**Supplementary Material**

**The role of multimorbidity in patients with heart failure across the left ventricular ejection fraction spectrum: data from the Swedish Heart Failure Registry**

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**Abbreviations:**

AF, atrial fibrillation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildy reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MAP, mean arterial pressure; MRA, mineralcorticoid receptor antagonist; NYHA, New York Heart Association; NPR, National Patient Register; NTproBNP, N-terminal pro B type natriuretic peptide; PAD, peripheral artery disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

**Supplementary Figures**

**Supplemetary Figure 1. Study population flow-chart**

Immagine che contiene testo, schermata, Carattere, ricevuta

Descrizione generata automaticamente

**Supplementary Figure 2.a Kaplan Meier curve stratified by obesity**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 2.b Kaplan Meier curve stratified by obesity in different EF categories**

Immagine che contiene testo, schermata, Carattere, linea

Descrizione generata automaticamente

**Supplementary Figure 3.a Kaplan Meier curve stratified by hypertension**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 3.b Kaplan Meier curve stratified by hypertension in different EF categories**

Immagine che contiene testo, schermata, linea, Carattere

Descrizione generata automaticamente

**Supplementary Figure 4.a Kaplan Meier curve stratified by diabetes**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 4.b Kaplan Meier curve stratified by diabetes in different EF categories**

Immagine che contiene testo, schermata, linea, Carattere

Descrizione generata automaticamente

**Supplementary Figure 5.a Kaplan Meier curve stratified by CAD**

Immagine che contiene testo, schermata, linea, Carattere

Descrizione generata automaticamente

**Supplementary Figure 5.b Kaplan Meier curve stratified by CAD in different EF categories**

Immagine che contiene testo, schermata, Carattere, numero

Descrizione generata automaticamente

**Supplementary Figure 6.a Kaplan Meier curve stratified by atrial fibrillation**

Immagine che contiene testo, linea, schermata, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 6.b Kaplan Meier curve stratified by atrial fibrillation in different EF categories**

Immagine che contiene testo, schermata, linea, Carattere

Descrizione generata automaticamente

**Supplementary Figure 7.a Kaplan Meier curve stratified by valvular heart disease**

Immagine che contiene testo, linea, schermata, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 7.b Kaplan Meier curve stratified by valvular heart disease (VHD) in different EF categories**

Immagine che contiene testo, schermata, linea, Carattere

Descrizione generata automaticamente

**Supplementary Figure 8.a Kaplan Meier curve stratified by chronic kidney disease (CKD)**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 8.b Kaplan Meier curve stratified by CKD in different EF categories**

Immagine che contiene testo, schermata, numero, linea

Descrizione generata automaticamente

**Supplementary Figure 9.a Kaplan Meier curve stratified by anaemia**

Immagine che contiene testo, linea, schermata, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 9.b Kaplan Meier curve stratified by anaemia in different EF categories**

Immagine che contiene testo, schermata, linea, numero

Descrizione generata automaticamente

**Supplementary Figure 10.a Kaplan Meier curve stratified by COPD**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 10.b Kaplan Meier curve stratified by COPD in different EF categories**

Immagine che contiene testo, schermata, linea, diagramma

Descrizione generata automaticamente

**Supplementary Figure 11.a Kaplan Meier curve stratified by liver disease**

Immagine che contiene testo, schermata, linea, diagramma

Descrizione generata automaticamente

**Supplementary Figure 11.b Kaplan Meier curve stratified by liver disease in different EF categories**

Immagine che contiene testo, schermata, linea, numero

Descrizione generata automaticamente

**Supplementary Figure 12.a Kaplan Meier curve stratified by PAD**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 12.b Kaplan Meier curve stratified by PAD in different EF categories**

Immagine che contiene testo, schermata, Carattere, linea

Descrizione generata automaticamente

**Supplementary Figure 13.a Kaplan Meier curve stratified by history of stroke/TIA**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 13.b Kaplan Meier curve stratified by history of stroke/TIA in different EF categories**

Immagine che contiene testo, schermata, linea, Carattere

Descrizione generata automaticamente

**Supplementary Figure 14.a Kaplan Meier curve stratified by depression**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 14.b Kaplan Meier curve stratified by depression in different EF categories**

Immagine che contiene testo, schermata, numero, linea

Descrizione generata automaticamente

**Supplementary Figure 15.a Kaplan Meier curve stratified by dementia**

Immagine che contiene testo, linea, schermata, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 15.b Kaplan Meier curve stratified by dementia in different EF categories**

Immagine che contiene testo, schermata, linea, diagramma

Descrizione generata automaticamente

**Supplementary Figure 16.a Kaplan Meier curve stratified by history of cancer ( within 3 years)**

Immagine che contiene testo, schermata, linea, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 16.b Kaplan Meier curve stratified by history of cancer (within 3 years) in different EF categories**

Immagine che contiene testo, schermata, numero, linea

Descrizione generata automaticamente

**Supplementary Figure 17.a Kaplan Meier curve stratified by muscoloskeletal disease**

Immagine che contiene testo, linea, schermata, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 17.b Kaplan Meier curve stratified by muscoloskeletal disease in different EF categories**

Immagine che contiene testo, schermata, linea, Carattere

Descrizione generata automaticamente

**Supplementary Figure 18.a Kaplan Meier curve stratified by dysthyroidism**

Immagine che contiene testo, linea, schermata, Diagramma

Descrizione generata automaticamente

**Supplementary Figure 18.b Kaplan Meier curve stratified by dysthyroidism in different EF categories**

Immagine che contiene testo, schermata, linea, numero

Descrizione generata automaticamente

**Supplementary Tables**

**Supplementary Table 1. Definition of comorbidities and sources**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Comorbidity** | **Definition** | **Source** | **Time period** | **Position of ICD codes** |
| Obesity | BMI>30Kg/m2 | SwedeHF | Baseline registration | - |
| Hypertension | ICD-10 codes:I10-I15 | National Patient Register | Within 5 years | All |
| Diabetes | ICD-10 codes: E10-E14 | National Patient Register | Within 5 years | All |
| CAD | ICD-10 codes: 410-1, I20-5 | National Patient Register | Within 5 years | All |
| AF | ICD-10 code: I48 | National Patient Register | Within 5 years | All |
| VHD | Diagnosis in SwedeHF or in NPR (ICD-10 codes: A520, I05-I08, I091, I098, I34-I39, Q230-Q233, Z952, Z954) | SwedeHF and National Patient Register | Within 5 years | All |
| CKD | estimated GFR (eGFR) <60 mL/min/1.73 m2 (according to CKD-EPI 2021)a | SwedeHF | Baseline registration | - |
| Anaemia | haemoglobin <13 g/L (8.1 mmol/L) in men and <12 g/L (7.5 mmol/L) in non-pregnant women | SwedeHF | Baseline registration | - |
| COPD | ICD-10 codes: J40-4 | National Patient Register | Within 5 years | All |
| Liver disease | ICD-10 codes: B18, I85, I864, I982, K70, K710, K711, K713-7, K72-4, K760, K762-9 | National Patient Register | Within 5 years | All |
| PAD | ICD:I70-3 | National Patient Register | Within 5 years | All |
| Stroke or TIA | ICD-9 codes: 430-4, 438; ICD-10 codes: I60-4, I690-4, G45 | National Patient Register | Within 5 years | All |
| Depression | ICD-10 codes: F32,F33 | National Patient Register | Within 5 years | All |
| Dementia | ICD-10 codes: F00-F03 | National Patient Register | Within 5 years | All |
| Cancer <3years | ICD-10 codes: C | National Patient Register | Within 3 years | All |
| Muscolo-skeletal <3years | ICD-10 codes: M00-M99 | National Patient Register | Within 3 years | All |
| Dysthyroidism | ICD codes: E00-E07 | National Patient Register | Within 5 years | All |

aInker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, Grams ME, Greene T, Grubb A, Gudnason V, Gutiérrez OM, Kalil R, Karger AB, Mauer M, Navis G, Nelson RG, Poggio ED, Rodby R, Rossing P, Rule AD, Selvin E, Seegmiller JC, Shlipak MG, Torres VE, Yang W, Ballew SH, Couture SJ, Powe NR, Levey AS; Chronic Kidney Disease Epidemiology Collaboration. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385:1737-1749.

