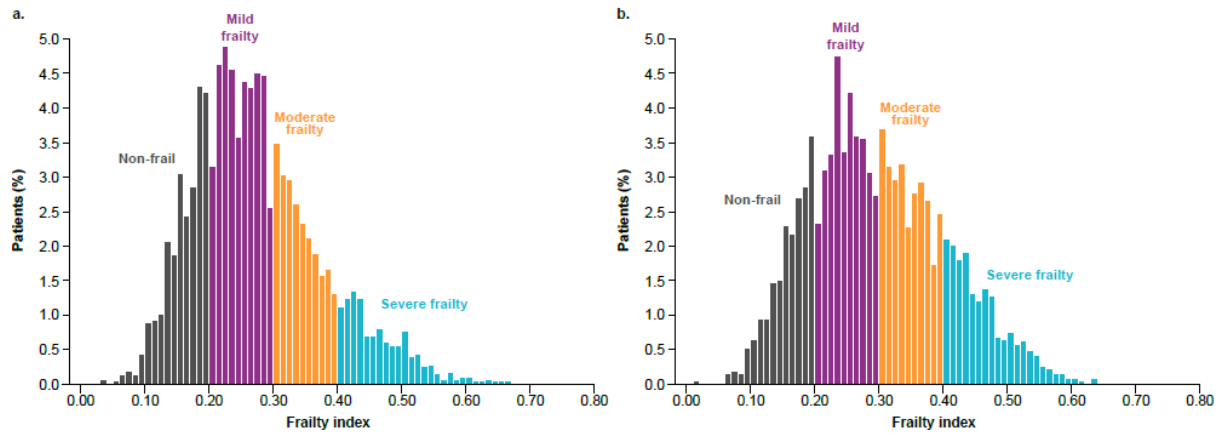
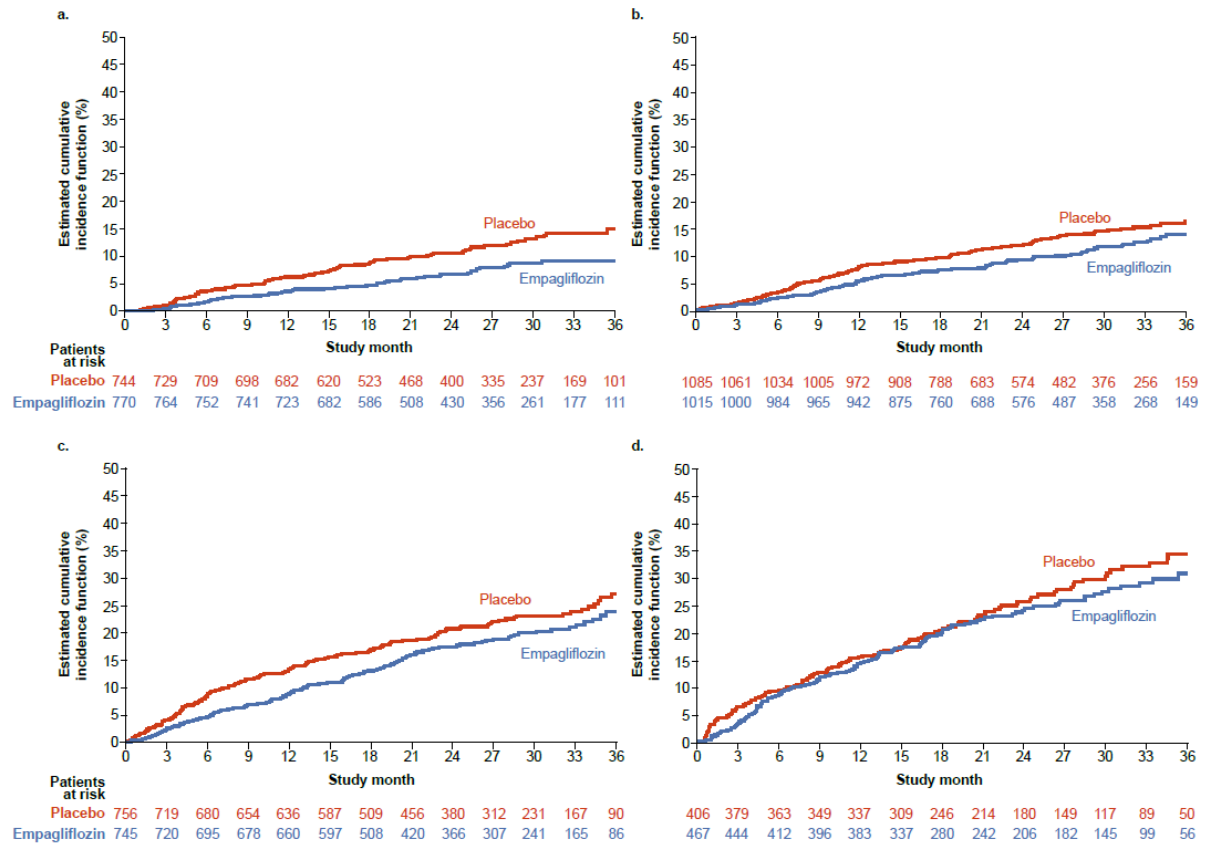


