

Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials

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Supplementary Tables and Figures

eTable 1. Patient Baseline Characteristics According to Age and Sex Stratified by Treatment Group

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (n=6519)	PBO (n=6507)	FIN (n=2958)	PBO (n=2931)	FIN (n=2635)	PBO (n=2586)	FIN (n=926)	PBO (n=990)	FIN (n=4481)	PBO (n=4607)	FIN (n=163)	PBO (n=160)	FIN (n=1875)	PBO (n=1740)
Age, y, mean ± SD	64.7 ± 9.4	64.8 ± 9.7	56.5 ± 6.4	56.3 ± 6.7	69.1 ± 2.7	69.2 ± 2.8	78.4 ± 3.0	78.4 ± 3.1	64.8 ± 9.3	64.9 ± 9.6	45.3 ± 4.4	44.9 ± 5.4	66.2 ± 8.0	66.4 ± 8.0
Sex, n (%)														
Female	2038 (31.3)	1900 (29.2)	959 (32.4)	880 (30.0)	772 (29.3)	729 (28.2)	307 (33.2)	291 (29.4)	0 (0.0)	0 (0.0)	163 (100)	160 (100)	1875 (100)	1740 (100)
Male	4481 (68.7)	4607 (70.8)	1999 (67.6)	2051 (70.0)	1863 (70.7)	1857 (71.8)	619 (66.8)	699 (70.6)	4481 (100)	4607 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)														
Asian	1432 (22.0)	1462 (22.5)	772 (26.1)	819 (27.9)	518 (19.7)	479 (18.5)	142 (15.3)	164 (16.6)	1032 (23.0)	1104 (24.0)	45 (27.6)	42 (26.3)	355 (18.9)	316 (18.2)
Black/African American	253 (3.9)	269 (4.1)	158 (5.3)	151 (5.2)	75 (2.8)	85 (3.3)	20 (2.2)	33 (3.3)	137 (3.1)	147 (3.2)	17 (10.4)	20 (12.5)	99 (5.3)	102 (5.9)
White	4449 (68.2)	4420 (67.9)	1827 (61.8)	1765 (60.2)	1908 (72.4)	1909 (73.8)	714 (77.1)	746 (75.4)	3099 (69.2)	3132 (68.0)	84 (51.5)	83 (51.9)	1266 (67.5)	1205 (69.3)
Other ^a	385 (5.9)	356 (5.5)	201 (6.8)	196 (6.7)	134 (5.1)	113 (4.4)	50 (5.4)	47 (4.7)	213 (4.8)	224 (4.9)	17 (10.4)	15 (9.4)	155 (8.3)	117 (6.7)
Systolic blood pressure, mm Hg, mean (SD)	136.8 ± 14.2	136.7 ± 14.3	135.7 ± 13.9	135.5 ± 14.1	137.4 ± 14.2	137.5 ± 14.2	138.4 ± 14.6	138.5 ± 14.6	136.9 ± 14.1	136.7 ± 14.3	131.6 ± 13.1	134.4 ± 14.7	136.8 ± 14.4	136.9 ± 14.0
Diastolic blood pressure,	76.3 ± 9.6	76.4 ± 9.6	78.7 ± 9.2	79.0 ± 8.9	74.8 ± 9.4	74.9 ± 9.4	73.2 ± 9.8	72.4 ± 9.8	76.6 ± 9.7	76.5 ± 9.7	78.7 ± 8.2	81.6 ± 8.4	75.6 ± 9.6	75.6 ± 9.4

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (n=6519)	PBO (n=6507)	FIN (n=2958)	PBO (n=2931)	FIN (n=2635)	PBO (n=2586)	FIN (n=926)	PBO (n=990)	FIN (n=4481)	PBO (n=4607)	FIN (n=163)	PBO (n=160)	FIN (n=1875)	PBO (n=1740)
mm Hg, mean (SD)														
Duration of diabetes, y, mean (SD)	15.4 ± 8.7	15.4 ± 8.7	13.6 ± 7.6	13.3 ± 7.7	16.4 ± 8.7	16.5 ± 8.5	18.7 ± 10.7	18.5 ± 10.2	15.4 ± 8.6	15.3 ± 8.4	11.0 ± 7.4	10.1 ± 6.5	15.9 ± 9.0	16.0 ± 9.2
HbA1c, %, mean (SD)	7.7 ± 1.4	7.7 ± 1.4	7.9 ± 1.5	7.9 ± 1.5	7.6 ± 1.3	7.6 ± 1.3	7.5 ± 1.2	7.4 ± 1.2	7.6 ± 1.3	7.6 ± 1.3	8.1 ± 1.7	8.3 ± 1.6	7.9 ± 1.4	7.9 ± 1.5
Serum potassium, mmol/L, mean (SD)	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	4.3 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4
eGFR, mL/min/1.73 m ² , mean (SD)	57.5 ± 21.6	57.7 ± 21.8	63.9 ± 23.9	64.6 ± 24.0	53.7 ± 18.4	53.3 ± 18.6	48.0 ± 15.5	48.3 ± 14.8	57.8 ± 21.0	57.7 ± 21.4	76.3 ± 28.7	77.5 ± 29.1	55.3 ± 21.5	55.8 ± 21.1
eGFR, mL/min/1.73 m ² , n (%) ^b														
<25	81 (1.2)	81 (1.2)	24 (0.8)	29 (1.0)	35 (1.3)	37 (1.4)	22 (2.4)	15 (1.5)	44 (1.0)	54 (1.2)	0	2 (1.3)	37 (2.0)	25 (1.4)
25–<45	2117 (32.5)	2115 (32.5)	744 (25.2)	704 (24.0)	937 (35.6)	961 (37.2)	436 (47.1)	450 (45.5)	1392 (31.1)	1479 (32.1)	31 (19.0)	26 (16.3)	694 (37.0)	610 (35.1)
45–<60	1717 (26.3)	1717 (26.4)	666 (22.5)	649 (22.1)	775 (29.4)	739 (28.6)	276 (29.8)	329 (33.2)	1240 (27.7)	1228 (26.7)	26 (16.0)	24 (15.0)	451 (24.1)	465 (26.7)
≥60	2603 (39.9)	2592 (39.8)	1523 (51.5)	1548 (52.8)	888 (33.7)	848 (32.8)	192 (20.7)	196 (19.8)	1805 (40.3)	1846 (40.1)	106 (65.0)	108 (67.5)	692 (36.9)	638 (36.7)
UACR, mg/g, median (Q1–Q3)	514.2 (197.5–1129.4)	514.9 (198.2–1163.4)	649.2 (308.0–1331.8)	651.4 (322.5–1382.2)	433.8 (150.7–1025.7)	441.3 (157.8–1032.8)	325.6 (107.00–802.7)	340.5 (109.8–871.7)	514.5 (205.3–1116.5)	509.2 (195.4–1143.0)	733.0 (336.3–1522.7)	868.4 (398.5–1604.2)	496.4 (169.9–1124.4)	509.1 (185.0–1174.5)
UACR, mg/g, n (%) ^c														
<30	120 (1.8)	110 (1.7)	39 (1.3)	40 (1.4)	53 (2.0)	50 (1.9)	28 (3.0)	20 (2.0)	69 (1.5)	68 (1.5)	2 (1.2)	1 (0.6)	49 (2.6)	41 (2.4)
30–<300	2076 (31.8)	2023 (31.1)	686 (23.2)	645 (22.0)	971 (36.9)	936 (36.2)	419 (45.2)	442 (44.6)	1422 (31.7)	1459 (31.7)	34 (20.9)	20 (12.5)	620 (33.1)	544 (31.3)