**Supplementary Table 2. Baseline characteristics of the whole study population and stratified by EF categories (HFrEF, HFmrEF and HFpEF).**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Missing (%)** | **Level** | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-value** |
| N |  |  | 91463 | 49589 (54%) | 20921 (23%) | 20953 (23%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |
| Sex | 0 | Female | 33334 (36.4%) | 14369 (29.0%) | 7905 (37.8%) | 11060 (52.8%) | <0.001 |
|  |  | Male | 58129 (63.6%) | 35220 (71.0%) | 13016 (62.2%) | 9893 (47.2%) |  |
| Age, median (IQR) | 0 |  | 76 (67, 82) | 73 (64, 81) | 76 (68, 83) | 80 (73, 85) | <0.001 |
| Family type | 0.1 | Cohabitating | 47512 (52.0%) | 26785 (54.1%) | 11186 (53.5%) | 9541 (45.6%) | <0.001 |
|  |  | Living alone | 43823 (48.0%) | 22711 (45.9%) | 9714 (46.5%) | 11398 (54.4%) |  |
| Smoking | 19 |  | 8554 (11.9%) | 5638 (14.0%) | 1709 (10.3%) | 1207 (7.9%) | <0.001 |
| Alcohol user | 38 |  | 2687 (4.8%) | 1719 (5.3%) | 567 (4.4%) | 401 (3.6%) | <0.001 |
| Location of care | 0 | Out-patient | 50100 (54.8%) | 28499 (57.5%) | 12409 (59.3%) | 9192 (43.9%) | <0.001 |
|  |  | In-patient | 41363 (45.2%) | 21090 (42.5%) | 8512 (40.7%) | 11761 (56.1%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months | 0 |  | 57671 (63.1%) | 32306 (65.1%) | 11268 (53.9%) | 14097 (67.3%) | <0.001 |
| Duration of HF | 2.4 | <6mo | 47622 (53.3%) | 27673 (56.9%) | 10518 (51.5%) | 9431 (46.6%) | <0.001 |
|  |  | >=6mo | 41660 (46.7%) | 20970 (43.1%) | 9901 (48.5%) | 10789 (53.4%) |  |
| Follow-up location | 4.1 | Primary care | 28126 (32.1%) | 10747 (22.5%) | 7268 (36.1%) | 10111 (51.1%) | <0.001 |
|  |  | Hospital | 59598 (67.9%) | 37080 (77.5%) | 12841 (63.9%) | 9677 (48.9%) |  |
| NYHA functional class | 27.5 | I-II | 40079 (60.4%) | 21716 (57.2%) | 10499 (68.4%) | 7864 (60.4%) | <0.001 |
|  |  | III-IV | 26263 (39.6%) | 16273 (42.8%) | 4841 (31.6%) | 5149 (39.6%) |  |
| BMI, median (IQR) | 0 |  | 26 (23, 30) | 26 (23, 30) | 27 (24, 30) | 27 (24, 31) | <0.001 |
| SBP, median (IQR) | 0.8 |  | 125 (111, 140) | 120 (110, 138) | 130 (115, 140) | 130 (120, 145) | <0.001 |
| DBP, median (IQR) | 0.7 |  | 72 (65, 80) | 71 (65, 80) | 74 (65, 80) | 71 (65, 80) | <0.001 |
| MAP, median (IQR) | 0.7 |  | 90 (82, 100) | 90 (81, 99) | 92 (83, 100) | 93 (83, 101) | <0.001 |
| Heart rate, median (IQR) | 3.4 |  | 72 (63, 82) | 72 (64, 84) | 70 (62, 81) | 72 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |
| eGFR, median (IQR) | 0 |  | 67 (49, 86) | 69 (51, 87) | 67 (50, 86) | 61 (45, 80) | <0.001 |
| Potassium categories | 19 | Normakalemia | 68693 (92.8%) | 37193 (93.3%) | 16072 (93.0%) | 15428 (91.4%) | <0.001 |
|  |  | Hypokalemia | 3275 (4.4%) | 1494 (3.7%) | 758 (4.4%) | 1023 (6.1%) |  |
|  |  | Hyperkalemia | 2056 (2.8%) | 1185 (3.0%) | 451 (2.6%) | 420 (2.5%) |  |
| Haemoglobin, median (IQR) | 0 |  | 133 (120, 145) | 135 (123, 147) | 132 (120, 144) | 127 (115, 139) | <0.001 |
| NT-proBNP, median (IQR) | 42.3 |  | 2300 (1005, 5119) | 2730 (1184, 6123) | 1880 (762, 4126) | 2007 (920, 4088) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI | 1.1 |  | 77270 (85.4%) | 44924 (91.6%) | 17576 (84.8%) | 14770 (71.3%) | <0.001 |
| Beta-blockers | 0.3 |  | 80628 (88.4%) | 45530 (92.0%) | 18168 (87.0%) | 16930 (81.1%) | <0.001 |
| MRA | 0.5 |  | 32075 (35.2%) | 19757 (40.0%) | 5892 (28.3%) | 6426 (30.9%) | <0.001 |
| Diuretics | 0.3 |  | 69378 (76.1%) | 37525 (75.9%) | 14506 (69.5%) | 17347 (83.1%) | <0.001 |
| Digoxin | 0.3 |  | 12170 (13.4%) | 6778 (13.7%) | 2495 (12.0%) | 2897 (13.9%) | <0.001 |
| Antiplatelet therapy | 0.4 |  | 38029 (41.7%) | 21923 (44.4%) | 8895 (42.7%) | 7211 (34.6%) | <0.001 |
| Anticoagulant therapy | 0.4 |  | 42363 (46.5%) | 22092 (44.7%) | 9740 (46.7%) | 10531 (50.5%) | <0.001 |
| Statins | 0.3 |  | 44335 (48.6%) | 24828 (50.2%) | 10667 (51.1%) | 8840 (42.3%) | <0.001 |
| Nitrates | 0.4 |  | 11585 (12.7%) | 5740 (11.6%) | 2718 (13.0%) | 3127 (15.0%) | <0.001 |
| HF devices | 1.4 |  | 4938 (5.5%) | 3979 (8.1%) | 661 (3.2%) | 298 (1.5%) | <0.001 |
| **Comorbidities** |  |  |  |  |  |  |  |
| Obesity | 0 |  | 23971 (26.2%) | 11719 (23.6%) | 5822 (27.8%) | 6430 (30.7%) | <0.001 |
| Hypertension | 0 |  | 59383 (64.9%) | 29092 (58.7%) | 14212 (67.9%) | 16079 (76.7%) | <0.001 |
| Diabetes | 0 |  | 23830 (26.1%) | 12628 (25.5%) | 5281 (25.2%) | 5921 (28.3%) | <0.001 |
| CAD | 0 |  | 47933 (52.4%) | 26679 (53.8%) | 11591 (55.4%) | 9663 (46.1%) | <0.001 |
| AF | 0 |  | 51261 (56.0%) | 25313 (51.0%) | 12127 (58.0%) | 13821 (66.0%) | <0.001 |
| VHD | 0 |  | 24373 (26.6%) | 11560 (23.3%) | 5580 (26.7%) | 7233 (34.5%) | <0.001 |
| CKD | 0 |  | 36579 (40.0%) | 18239 (36.8%) | 8223 (39.3%) | 10117 (48.3%) | <0.001 |
| Anaemia | 0 |  | 31188 (34.1%) | 15118 (30.5%) | 7257 (34.7%) | 8813 (42.1%) | <0.001 |
| COPD | 0 |  | 11597 (12.7%) | 5624 (11.3%) | 2647 (12.7%) | 3326 (15.9%) | <0.001 |
| Liver disease | 0 |  | 1916 (2.1%) | 1060 (2.1%) | 379 (1.8%) | 477 (2.3%) | 0.002 |
| PAD | 0 |  | 7916 (8.7%) | 4107 (8.3%) | 1854 (8.9%) | 1955 (9.3%) | <0.001 |
| Stroke or TIA | 0 |  | 14660 (16.0%) | 7402 (14.9%) | 3360 (16.1%) | 3898 (18.6%) | <0.001 |
| Depression | 0 |  | 3262 (3.6%) | 1738 (3.5%) | 702 (3.4%) | 822 (3.9%) | 0.004 |
| Dementia | 0 |  | 1400 (1.5%) | 674 (1.4%) | 292 (1.4%) | 434 (2.1%) | <0.001 |
| Cancer <3years | 0 |  | 11364 (12.4%) | 5663 (11.4%) | 2742 (13.1%) | 2959 (14.1%) | <0.001 |
| Muscolo-skeletal <3years | 0 |  | 28120 (30.7%) | 13438 (27.1%) | 6752 (32.3%) | 7930 (37.8%) | <0.001 |
| Dysthyroidism | 0 |  | 6861 (7.5%) | 3128 (6.3%) | 1578 (7.5%) | 2155 (10.3%) | <0.001 |
| Charlson Comorbidity Index | 0 | 0-1 | 26863 (29.4%) | 15115 (30.5%) | 6072 (29.0%) | 5676 (27.1%) | <0.001 |
|  |  | 2-3 | 35155 (38.4%) | 19428 (39.2%) | 8012 (38.3%) | 7715 (36.8%) |  |
|  |  | 4-7 | 24204 (26.5%) | 12510 (25.2%) | 5586 (26.7%) | 6108 (29.2%) |  |
|  |  | >=8 | 5241 (5.7%) | 2536 (5.1%) | 1251 (6.0%) | 1454 (6.9%) |  |
| N of comorbidities | 0 | 0 | 1690 (1.9%) | 1283 (2.6%) | 282 (1.3%) | 125 (0.6%) | <0.001 |
|  |  | 1 | 6542 (7.2%) | 4628 (9.3%) | 1285 (6.1%) | 629 (3.0%) |  |
|  |  | 2 | 11880 (13.0%) | 7626 (15.4%) | 2600 (12.4%) | 1654 (7.9%) |  |
|  |  | 3 | 15386 (16.8%) | 8884 (17.9%) | 3534 (16.9%) | 2968 (14.2%) |  |
|  |  | 4 | 16573 (18.1%) | 8894 (17.9%) | 3882 (18.6%) | 3797 (18.1%) |  |
|  |  | 5 | 14997 (16.4%) | 7482 (15.1%) | 3479 (16.6%) | 4036 (19.3%) |  |
|  |  | 6 | 11401 (12.5%) | 5283 (10.7%) | 2692 (12.9%) | 3426 (16.4%) |  |
|  |  | 7 | 7304 (8.0%) | 3163 (6.4%) | 1802 (8.6%) | 2339 (11.2%) |  |
|  |  | 8 | 3621 (4.0%) | 1546 (3.1%) | 846 (4.0%) | 1229 (5.9%) |  |
|  |  | 9 | 1469 (1.6%) | 590 (1.2%) | 369 (1.8%) | 510 (2.4%) |  |
|  |  | 10 | 473 (0.5%) | 168 (0.3%) | 125 (0.6%) | 180 (0.9%) |  |
|  |  | 11 | 103 (0.1%) | 37 (0.1%) | 17 (0.1%) | 49 (0.2%) |  |
|  |  | 12 | 21 (<1%) | <10 (<1%) | <10 (<1%) | <10 (<1%) |  |
|  |  | 13 | <5 (<1%) | 0 (0.0%) | <5 (<1%) | <5 (<1%) |  |
| N of CV comorbidities | 0 | 0 | 5735 (6.3%) | 4114 (8.3%) | 1003 (4.8%) | 618 (2.9%) | <0.001 |
|  |  | 1 | 19449 (21.3%) | 12193 (24.6%) | 4068 (19.4%) | 3188 (15.2%) |  |
|  |  | 2 | 29489 (32.2%) | 15655 (31.6%) | 7013 (33.5%) | 6821 (32.6%) |  |
|  |  | 3 | 23211 (25.4%) | 11322 (22.8%) | 5473 (26.2%) | 6416 (30.6%) |  |
|  |  | 4 | 10712 (11.7%) | 4978 (10.0%) | 2680 (12.8%) | 3054 (14.6%) |  |
|  |  | 5 | 2584 (2.8%) | 1190 (2.4%) | 613 (2.9%) | 781 (3.7%) |  |
|  |  | 6 | 283 (0.3%) | 137 (0.3%) | 71 (0.3%) | 75 (0.4%) |  |
| N of non-CV comorbidities | 0 | 0 | 13574 (14.8%) | 8662 (17.5%) | 3010 (14.4%) | 1902 (9.1%) | <0.001 |
|  |  | 1 | 24110 (26.4%) | 14239 (28.7%) | 5488 (26.2%) | 4383 (20.9%) |  |
|  |  | 2 | 23888 (26.1%) | 12858 (25.9%) | 5469 (26.1%) | 5561 (26.5%) |  |
|  |  | 3 | 16771 (18.3%) | 8267 (16.7%) | 3872 (18.5%) | 4632 (22.1%) |  |
|  |  | 4 | 8870 (9.7%) | 3932 (7.9%) | 2040 (9.8%) | 2898 (13.8%) |  |
|  |  | 5 | 3270 (3.6%) | 1298 (2.6%) | 815 (3.9%) | 1157 (5.5%) |  |
|  |  | 6 | 818 (0.9%) | 281 (0.6%) | 194 (0.9%) | 343 (1.6%) |  |
|  |  | 7 | 148 (0.2%) | 48 (0.1%) | 31 (0.1%) | 69 (0.3%) |  |
|  |  | 8 | 11 (<1%) | <5 (<1%) | <5 (<1%) | <10 (<1%) |  |
|  |  | 9 | <5 (<1%) | <5 (<1%) | <5 (<1%) | <5 (<1%) |  |
| Any Comorbidity | 0 |  | 89773 (98.2%) | 48306 (97.4%) | 20639 (98.7%) | 20828 (99.4%) | <0.001 |
| Any CV comorbidity | 0 |  | 85728 (93.7%) | 45475 (91.7%) | 19918 (95.2%) | 20335 (97.1%) | <0.001 |
| Any Non CV comorbidity | 0 |  | 77889 (85.2%) | 40927 (82.5%) | 17911 (85.6%) | 19051 (90.9%) | <0.001 |
| Multimorbidity groups | 0 | No comorbidities | 1690 (1.8%) | 1283 (2.6%) | 282 (1.3%) | 125 (0.6%) | <0.001 |
|  |  | 1 to 3 comorbidities | 33808 (37.0%) | 21138 (42.6%) | 7419 (35.5%) | 5251 (25.1%) |  |
|  |  | 4 to 6 comorbidities | 42971 (47.0%) | 21659 (43.7%) | 10053 (48.1%) | 11259 (53.7%) |  |
|  |  | >6 comorbidities | 12994 (14.2%) | 5509 (11.1%) | 3167 (15.1%) | 4318 (20.6%) |  |
| Non CV multimorbidity groups | 0 | No comorbidities | 13574 (14.8%) | 8662 (17.5%) | 3010 (14.4%) | 1902 (9.1%) | <0.001 |
|  |  | 1 to 3 comorbidities | 64769 (70.8%) | 35364 (71.3%) | 14829 (70.9%) | 14576 (69.6%) |  |
|  |  | 4 to 6 comorbidities | 12958 (14.2%) | 5511 (11.1%) | 3049 (14.6%) | 4398 (21.0%) |  |
|  |  | >6 comorbidities | 162 (0.2%) | 52 (0.1%) | 33 (0.2%) | 77 (0.4%) |  |
| CV multimorbidity groups | 0 | No comorbidities | 5735 (6.3%) | 4114 (8.3%) | 1003 (4.8%) | 618 (2.9%) | <0.001 |
|  |  | 1 to 3 comorbidities | 72149 (78.9%) | 39170 (79.0%) | 16554 (79.1%) | 16425 (78.4%) |  |
|  |  | 4 to 6 comorbidities | 13579 (14.8%) | 6305 (12.7%) | 3364 (16.1%) | 3910 (18.7%) |  |

