

SUPPLEMENTAL MATERIAL

Table S1. Demographic characteristics by quintile of galectin-3 (N = 2873).

	Quintile 1 ≤ 9.11 pg/mL (N = 576)	Quintile 2 9.12 – 12.2 pg/mL (N = 573)	Quintile 3 12.3 – 15.4 pg/mL (N = 575)	Quintile 4 15.5 – 20.1 pg/mL (N = 574)	Quintile 5 > 20.1 pg/mL (N = 575)
Demographics					
Age	57 (10.9)	59 (11.3)	59 (10.7)	60 (10.7)	61 (10.1)
Male	376 (65)	345 (60)	300 (52)	298 (52)	239 (42)
Race/ethnicity					
Non-Hispanic white	341 (59)	296 (52)	266 (46)	224 (39)	187 (33)
Non-Hispanic black	179 (31)	197 (34)	232 (40)	236 (41)	267 (46)
Hispanic	32 (6)	51 (9)	55 (10)	86 (15)	100 (17)
Other	24 (4)	29 (5)	22 (4)	28 (5)	21 (4)
Comorbidities					
Cardiovascular disease	125 (22)	140 (24)	157 (27)	171 (30)	213 (37)
MI/prior revascularization	83 (14)	100 (17)	106 (18)	110 (19)	131 (23)
COPD	21 (4)	28 (5)	22 (4)	22 (4)	28 (5)
Atrial fibrillation	72 (12)	89 (16)	75 (13)	87 (15)	96 (17)
Stroke	42 (7)	37 (6)	57 (10)	59 (10)	74 (13)
Diabetes	206 (36)	211 (37)	263 (46)	296 (52)	365 (63)
Clinical variables					
Systolic blood pressure (mmHg)	120.2 (19.7)	124.1 (19.4)	126.0 (21.0)	129.7 (22.2)	132.2 (22.2)
BMI (kg/m ²)	31 (6.4)	31 (7.6)	32 (7.2)	33 (8.1)	34 (8.3)
Current smoking	41 (7)	59 (10)	88 (15)	67 (12)	85 (15)
Laboratory and imaging variables					
eGFR (CKD-EPI) (mL/min/1.73m ²)	51.8 (15.2)	45.8 (15.0)	43.8 (15.1)	39.4 (13.8)	35.0 (14.0)
Urinary protein to creatinine ratio from 24hr urine test	74 (41-259)	93 (46-513)	113 (53-577)	144 (58-622)	339 (83-1330)
Ejection fraction (%)	54.9 (7.4)	55.5 (7.1)	55.5 (7.3)	55.2 (7.5)	55.2 (7.0)
Left ventricular mass index (g)	57.5 (20.3)	61.9 (21.5)	61.9 (21.8)	65.0 (23.1)	68.6 (23.4)
Medications					
ACEi/ARB	361 (63)	391 (68)	397 (69)	408 (71)	415 (72)
Diuretics	253 (44)	301 (53)	300 (52)	372 (65)	390 (68)
Beta blockers	221 (38)	258 (45)	264 (46)	301 (52)	305 (53)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.

MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S2. Demographic characteristics by quintile of sST-2 (N = 2873).