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (n=6519)	PBO (n=6507)	FIN (n=2958)	PBO (n=2931)	FIN (n=2635)	PBO (n=2586)	FIN (n=926)	PBO (n=990)	FIN (n=4481)	PBO (n=4607)	FIN (n=163)	PBO (n=160)	FIN (n=1875)	PBO (n=1740)
≥300	4321 (66.3)	4371 (67.2)	2231 (75.4)	2244 (76.6)	1611 (61.1)	1599 (61.8)	479 (51.7)	528 (53.3)	2989 (66.7)	3079 (66.8)	127 (77.9)	139 (86.9)	1205 (64.3)	1153 (66.3)
BMI, kg/m ² , mean (SD)	31.3 ± 6.0	31.3 ± 6.0	32.1 ± 6.5	32.0 ± 6.3	31.1 ± 5.7	31.1 ± 5.7	29.5 ± 4.8	29.6 ± 5.1	30.9 ± 5.6	30.9 ± 5.6	34.0 ± 7.9	34.3 ± 7.9	32.0 ± 6.7	32.1 ± 6.5
Current smoker, n (%)	1065 (16.3)	1028 (15.8)	657 (22.2)	626 (21.4)	351 (13.3)	335 (13.0)	57 (6.2)	67 (6.8)	874 (19.5)	856 (18.6)	17 (10.4)	18 (11.3)	174 (9.3)	154 (8.9)
History of CV disease, present, n (%)	2979 (45.7)	2956 (45.4)	1127 (38.1)	1061 (36.2)	1330 (50.5)	1337 (51.7)	522 (56.4)	558 (56.4)	2152 (48.0)	2222 (48.2)	36 (22.1)	20 (12.5)	791 (42.2)	714 (41.0)
History of heart failure	485 (7.4)	522 (8.0)	211 (7.1)	202 (6.9)	192 (7.3)	240 (9.3)	82 (8.9)	80 (8.1)	302 (6.7)	328 (7.1)	11 (6.7)	11 (6.9)	172 (9.2)	183 (10.5)
History of atrial fibrillation/atrial flutter	568 (8.7)	538 (8.3)	144 (4.9)	122 (4.2)	280 (10.6)	267 (10.3)	144 (15.6)	149 (15.1)	439 (9.8)	428 (9.3)	0	0	129 (6.9)	110 (6.3)
Baseline medications, n (%) ^d														
RAS inhibitors (ACEis/ARBs)	6508 (99.8)	6495 (99.8)	2951 (99.8)	2925 (99.8)	2631 (99.8)	2582 (99.8)	926 (100.0)	988 (99.8)	4473 (99.8)	4596 (99.8)	163 (100.0)	160 (100.0)	1872 (99.8)	1739 (>99.9)
Beta-blockers	3236 (49.6)	3268 (50.2)	1311 (44.3)	1308 (44.6)	1419 (53.9)	1430 (55.3)	506 (54.6)	530 (53.5)	2237 (49.9)	2308 (50.1)	57 (35.0)	54 (33.8)	942 (50.2)	906 (52.1)
Diuretics	3325 (51.0)	3385 (52.0)	1378 (46.6)	1412 (48.2)	1412 (53.6)	1401 (54.2)	535 (57.8)	572 (57.8)	2320 (51.8)	2386 (51.8)	67 (41.1)	70 (43.8)	938 (50.0)	929 (53.4)
Statins	4657 (71.4)	4742 (72.9)	1993 (67.4)	2040 (69.6)	1975 (75.0)	1945 (75.2)	689 (74.4)	757 (76.5)	3291 (73.4)	3405 (73.9)	93 (57.1)	110 (68.8)	1273 (67.9)	1227 (70.5)
Calcium channel blockers	3664 (56.2)	3694 (56.8)	1564 (52.9)	1563 (53.3)	1544 (58.6)	1508 (58.3)	556 (60.0)	623 (62.9)	2554 (57.0)	2654 (57.6)	74 (45.4%)	75 (46.9)	1036 (55.3)	965 (55.5)
≥1 glucose-lowering medication	6354 (97.5)	6366 (97.8)	2898 (98.0)	2881 (98.3)	2574 (97.7)	2537 (98.1)	882 (95.2)	948 (95.8)	4361 (97.3)	4499 (97.7)	161 (98.8)	156 (97.5)	1832 (97.7)	1711 (98.3)

