SUPPLEMENTARY MATERIAL

Supplementary Table 1: Variables used in frailty index and score assigned

Item #	Items	Response	Score
1.	Self-rated general health	Excellent Very Good Fair Poor	0 0.25 0.5 0.75 1
2.	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Accomplished less that you would like	None of the time A little of the time Some of the time Most of the time All of the time	0 0.25 0.50 0.75 1
3.	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all Slightly Moderately Quite a bit Extremely	0 0.25 0.50 0.75 1
4.	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all A little bit Moderately Quite a bit Extremely	0 0.25 0.50 0.75 1
5.	How much of the time during the past 4 weeks did you have a lot of energy?	All of the time Most of the time Some of the time A little of the time None of the time	0 0.25 0.50 0.75 1
6.	How much of the time during the past 4 weeks have you felt downhearted and depressed?	None of the time A little of the time Some of the time Most of the time All of the time	0 0.25 0.50 0.75 1
7.	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None of the time A little of the time Some of the time Most of the time All of the time	0 0.25 0.50 0.75 1
8.	The following questions are about activities you might do during a typical day. Does your health now limit you in these activities during a typical day? Bathing or dressing yourself	No, not limited at all Yes, limited a little Yes, limited a lot	0 0.5 1
9.	Sleep	I can sleep as well as usual I don't sleep as well as I used to I wake up 1-2 hours earlier than usual and find it hard to get back to sleep. I wake up several hours earlier than I used	0 0.33 0.67

		to and cannot get back to sleep	1
10.	Do you smoke cigarettes now?	No Yes	0 1
11.	Self-reported stroke	No Yes	0 1
12.	Self -reported heart attack	No Yes	0 1
13.	Self-reported cancer	No Yes	0 1
14.	Self-reported angina	No Yes	0 1
15.	Self-reported kidney failure	No Yes	0 1
16.	Albuminuria	0.3-2.9 mg/dl serum creatinine ≥3.0 mg/dl serum creatinine	0.5 1
17.	HDL-cholesterol	< 40 mg/dl (males) or <50 mg/dl (females)	1
18.	Total cholesterol	< 135.3 or >270.7 mg/dl	1
19.	Glucose	<50.5 or >198.2 mg/dl	1
20.	Overweight/obesity	BMI 25.0-29.9 kg/m^2 BMI ≥30.0 kg/m^2	0.5 1
21.	Systolic blood pressure	<140 mmHg 140-159 mmHg 160-179 mmHg ≥180 mmHg	0 0.33 0.67 1
22.	Diastolic blood pressure	≥90 mmHg	1
23.	How would you describe your ability to think and solve day to day problems, during the past four weeks: able to think clearly and solve problems, had a little difficulty, had some difficulty, had a great deal of difficulty, or unable to think or solve problems?	Able to think clearly and solve problems Had a little difficulty Had some difficulty Had a great deal of difficulty Unable to think or solve problems Don't know/Refused	0 0.25 0.50 0.75 1 Missing
24.	How would you describe your ability to remember things, during the past four weeks: able to remember most things, somewhat forgetful, very forgetful, or unable to remember anything at all?	Able to remember most things Somewhat forgetful Very forgetful Unable to remember anything at all Don't know/Refused	0 0.33 0.67 1 Missing
25.	Trouble making decisions?	I make decisions about as well as I ever could. I put off making decisions more than I used to. I have greater difficulty in making decisions than before I can't make decisions at all anymore.	0 0.33 0.67 1
26.	What degree of difficulty do you have walking on a flat surface?	None Mild Moderately Severe Extreme	0 0.25 0.50 0.75 1
27.	Are there times when you stop breathing during your sleep?	No Yes	0 1
28.	How severe is your stiffness after first wakening in the morning?	None Mild	0 0.25

