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| **Supplementary Table 1: Components of the Frailty Index (42 items)** | | | |
|  |  |  |  |
| ***Sl. No.*** | ***Component*** | ***Cut off / Sub-component*** | ***Score*** |
| 1. | Diastolic blood pressure – mmHg | >90 | 1 |
| 2. | Pulse pressure – mmHg | >55 | 1 |
| 3. | Systolic blood pressure - mmHg | <90/>140 | 1 |
| 4. | Body Mass Index – kg/m2 | ≥25/<30 | 0.5 |
| <18.8/≥30 | 1 |
|  |  |  |  |
| **Laboratory measures** | | | |
| 5. | Albumin- gm/L | <35/>55 | 1 |
| 6. | BUN – mmol/L | <3/>7.5 | 1 |
| 7. | Calcium – mmol/L | <2.2/>2.7 | 1 |
| 8. | Creatinine – umol/L | <40/>150 | 1 |
| 9. | HDL Cholesterol – mmol/L | <0.4/>1.5 | 1 |
| 10. | Potassium – mmol/L | <3.5/>6 | 1 |
| 11. | RBC count – X109/L | <3.5/>5.5 | 1 |
| 12. | Sodium – mmol/L | <135/>145 | 1 |
| 13. | Total Cholesterol – mmol/L | <3.5/>7 | 1 |
| 14. | Uric acid – umol/L | Males - <200/>430 | 1 |
|  |  | Females - <140/ >360 | 1 |
| 15. | Haemoglobin – gm/L | Males - <130/>175 | 1 |
|  |  | Females - <120/>155 | 1 |
| 16. | Platelet count - X109/L | <150/>400 | 1 |
| 17. | WBC count – X109/L | <4/>12 | 1 |
|  |  |  |  |
| **Comorbidities** | | | |
| 18. | Atrial Fibrillation |  | 1 |
| 19. | Hypertension |  | 1 |
| 20. | Myocardial Infarction |  | 1 |
| 21. | PCI or CABG |  | 1 |
| 22. | Unstable angina |  | 1 |
| 23. | Peripheral arterial disease |  | 1 |
| 24. | Stroke |  | 1 |
| 25. | Diabetes |  | 1 |
| 26. | Cancer |  | 1 |
| 27. | COPD |  | 1 |
|  |  |  |  |
| **Quality of life measures – Kansas City cardiomyopathy questionnaire (all responses with respect to the two weeks prior to questioning)** | | | |
| **Mobility** | | | |
| 28. | Limited activities due to heart failure | Dressing yourself: |  |
| *Not at all limited* | 0 |
| *Limited for other reasons or did not do the activity* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 29. | Showering/bathing: |  |
| *Not at all limited* | 0 |
| *Limited for other reasons or did not do the activity* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 30. | Walking 1 block on level ground: |  |
| *Not at all limited* | 0 |
| *Limited for other reasons or did not do the activity* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 31. | Doing yardwork, housework, or carrying groceries: |  |
| *Not at all limited* | 0 |
| *Limited for other reasons or did not do the activity* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 32. | Climbing a flight of stairs without stopping: |  |
| *Not at all limited* | 0 |
| *Limited for other reasons or did not do the activity* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 33. | Hurrying or jogging: |  |
| *Not at all limited* | 0 |
| *Limited for other reasons or did not do the activity* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| **Memory and cognitive abilities** | | | |
| 34. | Are you sure you know what to do or whom to call if your heart failure gets worse | Completely sure | 0 |
| Mostly sure | 0.25 |
| somewhat sure | 0.5 |
| Not very sure | 0.75 |
| Not at all sure | 1 |