	Quintile 1 ≤ 10.4 pg/mL (N = 577)	Quintile 2 10.5 – 13.4 pg/mL (N = 573)	Quintile 3 13.5 – 16.8 pg/mL (N = 574)	Quintile 4 16.9 – 22 pg/mL (N = 574)	Quintile 5 > 22 pg/mL (N = 575)
Demographics					
Age	57 (11.6)	59 (10.1)	60 (10.6)	60 (10.6)	60 (10.9)
Male	227 (39)	264 (46)	299 (52)	369 (64)	399 (69)
Race/ethnicity					
Non-Hispanic white	237 (41)	270 (47)	262 (46)	265 (46)	280 (49)
Non-Hispanic black	254 (44)	238 (42)	227 (40)	203 (35)	189 (33)
Hispanic	53 (9)	46 (8)	63 (11)	79 (14)	83 (14)
Other	33 (6)	19 (3)	22 (4)	27 (5)	23 (4)
Comorbidities					
Cardiovascular disease	108 (19)	161 (28)	152 (26)	188 (33)	197 (34)
MI/prior revascularization	65 (11)	104 (18)	96 (17)	129 (22)	136 (24)
COPD	25 (4)	27 (5)	23 (4)	19 (3)	27 (5)
Atrial fibrillation	64 (11)	93 (16)	86 (15)	89 (16)	87 (15)
Stroke	39 (7)	55 (10)	57 (10)	57 (10)	61 (11)
Diabetes	193 (33)	242 (42)	250 (44)	321 (56)	335 (58)
Clinical variables					
Systolic blood pressure (mmHg)	123.1 (19.9)	124.2 (20.1)	126.1 (20.9)	130.4 (22.9)	128.4 (21.9)
BMI (kg/m ²)	32 (7.7)	32 (7.8)	32 (7.3)	32 (7.9)	31 (7.3)
Current smoking	80 (14)	67 (12)	69 (12)	61 (11)	63 (11)
Laboratory and imaging variables					
eGFR (CKD-EPI) (mL/min/1.73m ²)	46.4 (16.6)	44.2 (15.3)	44.1 (15.2)	41.4 (15.7)	39.6 (14.8)
Urinary protein to creatinine ratio from 24hr urine test	78 (44-295)	99 (47-380)	98 (48-484)	183 (60-885)	293 (78-1303)
Ejection fraction (%)	55.9 (7.3)	55.2 (7.2)	55.4 (7.3)	55.1 (7.4)	54.7 (7.1)
Left ventricular mass index (g)	59.6 (22.5)	62.0 (22.3)	62.5 (22.5)	65.5 (21.7)	64.7 (22.0)
Medications					
ACEi/ARB	352 (61)	401 (70)	393 (68)	421 (73)	405 (70)
Diuretics	274 (47)	319 (56)	306 (53)	351 (61)	366 (64)
Beta blockers	228 (40)	246 (43)	275 (48)	289 (50)	311 (54)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.

MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S3. Demographic characteristics by category of hsTNT (N = 2873).

	<LLD ≤ 10 ng/L (N = 1023)	Tertile 1 10.1 – 14.7 ng/L (N = 572)	Tertile 2 14.8 – 23.9 ng/L (N = 631)	Tertile 3 >23.9 ng/L (N = 647)
Demographics				
Age	55 (11.4)	60 (10.1)	62 (9.8)	61 (9.6)
Male	357 (35)	309 (54)	407 (65)	485 (75)
Race/ethnicity				
Non-Hispanic white	526 (51)	296 (52)	280 (44)	212 (33)
Non-Hispanic black	349 (34)	198 (35)	257 (41)	307 (47)
Hispanic	89 (9)	58 (10)	69 (11)	108 (17)
Other	59 (6)	20 (3)	25 (4)	20 (3)
Comorbidities				
Cardiovascular disease	169 (17)	142 (25)	223 (35)	272 (42)
MI/prior revascularization	107 (10)	98 (17)	150 (24)	175 (27)
COPD	42 (4)	15 (3)	33 (5)	31 (5)
Atrial fibrillation	116 (11)	75 (13)	114 (18)	114 (18)
Stroke	63 (6)	46 (8)	76 (12)	84 (13)
Diabetes	267 (26)	240 (42)	344 (55)	490 (76)
Clinical variables				
Systolic blood pressure (mmHg)	120.1 (18.5)	124.9 (20.2)	130.5 (22.2)	133.9 (22.3)
BMI (kg/m ²)	31 (7.6)	32 (7.5)	33 (7.9)	33 (7.1)
Current smoking	119 (12)	73 (13)	70 (11)	78 (12)
Laboratory and imaging variables				
eGFR (CKD-EPI) (mL/min/1.73m ²)	50.2 (15.8)	43.6 (13.6)	40.0 (13.5)	34.6 (14.1)
Urinary protein to creatinine ratio from 24hr urine test	72 (42-218)	92 (49-350)	155 (63-745)	472 (128-1931)
Ejection fraction (%)	56.0 (6.3)	56.0 (7.2)	54.7 (7.7)	53.7 (8.1)
Left ventricular mass index (g)	53.6 (16.6)	61.4 (19.2)	67.5 (22.9)	75.9 (25.3)
Medications				
ACEi/ARB	616 (60)	408 (71)	475 (75)	473 (73)
Diuretics	419 (41)	314 (55)	405 (64)	478 (74)
Beta blockers	374 (37)	268 (47)	333 (53)	374 (58)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.