		Moderately	0.50
		Severe	0.75
		Extreme	1
29.	How severe is your stiffness after sitting, lying or resting later in the day?	None	0
		Mild	0.25
		Moderately	0.50
		Severe	0.75
		Extreme	1
30.	Have you leaked even a small amount of urine or wet yourself in the past 7 days?	No	0
		Yes	1
31.	Insulin use	No	0
		Yes	1
32.	During the past four weeks, have you been able to hear what is said in a group conversation with at least three other people without a hearing aid?	No	0
		Yes	1
		Don't know/Refused	Missing
33.	Worsening of your eyesight?	Did not occur	0
		Mild	0.33
		Moderate	0.67
		Severe	1
34.	Sores on your feet that heal poorly?	Did not occur	0
		Mild	0.33
		Moderate	0.67
		Severe	1
35.	Has your doctor ever told you that you have diabetic neuropathy?	No	0
		Yes	1

Supplementary Table 2: Multivariable adjusted association of baseline frailty index categories with risk of incident overall HF, HFpEF, and HFrEF among men and women

Groups		Model 1		Model 2		Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Overall HF (referent: Tertile 1)							
Men	**Tertile 2**	2.96 (1.69-5.19)	<.001	2.48 (1.40-4.37)	0.002	2.01 (1.13-3.56)	0.02
	Tertile 3	6.45 (3.80-10.95)	<.001	4.80 (2.79-8.24)	<.001	3.09 (1.76-5.44)	<.001
Women	**Tertile 2**	1.32 (0.80-2.19)	0.28	1.17 (0.70-1.93)	0.55	0.95 (0.57-1.59)	0.83
	Tertile 3	1.98 (1.24-3.15)	0.004	1.49 (0.93-2.40)	0.10	0.95 (0.57-1.58)	0.83
HFpEF (referent: Tertile 1)							
Men	**Tertile 2**	3.91 (1.57-9.73)	0.004	3.28 (1.31-8.21)	0.01	2.51 (0.99-6.34)	0.05
	Tertile 3	9.72 (4.10-23.06)	<.001	7.13 (2.97-17.11)	<.001	4.34 (1.76-10.73)	0.002
Women	**Tertile 2**	1.54 (0.76-3.10)	0.23	1.36 (0.67- 2.76)	0.39	1.09 (0.53-2.24)	0.81
	Tertile 3	2.14 (1.10-4.16)	0.02	1.63 (0.83- 3.20)	0.15	1.04 (0.51-2.14)	0.91
HFrEF (referent: Tertile 1)							
Men	**Tertile 2**	2.24 (1.05-4.77)	0.04	2.06 (0.96-4.42)	0.06	1.63 (0.75-3.55)	0.22
	Tertile 3	3.78 (1.82-7.84)	<.001	3.25 (1.53-6.88)	0.002	2.08 (0.95-4.58)	0.07
Women	**Tertile 2**	0.89 (0.40 - 2.00)	0.78	0.80 (0.36-1.80)	0.60	0.64 (0.28 -1.47)	0.29
	Tertile 3	1.56 (0.76 - 3.17)	0.22	1.23 (0.59-2.54)	0.58	0.76 (0.34 -1.70)	0.51

Model 1: Adjusted for age, sex, race/ethnicity, and treatment arm;
Model 2: Model 1 + Baseline Estimated Fitness (METs)
Model 3: Model 2 + history of hypertension, systolic blood pressure, smoking status, drinking status, history of CVD, HbA1c, GFR, BMI
Abbreviations: CI, confidence interval; HF, heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HR, hazard ratio; SD, standard deviation; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; GFR, Glomerular filtration rate; BMI, Body mass index

Supplementary Table 3: Multivariable adjusted association of baseline frailty index (continuous) with risk of incident overall HF, HFpEF, and HFrEF among men and women

Groups	Model 1		Model 2		Model 3	
	HR (95% CI) Per 1 SD higher FI	P-value	HR (95% CI) Per 1 SD higher FI	P-value	HR (95% CI) Per 1 SD higher FI	P-value
Overall HF						
Men	1.92 (1.66-2.21)	<.001	1.74 (1.49, 2.03)	<.001	1.49 (1.26, 1.76)	<.001
Women	1.50 (1.26- 1.78)	<.001	1.32 (1.10, 1.58)	0.003	1.10 (0.91, 1.35)	0.33
HFpEF						
Men	2.05 (1.68- 2.51)	<.001	1.86 (1.50, 2.30)	<.001	1.601 (1.26, 2.03)	<.001
Women	1.54 (1.22-1.94)	<.001	1.37 (1.08, 1.74)	0.01	1.13 (0.87, 1.47)	0.35
HFrEF						
Men	1.76 (1.39, 2.22)	<.001	1.67 (1.31, 2.14)	<.001	1.45 (1.11, 1.90)	0.007
Women	1.34 (1.00, 1.81)	0.05	1.20 (0.88, 1.64)	0.24	0.98 (0.69, 1.39)	0.91

