

Supplementary Table 1: Components of the Frailty Index (42 items)

<i>Sl.</i>	<i>N</i>	<i>Component</i>	<i>Cut off / Sub-component</i>	<i>Score</i>
	<i>o.</i>			
1.		Diastolic blood pressure – mmHg	>90	1
2.		Pulse pressure – mmHg	>55	1
3.		Systolic blood pressure - mmHg	<90/>140	1
4.		Body Mass Index – kg/m ²	≥25/<30 <18.8/≥30	0.5 1
Laboratory measures				
5.		Albumin- gm/L	<35/>55	1
6.		BUN – mmol/L	<3/>7.5	1
7.		Calcium – mmol/L	<2.2/>2.7	1
8.		Creatinine – umol/L	<40/>150	1
9.		HDL Cholesterol – mmol/L	<0.4/>1.5	1
10.		Potassium – mmol/L	<3.5/>6	1
11.		RBC count – X10 ⁹ /L	<3.5/>5.5	1
12.		Sodium – mmol/L	<135/>145	1
13.		Total Cholesterol – mmol/L	<3.5/>7	1
14.		Uric acid – umol/L	Males - <200/>430 Females - <140/ >360	1 1
15.		Haemoglobin – gm/L	Males - <130/>175 Females - <120/>155	1 1
16.		Platelet count - X10 ⁹ /L	<150/>400	1
17.		WBC count – X10 ⁹ /L	<4/>12	1
Comorbidities				
18.		Atrial Fibrillation		1
19.		Hypertension		1
20.		Myocardial Infarction		1

0.		
2	PCI or CABG	1
1.		
2	Unstable angina	1
2.		
2	Peripheral arterial disease	1
3.		
2	Stroke	1
4.		
2	Diabetes	1
5.		
2	Cancer	1
6.		
2	COPD	1
7.		

Quality of life measures – Kansas City cardiomyopathy questionnaire (all responses with respect to the two weeks prior to questioning)

Mobility

		<u>Dressing yourself:</u>	
		<i>Not at all limited</i>	0
		<i>Limited for other reasons or did not do the activity</i>	0.2
2		<i>Slightly limited</i>	0.4
8.		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8
		<i>Extremely limited</i>	1
		<u>Showering/bathing:</u>	
		<i>Not at all limited</i>	0
		<i>Limited for other reasons or did not do the activity</i>	0.2
2	Limited activities due to heart failure	<i>Slightly limited</i>	0.4
9.		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8
		<i>Extremely limited</i>	1
		<u>Walking 1 block on level ground:</u>	
		<i>Not at all limited</i>	0
		<i>Limited for other reasons or did not do the activity</i>	0.2
3		<i>Slightly limited</i>	0.4
0.		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8

		<i>Extremely limited</i>	1
		<u>Doing yardwork, housework, or carrying groceries:</u>	
		<i>Not at all limited</i>	0
3		<i>Limited for other reasons or did not do the activity</i>	0.2
1.		<i>Slightly limited</i>	0.4
		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8
		<i>Extremely limited</i>	1
		<u>Climbing a flight of stairs without stopping:</u>	
		<i>Not at all limited</i>	0
3		<i>Limited for other reasons or did not do the activity</i>	0.2
2.		<i>Slightly limited</i>	0.4
		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8
		<i>Extremely limited</i>	1
		<u>Hurrying or jogging:</u>	
		<i>Not at all limited</i>	0
3		<i>Limited for other reasons or did not do the activity</i>	0.2
3.		<i>Slightly limited</i>	0.4
		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8
		<i>Extremely limited</i>	1
Memory and cognitive abilities			
		Completely sure	0
		Mostly sure	0.2
3	Are you sure you know what to do or whom to call if your heart failure		5
4.	gets worse	somewhat sure	0.5
		Not very sure	0.7
		Not at all sure	1
		Completely understand	0
		Mostly understand	0.2
3	How well do you understand what things you can do to keep your heart		5
5.	failure symptoms from getting worse	Somewhat understand	0.5
		Do not understand very well	0.7
		Do not understand at all	1

