

Appendix Table 1. Comparison of biomarker group and rest of patients in ARISE-HF.

	Elevated Biomarker (907)	Echo abnormalities (556)	p	
Demographic/clinical variables	Age (mean (SD))	67.25 (7.48)	67.33 (7.59)	0.85
	Male (%)	496 (54.7)	301 (54.1)	0.88
	Race (%)			0.10
	White	597 (65.8)	328 (59.0)	
	Hispanic	179 (19.7)	121 (21.8)	
	Black	61 (6.7)	55 (9.9)	
	Asian	58 (6.4)	41 (7.4)	
	American Indian or Alaskan Native	3 (0.3)	2 (0.4)	
	Other	9 (1.0)	9 (1.6)	
	SBP (mean (SD))	130.31 (13.26)	129.87 (13.38)	0.62
DBP (mean (SD))	76.08 (8.87)	75.90 (8.79)	0.76	
Laboratory Tests	NT-proBNP (median [IQR])	77.00 [44.00, 138.00]	78.00 [34.00, 142.00]	0.68
	hs-cTnt (median [IQR])	9.00 [7.00, 13.00]	9.00 [7.00, 14.00]	0.79
	HBA1 (mean (SD))	7.22 (1.27)	7.11 (0.95)	0.07
	Hgb (mean (SD))	13.70 (1.50)	13.64 (1.43)	0.49
	eGFR (mean (SD))	77.72 (18.38)	79.27 (17.50)	0.11
Echocardiogram	LVEF (median [IQR])	63.00 [60.00, 66.00]	61.00 [58.00, 64.00]	<0.001
	GLS (median [IQR])	-18.80 [-20.20, -17.90]	-15.20 [-17.00, -14.20]	<0.001
	LAVI (median [IQR])	22.00 [18.60, 26.00]	25.10 [20.00, 34.10]	<0.001
	LVMI (median [IQR])	68.00 [60.00, 79.00]	83.00 [67.00, 98.00]	<0.001
	EE (median [IQR])	8.70 [7.38, 10.30]	10.30 [8.40, 13.90]	<0.001
	RVSP (median [IQR])	22.60 [18.80, 26.00]	24.05 [19.52, 30.60]	<0.001
CPET	PEAK VO2 (mean (SD))	16.52 (4.91)	15.99 (4.77)	0.10
	Duration of CPET test, min, mean ± SD	9.98 (2.79)	9.79 (2.93)	0.32
	Peak respiratory exchange rate, mean ± SD	1.16 (0.10)	1.16 (0.11)	0.84
Questionnaires	KCCQ physical limitation score, mean ± SD			
	KCCQ symptom stability score, mean ± SD			
	KCCQ symptom burden score, mean ± SD			
	KCCQ self-efficacy score, mean ± SD			
	KCCQ quality of life score, mean ± SD			
	KCCQ social limitation score, mean ± SD			
	KCCQ total symptom score, mean ± SD			
	KCCQ clinical summary score, mean ± SD			
	KCCQ overall summary score, mean ± SD			
	PASE score, mean ± SD			

Appendix Table 2. Comparison of biomarkers group with an NT-proBNP cut-off of 125 ng/L and the rest of the participants.

	Elevated Biomarkers	All	p
n	751	556	
AGE (mean (SD))	67.46 (7.49)	67.33 (7.59)	0.76
MALE (%)	441 (58.7)	301 (54.1)	0.11
RACE (%)			0.08
White	500 (66.6)	328 (59.0)	
Hispanic	148 (19.7)	121 (21.8)	
Black	53 (7.1)	55 (9.9)	
Asian	38 (5.1)	41 (7.4)	
American Indian or Alaskan Native	3 (0.4)	2 (0.4)	
Other	9 (1.2)	9 (1.6)	
SBP (mean (SD))	131 (14)	130 (13)	0.40
DBP (mean (SD))	76 (9)	76 (9)	0.66
Laboratory Test			
NT-proBNP (median [IQR])	80.00 [35.00, 148.00]	78.00 [34.00, 142.00]	0.55
hs-cTnt (median [IQR])	10.00 [7.00, 14.00]	9.00 [7.00, 14.00]	0.004
HbA1c (mean (SD))	7.20 (1.25)	7.11 (0.95)	0.17
Hgb (mean (SD))	13.73 (1.52)	13.64 (1.43)	0.26
eGFR (mean (SD))	77.02 (18.62)	79.27 (17.50)	0.03
Echocardiogram			
LVEF (median [IQR])	63.00 [60.00, 66.00]	61.00 [58.00, 64.00]	<0.001
GLS (median [IQR])	-18.90 [-20.40, -17.90]	-15.20 [-17.00, -14.20]	<0.001
LAVI (median [IQR])	22.10 [18.60, 26.17]	25.10 [20.00, 34.10]	<0.001
LVMI (median [IQR])	69.00 [60.30, 80.00]	83.00 [67.00, 98.00]	<0.001
EE (median [IQR])	8.80 [7.40, 10.40]	10.30 [8.40, 13.90]	<0.001
RVSP (median [IQR])	22.60 [18.90, 26.00]	24.05 [19.52, 30.60]	<0.001
CPET			
PEAKVO2 (mean (SD))	16.65 (5.08)	15.99 (4.77)	0.06
Duration of CPET test, min, mean \pm SD	1.16 (0.10)	1.16 (0.11)	0.84
Peak respiratory exchange rate, mean \pm SD	16.65 (5.08)	15.99 (4.77)	0.06