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (n=6519)	PBO (n=6507)	FIN (n=2958)	PBO (n=2931)	FIN (n=2635)	PBO (n=2586)	FIN (n=926)	PBO (n=990)	FIN (n=4481)	PBO (n=4607)	FIN (n=163)	PBO (n=160)	FIN (n=1875)	PBO (n=1740)
n (%) ^d														
Insulin	3866 (59.3)	3764 (57.8)	1848 (62.5)	1789 (61.0)	1539 (58.4)	1481 (57.3)	479 (51.7)	494 (49.9)	2598 (58.0)	2605 (56.5)	94 (57.7)	99 (61.9)	1174 (62.6)	1060 (60.9)
GLP-1RA	497 (7.6)	447 (6.9)	273 (9.2)	219 (7.5)	190 (7.2)	188 (7.3)	34 (3.7)	40 (4.0)	359 (8.0)	317 (6.9)	12 (7.4)	18 (11.3)	126 (6.7)	112 (6.4)
SGLT-2i	438 (6.7)	439 (6.7)	251 (8.5)	266 (9.1)	149 (5.7)	140 (5.4)	38 (4.1)	33 (3.3)	331 (7.4)	340 (7.4)	19 (11.7)	17 (10.6)	88 (4.7)	82 (4.7)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; eGFR = estimated

glomerular filtration rate; FIN = finerenone; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; PBO = placebo; Q = quartile;

RAS = renin-angiotensin system; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; UACR = urine albumin-to-creatinine ratio.

Values are based on available data.

^a Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific, not reported, multiple.

^b Missing (eGFR): <65 years, *n*=2; 65 to 74 years, *n*=1; postmenopausal female, *n*=3.

^c Missing (UACR): <65 years, *n*=4; 65 to 74 years, *n*=1; male, *n*=2; postmenopausal female, *n*=3.

^d Analysis allowed multiple drug groups for the same drug.

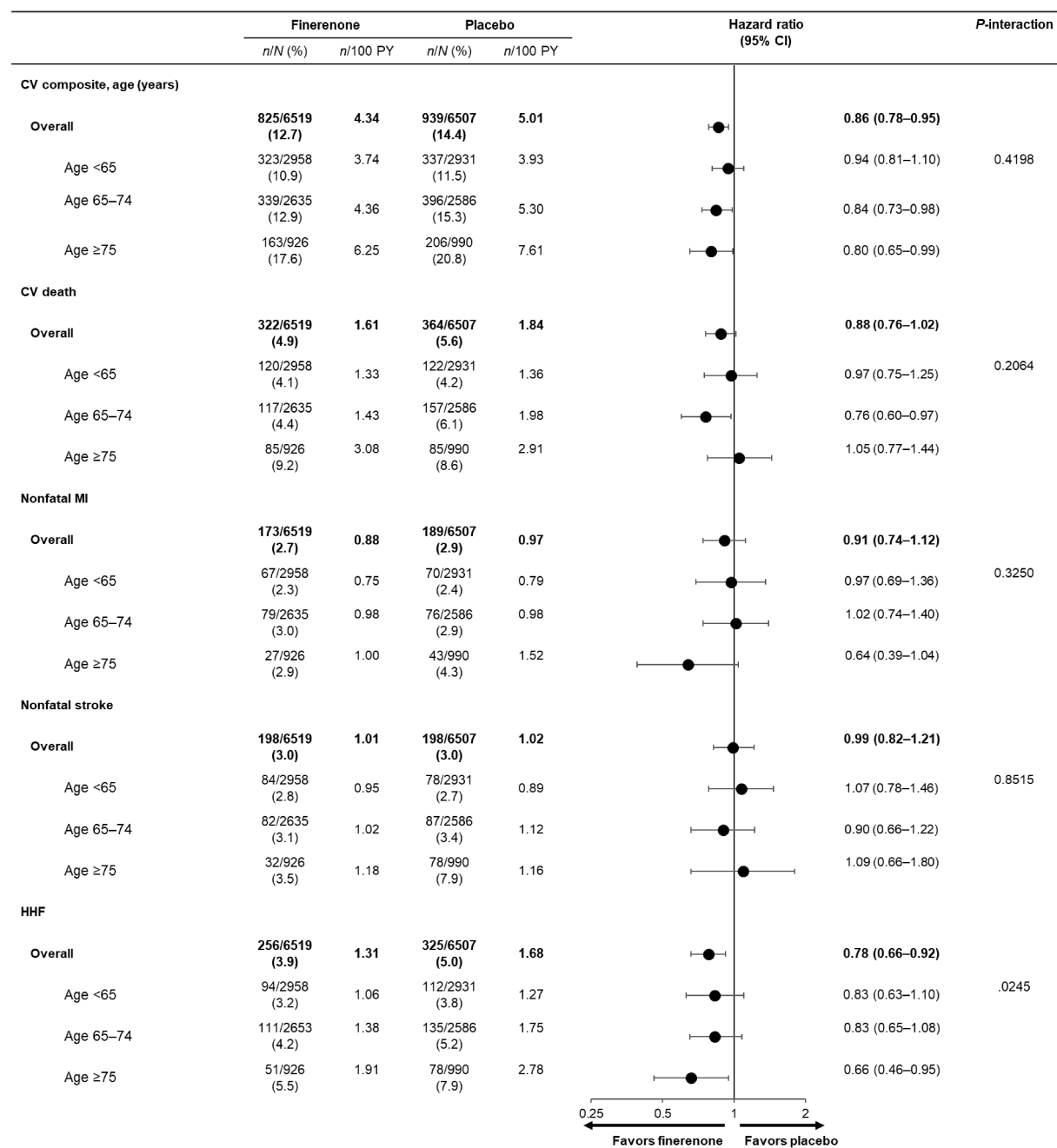
eTable 2. Treatment-Emergent AEs According to Age and Sex

