Supplement table 1: Baseline characteristics

(A) Alkaline Phosphatase

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | < T1 | T1 - < T2 | >= T2 | p-value for trend^ |
| Total [N (%)] | 1934 | 2024 | 2028 |  |
| Mean Age - yr | 72.0±9.2 | 72.0±9.5 | 71.7±9.6 | 0.3139 |
| Female sex — no. (%) | 722 ( 37.3)  | 926 ( 45.8) | 1028 ( 50.7) | <0.0001 |
| Race — no. (%) † |  |  |  | <0.0001 |
|  White | 1462 ( 75.6)  | 1533 ( 75.7) | 1546 ( 76.2) |  |
|  Black | 60 ( 3.1) | 97 ( 4.8) | 100 ( 4.9) |  |
|  Asian | 343 ( 17.7)  | 261 ( 12.9) | 220 ( 10.8) |  |
|  Other | 69 ( 3.6) | 132 ( 6.5) | 161 ( 7.9) |  |
| NYHA functional classification — no. (%) |  |  |  | <0.0001 |
|  Class I/II | 1633 ( 84.4)  | 1686 ( 83.3) | 1566 ( 77.2) |  |
|  Class III/IV | 301 ( 15.6)  | 338 ( 16.7) | 462 ( 22.8) |  |
| Body-mass index ‡ | 29.4±5.6 | 29.9±5.9 | 30.1±6.1 | 0.0002 |
| Heart rate — beats per minute | 69.9±12.0 | 70.3±11.9 | 70.9±11.7 | 0.0042 |
| Systolic blood pressure — mm Hg | 131.8±15.3 | 131.8±15.9 | 131.9±15.7 | 0.8131 |
| Left ventricular ejection fraction |  |  |  |  |
| Mean LVEF - % | 54.1±8.6 | 54.3±9.0 | 54.5±8.6 | 0.1054 |
|  LVEF >40% to <50% — no. (%) § | 655 ( 33.9)  | 694 ( 34.3) | 633 ( 31.2) | 0.1241 ## |
|  LVEF >=50% to <60% — no. (%) | 670 ( 34.6)  | 658 ( 32.5) | 730 ( 36.0) |  |
|  LVEF >=60% — no. (%) | 609 ( 31.5)  | 672 ( 33.2) | 665 ( 32.8) |  |
| Median NT-proBNP (interquartile range) — pg/ml | 901.5 (483-1585) | 922.0 (476-1645) | 1071.0 (562-2005) | <0.0001 # |
| Heart failure category — no. (%) |  |  |  | 0.2224 |
|  Ischemic | 695 ( 35.9)  | 729 ( 36.0) | 692 ( 34.1) |  |
|  Nonischemic | 1238 ( 64.0)  | 1295 ( 64.0) | 1336 ( 65.9) |  |
| Cardiovascular history – no. (%) |  |  |  |  |
|  Hospitalization for heart failure during previous 12 mo | 417 ( 21.6)  | 415 ( 20.5) | 535 ( 26.4) | 0.0002 |
|  Atrial fibrillation | 1001 ( 51.8)  | 986 ( 48.7) | 1070 ( 52.8) | 0.4553 |
|  Diabetes mellitus | 917 ( 47.4)  | 981 ( 48.5) | 1038 ( 51.2) | 0.0171 |
|  Hypertension | 1737 ( 89.8)  | 1833 ( 90.6) | 1852 ( 91.3) | 0.1044 |
| Mean eGFR - [mL/min/1.73m²] | 62.1±19.0 | 61.3±19.8 | 58.6±20.5 | <0.0001 |
| eGFR <60 ml/min/1.73 m2 — no. (%) | 901 ( 46.6)  | 979 ( 48.4) | 1108 ( 54.6) | <0.0001 |
| Alkaline Phosphatase [U/L] | 55.8±8.8 | 77.5±5.9 | 116.4±30.3 | NC |
| Albumin [g/dL] | 4.41±0.31 | 4.37±0.32 | 4.30±0.36 | <0.0001 |
|  Total Bilirubin [mg/dL] | 0.58±0.34 | 0.57±0.36 | 0.59±0.42 | 0.6647 |
| AST(SGOT) [U/L] | 21.3±8.0 | 21.2±7.4 | 23.1±13.3 | <0.0001 |
| ALT(SGPT) [U/L] | 19.0±10.0 | 19.3±9.9 | 20.4±16.3 | <0.0001 |

Baseline Alkaline Phosphatase [U/L]: T1: 68, T2: 89.