Supplementary Figures

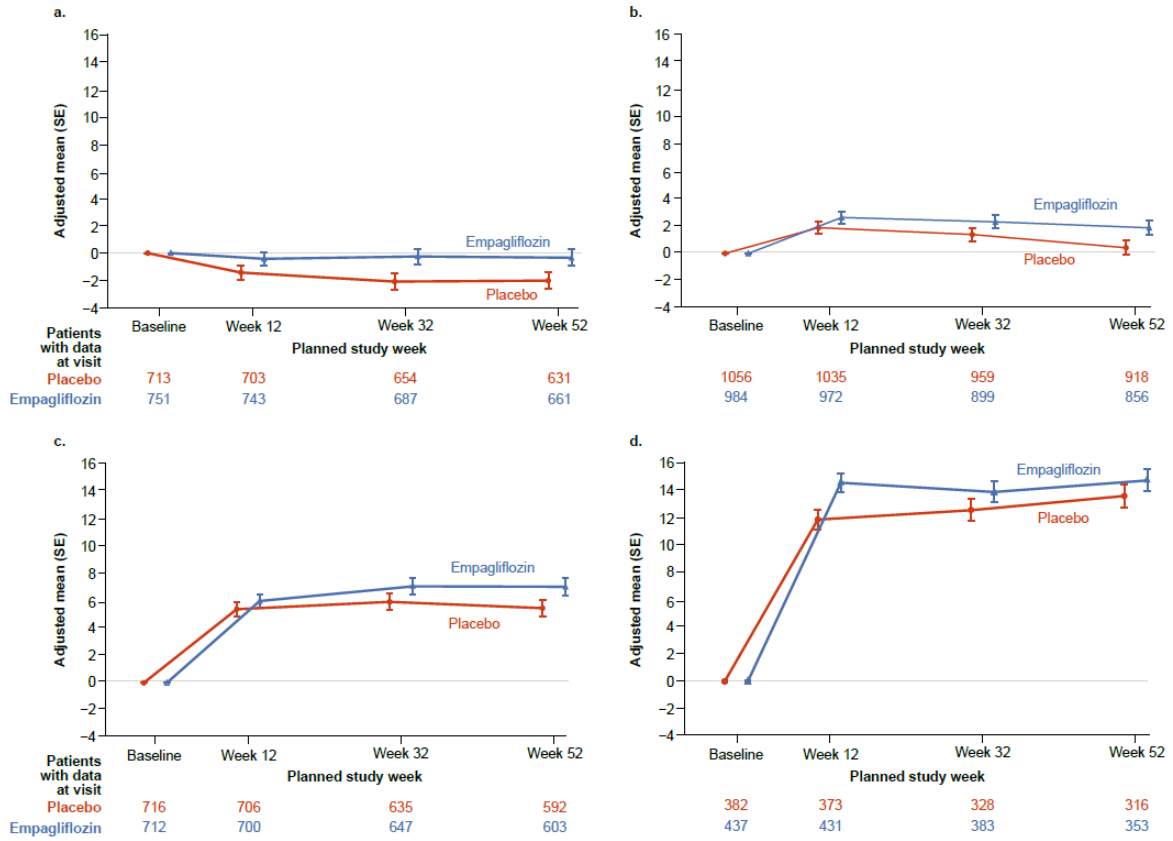
Supplementary Figure 1 Distribution of Frailty Index by sex a) Men b) Women