| 35. | How well do you understand what things you can do to keep your heart failure symptoms from getting worse | Completely understand | 0 |
| Mostly understand | 0.25 |
| Somewhat understand | 0.5 |
| Do not understand very well | 0.75 |
| Do not understand at all | 1 |
| **Mood vulnerabilities** | | | |
| 36. | How would you feel if you had to spend rest of life with heart failure the way it is right now | Completely satisfied | 0 |
| Mostly satisfied | 0.25 |
| Somewhat satisfied | 0.5 |
| Mostly dissatisfied | 0.75 |
| Completely dissatisfied | 1 |
| 37. | How often have you felt discouraged or down in dumps because of your heart failure | I never felt that way | 0 |
| I have rarely felt that way | 0.25 |
| I have occasionally felt that way | 0.5 |
| I have felt that way most of the time | 0.75 |
| I have felt that way all the time | 1 |
| **Functional abilities** | | | |
| 38. | How much has heart failure limited enjoyment of life | It has not limited my enjoyment of life at all | 0 |
| It has slightly limited my enjoyment of life | 0.25 |
| It has moderately limited my enjoyment of life | 0.5 |
| It has limited my enjoyment of life quite a bit | 0.75 |
| It has extremely limited my enjoyment of life | 1 |
| 39. | How does heart failure affect lifestyle | Hobbies, recreational activities: |  |
| *Did not limit at all* | 0 |
| *Does not apply or did not do for other reasons* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 40. | Working or doing household chores: |  |
| *Did not limit at all* | 0 |
| *Does not apply or did not do for other reasons* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 41. | Visiting family or friends out of your home: |  |
| *Did not limit at all* | 0 |
| *Does not apply or did not do for other reasons* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| 42. | Intimate relationships with loved ones: |  |
| *Did not limit at all* | 0 |
| *Does not apply or did not do for other reasons* | 0.2 |
| *Slightly limited* | 0.4 |
| *Moderately limited* | 0.6 |
| *Quite a bit limited* | 0.8 |
| *Extremely limited* | 1 |
| BUN – Blood urea nitrogen, HDL – High density lipoprotein, WBC – White blood cell, PCI – Primary coronary intervention, CABG – Coronary artery bypass graft, COPD – Chronic obstructive pulmonary disease, BMI – Body mass index. | | | |

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| --- | --- | --- | --- | --- |
| **Supplementary Table 2: State of Health Score (EQ-5D-3L) (PARADIGM-HF only) – no. (%)** | | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** | **p-value for trend** |
|  | n=2836 | n=2663 | n=1972 |  |
|  | (≤0.210) | (0.211 – 0.310) | (≥0.311) |  |
|  |  |  |  |  |
| Mobility |  |  |  | <0.001 |
| I have no problems in walking about | 2305 (81.4) | 1374 (51.7) | 451 (22.9) |  |
| I have some problems in walking about | 524 (18.5) | 1280 (48.1) | 1506 (76.6) |  |
| I am confined to bed | 1 (0.1) | 5 (0.2) | 10 (0.5) |  |
| Self-care |  |  |  | <0.001 |
| I have no problems with self-care | 2745 (97.0) | 2280 (85.7) | 1172 (59.6) |  |
| I have some problems washing or dressing myself | 84 (3.0) | 370 (13.9) | 776 (39.5) |  |