LLD - Lower Limit of Detection; MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S4. Demographic characteristics by quintile of NT-proBNP (N = 2873).

	Quintile 1 ≤ 30.9 pg/mL (N = 575)	Quintile 2 31 – 76 pg/mL (N = 574)	Quintile 3 76.1 – 158 pg/mL (N = 575)	Quintile 4 158.1 – 370 pg/mL (N = 574)	Quintile 5 > 370 pg/mL (N = 575)
Demographics					
Age	54 (11.4)	58 (10.7)	60 (10.7)	61 (10.0)	62 (9.4)
Male	376 (65)	296 (52)	311 (54)	264 (46)	311 (54)
Race/ethnicity					
Non-Hispanic white	253 (44)	264 (46)	277 (48)	290 (51)	230 (40)
Non-Hispanic black	257 (45)	234 (41)	216 (38)	191 (33)	213 (37)
Hispanic	34 (6)	48 (8)	63 (11)	69 (12)	110 (19)
Other	31 (5)	28 (5)	19 (3)	24 (4)	22 (4)
Comorbidities					
Cardiovascular disease	76 (13)	112 (20)	156 (27)	182 (32)	280 (49)
MI/prior revascularization	46 (8)	65 (11)	96 (17)	129 (22)	194 (34)
COPD	15 (3)	25 (4)	19 (3)	34 (6)	28 (5)
Atrial fibrillation	52 (9)	62 (11)	74 (13)	90 (16)	141 (25)
Stroke	25 (4)	42 (7)	52 (9)	67 (12)	83 (14)
Diabetes	197 (34)	248 (43)	268 (47)	290 (51)	338 (59)
Clinical variables					
Systolic blood pressure (mmHg)	120.1 (17.7)	123.1 (19.2)	125.0 (20.4)	130.1 (22.1)	134.0 (23.8)
BMI (kg/m ²)	32 (7.0)	32 (7.1)	32 (7.7)	32 (8.4)	32 (7.7)
Current smoking	53 (9)	57 (10)	62 (11)	72 (13)	96 (17)
Laboratory and imaging variables					
eGFR (CKD-EPI) (mL/min/1.73m ²)	53.3 (14.6)	46.5 (14.5)	42.8 (15.1)	39.6 (13.7)	33.5 (13.2)
Urinary protein to creatinine ratio from 24hr urine test	69 (42-214)	96 (48-456)	128 (54-543)	140 (56-739)	329 (85-1390)
Ejection fraction (%)	55.6 (6.3)	56.2 (6.2)	55.6 (6.9)	55.4 (7.4)	53.2 (9.0)
Left ventricular mass index (g)	55.2 (17.6)	59.3 (20.1)	62.0 (21.4)	62.9 (20.9)	76.3 (25.8)
Medications					
ACEi/ARB	394 (69)	387 (67)	416 (72)	390 (68)	385 (67)
Diuretics	246 (43)	294 (51)	330 (57)	343 (60)	403 (70)
Beta blockers	150 (26)	215 (37)	258 (45)	336 (59)	390 (68)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.

MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S5. Correlations of log-transformed biomarkers adjusted for age and sex.

	GDF-15	Galectin-3	sST-2	hsTnT	NT-proBNP
GDF-15	1.00	0.35	0.28	0.32	0.31
Galectin-3		1.00	0.12	0.17	0.15
sST-2			1.00	0.13	0.11
hsTnT				1.00	0.24
NT-proBNP					1.00

Entries are the partial correlation between the log-transformed biomarkers adjusting for age and sex.

Table S6. Effect of adjustment for LV mass index, ejection fraction, and baseline KCCQ scores on the associations of biomarkers with year 1 KCCQ <75 and incident decline in KCCQ scores.