Mood vulnerabilities

		Completely satisfied	0
		Mostly satisfied	0.2
3	How would you feel if you had to spend rest of life with heart failure the		5
6.	way it is right now	Somewhat satisfied	0.5
		Mostly dissatisfied	0.7
			5
		Completely dissatisfied	1
		I never felt that way	0
		I have rarely felt that way	0.2
			5
3	How often have you felt discouraged or down in dumps because of your	I have occasionally felt that way	0.5
7.	heart failure	I have felt that way most of the	0.7
		time	5
		I have felt that way all the time	1

Functional abilities

		It has not limited my enjoyment	0
		of life at all	
		It has slightly limited my	0.2
		enjoyment of life	5
3	How much has heart failure limited enjoyment of life	It has moderately limited my	0.5
8.		enjoyment of life	
		It has limited my enjoyment of	0.7
		life quite a bit	5
		It has extremely limited my	1
		enjoyment of life	
		<u>Hobbies, recreational activities:</u>	
		<i>Did not limit at all</i>	0
		<i>Does not apply or did not do for</i>	0.2
3		<i>other reasons</i>	
9.		<i>Slightly limited</i>	0.4
		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8
		<i>Extremely limited</i>	1
	How does heart failure affect lifestyle	<u>Working or doing household</u>	
		<u>chores:</u>	
		<i>Did not limit at all</i>	0
4		<i>Does not apply or did not do for</i>	0.2
0.		<i>other reasons</i>	
		<i>Slightly limited</i>	0.4
		<i>Moderately limited</i>	0.6
		<i>Quite a bit limited</i>	0.8

	<i>Extremely limited</i>	1
	<u>Visiting family or friends out of your home:</u>	
	<i>Did not limit at all</i>	0
4	<i>Does not apply or did not do for other reasons</i>	0.2
1.	<i>Slightly limited</i>	0.4
	<i>Moderately limited</i>	0.6
	<i>Quite a bit limited</i>	0.8
	<i>Extremely limited</i>	1
	<u>Intimate relationships with loved ones:</u>	
	<i>Did not limit at all</i>	0
4	<i>Does not apply or did not do for other reasons</i>	0.2
2.	<i>Slightly limited</i>	0.4
	<i>Moderately limited</i>	0.6
	<i>Quite a bit limited</i>	0.8
	<i>Extremely limited</i>	1

BUN – Blood urea nitrogen, HDL – High density lipoprotein, WBC – White blood cell, PCI – Primary coronary intervention, CABG – Coronary artery bypass graft, COPD – Chronic obstructive pulmonary disease, BMI – Body mass index.

Supplementary Table 2: State of Health Score (EQ-5D-3L) (PARADIGM-HF only) – no. (%)

	FI Class 1	FI Class 2	FI Class 3	p-value for trend
	n=2836 (≤0.210)	n=2663 (0.211 – 0.310)	n=1972 (≥0.311)	
Mobility				<0.001
I have no problems in walking about	2305 (81.4)	1374 (51.7)	451 (22.9)	
I have some problems in walking about	524 (18.5)	1280 (48.1)	1506 (76.6)	
I am confined to bed	1 (0.1)	5 (0.2)	10 (0.5)	
Self-care				<0.001
I have no problems with self-care	2745 (97.0)	2280 (85.7)	1172 (59.6)	
I have some problems washing or dressing myself	84 (3.0)	370 (13.9)	776 (39.5)	
I am unable to wash or dress myself	1 (0.0)	9 (0.3)	19 (1.0)	
Usual activities				<0.001
I have no problems with performing my usual activities	2371 (83.8)	1409 (53.0)	481 (24.5)	
I have some problems with performing my usual activities	450 (15.9)	1216 (45.7)	1344 (68.3)	
I am unable to perform my usual activities	9 (0.3)	33 (1.2)	142 (7.2)	
Pain/ Discomfort				<0.001
I have no pain or discomfort	2095 (74.0)	1433 (53.9)	617 (31.4)	
I have moderate pain or discomfort	716 (25.3)	1188 (44.7)	1255 (63.8)	
I have extreme pain or discomfort	19 (0.7)	37 (1.4)	95 (4.8)	
Anxiety/ Depression				<0.001
I am not anxious or depressed	2300	1750 (65.8)	912 (46.4)	

