# Supplementary Online Content

Cotter G, Deniau B, Davison B, et al. Optimization of evidence-based heart failure medications after an acute heart failure admission: a secondary analysis of the STRONG-HF randomized clinical trial. *JAMA Cardiol*. Published online December 27, 2023. doi:10.1001/jamacardio.2023.4553

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1. Changes from week 2 to day 90 in vital signs and laboratory data by average optimal dose categories at week 2**

| Parameter | Statistic | Average Dose <50% (n= 39) | Average Dose >=50-<90% (n=254) | Average Dose >=90% (n=222) |
|---|---|---|---|---|
| Vital Signs | | | | |
| Systolic Blood Pressure, mmHg | | | | |
| Week 2 | Mean (SD) | 110.60 ( 15.62) | 119.81 ( 16.28) | 124.90 ( 13.64) |
| Day 90 | Mean (SD) | 121.62 ( 17.52) | 118.94 ( 14.98) | 118.14 ( 16.28) |
| Adjusted Mean Change | LS Mean (SE) | 4.38 ( 2.40) | -1.65 ( 0.91) | -4.93 ( 0.96) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -6.03 (-11.05, -1.00) | -9.31 (-14.43, -4.18) |
| P-value (vs. reference) | | -- | 0.02 | <0.001 |
| Diastolic Blood Pressure, mmHg | | | | |
| Week 2 | Mean (SD) | 68.34 ( 11.53) | 74.28 ( 10.77) | 78.13 ( 9.90) |
| Day 90 | Mean (SD) | 73.65 ( 9.58) | 73.42 ( 10.38) | 74.53 ( 10.35) |
| Adjusted Mean Change | LS Mean (SE) | 1.18 ( 1.63) | -1.44 ( 0.62) | -1.99 ( 0.65) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -2.62 ( -6.03, 0.78) | -3.18 ( -6.66, 0.31) |
| P-value (vs. reference) | | -- | 0.13 | 0.07 |
| Heart Rate, beats/min | | | | |
| Week 2 | Mean (SD) | 74.31 (14.74) | 74.00 (13.17) | 76.26 (10.11) |
| Day 90 | Mean (SD) | 71.32 (14.21) | 71.11 (13.55) | 71.30 (12.79) |
| Adjusted Mean Change | LS Mean (SE) | -3.24 ( 2.09) | -2.89 ( 0.81) | -3.98 ( 0.85) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 0.36 ( -4.05, 4.77) | -0.74 ( -5.18, 3.70) |
| P-value (vs. reference) | | -- | 0.87 | 0.74 |
| Respiratory Rate, breaths/min | | | | |
| Week 2 | Mean (SD) | 18.18 ( 2.26) | 17.62 ( 2.23) | 16.83 ( 2.33) |
| Day 90 | Mean (SD) | 18.03 ( 2.80) | 17.62 ( 2.45) | 16.57 ( 2.15) |
| Adjusted Mean Change | LS Mean (SE) | 0.26 ( 0.32) | 0.13 ( 0.12) | -0.38 ( 0.13) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -0.13 ( -0.79, 0.53) | -0.64 ( -1.31, 0.03) |

| Parameter | Statistic | Average Dose <50% (n= 39) | Average Dose >=50-<90% (n=254) | Average Dose >=90% (n=222) |
|---|---|---|---|---|
| P-value (vs. reference) | | -- | 0.70 | 0.06 |
| | | | | |
| Weight, kg | | | | |
| Week 2 | Mean (SD) | 80.12 (20.21) | 82.81 (19.42) | 77.67 (20.99) |
| Day 90 | Mean (SD) | 77.72 (19.10) | 82.59 (19.42) | 77.11 (20.63) |
| Adjusted Mean Change | LS Mean (SE) | -2.85 ( 0.65) | -0.34 ( 0.25) | -0.98 ( 0.26) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 2.51 ( 1.14, 3.87) | 1.87 ( 0.49, 3.24) |
| P-value (vs. reference) | | -- | <0.001 | 0.008 |
| | | | | |
| Local Laboratory | | | | |
| Hemoglobin, g/L | | | | |
| Week 2 | Mean (SD) | 129.1 (19.83) | 137.4 (19.26) | 133.4 (16.95) |
| Day 90 | Mean (SD) | 127.3 (17.69) | 134.0 (17.98) | 130.6 (15.54) |
| Adjusted Mean Change | LS Mean (SE) | -3.88 ( 2.20) | -3.41 ( 0.83) | -3.22 ( 0.86) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 0.47 ( -4.16, 5.10) | 0.66 ( -3.97, 5.29) |
| P-value (vs. reference) | | -- | 0.84 | 0.78 |
| | | | | |
| White Blood Cells,10/L | | | | |
| Week 2 | Mean (SD) | 6.74 ( 2.18) | 7.24 ( 1.94) | 6.70 ( 1.82) |
| Day 90 | Mean (SD) | 6.96 ( 1.76) | 7.12 ( 1.93) | 6.57 ( 1.61) |
| Adjusted Mean Change | LS Mean (SE) | -0.07 ( 0.26) | -0.01 ( 0.10) | -0.22 ( 0.10) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 0.07 ( -0.48, 0.62) | -0.15 ( -0.70, 0.40) |
| P-value (vs. reference) | | -- | 0.81 | 0.60 |
| | | | | |
| Lymphocytes,% | | | | |
| Week 2 | Mean (SD) | 25.88 ( 8.06) | 27.67 ( 8.83) | 28.66 ( 8.88) |
| Day 90 | Mean (SD) | 25.17 ( 9.01) | 27.73 ( 8.82) | 29.02 ( 8.38) |
| Adjusted Mean Change | LS Mean (SE) | -1.29 ( 1.32) | -0.08 ( 0.50) | 0.36 ( 0.53) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 1.21 ( -1.57, 3.98) | 1.64 ( -1.16, 4.45) |
| P-value (vs. reference) | | -- | 0.39 | 0.25 |
| | | | | |
| Glucose, mmol/L | | | | |

| Parameter | Statistic | Average Dose <50% (n= 39) | Average Dose >=50-<90% (n=254) | Average Dose >=90% (n=222) |
|---|---|---|---|---|
| Week 2 | Mean (SD) | 7.03 ( 3.63) | 6.50 ( 2.58) | 5.79 ( 1.95) |
| Day 90 | Mean (SD) | 6.34 ( 2.25) | 6.74 ( 2.85) | 5.85 ( 1.90) |
| Adjusted Mean Change | LS Mean (SE) | -0.19 ( 0.36) | 0.34 ( 0.13) | -0.12 ( 0.14) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 0.53 ( -0.21, 1.28) | 0.07 ( -0.68, 0.81) |
| P-value (vs. reference) | | -- | 0.16 | 0.86 |
| | | | | |
| Sodium, mmol/L | | | | |
| Week 2 | Mean (SD) | 140.1 ( 5.18) | 140.7 ( 4.23) | 139.6 ( 3.69) |
| Day 90 | Mean (SD) | 141.3 ( 5.34) | 141.1 ( 4.71) | 139.7 ( 3.37) |
| Adjusted Mean Change | LS Mean (SE) | 1.09 ( 0.61) | 0.58 ( 0.23) | -0.10 ( 0.25) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -0.51 ( -1.80, 0.78) | -1.19 ( -2.49, 0.10) |
| P-value (vs. reference) | | -- | 0.44 | 0.07 |
| | | | | |
| Potassium, mmol/L | | | | |
| Week 2 | Mean (SD) | 4.75 ( 0.66) | 4.60 ( 0.51) | 4.48 ( 0.38) |
| Day 90 | Mean (SD) | 4.65 ( 0.47) | 4.55 ( 0.54) | 4.65 ( 0.37) |
| Adjusted Mean Change | LS Mean (SE) | 0.02 ( 0.08) | -0.03 ( 0.03) | 0.12 ( 0.03) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -0.05 ( -0.21, 0.11) | 0.10 ( -0.06, 0.27) |
| P-value (vs. reference) | | -- | 0.53 | 0.22 |
| | | | | |
| Urea, mmol/L | | | | |
| Week 2 | Mean (SD) | 10.63 ( 5.85) | 8.32 ( 3.89) | 6.80 ( 2.62) |
| Day 90 | Mean (SD) | 10.00 ( 5.66) | 8.35 ( 3.99) | 6.86 ( 2.90) |
| Adjusted Mean Change | LS Mean (SE) | 0.35 ( 0.52) | 0.11 ( 0.19) | -0.58 ( 0.20) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -0.24 ( -1.31, 0.84) | -0.93 ( -2.03, 0.18) |
| P-value (vs. reference) | | -- | 0.67 | 0.10 |
| | | | | |
| eGFR, ml/min/1.732 | | | | |
| Week 2 | Mean (SD) | 56.35 (24.49) | 62.30 (22.44) | 68.33 (21.28) |
| Day 90 | Mean (SD) | 59.95 (22.56) | 62.86 (22.64) | 66.79 (21.45) |
| Adjusted Mean Change | LS Mean (SE) | 2.91 ( 2.45) | 0.23 ( 0.92) | -0.37 ( 0.96) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -2.69 ( -7.82, 2.45) | -3.28 ( -8.48, 1.92) |

