

Online-only supplement

Efficacy and Safety of Sacubitril/Valsartan According to Frailty in Heart Failure With Preserved Ejection Fraction: A Post Hoc Analysis of the PARAGON-HF Trial

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Supplementary Table 1. Components of the Frailty Index

Number	Component	Cut-off	Score
<i>Vital signs</i>			
1	Body mass index, kg/m ²	<18.5 or ≥30	1
		25-29	0.5
2	Systolic blood pressure, mmHg	≤90 or ≥140	1
3	Diastolic blood pressure, mmHg	≥90	1
4	Pulse pressure, mmHg	>55	1
<i>Comorbidities</i>			
5	Myocardial infarction	Present/history	1
6	PCI or CABG	Present/history	1
7	Unstable angina pectoris	Present/history	1
8	Peripheral artery disease	Present/history	1
9	Atrial fibrillation/flutter*	Present/history	1
10	Left bundle branch block	Present/history	1
11	Pacemaker	Present/history	1
12	Diabetes	Present/history	1
13	Hypertension	Present/history	1
14	Chronic obstructive pulmonary disease	Present/history	1
15	Stroke	Present/history	1
16	Carotid artery disease	Present/history	1
17	Cancer	Present/history	1
18	Chronic kidney disease	Present/history	1
19	Sleep apnea	Present/history	1
20	Osteoporosis	Present/history	1

Quality of life measures			
21	Mobility	I have no problems in walking about	0
		I have some problems in walking about	0.5
		I am confined to bed	1
22	Self-care	I have no problems with self-care	0
		I have some problems washing or dressing myself	0.5
		I am unable to wash or dress myself	1
23	Usual activities	I have no problems with performing my usual activities	0
		I have some problems with performing my usual activities	0.5
		I am unable to perform my usual activities	1
24	Pain/discomfort	I have no pain or discomfort	0
		I have moderate pain or discomfort	0.5
		I have extreme pain or discomfort	1
25	Anxiety or depression	I am not anxious or depressed	0
		I am moderately anxious or depressed	0.5
		I am extremely anxious or depressed	1
Laboratory measures			
26	Creatinine, umol/L	<40 or >150	1
27	Sodium, mmol/L	<135 or >145	1
28	Potassium, mmol/L	<3.5 or >6	1
29	Hemoglobin, g/L	Men: <130 or >175 Women: <120 or >155	1
30	Alanine aminotransferase, U/L	<7 or >55	1
31	Bilirubin, mg/dL	<0.1 or >1.2	1

32	Alkaline phosphatase, U/L	<40 or >129	1
33	Albumin, g/L	<35 or >55	1
34	Blood urea nitrogen, mmol/L	<3 or >7.5	1
35	Total cholesterol, mmol/L	<3.5 or >7	1
36	HDL cholesterol, mmol/L	<0.4 or >1.5	1
37	Calcium, mmol/L	<2.2 or >2.7	1
38	Uric acid, umol/L	Men: <200 or >430 Women: <140 or >360	1
39	Platelet count, 10 ⁹ /L	<150 or >400	1
40	White blood cell count, 10 ⁹ /L	<4 or >12	1
41	HbA1c, %	<4 or >6.4	1

CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

**A history of atrial fibrillation/flutter or atrial fibrillation/flutter on electrocardiogram at randomization.*

Supplementary Table 2. Biomarkers and EQ-5D questionnaire responses at baseline according to Frailty Index