| I am unable to wash or dress myself | 1 (0.0) | 9 (0.3) | 19 (1.0) |  |
| Usual activities |  |  |  | <0.001 |
| I have no problems with performing my usual activities | 2371 (83.8) | 1409 (53.0) | 481 (24.5) |  |
| I have some problems with performing my usual activities | 450 (15.9) | 1216 (45.7) | 1344 (68.3) |  |
| I am unable to perform my usual activities | 9 (0.3) | 33 (1.2) | 142 (7.2) |  |
| Pain/ Discomfort |  |  |  | <0.001 |
| I have no pain or discomfort | 2095 (74.0) | 1433 (53.9) | 617 (31.4) |  |
| I have moderate pain or discomfort | 716 (25.3) | 1188 (44.7) | 1255 (63.8) |  |
| I have extreme pain or discomfort | 19 (0.7) | 37 (1.4) | 95 (4.8) |  |
| Anxiety/ Depression |  |  |  | <0.001 |
| I am not anxious or depressed | 2300 (81.3) | 1750 (65.8) | 912 (46.4) |  |
| I am moderately anxious or depressed | 505 (17.8) | 882 (33.2) | 970 (49.3) |  |
| I am extremely anxious or depressed | 25 (0.9) | 27 (1.0) | 85 (4.3) |  |
| Overall Score – mean (SD) | 75.1 ± 18.9 | 66.1 ± 18.0 | 56.0 ± 17.9 | <<0.001 |

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| **Supplementary Table 3: Biomarkers (PARADIGM-HF only)** | | | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** | **p-value for trend** | **Missing** |
|  | n=2836 | n=2663 | n=1972 |  |  |
|  | (≤0.210) | (0.211 – 0.310) | (≥0.311) |  |  |
|  |  |  |  |  |  |
| HbA1C – no (%) |  |  |  | <0.001 | 67 |
| Prediabetes (6-6.4) | 700 (32.4) | 612 (36.6) | 402 (40.9) |  |  |
| Undiagnosed Diabetes (>6.4) | 299 (13.8) | 282 (16.8) | 158 (16.1) |  |  |
|  |  |  |  |  |  |
| NT-proBNP (pg/ml) | 1364 (817 – 2736) | 1653 (906 – 3204) | 1885 (1037 – 3961) | <0.001 | 14 |
| BNP (pg/ml) | 66 (41 – 121) | 73 (45 – 132) | 82 (49 – 149) | <0.001 | 55 |
|  |  |  |  |  |  |
| MMP2 (ng/mL) | 128 (113 - 148) | 136 (116 - 159) | 138 (120 - 162) | <0.001 | 6130 |
| MMP9 (ng/mL) | 62 (39 - 132) | 64 (41 - 124) | 63 (37 - 126) | 0.562 | 6131 |
| hsTropT (ng/L) | 14 (9 - 20) | 16 (11 - 24) | 21 (13 - 31) | <0.001 | 5919 |
| GDF 15 (ng/L) | 1387 (1020 - 1914) | 1645 (1148 - 2287) | 2035 (1440 - 3038) | <0.001 | 5991 |
| KIM-1 (pg/mL) | 108 (74 - 159) | 133 (91 - 189) | 154 (101 - 233) | <0.001 | 5986 |
| ST2 (ng/mL) | 31 (25 - 39) | 32 (26 - 41) | 34 (27 - 45) | <0.001 | 5948 |
| TIMP 1 (ng/mL) | 116 (99 - 141) | 124 (105 - 147) | 136 (114 - 165) | <0.001 | 6115 |
| Galectin – 3 (ng/mL) | 16 (13 - 19) | 17 (14 - 21) | 19 (15 - 23) | <0.001 | 5920 |
| All values presented as median (IQR) except where indicated.  HbA1c is randomization.  BNP and NTproBNP are screening values.  Remaining biomarkers are from visit 2 (after screening). | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Supplementary Table 4: Immunization and lifestyle management history (PARADIGM-HF only) – no. (%)** | | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** | **p-value for trend** |
|  | n=2836 | n=2663 | n=1972 |  |
|  | (≤0.210) | (0.211 – 0.310) | (≥0.311) |  |
|  |  |  |  |  |
| Influenza vaccination in past 12 months | 557 (19.6) | 603 (22.6) | 526 (26.7) | <0.001 |