	(81.3)			
I am moderately anxious or depressed	505 (17.8)	882 (33.2)	970 (49.3)	
I am extremely anxious or depressed	25 (0.9)	27 (1.0)	85 (4.3)	
Overall Score – mean (SD)	75.1 ± 18.9	66.1 ± 18.0	56.0 ± 17.9	<<0.001

Supplementary Table 3: Biomarkers (PARADIGM-HF only)

	FI Class 1	FI Class 2	FI Class 3	p-value for trend	Missing
	n=2836 (≤0.210)	n=2663 (0.211 – 0.310)	n=1972 (≥0.311)		
HbA1C – no (%)				<0.001	67
Prediabetes (6-6.4)	700 (32.4)	612 (36.6)	402 (40.9)		
Undiagnosed Diabetes (>6.4)	299 (13.8)	282 (16.8)	158 (16.1)		
NT-proBNP (pg/ml)	1364 (817 – 2736)	1653 (906 – 3204)	1885 (1037 – 3961)	<0.001	14
BNP (pg/ml)	66 (41 – 121)	73 (45 – 132)	82 (49 – 149)	<0.001	55
MMP2 (ng/mL)	128 (113 - 148)	136 (116 - 159)	138 (120 - 162)	<0.001	6130
MMP9 (ng/mL)	62 (39 - 132)	64 (41 - 124)	63 (37 - 126)	0.562	6131
hsTropT (ng/L)	14 (9 - 20)	16 (11 - 24)	21 (13 - 31)	<0.001	5919
GDF 15 (ng/L)	1387 (1020 - 1914)	1645 (1148 - 2287)	2035 (1440 - 3038)	<0.001	5991
KIM-1 (pg/mL)	108 (74 - 159)	133 (91 - 189)	154 (101 - 233)	<0.001	5986
ST2 (ng/mL)	31 (25 - 39)	32 (26 - 41)	34 (27 - 45)	<0.001	5948
TIMP 1 (ng/mL)	116 (99 - 141)	124 (105 - 147)	136 (114 - 165)	<0.001	6115
Galectin – 3 (ng/mL)	16 (13 - 19)	17 (14 - 21)	19 (15 - 23)	<0.001	5920

All values presented as median (IQR) except where indicated.

HbA1c is randomization.

BNP and NTproBNP are screening values.

Remaining biomarkers are from visit 2 (after screening).

Supplementary Table 4: Immunization and lifestyle management history (PARADIGM-HF only) – no. (%)

	FI Class 1	FI Class 2	FI Class 3	p-value for trend
	n=2836 (≤0.210)	n=2663 (0.211 – 0.310)	n=1972 (≥0.311)	
Influenza vaccination in past 12 months	557 (19.6)	603 (22.6)	526 (26.7)	<0.001
Pneumococcal Vaccination in past 12 months	155 (5.5)	161 (6.0)	144 (7.3)	0.010
Patient been prescribed an exercise regimen	532 (18.8)	456 (17.1)	385 (19.5)	0.658
Patient enrolled in structured disease management program	418 (14.7)	461 (17.3)	352 (17.8)	0.003

Supplementary Table 5a: Clinical outcomes according to age and FI in patients with HFReF