| Parameter | Statistic | Average Dose <50% (n= 39) | Average Dose >=50-<90% (n=254) | Average Dose >=90% (n=222) |
|---|---|---|---|---|
| P-value (vs. reference) | | -- | 0.30 | 0.22 |
| | | | | |
| Uric Acid, umol/L | | | | |
| Week 2 | Mean (SD) | 433.0 (105.9) | 412.8 (123.0) | 405.4 (83.97) |
| Day 90 | Mean (SD) | 412.7 (115.0) | 392.2 (110.0) | 404.4 (94.76) |
| Adjusted Mean Change | LS Mean (SE) | -12.2 (17.23) | -17.8 ( 6.55) | -5.83 ( 6.48) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -5.60 (-41.87, 30.66) | 6.33 (-29.88, 42.54) |
| P-value (vs. reference) | | -- | 0.76 | 0.73 |
| | | | | |
| AST, U/L | | | | |
| Week 2 | Mean (SD) | 25.73 (13.04) | 26.69 (13.30) | 23.24 (16.42) |
| Day 90 | Mean (SD) | 33.17 (46.71) | 24.48 (10.91) | 24.27 (44.05) |
| Adjusted Mean Change | LS Mean (SE) | 7.88 ( 5.32) | -2.15 ( 2.09) | 1.36 ( 2.19) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -10.04 (-21.27, 1.20) | -6.53 (-17.85, 4.79) |
| P-value (vs. reference) | | -- | 0.08 | 0.26 |
| | | | | |
| ALT, U/L | | | | |
| Week 2 | Mean (SD) | 22.90 (12.75) | 28.09 (30.68) | 22.42 (21.50) |
| Day 90 | Mean (SD) | 41.55 (115.6) | 23.44 (12.30) | 20.92 (13.71) |
| Adjusted Mean Change | LS Mean (SE) | 19.50 ( 6.24) | -1.99 ( 2.47) | -3.70 ( 2.58) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -21.49 (-34.69, -8.29) | -23.21 (-36.46, -9.95) |
| P-value (vs. reference) | | -- | 0.002 | <0.001 |
| | | | | |
| Total Bilirubin, umol/L | | | | |
| Week 2 | Mean (SD) | 15.94 ( 8.43) | 15.70 ( 9.77) | 12.31 ( 5.44) |
| Day 90 | Mean (SD) | 15.65 ( 9.54) | 15.24 ( 9.96) | 12.91 ( 7.33) |
| Adjusted Mean Change | LS Mean (SE) | 0.13 ( 1.58) | 0.68 ( 0.59) | -0.44 ( 0.62) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 0.55 ( -2.76, 3.86) | -0.56 ( -3.92, 2.79) |
| P-value (vs. reference) | | -- | 0.74 | 0.74 |

| Parameter | Statistic | Average Dose <50% (n= 39) | Average Dose >=50-<90% (n=254) | Average Dose >=90% (n=222) |
|---|---|---|---|---|
| Total Cholesterol, mmol/L | | | | |
| Week 2 | Mean (SD) | 4.13 ( 1.18) | 4.23 ( 1.07) | 4.59 ( 1.09) |
| Day 90 | Mean (SD) | 4.35 ( 1.23) | 4.38 ( 1.13) | 4.46 ( 0.90) |
| Adjusted Mean Change | LS Mean (SE) | 0.15 ( 0.16) | 0.05 ( 0.06) | -0.05 ( 0.06) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | -0.09 ( -0.43, 0.25) | -0.20 ( -0.54, 0.14) |
| P-value (vs. reference) | | -- | 0.59 | 0.25 |
| | | | | |
| NT-proBNP, pg/mL | | | | |
| Week 2 | Geo. Mean (95% CI) | 3458.3 (2467.4, 4847.0) | 2885.9 (2551.8, 3263.9) | 1661.1 (1459.0, 1891.3) |
| Day 90 | Geo. Mean (95% CI) | 2325.1 (1657.0, 3262.6) | 1635.3 (1409.7, 1897.0) | 978.0 (840.2, 1138.3) |
| Adjusted Mean Change[a] | LS Mean (SE) | 0.73 (0.18) | 0.64 (0.07) | 0.51 (0.07) |
| LS Mean Difference | LS Mean Diff (95% CI) | [ref] | 0.87 (0.60, 1.27) | 0.70 (0.48, 1.03) |
| P-value (vs. reference) | | -- | 0.48 | 0.07 |

[a] Statistics are estimated based on an Analysis of Covariance (ANCOVA) model adjusted for Week 2 value.

**eTable 2. Clinical outcomes by average percentage optimal dose categories at week 2 in high intensity care patients**

| | | Unadjusted | | Adjusted | |
|---|---|---|---|---|---|
| Endpoint | n/N (KM%) | HR (95% CI) | P-value | HR (95% CI) | P-value |
| All-cause death or heart failure readmission by day 180 | | | 0.47 | | 0.75 |
| Average Dose <50% | 6/31 (18.9%) | [ref] | | [ref] | |
| Average Dose >=50% - <90% | 31/234 (13.3%) | 0.70 (0.27, 1.84) | | 0.76 (0.29, 2.01) | |
| Average Dose >=90% | 23/214 (11.3%) | 0.55 (0.20, 1.49) | | 0.68 (0.25, 1.86) | |
| Test of Proportional Hazards | | | 0.12 | | |
| All-cause death by day 180 | | | 0.81 | | 0.96 |
| Average Dose <50% | 3/34 (9.4%) | [ref] | | [ref] | |
| Average Dose >=50% - <90% | 14/235 (6.6%) | 0.70 (0.18, 2.73) | | 0.94 (0.22, 3.99) | |
| Average Dose >=90% | 12/214 (6.1%) | 0.63 (0.16, 2.54) | | 0.80 (0.18, 3.58) | |
| Test of Proportional Hazards | | | 0.87 | | |
| | LS-Mean (SE) | LS-Mean Difference (95% CI) | | LS-Mean Difference (95% CI) | |
| EQ-VAS Change from Baseline to Visit 7 | | | 0.001 | | 0.07 |
| Average Dose <50% | 7.01 (2.42) | [ref] | | [ref] | |
| Average Dose >=50% - <90% | 8.57 (0.94) | 1.56 (-3.50, 6.61) | | 0.10 (-4.88, 5.07) | |
| Average Dose >=90% | 13.51 (1.01) | 6.50 (1.39, 11.61) | | 3.13 (-1.98, 8.24) | |

**eTable 3. Clinical outcomes by average percentage optimal dose categories at week 2 in all subjects**

| | | Unadjusted | | Adjusted | |
|---|---|---|---|---|---|
| Endpoint | n/N (KM%) | HR (95% CI) | P-value | HR (95% CI) | P-value |
| All-cause death or heart failure readmission by day 180 | | | 0.009 | | 0.02 |
| Average Dose <50% | 92/444 (22.0%) | [ref] | | [ref] | |
| Average Dose >=50% - <90% | 49/317 (16.6%) | 0.73 (0.50, 1.07) | | 0.71 (0.49, 1.04) | |
| Average Dose >=90% | 23/215 (11.3%) | 0.46 (0.27, 0.77) | | 0.50 (0.29, 0.84) | |
| Test of Proportional Hazards | | | 0.17 | | |
| All-cause death by day 180 | | | 0.23 | | 0.36 |
| Average Dose <50% | 42/446 (9.8%) | [ref] | | [ref] | |
| Average Dose >=50% - <90% | 20/318 (7.2%) | 0.70 (0.39, 1.24) | | 0.76 (0.42, 1.35) | |
| Average Dose >=90% | 12/215 (6.1%) | 0.58 (0.28, 1.19) | | 0.62 (0.30, 1.29) | |
| Test of Proportional Hazards | | | 0.04 | | |
| | LS-Mean (SE) | LS-Mean Difference (95% CI) | | LS-Mean Difference (95% CI) | |
| EQ-VAS Change from Baseline to Visit 7 | | | <0.001 | | <0.001 |
| Average Dose <50% | 6.89 (0.98) | [ref] | | [ref] | |
| Average Dose >=50% - <90% | 8.68 (0.96) | 1.80 (-0.26, 3.85) | | 1.62 (-0.38, 3.62) | |
| Average Dose >=90% | 12.40 (1.14) | 5.51 (3.20, 7.82) | | 5.21 (2.97, 7.46) | |

**eTable 4. Treatment emergent adverse events by average percentage optimal dose categories at week 2**

| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|
| Any Adverse Event | n (%) | 21 (53.8%) | 98 (38.6%) | 51 (23.0%) | <0.001 |
| Blood And Lymphatic System Disorders | n (%) | 1 (2.6%) | 0 | 2 (0.9%) | |
| Anaemia | n (%) | 1 (2.6%) | 0 | 0 | |
| Anaemia Of Chronic Disease | n (%) | 0 | 0 | 1 (0.5%) | |
| Febrile Neutropenia | n (%) | 0 | 0 | 1 (0.5%) | |
| Leukocytosis | n (%) | 0 | 0 | 1 (0.5%) | |
| Cardiac Disorders | n (%) | 8 (20.5%) | 49 (19.3%) | 23 (10.4%) | 0.008 |
| Acute Coronary Syndrome | n (%) | 0 | 1 (0.4%) | 0 | |
| Acute Myocardial Infarction | n (%) | 1 (2.6%) | 1 (0.4%) | 1 (0.5%) | |
| Angina Unstable | n (%) | 0 | 1 (0.4%) | 0 | |
| Atrial Fibrillation | n (%) | 0 | 2 (0.8%) | 0 | |
| Atrioventricular Block Complete | n (%) | 1 (2.6%) | 0 | 0 | |
| Bradycardia | n (%) | 0 | 0 | 2 (0.9%) | |
| Cardiac Failure | n (%) | 5 (12.8%) | 43 (16.9%) | 19 (8.6%) | |
| Cardiac Failure Chronic | n (%) | 0 | 2 (0.8%) | 1 (0.5%) | |
| Myocardial Infarction | n (%) | 0 | 0 | 1 (0.5%) | |
| Ventricular Tachycardia | n (%) | 1 (2.6%) | 0 | 0 | |
| Gastrointestinal Disorders | n (%) | 0 | 6 (2.4%) | 4 (1.8%) | |
| Abdominal Pain | n (%) | 0 | 1 (0.4%) | 0 | |
| Abdominal Pain Upper | n (%) | 0 | 0 | 1 (0.5%) | |
| Constipation | n (%) | 0 | 0 | 1 (0.5%) | |
| Diarrhoea | n (%) | 0 | 2 (0.8%) | 2 (0.9%) | |
| Dry Mouth | n (%) | 0 | 0 | 1 (0.5%) | |
| Dyspepsia | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Eructation | n (%) | 0 | 1 (0.4%) | 0 | |

| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|
| Gastrointestinal Motility Disorder | n (%) | 0 | 1 (0.4%) | 0 | |
| Haemorrhoids | n (%) | 0 | 1 (0.4%) | 0 | |
| General Disorders And Administration Site Conditions | n (%) | 1 (2.6%) | 4 (1.6%) | 2 (0.9%) | |
| Asthenia | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Fatigue | n (%) | 0 | 1 (0.4%) | 0 | |
| Sudden Death | n (%) | 1 (2.6%) | 2 (0.8%) | 1 (0.5%) | |
| Hepatobiliary Disorders | n (%) | 0 | 0 | 1 (0.5%) | |
| Hepatitis Acute | n (%) | 0 | 0 | 1 (0.5%) | |
| Infections And Infestations | n (%) | 3 (7.7%) | 16 (6.3%) | 4 (1.8%) | |
| Bronchitis | n (%) | 0 | 1 (0.4%) | 0 | |
| Bursitis Infective | n (%) | 0 | 1 (0.4%) | 0 | |
| Corona Virus Infection | n (%) | 0 | 1 (0.4%) | 3 (1.4%) | |
| Gastroenteritis | n (%) | 0 | 1 (0.4%) | 0 | |
| Influenza | n (%) | 0 | 0 | 0 | |
| Lower Respiratory Tract Infection | n (%) | 1 (2.6%) | 0 | 0 | |
| Nasopharyngitis | n (%) | 0 | 5 (2.0%) | 0 | |
| Pneumonia | n (%) | 2 (5.1%) | 2 (0.8%) | 0 | |
| Pneumonia Viral | n (%) | 0 | 0 | 1 (0.5%) | |
| Pyelonephritis | n (%) | 0 | 0 | 1 (0.5%) | |
| Respiratory Tract Infection Viral | n (%) | 0 | 3 (1.2%) | 0 | |
| Urinary Tract Infection | n (%) | 0 | 1 (0.4%) | 0 | |
| Viral Infection | n (%) | 0 | 1 (0.4%) | 0 | |
| Vulvovaginal Mycotic Infection | n (%) | 0 | 1 (0.4%) | 0 | |
| Injury, Poisoning And Procedural Complications | n (%) | 0 | 4 (1.6%) | 1 (0.5%) | |
| Contusion | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Fall | n (%) | 0 | 1 (0.4%) | 0 | |
| Humerus Fracture | n (%) | 0 | 1 (0.4%) | 0 | |
| Toxicity To Various Agents | n (%) | 0 | 1 (0.4%) | 0 | |

| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|
| Investigations | n (%) | 2 (5.1%) | 5 (2.0%) | 5 (2.3%) | 0.64 |
| Blood Creatinine Increased | n (%) | 1 (2.6%) | 0 | 1 (0.5%) | |
| Blood Potassium Increased | n (%) | 1 (2.6%) | 1 (0.4%) | 0 | |
| Blood Pressure Increased | n (%) | 0 | 3 (1.2%) | 1 (0.5%) | |
| Glomerular Filtration Rate Decreased | n (%) | 0 | 0 | 2 (0.9%) | |
| N-Terminal Prohormone Brain Natriuretic Peptide Increased | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Platelet Count Decreased | n (%) | 1 (2.6%) | 0 | 0 | |
| Metabolism And Nutrition Disorders | n (%) | 5 (12.8%) | 9 (3.5%) | 3 (1.4%) | 0.002 |
| Decreased Appetite | n (%) | 0 | 1 (0.4%) | 0 | |
| Dehydration | n (%) | 0 | 1 (0.4%) | 0 | |
| Hyperkalaemia | n (%) | 4 (10.3%) | 6 (2.4%) | 3 (1.4%) | 0.01 |
| Hyperuricaemia | n (%) | 1 (2.6%) | 0 | 0 | |
| Hypoglycaemia | n (%) | 1 (2.6%) | 0 | 0 | |
| Hypokalaemia | n (%) | 0 | 1 (0.4%) | 0 | |
| Type 2 Diabetes Mellitus | n (%) | 0 | 1 (0.4%) | 0 | |
| Musculoskeletal And Connective Tissue Disorders | n (%) | 0 | 3 (1.2%) | 3 (1.4%) | |
| Arthritis | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Back Pain | n (%) | 0 | 0 | 1 (0.5%) | |
| Gouty Arthritis | n (%) | 0 | 1 (0.4%) | 0 | |
| Muscular Weakness | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Osteochondrosis | n (%) | 0 | 0 | 1 (0.5%) | |
| Nervous System Disorders | n (%) | 0 | 7 (2.8%) | 5 (2.3%) | 0.82 |
| Cerebrovascular Accident | n (%) | 0 | 2 (0.8%) | 1 (0.5%) | 1.00 |
| Dizziness | n (%) | 0 | 3 (1.2%) | 0 | |
| Dizziness Exertional | n (%) | 0 | 1 (0.4%) | 0 | |
| Dizziness Postural | n (%) | 0 | 1 (0.4%) | 0 | |
| Dysgeusia | n (%) | 0 | 0 | 1 (0.5%) | |
| Headache | n (%) | 0 | 0 | 2 (0.9%) | |

| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|
| Hemianopia Homonymous | n (%) | 0 | 1 (0.4%) | 0 | |
| Loss Of Consciousness | n (%) | 0 | 1 (0.4%) | 0 | |
| Paraesthesia | n (%) | 0 | 0 | 2 (0.9%) | |
| Somnolence | n (%) | 0 | 1 (0.4%) | 0 | |
| Renal And Urinary Disorders | n (%) | 4 (10.3%) | 6 (2.4%) | 4 (1.8%) | 0.05 |
| Acute Kidney Injury | n (%) | 1 (2.6%) | 1 (0.4%) | 0 | |
| Chronic Kidney Disease | n (%) | 1 (2.6%) | 0 | 0 | |
| Renal Failure | n (%) | 0 | 0 | 1 (0.5%) | |
| Renal Impairment | n (%) | 2 (5.1%) | 5 (2.0%) | 3 (1.4%) | |
| Reproductive System And Breast Disorders | n (%) | 0 | 0 | 1 (0.5%) | |
| Gynaecomastia | n (%) | 0 | 0 | 1 (0.5%) | |
| Respiratory, Thoracic And Mediastinal Disorders | n (%) | 1 (2.6%) | 2 (0.8%) | 1 (0.5%) | |
| Cough | n (%) | 0 | 1 (0.4%) | 0 | |
| Dyspnoea | n (%) | 1 (2.6%) | 0 | 0 | |
| Pulmonary Embolism | n (%) | 0 | 0 | 1 (0.5%) | |
| Pulmonary Oedema | n (%) | 0 | 1 (0.4%) | 0 | |
| Skin And Subcutaneous Tissue Disorders | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Rash | n (%) | 0 | 0 | 1 (0.5%) | |
| Stasis Dermatitis | n (%) | 0 | 1 (0.4%) | 0 | |
| Surgical And Medical Procedures | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Chemotherapy | n (%) | 0 | 0 | 1 (0.5%) | |
| High Frequency Ablation | n (%) | 0 | 1 (0.4%) | 0 | |
| Vascular Disorders | n (%) | 2 (5.1%) | 14 (5.5%) | 4 (1.8%) | 0.07 |
| Hypertension | n (%) | 0 | 0 | 1 (0.5%) | |
| Hypertensive Crisis | n (%) | 0 | 3 (1.2%) | 1 (0.5%) | |
| Hypotension | n (%) | 2 (5.1%) | 10 (3.9%) | 2 (0.9%) | 0.05 |
| Orthostatic Hypotension | n (%) | 0 | 2 (0.8%) | 0 | |

| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|

Including adverse events with onset date equal to or greater than Day 14 through 90 days post-randomization.
#: Cochran-Armitage trend test. Exact p-value when <5 events in any category