n (%)	ALL		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (n=6510)	PBO (n=6489)	FIN (n=2953)	PBO (n=2926)	FIN (n=2631)	PBO (n=2578)	FIN (n=926)	PBO (n=985)	FIN (n=4476)	PBO (n=4595)	FIN (n=163)	PBO (n=160)	FIN (n=1871)	PBO (n=1734)
Any AE	5602 (86.1)	5607 (86.4)	2494 (84.5)	2523 (86.2)	2301 (87.5)	2225 (86.3)	807 (87.1)	859 (87.2)	3899 (87.1)	4011 (87.3)	137 (84.0)	138 (86.3)	1566 (83.7)	1458 (84.1)
Related to study drug	1206 (18.5)	862 (13.3)	478 (16.2)	384 (13.1)	558 (21.2)	337 (13.1)	170 (18.4)	141 (14.3)	884 (19.7)	612 (13.3)	21 (12.9)	20 (12.5)	301 (16.1)	230 (13.3)
Leading to discontinuation	414 (6.4)	351 (5.4)	128 (4.3)	124 (4.2)	212 (8.1)	153 (5.9)	74 (8.0)	74 (7.5)	313 (7.0)	249 (5.4)	9 (5.5)	7 (4.4)	92 (4.9)	95 (5.5)
Any SAE	2060 (31.6)	2186 (33.7)	856 (29.0)	938 (32.1)	871 (33.1)	876 (34.0)	333 (36.0)	372 (37.8)	1487 (33.2)	1590 (34.6)	33 (20.2)	42 (26.3)	540 (28.9)	554 (31.9)
Related to study drug	83 (1.3)	61 (0.9)	29 (1.0)	27 (0.9)	39 (1.5)	17 (0.7)	15 (1.6)	17 (1.7)	56 (1.3)	46 (1.0)	0	1 (0.6)	27 (1.4)	14 (0.8)
Leading to discontinuation	145 (2.2)	154 (2.4)	41 (1.4)	48 (1.6)	75 (2.9)	71 (2.8)	29 (3.1)	35 (3.6)	115 (2.6)	112 (2.4)	1 (0.6)	2 (1.3)	29 (1.5)	40 (2.3)
Any AE leading to death	110 (1.7)	151 (2.3)	43 (1.5)	55 (1.9)	42 (1.6)	62 (2.4)	25 (2.7)	34 (3.5)	73 (1.6)	115 (2.5)	0	3 (1.9)	37 (2.0)	33 (1.9)
AEs of interest														
Hypotension	282(4.3)	177 (2.7)	101 (3.4)	70 (2.4)	127 (4.8)	76 (2.9)	54 (5.8)	31 (3.1)	216 (4.8)	131 (2.9)	3 (1.8)	0	63 (3.4)	46 (2.7)
Orthostatic hypotension	46 (0.7)	39 (0.6)	18 (0.6)	15 (0.5)	23 (0.9)	15 (0.6)	5 (0.5)	9 (0.9)	34 (0.8)	30 (0.7)	0	2 (1.3)	12 (0.6)	7 (0.4)
Hyperkalemia	912 (14.0)	448 (6.9)	360 (12.2)	238 (8.1)	420 (16.0)	158 (6.1)	132 (14.3)	52 (5.3)	647 (14.5)	304 (6.6)	14 (8.6)	16 (10.0)	251 (13.4)	128 (7.4)
Leading to permanent discontinuation	110 (1.7)	38 (0.6)	31 (1.0)	13 (0.4)	54 (2.1)	19 (0.7)	25 (2.7)	6 (0.6)	83 (1.9)	28 (0.6)	4 (2.5)	1 (0.6)	23 (1.2)	9 (0.5)
Classified as a serious AE	69 (1.1)	16 (0.2)	28 (0.9)	8 (0.3)	29 (1.1)	5 (0.2)	12 (1.3)	3 (0.3)	45 (1.0)	9 (0.2)	1 (0.6)	0	23 (1.2)	7 (0.4)
Leading to hospitalization	61 (0.9)	10 (0.2)	26 (0.9)	6 (0.2)	25 (1.0)	2 (<0.1)	10 (1.1)	2 (0.2)	38 (0.8)	5 (0.1)	1 (0.6)	0	22 (1.2)	5 (0.3)
Gynecomastia	8 (0.1)	11 (0.2)	2 (<0.1)	4 (0.1)	5 (0.2)	3 (0.1)	1 (0.1)	4 (0.4)	8 (0.2)	11 (0.2)	NA	NA	NA	NA
Central laboratory assessments, n/N (%)^a														