	FI Class 1 n=4882 (≤0.210)	FI Class 2 n=4770 (0.211 – 0.310)	FI Class 3 n=3613 (≥0.311)
<u>18 – 60 years</u>			
Primary outcome – event rate	8.9 (8.2 – 9.7)	11.6 (10.6 – 12.8)	15.1 (13.6 – 16.9)
– sHR	1.00 (ref.)	1.33 (1.17 – 1.52) <0.001	1.76 (1.51 – 2.05) <0.001
HF hospitalization – event rate	5.0 (5.9 – 7.5)	6.6 (5.9 – 7.5)	9.4 (8.2 – 10.8)
– sHR	1.00 (ref.)	1.24 (1.04 – 1.47) 0.014	1.64 (1.36 – 1.99) <0.001
Cardiovascular death – event rate	5.3 (4.8 – 5.9)	6.4 (5.7 – 7.3)	8.3 (7.2 – 9.5)
– sHR	1.00 (ref.)	1.33 (1.12 – 1.57) 0.001	1.84 (1.52 – 2.23) <0.001
All-cause death – event rate	6.0 (5.4 – 6.7)	7.2 (6.4 – 8.0)	9.6 (8.4 – 10.9)
- HR	1.00 (ref.)	1.29 (1.10 – 1.51) 0.002	1.85 (1.55 – 2.21) <0.001
<u>61 – 70 years</u>			
Primary outcome – event rate	8.2 (7.3 – 9.1)	11.9 (10.8 – 13.0)	16.1 (14.6 – 17.7)
– sHR	1.00 (ref.)	1.48 (1.28 – 1.71) <0.001	2.04 (1.75 – 2.37) <0.001
HF hospitalization – event rate	4.8 (4.2 – 5.5)	7.1 (6.3 – 8.0)	9.7 (8.5 – 11.0)
– sHR	1.00 (ref.)	1.42 (1.18 – 1.70) <0.001	1.87 (1.54 – 2.28) <0.001
Cardiovascular death – event rate	4.6 (4.0 – 5.3)	6.6 (5.9 – 7.4)	9.3 (8.3 – 10.5)
– sHR	1.00 (ref.)	1.48 (1.23 – 1.78) <0.001	2.20 (1.81 – 2.67) <0.001
All-cause death – event rate	5.8 (5.1 – 6.5)	8.1 (7.3 – 9.0)	11.3 (10.1 – 12.6)
- HR	1.00 (ref.)	1.47 (1.25 – 1.74) <0.001	2.15 (1.81 – 2.56) <0.001

71 – 96 years

Primary outcome – event rate	9.6 (8.5 – 10.8)	11.4 (10.4 – 12.5)	19.2 (17.7 – 20.8)
– sHR	1.00 (ref.)	1.20 (1.03 – 1.40) 0.018	1.99 (1.71 – 2.31) <0.001
HF hospitalization – event rate	5.2 (4.4 – 6.2)	6.2 (5.5 – 7.1)	11.3 (10.1 – 12.5)
– sHR	1.00 (ref.)	1.13 (0.92 – 1.40) 0.233	1.87 (1.53 – 2.29) <0.001
Cardiovascular death – event rate	6.1 (5.2 – 7.0)	7.3 (6.5 – 8.2)	11.8 (10.7 – 13.0)
– sHR	1.00 (ref.)	1.26 (1.05 – 1.52) 0.014	2.07 (1.73 – 2.49) <0.001
All-cause death – event rate	7.6 (6.7 – 8.7)	9.3 (8.4 – 10.3)	14.8 (13.5 – 16.1)
- HR	1.00 (ref.)	1.30 (1.10 – 1.53) 0.002	2.17 (1.84 – 2.55) <0.001

Supplementary Table 5b: Clinical outcomes according to age and FI in patients with HFref (≥60 years)