**eTable 5. Treatment emergent serious adverse events by average percentage optimal dose categories at week 2**

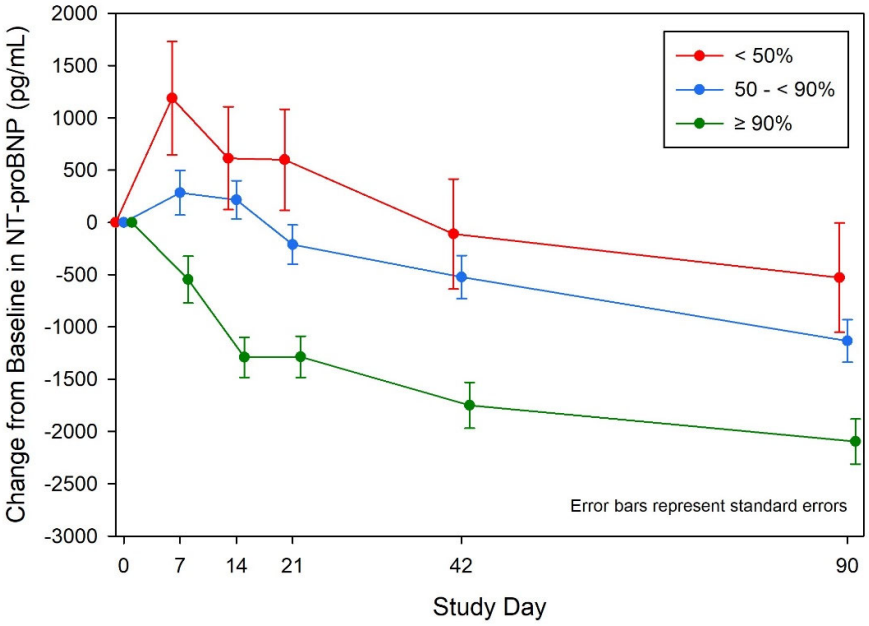
| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|
| Any Serious Adverse Event | n (%) | 9 (23.1%) | 37 (14.6%) | 21 (9.5%) | 0.012 |
| Blood And Lymphatic System Disorders | n (%) | 0 | 0 | 1 (0.5%) | |
| Febrile Neutropenia | n (%) | 0 | 0 | 1 (0.5%) | |
| Cardiac Disorders | n (%) | 5 (12.8%) | 24 (9.4%) | 12 (5.4%) | 0.05 |
| Acute Coronary Syndrome | n (%) | 0 | 1 (0.4%) | 0 | |
| Acute Myocardial Infarction | n (%) | 1 (2.6%) | 1 (0.4%) | 1 (0.5%) | 0.37 |
| Atrial Fibrillation | n (%) | 0 | 1 (0.4%) | 0 | |
| Atrioventricular Block Complete | n (%) | 1 (2.6%) | 0 | 0 | |
| Cardiac Failure | n (%) | 2 (5.1%) | 21 (8.3%) | 10 (4.5%) | 0.31 |
| Cardiac Failure Chronic | n (%) | 0 | 0 | 1 (0.5%) | |
| Myocardial Infarction | n (%) | 0 | 0 | 1 (0.5%) | |
| Ventricular Tachycardia | n (%) | 1 (2.6%) | 0 | 0 | |
| Gastrointestinal Disorders | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Abdominal Pain | n (%) | 0 | 1 (0.4%) | 0 | |
| Abdominal Pain Upper | n (%) | 0 | 0 | 1 (0.5%) | |
| Diarrhoea | n (%) | 0 | 0 | 1 (0.5%) | |
| General Disorders And Administration Site Conditions | n (%) | 1 (2.6%) | 2 (0.8%) | 1 (0.5%) | |
| Sudden Death | n (%) | 1 (2.6%) | 2 (0.8%) | 1 (0.5%) | |
| Hepatobiliary Disorders | n (%) | 0 | 0 | 1 (0.5%) | |
| Hepatitis Acute | n (%) | 0 | 0 | 1 (0.5%) | |
| Infections And Infestations | n (%) | 3 (7.7%) | 6 (2.4%) | 3 (1.4%) | 0.06 |

| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|
| Bronchitis | n (%) | 0 | 1 (0.4%) | 0 | |
| Bursitis Infective | n (%) | 0 | 1 (0.4%) | 0 | |
| Corona Virus Infection | n (%) | 0 | 1 (0.4%) | 2 (0.9%) | |
| Gastroenteritis | n (%) | 0 | 1 (0.4%) | 0 | |
| Lower Respiratory Tract Infection | n (%) | 1 (2.6%) | 0 | 0 | |
| Pneumonia | n (%) | 2 (5.1%) | 2 (0.8%) | 0 | |
| Pneumonia Viral | n (%) | 0 | 0 | 1 (0.5%) | |
| Pyelonephritis | n (%) | 0 | 0 | 1 (0.5%) | |
| Urinary Tract Infection | n (%) | 0 | 1 (0.4%) | 0 | |
| Injury, Poisoning And Procedural Complications | n (%) | 0 | 1 (0.4%) | 0 | |
| Fall | n (%) | 0 | 1 (0.4%) | 0 | |
| Investigations | n (%) | 1 (2.6%) | 0 | 0 | |
| Blood Creatinine Increased | n (%) | 1 (2.6%) | 0 | 0 | |
| Metabolism And Nutrition Disorders | n (%) | 1 (2.6%) | 0 | 0 | |
| Hyperkalaemia | n (%) | 1 (2.6%) | 0 | 0 | |
| Hypoglycaemia | n (%) | 1 (2.6%) | 0 | 0 | |
| Musculoskeletal And Connective Tissue Disorders | n (%) | 0 | 0 | 1 (0.5%) | |
| Osteochondrosis | n (%) | 0 | 0 | 1 (0.5%) | |
| Nervous System Disorders | n (%) | 0 | 3 (1.2%) | 1 (0.5%) | |
| Cerebrovascular Accident | n (%) | 0 | 2 (0.8%) | 1 (0.5%) | |
| Hemianopia Homonymous | n (%) | 0 | 1 (0.4%) | 0 | |
| Renal And Urinary Disorders | n (%) | 2 (5.1%) | 0 | 1 (0.5%) | 0.07 |
| Chronic Kidney Disease | n (%) | 1 (2.6%) | 0 | 0 | |
| Renal Impairment | n (%) | 1 (2.6%) | 0 | 1 (0.5%) | |
| Respiratory, Thoracic And Mediastinal Disorders | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |

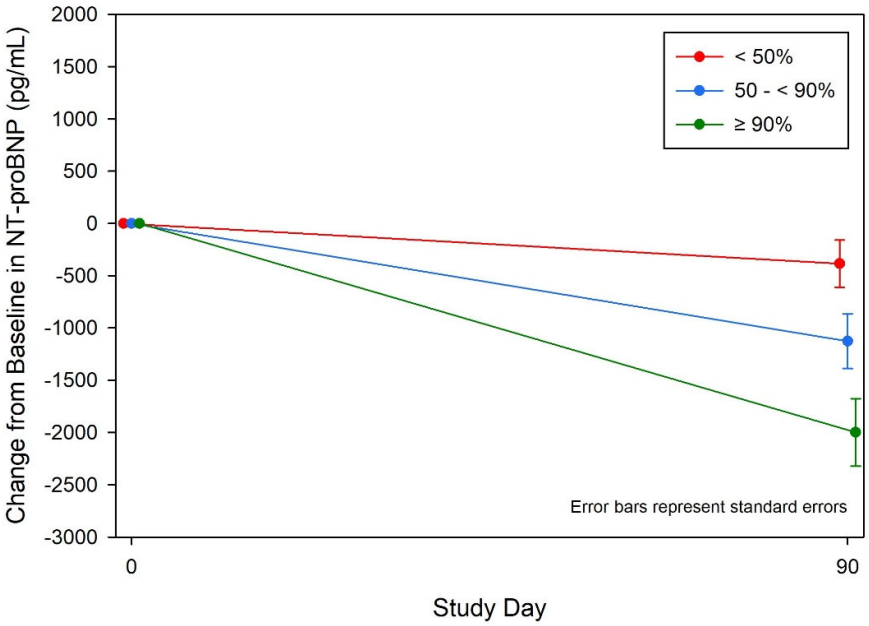
| System Organ Class<br>Preferred Term | Statistic | Average Dose <50% (N=39) | Average Dose >=50-<90% (N=254) | Average Dose >=90% (N=222) | Trend P-value[#] |
|---|---|---|---|---|---|
| Pulmonary Embolism | n (%) | 0 | 0 | 1 (0.5%) | |
| Pulmonary Oedema | n (%) | 0 | 1 (0.4%) | 0 | |
| Surgical And Medical Procedures | n (%) | 0 | 1 (0.4%) | 1 (0.5%) | |
| Chemotherapy | n (%) | 0 | 0 | 1 (0.5%) | |
| High Frequency Ablation | n (%) | 0 | 1 (0.4%) | 0 | |

Including serious adverse events with onset date equal to or greater than Day 14 through 90 days post-randomization.
#: Cochran-Armitage trend test. Exact p-value when <5 events in any category

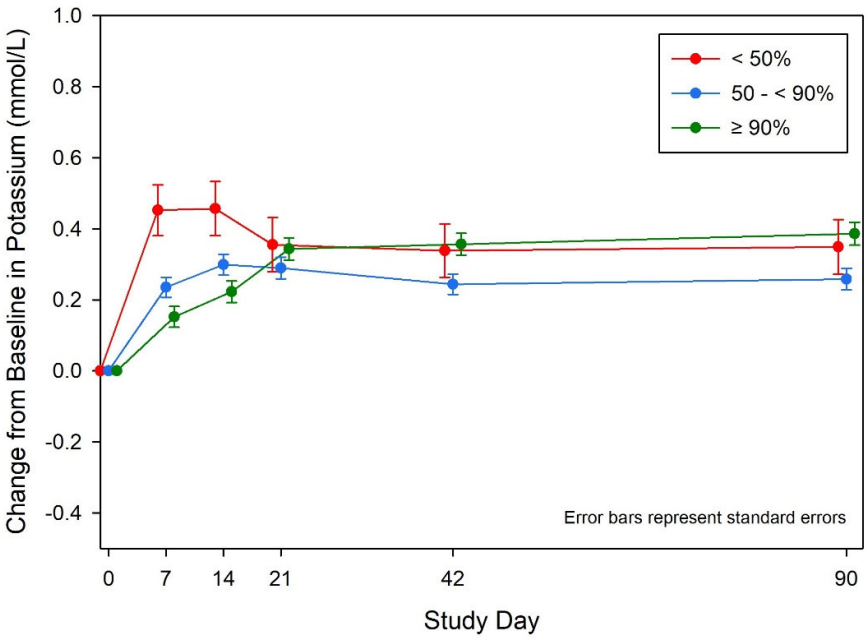
**eFigure 1. Change in NT-proBNP by average percentage optimal dose group at Week 2- High Intensity Care Subjects**