| Pneumococcal Vaccination in past 12 months | 155 (5.5) | 161 (6.0) | 144 (7.3) | 0.010 |
| Patient been prescribed an exercise regimen | 532 (18.8) | 456 (17.1) | 385 (19.5) | 0.658 |
| Patient enrolled in structured disease management program | 418 (14.7) | 461 (17.3) | 352 (17.8) | 0.003 |

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| **Supplementary Table 5a: Clinical outcomes according to age and FI in patients with HFrEF** | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** |
|  | **n=4882** | **n=4770** | **n=3613** |
|  | **(≤0.210)** | **(0.211 – 0.310)** | **(≥0.311)** |
|  |  |  |  |
| **18 – 60 years** |  |  |  |
| **Primary outcome** – event rate | 8.9 (8.2 – 9.7) | 11.6 (10.6 – 12.8) | 15.1 (13.6 – 16.9) |
| – sHR | 1.00 (ref.) | 1.33 (1.17 – 1.52)  <0.001 | 1.76 (1.51 – 2.05)  <0.001 |
| **HF hospitalization** – event rate | 5.0 (5.9 – 7.5) | 6.6 (5.9 – 7.5) | 9.4 (8.2 – 10.8) |
| – sHR | 1.00 (ref.) | 1.24 (1.04 – 1.47)  0.014 | 1.64 (1.36 – 1.99)  <0.001 |
| **Cardiovascular death** – event rate | 5.3 (4.8 – 5.9) | 6.4 (5.7 – 7.3) | 8.3 (7.2 – 9.5) |
| – sHR | 1.00 (ref.) | 1.33 (1.12 – 1.57)  0.001 | 1.84 (1.52 – 2.23)  <0.001 |
| **All-cause death** – event rate | 6.0 (5.4 – 6.7) | 7.2 (6.4 – 8.0) | 9.6 (8.4 – 10.9) |
| - HR | 1.00 (ref.) | 1.29 (1.10 – 1.51)  0.002 | 1.85 (1.55 – 2.21)  <0.001 |
|  |  |  |  |
| **61 – 70 years** |  |  |  |
| **Primary outcome** – event rate | 8.2 (7.3 – 9.1) | 11.9 (10.8 – 13.0) | 16.1 (14.6 – 17.7) |
| – sHR | 1.00 (ref.) | 1.48 (1.28 – 1.71)  <0.001 | 2.04 (1.75 – 2.37)  <0.001 |
| **HF hospitalization** – event rate | 4.8 (4.2 – 5.5) | 7.1 (6.3 – 8.0) | 9.7 (8.5 – 11.0) |
| – sHR | 1.00 (ref.) | 1.42 (1.18 – 1.70)  <0.001 | 1.87 (1.54 – 2.28)  <0.001 |
| **Cardiovascular death** – event rate | 4.6 (4.0 – 5.3) | 6.6 (5.9 – 7.4) | 9.3 (8.3 – 10.5) |
| – sHR | 1.00 (ref.) | 1.48 (1.23 – 1.78)  <0.001 | 2.20 (1.81 – 2.67)  <0.001 |
| **All-cause death** – event rate | 5.8 (5.1 – 6.5) | 8.1 (7.3 – 9.0) | 11.3 (10.1 – 12.6) |
| - HR | 1.00 (ref.) | 1.47 (1.25 – 1.74)  <0.001 | 2.15 (1.81 – 2.56)  <0.001 |
|  |  |  |  |
| **71 – 96 years** |  |  |  |
| **Primary outcome** – event rate | 9.6 (8.5 – 10.8) | 11.4 (10.4 – 12.5) | 19.2 (17.7 – 20.8) |
| – sHR | 1.00 (ref.) | 1.20 (1.03 – 1.40)  0.018 | 1.99 (1.71 – 2.31)  <0.001 |
| **HF hospitalization** – event rate | 5.2 (4.4 – 6.2) | 6.2 (5.5 – 7.1) | 11.3 (10.1 – 12.5) |
| – sHR | 1.00 (ref.) | 1.13 (0.92 – 1.40)  0.233 | 1.87 (1.53 – 2.29)  <0.001 |
| **Cardiovascular death** – event rate | 6.1 (5.2 – 7.0) | 7.3 (6.5 – 8.2) | 11.8 (10.7 – 13.0) |
| – sHR | 1.00 (ref.) | 1.26 (1.05 – 1.52)  0.014 | 2.07 (1.73 – 2.49)  <0.001 |
| **All-cause death** – event rate | 7.6 (6.7 – 8.7) | 9.3 (8.4 – 10.3) | 14.8 (13.5 – 16.1) |
| - HR | 1.00 (ref.) | 1.30 (1.10 – 1.53)  0.002 | 2.17 (1.84 – 2.55)  <0.001 |
| **Supplementary Table 5b: Clinical outcomes according to age and FI in patients with HFrEF (≥60 years)** | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** |
|  | **n=2836** | **n=3369** | **n=2878** |
|  | **(<=0.210)** | **(0.211 – 0.310)** | **(>=0.311)** |
|  |  |  |  |