**Supplementary Table 3. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by obesity.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  | | | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 67492 (74%) | 23971 (26%) |  | 37870 (76%) | 11719 (24%) | 15099 (72%) | 5822 (28%) | 14523 (69%) | 6430 (31%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 24152 (35.8%) | 9182 (38.3%) | <0.001 | 10958 (28.9%) | 3411 (29.1%) | 5627 (37.3%) | 2278 (39.1%) | 7567 (52.1%) | 3493 (54.3%) | <0.001 |
|  | Male | 43340 (64.2%) | 14789 (61.7%) |  | 26912 (71.1%) | 8308 (70.9%) | 9472 (62.7%) | 3544 (60.9%) | 6956 (47.9%) | 2937 (45.7%) |  |
| Age, median (IQR) |  | 77 (68, 83) | 72 (63, 79) | <0.001 | 75 (66, 82) | 68 (59, 76) | 78 (69, 84) | 72 (64, 79) | 81 (75, 86) | 76 (69, 82) | <0.001 |
| Family type | Cohabitating | 35245 (52.3%) | 12267 (51.2%) | 0.005 | 20531 (54.3%) | 6254 (53.4%) | 8112 (53.8%) | 3074 (52.9%) | 6602 (45.5%) | 2939 (45.7%) | <0.001 |
|  | Living alone | 32146 (47.7%) | 11677 (48.8%) |  | 17262 (45.7%) | 5449 (46.6%) | 6973 (46.2%) | 2741 (47.1%) | 7911 (54.5%) | 3487 (54.3%) |  |
| Smoking |  | 6538 (12.3%) | 2016 (10.6%) | <0.001 | 4448 (14.5%) | 1190 (12.3%) | 1237 (10.4%) | 472 (10.2%) | 853 (8.1%) | 354 (7.5%) | <0.001 |
| Alcohol user |  | 1864 (4.5%) | 823 (5.5%) | <0.001 | 1262 (5.2%) | 457 (5.7%) | 365 (3.9%) | 202 (5.5%) | 237 (3.1%) | 164 (4.7%) | <0.001 |
| Location of care | Out-patient | 36234 (53.7%) | 13866 (57.8%) | <0.001 | 21224 (56.0%) | 7275 (62.1%) | 8823 (58.4%) | 3586 (61.6%) | 6187 (42.6%) | 3005 (46.7%) | <0.001 |
|  | In-patient | 31258 (46.3%) | 10105 (42.2%) |  | 16646 (44.0%) | 4444 (37.9%) | 6276 (41.6%) | 2236 (38.4%) | 8336 (57.4%) | 3425 (53.3%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 43129 (63.9%) | 14542 (60.7%) | <0.001 | 25029 (66.1%) | 7277 (62.1%) | 8206 (54.3%) | 3062 (52.6%) | 9894 (68.1%) | 4203 (65.4%) | <0.001 |
| Duration of HF | <6mo | 35670 (54.1%) | 11952 (51.2%) | <0.001 | 21257 (57.2%) | 6416 (55.9%) | 7775 (52.7%) | 2743 (48.3%) | 6638 (47.4%) | 2793 (45.0%) | <0.001 |
|  | >=6mo | 30252 (45.9%) | 11408 (48.8%) |  | 15912 (42.8%) | 5058 (44.1%) | 6966 (47.3%) | 2935 (51.7%) | 7374 (52.6%) | 3415 (55.0%) |  |
| Follow-up location | Primary care | 21044 (32.5%) | 7082 (30.8%) | <0.001 | 8706 (23.9%) | 2041 (18.0%) | 5264 (36.3%) | 2004 (35.7%) | 7074 (51.5%) | 3037 (50.1%) | <0.001 |
|  | Hospital | 43650 (67.5%) | 15948 (69.2%) |  | 27767 (76.1%) | 9313 (82.0%) | 9232 (63.7%) | 3609 (64.3%) | 6651 (48.5%) | 3026 (49.9%) |  |
| NYHA functional class | I-II | 30065 (61.6%) | 10014 (57.2%) | <0.001 | 16745 (58.1%) | 4971 (54.3%) | 7753 (70.3%) | 2746 (63.6%) | 5567 (62.1%) | 2297 (56.8%) | <0.001 |
|  | III-IV | 18758 (38.4%) | 7505 (42.8%) |  | 12087 (41.9%) | 4186 (45.7%) | 3268 (29.7%) | 1573 (36.4%) | 3403 (37.9%) | 1746 (43.2%) |  |
| BMI, median (IQR) |  | 25 (22, 27) | 33 (31, 36) | <0.001 | 25 (22, 27) | 33 (31, 36) | 25 (23, 27) | 33 (31, 36) | 25 (22, 27) | 34 (32, 37) | <0.001 |
| SBP, median (IQR) |  | 125 (110, 140) | 130 (115, 140) | <0.001 | 120 (110, 136) | 125 (110, 140) | 130 (115, 140) | 130 (120, 143) | 130 (118, 145) | 130 (120, 145) | <0.001 |
| DBP, median (IQR) |  | 70 (65, 80) | 75 (69, 82) | <0.001 | 70 (65, 80) | 75 (70, 84) | 71 (65, 80) | 75 (70, 83) | 70 (65, 80) | 75 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (82, 100) | 93 (84, 102) | <0.001 | 89 (80, 98) | 93 (83, 101) | 92 (83, 100) | 93 (86, 103) | 92 (83, 100) | 93 (85, 102) | <0.001 |
| Heart rate, median (IQR) |  | 71 (63, 82) | 73 (64, 84) | <0.001 | 72 (63, 83) | 74 (65, 85) | 70 (62, 80) | 72 (63, 82) | 71 (63, 82) | 72 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 66 (49, 85) | 69 (50, 88) | <0.001 | 68 (50, 86) | 73 (53, 91) | 67 (49, 85) | 68 (50, 88) | 61 (45, 79) | 62 (44, 81) | <0.001 |
| Potassium categories | Normakalemia | 50061 (92.6%) | 18632 (93.3%) | 0.006 | 27983 (93.1%) | 9210 (93.9%) | 11508 (92.9%) | 4564 (93.3%) | 10570 (91.2%) | 4858 (92.0%) | <0.001 |
|  | Hypokalemia | 2467 (4.6%) | 808 (4.0%) |  | 1171 (3.9%) | 323 (3.3%) | 558 (4.5%) | 200 (4.1%) | 738 (6.4%) | 285 (5.4%) |  |
|  | Hyperkalemia | 1517 (2.8%) | 539 (2.7%) |  | 913 (3.0%) | 272 (2.8%) | 322 (2.6%) | 129 (2.6%) | 282 (2.4%) | 138 (2.6%) |  |
| Haemoglobin, median (IQR) |  | 132 (119, 144) | 136 (123, 148) | <0.001 | 134 (122, 146) | 140 (127, 151) | 131 (119, 143) | 135 (122, 147) | 126 (114, 138) | 129 (117, 141) | <0.001 |
| NT-proBNP, median (IQR) |  | 2707 (1194, 5940) | 1540 (693, 3240) | <0.001 | 3180 (1400, 7015) | 1700 (756, 3665) | 2160 (870, 4650) | 1350 (586, 2876) | 2315 (1081, 4700) | 1453 (694, 2943) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 56440 (84.6%) | 20830 (87.8%) | <0.001 | 34022 (90.9%) | 10902 (94.0%) | 12493 (83.5%) | 5083 (88.2%) | 9925 (69.2%) | 4845 (76.2%) | <0.001 |
| Beta-blockers |  | 59128 (87.8%) | 21500 (89.9%) | <0.001 | 34536 (91.4%) | 10994 (94.0%) | 12994 (86.3%) | 5174 (89.0%) | 11598 (80.2%) | 5332 (83.2%) | <0.001 |
| MRA |  | 22801 (34.0%) | 9274 (38.9%) | <0.001 | 14492 (38.4%) | 5265 (45.1%) | 4050 (26.9%) | 1842 (31.8%) | 4259 (29.5%) | 2167 (33.8%) | <0.001 |
| DIuretics |  | 50186 (74.6%) | 19192 (80.3%) | <0.001 | 28298 (75.0%) | 9227 (79.0%) | 10128 (67.3%) | 4378 (75.4%) | 11760 (81.3%) | 5587 (87.1%) | <0.001 |
| Digoxin |  | 9302 (13.8%) | 2868 (12.0%) | <0.001 | 5254 (13.9%) | 1524 (13.1%) | 1855 (12.3%) | 640 (11.0%) | 2193 (15.2%) | 704 (11.0%) | <0.001 |
| Antiplatelet therapy |  | 29005 (43.1%) | 9024 (37.8%) | <0.001 | 17268 (45.8%) | 4655 (39.8%) | 6573 (43.7%) | 2322 (40.0%) | 5164 (35.7%) | 2047 (32.0%) | <0.001 |
| Anticoagulant therapy |  | 30335 (45.1%) | 12028 (50.3%) | <0.001 | 16392 (43.4%) | 5700 (48.8%) | 6852 (45.5%) | 2888 (49.8%) | 7091 (49.1%) | 3440 (53.7%) | <0.001 |
| Statins |  | 31472 (46.8%) | 12863 (53.8%) | <0.001 | 18456 (48.9%) | 6372 (54.5%) | 7412 (49.2%) | 3255 (56.1%) | 5604 (38.7%) | 3236 (50.5%) | <0.001 |
| Nitrates |  | 8643 (12.9%) | 2942 (12.3%) | 0.029 | 4512 (12.0%) | 1228 (10.5%) | 1966 (13.1%) | 752 (13.0%) | 2165 (15.0%) | 962 (15.0%) | <0.001 |
| HF devices |  | 3574 (5.4%) | 1364 (5.8%) | 0.018 | 2890 (7.7%) | 1089 (9.4%) | 477 (3.2%) | 184 (3.2%) | 207 (1.5%) | 91 (1.4%) | <0.001 |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 0 (0.0%) | 23971 (100.0%) | <0.001 | 0 (0.0%) | 11719 (100.0%) | 0 (0.0%) | 5822 (100.0%) | 0 (0.0%) | 6430 (100.0%) | <0.001 |
| Hypertension |  | 41604 (61.6%) | 17779 (74.2%) | <0.001 | 21222 (56.0%) | 7870 (67.2%) | 9744 (64.5%) | 4468 (76.7%) | 10638 (73.2%) | 5441 (84.6%) | <0.001 |
| Diabetes |  | 14430 (21.4%) | 9400 (39.2%) | <0.001 | 8202 (21.7%) | 4426 (37.8%) | 3063 (20.3%) | 2218 (38.1%) | 3165 (21.8%) | 2756 (42.9%) | <0.001 |
| CAD |  | 36190 (53.6%) | 11743 (49.0%) | <0.001 | 20915 (55.2%) | 5764 (49.2%) | 8465 (56.1%) | 3126 (53.7%) | 6810 (46.9%) | 2853 (44.4%) | <0.001 |
| AF |  | 37616 (55.7%) | 13645 (56.9%) | 0.001 | 19239 (50.8%) | 6074 (51.8%) | 8707 (57.7%) | 3420 (58.7%) | 9670 (66.6%) | 4151 (64.6%) | <0.001 |
| VHD |  | 19493 (28.9%) | 4880 (20.4%) | <0.001 | 9526 (25.2%) | 2034 (17.4%) | 4382 (29.0%) | 1198 (20.6%) | 5585 (38.5%) | 1648 (25.6%) | <0.001 |
| CKD |  | 27409 (40.6%) | 9170 (38.3%) | <0.001 | 14358 (37.9%) | 3881 (33.1%) | 6014 (39.8%) | 2209 (37.9%) | 7037 (48.5%) | 3080 (47.9%) | <0.001 |
| Anaemia |  | 24428 (36.2%) | 6760 (28.2%) | <0.001 | 12443 (32.9%) | 2675 (22.8%) | 5589 (37.0%) | 1668 (28.6%) | 6396 (44.0%) | 2417 (37.6%) | <0.001 |
| COPD |  | 8342 (12.4%) | 3255 (13.6%) | <0.001 | 4269 (11.3%) | 1355 (11.6%) | 1872 (12.4%) | 775 (13.3%) | 2201 (15.2%) | 1125 (17.5%) | <0.001 |
| Liver disease |  | 1421 (2.1%) | 495 (2.1%) | 0.71 | 833 (2.2%) | 227 (1.9%) | 284 (1.9%) | 95 (1.6%) | 304 (2.1%) | 173 (2.7%) | <0.001 |
| PAD |  | 6241 (9.2%) | 1675 (7.0%) | <0.001 | 3375 (8.9%) | 732 (6.2%) | 1419 (9.4%) | 435 (7.5%) | 1447 (10.0%) | 508 (7.9%) | <0.001 |
| Stroke or TIA |  | 11312 (16.8%) | 3348 (14.0%) | <0.001 | 5956 (15.7%) | 1446 (12.3%) | 2529 (16.7%) | 831 (14.3%) | 2827 (19.5%) | 1071 (16.7%) | <0.001 |
| Depression |  | 2275 (3.4%) | 987 (4.1%) | <0.001 | 1267 (3.3%) | 471 (4.0%) | 465 (3.1%) | 237 (4.1%) | 543 (3.7%) | 279 (4.3%) | <0.001 |
| Dementia |  | 1158 (1.7%) | 242 (1.0%) | <0.001 | 591 (1.6%) | 83 (0.7%) | 228 (1.5%) | 64 (1.1%) | 339 (2.3%) | 95 (1.5%) | <0.001 |
| Cancer <3years |  | 9091 (13.5%) | 2273 (9.5%) | <0.001 | 4659 (12.3%) | 1004 (8.6%) | 2159 (14.3%) | 583 (10.0%) | 2273 (15.7%) | 686 (10.7%) | <0.001 |
| Muscolo-skeletal <3years |  | 19987 (29.6%) | 8133 (33.9%) | <0.001 | 10005 (26.4%) | 3433 (29.3%) | 4721 (31.3%) | 2031 (34.9%) | 5261 (36.2%) | 2669 (41.5%) | <0.001 |
| Dysthyroidism |  | 4967 (7.4%) | 1894 (7.9%) | 0.006 | 2397 (6.3%) | 731 (6.2%) | 1103 (7.3%) | 475 (8.2%) | 1467 (10.1%) | 688 (10.7%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 19096 (28.3%) | 7767 (32.4%) | <0.001 | 10889 (28.8%) | 4226 (36.1%) | 4305 (28.5%) | 1767 (30.4%) | 3902 (26.9%) | 1774 (27.6%) | <0.001 |
|  | 2-3 | 26662 (39.5%) | 8493 (35.4%) |  | 15298 (40.4%) | 4130 (35.2%) | 5895 (39.0%) | 2117 (36.4%) | 5469 (37.7%) | 2246 (34.9%) |  |
|  | 4-7 | 17942 (26.6%) | 6262 (26.1%) |  | 9749 (25.7%) | 2761 (23.6%) | 4019 (26.6%) | 1567 (26.9%) | 4174 (28.7%) | 1934 (30.1%) |  |
|  | >=8 | 3792 (5.6%) | 1449 (6.0%) |  | 1934 (5.1%) | 602 (5.1%) | 880 (5.8%) | 371 (6.4%) | 978 (6.7%) | 476 (7.4%) |  |