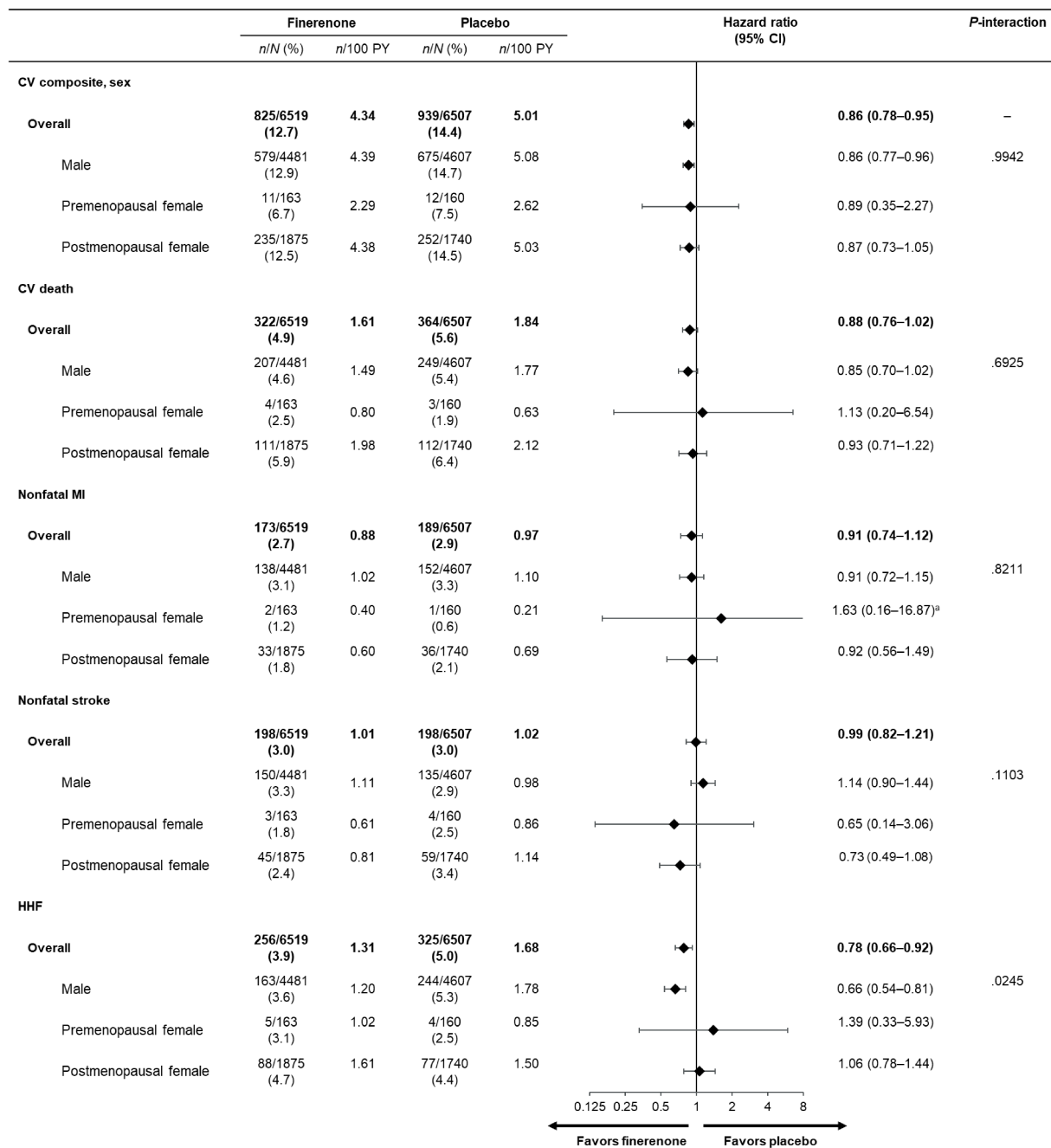
Serum potassium >5.5 mmol/L	1075/6402 (16.8)	470/6370 (7.4)	444/2904 (15.3)	233/2871 (8.1)	460/2585 (17.8)	180/2529 (7.1)	171/913 (18.7)	57/970 (5.9)	720/4403 (16.4)	308/4523 (6.8)	16/159 (10.1)	8/154 (5.2)	339/1840 (18.4)	154/1693 (9.1)
Serum potassium >6.0 mmol/L	211/6439 (3.3)	80/6413 (1.2)	90/2926 (3.1)	44/2896 (1.5)	89/2598 (3.4)	31/2544 (1.2)	32/915 (3.5)	5/973 (0.5)	143/4428 (3.2)	48/4544 (1.1)	4/160 (2.5)	1/156 (0.6)	64/1851 (3.5)	31/1713 (1.8)

AE = adverse event; FIN = finerenone; NA = not applicable; PBO = placebo; SAE = serious adverse event.

^a The “*n*” numerator represents the number of patients at risk with ≥ 1 treatment-emergent laboratory assessment meeting the criterion. The “*N*” denominator represents all patients at risk for a treatment-emergent laboratory abnormality. Patients had both a baseline and postbaseline treatment-emergent value while the baseline value did not exceed the displayed threshold.

eFigure 1. Analysis of CV composite outcome and subcomponents according to (A) age and (B) sex.**A.**

B.



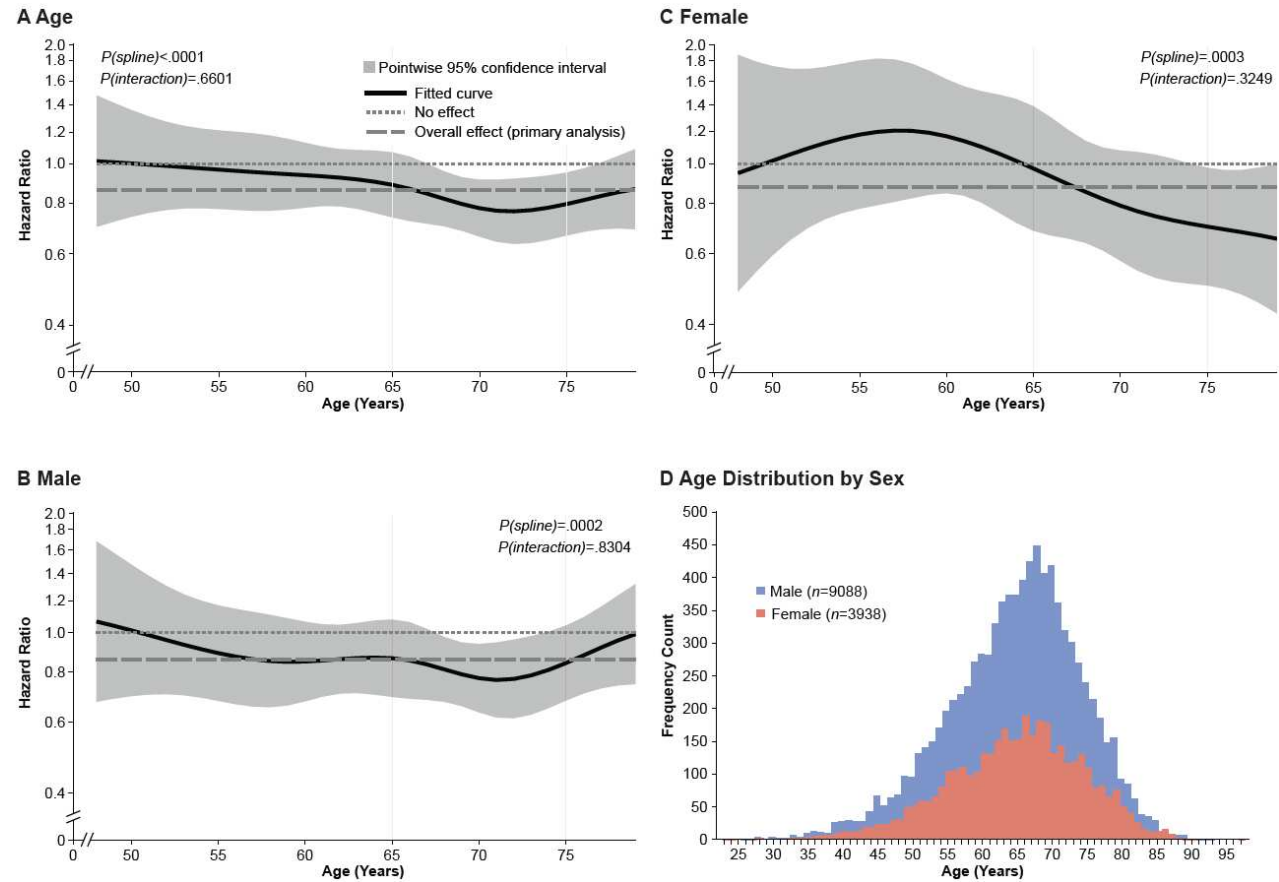
A stratified Cox proportional hazards model including treatment was calculated separately by subgroup category. The $P_{\text{interaction}}$ is based on a stratified Cox proportional hazards model including treatment, subgroup, and treatment by subgroup interaction.