Model 1: Adjusted for age, sex, race/ethnicity, and treatment arm;
Model 2: Model 1 + Baseline Estimated Fitness (METs)
Model 3: Model 2 + history of hypertension, systolic blood pressure, smoking status, drinking status, history of CVD, HbA1c, GFR, BMI
Abbreviations: CI, confidence interval; HF, heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HR, hazard ratio; SD, standard deviation; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; GFR, Glomerular filtration rate; BMI, Body mass index

Supplementary Table 4: Multivariable adjusted association of baseline frailty index (continuous) with risk of incident overall HF across tertiles of BMI

BMI tertiles	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Continuous frailty measure (HR Per 1 SD (0.07) higher)						
Tertile 1: BMI 24.53 to 32.62 kg/m²	1.77 (1.41, 2.21)	<0.001	1.61 (1.28, 2.02)	<0.001	1.38 (1.06, 1.80)	0.02
Tertile 2: BMI 32.62 to 37.78 kg/m²	1.74 (1.44, 2.11)	<0.001	1.62 (1.33, 1.98)	<0.001	1.34 (1.08, 1.66)	0.009
Tertile 3: 37.78 to 63.53 kg/m²	1.53 (1.28, 1.84)	<0.001	1.42 (1.18, 1.72)	<0.001	1.24 (1.01, 1.53)	0.04

Model 1: Adjusted for age, sex, race/ethnicity, and treatment arm
Model 2: Model 1 + Baseline Estimated Fitness (METs)
Model 3: Model 2 + history of hypertension, systolic blood pressure, smoking status, drinking status, history of CVD, HbA1c, GFR
Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio; SD, standard deviation; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; GFR, Glomerular filtration rate; BMI, Body mass index

Supplementary Table 5: Multivariable adjusted association of baseline frailty index with risk of incident overall HF, HFpEF, and HFrEF at 2 years

	Model 1		Model 2		Model 3	
	HR (95% CI) Per 1 SD higher FI	**P-value**	**HR (95% CI) Per 1 SD higher FI**	**P-value**	**HR (95% CI) Per 1 SD higher FI**	**P-value**
Overall HF	1.68 (1.50-1.89)	<.001	1.52 (1.34-1.72)	<.001	1.28(1.11- 1.46)	<.001
HFpEF	1.78 (1.51-2.09)	<.001	1.59 (1.34-1.88)	<.001	1.34 (1.12- 1.62)	0.002
HFrEF	1.51 (1.25-1.82)	<.001	1.40 (1.15-1.71)	<.001	1.16 (0.93- 1.45)	0.18

Model 1: Adjusted for age, sex, race/ethnicity, and treatment arm;
Model 2: Model 1 + Baseline Estimated Fitness (METs)
Model 3: Model 2 + history of hypertension, systolic blood pressure, smoking status, drinking status, history of CVD, HbA1c, GFR, BMI
Abbreviations: CI, confidence interval; HF, heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HR, hazard ratio; SD, standard deviation; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; GFR, Glomerular filtration rate; BMI, Body mass index

Supplementary Table 6: Baseline and follow-up characteristics stratified by year 1 change in frailty index tertiles