(B) Albumin

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | < T1 | T1 - < T2 | >= T2 | p-value for trend^ |
| Total [N (%)] | 1417 | 2112 | 2399 |  |
| Mean Age - yr | 72.7±9.8 | 72.7±9.2 | 70.7±9.3 | <0.0001 |
| Female sex — no. (%) | 661 ( 46.6)  | 979 ( 46.4) | 1016 ( 42.4) | 0.0035 |
| Race — no. (%) † |  |  |  | <0.0001 |
|  White | 1035 ( 73.0)  | 1636 ( 77.5) | 1820 ( 75.9) |  |
|  Black | 89 ( 6.3) | 82 ( 3.9) | 85 ( 3.5) |  |
|  Asian | 156 ( 11.0)  | 266 ( 12.6) | 400 ( 16.7) |  |
|  Other | 136 ( 9.6)  | 127 ( 6.0) | 94 ( 3.9) |  |
| NYHA functional classification — no. (%) |  |  |  | <0.0001 |
|  Class I/II | 1113 ( 78.5)  | 1695 ( 80.3) | 2035 ( 84.8) |  |
|  Class III/IV | 304 ( 21.5)  | 417 ( 19.7) | 364 ( 15.2) |  |
| Body-mass index ‡ | 30.7±6.5 | 29.9±5.9 | 29.2±5.4 | <0.0001 |
| Heart rate — beats per minute | 70.9±12.2 | 70.3±11.8 | 70.1±11.8 | 0.0517 |
| Systolic blood pressure — mm Hg | 131.8±16.7 | 131.9±15.5 | 131.9±15.2 | 0.8685 |
| Left ventricular ejection fraction |  |  |  |  |
| Mean LVEF - % | 55.0±9.0 | 54.5±8.7 | 53.8±8.7 | <0.0001 |
|  LVEF >40% to <50% — no. (%) § | 421 ( 29.7)  | 689 ( 32.6) | 855 ( 35.6) | <0.0001 ## |
|  LVEF >=50% to <60% — no. (%) | 505 ( 35.6)  | 704 ( 33.3) | 825 ( 34.4) |  |
|  LVEF >=60% — no. (%) | 491 ( 34.7)  | 719 ( 34.0) | 719 ( 30.0) |  |
| Median NT-proBNP (interquartile range) — pg/ml | 1202.0 (607-2186) | 1000.5 (524.5-1725) | 830.0 (438-1504) | <0.0001 # |
| Heart failure category — no. (%) |  |  |  | 0.0008 |
|  Ischemic | 467 ( 33.0)  | 713 ( 33.8) | 907 ( 37.8) |  |
|  Nonischemic | 950 ( 67.0)  | 1398 ( 66.2) | 1492 ( 62.2) |  |
| Cardiovascular history – no. (%) |  |  |  |  |
|  Hospitalization for heart failure during previous 12 mo | 373 ( 26.3)  | 469 ( 22.2) | 518 ( 21.6) | 0.0023 |
|  Atrial fibrillation | 678 ( 47.8)  | 1138 ( 53.9) | 1218 ( 50.8) | 0.3270 |
|  Diabetes mellitus | 735 ( 51.9)  | 1010 ( 47.8) | 1158 ( 48.3) | 0.0730 |
|  Hypertension | 1304 ( 92.0)  | 1913 ( 90.6) | 2153 ( 89.7) | 0.0238 |
| Mean eGFR - [mL/min/1.73m²] |  |  |  |  |
| eGFR <60 ml/min/1.73 m2 — no. (%) | 815 ( 57.5)  | 1046 ( 49.5) | 1095 ( 45.6) | <0.0001 |
| Alkaline Phosphatase [U/L] | 91.5±36.2 | 82.7±29.0 | 79.9±29.0 | <0.0001 |
| Albumin [g/dL] | 3.92±0.23 | 4.31±0.08 | 4.67±0.17 | NC |
| Total Bilirubin [mg/dL] | 0.53±0.39 | 0.57±0.37 | 0.61±0.37 | <0.0001 |
| AST(SGOT) [U/L] | 21.1±9.4 | 21.5±10.8 | 22.6±9.7 | <0.0001 |
| ALT(SGPT) [U/L] | 18.2±10.8 | 19.1±14.7 | 20.9±11.1 | <0.0001 |