CV composite outcome includes CV death, nonfatal MI, nonfatal stroke, or HHF.

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; MI = myocardial infarction; PY = patient-years.

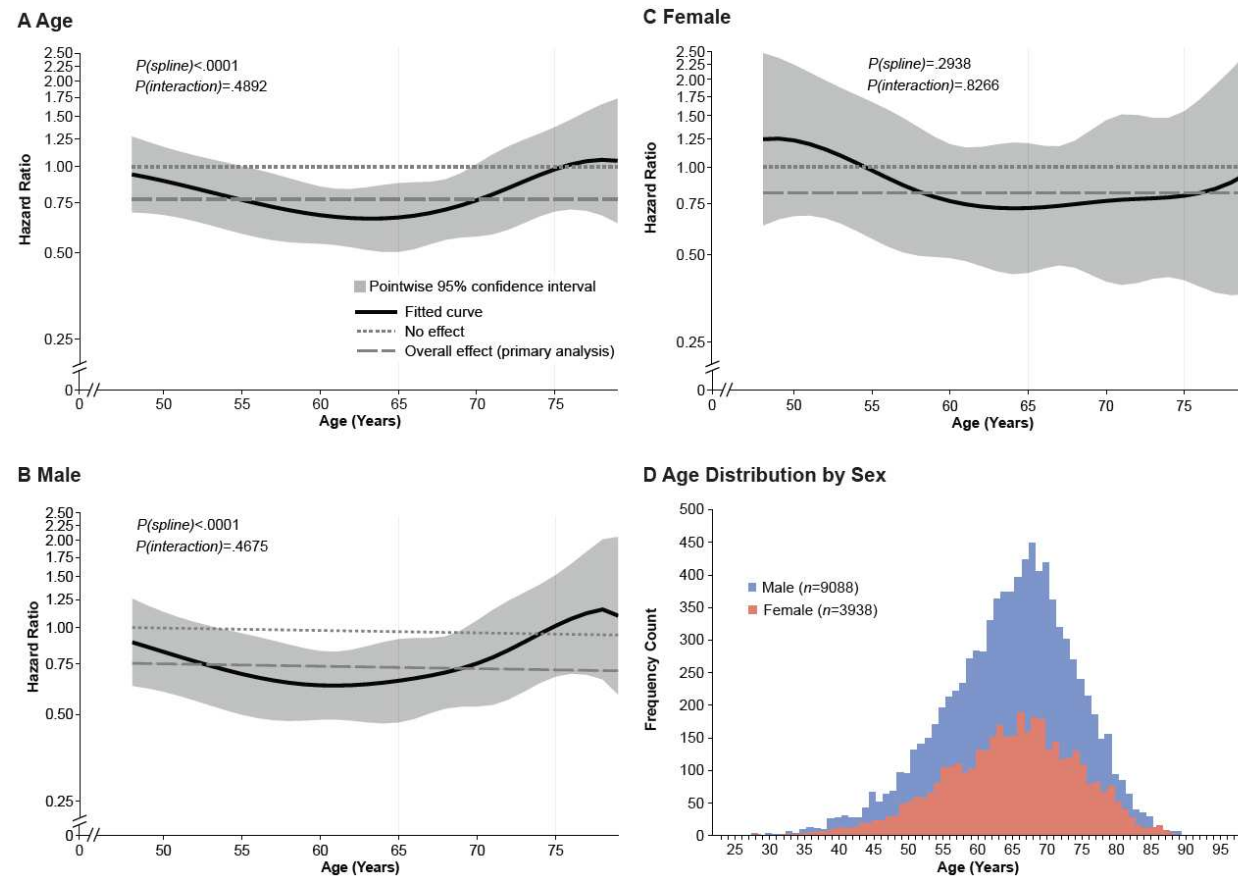
^a An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts and/or convergence issues.

eFigure 2. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for CV composite outcome by age (A), spline for hazard ratio of CV composite outcomes by sex (B, C), and age distribution by sex (D).