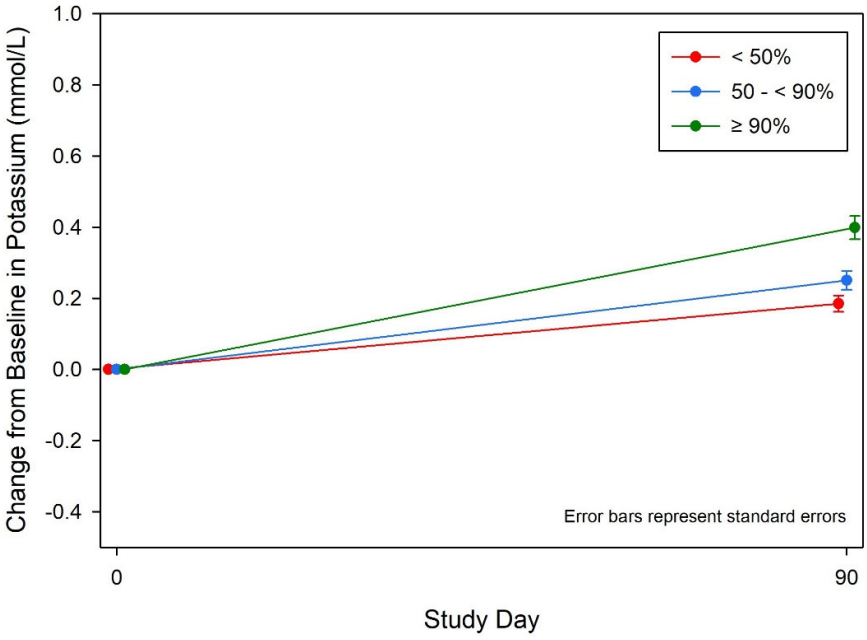

**eFigure 2. Change in NT-proBNP by average percentage optimal dose group at Week 2 (or Post-Rand for Usual Care)- All Subjects**



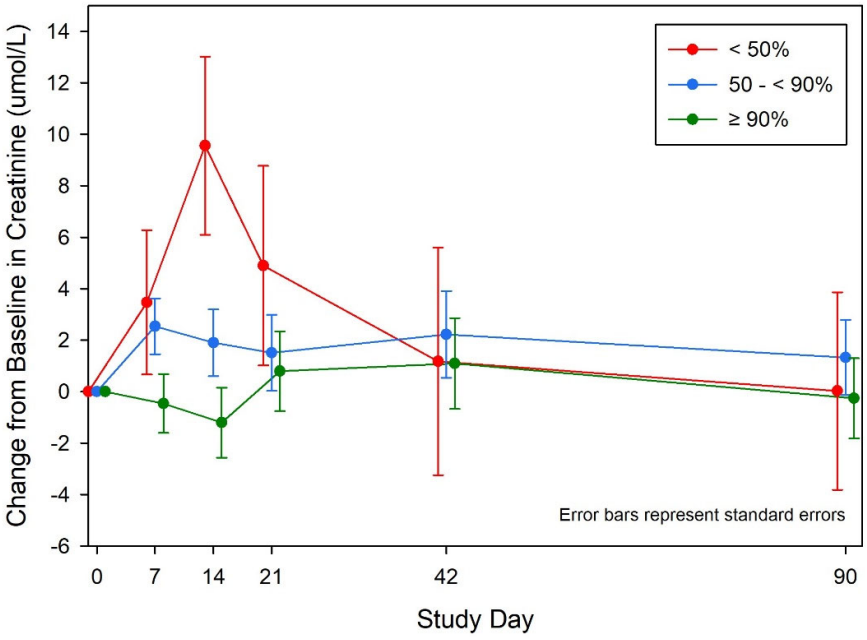
**eFigure 3. Change in Potassium by average percentage optimal dose group at Week 2- High Intensity Care Subjects**



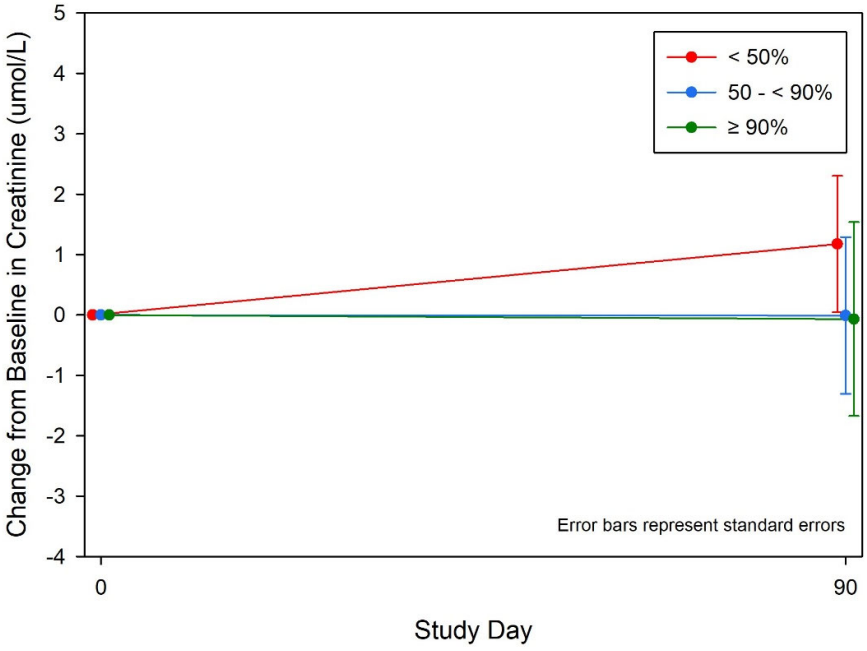

**eFigure 4. Change in Potassium by average percentage optimal dose group at Week 2 (or Post-Rand for Usual Care)- All Subjects**



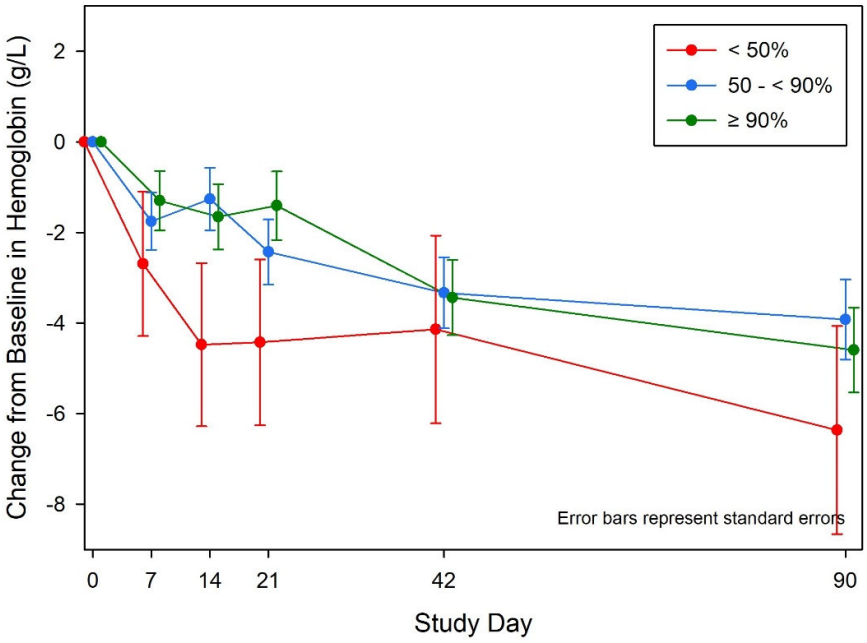
**eFigure 5. Change in Creatinine by average percentage optimal dose group at Week 2- High Intensity Care Subjects**



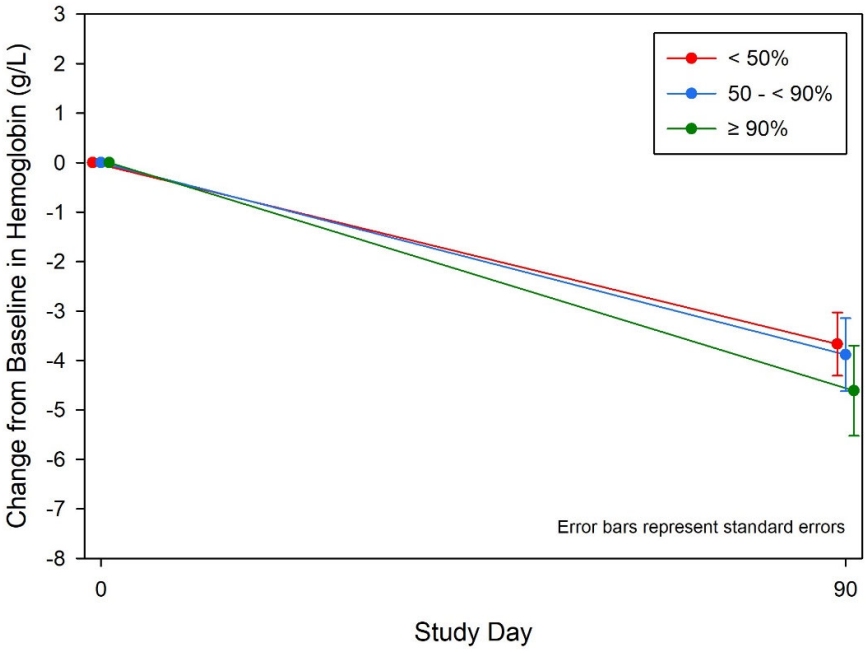

**eFigure 6. Change in Creatinine by average percentage optimal dose group at Week 2 (or Post-Rand for Usual Care)- All Subjects**



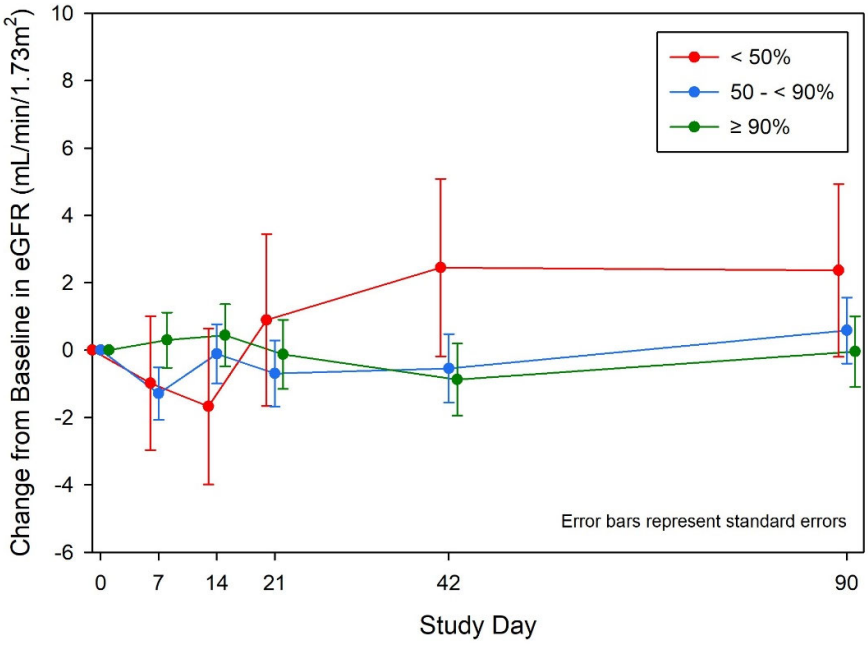
**eFigure 7. Change in Hemoglobin by average percentage optimal dose group at Week 2- High Intensity Care Subjects**