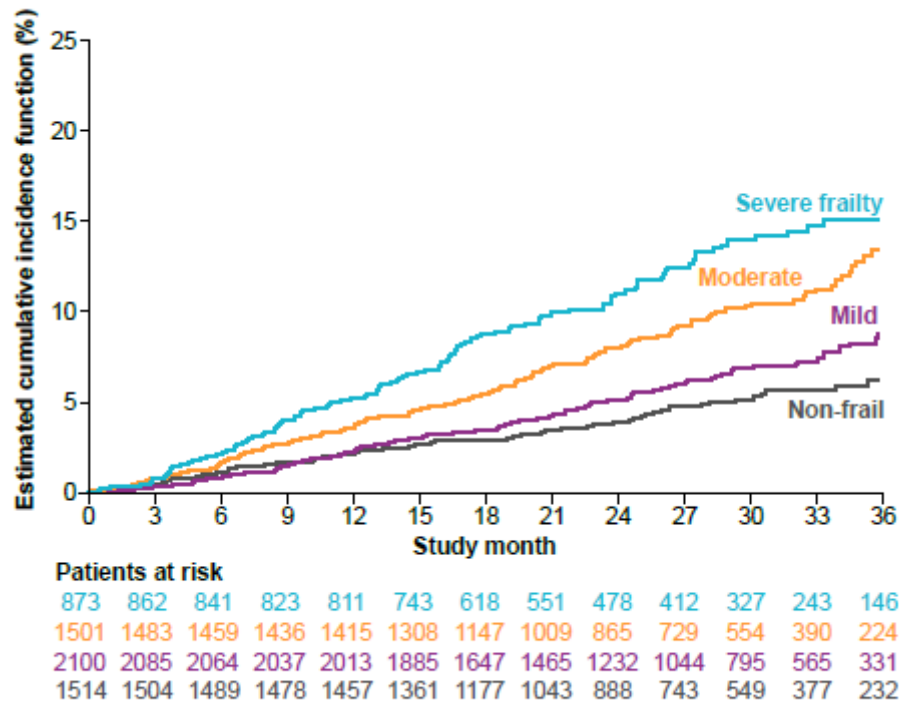
Supplementary Figure 2: Effect of Empagliflozin vs. Placebo: CV Death or HHF (Primary Outcome) by Baseline Frailty a) Non-frail (<0.21) b) Mild Frailty (0.21-<0.3) c) Moderate Frailty (0.3-<0.4) d) Severe Frailty (>=0.4)



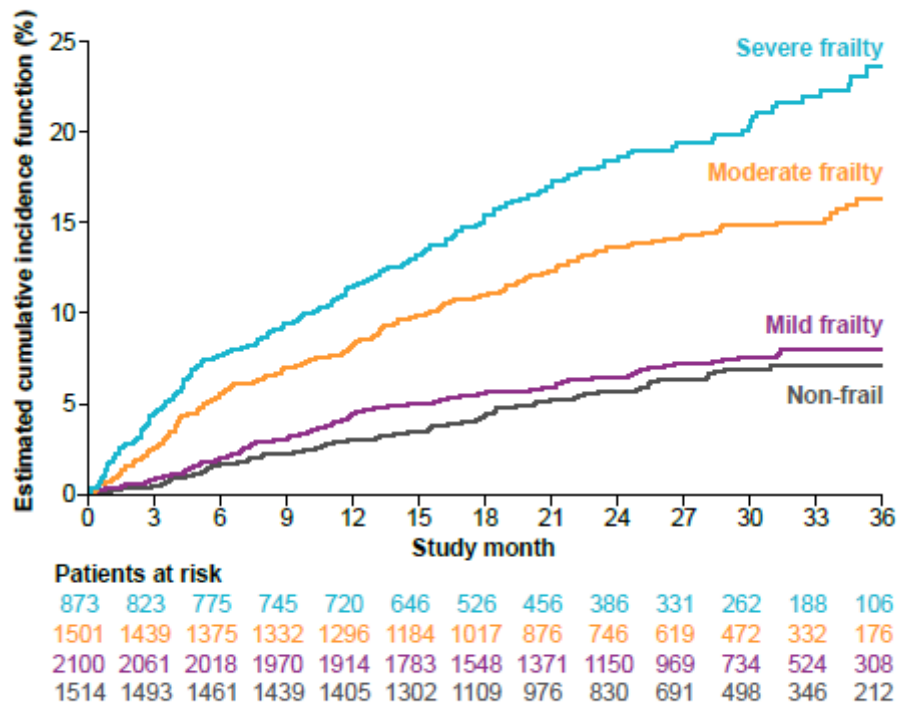
Supplementary Figure 3: Effect of Empagliflozin vs. Placebo: KCCQ-CSS Change From Baseline by Baseline Frailty a) Non-frail (<0.21) b) Mild Frailty (0.21-<0.3) c) Moderate Frailty (0.3-<0.4) d) Severe Frailty (>=0.4)