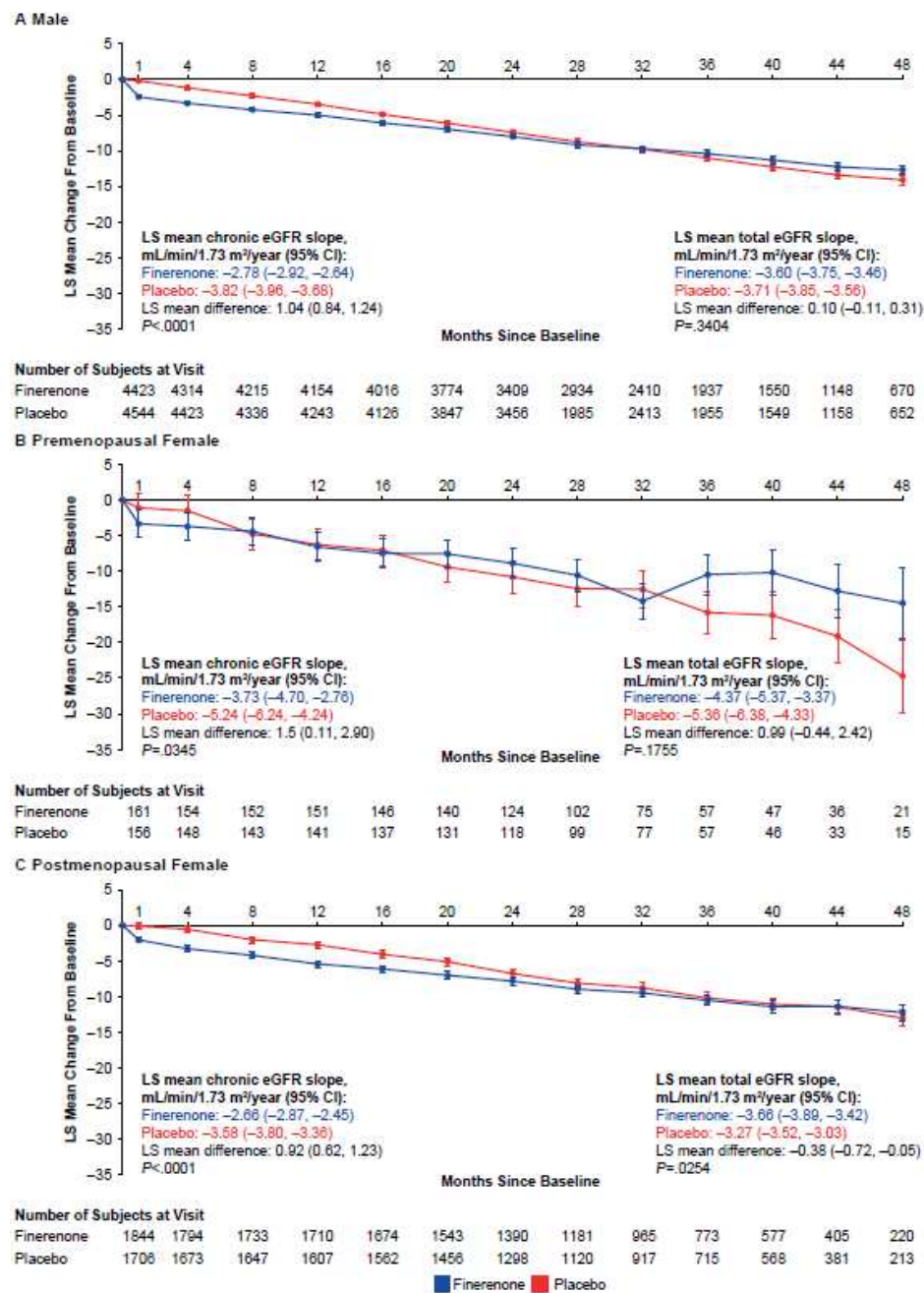


CV = cardiovascular.

eFigure 3. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for kidney composite outcome by age (A), spline for hazard ratio of kidney composite outcomes by sex (B, C), and age distribution by sex (D).

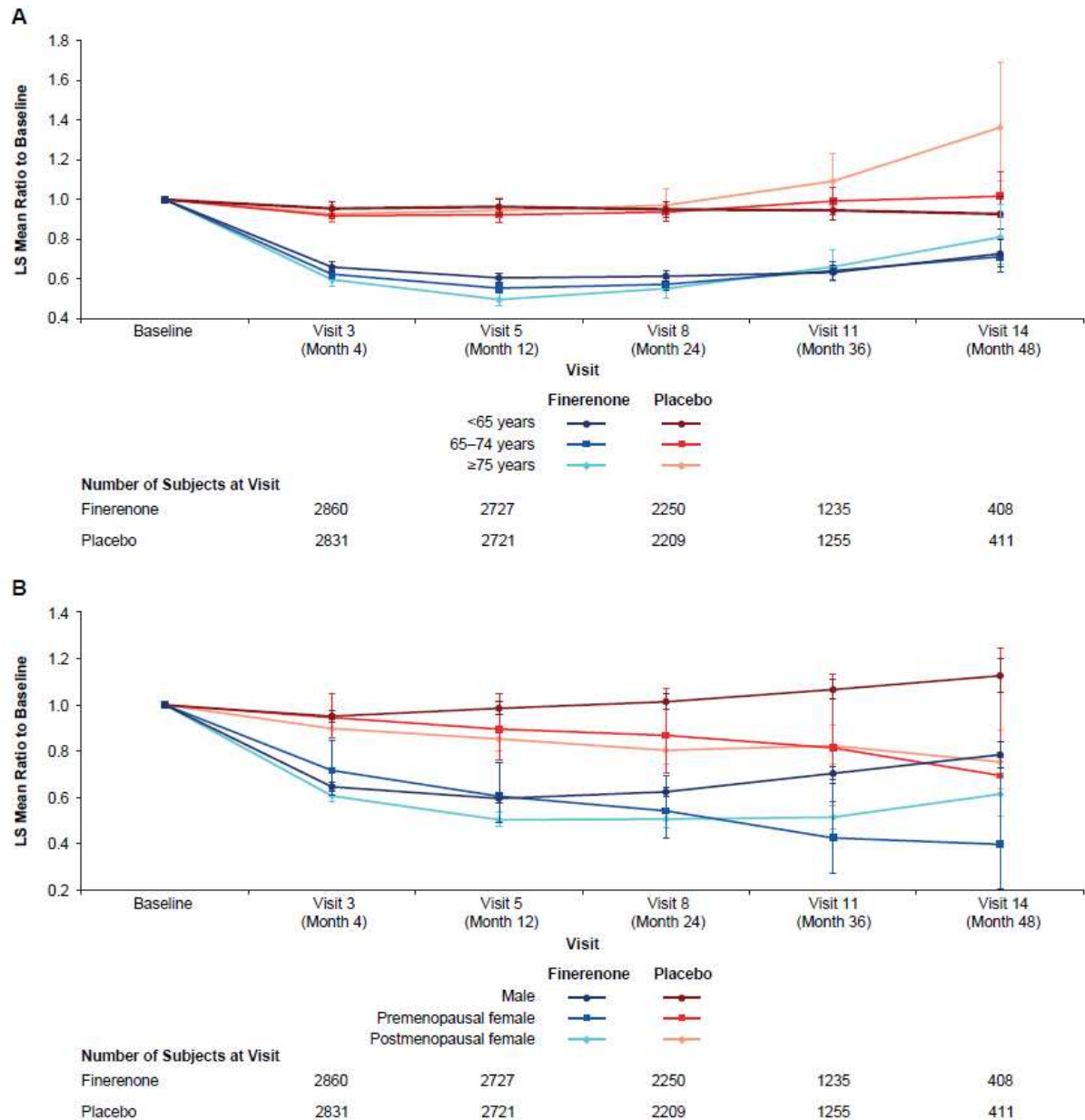


eFigure 4. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.