	FI \leq 0.210 (not frail) N=2,165	FI 0.211-0.310 (more frail) N=2,084	FI \geq 0.311 (most frail) N=546	P-value
Biomarkers, median (25 th -75 th percentile)				
NT-proBNP, pg/mL	782.5 (425.5-1434.5)	983.0 (497.0-1725.5)	1085.5 (584.0-1940.5)	<0.001
Creatinine, μ mol/L	84.9 (72.0-100.8)	96.0 (80.0-117.6)	112.3 (93.7-137.0)	<0.001
Estimated glomerular filtration rate, mL/min/1.73m ²	66.2 (55.2-78.3)	57.5 (45.7-70.8)	47.3 (38.6-58.9)	<0.001
Albumin, g/L	43.0 (41.0-44.0)	42.0 (40.0-44.0)	42.0 (40.0-44.0)	<0.001
Blood urea nitrogen, mmol/L	6.6 (5.5-8.0)	8.1 (6.3-10.2)	9.8 (7.9-12.2)	<0.001
Calcium, mmol/L	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.3 (2.2-2.4)	0.02
Uric acid, μ mol/L	360.0 (300.0-430.0)	392.6 (330.0-480.0)	440.0 (360.0-511.5)	<0.001
Sodium, mmol/L	141.0 (140.0-143.0)	141.0 (139.0-143.0)	141.0 (139.0-143.0)	0.09
Potassium, mmol/L	4.5 (4.2-4.8)	4.5 (4.2-4.8)	4.5 (4.2-4.8)	0.30
Total cholesterol, mmol/L	4.5 (3.9-5.3)	4.3 (3.6-5.1)	3.9 (3.3-4.8)	<0.001
HDL cholesterol, mmol/L	1.3 (1.1-1.5)	1.3 (1.0-1.6)	1.3 (1.0-1.6)	0.12
Hemoglobin, g/L	138.0 (129.0-147.0)	133.0 (123.0-143.0)	125.0 (116.0-136.0)	<0.001
Red cell distribution width, %	14.0 (13.4-14.7)	14.3 (13.6-15.2)	14.7 (13.9-15.6)	<0.001
White blood cell count, 10 ⁹ /L	6.3 (5.3-7.5)	6.5 (5.4-7.7)	6.6 (5.3-8.0)	0.001
Lymphocyte count, 10 ⁹ /L	1.7 (1.4-2.1)	1.6 (1.3-2.0)	1.5 (1.1-1.9)	0.001
Neutrophil count, 10 ⁹ /L	3.9 (3.2-4.8)	4.1 (3.3-5.2)	4.3 (3.3-5.4)	0.001
Neutrophil/lymphocyte ratio	2.3 (1.8-3.1)	2.6 (1.9-3.5)	2.8 (2.0-3.9)	0.001
Platelet count, 10 ⁹ /L	210.0 (175.0-249.0)	205.0 (167.0-249.0)	203.0 (163.0-253.0)	0.001
HbA1c, %	6.0 (5.7-6.5)	6.3 (5.8-7.2)	6.7 (6.0-7.7)	<0.001
Alanine aminotransferase, U/L	17.0 (13.0-22.0)	16.0 (13.0-21.0)	16.0 (12.0-21.0)	<0.001
Alkaline phosphatase, U/L	71.0 (58.0-87.0)	74.0 (60.0-93.0)	78.0 (63.0-99.0)	<0.001

Bilirubin, mg/dL	9.0 (6.8-12.0)	8.6 (6.0-12.0)	8.0 (5.1-10.3)	<0.001
High-sensitivity troponin T, ug/L	0.013 (0.009-0.019)	0.018 (0.012-0.025)	0.023 (0.017-0.035)	<0.001
sST2, ng/mL	21.4 (17.7-25.6)	22.5 (18.6-27.6)	24.3 (18.8-29.0)	<0.001
Urine cGMP/creatinine ratio, nmol/mmol	117.8 (85.1-160.6)	112.9 (82.2-147.8)	92.5 (72.5-133.1)	<0.001
CITP, ug/L	5.1 (4.2-6.6)	6.4 (5.0-8.7)	7.4 (6.0-10.6)	<0.001
PINP, ug/L	37 (28-50)	39 (29-51)	41 (29-53)	0.04
PIIINP, ug/L	4.15 (3.44-5.21)	4.54 (3.64-5.65)	4.89 (3.81-6.01)	<0.001
TIMP-1, ng/mL	119.9 (101.8-140.5)	133.6 (111.0-161.3)	148.7 (124.1-180.0)	<0.001
EuroQoL-5 Domain questionnaire, N (%)				
Mobility				<0.001
I have no problems in walking about	1,338 (62.7)	745 (36.3)	101 (19.1)	
I have some problems in walking about	797 (37.3)	1,305 (63.6)	421 (79.7)	
I am confined to bed	0 (0.0)	2 (0.1)	6 (1.1)	
Self-care				<0.001
I have no problems with self-care	1,986 (93.0)	1,607 (78.3)	347 (65.7)	
I have some problems washing or dressing myself	145 (6.8)	425 (20.7)	164 (31.1)	
I am unable to wash or dress myself	4 (0.2)	20 (1.0)	17 (3.2)	
Usual activities				<0.001
I have no problems with performing my usual activities	1,465 (68.6)	977 (47.6)	159 (30.1)	
I have some problems with performing my usual activities	661 (31.0)	1,015 (49.5)	324 (61.4)	
I am unable to perform my usual activities	9 (0.4)	60 (2.9)	45 (8.5)	
Pain/discomfort				<0.001
I have no pain or discomfort	1,292 (60.5)	794 (38.7)	140 (26.5)	
I have moderate pain or discomfort	811 (38.0)	1,147 (56.0)	324 (61.4)	
I have extreme pain or discomfort	32 (1.5)	109 (5.3)	64 (12.1)	
Anxiety or depression				<0.001
I am not anxious or depressed	1,603 (75.1)	1,303 (63.5)	284 (53.8)	