| **60 – 66 years** |  |  |  |
| **Primary outcome** – event rate | 8.2 (7.3 – 9.3) | 11.5 (10.3 – 12.8) | 15.3 (13.7 – 17.2) |
| – sHR | 1.00 (ref.) | 1.44 (1.22 – 1.70)  <0.001 | 1.98 (1.66 – 2.37)  <0.001 |
| **HF hospitalization** – event rate | 4.7 (4.0 – 5.5) | 6.5 (5.6 – 7.5) | 9.5 (8.2 – 11.0) |
| – sHR | 1.00 (ref.) | 1.32 (1.06 – 1.65)  0.012 | 1.90 (1.51 – 2.38)  <0.001 |
| **Cardiovascular death** – event rate | 4.8 (4.1 – 5.6) | 6.4 (5.6 – 7.4) | 8.8 (7.6 – 10.2) |
| – sHR | 1.00 (ref.) | 1.44 (1.16 – 1.79)  0.001 | 2.09 (1.66 – 2.63)  <0.001 |
| **All-cause death** – event rate | 5.7 (4.9 – 6.5) | 7.8 (6.8 – 8.9) | 10.4 (9.1 – 11.8) |
| - HR | 1.00 (ref.) | 1.48 (1.22 – 1.80)  <0.001 | 2.08 (1.69 – 2.56)  <0.001 |
|  |  |  |  |
| **67 – 73 years** |  |  |  |
| **Primary outcome** – event rate | 8.7 (7.6 – 10.0) | 12.0 (10.7 – 13.4) | 16.6 (14.9 – 18.6) |
| – sHR | 1.00 (ref.) | 1.39 (1.17 – 1.66)  <0.001 | 1.93 (1.61 – 2.31)  <0.001 |
| **HF hospitalization** – event rate | 5.0 (4.1 – 5.9) | 7.2 (6.3 – 8.3) | 9.9 (8.6 – 11.5) |
| – sHR | 1.00 (ref.) | 1.43 (1.14 – 1.79)  0.002 | 1.86 (1.47 – 2.37)  <0.001 |
| **Cardiovascular death** – event rate | 5.1 (4.3 – 6.0) | 6.6 (5.7 – 7.6) | 10.1 (8.8 – 11.6) |
| – sHR | 1.00 (ref.) | 1.35 (1.08 – 1.69)  0.008 | 2.12 (1.70 – 2.66)  <0.001 |
| **All-cause death** – event rate | 6.5 (5.6 – 7.6) | 8.1 (7.1 – 9.1) | 12.5 (11.0 – 14.1) |
| - HR | 1.00 (ref.) | 1.29 (1.06 – 1.57)  0.012 | 2.11 (1.72 – 2.58)  <0.001 |
|  |  |  |  |
| **74 – 96 years** |  |  |  |
| **Primary outcome** – event rate | 9.3 (8.0 – 10.9) | 11.4 (10.1 – 12.7) | 20.5 (18.7 – 22.5) |
| – sHR | 1.00 (ref.) | 1.22 (1.00 – 1.48)  0.045 | 2.14 (1.78 – 2.58)  <0.001 |
| **HF hospitalization** – event rate | 5.0 (4.1 – 6.2) | 6.2 (5.3 – 7.2) | 11.8 (10.4 – 13.3) |
| – sHR | 1.00 (ref.) | 1.15 (0.88 – 1.49)  0.304 | 1.95 (1.52 – 2.51)  <0.001 |
| **Cardiovascular death** – event rate | 6.2 (5.2 – 7.4) | 7.7 (6.7 – 8.7) | 12.5 (11.2 – 14.0) |
| – sHR | 1.00 (ref.) | 1.28 (1.02 – 1.61)  0.034 | 2.12 (1.70 – 2.64)  <0.001 |
| **All-cause death** – event rate | 7.9 (6.7 – 9.3) | 10.0 (8.9 – 11.2) | 15.8 (14.3 – 17.4) |
| - HR | 1.00 (ref.) | 1.33 (1.09 – 1.63)  0.005 | 2.23 (1.83 – 2.72)  <0.001 |
| All events are reported as event rates per 100 patient years (95% confidence interval).  All sHRs reported are only adjusted for randomized treatment and region at baseline.  Age is categorized by tertiles of age. | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| **Supplementary Table 6: Clinical Outcomes according to frailty in patients aged ≥60 years** | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** |
|  | n=2836 | n=3369 | n=2787 |
|  | (≤0.210) | (0.211 – 0.310) | (≥0.311) |
|  |  |  |  |
| **Primary Outcome** |  |  |  |
| Events – no (%) | 633 (22.3) | 937 (27.8) | 1038 (37.2) |
| Event rate per 100 pt. years (CI) | 8.7 (8.0 - 9.4) | 11.6 (10.9 - 12.4) | 17.6 (16.6 - 18.8) |
| Unadjusted sHR | 1.00 (ref) | 1.37 (1.24 - 1.51)  <0.001 | 2.08 (1.88 - 2.31)  <0.001 |
| Adjusted sHR | 1.00 (ref) | 1.30 (1.17 - 1.44)  <0.001 | 1.85 (1.66 - 2.07)  <0.001 |