**Supplementary Table 4. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by hypertension.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** |  | **HFmrEF** |  | **HFpEF** |  |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 32080 (35%) | 59383 (65%) |  | 20497 (41%) | 29092 (59%) | 6709 (32%) | 14212 (68%) | 4874 (23%) | 16079 (77%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 10480 (32.7%) | 22854 (38.5%) | <0.001 | 5683 (27.7%) | 8686 (29.9%) | 2343 (34.9%) | 5562 (39.1%) | 2454 (50.3%) | 8606 (53.5%) | <0.001 |
|  | Male | 21600 (67.3%) | 36529 (61.5%) |  | 14814 (72.3%) | 20406 (70.1%) | 4366 (65.1%) | 8650 (60.9%) | 2420 (49.7%) | 7473 (46.5%) |  |
| Age, median (IQR) |  | 72 (62, 81) | 77 (69, 83) | <0.001 | 70 (61, 79) | 75 (67, 81) | 73 (62, 81) | 77 (70, 83) | 78 (69, 85) | 80 (73, 85) | <0.001 |
| Family type | Cohabitating | 17173 (53.7%) | 30339 (51.1%) | <0.001 | 11174 (54.7%) | 15611 (53.7%) | 3767 (56.3%) | 7419 (52.2%) | 2232 (45.9%) | 7309 (45.5%) | <0.001 |
|  | Living alone | 14824 (46.3%) | 28999 (48.9%) |  | 9264 (45.3%) | 13447 (46.3%) | 2928 (43.7%) | 6786 (47.8%) | 2632 (54.1%) | 8766 (54.5%) |  |
| Smoking |  | 3801 (14.7%) | 4753 (10.3%) | <0.001 | 2764 (16.4%) | 2874 (12.2%) | 673 (12.4%) | 1036 (9.3%) | 364 (10.3%) | 843 (7.2%) | <0.001 |
| Alcohol user |  | 1120 (5.6%) | 1567 (4.3%) | <0.001 | 823 (6.2%) | 896 (4.7%) | 200 (4.7%) | 367 (4.2%) | 97 (3.9%) | 304 (3.5%) | <0.001 |
| Location of care | Out-patient | 18057 (56.3%) | 32043 (54.0%) | <0.001 | 11719 (57.2%) | 16780 (57.7%) | 4235 (63.1%) | 8174 (57.5%) | 2103 (43.1%) | 7089 (44.1%) | <0.001 |
|  | In-patient | 14023 (43.7%) | 27340 (46.0%) |  | 8778 (42.8%) | 12312 (42.3%) | 2474 (36.9%) | 6038 (42.5%) | 2771 (56.9%) | 8990 (55.9%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 19903 (62.0%) | 37768 (63.6%) | <0.001 | 13376 (65.3%) | 18930 (65.1%) | 3262 (48.6%) | 8006 (56.3%) | 3265 (67.0%) | 10832 (67.4%) | <0.001 |
| Duration of HF | <6mo | 18794 (59.6%) | 28828 (49.9%) | <0.001 | 12623 (62.5%) | 15050 (52.9%) | 3803 (57.7%) | 6715 (48.6%) | 2368 (50.0%) | 7063 (45.6%) | <0.001 |
|  | >=6mo | 12718 (40.4%) | 28942 (50.1%) |  | 7559 (37.5%) | 13411 (47.1%) | 2791 (42.3%) | 7110 (51.4%) | 2368 (50.0%) | 8421 (54.4%) |  |
| Follow-up location | Primary care | 7985 (25.9%) | 20141 (35.4%) | <0.001 | 3958 (20.0%) | 6789 (24.2%) | 1887 (29.2%) | 5381 (39.4%) | 2140 (46.4%) | 7971 (52.5%) | <0.001 |
|  | Hospital | 22897 (74.1%) | 36701 (64.6%) |  | 15853 (80.0%) | 21227 (75.8%) | 4573 (70.8%) | 8268 (60.6%) | 2471 (53.6%) | 7206 (47.5%) |  |
| NYHA functional class | I-II | 15560 (64.2%) | 24519 (58.2%) | <0.001 | 9678 (60.7%) | 12038 (54.6%) | 3857 (74.4%) | 6642 (65.4%) | 2025 (64.9%) | 5839 (59.0%) | <0.001 |
|  | III-IV | 8684 (35.8%) | 17579 (41.8%) |  | 6260 (39.3%) | 10013 (45.4%) | 1330 (25.6%) | 3511 (34.6%) | 1094 (35.1%) | 4055 (41.0%) |  |
| BMI, median (IQR) |  | 25 (23, 29) | 27 (24, 31) | <0.001 | 25 (23, 29) | 27 (24, 30) | 26 (23, 29) | 27 (24, 31) | 26 (22, 29) | 27 (24, 32) | <0.001 |
| SBP, median (IQR) |  | 120 (109, 130) | 130 (118, 144) | <0.001 | 118 (105, 130) | 127 (114, 140) | 120 (110, 135) | 130 (120, 145) | 120 (110, 136) | 134 (120, 150) | <0.001 |
| DBP, median (IQR) |  | 70 (63, 80) | 75 (65, 80) | <0.001 | 70 (63, 80) | 75 (65, 80) | 70 (65, 80) | 75 (66, 80) | 70 (60, 80) | 73 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 87 (80, 96) | 93 (83, 102) | <0.001 | 87 (78, 95) | 92 (83, 100) | 88 (80, 97) | 93 (85, 103) | 88 (80, 97) | 93 (85, 103) | <0.001 |
| Heart rate, median (IQR) |  | 72 (62, 83) | 72 (63, 82) | 0.25 | 72 (63, 84) | 72 (64, 83) | 70 (61, 80) | 71 (62, 81) | 72 (63, 82) | 71 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 74 (56, 91) | 63 (46, 82) | <0.001 | 75 (58, 91) | 65 (47, 84) | 76 (58, 92) | 63 (47, 82) | 68 (51, 87) | 59 (43, 77) | <0.001 |
| Potassium categories | Normakalemia | 23214 (94.3%) | 45479 (92.0%) | <0.001 | 14880 (94.4%) | 22313 (92.5%) | 4985 (94.8%) | 11087 (92.2%) | 3349 (93.1%) | 12079 (91.0%) | <0.001 |
|  | Hypokalemia | 779 (3.2%) | 2496 (5.1%) |  | 446 (2.8%) | 1048 (4.3%) | 157 (3.0%) | 601 (5.0%) | 176 (4.9%) | 847 (6.4%) |  |
|  | Hyperkalemia | 617 (2.5%) | 1439 (2.9%) |  | 429 (2.7%) | 756 (3.1%) | 117 (2.2%) | 334 (2.8%) | 71 (2.0%) | 349 (2.6%) |  |
| Haemoglobin, median (IQR) |  | 135 (123, 147) | 131 (119, 144) | <0.001 | 137 (125, 148) | 134 (121, 146) | 135 (122, 146) | 131 (119, 143) | 129 (117, 141) | 127 (115, 139) | <0.001 |
| NT-proBNP, median (IQR) |  | 2130 (875, 4680) | 2392 (1069, 5340) | <0.001 | 2480 (1075, 5390) | 2901 (1260, 6660) | 1426 (522, 3239) | 2060 (879, 4473) | 1825 (730, 3838) | 2055 (980, 4129) | <0.001 |
| **Treatments** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 27299 (86.1%) | 49971 (85.0%) | <0.001 | 18714 (92.4%) | 26210 (91.0%) | 5586 (84.1%) | 11990 (85.1%) | 2999 (62.4%) | 11771 (74.0%) | <0.001 |
| Beta-blockers |  | 27864 (87.1%) | 52764 (89.1%) | <0.001 | 18624 (91.1%) | 26906 (92.7%) | 5629 (84.1%) | 12539 (88.4%) | 3611 (74.5%) | 13319 (83.2%) | <0.001 |
| MRA |  | 10614 (33.2%) | 21461 (36.3%) | <0.001 | 7590 (37.2%) | 12167 (42.0%) | 1573 (23.5%) | 4319 (30.5%) | 1451 (29.9%) | 4975 (31.1%) | <0.001 |
| DIuretics |  | 22121 (69.2%) | 47257 (79.8%) | <0.001 | 14521 (71.1%) | 23004 (79.3%) | 3865 (57.7%) | 10641 (75.1%) | 3735 (76.9%) | 13612 (85.0%) | <0.001 |
| Digoxin |  | 4846 (15.2%) | 7324 (12.4%) | <0.001 | 3130 (15.3%) | 3648 (12.6%) | 860 (12.9%) | 1635 (11.5%) | 856 (17.6%) | 2041 (12.7%) | <0.001 |
| Antiplatelet therapy |  | 12902 (40.4%) | 25127 (42.5%) | <0.001 | 8502 (41.6%) | 13421 (46.3%) | 2802 (41.9%) | 6093 (43.0%) | 1598 (32.9%) | 5613 (35.1%) | <0.001 |
| Anticoagulant therapy |  | 13890 (43.4%) | 28473 (48.1%) | <0.001 | 8848 (43.3%) | 13244 (45.7%) | 2798 (41.8%) | 6942 (49.0%) | 2244 (46.2%) | 8287 (51.8%) | <0.001 |
| Statins |  | 12762 (39.9%) | 31573 (53.3%) | <0.001 | 8514 (41.7%) | 16314 (56.2%) | 2849 (42.5%) | 7818 (55.2%) | 1399 (28.8%) | 7441 (46.4%) | <0.001 |
| Nitrates |  | 2976 (9.3%) | 8609 (14.6%) | <0.001 | 1808 (8.9%) | 3932 (13.6%) | 612 (9.2%) | 2106 (14.9%) | 556 (11.5%) | 2571 (16.1%) | <0.001 |
| HF devices |  | 2097 (6.6%) | 2841 (4.9%) | <0.001 | 1724 (8.5%) | 2255 (7.8%) | 269 (4.1%) | 392 (2.8%) | 104 (2.2%) | 194 (1.2%) | <0.001 |
| EF categories | HFrEF | 20497 (63.9%) | 29092 (49.0%) | <0.001 | 20497 (100.0%) | 29092 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 6709 (20.9%) | 14212 (23.9%) |  | 0 (0.0%) | 0 (0.0%) | 6709 (100.0%) | 14212 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 4874 (15.2%) | 16079 (27.1%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4874 (100.0%) | 16079 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 6192 (19.3%) | 17779 (29.9%) | <0.001 | 3849 (18.8%) | 7870 (27.1%) | 1354 (20.2%) | 4468 (31.4%) | 989 (20.3%) | 5441 (33.8%) | <0.001 |
| Hypertension |  | 0 (0.0%) | 59383 (100.0%) | <0.001 | 0 (0.0%) | 29092 (100.0%) | 0 (0.0%) | 14212 (100.0%) | 0 (0.0%) | 16079 (100.0%) | <0.001 |
| Diabetes |  | 4499 (14.0%) | 19331 (32.6%) | <0.001 | 3012 (14.7%) | 9616 (33.1%) | 816 (12.2%) | 4465 (31.4%) | 671 (13.8%) | 5250 (32.7%) | <0.001 |
| CAD |  | 14648 (45.7%) | 33285 (56.1%) | <0.001 | 9480 (46.3%) | 17199 (59.1%) | 3265 (48.7%) | 8326 (58.6%) | 1903 (39.0%) | 7760 (48.3%) | <0.001 |
| AF |  | 16306 (50.8%) | 34955 (58.9%) | <0.001 | 9688 (47.3%) | 15625 (53.7%) | 3516 (52.4%) | 8611 (60.6%) | 3102 (63.6%) | 10719 (66.7%) | <0.001 |
| VHD |  | 8361 (26.1%) | 16012 (27.0%) | 0.003 | 4685 (22.9%) | 6875 (23.6%) | 1757 (26.2%) | 3823 (26.9%) | 1919 (39.4%) | 5314 (33.0%) | <0.001 |
| CKD |  | 9470 (29.5%) | 27109 (45.7%) | <0.001 | 5775 (28.2%) | 12464 (42.8%) | 1842 (27.5%) | 6381 (44.9%) | 1853 (38.0%) | 8264 (51.4%) | <0.001 |
| Anaemia |  | 9484 (29.6%) | 21704 (36.5%) | <0.001 | 5571 (27.2%) | 9547 (32.8%) | 2013 (30.0%) | 5244 (36.9%) | 1900 (39.0%) | 6913 (43.0%) | <0.001 |
| COPD |  | 3603 (11.2%) | 7994 (13.5%) | <0.001 | 2093 (10.2%) | 3531 (12.1%) | 761 (11.3%) | 1886 (13.3%) | 749 (15.4%) | 2577 (16.0%) | <0.001 |
| Liver disease |  | 706 (2.2%) | 1210 (2.0%) | 0.10 | 472 (2.3%) | 588 (2.0%) | 125 (1.9%) | 254 (1.8%) | 109 (2.2%) | 368 (2.3%) | 0.005 |
| PAD |  | 1712 (5.3%) | 6204 (10.4%) | <0.001 | 1067 (5.2%) | 3040 (10.4%) | 364 (5.4%) | 1490 (10.5%) | 281 (5.8%) | 1674 (10.4%) | <0.001 |
| Stroke or TIA |  | 3511 (10.9%) | 11149 (18.8%) | <0.001 | 2143 (10.5%) | 5259 (18.1%) | 692 (10.3%) | 2668 (18.8%) | 676 (13.9%) | 3222 (20.0%) | <0.001 |
| Depression |  | 1067 (3.3%) | 2195 (3.7%) | 0.004 | 670 (3.3%) | 1068 (3.7%) | 215 (3.2%) | 487 (3.4%) | 182 (3.7%) | 640 (4.0%) | 0.003 |
| Dementia |  | 374 (1.2%) | 1026 (1.7%) | <0.001 | 196 (1.0%) | 478 (1.6%) | 76 (1.1%) | 216 (1.5%) | 102 (2.1%) | 332 (2.1%) | <0.001 |
| Cancer <3years |  | 3625 (11.3%) | 7739 (13.0%) | <0.001 | 2103 (10.3%) | 3560 (12.2%) | 849 (12.7%) | 1893 (13.3%) | 673 (13.8%) | 2286 (14.2%) | <0.001 |
| Muscolo-skeletal <3years |  | 8079 (25.2%) | 20041 (33.7%) | <0.001 | 4657 (22.7%) | 8781 (30.2%) | 1828 (27.2%) | 4924 (34.6%) | 1594 (32.7%) | 6336 (39.4%) | <0.001 |
| Dysthyroidism |  | 1873 (5.8%) | 4988 (8.4%) | <0.001 | 1041 (5.1%) | 2087 (7.2%) | 418 (6.2%) | 1160 (8.2%) | 414 (8.5%) | 1741 (10.8%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 12043 (37.5%) | 14820 (25.0%) | <0.001 | 7809 (38.1%) | 7306 (25.1%) | 2518 (37.5%) | 3554 (25.0%) | 1716 (35.2%) | 3960 (24.6%) | <0.001 |
|  | 2-3 | 12818 (40.0%) | 22337 (37.6%) |  | 8285 (40.4%) | 11143 (38.3%) | 2678 (39.9%) | 5334 (37.5%) | 1855 (38.1%) | 5860 (36.4%) |  |
|  | 4-7 | 6086 (19.0%) | 18118 (30.5%) |  | 3707 (18.1%) | 8803 (30.3%) | 1253 (18.7%) | 4333 (30.5%) | 1126 (23.1%) | 4982 (31.0%) |  |
|  | >=8 | 1133 (3.5%) | 4108 (6.9%) |  | 696 (3.4%) | 1840 (6.3%) | 260 (3.9%) | 991 (7.0%) | 177 (3.6%) | 1277 (7.9%) |  |