Variable	Tertile 1 (n=1583)	Tertile 2: (n=1570)	Tertile 3: (n=1598)	P-value
		Frailty Index		
Baseline Frailty Index	0.23 (0.07)	0.20 (0.06)	0.19 (0.06)	<.001
Change in Frailty Index by 1-year	-0.07 (0.03)	-0.01 (0.01)	0.05 (0.04)	<.001
Range of frailty change	-0.224 to -0.035	-0.035 to 0.008	0.008 to 0.277	
Baseline variables				
Age, years	58.6 (6.9)	58.8 (6.8)	58.9 (6.9)	0.40
Women, %	926 (58.5%)	917 (58.4%)	981 (61.4%)	0.15
White, %	950 (60.1%)	1033 (65.8%)	1041 (65.1%)	<.001
Weight, Kg	99.4 (19.1)	100.8 (19.5)	101.8 (19.2)	0.002
BMI, kg/m^^2	35.6 (5.8)	35.8 (5.9)	36.3 (5.9)	0.001
Estimated Fitness, METs	7.3 (2.0)	7.3 (1.9)	7.1 (2.0)	0.06
Systolic BP, mmHg	129.6 (18.1)	128.8 (16.5)	127.9 (16.5)	0.02
History of CVD, %	193 (12.2%)	194 (12.4%)	230 (14.4%)	0.12
History of Hypertension, %	1306 (82.5%)	1313 (83.6%)	1329 (83.2%)	0.70
Duration of Diabetes	6.6 (6.2)	6.5 (6.3)	7.1 (6.9)	0.03
HbA1c, %	7.3 (1.2)	7.2 (1.2)	7.2 (1.1)	0.006
GFR, mL/min per 1.73 m^^s	90.3 (15.6)	89.5 (15.8)	89.0 (16.3)	0.05
ILI treatment group, %	994 (62.8%)	804 (51.2%)	607 (38.0%)	<.001
Insulin Use, %	256 (16.7%)	202 (13.4%)	251 (16.3%)	0.03
LDL, mg/dL	112.6 (34.5)	111.7 (31.4)	111.7 (31.0)	0.66
1-Year follow up variables				
BMI, kg/m^^2	33.0 (6.0)	34.3 (6.1)	35.3 (6.1)	<.001
Change in BMI, %	-7.2 (7.7)	-4.3 (6.6)	-2.6 (6.2)	<.001
Change in Estimated Fitness, %	18.9 (29.8)	13.9 (25.1)	8.1 (24.3)	<.001
Change in Systolic BP, mmHg	-7.7 (17.0)	-4.5 (16.2)	-2.4 (17.3)	<.001
Change in Systolic BP, %	-5.0 (13.0)	-2.8 (12.6)	-1.2 (13.4)	<.001
Change in HbA1c, %	-7.7 (12.8)	-4.6 (11.9)	-1.6 (12.9)	<.001

