

Supplemental Material for Cunningham et al. “Effect of Sacubitril/Valsartan on Biomarkers of Extracellular Matrix Regulation in Patients with HFpEF”

Supplemental Table 1. Baseline characteristics of patients with or without available biomarker data

	Available Biomarker Data	Rest of Trial	
	n = 1,135	n = 3,661	
Age, years	73.5 ± 8.0	72.5 ± 8.5	<0.001
Female	586 (51.6%)	1893 (51.7%)	0.96
Race			<0.001
White	1,052 (92.7%)	2,855 (78.0%)	
Asian	37 (3.3%)	570 (15.6%)	
Black	15 (1.3%)	87 (2.4%)	
Other	31 (2.7%)	149 (4.1%)	
Region			0.27
Asia/Pacific	108 (9.5%)	654 (17.9%)	

Central Europe	538 (47.4%)	1,177 (32.1%)	
Latin America	13 (1.1%)	357 (9.8%)	
North America	138 (12.2%)	421 (11.5%)	
Western Europe	338 (29.8%)	1,052 (28.7%)	
Diabetes	471 (41.5%)	1,591 (43.5%)	0.24
Stroke	124 (11.0%)	384 (10.5%)	0.66
Hypertension	1,090 (96.0%)	3,494 (95.4%)	0.39
Prior myocardial infarction	242 (21.3%)	841 (23.0%)	0.25
Ischemic etiology	417 (36.7%)	1,306 (35.7%)	0.52
NYHA functional class			0.46
I	32 (2.8%)	105 (2.9%)	
II	868 (76.5%)	2,838 (77.6%)	
III	234 (20.6%)	698 (19.1%)	
IV	1 (0.1%)	18 (0.5%)	
Prior HF Hosp	409 (36.0%)	1,897 (51.8%)	<0.001
Body mass index, kg/m ²	30.7 ± 4.8	30.1 ± 5.1	<0.001
Left ventricular ejection	57.3 ± 7.5	57.6 ± 8.0	0.19

fraction			
ACEi/ARB	1,010 (89.0%)	3,129 (85.5%)	0.003
Mineralocorticoid antagonist	276 (24.3%)	963 (26.3%)	0.18
Diuretic	1,099 (96.8%)	3,486 (95.2%)	0.021
Beta-blocker	935 (82.4%)	2,886 (78.8%)	0.009
Atrial fibrillation	362 (32.0%)	1,190 (32.6%)	0.67
Systolic blood pressure, mm Hg	130.9 ± 15.3	130.5 ± 15.5	0.41
Diastolic blood pressure, mm Hg	74.4 ± 10.3	74.3 ± 10.6	0.68
Potassium, mEq/l	4.5 ± 0.4	4.5 ± 0.5	0.87
eGFR, ml/min/1.73m ²	60.2 ± 17.9	63.3 ± 19.4	<0.001
NT-proBNP, pg/ml	942.0 [506.0, 1,553.0]	892.0 [452.0, 1,639.0]	0.18
hsTNT, ng/l	17.0 [11.0, 26.0]	24.0 [11.0, 34.0]	0.12

Abbreviation: Biomarker substudy participation is defined as having data for at least 1 biomarker of ECM homeostasis at baseline. Normally distributed categorical variables are described as mean ± standard deviation. Skewed variables are described as median (interquartile range).

Categorical variables are described as number (percentage of total). Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; hsTNT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Supplemental Table 2. Median (95% confidence interval) baseline biomarker levels in men and women and patients with higher or lower left ventricular ejection fraction

A: Sex

	Men	Women	p Value
CITP	6.2 (4.7–8.7)	5.8 (4.6–7.5)	0.005
PINP	35 (27–47)	41 (31–54)	<0.001
PIIINP	4.5 (3.7–5.6)	4.3 (3.5–5.4)	0.018
sST2	25.3 (20.1–31.3)	22 (18.2–26.9)	<0.001
TIMP-1	131.3 (109.3–161.1)	126.2 (106–153.1)	0.011

