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/m2 | 30.7 ± 4.8 | 30.1 ± 5.1 | <0.001 |
| Left ventricular ejection fraction | 57.3 ± 7.5 | 57.6 ± 8.0 | 0.19 |
| 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/1.73m2 | 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)

|  |  |  |  |
| --- | --- | --- | --- |
|  |   | Unadjusted | Adjusted  |
|  | n | 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)

|  |  |  |  |
| --- | --- | --- | --- |
|  |   | Unadjusted | Adjusted  |
|  | n | 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.