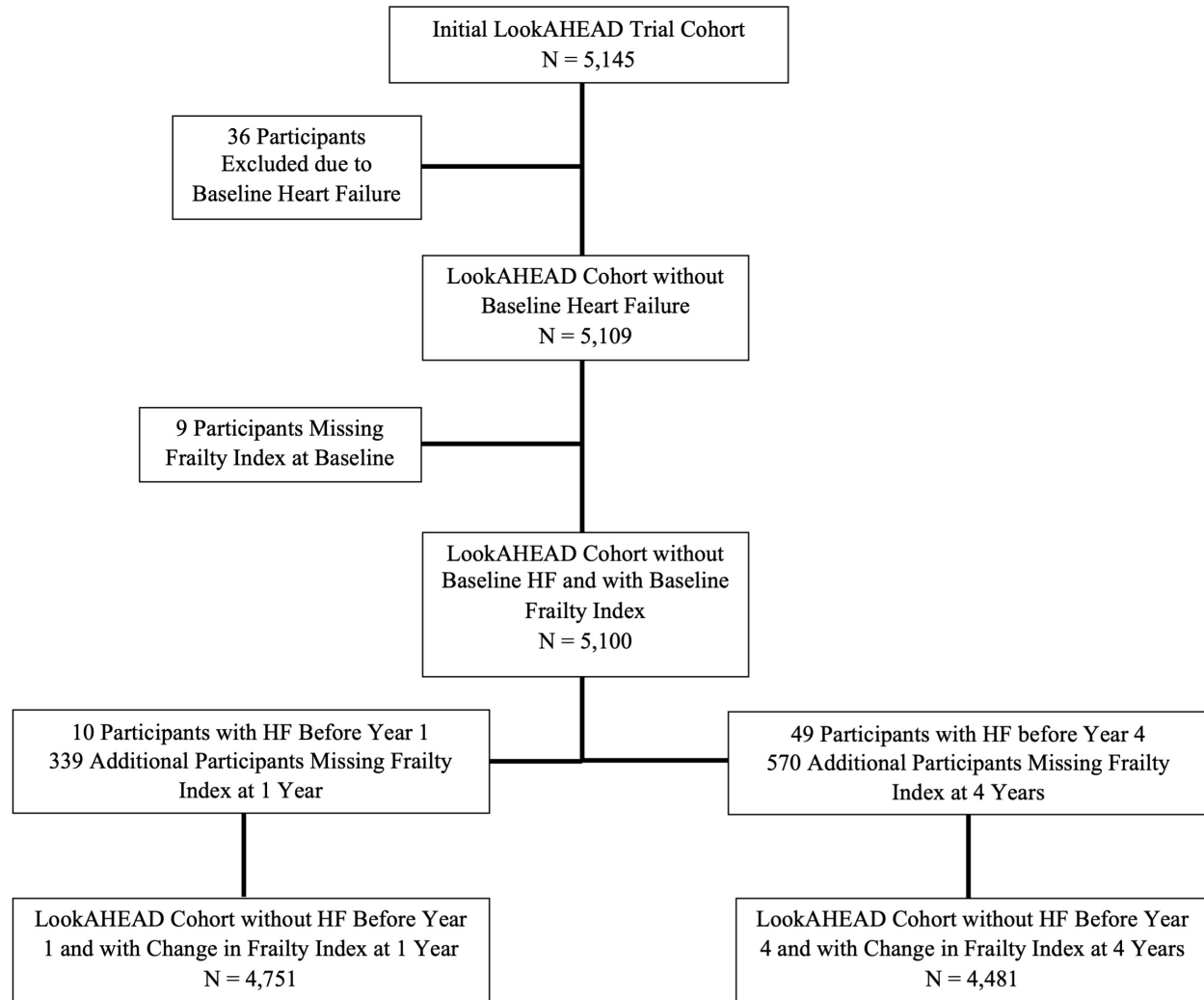| Variable	Frailty Index			
	Tertile 1 (n=1583)	Tertile 2: (n=1570)	Tertile 3: (n=1598)	P-value

Data presented as mean (SD) or %. Abbreviation: BMI, Body mass index; METs, Metabolic equivalents; CVD, Cardiovascular disease; GFR, Glomerular filtration rate; HbA1c, hemoglobin A1c; ILI, intensive lifestyle intervention; LDL, Low density lipoprotein

Supplementary Table 7: Baseline and follow-up characteristics stratified by year 4 change in frailty index tertiles