Baseline Albumin [g/dL]: T1: 4.2, T2: 4.5.

(C) Total Bilirubin

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | < T1 | T1 - < T2 | >= T2 | p-value for trend^ |
| Total [N (%)] | 1825 | 2115 | 1976 |  |
| Mean Age - yr | 70.2±10.0 | 72.4±9.1 | 72.9±9.0 | <0.0001 |
| Female sex — no. (%) | 1019 ( 55.8)  | 953 ( 45.1) | 681 ( 34.5) | <0.0001 |
| Race — no. (%) † |  |  |  | <0.0001 |
|  White | 1334 ( 73.1)  | 1643 ( 77.7) | 1505 ( 76.2) |  |
|  Black | 133 ( 7.3) | 83 ( 3.9) | 40 ( 2.0) |  |
|  Asian | 214 ( 11.7)  | 256 ( 12.1) | 352 ( 17.8) |  |
|  Other | 142 ( 7.8)  | 133 ( 6.3) | 79 ( 4.0) |  |
| NYHA functional classification — no. (%) |  |  |  | 0.3101 |
|  Class I/II | 1486 ( 81.4)  | 1761 ( 83.3) | 1586 ( 80.3) |  |
|  Class III/IV | 339 ( 18.6)  | 354 ( 16.7) | 390 ( 19.7) |  |
| Body-mass index ‡ | 30.5±6.0 | 29.9±6.0 | 29.2±5.5 | <0.0001 |
| Heart rate — beats per minute | 69.9±11.2 | 69.5±11.8 | 71.8±12.4 | <0.0001 |
| Systolic blood pressure — mm Hg | 132.6±16.2 | 131.8±15.7 | 131.3±15.1 | 0.0081 |
| Left ventricular ejection fraction |  |  |  |  |
| Mean LVEF - % | 54.9±9.0 | 54.1±8.8 | 54.1±8.5 | 0.0116 |
|  LVEF >40% to <50% — no. (%) § | 583 ( 31.9)  | 726 ( 34.3) | 651 ( 32.9) | 0.1849 ## |
|  LVEF >=50% to <60% — no. (%) | 610 ( 33.4)  | 725 ( 34.3) | 693 ( 35.1) |  |
|  LVEF >=60% — no. (%) | 632 ( 34.6)  | 664 ( 31.4) | 632 ( 32.0) |  |
| Median NT-proBNP (interquartile range) — pg/ml | 727.0 (413-1398) | 954.0 (491-1686) | 1256.0 (657-2075) | <0.0001 # |
| Heart failure category — no. (%) |  |  |  | <0.0001 |
|  Ischemic | 721 ( 39.5)  | 731 ( 34.6) | 629 ( 31.8) |  |
|  Nonischemic | 1104 ( 60.5)  | 1384 ( 65.4) | 1346 ( 68.1) |  |
| Cardiovascular history – no. (%) |  |  |  |  |
|  Hospitalization for heart failure during previous 12 mo | 400 ( 21.9)  | 460 ( 21.7) | 500 ( 25.3) | 0.0108 |
|  Atrial fibrillation | 598 ( 32.8)  | 1092 ( 51.6) | 1339 ( 67.8) | <0.0001 |
|  Diabetes mellitus | 1075 ( 58.9)  | 977 ( 46.2) | 843 ( 42.7) | <0.0001 |
|  Hypertension | 1699 ( 93.1)  | 1918 ( 90.7) | 1745 ( 88.3) | <0.0001 |
| Mean eGFR - [mL/min/1.73m²] | 58.3±21.6 | 61.0±19.4 | 62.6±18.3 | <0.0001 |
| eGFR <60 ml/min/1.73 m2 — no. (%) | 1001 ( 54.8)  | 1051 ( 49.7) | 897 ( 45.4) | <0.0001 |
| Alkaline Phosphatase [U/L] | 85.1±30.8 | 81.5±27.2 | 84.6±35.2 | 0.7664 |
| Albumin [g/dL] | 4.29±0.35 | 4.37±0.32 | 4.41±0.32 | <0.0001 |
| Total Bilirubin [mg/dL] | 0.27±0.07 | 0.49±0.07 | 0.97±0.40 | NC |
| AST(SGOT) [U/L] | 19.9±7.5 | 21.7±10.5 | 23.9±11.2 | <0.0001 |
| ALT(SGPT) [U/L] | 18.2±10.2 | 19.6±15.0 | 20.8±11.3 | <0.0001 |