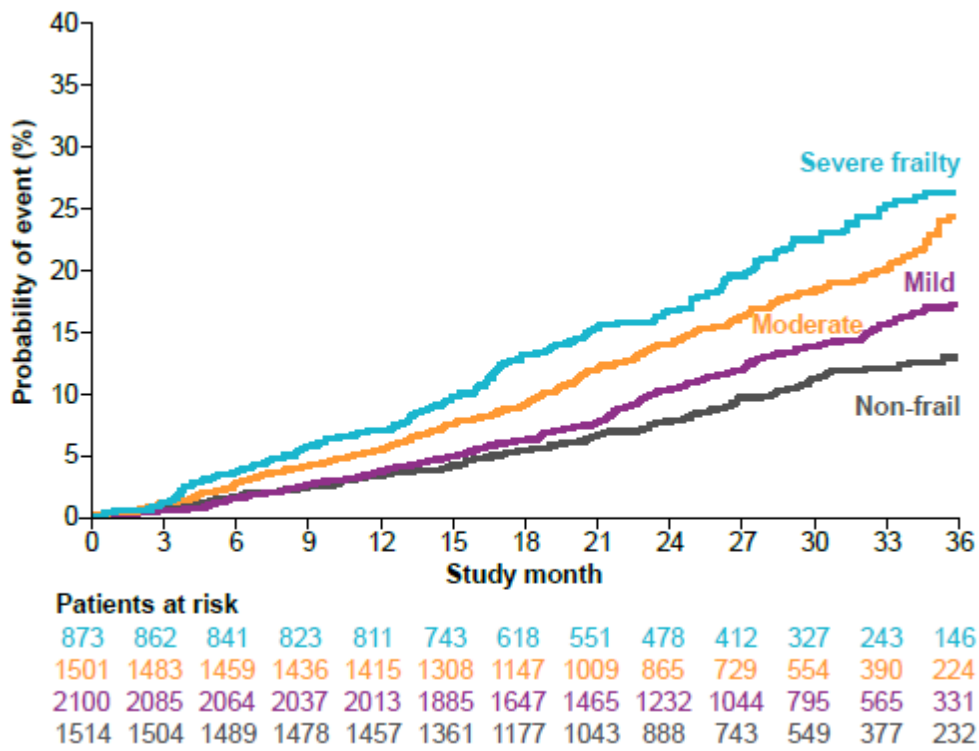
Supplementary Figure 4 Time to CV death by frailty index



Supplementary Figure 5 Time to first HHF by frailty index



Supplementary Figure 6: Time to all-cause mortality by frailty index



Supplementary tables

Supplementary Table 1: List of parameters to calculate Frailty Index

	Parameter	Response	Score
1	Body mass index (BMI) (kg/m ²)	≥35.0	1
		30.0 - <35.0	0.75
		22.0 - <30.0	0
		18.5 - <22.0	0.5
		< 18.5	1
2	Diastolic BP, high (mmHg)	≥90	1
3	eGFR (ml/min/1.73 m ²)	≥60	0
		45 to <60	0.5
		30 to <45	0.75
		<30	1.0
4	Fasting glucose (mmol/L)	>15 or <0.9	1
5	Hemoglobin (g/dl)	>18 or <10.5	1
6	Potassium (mmol/L)	>5.5 or <3.5	1
7	Sodium (mEq/L)	>150 or <135	1
8	Platelet count	<5th percentile or >95th percentile	1
9	Pulse pressure (mmHg)	>55	1
10	Systolic BP(mmHg)	≥140 or ≤90	1
11	White blood cell count	<5th percentile or >95th percentile	1
12	Albumin (g/dL)	<3.2 or >4.5	1
	Co-morbid Illness/ Medications at baseline		
13	Coronary artery disease	yes	1
14	Atrial fibrillation or flutter	yes	1
15	Diabetes	yes	1
16	Hypertension	yes	1
17	Myocardial infarction	yes	1
18	PCI or CABG	yes	1
19	Chronic obstructive pulmonary disease	yes	1
20	Stroke	yes	1
21	Lipid lowering drugs: Niacin, Fibrates, statins, Ezetimibe, PCSK9 or other lipid lowering drugs	yes	1
22	Total number medications at baseline (n)	n <8	0
		8 ≤ n <12	0.5
		n ≥12	1
23	History of HHF (in the last 12	Yes	1