		Model 2	Model 3	Model 4	Model 5
GDF-15 Continuous Model	KCCQ <75 OR (99% CI)	1.42 (1.19, 1.68)*	1.33 (1.12, 1.59)*	1.41 (1.19, 1.68)*	--
	Log(GDF-15) per 1 SD (0.58 pg/mL) increase	Incident Decline in KCCQ HR (99% CI)	1.36 (1.12, 1.65)*	1.32 (1.07, 1.61)*	1.34 (1.11, 1.63)*
Galectin-3 Continuous Model	KCCQ <75 OR (99% CI)	1.28 (1.12, 1.48)*	1.23 (1.07, 1.41)*	1.29 (1.12, 1.48)*	--
	Log(Galectin-3) per 1 SD (0.50 pg/mL) increase	Incident Decline in KCCQ [^] HR (99% CI)	1.08 (0.92, 1.26)	1.05 (0.90, 1.23)	1.08 (0.92, 1.26)
sST-2 Continuous Model	KCCQ <75 OR (99% CI)	1.12 (0.98, 1.28)	1.07 (0.94, 1.21)	1.12 (0.98, 1.28)	--
	Log(sST-2) per 1 SD (0.55 pg/mL) increase	Incident Decline in KCCQ HR (99% CI)	1.08 (0.92, 1.26)	1.04 (0.90, 1.22)	1.08 (0.93, 1.27)
hsTnT Continuous Model	KCCQ <75 OR (99% CI)	1.10 (0.93, 1.31)	1.01 (0.85, 1.20)	1.10 (0.92, 1.30)	--
	Log(hsTnT) per 1 SD (0.78 ng/L) increase	Incident Decline in KCCQ HR (99% CI)	1.20 (1.01, 1.44)*	1.15 (0.95, 1.39)	1.17 (0.97, 1.40)
NT-proBNP Continuous Model	KCCQ <75 OR (99% CI)	1.03 (0.88, 1.21)	0.97 (0.83, 1.14)	1.02 (0.87, 1.20)	--
	Log(NT-proBNP) per 1 SD (1.60pg/mL) increase	Incident Decline in KCCQ HR (99% CI)	1.30 (1.08, 1.56)*	1.26 (1.04, 1.51)*	1.25 (1.04, 1.51)*

* $P < 0.01$

Model 2: Age, sex, race/ethnicity (M1) + myocardial infarction, chronic obstructive pulmonary disease, atrial fibrillation, stroke, baseline diabetes, systolic blood pressure, body mass index, current smoking, eGFR, 24 hour urinary protein, ACEi/ARBs, diuretics, and beta blocker use.

Model 3: M2 + other cardiac biomarkers.

Model 4: M2 + LV Mass Index and Ejection Fraction.

Model 5: M2 + Year 1 KCCQ score.

[^]Incident Decline in KCCQ defined as participants with KCCQ ≥ 75 developing a KCCQ < 75 and having an average decline in KCCQ score of >3 points/year.

N = 2873 for year 1 KCCQ analysis.

N = 2132 for analysis of incident decline in KCCQ scores at year 5.

LV – left ventricular; KCCQ – Kansas City Cardiomyopathy Questionnaire; HF – heart failure; OR – odds ratio; CI – confidence interval; LLD - Lower Limit of Detection

Table S7. Association of cardiac biomarkers with incident decline in KCCQ scores[†], among participants with year 1 KCCQ \geq 60 (N = 2461).

