

Supplemental Material

Frailty Index

A deficit accumulation approach was used to calculate the frailty index in SPRINT.^{1,2} To construct the frailty index in SPRINT, the 25-item frailty index from the African-American Health Study (AAH)³ was modified based on 16 available items in SPRINT. An additional 20 items available in SPRINT and similar to the frailty index in Hypertension in the Very Elderly Trial (HYVET)⁴ were also included. The 36-item list and scoring system is found in Supplemental Table 1 below. Gait speed assessed by the 4-meter walk test and was included in the SPRINT FI for the subset of participants ≥ 75 years, in whom it was measured.

Supplemental Table 1. Items and scoring system for the SPRINT frailty index¹

Item #	Source	Item	Response	Score	Notes
1	AAH	Self-rated general health	Excellent	0	
			Very Good	0.25	
			Good	0.5	
			Fair	0.75	
			Poor	1	
2	AAH	Does your health limit you now in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	No, not limited at all	0	
			Yes, limited a little	0.5	
			Yes, limited a lot	1	
3	AAH	Does your health limit you now in climbing several flights of stairs?	No, not limited at all	0	
			Yes, limited a little	0.5	
			Yes, limited a lot	1	
4	AAH	During the past 4 weeks, have you accomplished less than you would like as a result of your physical health?	No, none of the time	0	
			Yes, a little of the time	0.25	
			Yes, some of the time	0.5	
			Yes, most of the time	0.75	
			Yes, all of the time	1	
5	AAH	During the past 4 weeks, did you not do work or other activities as carefully as usual due to emotional problems?	No, none of the time	0	
			Yes, a little of the time	0.25	
			Yes, some of the time	0.5	
			Yes, most of the time	0.75	
			Yes, all of the time	1	
6	HYVET	During the past 4 weeks, how much did pain interfere with your normal work?	Not at all	0	
			A little bit	0.25	
			Moderately	0.5	
			Quite a bit	0.75	
			Extremely	1	

7	AAH	How much of the time during the past 4 weeks did you have a lot of energy?	All of the time	0
			Most of the time	0.2
			A good bit of the time	0.4
			Some of the time	0.6
			A little of the time	0.8
			None of the time	1

Item #	Source	Item	Response	Score	Notes
8	AAH	How much of the time during the past 4 weeks have you felt downhearted and blue?	None of the time	0	
			A little of the time	0.2	
			Some of the time	0.4	
			A good bit of the time	0.6	
			Most of the time	0.8	
			All of the time	1	
9	HYVET	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities?	None of the time	0	
			A little of the time	0.25	
			Some of the time	0.5	
			Most of the time	0.75	
10	HYVET	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	
11	AAH	Over the last two weeks, have you had trouble falling or staying asleep, or sleeping too much?	Not at all	0	
			Several days	0.33	
			More than half the days	0.67	
			Nearly every day	1	
12	HYVET	Smoking status	Never smoker	0	
			Former smoker	0.5	
			Current smoker	1	
13	AAH	Self-reported history of stroke		1	
14	AAH	Self-reported history of diabetes		1	
15	AAH	Self-reported history of heart attack		1	

16	AAH	Self-reported history of cancer		1	
17	AAH	Self-reported history of heart failure		1	
18	AAH	Self-reported history of angina		1	
19	HYVET	Self-reported history of atrial fibrillation or atrial fibrillation detected on ECG reading		1	
Item #	Item	Response	Score	Notes	
20	AAH	Chronic Kidney Disease	eGFR <60 ml/min/1.73m ²	1	Based on CKD-EPI equation ⁹
21	SPRINT	Albuminuria	≥30 but less <300 mg/g Cr	0.5	
			≥300 mg/g Cr	1	
22	HYVET	HDL Cholesterol	<0.4 or >1.5 mmol/l	1	
23	HYVET	Total Cholesterol	<3.5 or >7 mmol/l	1	
24	HYVET	Potassium	<3.5 or >6 mmol/l	1	
25	HYVET	Sodium	<135 or >150 mmol/l	1	
26	HYVET	Glucose	<2.8 or >11 mmol/l	1	
27	HYVET	Blood Urea Nitrogen	<3 or >7.5 mmol/l	1	
28	HYVET	Overweight / Obesity	BMI ≥ 25 but <30 kg/m ²	0.5	
			BMI ≥ 30 kg/m ²	1	
29	HYVET	Underweight	BMI < 18.5 kg/m ²	1	
30	HYVET	Systolic Blood Pressure	≥ 180 mmHg	1	
31	HYVET	Diastolic Blood Pressure	≥ 90 mmHg	1	
32	HYVET	Orthostatic hypotension	Difference in seated - standing SBP ≥ 20 mmHg or seated - standing DBP ≥ 10 mmHg	1	
33	AAHS	Global Cognitive Status (MoCA)	< age and education specific 25th percentile	1	Estimated percentiles from Kenny et al. ² To correct for racial/ethnic differences, 2 points were added to the scores of African-American and Hispanic participants