I am moderately anxious or depressed	515 (24.1)	691 (33.7)	225 (42.6)	
I am extremely anxious or depressed	16 (0.7)	57 (2.8)	19 (3.6)	

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

High-sensitivity troponin T, N=1,260; sST2, N=1,228 Urine cGMP/creatinine ratio, N=1,195; CITP, N=1,102; PINP, N=1,116; PIIINP, N=1,108; TIMP-1, N=1,117.

CITP, PINP, PIIINP, and TIMP-1 were collected at the screening visit.

MMSE at randomization, N=2,895.

Mobility, selfcare, usual activities, N=4,715; pain/discomfort, anxiety or depression, N=4,713.

Supplementary Table 3. Outcomes according to Frailty Index

	FI \leq 0.210 (not frail) N=2,165	FI 0.211-0.310 (more frail) N=2,084	FI \geq 0.311 (most frail) N=546
Primary outcome (total HF hospitalizations or cardiovascular death)			
No. of events	419	992	491
Event rate per 100 person-years (95% CI)	6.6 (6.0-7.3)	16.6 (15.6-17.7)	32.4 (29.7-35.4)
RR (95% CI)*	Reference	2.44 (2.07-2.87)	4.14 (3.38-5.07)
RR (95% CI)**	Reference	2.19 (1.85-2.60)	3.29 (2.65-4.09)
Primary outcome and urgent HF visits			
No. of events	443	1,036	518
Event rate per 100 person-years (95% CI)	7.0 (6.3-7.6)	17.3 (16.3-18.4)	34.2 (31.4-37.3)
RR (95% CI)*	Reference	2.40 (2.05-2.82)	4.11 (3.36-5.02)
RR (95% CI)**	Reference	2.16 (1.83-2.54)	3.26 (2.64-4.04)
Total HF hospitalizations			
No. of events	310	769	407
Event rate per 100 person-years (95% CI)	4.9 (4.4-5.4)	12.9 (12.0-13.8)	26.9 (24.4-29.6)
RR (95% CI)*	Reference	2.50 (2.07-3.02)	4.37 (3.47-5.50)
RR (95% CI)**	Reference	2.31 (1.90-2.81)	3.62 (2.84-4.63)
Total cardiovascular hospitalizations			
No. of events	980	1,564	728
Event rate per 100 person-years (95% CI)	15.4 (14.5-16.4)	26.2 (24.9-27.5)	48.1 (44.7-51.7)
RR (95% CI)*	Reference	1.64 (1.46-1.84)	2.71 (2.32-3.16)
RR (95% CI)**	Reference	1.55 (1.38-1.75)	2.41 (2.05-2.83)
Total all-cause hospitalizations			
No. of events	2,017	3,286	1,472