	FI Class 1 n=2836 (<=0.210)	FI Class 2 n=3369 (0.211 – 0.310)	FI Class 3 n=2878 (>=0.311)
60 – 66 years			
Primary outcome – event rate	8.2 (7.3 – 9.3)	11.5 (10.3 – 12.8)	15.3 (13.7 – 17.2)
– sHR	1.00 (ref.)	1.44 (1.22 – 1.70) <0.001	1.98 (1.66 – 2.37) <0.001
HF hospitalization – event rate	4.7 (4.0 – 5.5)	6.5 (5.6 – 7.5)	9.5 (8.2 – 11.0)
– sHR	1.00 (ref.)	1.32 (1.06 – 1.65) 0.012	1.90 (1.51 – 2.38) <0.001
Cardiovascular death – event rate	4.8 (4.1 – 5.6)	6.4 (5.6 – 7.4)	8.8 (7.6 – 10.2)
– sHR	1.00 (ref.)	1.44 (1.16 – 1.79) 0.001	2.09 (1.66 – 2.63) <0.001
All-cause death – event rate	5.7 (4.9 – 6.5)	7.8 (6.8 – 8.9)	10.4 (9.1 – 11.8)
- HR	1.00 (ref.)	1.48 (1.22 – 1.80) <0.001	2.08 (1.69 – 2.56) <0.001

67 – 73 years

Primary outcome – event rate	8.7 (7.6 – 10.0)	12.0 (10.7 – 13.4)	16.6 (14.9 – 18.6)
– sHR	1.00 (ref.)	1.39 (1.17 – 1.66) <0.001	1.93 (1.61 – 2.31) <0.001
HF hospitalization – event rate	5.0 (4.1 – 5.9)	7.2 (6.3 – 8.3)	9.9 (8.6 – 11.5)
– sHR	1.00 (ref.)	1.43 (1.14 – 1.79) 0.002	1.86 (1.47 – 2.37) <0.001
Cardiovascular death – event rate	5.1 (4.3 – 6.0)	6.6 (5.7 – 7.6)	10.1 (8.8 – 11.6)
– sHR	1.00 (ref.)	1.35 (1.08 – 1.69) 0.008	2.12 (1.70 – 2.66) <0.001
All-cause death – event rate	6.5 (5.6 – 7.6)	8.1 (7.1 – 9.1)	12.5 (11.0 – 14.1)
- HR	1.00 (ref.)	1.29 (1.06 – 1.57) 0.012	2.11 (1.72 – 2.58) <0.001
<u>74 – 96 years</u>			
Primary outcome – event rate	9.3 (8.0 – 10.9)	11.4 (10.1 – 12.7)	20.5 (18.7 – 22.5)
– sHR	1.00 (ref.)	1.22 (1.00 – 1.48) 0.045	2.14 (1.78 – 2.58) <0.001
HF hospitalization – event rate	5.0 (4.1 – 6.2)	6.2 (5.3 – 7.2)	11.8 (10.4 – 13.3)
– sHR	1.00 (ref.)	1.15 (0.88 – 1.49) 0.304	1.95 (1.52 – 2.51) <0.001
Cardiovascular death – event rate	6.2 (5.2 – 7.4)	7.7 (6.7 – 8.7)	12.5 (11.2 – 14.0)
– sHR	1.00 (ref.)	1.28 (1.02 – 1.61) 0.034	2.12 (1.70 – 2.64) <0.001
All-cause death – event rate	7.9 (6.7 – 9.3)	10.0 (8.9 – 11.2)	15.8 (14.3 – 17.4)
- HR	1.00 (ref.)	1.33 (1.09 – 1.63) 0.005	2.23 (1.83 – 2.72) <0.001

All events are reported as event rates per 100 patient years (95% confidence interval).

All sHRs reported are only adjusted for randomized treatment and region at baseline.

Age is categorized by tertiles of age.