**Supplementary Table 5. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by diabetes.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 67633 (74%) | 23830 (26%) |  | 36961 (74%) | 12628 (26%) | 15640 (75%) | 5281 (25%) | 15032 (72%) | 5921 (28%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 25264 (37.4%) | 8070 (33.9%) | <0.001 | 11001 (29.8%) | 3368 (26.7%) | 6076 (38.8%) | 1829 (34.6%) | 8187 (54.5%) | 2873 (48.5%) | <0.001 |
|  | Male | 42369 (62.6%) | 15760 (66.1%) |  | 25960 (70.2%) | 9260 (73.3%) | 9564 (61.2%) | 3452 (65.4%) | 6845 (45.5%) | 3048 (51.5%) |  |
| Age, median (IQR) |  | 76 (66, 83) | 75 (67, 81) | <0.001 | 73 (64, 81) | 73 (65, 80) | 76 (67, 83) | 76 (69, 82) | 80 (73, 86) | 78 (71, 83) | <0.001 |
| Family type | Cohabitating | 35230 (52.2%) | 12282 (51.6%) | 0.14 | 20051 (54.4%) | 6734 (53.4%) | 8409 (53.8%) | 2777 (52.6%) | 6770 (45.1%) | 2771 (46.8%) | <0.001 |
|  | Living alone | 32307 (47.8%) | 11516 (48.4%) |  | 16841 (45.6%) | 5870 (46.6%) | 7215 (46.2%) | 2499 (47.4%) | 8251 (54.9%) | 3147 (53.2%) |  |
| Smoking |  | 6518 (12.1%) | 2036 (11.1%) | <0.001 | 4348 (14.3%) | 1290 (12.9%) | 1299 (10.4%) | 410 (10.1%) | 871 (7.9%) | 336 (7.9%) | <0.001 |
| Alcohol user |  | 2142 (5.0%) | 545 (3.9%) | <0.001 | 1398 (5.7%) | 321 (4.1%) | 443 (4.5%) | 124 (4.0%) | 301 (3.7%) | 100 (3.3%) | <0.001 |
| Location of care | Out-patient | 38416 (56.8%) | 11684 (49.0%) | <0.001 | 21773 (58.9%) | 6726 (53.3%) | 9703 (62.0%) | 2706 (51.2%) | 6940 (46.2%) | 2252 (38.0%) | <0.001 |
|  | In-patient | 29217 (43.2%) | 12146 (51.0%) |  | 15188 (41.1%) | 5902 (46.7%) | 5937 (38.0%) | 2575 (48.8%) | 8092 (53.8%) | 3669 (62.0%) |  |
| **Clnical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 41059 (60.7%) | 16612 (69.7%) | <0.001 | 23502 (63.6%) | 8804 (69.7%) | 7873 (50.3%) | 3395 (64.3%) | 9684 (64.4%) | 4413 (74.5%) | <0.001 |
| Duration of HF | <6mo | 37025 (56.0%) | 10597 (45.6%) | <0.001 | 21848 (60.3%) | 5825 (47.0%) | 8231 (53.9%) | 2287 (44.5%) | 6946 (47.8%) | 2485 (43.6%) | <0.001 |
|  | >=6mo | 29038 (44.0%) | 12622 (54.4%) |  | 14414 (39.7%) | 6556 (53.0%) | 7051 (46.1%) | 2850 (55.5%) | 7573 (52.2%) | 3216 (56.4%) |  |
| Follow-up location | Primary care | 20399 (31.4%) | 7727 (34.0%) | <0.001 | 7712 (21.6%) | 3035 (25.1%) | 5374 (35.7%) | 1894 (37.6%) | 7313 (51.4%) | 2798 (50.3%) | <0.001 |
|  | Hospital | 44629 (68.6%) | 14969 (66.0%) |  | 28024 (78.4%) | 9056 (74.9%) | 9695 (64.3%) | 3146 (62.4%) | 6910 (48.6%) | 2767 (49.7%) |  |
| NYHA functional class | I-II | 31561 (63.1%) | 8518 (52.1%) | <0.001 | 17224 (60.1%) | 4492 (48.2%) | 8334 (70.9%) | 2165 (60.5%) | 6003 (62.9%) | 1861 (53.7%) | <0.001 |
|  | III-IV | 18421 (36.9%) | 7842 (47.9%) |  | 11451 (39.9%) | 4822 (51.8%) | 3425 (29.1%) | 1416 (39.5%) | 3545 (37.1%) | 1604 (46.3%) |  |
| BMI, median (IQR) |  | 26 (23, 29) | 28 (25, 32) | <0.001 | 26 (23, 29) | 28 (25, 32) | 26 (23, 30) | 29 (25, 33) | 26 (23, 30) | 29 (26, 34) | <0.001 |
| SBP, median (IQR) |  | 125 (110, 140) | 130 (115, 140) | <0.001 | 120 (110, 137) | 123 (110, 140) | 130 (115, 140) | 130 (120, 145) | 130 (118, 144) | 135 (120, 150) | <0.001 |
| DBP, median (IQR) |  | 73 (65, 80) | 70 (65, 80) | <0.001 | 72 (65, 80) | 70 (65, 80) | 75 (65, 80) | 70 (65, 80) | 72 (65, 80) | 70 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (82, 100) | 90 (83, 100) | 0.34 | 90 (81, 99) | 90 (81, 98) | 92 (83, 100) | 92 (83, 100) | 93 (83, 100) | 93 (85, 101) | <0.001 |
| Heart rate, median (IQR) |  | 72 (62, 82) | 72 (64, 82) | <0.001 | 72 (63, 83) | 73 (65, 84) | 70 (61, 80) | 71 (64, 81) | 71 (63, 82) | 72 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 69 (51, 86) | 61 (43, 82) | <0.001 | 71 (53, 88) | 64 (46, 85) | 69 (52, 87) | 61 (43, 82) | 63 (47, 81) | 56 (40, 75) | <0.001 |
| Potassium categories | Normakalemia | 51060 (93.2%) | 17633 (91.6%) | <0.001 | 27900 (93.7%) | 9293 (92.0%) | 12091 (93.5%) | 3981 (91.6%) | 11069 (91.7%) | 4359 (90.7%) | <0.001 |
|  | Hypokalemia | 2401 (4.4%) | 874 (4.5%) |  | 1092 (3.7%) | 402 (4.0%) | 564 (4.4%) | 194 (4.5%) | 745 (6.2%) | 278 (5.8%) |  |
|  | Hyperkalemia | 1309 (2.4%) | 747 (3.9%) |  | 780 (2.6%) | 405 (4.0%) | 278 (2.1%) | 173 (4.0%) | 251 (2.1%) | 169 (3.5%) |  |
| Haemoglobin, median (IQR) |  | 134 (122, 146) | 128 (116, 141) | <0.001 | 137 (124, 148) | 131 (119, 144) | 134 (121, 145) | 127 (115, 140) | 129 (117, 140) | 124 (112, 136) | <0.001 |
| NT-proBNP, median (IQR) |  | 2290 (989, 5030) | 2333 (1047, 5367) | <0.001 | 2710 (1164, 6030) | 2800 (1242, 6340) | 1829 (715, 3899) | 2037 (895, 4730) | 2040 (934, 4100) | 1928 (899, 4040) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 57156 (85.4%) | 20114 (85.3%) | 0.71 | 33553 (91.8%) | 11371 (91.0%) | 13167 (85.0%) | 4409 (84.3%) | 10436 (70.2%) | 4334 (74.1%) | <0.001 |
| Beta-blockers |  | 59339 (88.0%) | 21289 (89.6%) | <0.001 | 33817 (91.7%) | 11713 (93.0%) | 13520 (86.6%) | 4648 (88.3%) | 12002 (80.2%) | 4928 (83.6%) | <0.001 |
| MRA |  | 23050 (34.2%) | 9025 (38.1%) | <0.001 | 14340 (39.0%) | 5417 (43.1%) | 4194 (26.9%) | 1698 (32.3%) | 4516 (30.2%) | 1910 (32.4%) | <0.001 |
| DIuretics |  | 49316 (73.1%) | 20062 (84.5%) | <0.001 | 26967 (73.2%) | 10558 (83.9%) | 10278 (65.9%) | 4228 (80.4%) | 12071 (80.6%) | 5276 (89.5%) | <0.001 |
| Digoxin |  | 9294 (13.8%) | 2876 (12.1%) | <0.001 | 5201 (14.1%) | 1577 (12.5%) | 1916 (12.3%) | 579 (11.0%) | 2177 (14.5%) | 720 (12.2%) | <0.001 |
| Antiplatelet therapy |  | 26508 (39.3%) | 11521 (48.5%) | <0.001 | 15329 (41.6%) | 6594 (52.4%) | 6307 (40.5%) | 2588 (49.2%) | 4872 (32.6%) | 2339 (39.7%) | <0.001 |
| Anticoagulant therapy |  | 31718 (47.1%) | 10645 (44.8%) | <0.001 | 16715 (45.4%) | 5377 (42.8%) | 7362 (47.2%) | 2378 (45.1%) | 7641 (51.0%) | 2890 (49.0%) | <0.001 |
| Statins |  | 28615 (42.4%) | 15720 (66.1%) | <0.001 | 16240 (44.1%) | 8588 (68.2%) | 7128 (45.7%) | 3539 (67.2%) | 5247 (35.0%) | 3593 (60.9%) | <0.001 |
| Nitrates |  | 7202 (10.7%) | 4383 (18.5%) | <0.001 | 3541 (9.6%) | 2199 (17.5%) | 1735 (11.1%) | 983 (18.7%) | 1926 (12.9%) | 1201 (20.4%) | <0.001 |
| HF devices |  | 3517 (5.3%) | 1421 (6.0%) | <0.001 | 2786 (7.6%) | 1193 (9.5%) | 497 (3.2%) | 164 (3.2%) | 234 (1.6%) | 64 (1.1%) | <0.001 |
| EF categories | HFrEF | 36961 (54.6%) | 12628 (53.0%) | <0.001 | 36961 (100.0%) | 12628 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 15640 (23.1%) | 5281 (22.2%) |  | 0 (0.0%) | 0 (0.0%) | 15640 (100.0%) | 5281 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 15032 (22.2%) | 5921 (24.8%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 15032 (100.0%) | 5921 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 14571 (21.5%) | 9400 (39.4%) | <0.001 | 7293 (19.7%) | 4426 (35.0%) | 3604 (23.0%) | 2218 (42.0%) | 3674 (24.4%) | 2756 (46.5%) | <0.001 |
| Hypertension |  | 40052 (59.2%) | 19331 (81.1%) | <0.001 | 19476 (52.7%) | 9616 (76.1%) | 9747 (62.3%) | 4465 (84.5%) | 10829 (72.0%) | 5250 (88.7%) | <0.001 |
| Diabetes |  | 0 (0.0%) | 23830 (100.0%) | <0.001 | 0 (0.0%) | 12628 (100.0%) | 0 (0.0%) | 5281 (100.0%) | 0 (0.0%) | 5921 (100.0%) | <0.001 |
| CAD |  | 32391 (47.9%) | 15542 (65.2%) | <0.001 | 18069 (48.9%) | 8610 (68.2%) | 8007 (51.2%) | 3584 (67.9%) | 6315 (42.0%) | 3348 (56.5%) | <0.001 |
| AF |  | 38188 (56.5%) | 13073 (54.9%) | <0.001 | 18976 (51.3%) | 6337 (50.2%) | 9122 (58.3%) | 3005 (56.9%) | 10090 (67.1%) | 3731 (63.0%) | <0.001 |
| VHD |  | 18560 (27.4%) | 5813 (24.4%) | <0.001 | 8775 (23.7%) | 2785 (22.1%) | 4312 (27.6%) | 1268 (24.0%) | 5473 (36.4%) | 1760 (29.7%) | <0.001 |
| CKD |  | 24973 (36.9%) | 11606 (48.7%) | <0.001 | 12549 (34.0%) | 5690 (45.1%) | 5619 (35.9%) | 2604 (49.3%) | 6805 (45.3%) | 3312 (55.9%) | <0.001 |
| Anaemia |  | 20772 (30.7%) | 10416 (43.7%) | <0.001 | 10158 (27.5%) | 4960 (39.3%) | 4842 (31.0%) | 2415 (45.7%) | 5772 (38.4%) | 3041 (51.4%) | <0.001 |
| COPD |  | 8145 (12.0%) | 3452 (14.5%) | <0.001 | 4018 (10.9%) | 1606 (12.7%) | 1847 (11.8%) | 800 (15.1%) | 2280 (15.2%) | 1046 (17.7%) | <0.001 |
| Liver disease |  | 1286 (1.9%) | 630 (2.6%) | <0.001 | 743 (2.0%) | 317 (2.5%) | 248 (1.6%) | 131 (2.5%) | 295 (2.0%) | 182 (3.1%) | <0.001 |
| PAD |  | 5016 (7.4%) | 2900 (12.2%) | <0.001 | 2570 (7.0%) | 1537 (12.2%) | 1202 (7.7%) | 652 (12.3%) | 1244 (8.3%) | 711 (12.0%) | <0.001 |
| Stroke or TIA |  | 9972 (14.7%) | 4688 (19.7%) | <0.001 | 5007 (13.5%) | 2395 (19.0%) | 2324 (14.9%) | 1036 (19.6%) | 2641 (17.6%) | 1257 (21.2%) | <0.001 |
| Depression |  | 2356 (3.5%) | 906 (3.8%) | 0.023 | 1284 (3.5%) | 454 (3.6%) | 496 (3.2%) | 206 (3.9%) | 576 (3.8%) | 246 (4.2%) | 0.002 |
| Dementia |  | 974 (1.4%) | 426 (1.8%) | <0.001 | 446 (1.2%) | 228 (1.8%) | 214 (1.4%) | 78 (1.5%) | 314 (2.1%) | 120 (2.0%) | <0.001 |
| Cancer <3years |  | 8509 (12.6%) | 2855 (12.0%) | 0.016 | 4294 (11.6%) | 1369 (10.8%) | 2077 (13.3%) | 665 (12.6%) | 2138 (14.2%) | 821 (13.9%) | <0.001 |
| Muscolo-skeletal <3years |  | 19913 (29.4%) | 8207 (34.4%) | <0.001 | 9479 (25.6%) | 3959 (31.4%) | 4890 (31.3%) | 1862 (35.3%) | 5544 (36.9%) | 2386 (40.3%) | <0.001 |
| Dysthyroidism |  | 4842 (7.2%) | 2019 (8.5%) | <0.001 | 2247 (6.1%) | 881 (7.0%) | 1106 (7.1%) | 472 (8.9%) | 1489 (9.9%) | 666 (11.2%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 23196 (34.3%) | 3667 (15.4%) | <0.001 | 13043 (35.3%) | 2072 (16.4%) | 5293 (33.8%) | 779 (14.8%) | 4860 (32.3%) | 816 (13.8%) | <0.001 |
|  | 2-3 | 27450 (40.6%) | 7705 (32.3%) |  | 15186 (41.1%) | 4242 (33.6%) | 6352 (40.6%) | 1660 (31.4%) | 5912 (39.3%) | 1803 (30.5%) |  |
|  | 4-7 | 14225 (21.0%) | 9979 (41.9%) |  | 7376 (20.0%) | 5134 (40.7%) | 3312 (21.2%) | 2274 (43.1%) | 3537 (23.5%) | 2571 (43.4%) |  |
|  | >=8 | 2762 (4.1%) | 2479 (10.4%) |  | 1356 (3.7%) | 1180 (9.3%) | 683 (4.4%) | 568 (10.8%) | 723 (4.8%) | 731 (12.3%) |  |