	months)		
	Quality of Life Measures		
	Kansas City Cardiomyopathy Questionnaire (KCCQ)		
24	KCCQ Q1: Indicate how much you are limited by heart failure in your ability to do the following activities over the last 2 weeks: a) Dressing yourself b) Showering/Bathing c) Walking 1 block on level ground d) Doing yardwork, housework or carrying groceries e) Climbing a flight of stairs without stopping f) Hurrying or jogging (as if to catch a bus)	Physical limitation score < 50	1
25	KCCQ Q2: Compared with 2 weeks ago, my symptoms of heart failure have become	Much worse	1
		Slightly worse	0.75
		Not changed	0.5
		Slightly better	0.25
		Much better/no symptoms	0
26	KCCQ Q3: Over the past 2 weeks, how many times did you have swelling in your feet, ankles, or legs when you woke up in the morning?	Every morning	1
		3 or more times per week but not every day	0.75
		1-2 times a week	0.5
		Less than once a week	0.25
		Never over the past 2 weeks	0
27	KCCQ Q4: Over the past 2 weeks, how much has swelling in your feet, ankles, or legs bothered you?	Extremely bothersome	1
		Quite a bit bothersome	0.75
		Moderately bothersome	0.5
		Slightly bothersome	0.25
		Not at all bother some/ No Swelling	0
28	KCCQ Q5: Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?	All of the time	1
		Several times per day	0.8
		At least once a day	0.6
		3 or more times per week, but not every day	0.4
		1-2 times per week	0.2
		Less than once a week or never over the past 2 weeks	0
29	KCCQ Q6: Over the past 2 weeks, how much has your fatigued bothered you?	Extremely bothersome	1
		Quite a bit bothersome	0.75
		Moderately bothersome	0.5
		Slightly bothersome	0.25
		Not bothersome at all, no fatigue	0
30	KCCQ Q7: Over the past 2 weeks, on average, how many times has shortness of breath (SOB) limited your ability to do what you wanted?	All of the time	1
		Several times per day	0.8
		At least once a day	0.6
		3 or more times per week, but not every day	0.4
		1-2 times per week	0.2

		Less than once a week, never	0
31	KCCQ Q8: Over the past 2 weeks, how much has your shortness of breath (SOB) bothered you?	Extremely bothersome	1
		Quite a bit bothersome	0.75
		Moderately bothersome	0.5
		Slightly bothersome	0.25
		Not bothersome at all, no SOB	0
32	KCCQ Q9: Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of SOB?	Every night	1
		3 or more times a week but not every day	0.75
		1-2 times per week	0.5
		Less than once a week	0.25
		Never	0
33	KCCQ Q10: How sure are you that you know what to do or whom to call if your heart failure gets worse?	Not at all sure	1
		Not very sure	0.75
		Somewhat sure	0.5
		Mostly sure	0.25
		Completely sure	0
34	KCCQ Q11: How well do you understand what things you are able to do to keep your heart failure symptom from getting worse?	Do not understand at all	1
		Do not understand 35very well	0.75
		Somewhat understand	0.5
		Mostly understand	0.25
		Completely understand	0
35	KCCQ Q12: Over the past 2 weeks, how much has your heart failure limited your enjoyment in life	Extremely	1
		Quite a bit	0.75
		Moderately	0.5
		Slightly	0.25
		Not at all	0
36	KCCQ Q13: If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?	Not at all satisfied	1
		Mostly dissatisfied	0.75
		Somewhat satisfied	0.5
		Mostly satisfied	0.25
		Completely satisfied	0
37	KCCQ Q14: Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?	All of the time	1
		Most of the time	0.75
		Occasionally	0.5
		Rarely	0.25
		Never	0
38	KCCQ Q 15: How has your heart failure limited your participation in the following activities over the past 2 weeks? a) Hobbies, recreational activities b) Working or doing household chores c) Visiting family or friends out of your home d) Intimate relationships with loved ones	Social limitation score <50	1
	EQ-5D		
39	EQ-5D (Mobility)	unable to walk	1
		severe problems walking	0.75
		moderate problems walking	0.5
		slight problems walking	0.25
		no problems walking	0
40	EQ-5D (Self-care)	unable to wash or dress myself	1