Baseline Bilirubin [mg/dL]: T1: 0.40, T2: 0.64.

(D) AST

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | < T1 | T1 - < T2 | >= T2 | p-value for trend^ |
| Total [N (%)] | 1896 | 1993 | 2097 |  |
| Mean Age - yr | 71.8±9.2 | 72.4±9.3 | 71.6±9.8 | 0.4251 |
| Female sex — no. (%) | 882 ( 46.5)  | 924 ( 46.4) | 870 ( 41.5) | 0.0011 |
| Race — no. (%) † |  |  |  | <0.0001 |
|  White | 1471 ( 77.6)  | 1542 ( 77.4) | 1528 ( 72.9) |  |
|  Black | 104 ( 5.5)  | 78 ( 3.9) | 75 ( 3.6) |  |
|  Asian | 173 ( 9.1)  | 255 ( 12.8) | 396 ( 18.9) |  |
|  Other | 147 ( 7.8)  | 118 ( 5.9) | 97 ( 4.6) |  |
| NYHA functional classification — no. (%) |  |  |  | 0.5018 |
|  Class I/II | 1526 ( 80.5)  | 1652 ( 82.9) | 1707 ( 81.4) |  |
|  Class III/IV | 370 ( 19.5)  | 341 ( 17.1) | 390 ( 18.6) |  |
| Body-mass index ‡ | 30.7±5.9 | 30.0±5.8 | 28.9±5.8 | <0.0001 |
| Heart rate — beats per minute | 70.3±11.5 | 70.1±12.1 | 70.7±11.9 | 0.2655 |
| Systolic blood pressure — mm Hg | 132.6±15.9 | 131.7±15.7 | 131.3±15.4 | 0.0110 |
| Left ventricular ejection fraction |  |  |  |  |
| Mean LVEF - % | 54.5±9.1 | 53.8±8.6 | 54.6±8.7 | 0.6944 |
|  LVEF >40% to <50% — no. (%) § | 631 ( 33.3)  | 693 ( 34.8) | 658 ( 31.4) | 0.4192 ## |
|  LVEF >=50% to <60% — no. (%) | 623 ( 32.9)  | 697 ( 35.0) | 738 ( 35.2) |  |
|  LVEF >=60% — no. (%) | 642 ( 33.9)  | 603 ( 30.3) | 701 ( 33.4) |  |
| Median NT-proBNP (interquartile range) — pg/ml | 874.5 (459-1587.5) | 981.0 (501.5-1694.5) | 1075.0 (543-1904) | <0.0001 # |
| Heart failure category — no. (%) |  |  |  | 0.0040 |
|  Ischemic | 702 ( 37.0)  | 727 ( 36.5) | 687 ( 32.8) |  |
|  Nonischemic | 1193 ( 62.9)  | 1266 ( 63.5) | 1410 ( 67.2) |  |
| Cardiovascular history – no. (%) |  |  |  |  |
|  Hospitalization for heart failure during previous 12 mo | 443 ( 23.4)  | 414 ( 20.8) | 510 ( 24.3) | 0.4001 |
|  Atrial fibrillation | 791 ( 41.7)  | 1051 ( 52.7) | 1215 ( 57.9) | <0.0001 |
|  Diabetes mellitus | 1122 ( 59.2)  | 923 ( 46.3) | 891 ( 42.5) | <0.0001 |
|  Hypertension | 1769 ( 93.3)  | 1822 ( 91.4) | 1831 ( 87.3) | <0.0001 |
| Mean eGFR - [mL/min/1.73m²] | 59.2±20.3 | 60.7±19.6 | 61.9±19.5 | <0.0001 |
| eGFR <60 ml/min/1.73 m2 — no. (%) | 1007 ( 53.1)  | 987 ( 49.5) | 994 ( 47.4) | 0.0003 |
| Alkaline Phosphatase [U/L] | 82.5±28.9 | 82.1±29.6 | 86.3±34.5 | <0.0001 |
| Albumin [g/dL] | 4.30±0.32 | 4.38±0.32 | 4.40±0.35 | <0.0001 |
| Total Bilirubin [mg/dL] | 0.49±0.31 | 0.57±0.35 | 0.66±0.43 | <0.0001 |
| AST(SGOT) [U/L] | 14.6±2.0 | 19.9±1.4 | 30.3±12.6 | NC |
| ALT(SGPT) [U/L] | 13.6±4.5 | 17.4±5.7 | 27.0±17.4 | <0.0001 |