| Variable | Frailty Index | | | |
	Tertile 1 (n=1493)	Tertile 2 (n=1494)	Tertile 3 (n=1494)	P-value for tertiles
Baseline Frailty Index	0.23 (0.07)	0.20 (0.06)	0.20 (0.06)	<.0001
Change in Frailty Index by 4-year	-0.06 (0.03)	0.00 (0.01)	0.08 (0.04)	<.0001
Range of change in frailty index	-0.256 to -0.02	-0.020 to 0.03	0.03 to 0.292	-
Baseline variables				
Age, years	58.2 (6.8)	58.8 (6.7)	59.0 (7.0)	0.01
Women, n (%)	892 (59.8)	896 (60.0)	910 (60.9)	0.79
White, n (%)	909 (60.9)	982 (65.7)	968 (64.8)	0.006
BMI, kg/m^2	35.4 (5.8)	35.8 (5.8)	36.5 (6.0)	<.001
Estimated Fitness, METs	7.4 (2.0)	7.3 (2.0)	7.0 (1.9)	<.001
Systolic BP, mmHg	129.3 (17.6)	128.5 (16.7)	128.0 (16.9)	0.09
History of CVD, n (%)	159 (10.7)	183 (12.3)	217 (14.5)	0.006
History of Hypertension, n (%)	1219 (81.7)	1231 (82.4)	1254 (83.9)	0.24
Duration of Diabetes, years	6.6 (6.2)	6.5 (6.4)	7.1 (6.7)	0.02
HbA1c, n (%)	7.3 (1.2)	7.2 (1.1)	7.2 (1.2)	<.001
GFR, mL/min per 1.73 m^2	90.9 (15.4)	90.1 (15.5)	88.5 (16.5)	<.001
ILI treatment group, n (%)	869 (58.2)	738 (49.4)	645 (43.2)	<.001
Insulin Use, n (%)	245 (17.0)	183 (12.8)	231 (16.0)	0.004
LDL, mg/dL	113.2 (33.9)	111.0 (31.6)	111.4 (31.1)	0.14
4-year follow up variables				
BMI, kg/m^2	33.6 (6.1)	34.9 (6.2)	36.3 (6.5)	<.001
Change in BMI, %	-4.7 (9.7)	-2.4 (7.7)	-0.3 (9.0)	<.001
Change in Estimated Fitness, %	6.6 (29.4)	2.0 (24.6)	-1.6 (24.6)	<.001
Change in Systolic BP, mmHg	-6.7 (17.8)	-4.1 (18.2)	-1.4 (20.7)	<.001
Change in Systolic BP, %	-4.3 (13.6)	-2.3 (14.3)	-0.1 (16.1)	<.001
Change in HbA1c, %	-5.4 (15.2)	-0.6 (16.5)	2.4 (19.6)	<.001

Data presented as mean (SD) or %. Abbreviation: BMI, Body mass index; METs, Metabolic equivalents; CVD, Cardiovascular disease; GFR, Glomerular filtration rate; HbA1c, hemoglobin A1c; ILI, intensive lifestyle intervention; LDL, Low density lipoprotein

Supplementary Figure 1: Consort diagram showing the selection of participants included in the study.
Participants who had follow-up data for calculation of frailty index at year 1 and year 4 and were free of heart failure at the time of follow-up visit were included in the study.

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                          ┌─────────────────────────────┐
                          │  Initial LookAHEAD Trial     │
                          │  Cohort                      │
                          │  N = 5,145                   │
                          └─────────────────────────────┘
                                       │
   ┌──────────────────────┐            │
   │ 36 Participants       │───────────┤
   │ Excluded due to       │           │
   │ Baseline Heart Failure│           │
   └──────────────────────┘           │
                          ┌─────────────────────────────┐
                          │  LookAHEAD Cohort without    │
                          │  Baseline Heart Failure      │
                          │  N = 5,109                   │
                          └─────────────────────────────┘
                                       │
   ┌──────────────────────┐            │
   │ 9 Participants Missing│───────────┤
   │ Frailty Index at      │           │
   │ Baseline              │           │
   └──────────────────────┘           │
                          ┌─────────────────────────────┐
                          │  LookAHEAD Cohort without    │
                          │  Baseline HF and with Baseline│
                          │  Frailty Index               │
                          │  N = 5,100                   │
                          └─────────────────────────────┘
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| 10 Participants with HF Before Year 1 | 49 Participants with HF before Year 4 |
| 339 Additional Participants Missing Frailty Index at 1 Year | 570 Additional Participants Missing Frailty Index at 4 Years |

| LookAHEAD Cohort without HF Before Year 1 and with Change in Frailty Index at 1 Year N = 4,751 | LookAHEAD Cohort without HF Before Year 4 and with Change in Frailty Index at 4 Years N = 4,481 |