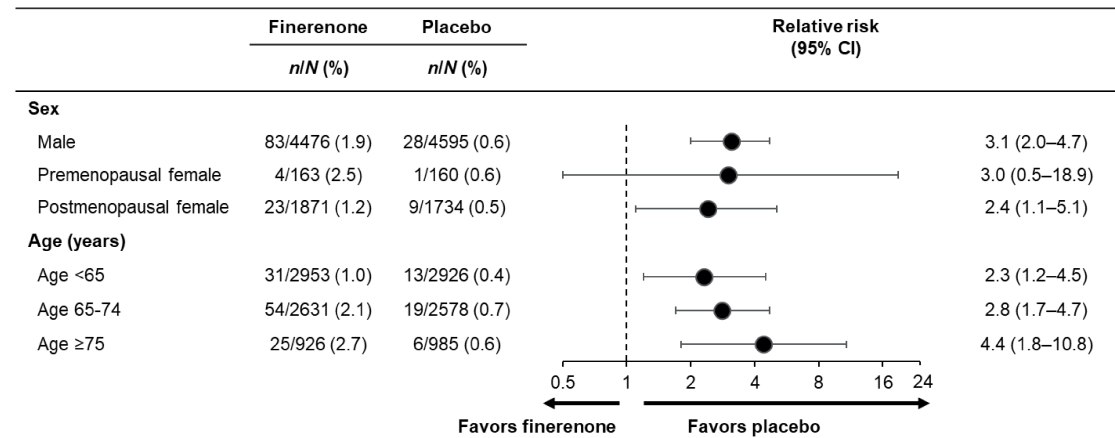
Chronic eGFR slope from month 4 to end-of-study visit.

CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

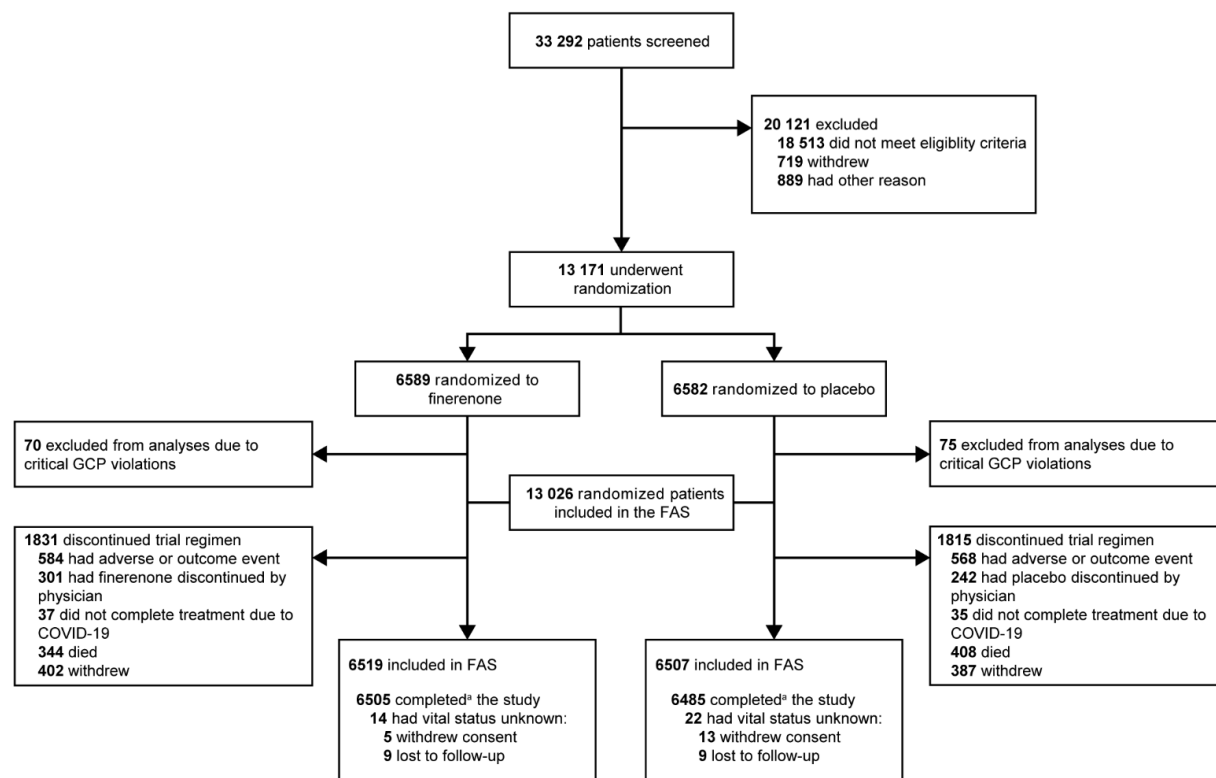
eFigure 5. LS mean ratio to baseline UACR over time by age and sex

LS = least-squares; UACR = urine albumin-to-creatinine ratio.

eFigure 6. Relative risk of treatment-emergent hyperkalemia causing permanent discontinuation of study drug by age and sex



Relative risk values based on Mantel-Haenszel estimates (stratified by study). For the relative risk, a treatment-arm-size zero cell correction with zero term = 0.5 was applied.

eFigure 7. FIDELITY CONSORT diagram.

^a The patient was considered as having completed the study if there was a contact with the patient after the end-of-study notification or if the patient died.

CONSORT = Consolidated Standards of Reporting Trials; COVID-19, coronavirus disease of 2019;

FAS, full analysis set; FIDELITY = The Finerenone in chronic kidney disease and type 2 diabetes:

Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis; GCP, Good Clinical Practice.