Appendix Table 3. Comparison of phenotype groups in the screened cohort.

	Elevated Biomarkers of Heart disease	Systolic/LVH cluster	P (biomarkers vs systolic)	Diastolic + Overlap	P (biomarkers vs diastolic+overlap)	P (systolic vs diastolic+overlap)
n	907	301		255		
AGE (mean (SD))	67.25 (7.48)	66.05 (7.36)	0.02	68.91 (7.58)	0.03	<0.01
MALE (%)	496 (54.7)	178 (59.1)	0.20	123 (48.2)	0.08	0.01
Race (%)			0.02		0.31	0.07
White	597 (65.8)	175 (58.1)		153 (60.0)		
Hispanic	179 (19.7)	58 (19.3)		63 (24.7)		
Black	61 (6.7)	39 (13.0)		16 (6.3)		
Asian	58 (6.4)	23 (7.6)		18 (7.1)		
American Indian/Alaskan	3 (0.3)	2 (0.7)		0 (0.0)		
Other	9 (1.0)	4 (1.3)		5 (2.0)		
SBP (mean (SD))	130.31 (13.26)	127.81 (12.18)	0.02	131.96 (14.21)	0.14	0.01
DBP (mean (SD))	76.08 (8.87)	76.18 (8.63)	0.89	75.62 (8.96)	0.53	0.51
Laboratory Tests						
NT-proBNP (median [IQR])	77 [44, 138]	62 [29, 118]	<.0001	101 [47, 173]	<.0001	<.0001
hs-cTnt (median [IQR])	9 [7, 13]	9 [6, 13.25]	0.13	10 [7, 14]	0.24	0.04
HbA1c (% , mean (SD))	7.22 (1.27)	7.20 (1.01)	0.75	7.01 (0.86)	0.01	0.02
Hb (mean (SD))	13.70 (1.50)	13.76 (1.48)	0.51	13.50 (1.37)	0.06	0.03
eGFR (mean (SD))	77.72 (18.38)	80.71 (17.66)	0.01	77.58 (17.19)	0.91	0.04
Echocardiogram						
LVEF (median [IQR])	63 [60, 66]	60 [57, 63]	<.0001	63 [60, 66]	0.45	<.0001
GLS (median [IQR])	-18.8 [-20.2, -17.9]	-14.8 [-15.5, -13.9]	<.0001	-18.1 [-20, -15.5]	<.0001	<.0001
LAVI (median [IQR])	22 [19, 26]	22 [18, 26]	0.26	34 [25, 37]	<.0001	<.0001
LVMI (median [IQR])	68 [60, 79]	74 [63, 91]	<.01	92 [74, 102]	<.0001	<.0001
EE (median [IQR])	8.7 [7.4, 10.3]	8.9 [7.4, 10.2]	0.42	14 [11.5, 15.7]	<.0001	<.0001
RVSP (median [IQR])	22.6 [18.8, 26]	22.3 [18.2, 25.7]	0.40	27.9 [21.9, 35]	<.0001	<.0001
CPET						
PEAK VO2 (mean (SD))	16.52 (4.91)	16.35 (4.58)	0.66	15.63 (4.93)	0.03	0.12
Duration of CPET test, min, mean ± SD	9.98 (2.79)	10.08 (2.94)	0.66	9.49 (2.89)	0.04	0.04
Pk RER, mean ± SD	1.16 (0.10)	1.17 (0.11)	0.18	1.15 (0.11)	0.32	0.05

Appendix Table 4. Distribution of phenotypes in randomized (impaired exercise capacity) and screen-failure patients. The randomized group had a greater proportion of patients with elevated biomarkers alone, and a smaller number of patients with a mixed phenotype (p<0.0001).