B: Left ventricular ejection fraction

	LVEF ≤ 57%	LVEF > 57%	p Value
CITP	6.0 (4.7–8.2)	6.0 (4.7–7.8)	0.64
PINP	39 (29–52)	37 (29–50)	0.41
PIIINP	4.5 (3.6–5.5)	4.4 (3.5–5.5)	0.91
sST2	24.1 (18.9–29.4)	23.2 (18.9–28.2)	0.16
TIMP-1	126.9 (106.3–156.4)	129.5 (108.6–155.9)	0.61

Supplemental Table 3. Association of baseline biomarker levels with components of the primary endpoint

A: CV death (74 events)

	n	Unadjusted		Adjusted	
		Hazard Ratio (95% CI) per SD	p Value	Hazard Ratio (95% CI) per SD	p Value
TIMP-1	1,117	1.59 (1.3–1.96)	<0.001	1.27 (0.99–1.63)	0.06
sST2	1,120	1.43 (1.19–1.72)	<0.001	1.25 (1.03–1.52)	0.03
PIIINP	1,108	1.11 (0.88–1.40)	0.38	0.86 (0.67–1.1)	0.23
PINP	1,116	1.01 (0.8–1.27)	0.95	0.85 (0.66–1.08)	0.17
CITP	1,096	1.37 (1.11–1.69)	0.004	0.93 (0.70–1.24)	0.64

B: Recurrent heart failure hospitalization (261 events)

	n	Unadjusted		Adjusted	
		Rate Ratio (95% CI) per SD	p Value	Rate Ratio (95% CI) per SD	p Value
TIMP-1	1,117	1.74 (1.51–2)	<0.001	1.38 (1.16–1.65)	<0.001

sST2	1,120	1.42 (1.26–1.61)	<0.001	1.11 (0.97–1.28)	0.13
PIIINP	1,108	1.38 (1.15–1.67)	0.001	1.09 (0.89–1.34)	0.39
PINP	1,116	1.07 (0.87–1.33)	0.52	0.94 (0.76–1.15)	0.53
CITP	1,096	1.60 (1.33–1.93)	<0.001	1.07 (0.85–1.34)	0.56

Hazard ratios and rate ratios with 95% confidence interval refers to increase in expected event rate per log increase in biomarker level. The following covariates were included: NT-proBNP, high sensitivity troponin, age, sex, region, history of stroke diabetes, hypertension, MI, ischemic cause of HF or AF, NYHA, LVEF, medications (MRA, Diuretic, BB), systolic and BP, eGFR and serum potassium. Abbreviations: CI, confidence interval; HR, hazard ratio; RR, rate ratio; SD, standard deviation.

Supplemental Table 4. Association of change in biomarker from baseline to 16 weeks after randomization versus subsequent primary endpoints

	Adjusted Baseline Value		Adjusted for Baseline and Clinical Covariates	
	Rate Ratio per SD Change	p Value	Rate Ratio per SD Change	p Value
TIMP-1	1.31 (1.11–1.54)	0.001	1.23 (1.03–1.47)	0.023
sST2	1.18 (1.04–1.32)	0.008	1.15 (1.02–1.31)	0.028
PIIINP	1.27 (1.05–1.54)	0.015	1.09 (0.90–1.31)	0.366
PINP	1.25 (1.03–1.53)	0.028	1.13 (0.95–1.36)	0.173
CITP	1.36 (1.13–1.64)	0.001	1.26 (1.03–1.55)	0.027

Rate ratios with 95% confidence interval refers to increase in expected event rate per standard deviation of log-transformed change in biomarker between baseline and 16 weeks after randomization, adjusted for baseline value alone (left columns) or baseline value and clinical covariates (right column). The following covariates were included: treatment group, age, sex, region, history of stroke diabetes, hypertension, MI, ischemic cause of HF or AF, NYHA, LVEF, medications (MRA, Diuretic, BB), systolic and BP, eGFR and serum potassium, NT-proBNP, and high sensitivity troponin. There were 292 primary endpoint events after the week 16 visit.

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, rate ratio; SD, standard deviation.