Event rate per 100 person-years (95% CI)	31.7 (30.4-33.1)	55.0 (53.2-56.9)	97.3 (92.4-102.4)
RR (95% CI)*	Reference	1.67 (1.53-1.82)	2.62 (2.32-2.95)
RR (95% CI)**	Reference	1.58 (1.44-1.73)	2.35 (2.07-2.67)
Cardiovascular death			
N (%)	109 (5.0)	223 (10.7)	84 (15.4)
Event rate per 100 person-years (95% CI)	1.7 (1.4-2.1)	3.7 (3.3-4.3)	5.5 (4.5-6.9)
HR (95% CI)*	Reference	2.26 (1.80-2.85)	3.40 (2.53-4.56)
HR (95% CI)**	Reference	1.87 (1.48-2.36)	2.31 (1.70-3.14)
Non-cardiovascular death			
N (%)	84 (3.9)	141 (6.8)	49 (9.0)
Event rate per 100 person-years (95% CI)	1.3 (1.1-1.6)	2.4 (2.0-2.8)	3.2 (2.4-4.3)
HR (95% CI)*	Reference	1.83 (1.40-2.41)	2.71 (1.88-3.89)
HR (95% CI)**	Reference	1.61 (1.22-2.13)	2.36 (1.62-3.43)
All-cause death			
N (%)	193 (8.9)	364 (17.5)	133 (24.4)
Event rate per 100 person-years (95% CI)	3.0 (2.6-3.5)	6.1 (5.5-6.7)	8.8 (7.4-10.4)
HR (95% CI)*	Reference	2.08 (1.74-2.48)	3.10 (2.47-3.89)
HR (95% CI)**	Reference	1.75 (1.46-2.09)	2.31 (1.83-2.93)
First HF hospitalization or cardiovascular death			
N (%)	301 (13.9)	559 (26.8)	222 (40.7)
Event rate per 100 person-years (95% CI)	5.0 (4.4-5.6)	10.5 (9.6-11.4)	17.8 (15.6-20.3)
HR (95% CI)*	Reference	2.09 (1.82-2.41)	3.28 (2.74-3.92)
HR (95% CI)**	Reference	1.86 (1.61-2.15)	2.56 (2.12-3.09)
First HF hospitalization			
N (%)	218 (10.1)	437 (21.0)	182 (33.3)
Event rate per 100 person-years (95% CI)	3.6 (3.2-4.1)	8.2 (7.4-9.0)	14.6 (12.6-16.9)
HR (95% CI)*	Reference	2.20 (1.87-2.60)	3.48 (2.84-4.26)

HR (95% CI)**	Reference	2.00 (1.69-2.36)	2.84 (2.29-3.52)
Renal composite outcome			
N (%)	19 (0.9)	62 (3.0)	16 (2.9)
Event rate per 100 person-years (95% CI)	0.3 (0.2-0.5)	1.0 (0.8-1.3)	1.1 (0.7-1.7)
HR (95% CI)*	Reference	3.65 (2.17-6.13)	3.54 (1.79-6.99)
HR (95% CI)**	Reference	4.16 (2.43-7.11)	4.11 (2.01-8.38)

CI, confidence interval; FI, frailty index; HF, heart failure; HR, hazard ratio; OR, odds ratio; RR, rate ratio.

**Stratified by region and adjusted for treatment assignment.*

***Stratified by region and adjusted for treatment assignment, age, sex, log of NT-proBNP, HF etiology, HF duration, left ventricular ejection fraction, NYHA functional class.*

P-values and 95% CIs have not been adjusted for multiplicity.