	Elevated Biomarkers (907)		Systolic/LVH (301)		Diastolic (162)		Overlap (93)	
n	Trial 347 (23.7%)	S/Fail 560 (38.3%)	Trial 169 (11.6%)	S/Fail 132 (9.0%)	Trial 86 (5.9%)	S/Fail 76 (5.2%)	Trial 67 (4.6%)	S/Fail 26 (1.8%)
Age (mean (SD))	67.70 (7.01)	66.97 (7.75)	66.88 (7.11)	64.99 (7.56)	66.27 (7.73)	71.01 (7.56)	69.06 (6.93)	70.88 (6.62)
Male (%)	168 (48.4)	328 (58.6)	96 (56.8)	82 (62.1)	52 (60.5)	38 (50.0)	21 (31.3)	12 (46.2)
Race (%)								
Black or African American	19 (5.5)	47 (8.4)	19 (11.2)	21 (15.9)	6 (7.0)	4 (5.3)	4 (6.0)	3 (11.5)
Other	30 (8.6)	146 (26.1)	19 (11.2)	34 (25.8)	7 (8.1)	24 (31.5)	7 (10.4)	14 (53.9)
White	298 (85.9)	367 (65.5)	131 (77.5)	77 (58.3)	73 (84.9)	48 (63.2)	56 (83.6)	9 (34.6)
BMI (mean (SD))	30 (4)	N/A	30.33 (4.13)	N/A	31.03 (4.87)	N/A	31.88 (4.89)	N/A
SBP (mean (SD))	130 (12)	131 (17)	127 (11)	130 (17)	130(10)	137 (15)	128(12)	148 (28)
Medical History								
Duration of T2DM, yrs (mean (SD))	12.92 (10.13)	N/A	14.91 (8.08)	N/A	15.38 (10.82)	N/A	16.20 (10.30)	N/A
Hypertension(%)	259 (74.6)	N/A	129 (76.3)	N/A	67 (77.9)	N/A	54 (80.6)	N/A
Dyslipidemia (%)	52 (15.0)	N/A	30 (17.8)	N/A	17 (19.8)	N/A	13 (19.4)	N/A
Medications								
ACEi-ARBs (%)	256 (73.8)	N/A	120 (71.0)	N/A	73 (84.9)	N/A	53 (79.1)	N/A
B-Blockers (%)	90 (25.9)	N/A	30 (17.8)	N/A	23 (26.7)	N/A	17 (25.4)	N/A
MRA (%)	9 (2.6)	N/A	4 (2.4)	N/A	2 (2.3)	N/A	4 (6.0)	N/A
Hydrochlorothiazide (%)	60 (17.3)	N/A	32 (18.9)	N/A	25 (29.1)	N/A	11 (16.4)	N/A
SGLT2 (%)	110 (31.7)	N/A	54 (32.0)	N/A	26 (30.2)	N/A	20 (29.9)	N/A
GLP1 (%)	78 (22.5)	N/A	57 (33.7)	N/A	20 (23.3)	N/A	14 (20.9)	N/A
Statin(%)	271 (78.1)	N/A	148 (87.6)	N/A	66 (76.7)	N/A	50 (74.6)	N/A
Metformin(%)	266 (76.7)	N/A	129 (76.3)	N/A	60 (69.8)	N/A	45 (67.2)	N/A
Sulfonylureas (%)	88 (25.4)	N/A	30 (17.8)	N/A	18 (20.9)	N/A	16 (23.9)	N/A
Insulin (%)	78 (22.5)	N/A	49 (29.0)	N/A	31 (36.0)	N/A	18 (26.9)	N/A
DDP4 (%)	40 (11.5)	N/A	22 (13.0)	N/A	5 (5.8)	N/A	12 (17.9)	N/A
Laboratory Test								
NT-proBNP (median [IQR])	77.00 [46.00, 141.50]	77.00 [42.00, 132.00]	61.00 [28.00, 117.50]	64.00 [29.00, 122.25]	70.00 [37.00, 125.25]	107.00 [59.50, 189.00]	98.00 [42.50, 161.00]	184.00 [119.25, 358.50]
hs-cTnt (median [IQR])	9.00 [6.00, 12.00]	10.00 [7.00, 14.00]	8.00 [6.00, 12.00]	9.00 [6.00, 15.00]	11.00 [8.00, 13.75]	11.50 [8.00, 16.00]	8.00 [6.00, 10.00]	13.00 [8.25, 19.75]
HbA1c (% , mean (SD))	6.95 (0.81)	7.39 (1.47)	7.02 (0.81)	7.43 (1.19)	7.11 (0.81)	6.97 (0.85)	6.84 (0.57)	7.19 (1.46)
Hgb (mean (SD))	13.71 (1.37)	13.69 (1.57)	13.70 (1.49)	13.85 (1.47)	13.68 (1.34)	13.55 (1.34)	13.29 (1.32)	13.26 (1.61)
eGFR (mean (SD))	79.67 (16.02)	76.51 (19.63)	81.85 (16.16)	79.26 (19.39)	81.10 (16.83)	76.46 (15.93)	77.63 (15.82)	69.04 (22.27)

Appendix Table 5. Evolution of peak VO2 and functional status over 15 month follow-up in participants treated with placebo.