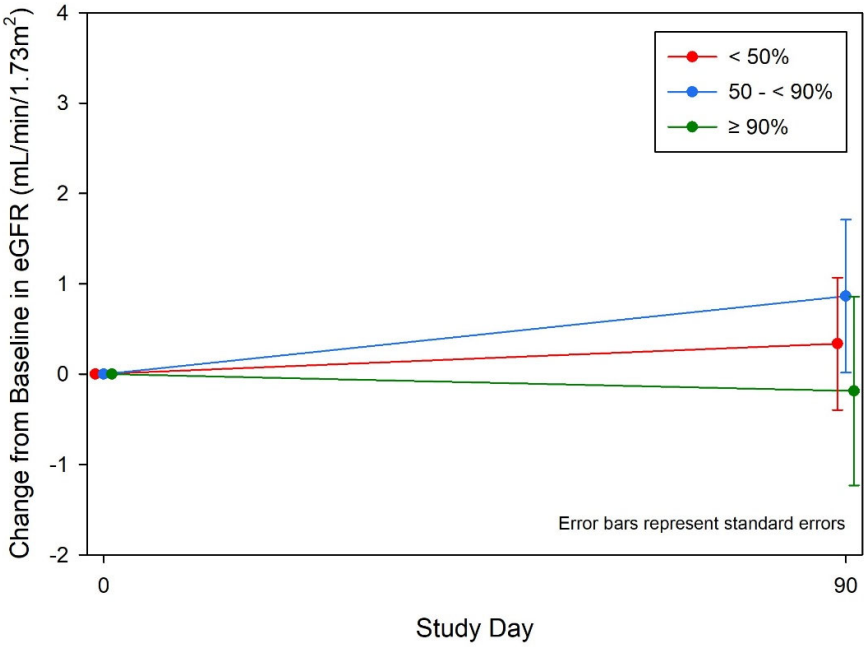

**eFigure 8. Change in Hemoglobin by average percentage optimal dose group at Week 2 (or Post-Rand for Usual Care)- All Subjects**



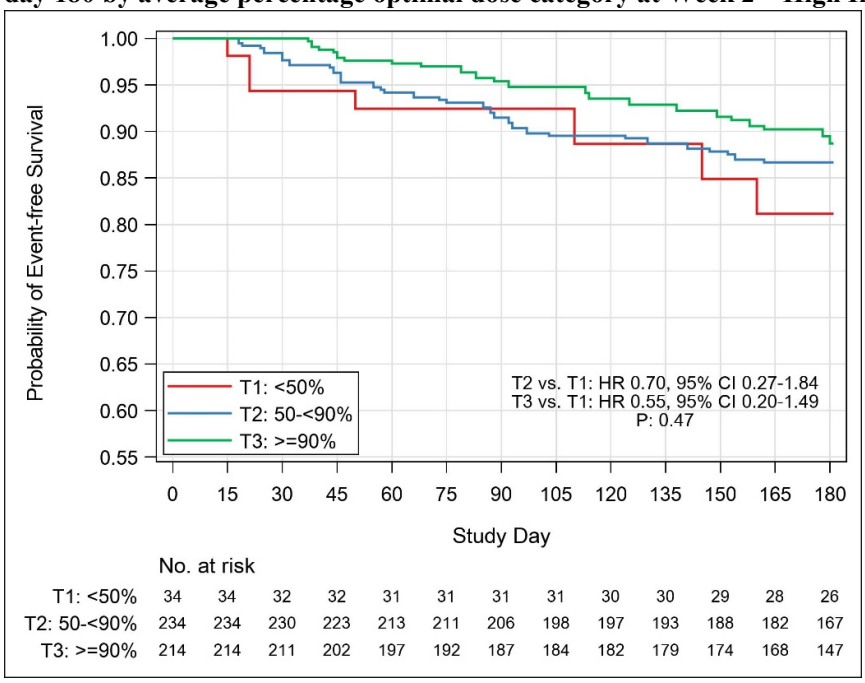
**eFigure 9. Change in eGFR by average percentage optimal dose group at Week 2- High Intensity Care Subjects**



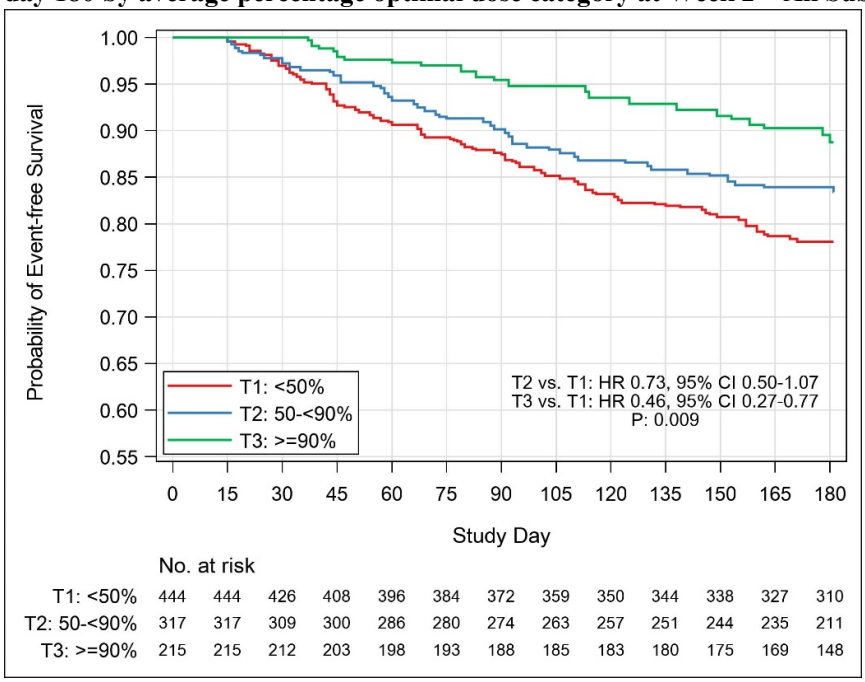

**eFigure 10. Change in eGFR by average percentage optimal dose group at Week 2 (or Post-Rand for Usual Care)- All Subjects**



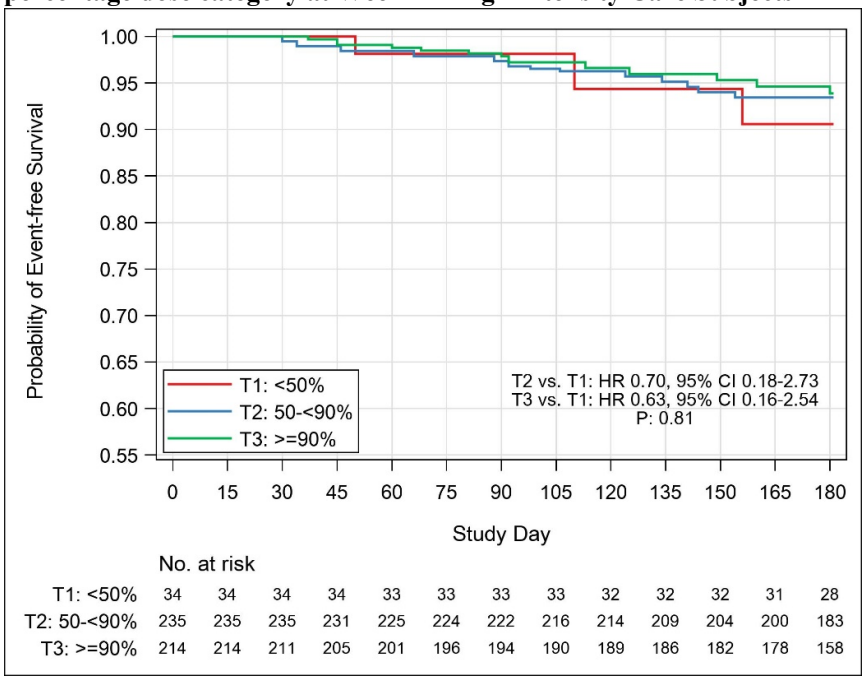
**eFigure 11. Kaplan-Meier curves for all-cause mortality or heart failure readmission through day 180 by average percentage optimal dose category at Week 2 – High Intensity Care Subjects**