Supplementary Table 4. Adverse events according to Frailty Index

	FI \leq 0.210 (not frail) N=2,165	FI 0.211-0.310 (more frail) N=2,084	FI \geq 0.311 (most frail) N=546
Hypotension			
N (%)	305 (14.1)	255 (12.2)	77 (14.1)
OR (95% CI)*	Reference	0.80 (0.66-0.96)	0.76 (0.57-1.01)
Elevated serum creatinine, mg/dL			
\geq 2.0			
N (%)	111 (5.1)	317 (15.2)	161 (29.5)
OR (95% CI)*	Reference	3.25 (2.58-4.07)	6.77 (5.15-8.91)
\geq 2.5			
N (%)	30 (1.4)	114 (5.5)	62 (11.4)
OR (95% CI)*	Reference	4.12 (2.74-6.20)	8.32 (5.25-13.2)
\geq 3.0			
N (%)	10 (0.5)	45 (2.2)	23 (4.2)
OR (95% CI)*	Reference	4.75 (2.38-9.47)	8.58 (3.98-18.50)
Elevated serum potassium, mmol/L			
>5.5			
N (%)	270 (12.5)	311 (14.9)	96 (17.6)
OR (95% CI)*	Reference	1.24 (1.04-1.48)	1.59 (1.23-2.07)
>6.0			
N (%)	61 (2.8)	91 (4.4)	24 (4.4)
OR (95% CI)*	Reference	1.58 (1.13-2.21)	1.66 (1.01-2.72)
Angioedema			
N (%)	8 (0.4)	7 (0.3)	3 (0.5)
OR (95% CI)*	Reference	0.88 (0.32-2.46)	1.26 (0.31-5.10)

Liver-related adverse event			
N (%)	128 (5.9)	144 (6.9)	57 (10.4)
OR (95% CI)*	Reference	1.19 (0.93-1.53)	1.76 (1.25-2.47)
Discontinuation for reasons other than death			
N (%)	434 (20.0)	611 (29.3)	202 (37.0)
OR (95% CI)*	Reference	1.57 (1.36-1.81)	2.00 (1.62-2.46)
Falls			
N (%)	70 (3.2)	124 (6.0)	51 (9.3)
OR (95% CI)*	Reference	1.56 (1.15-2.12)	1.72 (1.16-2.55)
Fractures			
N (%)	125 (5.8)	154 (7.4)	50 (9.2)
OR (95% CI)*	Reference	1.19 (0.93-1.52)	1.24 (0.87-1.77)

CI, confidence interval; FI, frailty index; OR, odds ratio.

**Stratified by region and adjusted for randomized treatment.*

P-values and 95% CIs have not been adjusted for multiplicity.

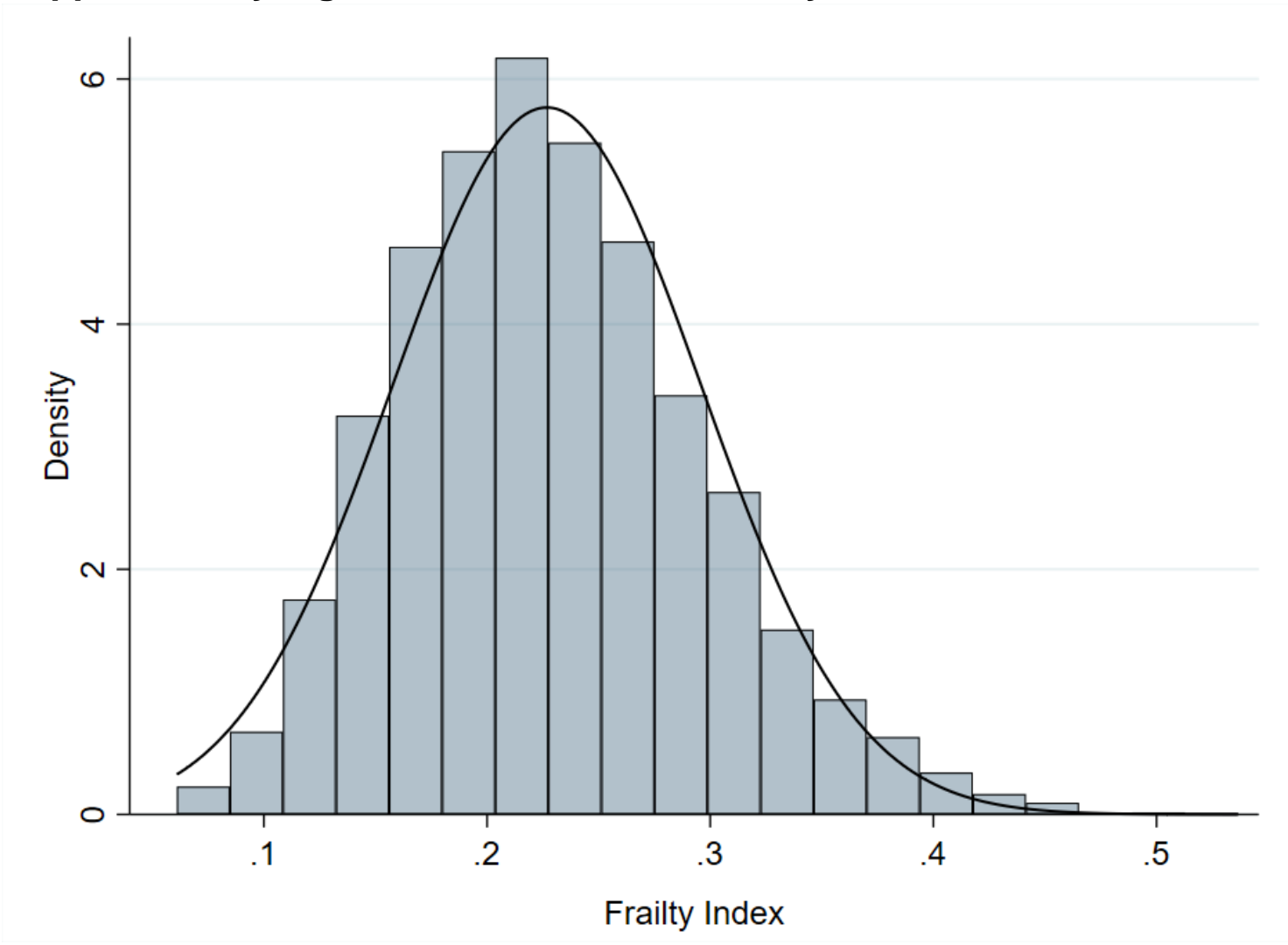
Supplementary Table 5. Adverse events in patients assigned to sacubitril/valsartan or valsartan according to Frailty Index