Phenogroup (n)	Elevated Biomarkers N = 117	Systolic/ LVH N = 54	p	Diastolic N = 28	P	Overlap N = 24	P
Primary Endpoint							
Peak VO2, Month 15, mL/Kg/min, mean ± SD	15.50 (3.92)	15.40 (4.48)	0.90	15.80 (4.28)	0.75	12.32 (3.90)	0.001
Peak VO2, Change, mL/Kg/min, mean ± SD	-0.43 (2.25)	-0.43 (2.39)	0.98	0.14 (2.24)	0.31	-0.90 (1.73)	0.37
PASE Score, Month 15							
PASE score, Month 15, mean ± SD	150.35 (81.79)	163.48 (116.30)	0.43	176.47 (81.48)	0.19	135.81 (77.56)	0.47
PASE score, change, mean ± SD	-8.11 (86.64)	-7.38 (97.97)	0.97	19.98 (73.50)	0.19	11.99 (73.63)	0.36
KCCQ Score, Month 15							
KCCQ physical limitation score, mean ± SD	87.43 (17.95)	84.01 (21.06)	0.30	96.03 (7.62)	0.03	78.92 (22.71)	0.07
KCCQ symptom stability score, mean ± SD	51.49 (15.34)	54.41 (11.94)	0.24	52.38 (10.91)	0.80	51.25 (9.85)	0.95
KCCQ symptom burden score, mean ± SD	89.32 (17.24)	88.89 (15.43)	0.88	96.03 (6.78)	0.08	85.83 (19.52)	0.42
KCCQ self-efficacy score, mean ± SD	83.75 (25.34)	78.92 (28.12)	0.29	88.10 (25.15)	0.48	91.88 (13.00)	0.17
KCCQ quality of life score, mean ± SD	87.54 (19.28)	83.82 (19.47)	0.27	93.65 (9.83)	0.16	84.17 (23.55)	0.49
KCCQ social limitation score, mean ± SD	90.77 (18.43)	86.48 (20.70)	0.24	96.98 (6.32)	0.14	84.72 (25.83)	0.24
KCCQ total symptom score, mean ± SD	88.72 (17.24)	89.26 (14.14)	0.85	96.03 (5.63)	0.06	84.53 (18.78)	0.33
KCCQ clinical summary score, mean ± SD	88.07 (16.87)	86.63 (16.06)	0.62	96.03 (5.26)	0.04	81.72 (18.86)	0.13
KCCQ overall summary score, mean ± SD	88.79 (16.18)	86.18 (16.18)	0.35	95.68 (5.26)	0.06	83.17 (20.22)	0.18
KCCQ Score, Change month 0- 15							
KCCQ physical limitation score, mean ± SD	-0.73 (11.54)	-6.42 (19.36)	0.03	0.79 (11.07)	0.58	-4.68 (11.80)	0.19
KCCQ symptom stability score, mean ± SD	-2.00 (16.55)	2.45 (13.47)	0.10	-1.19 (16.73)	0.84	-2.50 (16.02)	0.90
KCCQ symptom burden score, mean ± SD	-1.86 (12.73)	-4.08 (14.47)	0.33	-1.19 (7.11)	0.82	-3.75 (11.30)	0.54
KCCQ self-efficacy score, mean ± SD	-2.27 (24.83)	1.25 (30.54)	0.45	1.79 (14.94)	0.47	-3.12 (14.55)	0.88
KCCQ quality of life score, mean ± SD	0.58 (16.04)	0.49 (21.24)	0.98	-0.99 (11.63)	0.67	-2.92 (19.55)	0.39
KCCQ social limitation score, mean ± SD	-0.73 (13.91)	-3.42 (16.13)	0.36	0.81 (10.03)	0.66	-3.85 (19.35)	0.49
KCCQ total symptom score, mean ± SD	-2.21 (11.89)	-3.43 (13.38)	0.57	-0.69 (5.67)	0.57	-5.31 (11.47)	0.29
KCCQ clinical summary score, mean ± SD	-1.47 (9.19)	-4.61 (15.35)	0.12	0.05 (7.09)	0.48	-5.70 (11.94)	0.08
KCCQ overall summary score, mean ± SD	-0.59 (8.89)	-3.24 (15.28)	0.18	-0.12 (5.83)	0.82	-4.29 (13.08)	0.12