34	HYVET	MoCA Orientation Score	≤ 4 out of 6	1
35	SPRINT	Logical Memory Delayed Recall	1.5 SD or more below normative mean for age ^a	1
36	SPRINT	Digit Symbol - Copy	1.5 SD or more below normative mean for age ^b	1

Item #	Item	Response	Score	Notes	
37	SPRINT	Gait Speed	≥ 1.0 m/s	0	Only measured in participants 75 years and older at time of randomization
			≥ 0.8 but < 1.0 m/s	0.33	
			≥ 0.6 but < 0.8 m/s	0.67	
			< 0.6 m/s	1	

References

1. Pajewski NM, Williamson JD, Applegate WB, et al. Characterizing frailty status in the systolic blood pressure intervention trial. *J Gerontol A Biol Sci Med Sci.* 2016;71(5):649-655.
2. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci.* 2007;62(7):722-727.
3. Malmstrom TK, Miller DK, Morley JE. A comparison of four frailty models. *J Am Geriatr Soc.* 2014;62(4):721-726.
4. Warwick J, Falaschetti E, Rockwood, K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the in the Hypertension in the Very Elderly Trial (HIVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 or over. *BMC medicine.* 2015;13(78):1-8.

Supplemental Table 2. Baseline characteristics among SPRINT participants with CKD by fall

	No Falls N = 2274	Falls N = 102
Age, years	73 ± 9	80 ± 9
Female	900 (40)	48 (47)
Race, White	1482 (65)	77 (76)
Treatment randomization		
Standard	1113 (49)	55 (54)
Intensive	1161 (51)	47 (46)
Prevalent CVD	567 (25)	38 (37)
Prevalent heart failure	139 (6)	14 (14)
eGFR-CrCys, mL/min/1.73m²	49 ± 11	48 ± 12
UACR, mg/g	87 ± 253	93 ± 243
SBP, mmHg	140 ± 16	143 ± 18
DBP, mmHg	75 ± 12	72 ± 12
Antihypertensive medication, number	2.1 ± 1.0	2.2 ± 1.0
Smoking		
Never	1037 (46)	38 (37)
Former	1031 (45)	56 (55)
Current	206 (9)	8 (8)
Body mass index, m/kg²	30 ± 6	27 ± 5
Serum Calcium, mg/mL	9.6 ± 0.5	9.6 ± 0.5
Serum Phosphate, mg/mL	3.5 ± 0.6	3.6 ± 0.5
Serum PTH, pg/mL	56 ± 33	56 ± 36
Serum FGF23, pg/mL	66 [52 – 87]	80 [59 – 102]
Frailty		

Non-frail	254 (11)	11 (11)
Pre-frail	1209 (53)	38 (37)
Frail	811 (36)	53 (52)

Data presented as N (%), mean \pm SD, or median [IQR]

Abbreviations: FGF23, fibroblast growth factor 23; eGFR-CrCys, estimated glomerular filtration rate; UACR, urine albumin-creatinine-ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone

Supplemental Table 3. Baseline characteristics among SPRINT participants ≥ 75 years with CKD