|  |  |  |  |
| **HF Hospitalization** |  |  |  |
| Events – no (%) | 356 (12.6) | 536 (15.9) | 616 (22.1) |
| Event rate per 100 pt. years | 4.9 (4.4 - 5.4) | 6.6 (6.1 - 7.2) | 10.5 (9.7 - 11.3) |
| Unadjusted sHR | 1.00 (ref) | 1.33 (1.17 - 1.53)  <0.001 | 2.01 (1.75 - 2.30)  <0.001 |
| Adjusted sHR | 1.00 (ref) | 1.29 (1.12 - 1.48)  <0.001 | 1.88 (1.62 - 2.17)  <0.001 |
|  |  |  |  |
| **CV Death** |  |  |  |
| Events – no (%) | 405 (14.3) | 603 (17.9) | 705 (25.3) |
| Event rate per 100 pt. years | 5.2 (4.7 - 5.8) | 6.9 (6.3 - 7.4) | 10.6 (9.8 - 11.4) |
| Unadjusted sHR | 1.00 (ref) | 1.39 (1.22 - 1.57)  <0.001 | 2.21 (1.94 - 2.51)  <0.001 |
| Adjusted sHR | 1.00 (ref) | 1.30 (1.14 - 1.48)  <0.001 | 1.85 (1.61 - 2.13)  <0.001 |
|  |  |  |  |
| **All-cause Death** |  |  |  |
| Events – no (%) | 503 (17.7) | 752 (22.3) | 869 (31.2) |
| Event rate per 100 pt. years | 6.5 (6.0 - 7.1) | 8.6 (8.0 - 9.2) | 13.1 (12.2 - 14.0) |
| Unadjusted HR | 1.00 (ref) | 1.41 (1.25 - 1.58)  <0.001 | 2.26 (2.01 - 2.53)  <0.001 |
| Adjusted HR | 1.00 (ref) | 1.31 (1.17 - 1.48)  <0.001 | 1.92 (1.70 - 2.18)  <0.001 |
|  |  |  |  |
| **Fall in KCCQ clinical summary score ≥5 at 12 months** |  |  |  |
| No. (%) | 950 (34.5) | 1179 (36.4) | 980 (37.4) |
| Adjusted OR1 | 1.00 (ref.) | 1.33 (1.18 - 1.49)  <0.001 | 1.88 (1.60 - 2.20)  <0.001 |
| Adjusted OR2 | 1.00 (ref.) | 1.24 (1.10 - 1.40)  0.001 | 1.70 (1.44 - 2.00)  <0.001 |
| Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause death]  Event rates per 100 patient years with 95% confidence interval  All sHRs adjusted for region and randomized treatment at baseline  Adjusted sHRs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class I/II vs. II/IV, duration of heart failure and ejection fraction.  Heart failure hospitalization additionally adjusted for previous hospitalization for heart failure.  Odds ratio reported as OR (95% confidence interval)  ORs adjusted for region and randomized treatment at baseline  Adjusted OR1 additionally adjusted for: KCCQ clinical summary score at baseline  Adjusted OR2 additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class and ejection fraction. | | | |

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| **Supplementary Table 7: Clinical Outcomes according to every 0.010 increase in the Frailty Index score** | | |
|  | **Unadjusted sHR** | **Adjusted sHR** |
|  |  |  |
| **Primary Outcome** | 1.032 (1.028 – 1.036)  <0.001 | 1.026 (1.022 – 1.030)  <0.001 |
|  |  |  |
| **HF Hospitalization** | 1.030 (1.025 – 1.034)  <0.001 | 1.025 (1.020 – 1.030)  <0.001 |
|  |  |  |
| **CV Death** | 1.034 (1.029 – 1.038)  <0.001 | 1.025 (1.020 – 1.030)  <0.001 |
|  |  |  |
| **All-cause Death** | 1.035 (1.031 – 1.039)  <0.001 | 1.026 (1.022 – 1.030)  <0.001 |
| Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause death]  All sHRs adjusted for region and randomized treatment at baseline  Adjusted sHRs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class I/II vs. II/IV, duration of heart failure and ejection fraction.  Heart failure hospitalization additionally adjusted for previous hospitalization for heart failure.  Odds ratio reported as OR (95% confidence interval)  ORs adjusted for region and randomized treatment at baseline  Adjusted OR1 additionally adjusted for: KCCQ clinical summary score at baseline  Adjusted OR2 additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class and ejection fraction. | | |

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| **Supplementary Table 8: Number of hospitalizations in patients according to Frailty – no. (%)** | | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** | **p-value for trend** |
|  | n=4882 | n=4770 | n=3613 |  |
|  | (≤0.210) | (0.211 – 0.310) | (≥0.311) |  |
| **HF Hospitalization** | | | | <0.001 |
| 0 | 4257 (87.2) | 4011 (84.1) | 2826 (78.2) |  |
| 1 | 429 (8.8) | 484 (10.1) | 476 (13.2) |  |
| ≥2 | 196 (4.0) | 275 (5.8) | 311 (8.6) |  |
| **CV Hospitalization** | | | | <0.001 |
| 0 | 3576 (73.2) | 3165 (66.4) | 2136 (59.1) |  |
| 1 | 780 (16.0) | 905 (19.0) | 775 (21.5) |  |
| ≥2 | 526 (10.8) | 700 (14.7) | 702 (19.4) |  |
| **Non-CV Hospitalization** |  |  |  | <0.001 |
| 0 | 3794 (77.7) | 3509 (73.6) | 2455 (67.9) |  |
| 1 | 730 (15.0) | 800 (16.8) | 660 (18.3) |  |
| ≥2 | 358 (7.3) | 461 (9.7) | 498 (13.8) |  |
| **Non-CV Hospitalization** | | | | <0.001 |
| 0 | 2913 (59.7) | 2502 (52.5) | 1589 (44.0) |  |
| 1 | 1054 (21.6) | 1069 (22.4) | 861 (23.8) |  |
| ≥2 | 915 (18.7) | 1199 (25.1) | 1163 (32.2) |  |

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| **Supplementary Table 9: Falls and Fractures** | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** |
|  | n=4882 | n=4770 | n=3613 |
|  | (≤0.210) | (0.211 – 0.310) | (≥0.311) |
|  |  |  |  |
| **Falls** |  |  |  |
| Events – no. (%) | 52 (1.1) | 95 (2.0) | 92 (2.5) |
| Unadjusted OR | 1.00 (ref.) | 1.76 (1.24 – 2.49)  0.001 | 2.07 (1.45 – 2.95)  <0.001 |
| Adjusted OR | 1.00 (ref.) | 1.71 (1.19 - 2.45)  0.004 | 1.94 (1.32 - 2.85)  0.001 |
|  |  |  |  |
| **Fractures** |  |  |  |
| Events – no. (%) | 116 (2.4) | 158 (3.4) | 157 (4.3) |
| Unadjusted OR | 1.00 (ref.) | 1.32 (1.03 – 1.69)  0.030 | 1.68 (1.30 – 2.17)  <0.001 |
| Adjusted OR | 1.00 (ref.) | 1.28 (0.99 - 1.65)  0.061 | 1.57 (1.19 - 2.07)  0.001 |
| Odds ratio reported as OR (95% confidence interval)  All ORs adjusted for region and randomized treatment at baseline  Adjusted ORs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class, ejection fraction and duration of HF. | | | |

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| **Supplementary Table 10: Adverse Events – no. (%)** | | | | |
|  | **FI Class 1** | **FI Class 2** | **FI Class 3** | **p-value for trend** |
|  | n=4882 | n=4770 | n=3613 |  |
|  | (≤0.210) | (0.211 – 0.310) | (≥0.311) |  |
|  |  |  |  |  |
| Cough | 573 (11.7) | 482 (10.1) | 391 (10.8) | 0.126 |
| Hypotension | 520 (10.7) | 578 (12.1) | 510 (14.1) | <0.001 |
| Hyperkalaemia | 400 (8.2) | 596 (12.5) | 458 (12.7) | <0.001 |
| Angioedema | 11 (0.2) | 12 (0.3) | 9 (0.2) | 0.813 |
| Any adverse event leading to treatment withdrawal | 662 (13.6) | 784 (16.4) | 728 (20.1) | <0.001 |