Supplementary Table 6: Clinical Outcomes according to frailty in patients aged ≥60 years

	FI Class 1	FI Class 2	FI Class 3
	n=2836	n=3369	n=2787
	(≤0.210)	(0.211 – 0.310)	(≥0.311)
Primary Outcome			
Events – no (%)	633 (22.3)	937 (27.8)	1038 (37.2)
Event rate per 100 pt. years (CI)	8.7 (8.0 - 9.4)	11.6 (10.9 - 12.4)	17.6 (16.6 - 18.8)
Unadjusted sHR	1.00 (ref)	1.37 (1.24 - 1.51)	2.08 (1.88 - 2.31)
		<0.001	<0.001
Adjusted sHR	1.00 (ref)	1.30 (1.17 - 1.44)	1.85 (1.66 - 2.07)
		<0.001	<0.001
HF Hospitalization			
Events – no (%)	356 (12.6)	536 (15.9)	616 (22.1)
Event rate per 100 pt. years	4.9 (4.4 - 5.4)	6.6 (6.1 - 7.2)	10.5 (9.7 - 11.3)
Unadjusted sHR	1.00 (ref)	1.33 (1.17 - 1.53)	2.01 (1.75 - 2.30)
		<0.001	<0.001
Adjusted sHR	1.00 (ref)	1.29 (1.12 - 1.48)	1.88 (1.62 - 2.17)
		<0.001	<0.001
CV Death			
Events – no (%)	405 (14.3)	603 (17.9)	705 (25.3)
Event rate per 100 pt. years	5.2 (4.7 - 5.8)	6.9 (6.3 - 7.4)	10.6 (9.8 - 11.4)
Unadjusted sHR	1.00 (ref)	1.39 (1.22 - 1.57)	2.21 (1.94 - 2.51)
		<0.001	<0.001
Adjusted sHR	1.00 (ref)	1.30 (1.14 - 1.48)	1.85 (1.61 - 2.13)
		<0.001	<0.001
All-cause Death			
Events – no (%)	503 (17.7)	752 (22.3)	869 (31.2)
Event rate per 100 pt. years	6.5 (6.0 - 7.1)	8.6 (8.0 - 9.2)	13.1 (12.2 - 14.0)
Unadjusted HR	1.00 (ref)	1.41 (1.25 - 1.58)	2.26 (2.01 - 2.53)
		<0.001	<0.001
Adjusted HR	1.00 (ref)	1.31 (1.17 - 1.48)	1.92 (1.70 - 2.18)
		<0.001	<0.001
Fall in KCCQ clinical summary score ≥5 at			
12 months			
No. (%)	950 (34.5)	1179 (36.4)	980 (37.4)
Adjusted OR1	1.00 (ref.)	1.33 (1.18 - 1.49)	1.88 (1.60 - 2.20)
		<0.001	<0.001

Adjusted OR2	1.00 (ref.)	1.24 (1.10 - 1.40)	1.70 (1.44 - 2.00)
		0.001	<0.001

Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause death]

Event rates per 100 patient years with 95% confidence interval

All sHRs adjusted for region and randomized treatment at baseline

Adjusted sHRs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class I/II vs. II/IV, duration of heart failure and ejection fraction.

Heart failure hospitalization additionally adjusted for previous hospitalization for heart failure.

Odds ratio reported as OR (95% confidence interval)

ORs adjusted for region and randomized treatment at baseline

Adjusted OR1 additionally adjusted for: KCCQ clinical summary score at baseline

Adjusted OR2 additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class and ejection fraction.

Supplementary Table 7: Clinical Outcomes according to every 0.010 increase in the Frailty Index score

	Unadjusted sHR	Adjusted sHR
Primary Outcome	1.032 (1.028 – 1.036) <0.001	1.026 (1.022 – 1.030) <0.001
HF Hospitalization	1.030 (1.025 – 1.034) <0.001	1.025 (1.020 – 1.030) <0.001
CV Death	1.034 (1.029 – 1.038) <0.001	1.025 (1.020 – 1.030) <0.001
All-cause Death	1.035 (1.031 – 1.039) <0.001	1.026 (1.022 – 1.030) <0.001

Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause death]

All sHRs adjusted for region and randomized treatment at baseline

Adjusted sHRs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class I/II vs. II/IV, duration of heart failure and ejection fraction.

