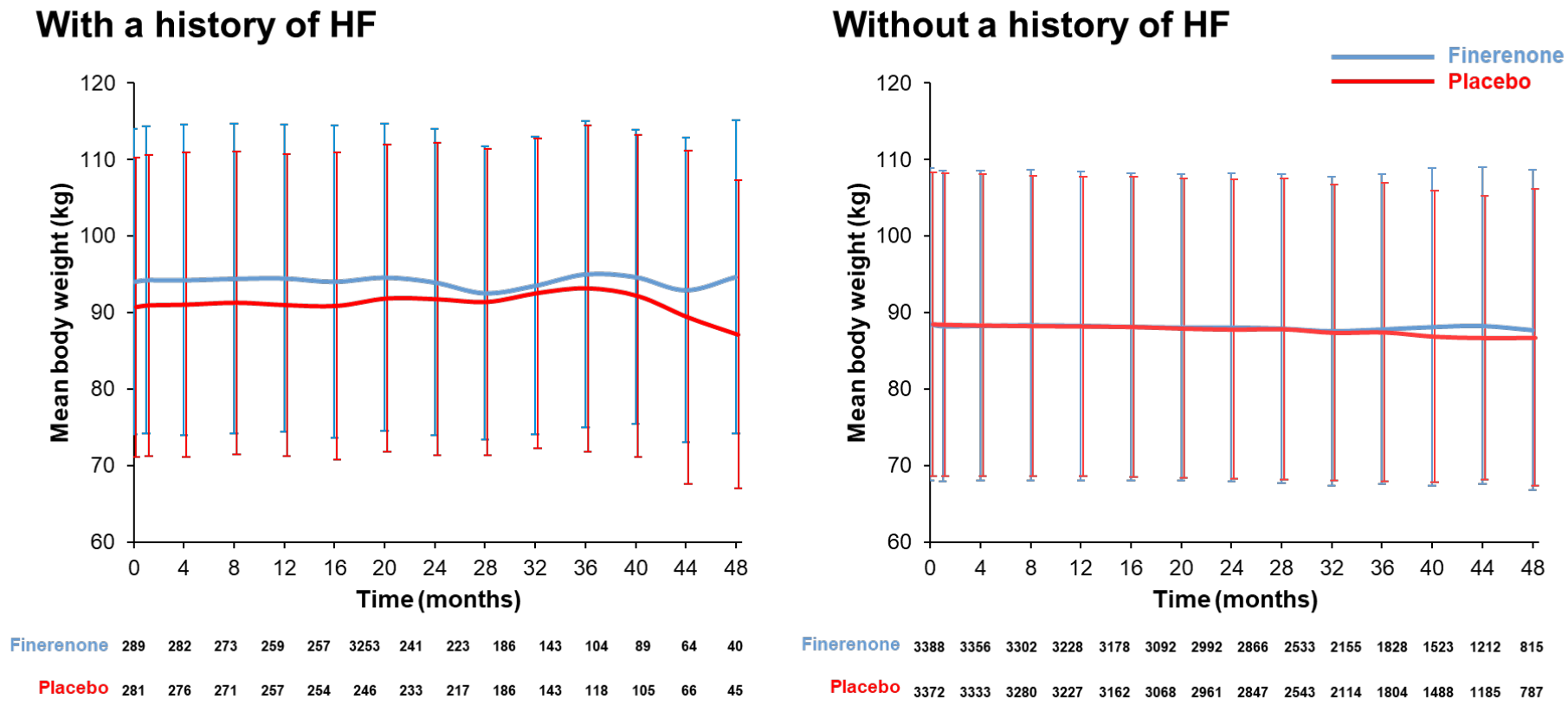
CI indicates confidence interval; CV, cardiovascular; HF, heart failure; and PY, patient-years.
* Time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF: stratified log-rank test and hazard ratio by history of HF (full analysis set).



Supplemental Figure IV. Systolic blood pressure over time by history of HF.

Data presented as mean systolic blood pressure ± standard deviation.

HF indicates heart failure.



Supplemental Figure V. Body weight over time by history of HF.

HF indicates heart failure.