Baseline AST [U/L]: T1: 18, T2: 23.

(E) ALT

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | < T1 | T1 - < T2 | >= T2 | p-value for trend^ |
| Total [N (%)] | 1661 | 2074 | 2251 |  |
| Mean Age - yr | 73.9±8.9 | 72.6±9.3 | 69.7±9.5 | <0.0001 |
| Female sex — no. (%) | 901 ( 54.2)  | 932 ( 44.9) | 843 ( 37.5) | <0.0001 |
| Race — no. (%) † |  |  |  | <0.0001 |
|  White | 1184 ( 71.3)  | 1577 ( 76.0) | 1780 ( 79.1) |  |
|  Black | 87 ( 5.2)  | 90 ( 4.3) | 80 ( 3.6) |  |
|  Asian | 271 ( 16.3)  | 273 ( 13.2) | 280 ( 12.4) |  |
|  Other | 119 ( 7.2)  | 133 ( 6.4) | 110 ( 4.9) |  |
| NYHA functional classification — no. (%) |  |  |  | 0.2251 |
|  Class I/II | 1331 ( 80.1)  | 1711 ( 82.5) | 1843 ( 81.9) |  |
|  Class III/IV | 330 ( 19.9)  | 363 ( 17.5) | 408 ( 18.1) |  |
| Body-mass index ‡ | 29.5±6.1 | 29.7±5.7 | 30.2±5.8 | <0.0001 |
| Heart rate — beats per minute | 70.5±12.0 | 70.3±11.8 | 70.4±11.8 | 0.8317 |
| Systolic blood pressure — mm Hg | 131.6±15.7 | 131.9±15.8 | 132.0±15.4 | 0.4951 |
| Left ventricular ejection fraction |  |  |  |  |
| Mean LVEF - % | 55.4±9.0 | 54.2±8.9 | 53.7±8.4 | <0.0001 |
|  LVEF >40% to <50% — no. (%) § | 484 ( 29.1)  | 712 ( 34.3) | 786 ( 34.9) | <0.0001 ## |
|  LVEF >=50% to <60% — no. (%) | 563 ( 33.9)  | 701 ( 33.8) | 794 ( 35.3) |  |
|  LVEF >=60% — no. (%) | 614 ( 37.0)  | 661 ( 31.9) | 671 ( 29.8) |  |
| Median NT-proBNP (interquartile range) — pg/ml | 1061.0 (557-1908) | 1009.0 (518-1746) | 876.0 (447-1630) | <0.0001 # |
| Heart failure category — no. (%) |  |  |  | 0.0003 |
|  Ischemic | 532 ( 32.0)  | 734 ( 35.4) | 850 ( 37.8) |  |
|  Nonischemic | 1128 ( 67.9)  | 1340 ( 64.6) | 1401 ( 62.2) |  |
| Cardiovascular history – no. (%) |  |  |  |  |
|  Hospitalization for heart failure during previous 12 mo | 378 ( 22.8)  | 460 ( 22.2) | 529 ( 23.5) | 0.5087 |
|  Atrial fibrillation | 807 ( 48.6)  | 1108 ( 53.4) | 1142 ( 50.7) | 0.3527 |
|  Diabetes mellitus | 764 ( 46.0)  | 995 ( 48.0) | 1177 ( 52.3) | <0.0001 |
|  Hypertension | 1525 ( 91.8)  | 1881 ( 90.7) | 2016 ( 89.6) | 0.0167 |
| Mean eGFR - [mL/min/1.73m²] | 57.1±19.8 | 60.1±19.5 | 63.7±19.6 | <0.0001 |
| eGFR <60 ml/min/1.73 m2 — no. (%) | 972 ( 58.5)  | 1040 ( 50.1) | 976 ( 43.4) | <0.0001 |
| Alkaline Phosphatase [U/L] | 83.5±29.4 | 82.2±30.3 | 85.1±33.2 | 0.0519 |
| Albumin [g/dL] | 4.30±0.33 | 4.35±0.32 | 4.41±0.33 | <0.0001 |
| Total Bilirubin [mg/dL] | 0.52±0.33 | 0.58±0.39 | 0.62±0.39 | <0.0001 |
| AST(SGOT) [U/L] | 16.7±4.2 | 19.8±4.7 | 27.6±13.3 | <0.0001 |
| ALT(SGPT) [U/L] | 10.7±2.0 | 16.3±1.7 | 29.2±15.7 | NC |