		severe problems walking	0.75
		moderate problems walking	0.5
		slight problems walking	0.25
		no problems walking	0
41	EQ-5D (Usual activities)	unable to do my usual activities	1
		severe problems doing my usual activities	0.75
		moderate problems doing my usual activities	0.5
		slight problems doing my usual activities	0.25
		no problems doing my usual activities	0
42	EQ-5D (Pain / Discomfort)	extreme pain or discomfort	1
		severe pain or discomfort	0.75
		moderate pain or discomfort	0.5
		slight pain or discomfort	0.25
		no pain or discomfort	0
43	EQ-5D (Anxiety / Depression)	extremely anxious or depressed	1
		severely anxious or depressed	0.75
		moderately anxious or depressed	0.5
		slightly anxious or depressed	0.25
		not anxious or depressed	0
44	NYHA class	III or IV	1
		II	0.5
		I	0

Supplementary Table 2: Secondary HF outcomes and mortality by Frailty Index.

Outcome by frailty index subgroup	Empagliflozin (N=2997)			Placebo (N=2991)			HR (95% CI)	P trend
	n/N	%	Rate/100 PY	n/N	%	Rate/100 PY		
Time to first HHF								
Overall	259/2997	8.6	4.28	352/2991	11.8	5.97	0.71 (0.60, 0.83)	
Non-frail (<0.21)	33/770	4.3	2.04	56/744	7.5	3.72	0.56 (0.36, 0.86)	
Mild Frailty (0.21-<0.3)	51/1015	5.0	2.39	94/1085	8.7	4.26	0.56 (0.40, 0.79)	0.114
Moderate Frailty (0.3-<0.4)	97/745	13.0	6.71	112/756	14.8	7.77	0.81 (0.62, 1.07)	
Severe Frailty (>=0.4)	78/467	16.7	9.16	90/406	22.2	12.14	0.75 (0.55,1.02)	
Time to CV death								
Overall	219/2997	7.3	3.42	244/2991	8.2	3.81	0.91 (0.76,1.09)	
Non-frail (<0.21)	29/770	3.8	1.74	43/744	5.8	2.71	0.65 (0.41,1.05)	0.149
Mild Frailty (0.21-<0.3)	63/1015	6.2	2.86	68/1085	6.3	2.91	0.99 (0.71,1.40)	

Moderate Frailty (0.3-<0.4)	64/745	8.6	4.09	87/756	11.5	5.40	0.76 (0.55, 1.05)
Severe Frailty (≥0.4)	63/467	13.5	6.59	46/406	11.3	5.33	1.22 (0.83, 1.78)

Time to all-cause mortality

Overall	422/2997	14.1	6.60	427/2991	14.3	6.67	1.00 (0.87, 1.15)	
Non-frail (<0.21)	65/770	8.4	3.89	78/744	10.5	4.91	0.81 (0.58, 1.13)	
Mild Frailty (0.21-<0.3)	133/1015	13.1	6.03	126/1085	11.6	5.39	1.14 (0.89, 1.45)	0.369
Moderate Frailty (0.3-<0.4)	119/745	16.0	7.60	146/756	19.3	9.06	0.85 (0.67, 1.08)	
Severe Frailty (≥0.4)	105/467	22.5	10.98	77/406	19.0	8.92	1.20 (0.89, 1.60)	

Time to composite renal endpoint

Overall	108/2997	3.6	2.13	112/2991	3.7	2.23	0.95 (0.73, 1.24)	
Non-frail (<0.21)	13/770	1.7	0.94	16/744	2.2	1.26	0.75 (0.36, 1.56)	
Mild Frailty (0.21-<0.3)	29/1015	2.9	1.62	39/1085	3.6	2.08	0.84 (0.52, 1.37)	1.000
Moderate Frailty (0.3-<0.4)	44/745	5.9	3.64	28/756	3.7	2.25	1.54 (0.96, 2.48)	

Severe Frailty
(≥ 0.4)

22/467

4.7

3.09

29/406

7.1

4.55

0.63 (0.36, 1.10)