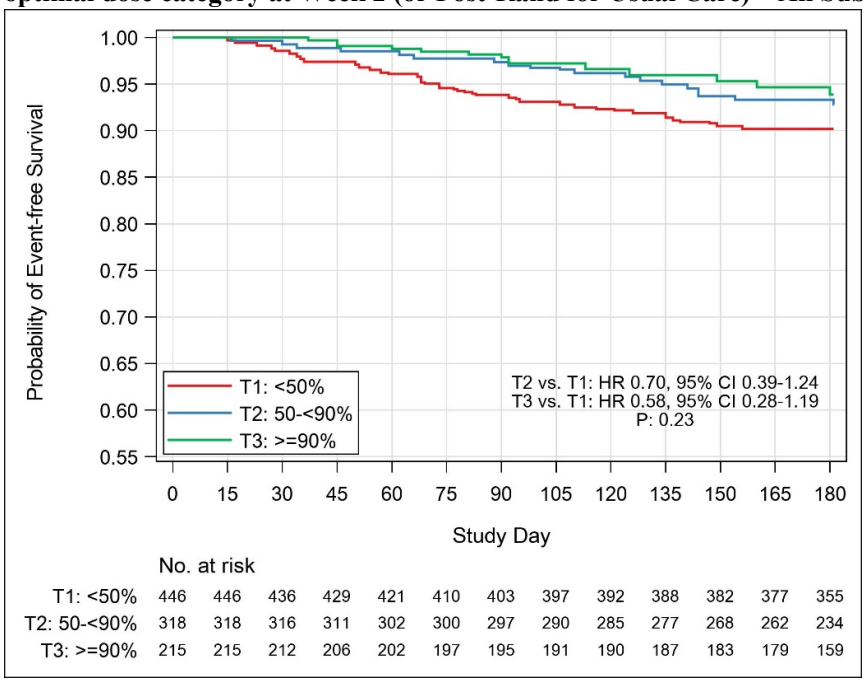

**eFigure 12. Kaplan-Meier curves for all-cause mortality or heart failure readmission through day 180 by average percentage optimal dose category at Week 2 – All Subjects**



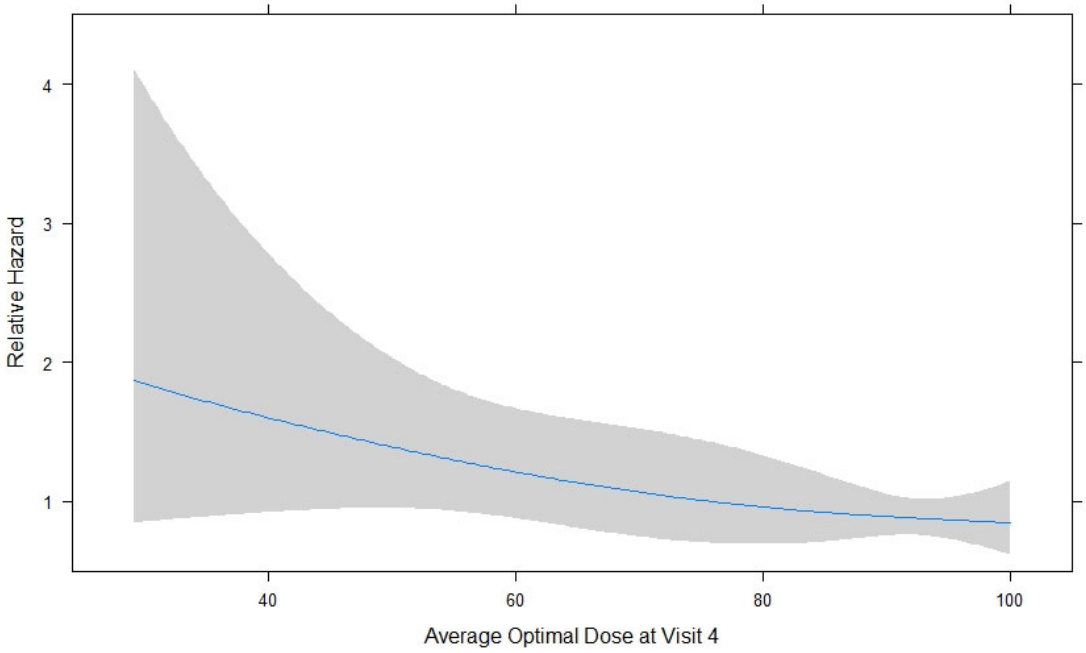
**eFigure 13. Kaplan-Meier curves for all-cause mortality through day 180 by average optimal percentage dose category at Week 2 – High Intensity Care Subjects**



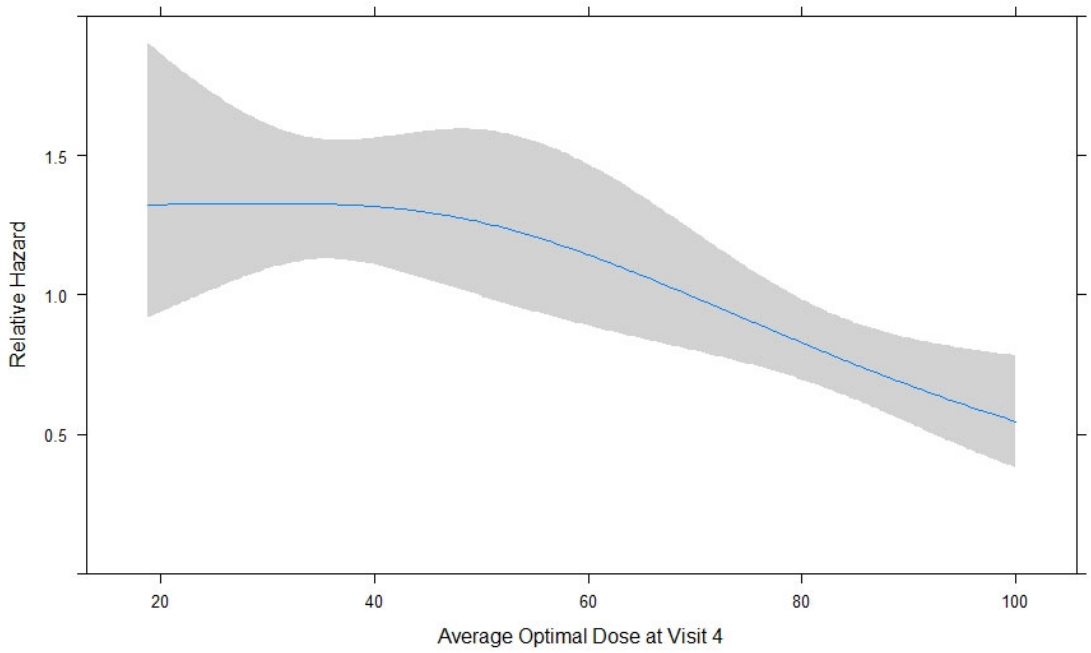

**eFigure 14. Kaplan-Meier curves for all-cause mortality through day 180 by average percentage optimal dose category at Week 2 (or Post-Rand for Usual Care) – All Subjects**



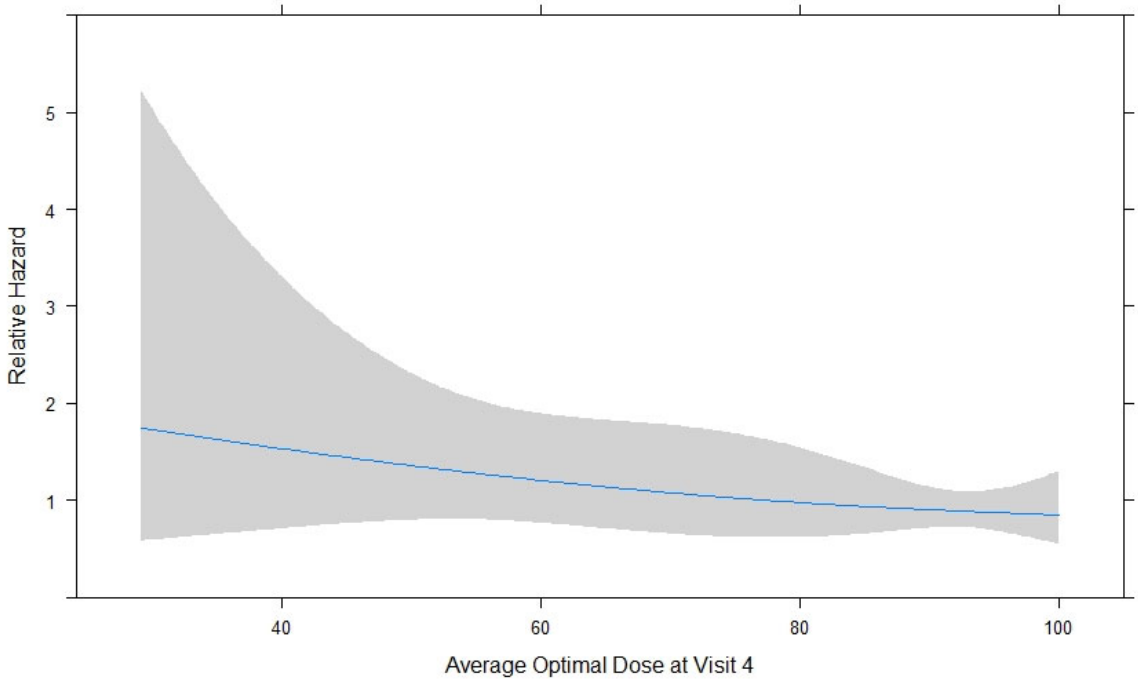
**eFigure 15. Relative hazard of all-cause mortality or heart failure readmission through day 180 by average percentage optimal dose at week 2 in HIC patients**