**Supplementary Table 6. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by coronary artery disease (CAD)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 43530 (48%) | 47933 (52%) |  | 22910 (46%) | 26679 (54%) | 9330 (45%) | 11591 (55%) | 11290 (54%) | 9663 (46%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 17754 (40.8%) | 15580 (32.5%) | <0.001 | 7416 (32.4%) | 6953 (26.1%) | 4002 (42.9%) | 3903 (33.7%) | 6336 (56.1%) | 4724 (48.9%) | <0.001 |
|  | Male | 25776 (59.2%) | 32353 (67.5%) |  | 15494 (67.6%) | 19726 (73.9%) | 5328 (57.1%) | 7688 (66.3%) | 4954 (43.9%) | 4939 (51.1%) |  |
| Age, median (IQR) |  | 74 (64, 82) | 77 (69, 83) | <0.001 | 70 (60, 79) | 75 (68, 82) | 75 (66, 82) | 77 (69, 83) | 79 (72, 85) | 80 (74, 86) | <0.001 |
| Family type | Cohabitating | 22239 (51.2%) | 25273 (52.8%) | <0.001 | 12219 (53.4%) | 14566 (54.7%) | 4969 (53.3%) | 6217 (53.7%) | 5051 (44.8%) | 4490 (46.5%) | <0.001 |
|  | Living alone | 21218 (48.8%) | 22605 (47.2%) |  | 10643 (46.6%) | 12068 (45.3%) | 4348 (46.7%) | 5366 (46.3%) | 6227 (55.2%) | 5171 (53.5%) |  |
| Smoking |  | 4356 (12.6%) | 4198 (11.1%) | <0.001 | 2857 (15.1%) | 2781 (12.9%) | 829 (11.2%) | 880 (9.6%) | 670 (8.2%) | 537 (7.6%) | <0.001 |
| Alcohol user |  | 1719 (6.1%) | 968 (3.4%) | <0.001 | 1115 (7.0%) | 604 (3.7%) | 332 (5.5%) | 235 (3.4%) | 272 (4.4%) | 129 (2.6%) | <0.001 |
| Location of care | Out-patient | 25260 (58.0%) | 24840 (51.8%) | <0.001 | 14006 (61.1%) | 14493 (54.3%) | 5908 (63.3%) | 6501 (56.1%) | 5346 (47.4%) | 3846 (39.8%) | <0.001 |
|  | In-patient | 18270 (42.0%) | 23093 (48.2%) |  | 8904 (38.9%) | 12186 (45.7%) | 3422 (36.7%) | 5090 (43.9%) | 5944 (52.6%) | 5817 (60.2%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 27105 (62.3%) | 30566 (63.8%) | <0.001 | 15096 (65.9%) | 17210 (64.5%) | 4819 (51.7%) | 6449 (55.6%) | 7190 (63.7%) | 6907 (71.5%) | <0.001 |
| Duration of HF | <6mo | 26050 (61.5%) | 21572 (46.0%) | <0.001 | 15511 (69.1%) | 12162 (46.4%) | 5126 (56.5%) | 5392 (47.5%) | 5413 (49.8%) | 4018 (43.0%) | <0.001 |
|  | >6mo | 16331 (38.5%) | 25329 (54.0%) |  | 6929 (30.9%) | 14041 (53.6%) | 3949 (43.5%) | 5952 (52.5%) | 5453 (50.2%) | 5336 (57.0%) |  |
| Follow-up location | Primary care | 12932 (30.8%) | 15194 (33.2%) | <0.001 | 4255 (19.1%) | 6492 (25.4%) | 3219 (35.8%) | 4049 (36.4%) | 5458 (51.1%) | 4653 (51.1%) | <0.001 |
|  | Hospital | 28997 (69.2%) | 30601 (66.8%) |  | 18008 (80.9%) | 19072 (74.6%) | 5768 (64.2%) | 7073 (63.6%) | 5221 (48.9%) | 4456 (48.9%) |  |
| NYHA functional class | I-II | 20898 (64.4%) | 19181 (56.6%) | <0.001 | 11287 (62.3%) | 10429 (52.5%) | 5038 (71.2%) | 5461 (66.0%) | 4573 (63.2%) | 3291 (57.0%) | <0.001 |
|  | III-IV | 11530 (35.6%) | 14733 (43.4%) |  | 6833 (37.7%) | 9440 (47.5%) | 2034 (28.8%) | 2807 (34.0%) | 2663 (36.8%) | 2486 (43.0%) |  |
| BMI, median (IQR) |  | 27 (23, 31) | 26 (23, 30) | <0.001 | 26 (23, 30) | 26 (23, 29) | 27 (23, 31) | 27 (24, 30) | 27 (24, 31) | 27 (24, 31) | <0.001 |
| SBP, median (IQR) |  | 125 (112, 140) | 125 (110, 140) | <0.001 | 121 (110, 140) | 120 (110, 136) | 130 (115, 141) | 130 (115, 140) | 130 (120, 145) | 130 (120, 147) | <0.001 |
| DBP, median (IQR) |  | 75 (67, 80) | 70 (64, 80) | <0.001 | 75 (68, 82) | 70 (63, 80) | 75 (68, 82) | 70 (65, 80) | 73 (65, 80) | 70 (64, 80) | <0.001 |
| MAP, median (IQR) |  | 92 (83, 101) | 90 (82, 98) | <0.001 | 91 (83, 100) | 88 (80, 97) | 93 (84, 102) | 91 (83, 100) | 93 (83, 102) | 92 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 74 (64, 85) | 70 (62, 80) | <0.001 | 75 (65, 87) | 70 (62, 80) | 73 (64, 84) | 70 (60, 80) | 73 (64, 84) | 70 (62, 80) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 71 (53, 88) | 63 (46, 82) | <0.001 | 74 (57, 91) | 64 (47, 84) | 71 (53, 88) | 65 (47, 83) | 64 (47, 82) | 58 (42, 76) | <0.001 |
| Potassium categories | Normakalemia | 33436 (92.9%) | 35257 (92.7%) | 0.039 | 17694 (93.6%) | 19499 (93.0%) | 7319 (93.0%) | 8753 (93.0%) | 8423 (91.3%) | 7005 (91.7%) | <0.001 |
|  | Hypokalemia | 1624 (4.5%) | 1651 (4.3%) |  | 675 (3.6%) | 819 (3.9%) | 365 (4.6%) | 393 (4.2%) | 584 (6.3%) | 439 (5.7%) |  |
|  | Hyperkalemia | 948 (2.6%) | 1108 (2.9%) |  | 537 (2.8%) | 648 (3.1%) | 189 (2.4%) | 262 (2.8%) | 222 (2.4%) | 198 (2.6%) |  |
| Haemoglobin, median (IQR) |  | 135 (123, 147) | 130 (118, 142) | <0.001 | 139 (127, 150) | 132 (120, 144) | 135 (122, 146) | 131 (118, 142) | 129 (116, 141) | 126 (114, 137) | <0.001 |
| NT-proBNP, median (IQR) |  | 2186 (962, 4673) | 2439 (1048, 5613) | <0.001 | 2564 (1130, 5636) | 2910 (1240, 6666) | 1770 (685, 3793) | 1991 (832, 4431) | 1960 (910, 3842) | 2071 (938, 4450) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 36834 (85.5%) | 40436 (85.3%) | 0.51 | 21098 (93.1%) | 23826 (90.3%) | 7850 (84.9%) | 9726 (84.7%) | 7886 (70.6%) | 6884 (72.2%) | <0.001 |
| Beta-blockers |  | 37700 (86.8%) | 42928 (89.8%) | <0.001 | 20994 (91.9%) | 24536 (92.2%) | 7881 (84.7%) | 10287 (88.9%) | 8825 (78.5%) | 8105 (84.3%) | <0.001 |
| MRA |  | 15313 (35.3%) | 16762 (35.1%) | 0.53 | 9023 (39.6%) | 10734 (40.4%) | 2651 (28.5%) | 3241 (28.1%) | 3639 (32.4%) | 2787 (29.1%) | <0.001 |
| DIuretics |  | 32680 (75.3%) | 36698 (76.8%) | <0.001 | 17005 (74.5%) | 20520 (77.1%) | 6389 (68.6%) | 8117 (70.2%) | 9286 (82.5%) | 8061 (83.8%) | <0.001 |
| Digoxin |  | 7085 (16.3%) | 5085 (10.6%) | <0.001 | 3873 (17.0%) | 2905 (10.9%) | 1428 (15.3%) | 1067 (9.2%) | 1784 (15.9%) | 1113 (11.6%) | <0.001 |
| Antiplatelet therapy |  | 9703 (22.4%) | 28326 (59.3%) | <0.001 | 5357 (23.5%) | 16566 (62.3%) | 1909 (20.5%) | 6986 (60.4%) | 2437 (21.7%) | 4774 (49.6%) | <0.001 |
| Anticoagulant therapy |  | 22322 (51.4%) | 20041 (42.0%) | <0.001 | 11191 (49.0%) | 10901 (41.0%) | 5066 (54.5%) | 4674 (40.5%) | 6065 (53.9%) | 4466 (46.5%) | <0.001 |
| Statins |  | 11583 (26.7%) | 32752 (68.5%) | <0.001 | 5974 (26.2%) | 18854 (70.8%) | 2511 (27.0%) | 8156 (70.5%) | 3098 (27.5%) | 5742 (59.6%) | <0.001 |
| Nitrates |  | 1182 (2.7%) | 10403 (21.8%) | <0.001 | 483 (2.1%) | 5257 (19.8%) | 249 (2.7%) | 2469 (21.4%) | 450 (4.0%) | 2677 (27.8%) | <0.001 |
| HF devices |  | 1467 (3.4%) | 3471 (7.3%) | <0.001 | 1091 (4.8%) | 2888 (10.9%) | 245 (2.7%) | 416 (3.6%) | 131 (1.2%) | 167 (1.8%) | <0.001 |
| EF categories | HFrEF | 22910 (52.6%) | 26679 (55.7%) | <0.001 | 22910 (100.0%) | 26679 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 9330 (21.4%) | 11591 (24.2%) |  | 0 (0.0%) | 0 (0.0%) | 9330 (100.0%) | 11591 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 11290 (25.9%) | 9663 (20.2%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 11290 (100.0%) | 9663 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 12228 (28.1%) | 11743 (24.5%) | <0.001 | 5955 (26.0%) | 5764 (21.6%) | 2696 (28.9%) | 3126 (27.0%) | 3577 (31.7%) | 2853 (29.5%) | <0.001 |
| Hypertension |  | 26098 (60.0%) | 33285 (69.4%) | <0.001 | 11893 (51.9%) | 17199 (64.5%) | 5886 (63.1%) | 8326 (71.8%) | 8319 (73.7%) | 7760 (80.3%) | <0.001 |
| Diabetes |  | 8288 (19.0%) | 15542 (32.4%) | <0.001 | 4018 (17.5%) | 8610 (32.3%) | 1697 (18.2%) | 3584 (30.9%) | 2573 (22.8%) | 3348 (34.6%) | <0.001 |
| CAD |  | 0 (0.0%) | 47933 (100.0%) | <0.001 | 0 (0.0%) | 26679 (100.0%) | 0 (0.0%) | 11591 (100.0%) | 0 (0.0%) | 9663 (100.0%) | <0.001 |
| AF |  | 26252 (60.3%) | 25009 (52.2%) | <0.001 | 12402 (54.1%) | 12911 (48.4%) | 6099 (65.4%) | 6028 (52.0%) | 7751 (68.7%) | 6070 (62.8%) | <0.001 |
| VHD |  | 11270 (25.9%) | 13103 (27.3%) | <0.001 | 4895 (21.4%) | 6665 (25.0%) | 2548 (27.3%) | 3032 (26.2%) | 3827 (33.9%) | 3406 (35.2%) | <0.001 |
| CKD |  | 14721 (33.8%) | 21858 (45.6%) | <0.001 | 6554 (28.6%) | 11685 (43.8%) | 3198 (34.3%) | 5025 (43.4%) | 4969 (44.0%) | 5148 (53.3%) | <0.001 |
| Anaemia |  | 12217 (28.1%) | 18971 (39.6%) | <0.001 | 5146 (22.5%) | 9972 (37.4%) | 2727 (29.2%) | 4530 (39.1%) | 4344 (38.5%) | 4469 (46.2%) | <0.001 |
| COPD |  | 4684 (10.8%) | 6913 (14.4%) | <0.001 | 2065 (9.0%) | 3559 (13.3%) | 1033 (11.1%) | 1614 (13.9%) | 1586 (14.0%) | 1740 (18.0%) | <0.001 |
| Liver disease |  | 1020 (2.3%) | 896 (1.9%) | <0.001 | 542 (2.4%) | 518 (1.9%) | 201 (2.2%) | 178 (1.5%) | 277 (2.5%) | 200 (2.1%) | <0.001 |
| PAD |  | 2327 (5.3%) | 5589 (11.7%) | <0.001 | 1045 (4.6%) | 3062 (11.5%) | 521 (5.6%) | 1333 (11.5%) | 761 (6.7%) | 1194 (12.4%) | <0.001 |
| Stroke or TIA |  | 5561 (12.8%) | 9099 (19.0%) | <0.001 | 2513 (11.0%) | 4889 (18.3%) | 1284 (13.8%) | 2076 (17.9%) | 1764 (15.6%) | 2134 (22.1%) | <0.001 |
| Depression |  | 1489 (3.4%) | 1773 (3.7%) | 0.023 | 810 (3.5%) | 928 (3.5%) | 292 (3.1%) | 410 (3.5%) | 387 (3.4%) | 435 (4.5%) | <0.001 |
| Dementia |  | 564 (1.3%) | 836 (1.7%) | <0.001 | 244 (1.1%) | 430 (1.6%) | 109 (1.2%) | 183 (1.6%) | 211 (1.9%) | 223 (2.3%) | <0.001 |
| Cancer <3years |  | 5360 (12.3%) | 6004 (12.5%) | 0.33 | 2496 (10.9%) | 3167 (11.9%) | 1303 (14.0%) | 1439 (12.4%) | 1561 (13.8%) | 1398 (14.5%) | <0.001 |
| Muscolo-skeletal <3years |  | 12415 (28.5%) | 15705 (32.8%) | <0.001 | 5553 (24.2%) | 7885 (29.6%) | 2834 (30.4%) | 3918 (33.8%) | 4028 (35.7%) | 3902 (40.4%) | <0.001 |
| Dysthyroidism |  | 3177 (7.3%) | 3684 (7.7%) | 0.026 | 1385 (6.0%) | 1743 (6.5%) | 685 (7.3%) | 893 (7.7%) | 1107 (9.8%) | 1048 (10.8%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 20068 (46.1%) | 6795 (14.2%) | <0.001 | 11686 (51.0%) | 3429 (12.9%) | 4150 (44.5%) | 1922 (16.6%) | 4232 (37.5%) | 1444 (14.9%) | <0.001 |
|  | 2-3 | 14523 (33.4%) | 20632 (43.0%) |  | 7289 (31.8%) | 12139 (45.5%) | 3114 (33.4%) | 4898 (42.3%) | 4120 (36.5%) | 3595 (37.2%) |  |
|  | 4-7 | 7336 (16.9%) | 16868 (35.2%) |  | 3285 (14.3%) | 9225 (34.6%) | 1675 (18.0%) | 3911 (33.7%) | 2376 (21.0%) | 3732 (38.6%) |  |
|  | >=8 | 1603 (3.7%) | 3638 (7.6%) |  | 650 (2.8%) | 1886 (7.1%) | 391 (4.2%) | 860 (7.4%) | 562 (5.0%) | 892 (9.2%) |  |

