

SUPPLEMENTAL MATERIAL

Supplemental Table 1A: Baseline characteristics, by quartile of soluble ST2

Characteristic	Quartile 1 (N=857)	Quartile 2 (N=856)	Quartile 3 (N=858)	Quartile 4 (N=857)
Soluble ST2 range, ng/mL				
Men	5.78-19.20	19.21-23.58	23.59-29.07	29.08-119.55
Women	3.16-15.27	15.28-18.77	18.78-23.15	23.16-86.89
Age, years	57 ± 9	59 ± 10	60 ± 10	61 ± 10
Women, %	53	53	53	53
Body-mass index, kg/m²	27.5 ± 4.7	27.6 ± 4.7	28.0 ± 5.3	28.5 ± 5.8
Systolic blood pressure, mm Hg	126 ± 18	128 ± 18	128 ± 19	131 ± 20
Use of anti-hypertensive therapy, %	21	27	28	35
Diabetes, %	7	9	12	19
Cigarette smoking, %	16	17	14	14
Total cholesterol, mg/dl	207 ± 36	203 ± 36	207 ± 40	207 ± 48
HDL cholesterol, mg/dl	52 ± 16	51 ± 17	51 ± 15	50 ± 17
Atrial fibrillation, %	2	3	3	4
Prevalent CVD, %	5	5	5	6
ECG LVH, %	0.2	0.8	0.9	0.6
Significant murmur, %	2	3	3	3

HDL: high density lipoprotein; CVD: cardiovascular disease; ECG: electrocardiography; LVH: left ventricular hypertrophy. For continuous variables, values are mean ± SD or medians (Q1 to Q3).

Supplemental Table 1B: Baseline characteristics, by quartile of Growth Differentiation Factor-15

Characteristic	Quartile 1 (N=857)	Quartile 2 (N=857)	Quartile 3 (N=858)	Quartile 4 (N=856)
GDF-15 range, ng/L				
Men	306 – 820	821 – 1065	1066 – 1414	1415 – 14493
Women	308 – 811	812 – 1021	1022 – 1304	1305 – 16074
Age, years	51 ± 7	57 ± 8	62 ± 9	66 ± 8
Women, %	53	53	53	53
Body-mass index, kg/m²	27.6 ± 4.9	27.7 ± 5.3	28.0 ± 5.0	28.3 ± 5.3
Systolic blood pressure, mm Hg	122 ± 17	127 ± 18	131 ± 18	134 ± 20
Use of anti-hypertensive therapy, %	15	21	32	43
Diabetes, %	6	6	12	23
Cigarette smoking, %	9	15	18	20
Total cholesterol, mg/dL	204 ± 37	208 ± 37	207 ± 39	204 ± 48
HDL cholesterol, mg/dL	52 ± 15	53 ± 17	51 ± 16	49 ± 16
Atrial fibrillation, %	0.4	2	3	7
Prevalent CVD, %	2	2	6	12
ECG LVH, %	0.1	0.5	0.6	1
Significant murmur, %	1	3	3	5

HDL: high density lipoprotein; CVD: cardiovascular disease; ECG: electrocardiography; LVH: left ventricular hypertrophy. For continuous variables, values are mean ± SD or medians (Q1 to Q3).

Supplemental Table 1C: Baseline characteristics, by quartile of high-sensitivity troponin I

Characteristic	Quartile 1 (N=878)	Quartile 2 (N=832)	Quartile 3 (N=862)	Quartile 4 (N=856)
hsTnI range, pg/mL				
Men	nd – 1.05	1.06 – 1.63	1.64 – 2.64	2.65 – 249.86
Women	nd – 0.78	0.79 – 1.14	1.15 – 1.90	1.91 – 578.27
Age, years	55 ± 8	58 ± 9	61 ± 9	62 ± 10
Women, %	54	51	54	53
Body-mass index, kg/m²	27.3 ± 4.8	28.2 ± 5.4	28.1 ± 5.0	28.0 ± 5.3
Systolic blood pressure, mm Hg	124 ± 17	128 ± 17	130 ± 19	132 ± 21
Use of anti-hypertensive therapy, %	16	27	32	37
Diabetes, %	7	11	10	18
Cigarette smoking, %	19	16	13	13
Total cholesterol, mg/dL	207 ± 42	205 ± 38	207 ± 39	205 ± 42
HDL cholesterol, mg/dL	52 ± 16	51 ± 16	52 ± 16	50 ± 17
Atrial fibrillation, %	1	2	3	6
Prevalent CVD, %	2	2	7	10
ECG LVH, %	0.2	0.1	0.2	2
Significant murmur, %	1	2	2	6