Baseline ALT [U/L]: T1: 14, T2: 20.

^ p−values from ordinal regression likelihood ratio test. # based on log−transformed results ## parameter in rows modelled ordinally

\* Plus–minus values are means ±SD. The abbreviation eGFR denotes estimated glomerular filtration rate, LVEF left

ventricular ejection fraction NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

† Race was reported by the patient; patients who identified with more than one race or with no race were classified as other.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Two patients with an ejection fraction of exactly 40% underwent randomization and were included in the analysis

Supplement table 2: Statistical analysis of liver tests over time

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **p-value** | **Week 4** | **Week 12** | **Week 32** | **Week 52** | **Week 76** | **Week 100** | **Week 124** | **Week 148** | **Week 172** |
| **Alkaline Phosphatase** | 0.0678 | 0.3170 | 0.9350 | 0.2468 | 0.7811 | 0.1680 | 0.7385 | 0.6538 | 0.9588 |
| **Albumin** | <0.0001 | <0.0001 | 0.0376 | <0.0001 | 0.0288 | 0.0268 | 0.0330 | 0.4246 | 0.3667 |
| **Bilirubin** | 0.1493 | 0.0759 | 0.8854 | 0.2904 | 0.2271 | 0.5869 | 0.0257 | 0.6254 | 0.1709 |
| **AST** | 0.4868 | 0.3210 | 0.3864 | 0.9975 | 0.9717 | 0.4838 | 0.9965 | 0.4525 | 0.5048 |
| **ALT** | 0.0119 | 0.7314 | 0.1908 | 0.3015 | 0.5385 | 0.8283 | 0.8549 | 0.7837 | 0.1567 |

*ALT Alanine Transaminase; AST Aspartate Transaminase.*

*p-value for treatment comparison from MMRM model with factors age, baseline eGFR (CKD−EPI), baseline LVEF as linear covariate(s) and region,
baseline diabetes status, sex, week reachable,treatment by visit interaction and baseline value of intrest by visit interaction as fixed effect(s).*