Supplementary Figure 2: Cumulative incidence of heart failure across baseline frailty index tertiles.
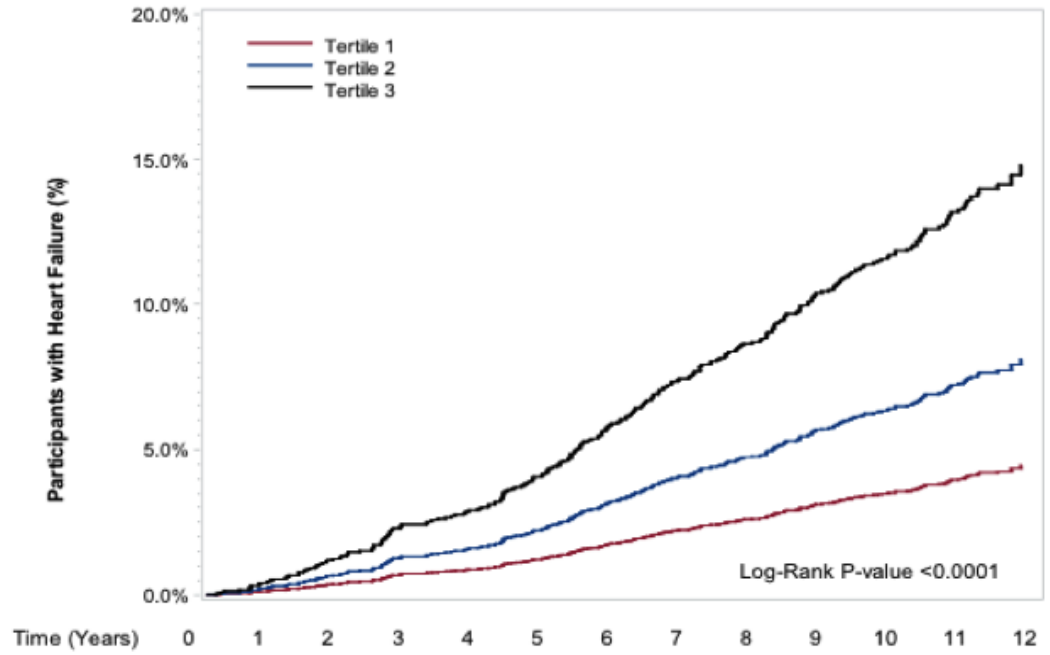
Supplementary Figure 3: Cumulative incidence of heart failure with preserved ejection fraction (A), and heart failure with reduced ejection fraction (B) across tertiles of baseline frailty index
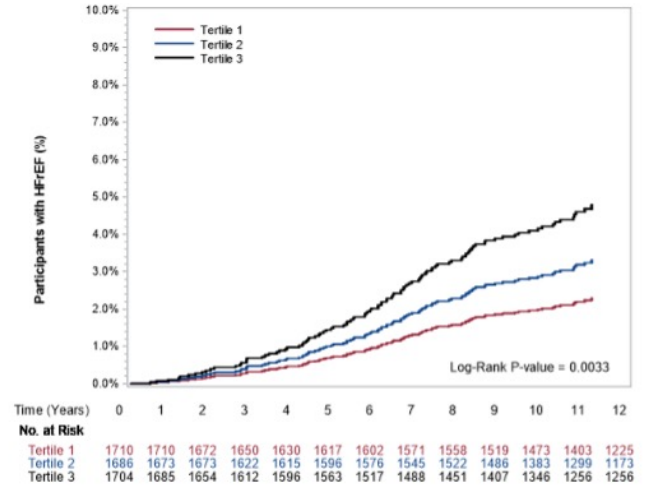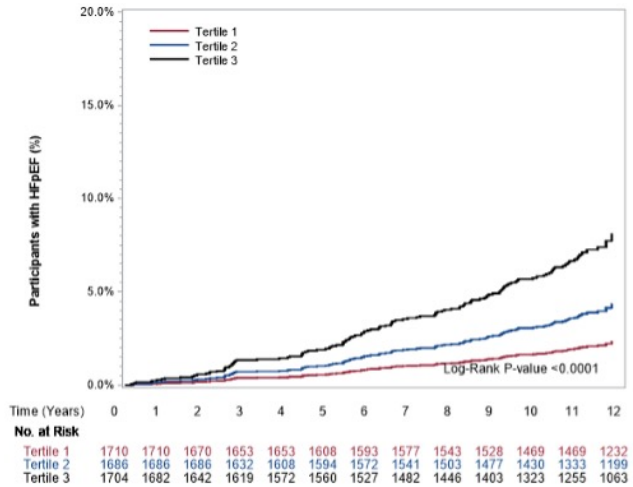
Appendix:

Look AHEAD Research Group at End of Continuation

Clinical Sites

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