HDL: high density lipoprotein; CVD: cardiovascular disease; ECG: electrocardiography; LVH: left ventricular hypertrophy; nd: non-detectable. For continuous variables, values are mean ± SD or medians (Q1 to Q3).

Supplemental Table 2: Relation of new cardiovascular biomarkers with death and cardiovascular events in quartile models

	Death	Heart failure	Major cardiovascular events
<i>sST2</i>			
1st quartile	Referent	Referent	Referent
2nd quartile	1.06 (0.79-1.42)	1.10 (0.60-2.01)	0.96 (0.67-1.38)
3rd quartile	1.27 (0.96-1.69)	1.98 (1.13-3.45)	1.50 (1.07-2.10)
4th quartile	1.74 (1.33-2.27)	2.48 (1.45-4.23)	1.67 (1.20-2.31)
P for trend	<0.001	<0.001	<0.001
<i>GDF-15</i>			
1st quartile	Referent	Referent	Referent
2nd quartile	1.52 (0.94-2.47)	0.97 (0.40-2.36)	0.82 (0.53-1.28)
3rd quartile	2.22 (1.40-3.52)	1.84 (0.83-4.07)	1.39 (0.93-2.08)
4th quartile	3.70 (2.34-5.86)	3.04 (1.38-6.71)	1.56 (1.03-2.36)
P for trend	<0.001	<0.001	0.002
<i>HsTnI</i>			
1st quartile	Referent	Referent	Referent
2nd quartile	0.95 (0.69-1.30)	1.48 (0.74-2.97)	0.78 (0.54-1.13)
3rd quartile	1.05 (0.78-1.42)	1.41 (0.71-2.78)	0.95 (0.67-1.35)
4th quartile	1.29 (0.97-1.73)	2.96 (1.57-5.56)	1.50 (1.08-2.08)
P for trend	0.03	<0.001	<0.001

Values are hazards ratios (HR), with 95% confidence interval, from multivariable models adjusting for age, sex, body mass index, systolic blood pressure, hypertension therapy, diabetes, cigarette smoking, total cholesterol, HDL cholesterol, prevalent atrial fibrillation (heart failure and death analyses only), prevalent cardiovascular disease (heart failure and death analyses), electrocardiographic left ventricular hypertrophy (heart failure and death analyses), and heart murmur (heart failure analysis only).

Supplemental Table 3: Exclusion of individuals with diabetes or left ventricular hypertrophy

	Death		Heart Failure		Major cardiovascular events	
	Full sample	Excluding individuals with diabetes or LVH	Full sample	Excluding individuals with diabetes or LVH	Full sample	Excluding individuals with diabetes or LVH
Multimarker score						
Per 1-unit	1.80 (1.64-1.98)	1.71 (1.53-1.92)	1.83 (1.55-2.16)	1.70 (1.39-2.09)	1.43 (1.28-1.61)	1.37 (1.20-1.57)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
By quartile						
1st quartile	Referent	Referent	Referent	Referent	Referent	Referent
2nd quartile	1.26 (0.82-1.92)	0.92 (0.57-1.52)	1.52 (0.57-4.06)	3.03 (0.86-10.69)	1.01 (0.67-1.53)	1.22 (0.78-1.93)
3rd quartile	1.55 (1.04-2.30)	1.65 (1.07-2.54)	2.19 (0.88-5.42)	2.54 (0.72-9.96)	1.10 (0.74-1.63)	1.03 (0.65-1.62)
4th quartile	3.20 (2.18-4.70)	2.68 (1.75-4.11)	6.25 (2.63-14.82)	7.49 (2.25-24.87)	1.87 (1.28-2.73)	1.85 (1.21-2.83)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.001

Values shown are multivariable-adjusted hazard ratios, with 95% confidence interval. All models adjust for age, sex, body mass index, systolic blood pressure, hypertension therapy, diabetes, cigarette smoking, total cholesterol, HDL cholesterol, prevalent atrial fibrillation (heart failure and death analyses), electrocardiographic left ventricular hypertrophy (heart failure and death analyses), and heart murmur (heart failure analysis). LVH: electrocardiographic left ventricular hypertrophy.