Heart failure hospitalization additionally adjusted for previous hospitalization for heart failure.

Odds ratio reported as OR (95% confidence interval)

ORs adjusted for region and randomized treatment at baseline

Adjusted OR1 additionally adjusted for: KCCQ clinical summary score at baseline

Adjusted OR2 additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class and ejection fraction.

Supplementary Table 8: Number of hospitalizations in patients according to Frailty – no. (%)

	FI Class 1 n=4882 (≤0.210)	FI Class 2 n=4770 (0.211 – 0.310)	FI Class 3 n=3613 (≥0.311)	p-value for trend
HF Hospitalization				<0.001
0	4257 (87.2)	4011 (84.1)	2826 (78.2)	
1	429 (8.8)	484 (10.1)	476 (13.2)	
≥2	196 (4.0)	275 (5.8)	311 (8.6)	
CV Hospitalization				<0.001
0	3576 (73.2)	3165 (66.4)	2136 (59.1)	
1	780 (16.0)	905 (19.0)	775 (21.5)	
≥2	526 (10.8)	700 (14.7)	702 (19.4)	
Non-CV Hospitalization				<0.001
0	3794 (77.7)	3509 (73.6)	2455 (67.9)	
1	730 (15.0)	800 (16.8)	660 (18.3)	
≥2	358 (7.3)	461 (9.7)	498 (13.8)	
Non-CV Hospitalization				<0.001
0	2913 (59.7)	2502 (52.5)	1589 (44.0)	
1	1054 (21.6)	1069 (22.4)	861 (23.8)	
≥2	915 (18.7)	1199 (25.1)	1163 (32.2)	

Supplementary Table 9: Falls and Fractures

	FI Class 1	FI Class 2	FI Class 3
	n=4882	n=4770	n=3613
	(≤0.210)	(0.211 – 0.310)	(≥0.311)
Falls			
Events – no. (%)	52 (1.1)	95 (2.0)	92 (2.5)
Unadjusted OR	1.00 (ref.)	1.76 (1.24 – 2.49)	2.07 (1.45 – 2.95)
		0.001	<0.001
Adjusted OR	1.00 (ref.)	1.71 (1.19 - 2.45)	1.94 (1.32 - 2.85)
		0.004	0.001
Fractures			
Events – no. (%)	116 (2.4)	158 (3.4)	157 (4.3)
Unadjusted OR	1.00 (ref.)	1.32 (1.03 – 1.69)	1.68 (1.30 – 2.17)
		0.030	<0.001
Adjusted OR	1.00 (ref.)	1.28 (0.99 - 1.65)	1.57 (1.19 - 2.07)
		0.061	0.001

Odds ratio reported as OR (95% confidence interval)

All ORs adjusted for region and randomized treatment at baseline

Adjusted ORs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class, ejection fraction and duration of HF.

Supplementary Table 10: Adverse Events – no. (%)

	FI Class 1	FI Class 2	FI Class 3	p-value for trend
	n=4882	n=4770	n=3613	
	(≤0.210)	(0.211 – 0.310)	(≥0.311)	
Cough	573 (11.7)	482 (10.1)	391 (10.8)	0.126
Hypotension	520 (10.7)	578 (12.1)	510 (14.1)	<0.001
Hyperkalaemia	400 (8.2)	596 (12.5)	458 (12.7)	<0.001
Angioedema	11 (0.2)	12 (0.3)	9 (0.2)	0.813
Any adverse event leading to treatment withdrawal	662 (13.6)	784 (16.4)	728 (20.1)	<0.001