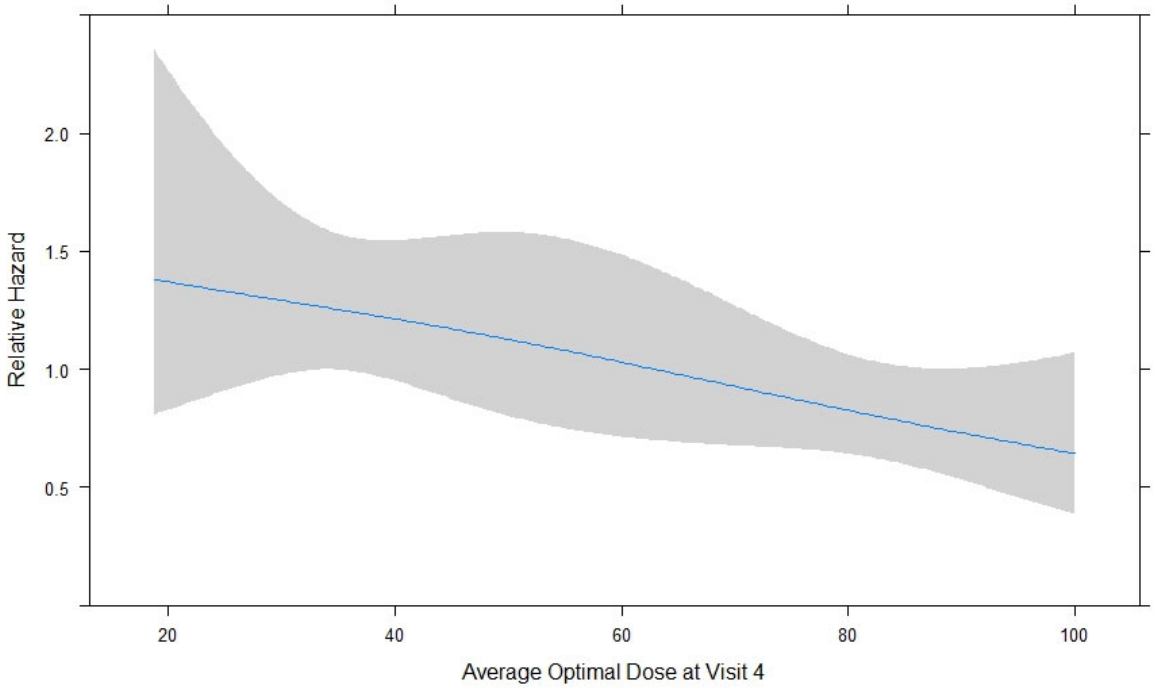
**eFigure 16. Relative hazard of all-cause mortality or heart failure readmission through day 180 by average percentage optimal dose at week 2 in all subjects**



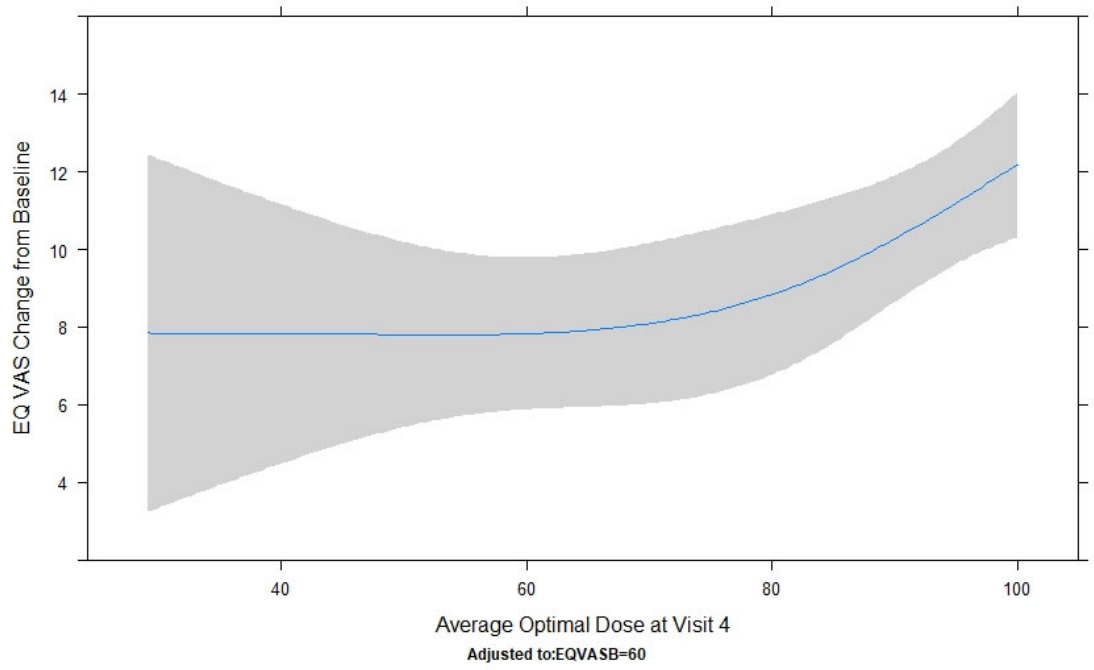
**eFigure 17. Relative hazard of all-cause mortality through day 180 by average percentage optimal dose at week 2 in HIC patients.**



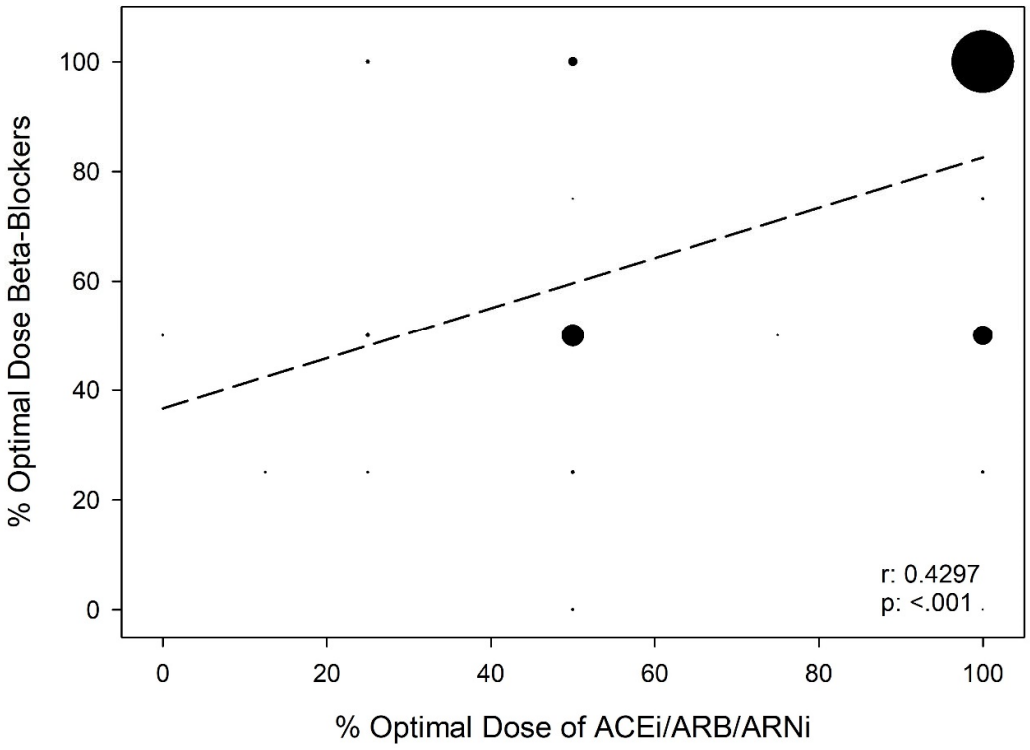
**eFigure 18. Relative hazard of all-cause mortality through day 180 by average percentage optimal dose at week 2 in all patients**



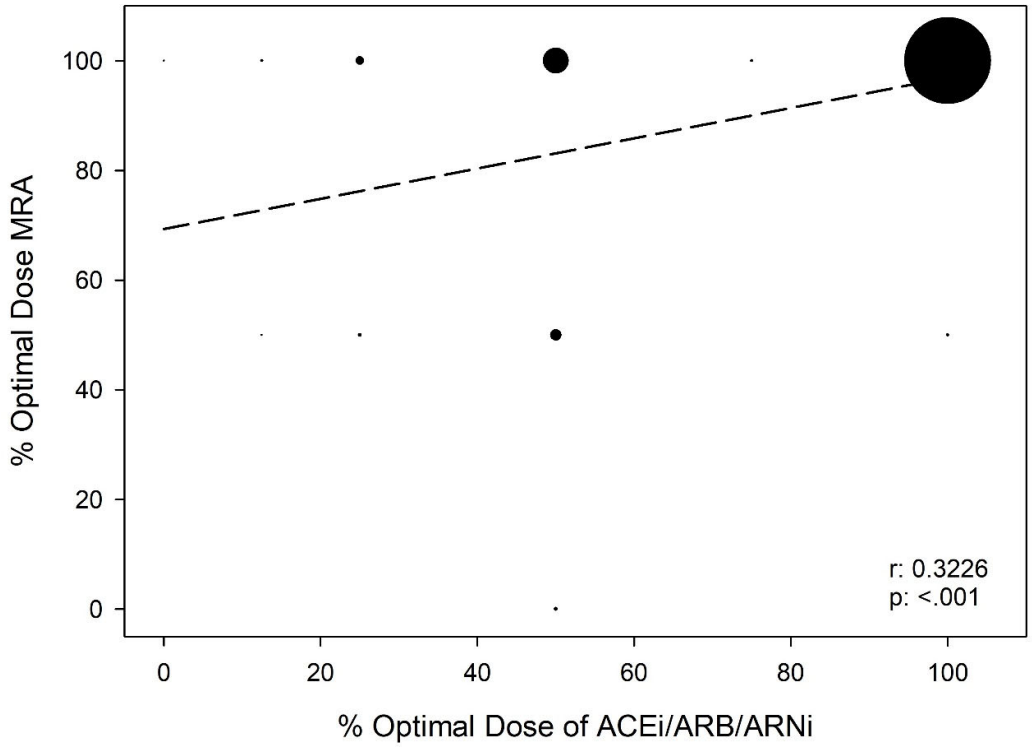
**eFigure 19. Change from baseline in EQ-VAS to day 90 by average percentage optimal dose at week 2 in HIC patients**




**eFigure 20. Bubble Plot of Percent Optimal Dose of RASi by Beta-Blockers at Week 2**



**eFigure 21. Bubble Plot of Percent Optimal Dose of RASi by MRA at Week 2**



**eFigure 22. Bubble Plot of Percent Optimal Dose of β-Blockers by MRA at Week 2**