	Incident Decline in KCCQ[†] Model 0 HR (99% CI)	Incident Decline in KCCQ Model 1 aHR (99% CI)	Incident Decline in KCCQ Model 2 aHR (99% CI)
GDF-15 Continuous Model Log(GDF-15) per 1 SD (0.58 pg/mL) increase	1.65 (1.39, 1.95)*	1.58 (1.31, 1.89)*	1.41 (1.13, 1.76)*
GDF-15 Categorical Model			
Quintile 1 (\leq 856 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (857 – 1200 pg/mL)	2.01 (1.05, 3.85)*	1.88 (0.97, 3.65)	1.69 (0.84, 3.37)
Quintile 3 (1201 – 1570 pg/mL)	2.79 (1.49, 5.23)*	2.65 (1.39, 5.05)*	2.11 (1.05, 4.24)*
Quintile 4 (1571 – 2220 pg/mL)	3.70 (1.99, 6.86)*	3.39 (1.77, 6.50)*	2.32 (1.10, 4.89)*
Quintile 5 ($>$ 2220 pg/mL)	5.04 (2.72, 9.35)*	4.59 (2.39, 8.81)*	3.37 (1.57, 7.23)*
Galectin-3 Continuous Model Log(Galectin-3) per 1 SD (0.50 pg/mL) increase	1.33 (1.11, 1.58)*	1.17 (0.98, 1.40)	1.03 (0.86, 1.23)
Galectin-3 Categorical Model			
Quintile 1 (\leq 9.11 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (9.12 – 12.2 pg/mL)	1.58 (0.89, 2.78)	1.42 (0.80, 2.51)	1.31 (0.74, 2.34)
Quintile 3 (12.3 – 15.4 pg/mL)	1.80 (1.03, 3.16)*	1.53 (0.87, 2.69)	1.32 (0.75, 2.32)
Quintile 4 (15.5 – 20.1 pg/mL)	2.08 (1.20, 3.62)*	1.61 (0.92, 2.82)	1.22 (0.69, 2.16)
Quintile 5 ($>$ 20.1 pg/mL)	2.57 (1.47, 4.49)*	1.83 (1.03, 3.24)*	1.28 (0.71, 2.30)
sST-2 Continuous Model Log(sST-2) per 1 SD (0.55 pg/mL) increase	1.16 (0.97, 1.38)	1.24 (1.02, 1.49)*	1.14 (0.93, 1.38)
sST-2 Categorical Model			
Quintile 1 (\leq 10.4 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (10.5 – 13.4 pg/mL)	1.42 (0.84, 2.41)	1.50 (0.88, 2.56)	1.25 (0.73, 2.14)
Quintile 3 (13.5 – 16.8 pg/mL)	1.41 (0.83, 2.42)	1.53 (0.89, 2.63)	1.24 (0.72, 2.14)
Quintile 4 (16.9 – 22 pg/mL)	1.39 (0.80, 2.40)	1.58 (0.91, 2.77)	1.13 (0.64, 2.00)
Quintile 5 ($>$ 22 pg/mL)	1.59 (0.93, 2.72)	2.01 (1.15, 3.50)*	1.58 (0.90, 2.79)
hsTnT Continuous Model Log(hsTnT) per 1 SD (0.78 ng/L) increase	1.41 (1.19, 1.66)*	1.48 (1.24, 1.77)*	1.25 (1.01, 1.56)*
hsTnT Categorical Model			
< LLD ($<$ 10 ng/L)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Tertile 1 (10.1 – 14.7 ng/L)	1.38 (0.87, 2.20)	1.51 (0.93, 2.43)	1.25 (0.76, 2.04)
Tertile 2 (14.8 – 23.9 ng/L)	1.47 (0.93, 2.33)	1.66 (1.02, 2.71)*	1.17 (0.70, 1.97)
Tertile 3 ($>$ 23.9 ng/L)	2.50 (1.62, 3.84)*	2.90 (1.79, 4.69)*	1.90 (1.10, 3.26)*
NT-proBNP Continuous Model Log(NT-proBNP) per 1 SD (1.60 pg/mL) increase	1.46 (1.22, 1.75)*	1.40 (1.16, 1.69)*	1.14 (0.91, 1.41)
NT-proBNP Categorical Model			
Quintile 1 (\leq 31.9 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (31 – 76 pg/mL)	1.19 (0.67, 2.10)	1.12 (0.63, 1.99)	0.99 (0.55, 1.79)
Quintile 3 (76.1 – 158 pg/mL)	1.39 (0.79, 2.44)	1.32 (0.74, 2.33)	0.98 (0.54, 1.77)
Quintile 4 (158.1 – 370 pg/mL)	1.92 (1.12, 3.29)*	1.84 (1.05, 3.20)*	1.27 (0.71, 2.30)
Quintile 5 ($>$ 370 pg/mL)	2.78 (1.64, 4.69)*	2.41 (1.39, 4.16)*	1.43 (0.77, 2.66)

* $P < 0.01$

[†]Incident Decline in KCCQ defined as participants with KCCQ \geq 60 developing a KCCQ $<$ 60 and having an average decline in KCCQ score of $>$ 5 points/year.

Model 0: Unadjusted.

Model 1: Age, sex, race/ethnicity.

Model 2: M1 + myocardial infarction, chronic obstructive pulmonary disease, atrial fibrillation, stroke, baseline diabetes, systolic blood pressure, body mass index, current smoking, eGFR, 24h urinary protein, ACEi/ARBs, diuretics, and beta blocker use.

HF – heart failure; KCCQ – Kansas City Cardiomyopathy Questionnaire; HR – hazard ratio; CI – confidence interval;

aHR – adjusted hazard ratio;LLD - Lower Limit of Detection