**Supplementary Table 7. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by atrial fibrillation.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | |  |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 40202 (44%) | 51261 (56%) |  | 24276 (49%) | 25313 (51%) | 8794 (42%) | 12127 (58%) | 7132 (34%) | 13821 (66%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 14956 (37.2%) | 18378 (35.9%) | <0.001 | 7736 (31.9%) | 6633 (26.2%) | 3369 (38.3%) | 4536 (37.4%) | 3851 (54.0%) | 7209 (52.2%) | <0.001 |
|  | Male | 25246 (62.8%) | 32883 (64.1%) |  | 16540 (68.1%) | 18680 (73.8%) | 5425 (61.7%) | 7591 (62.6%) | 3281 (46.0%) | 6612 (47.8%) |  |
| Age, median (IQR) |  | 72 (62, 80) | 78 (70, 84) | <0.001 | 70 (61, 79) | 76 (68, 82) | 72 (62, 80) | 78 (72, 84) | 77 (68, 84) | 81 (75, 86) | <0.001 |
| Family type | Cohabitating | 21234 (52.9%) | 26278 (51.3%) | <0.001 | 13112 (54.1%) | 13673 (54.1%) | 4822 (54.9%) | 6364 (52.5%) | 3300 (46.3%) | 6241 (45.2%) | <0.001 |
|  | Living alone | 18895 (47.1%) | 24928 (48.7%) |  | 11106 (45.9%) | 11605 (45.9%) | 3964 (45.1%) | 5750 (47.5%) | 3825 (53.7%) | 7573 (54.8%) |  |
| Smoking |  | 4968 (15.2%) | 3586 (9.1%) | <0.001 | 3414 (16.9%) | 2224 (11.1%) | 951 (13.3%) | 758 (8.1%) | 603 (11.4%) | 604 (6.1%) | <0.001 |
| Alcohol user |  | 1214 (4.8%) | 1473 (4.7%) | 0.92 | 828 (5.1%) | 891 (5.5%) | 249 (4.5%) | 318 (4.3%) | 137 (3.6%) | 264 (3.6%) | <0.001 |
| Location of care | Out-patient | 23623 (58.8%) | 26477 (51.7%) | <0.001 | 14612 (60.2%) | 13887 (54.9%) | 5709 (64.9%) | 6700 (55.2%) | 3302 (46.3%) | 5890 (42.6%) | <0.001 |
|  | In-patient | 16579 (41.2%) | 24784 (48.3%) |  | 9664 (39.8%) | 11426 (45.1%) | 3085 (35.1%) | 5427 (44.8%) | 3830 (53.7%) | 7931 (57.4%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 24091 (59.9%) | 33580 (65.5%) | <0.001 | 15461 (63.7%) | 16845 (66.5%) | 4127 (46.9%) | 7141 (58.9%) | 4503 (63.1%) | 9594 (69.4%) | <0.001 |
| Duration of HF | <6mo | 23655 (60.1%) | 23967 (48.0%) | <0.001 | 14918 (62.6%) | 12755 (51.4%) | 5044 (58.6%) | 5474 (46.3%) | 3693 (53.6%) | 5738 (43.1%) | <0.001 |
|  | >6mo | 15682 (39.9%) | 25978 (52.0%) |  | 8918 (37.4%) | 12052 (48.6%) | 3561 (41.4%) | 6340 (53.7%) | 3203 (46.4%) | 7586 (56.9%) |  |
| Follow-up location | Primary care | 10622 (27.4%) | 17504 (35.7%) | <0.001 | 4613 (19.6%) | 6134 (25.2%) | 2646 (31.2%) | 4622 (39.8%) | 3363 (49.6%) | 6748 (51.9%) | <0.001 |
|  | Hospital | 28124 (72.6%) | 31474 (64.3%) |  | 18868 (80.4%) | 18212 (74.8%) | 5845 (68.8%) | 6996 (60.2%) | 3411 (50.4%) | 6266 (48.1%) |  |
| NYHA functional class | I-II | 19510 (65.2%) | 20569 (56.5%) | <0.001 | 11537 (61.2%) | 10179 (53.2%) | 5034 (75.8%) | 5465 (62.8%) | 2939 (66.1%) | 4925 (57.5%) | <0.001 |
|  | III-IV | 10436 (34.8%) | 15827 (43.5%) |  | 7324 (38.8%) | 8949 (46.8%) | 1608 (24.2%) | 3233 (37.2%) | 1504 (33.9%) | 3645 (42.5%) |  |
| BMI, median (IQR) |  | 26 (23, 30) | 27 (23, 30) | <0.001 | 26 (23, 30) | 26 (23, 30) | 27 (24, 30) | 27 (24, 31) | 27 (23, 32) | 27 (24, 31) | <0.001 |
| SBP, median (IQR) |  | 126 (112, 140) | 125 (110, 140) | <0.001 | 121 (110, 140) | 120 (110, 135) | 130 (118, 145) | 130 (115, 140) | 135 (120, 150) | 130 (117, 142) | <0.001 |
| DBP, median (IQR) |  | 70 (65, 80) | 73 (65, 80) | <0.001 | 70 (65, 80) | 73 (65, 80) | 72 (65, 80) | 75 (66, 80) | 70 (64, 80) | 72 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (82, 100) | 90 (83, 100) | 0.20 | 90 (80, 99) | 90 (82, 99) | 92 (83, 100) | 92 (83, 100) | 93 (85, 102) | 92 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 70 (61, 80) | 74 (65, 85) | <0.001 | 70 (62, 80) | 75 (65, 87) | 68 (60, 76) | 74 (64, 85) | 69 (61, 79) | 73 (64, 84) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 72 (53, 90) | 63 (47, 81) | <0.001 | 73 (55, 91) | 65 (49, 83) | 74 (55, 91) | 63 (47, 81) | 64 (46, 85) | 60 (44, 77) | <0.001 |
| Potassium categories | Normakalemia | 30482 (93.5%) | 38211 (92.3%) | <0.001 | 18366 (93.6%) | 18827 (92.9%) | 6928 (94.3%) | 9144 (92.1%) | 5188 (91.8%) | 10240 (91.3%) | <0.001 |
|  | Hypokalemia | 1225 (3.8%) | 2050 (5.0%) |  | 680 (3.5%) | 814 (4.0%) | 245 (3.3%) | 513 (5.2%) | 300 (5.3%) | 723 (6.4%) |  |
|  | Hyperkalemia | 907 (2.8%) | 1149 (2.8%) |  | 567 (2.9%) | 618 (3.1%) | 177 (2.4%) | 274 (2.8%) | 163 (2.9%) | 257 (2.3%) |  |
| Haemoglobin, median (IQR) |  | 133 (121, 145) | 132 (120, 145) | <0.001 | 135 (123, 146) | 136 (123, 148) | 133 (120, 144) | 132 (119, 144) | 127 (115, 139) | 127 (115, 139) | <0.001 |
| NT-proBNP, median (IQR) |  | 1701 (612, 4608) | 2699 (1380, 5450) | <0.001 | 2230 (852, 5532) | 3142 (1562, 6635) | 1040 (365, 3110) | 2391 (1240, 4610) | 1126 (430, 3090) | 2351 (1272, 4400) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 35111 (88.3%) | 42159 (83.2%) | <0.001 | 22322 (93.0%) | 22602 (90.3%) | 7684 (88.2%) | 9892 (82.4%) | 5105 (72.4%) | 9665 (70.8%) | <0.001 |
| Beta-blockers |  | 34810 (86.8%) | 45818 (89.6%) | <0.001 | 22102 (91.2%) | 23428 (92.8%) | 7453 (85.0%) | 10715 (88.5%) | 5255 (74.0%) | 11675 (84.8%) | <0.001 |
| MRA |  | 13337 (33.3%) | 18738 (36.8%) | <0.001 | 9520 (39.4%) | 10237 (40.7%) | 2062 (23.5%) | 3830 (31.7%) | 1755 (24.7%) | 4671 (34.0%) | <0.001 |
| DIuretics |  | 27519 (68.7%) | 41859 (81.9%) | <0.001 | 17146 (70.9%) | 20379 (80.8%) | 4979 (56.8%) | 9527 (78.8%) | 5394 (75.9%) | 11953 (86.8%) | <0.001 |
| Digoxin |  | 891 (2.2%) | 11279 (22.1%) | <0.001 | 660 (2.7%) | 6118 (24.2%) | 108 (1.2%) | 2387 (19.7%) | 123 (1.7%) | 2774 (20.1%) | <0.001 |
| Antiplatelet therapy |  | 25230 (63.0%) | 12799 (25.1%) | <0.001 | 15193 (62.8%) | 6730 (26.7%) | 5929 (67.6%) | 2966 (24.6%) | 4108 (57.8%) | 3103 (22.6%) | <0.001 |
| Anticoagulant therapy |  | 4673 (11.7%) | 37690 (73.8%) | <0.001 | 3312 (13.7%) | 18780 (74.4%) | 758 (8.6%) | 8982 (74.3%) | 603 (8.5%) | 9928 (72.1%) | <0.001 |
| Statins |  | 22172 (55.3%) | 22163 (43.4%) | <0.001 | 13388 (55.3%) | 11440 (45.3%) | 5315 (60.6%) | 5352 (44.3%) | 3469 (48.8%) | 5371 (39.0%) | <0.001 |
| Nitrates |  | 5129 (12.8%) | 6456 (12.7%) | 0.48 | 2811 (11.6%) | 2929 (11.6%) | 1135 (13.0%) | 1583 (13.1%) | 1183 (16.7%) | 1944 (14.1%) | <0.001 |
| HF devices |  | 2149 (5.4%) | 2789 (5.5%) | 0.50 | 1773 (7.4%) | 2206 (8.8%) | 263 (3.0%) | 398 (3.3%) | 113 (1.6%) | 185 (1.4%) | <0.001 |
| EF categories | HFrEF | 24276 (60.4%) | 25313 (49.4%) | <0.001 | 24276 (100.0%) | 25313 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 8794 (21.9%) | 12127 (23.7%) |  | 0 (0.0%) | 0 (0.0%) | 8794 (100.0%) | 12127 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 7132 (17.7%) | 13821 (27.0%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 7132 (100.0%) | 13821 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 10326 (25.7%) | 13645 (26.6%) | 0.001 | 5645 (23.3%) | 6074 (24.0%) | 2402 (27.3%) | 3420 (28.2%) | 2279 (32.0%) | 4151 (30.0%) | <0.001 |
| Hypertension |  | 24428 (60.8%) | 34955 (68.2%) | <0.001 | 13467 (55.5%) | 15625 (61.7%) | 5601 (63.7%) | 8611 (71.0%) | 5360 (75.2%) | 10719 (77.6%) | <0.001 |
| Diabetes |  | 10757 (26.8%) | 13073 (25.5%) | <0.001 | 6291 (25.9%) | 6337 (25.0%) | 2276 (25.9%) | 3005 (24.8%) | 2190 (30.7%) | 3731 (27.0%) | <0.001 |
| CAD |  | 22924 (57.0%) | 25009 (48.8%) | <0.001 | 13768 (56.7%) | 12911 (51.0%) | 5563 (63.3%) | 6028 (49.7%) | 3593 (50.4%) | 6070 (43.9%) | <0.001 |
| AF |  | 0 (0.0%) | 51261 (100.0%) | <0.001 | 0 (0.0%) | 25313 (100.0%) | 0 (0.0%) | 12127 (100.0%) | 0 (0.0%) | 13821 (100.0%) | <0.001 |
| VHD |  | 8568 (21.3%) | 15805 (30.8%) | <0.001 | 4718 (19.4%) | 6842 (27.0%) | 1761 (20.0%) | 3819 (31.5%) | 2089 (29.3%) | 5144 (37.2%) | <0.001 |
| CKD |  | 13613 (33.9%) | 22966 (44.8%) | <0.001 | 7684 (31.7%) | 10555 (41.7%) | 2772 (31.5%) | 5451 (44.9%) | 3157 (44.3%) | 6960 (50.4%) | <0.001 |
| Anaemia |  | 13061 (32.5%) | 18127 (35.4%) | <0.001 | 7217 (29.7%) | 7901 (31.2%) | 2860 (32.5%) | 4397 (36.3%) | 2984 (41.8%) | 5829 (42.2%) | <0.001 |
| COPD |  | 4946 (12.3%) | 6651 (13.0%) | 0.002 | 2731 (11.2%) | 2893 (11.4%) | 1029 (11.7%) | 1618 (13.3%) | 1186 (16.6%) | 2140 (15.5%) | <0.001 |
| Liver disease |  | 851 (2.1%) | 1065 (2.1%) | 0.68 | 515 (2.1%) | 545 (2.2%) | 146 (1.7%) | 233 (1.9%) | 190 (2.7%) | 287 (2.1%) | <0.001 |
| PAD |  | 3355 (8.3%) | 4561 (8.9%) | 0.003 | 1883 (7.8%) | 2224 (8.8%) | 749 (8.5%) | 1105 (9.1%) | 723 (10.1%) | 1232 (8.9%) | <0.001 |
| Stroke or TIA |  | 5088 (12.7%) | 9572 (18.7%) | <0.001 | 2877 (11.9%) | 4525 (17.9%) | 1096 (12.5%) | 2264 (18.7%) | 1115 (15.6%) | 2783 (20.1%) | <0.001 |
| Depression |  | 1635 (4.1%) | 1627 (3.2%) | <0.001 | 961 (4.0%) | 777 (3.1%) | 341 (3.9%) | 361 (3.0%) | 333 (4.7%) | 489 (3.5%) | <0.001 |
| Dementia |  | 500 (1.2%) | 900 (1.8%) | <0.001 | 274 (1.1%) | 400 (1.6%) | 96 (1.1%) | 196 (1.6%) | 130 (1.8%) | 304 (2.2%) | <0.001 |
| Cancer <3years |  | 4527 (11.3%) | 6837 (13.3%) | <0.001 | 2529 (10.4%) | 3134 (12.4%) | 1068 (12.1%) | 1674 (13.8%) | 930 (13.0%) | 2029 (14.7%) | <0.001 |
| Muscolo-skeletal <3years |  | 11443 (28.5%) | 16677 (32.5%) | <0.001 | 6216 (25.6%) | 7222 (28.5%) | 2645 (30.1%) | 4107 (33.9%) | 2582 (36.2%) | 5348 (38.7%) | <0.001 |
| Dysthyroidism |  | 2575 (6.4%) | 4286 (8.4%) | <0.001 | 1338 (5.5%) | 1790 (7.1%) | 589 (6.7%) | 989 (8.2%) | 648 (9.1%) | 1507 (10.9%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 12072 (30.0%) | 14791 (28.9%) | <0.001 | 7530 (31.0%) | 7585 (30.0%) | 2548 (29.0%) | 3524 (29.1%) | 1994 (28.0%) | 3682 (26.6%) | <0.001 |
|  | 2-3 | 15935 (39.6%) | 19220 (37.5%) |  | 9841 (40.5%) | 9587 (37.9%) | 3566 (40.6%) | 4446 (36.7%) | 2528 (35.4%) | 5187 (37.5%) |  |
|  | 4-7 | 10080 (25.1%) | 14124 (27.6%) |  | 5780 (23.8%) | 6730 (26.6%) | 2193 (24.9%) | 3393 (28.0%) | 2107 (29.5%) | 4001 (28.9%) |  |
|  | >=8 | 2115 (5.3%) | 3126 (6.1%) |  | 1125 (4.6%) | 1411 (5.6%) | 487 (5.5%) | 764 (6.3%) | 503 (7.1%) | 951 (6.9%) |  |