Adverse event	FI \leq 0.210 (not frail) N=2,165		FI 0.211-0.310 (more frail) N=2,084		FI \geq 0.311 (most frail) N=546		P-value for interaction
	Valsartan N=1,081	Sac/val N=1,084	Valsartan N=1,030	Sac/val N=1,054	Valsartan N=277	Sac/val N=269	
Hypotension	126 (11.7)	179 (16.5)	95 (9.2)	160 (15.2)	36 (13.0)	41 (15.2)	0.44
Elevated serum creatinine, mg/dL							
\geq 2.0	58 (5.4)	53 (4.9)	173 (16.8)	144 (13.7)	97 (35.0)	64 (23.8)	0.23
\geq 2.5	14 (1.3)	16 (1.5)	58 (5.6)	56 (5.3)	37 (13.4)	25 (9.3)	0.44
\geq 3.0	5 (0.5)	5 (0.5)	20 (1.9)	25 (2.4)	15 (5.4)	8 (3.0)	0.30
Elevated serum potassium, mmol/L							
$>$ 5.5	147 (13.6)	123 (11.3)	158 (15.3)	153 (14.5)	56 (20.2)	40 (14.9)	0.38
$>$ 6.0	41 (3.8)	20 (1.8)	48 (4.7)	43 (4.1)	12 (4.3)	12 (4.5)	0.15
Angioedema	2 (0.2)	6 (0.5)	0 (0.0)	7 (0.7)	2 (0.7)	1 (0.4)	N/A
Liver-related adverse event	67 (6.2)	61 (5.6)	78 (7.6)	66 (6.3)	33 (11.9)	24 (8.9)	0.81
Discontinuation for reasons other than death	217 (20.1)	217 (20.0)	309 (30.0)	302 (28.7)	111 (40.1)	91 (33.8)	0.45
Falls	28 (2.6)	42 (3.9)	53 (5.1)	71 (6.7)	29 (10.5)	22 (8.2)	0.13
Fractures	69 (6.4)	56 (5.2)	71 (6.9)	83 (7.9)	27 (9.7)	23 (8.6)	0.30

CI, confidence interval; FI, frailty index.

P-values and 95% CIs have not been adjusted for multiplicity.

Supplementary Figure 1. Distribution of Frailty Index



Higher Frailty Index indicates greater frailty.