Supplemental Table 4: Reclassification table for death

Individuals who develop an event during the first 10 years of follow up

Clinical covariates	Model with clinical covariates and biomarker score			
	<10%	10% to <20%	≥20%	Total
<10%	69	12	6	87
10% to <20%	18	49	24	91
≥20%	0	17	146	163
Total	87	78	176	341

Individuals who do not have an event during the first 10 years of follow up

Clinical covariates	Model with clinical covariates and biomarker score			
	<10%	10% to <20%	≥20%	Total
<10%	1961	77	10	2048
10% to <20%	186	288	69	543
≥20%	11	87	222	320
Total	2158	452	301	2911

The number of events differs from the main analyses, because the table is restricted to events occurring during the first 10 years of follow up. Percentages in row and column headers denote predicted 10-year risk of events.

Supplemental Table 5: Reclassification table for heart failure

Individuals who develop an event during the first 10 years of follow up

Clinical covariates	Model with clinical covariates and biomarker score			
	<3%	3% to <8%	≥8%	Total
<3%	14	7	1	22
3% to <8%	1	22	7	30
≥8%	0	4	62	66
Total	15	33	70	118

Individuals who do not have an event during the first 10 years of follow up

Clinical covariates	Model with clinical covariates and biomarker score			
	<3%	3% to <8%	≥8%	Total
<3%	2017	102	7	2126
3% to <8%	216	349	72	637
≥8%	6	101	224	331
Total	2239	552	303	3094

The number of events differs from the main analyses, because the table is restricted to events occurring during the first 10 years of follow up. Percentages in row and column headers denote predicted 10-year risk of events.

Supplemental Table 6: Reclassification table for first major cardiovascular events

Individuals who develop an event during the first 10 years of follow up

Clinical covariates	Model with clinical covariates and biomarker score			
	<10%	10% to <20%	≥20%	Total
<10%	68	14	0	82
10% to <20%	9	53	17	79
≥20%	0	14	75	89
Total	77	81	92	250

Individuals who do not have an event during the first 10 years of follow up

Clinical covariates	Model with clinical covariates and biomarker score			
	<10%	10% to <20%	≥20%	Total
<10%	2080	75	5	2160
10% to <20%	120	308	64	492
≥20%	1	51	170	222
Total	2201	434	239	2874

The number of events differs from the main analyses, because the table is restricted to events occurring during the first 10 years of follow up. Percentages in row and column headers denote predicted 10-year risk of events.

Supplemental Table 7: Association of biomarkers with events in subsets of the sample

Biomarkers	Death		Heart Failure		Major cardiovascular events
	Adjusted for major and non-major CVD	Excluding anyone with baseline major or non-major CVD	Adjusted for major and non-major CVD	Excluding anyone with baseline major or non-major CVD	Excluding anyone with baseline major or non-major CVD
sST2	1.32 (1.20-1.45)	1.32 (1.18-1.48)	1.40 (1.19-1.65)	1.48 (1.20-1.83)	1.27 (1.12-1.44)
GDF-15	1.65 (1.51-1.81)	1.69 (1.51-1.88)	1.48 (1.26-1.74)	1.64 (1.34-2.00)	1.19 (1.05-1.36)
hsTnI	1.16 (1.07-1.26)	1.11 (1.01-1.22)	1.27 (1.12-1.44)	1.20 (1.03-1.39)	1.15 (1.04-1.27)

Values shown are multivariable-adjusted hazard ratios, with 95% confidence interval, per standard deviation increment in the biomarker. All models adjust for age, sex, body mass index, systolic blood pressure, hypertension therapy, diabetes, cigarette smoking, total cholesterol, HDL cholesterol, prevalent atrial fibrillation (heart failure and death analyses), electrocardiographic left ventricular hypertrophy (heart failure and death analyses), and heart murmur (heart failure analysis).