	Total Cohort N = 1192	FGF23 Q1 N = 298	FGF23 Q2 N = 298	FGF23 Q3 N = 297	FGF23 Q4 N = 299
FGF23, pg/mL	66.3 [52.7-88.6]	<52.8	52.8-67.2	67.3-89.0	≥ 89.1
Age, years	81 \pm 4	81 \pm 4	80 \pm 4	81 \pm 5	81 \pm 4
Female	446 (37)	104 (35)	104 (35)	116 (39)	122 (41)
Race, White	894 (75)	208 (70)	233 (78)	229 (77)	224 (75)
Treatment randomization					
Standard	593 (50)	140 (47)	149 (50)	157 (53)	153 (51)
Intensive	599 (50)	158 (53)	149 (50)	140 (47)	146 (49)
Prevalent CVD	344 (29)	73 (25)	88 (29)	98 (33)	85 (28)
Prevalent heart failure	77 (7)	14 (15)	18 (6)	20 (7)	25 (8)
eGFR-CrCys, mL/min/1.73m²	50 \pm 11	54 \pm 10	52 \pm 9	50 \pm 11	43 \pm 12
UACR, mg/g	75 \pm 213	45 \pm 113	53 \pm 150	73 \pm 189	127 \pm 326
SBP, mmHg	142 \pm 17	142 \pm 16	142 \pm 15	141 \pm 18	141 \pm 18
DBP, mmHg	70 \pm 12	72 \pm 12	71 \pm 11	70 \pm 12	69 \pm 11
Antihypertensive medication, number	2.2 \pm 1.0	2.0 \pm 1.0	2.1 \pm 1.0	2.2 \pm 1.0	2.3 \pm 1.0
Smoking					
Never	556 (47)	135 (45)	138 (46)	139 (47)	144 (48)
Former	591 (50)	147 (49)	152 (51)	148 (50)	144 (48)
Current	45 (4)	16 (5)	8 (3)	10 (3)	11 (4)
Body mass index, kg/m²	30 \pm 6	28 \pm 5	28 \pm 5	28 \pm 5	28 \pm 6
Serum Calcium, mg/mL	9.6 \pm 0.5	9.5 \pm 0.4	9.5 \pm 0.4	9.6 \pm 0.5	9.6 \pm 0.5
Serum Phosphate, mg/mL	3.5 \pm 0.5	3.4 \pm 0.5	3.5 \pm 0.5	3.6 \pm 0.5	3.6 \pm 0.5

Serum PTH, pg/mL	55 ± 31	48 ± 19	50 ± 23	55 ± 31	66 ± 43
Gait speed, seconds	5.9 ± 213	5.8 ± 6.6	6.2 ± 9.5	6.4 ± 12.4	5.3 ± 2
Frailty					
Non-frail	143 (12)	39 (13)	47 (16)	27 (9)	30 (10)
Pre-frail	625 (52)	167 (56)	157 (53)	159 (54)	142 (48)
Frail	424 (36)	92 (31)	94 (32)	11 (37)	127 (43)

Supplemental Table 4. Baseline characteristics of SPRINT participants ≥ 75 years with CKD by fall

	No Falls N = 1111	Falls N = 81
Age, years	80 \pm 4	83 \pm 5
Female	411 (37)	35 (43)
Race, White	831 (75)	63 (78)
Treatment randomization		
Standard	552 (50)	47 (58)
Intensive	559 (50)	34 (42)
Prevalent CVD	311 (28)	33 (40)
Prevalent heart failure	66 (6)	11 (14)
eGFR-CrCys, mL/min/1.73m²	50 \pm 11	49 \pm 11
UACR, mg/g	76 \pm 219	58 \pm 109
SBP, mmHg	141 \pm 17	144 \pm 17
DBP, mmHg	70 \pm 12	69 \pm 11
Antihypertensive medication, number	2.1 \pm 1.0	2.2 \pm 1.0
Smoking		
Never	526 (47)	30 (37)
Former	544 (49)	47 (58)
Current	41 (4)	4 (5)
Body mass index, m/kg²	28 \pm 5	27 \pm 5
Serum Calcium, mg/mL	9.6 \pm 0.5	9.6 \pm 0.5
Serum Phosphate, mg/mL	3.6 \pm 0.6	3.5 \pm 0.5
Serum PTH, pg/mL	55 \pm 31	53 \pm 35
Serum FGF23, pg/mL	66 [53 – 88]	71 [57 – 98]
Gait speed, seconds	5.8 \pm 8.2	7.7 \pm 12

Frailty

Non-frail	133 (12)	10 (12)
Pre-frail	596 (54)	29 (36)
Frail	382 (34)	42 (52)

Supplemental Table 5. Association of FGF23 concentrations and risk of falls among SPRINT participants <75 years with CKD (N = 1184)

	<u>Unadjusted</u>	<u>Model 1</u>	<u>Model 2</u>
Log ₂ FGF23	2.78 (1.67 – 4.64)	4.37 (2.02 – 9.47)	4.38 (2.02 – 9.48)
Quartile 1	REFERENCE	REFERENCE	REFERENCE
Quartile 2	1.60 (0.27 – 9.59)	1.78 (0.29 – 10.94)	1.79 (0.29 – 10.98)
Quartile 3	1.99 (0.0.37 – 10.88)	2.20 (0.39 – 12.52)	2.20 (0.39 – 12.47)
Quartile 4	5.91 (1.31 – 26.66)	7.08 (1.41 – 35.58)	7.02 (1.40 – 35.16)

Model 1: adjusted for age, gender, race, randomized treatment arm, smoking, CVD, CHF, body mass index, systolic and diastolic blood pressures, eGFR, UACR, # antihypertensive medications at baseline, and serum calcium, phosphorus, and PTH concentrations. Model 2: adjusted for covariables in model 1 plus frailty index