**Supplementary Table 8. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by valvular heart disease.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 67090 (73%) | 24373 (27%) |  | 38029 (77%) | 11560 (23%) | 15341 (73%) | 5580 (27%) | 13720 (65%) | 7233 (35%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 23456 (35.0%) | 9878 (40.5%) | <0.001 | 10722 (28.2%) | 3647 (31.5%) | 5663 (36.9%) | 2242 (40.2%) | 7071 (51.5%) | 3989 (55.2%) | <0.001 |
|  | Male | 43634 (65.0%) | 14495 (59.5%) |  | 27307 (71.8%) | 7913 (68.5%) | 9678 (63.1%) | 3338 (59.8%) | 6649 (48.5%) | 3244 (44.8%) |  |
| Age, median (IQR) |  | 74 (65, 82) | 78 (71, 84) | <0.001 | 72 (63, 80) | 77 (68, 83) | 75 (67, 82) | 79 (71, 84) | 79 (72, 85) | 81 (75, 86) | <0.001 |
| Family type | Cohabitating | 35195 (52.5%) | 12317 (50.6%) | <0.001 | 20636 (54.4%) | 6149 (53.3%) | 8280 (54.0%) | 2906 (52.1%) | 6279 (45.8%) | 3262 (45.1%) | <0.001 |
|  | Living alone | 31792 (47.5%) | 12031 (49.4%) |  | 17315 (45.6%) | 5396 (46.7%) | 7046 (46.0%) | 2668 (47.9%) | 7431 (54.2%) | 3967 (54.9%) |  |
| Smoking |  | 6901 (12.9%) | 1653 (8.9%) | <0.001 | 4639 (14.8%) | 999 (11.0%) | 1383 (11.2%) | 326 (7.7%) | 879 (8.7%) | 328 (6.3%) | <0.001 |
| Alcohol user |  | 2153 (5.1%) | 534 (3.8%) | <0.001 | 1395 (5.5%) | 324 (4.7%) | 454 (4.7%) | 113 (3.4%) | 304 (4.2%) | 97 (2.6%) | <0.001 |
| Location of care | Out-patient | 38546 (57.5%) | 11554 (47.4%) | <0.001 | 22854 (60.1%) | 5645 (48.8%) | 9428 (61.5%) | 2981 (53.4%) | 6264 (45.7%) | 2928 (40.5%) | <0.001 |
|  | In-patient | 28544 (42.5%) | 12819 (52.6%) |  | 15175 (39.9%) | 5915 (51.2%) | 5913 (38.5%) | 2599 (46.6%) | 7456 (54.3%) | 4305 (59.5%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 40792 (60.8%) | 16879 (69.3%) | <0.001 | 24040 (63.2%) | 8266 (71.5%) | 7827 (51.0%) | 3441 (61.7%) | 8925 (65.1%) | 5172 (71.5%) | <0.001 |
| Duration of HF | <6mo | 37082 (56.6%) | 10540 (44.4%) | <0.001 | 22491 (60.3%) | 5182 (45.7%) | 8152 (54.4%) | 2366 (43.5%) | 6439 (48.7%) | 2992 (42.8%) | <0.001 |
|  | >=6mo | 28438 (43.4%) | 13222 (55.6%) |  | 14821 (39.7%) | 6149 (54.3%) | 6830 (45.6%) | 3071 (56.5%) | 6787 (51.3%) | 4002 (57.2%) |  |
| Follow-up location | Primary care | 20228 (31.4%) | 7898 (33.8%) | <0.001 | 7789 (21.2%) | 2958 (26.6%) | 5382 (36.5%) | 1886 (35.2%) | 7057 (54.7%) | 3054 (44.4%) | <0.001 |
|  | Hospital | 44132 (68.6%) | 15466 (66.2%) |  | 28911 (78.8%) | 8169 (73.4%) | 9366 (63.5%) | 3475 (64.8%) | 5855 (45.3%) | 3822 (55.6%) |  |
| NYHA functional class | I-II | 31283 (62.8%) | 8796 (53.2%) | <0.001 | 17697 (59.5%) | 4019 (48.6%) | 8136 (70.9%) | 2363 (61.2%) | 5450 (63.5%) | 2414 (54.5%) | <0.001 |
|  | III-IV | 18510 (37.2%) | 7753 (46.8%) |  | 12030 (40.5%) | 4243 (51.4%) | 3343 (29.1%) | 1498 (38.8%) | 3137 (36.5%) | 2012 (45.5%) |  |
| BMI, median (IQR) |  | 27 (24, 31) | 25 (23, 29) | <0.001 | 26 (23, 30) | 25 (22, 29) | 27 (24, 31) | 26 (23, 29) | 28 (24, 32) | 26 (23, 30) | <0.001 |
| SBP, median (IQR) |  | 125 (112, 140) | 125 (110, 140) | <0.001 | 120 (110, 140) | 120 (110, 135) | 130 (116, 141) | 129 (115, 140) | 130 (120, 147) | 130 (115, 142) | <0.001 |
| DBP, median (IQR) |  | 74 (65, 80) | 70 (62, 80) | <0.001 | 73 (65, 80) | 70 (62, 80) | 75 (66, 80) | 70 (64, 80) | 74 (65, 80) | 70 (61, 80) | <0.001 |
| MAP, median (IQR) |  | 92 (83, 100) | 90 (80, 98) | <0.001 | 90 (82, 100) | 87 (80, 97) | 93 (84, 102) | 90 (82, 100) | 93 (85, 102) | 90 (82, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 72 (64, 82) | <0.001 | 72 (63, 84) | 73 (64, 83) | 70 (62, 80) | 72 (63, 82) | 71 (62, 82) | 72 (64, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 69 (51, 87) | 62 (45, 80) | <0.001 | 71 (53, 89) | 63 (46, 82) | 69 (52, 87) | 62 (45, 80) | 62 (45, 81) | 59 (43, 77) | <0.001 |
| Potassium categories | Normakalemia | 50962 (93.1%) | 17731 (91.9%) | <0.001 | 28959 (93.5%) | 8234 (92.6%) | 11896 (93.4%) | 4176 (92.0%) | 10107 (91.7%) | 5321 (90.9%) | <0.001 |
|  | Hypokalemia | 2319 (4.2%) | 956 (5.0%) |  | 1121 (3.6%) | 373 (4.2%) | 542 (4.3%) | 216 (4.8%) | 656 (6.0%) | 367 (6.3%) |  |
|  | Hyperkalemia | 1455 (2.7%) | 601 (3.1%) |  | 898 (2.9%) | 287 (3.2%) | 302 (2.4%) | 149 (3.3%) | 255 (2.3%) | 165 (2.8%) |  |
| Haemoglobin, median (IQR) |  | 135 (122, 146) | 128 (116, 140) | <0.001 | 137 (124, 148) | 131 (119, 143) | 134 (121, 145) | 128 (115, 140) | 129 (117, 141) | 124 (113, 136) | <0.001 |
| NT-proBNP, median (IQR) |  | 2120 (900, 4696) | 2951 (1370, 6454) | <0.001 | 2496 (1075, 5562) | 3784 (1711, 8523) | 1667 (651, 3716) | 2511 (1160, 5230) | 1825 (809, 3720) | 2427 (1188, 4840) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 58322 (87.9%) | 18948 (78.6%) | <0.001 | 35152 (93.5%) | 9772 (85.5%) | 13237 (87.1%) | 4339 (78.5%) | 9933 (73.3%) | 4837 (67.5%) | <0.001 |
| Beta-blockers |  | 59737 (89.3%) | 20891 (86.0%) | <0.001 | 35215 (92.8%) | 10315 (89.5%) | 13403 (87.6%) | 4765 (85.6%) | 11119 (81.4%) | 5811 (80.6%) | <0.001 |
| MRA |  | 22927 (34.3%) | 9148 (37.7%) | <0.001 | 14965 (39.5%) | 4792 (41.7%) | 4049 (26.5%) | 1843 (33.3%) | 3913 (28.7%) | 2513 (34.9%) | <0.001 |
| DIuretics |  | 49174 (73.5%) | 20204 (83.2%) | <0.001 | 28006 (73.9%) | 9519 (82.6%) | 10071 (65.8%) | 4435 (79.8%) | 11097 (81.2%) | 6250 (86.7%) | <0.001 |
| Digoxin |  | 8440 (12.6%) | 3730 (15.4%) | <0.001 | 5006 (13.2%) | 1772 (15.4%) | 1670 (10.9%) | 825 (14.8%) | 1764 (12.9%) | 1133 (15.7%) | <0.001 |
| Antiplatelet therapy |  | 28993 (43.4%) | 9036 (37.2%) | <0.001 | 17183 (45.4%) | 4740 (41.2%) | 6914 (45.2%) | 1981 (35.7%) | 4896 (35.8%) | 2315 (32.2%) | <0.001 |
| Anticoagulant therapy |  | 29568 (44.2%) | 12795 (52.7%) | <0.001 | 16337 (43.1%) | 5755 (50.0%) | 6633 (43.4%) | 3107 (55.9%) | 6598 (48.3%) | 3933 (54.5%) | <0.001 |
| Statins |  | 33411 (49.9%) | 10924 (45.0%) | <0.001 | 19389 (51.1%) | 5439 (47.3%) | 8147 (53.2%) | 2520 (45.3%) | 5875 (43.0%) | 2965 (41.1%) | <0.001 |
| Nitrates |  | 8317 (12.4%) | 3268 (13.5%) | <0.001 | 4227 (11.2%) | 1513 (13.1%) | 1982 (13.0%) | 736 (13.3%) | 2108 (15.4%) | 1019 (14.1%) | <0.001 |
| HF devices |  | 3813 (5.8%) | 1125 (4.7%) | <0.001 | 3097 (8.2%) | 882 (7.7%) | 503 (3.3%) | 158 (2.9%) | 213 (1.6%) | 85 (1.2%) | <0.001 |
| EF categories | HFrEF | 38029 (56.7%) | 11560 (47.4%) | <0.001 | 38029 (100.0%) | 11560 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 15341 (22.9%) | 5580 (22.9%) |  | 0 (0.0%) | 0 (0.0%) | 15341 (100.0%) | 5580 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 13720 (20.5%) | 7233 (29.7%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 13720 (100.0%) | 7233 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 19091 (28.5%) | 4880 (20.0%) | <0.001 | 9685 (25.5%) | 2034 (17.6%) | 4624 (30.1%) | 1198 (21.5%) | 4782 (34.9%) | 1648 (22.8%) | <0.001 |
| Hypertension |  | 43371 (64.6%) | 16012 (65.7%) | 0.003 | 22217 (58.4%) | 6875 (59.5%) | 10389 (67.7%) | 3823 (68.5%) | 10765 (78.5%) | 5314 (73.5%) | <0.001 |
| Diabetes |  | 18017 (26.9%) | 5813 (23.9%) | <0.001 | 9843 (25.9%) | 2785 (24.1%) | 4013 (26.2%) | 1268 (22.7%) | 4161 (30.3%) | 1760 (24.3%) | <0.001 |
| CAD |  | 34830 (51.9%) | 13103 (53.8%) | <0.001 | 20014 (52.6%) | 6665 (57.7%) | 8559 (55.8%) | 3032 (54.3%) | 6257 (45.6%) | 3406 (47.1%) | <0.001 |
| AF |  | 35456 (52.8%) | 15805 (64.8%) | <0.001 | 18471 (48.6%) | 6842 (59.2%) | 8308 (54.2%) | 3819 (68.4%) | 8677 (63.2%) | 5144 (71.1%) | <0.001 |
| VHD |  | 0 (0.0%) | 24373 (100.0%) | <0.001 | 0 (0.0%) | 11560 (100.0%) | 0 (0.0%) | 5580 (100.0%) | 0 (0.0%) | 7233 (100.0%) | <0.001 |
| CKD |  | 24968 (37.2%) | 11611 (47.6%) | <0.001 | 12951 (34.1%) | 5288 (45.7%) | 5580 (36.4%) | 2643 (47.4%) | 6437 (46.9%) | 3680 (50.9%) | <0.001 |
| Anaemia |  | 20817 (31.0%) | 10371 (42.6%) | <0.001 | 10594 (27.9%) | 4524 (39.1%) | 4854 (31.6%) | 2403 (43.1%) | 5369 (39.1%) | 3444 (47.6%) | <0.001 |
| COPD |  | 8448 (12.6%) | 3149 (12.9%) | 0.19 | 4261 (11.2%) | 1363 (11.8%) | 1923 (12.5%) | 724 (13.0%) | 2264 (16.5%) | 1062 (14.7%) | <0.001 |
| Liver disease |  | 1330 (2.0%) | 586 (2.4%) | <0.001 | 790 (2.1%) | 270 (2.3%) | 245 (1.6%) | 134 (2.4%) | 295 (2.2%) | 182 (2.5%) | <0.001 |
| PAD |  | 5093 (7.6%) | 2823 (11.6%) | <0.001 | 2738 (7.2%) | 1369 (11.8%) | 1197 (7.8%) | 657 (11.8%) | 1158 (8.4%) | 797 (11.0%) | <0.001 |
| Stroke or TIA |  | 10204 (15.2%) | 4456 (18.3%) | <0.001 | 5399 (14.2%) | 2003 (17.3%) | 2318 (15.1%) | 1042 (18.7%) | 2487 (18.1%) | 1411 (19.5%) | <0.001 |
| Depression |  | 2416 (3.6%) | 846 (3.5%) | 0.35 | 1323 (3.5%) | 415 (3.6%) | 525 (3.4%) | 177 (3.2%) | 568 (4.1%) | 254 (3.5%) | 0.004 |
| Dementia |  | 950 (1.4%) | 450 (1.8%) | <0.001 | 477 (1.3%) | 197 (1.7%) | 194 (1.3%) | 98 (1.8%) | 279 (2.0%) | 155 (2.1%) | <0.001 |
| Cancer <3years |  | 8238 (12.3%) | 3126 (12.8%) | 0.027 | 4246 (11.2%) | 1417 (12.3%) | 2007 (13.1%) | 735 (13.2%) | 1985 (14.5%) | 974 (13.5%) | <0.001 |
| Muscolo-skeletal <3years |  | 20076 (29.9%) | 8044 (33.0%) | <0.001 | 10054 (26.4%) | 3384 (29.3%) | 4839 (31.5%) | 1913 (34.3%) | 5183 (37.8%) | 2747 (38.0%) | <0.001 |
| Dysthyroidism |  | 4789 (7.1%) | 2072 (8.5%) | <0.001 | 2277 (6.0%) | 851 (7.4%) | 1137 (7.4%) | 441 (7.9%) | 1375 (10.0%) | 780 (10.8%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 20356 (30.3%) | 6507 (26.7%) | <0.001 | 12062 (31.7%) | 3053 (26.4%) | 4581 (29.9%) | 1491 (26.7%) | 3713 (27.1%) | 1963 (27.1%) | <0.001 |
|  | 2-3 | 25845 (38.5%) | 9310 (38.2%) |  | 14910 (39.2%) | 4518 (39.1%) | 5894 (38.4%) | 2118 (38.0%) | 5041 (36.7%) | 2674 (37.0%) |  |
|  | 4-7 | 17166 (25.6%) | 7038 (28.9%) |  | 9193 (24.2%) | 3317 (28.7%) | 3966 (25.9%) | 1620 (29.0%) | 4007 (29.2%) | 2101 (29.0%) |  |
|  | >=8 | 3723 (5.5%) | 1518 (6.2%) |  | 1864 (4.9%) | 672 (5.8%) | 900 (5.9%) | 351 (6.3%) | 959 (7.0%) | 495 (6.8%) |  |

**Supplementary Table 9. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by diabetes by chronic kidney disease (CKD)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 54884 (60%) | 36579 (40%) |  | 31350 (63%) | 18239 (37%) | 12698 (61%) | 8223 (39%) | 10836 (52%) | 10117 (48%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 17462 (31.8%) | 15872 (43.4%) | <0.001 | 8051 (25.7%) | 6318 (34.6%) | 4217 (33.2%) | 3688 (44.8%) | 5194 (47.9%) | 5866 (58.0%) | <0.001 |
|  | Male | 37422 (68.2%) | 20707 (56.6%) |  | 23299 (74.3%) | 11921 (65.4%) | 8481 (66.8%) | 4535 (55.2%) | 5642 (52.1%) | 4251 (42.0%) |  |
| Age, median (IQR) |  | 71 (62, 79) | 80 (74, 85) | <0.001 | 69 (60, 77) | 79 (73, 84) | 72 (63, 79) | 81 (75, 86) | 77 (69, 83) | 82 (77, 87) | <0.001 |
| Family type | Cohabitating | 29929 (54.6%) | 17583 (48.1%) | <0.001 | 17416 (55.7%) | 9369 (51.4%) | 7199 (56.8%) | 3987 (48.5%) | 5314 (49.1%) | 4227 (41.8%) | <0.001 |
|  | Living alone | 24860 (45.4%) | 18963 (51.9%) |  | 13863 (44.3%) | 8848 (48.6%) | 5486 (43.2%) | 4228 (51.5%) | 5511 (50.9%) | 5887 (58.2%) |  |
| Smoking |  | 6504 (14.6%) | 2050 (7.5%) | <0.001 | 4372 (16.6%) | 1266 (9.0%) | 1320 (12.7%) | 389 (6.3%) | 812 (10.1%) | 395 (5.5%) | <0.001 |
| Alcohol user |  | 2113 (5.9%) | 574 (2.8%) | <0.001 | 1408 (6.6%) | 311 (2.9%) | 439 (5.3%) | 128 (2.7%) | 266 (4.5%) | 135 (2.6%) | <0.001 |
| Location of care | Out-patient | 32985 (60.1%) | 17115 (46.8%) | <0.001 | 19386 (61.8%) | 9113 (50.0%) | 8329 (65.6%) | 4080 (49.6%) | 5270 (48.6%) | 3922 (38.8%) | <0.001 |
|  | In-patient | 21899 (39.9%) | 19464 (53.2%) |  | 11964 (38.2%) | 9126 (50.0%) | 4369 (34.4%) | 4143 (50.4%) | 5566 (51.4%) | 6195 (61.2%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 31615 (57.6%) | 26056 (71.2%) | <0.001 | 19142 (61.1%) | 13164 (72.2%) | 5871 (46.2%) | 5397 (65.6%) | 6602 (60.9%) | 7495 (74.1%) | <0.001 |
| Duration of HF | <6mo | 32558 (60.8%) | 15064 (42.2%) | <0.001 | 19830 (64.5%) | 7843 (43.8%) | 7253 (58.5%) | 3265 (40.7%) | 5475 (52.4%) | 3956 (40.5%) | <0.001 |
|  | >=6mo | 21001 (39.2%) | 20659 (57.8%) |  | 10894 (35.5%) | 10076 (56.2%) | 5138 (41.5%) | 4763 (59.3%) | 4969 (47.6%) | 5820 (59.5%) |  |
| Follow-up location | Primary care | 13707 (25.9%) | 14419 (41.5%) | <0.001 | 5136 (16.9%) | 5611 (32.2%) | 3701 (30.1%) | 3567 (45.8%) | 4870 (47.4%) | 5241 (55.1%) | <0.001 |
|  | Hospital | 39288 (74.1%) | 20310 (58.5%) |  | 25263 (83.1%) | 11817 (67.8%) | 8612 (69.9%) | 4229 (54.2%) | 5413 (52.6%) | 4264 (44.9%) |  |
| NYHA functional class | I-II | 27622 (67.0%) | 12457 (49.5%) | <0.001 | 15681 (63.9%) | 6035 (44.8%) | 7303 (75.1%) | 3196 (57.0%) | 4638 (66.8%) | 3226 (53.2%) | <0.001 |
|  | III-IV | 13576 (33.0%) | 12687 (50.5%) |  | 8841 (36.1%) | 7432 (55.2%) | 2426 (24.9%) | 2415 (43.0%) | 2309 (33.2%) | 2840 (46.8%) |  |
| BMI, median (IQR) |  | 27 (24, 30) | 26 (23, 30) | <0.001 | 26 (23, 30) | 26 (23, 29) | 27 (24, 31) | 27 (23, 30) | 27 (24, 31) | 27 (24, 31) | <0.001 |
| SBP, median (IQR) |  | 125 (111, 140) | 125 (110, 140) | 0.18 | 120 (110, 138) | 120 (110, 138) | 130 (115, 140) | 130 (115, 140) | 130 (120, 145) | 130 (120, 146) | <0.001 |
| DBP, median (IQR) |  | 75 (66, 80) | 70 (62, 80) | <0.001 | 75 (65, 80) | 70 (61, 80) | 75 (68, 80) | 70 (64, 80) | 75 (66, 80) | 70 (62, 80) | <0.001 |
| MAP, median (IQR) |  | 92 (83, 100) | 90 (81, 98) | <0.001 | 90 (82, 100) | 88 (80, 97) | 93 (85, 102) | 90 (83, 100) | 93 (85, 102) | 92 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 83) | 72 (63, 82) | 0.27 | 72 (63, 84) | 72 (64, 83) | 70 (61, 80) | 71 (63, 82) | 72 (63, 82) | 71 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 82 (70, 93) | 45 (35, 53) | <0.001 | 82 (71, 94) | 46 (36, 53) | 82 (70, 92) | 45 (36, 53) | 79 (69, 90) | 44 (34, 52) | <0.001 |
| Potassium categories | Normakalemia | 43041 (94.5%) | 25652 (90.1%) | <0.001 | 24662 (95.0%) | 12531 (90.2%) | 10185 (94.9%) | 5887 (89.9%) | 8194 (92.6%) | 7234 (90.2%) | <0.001 |
|  | Hypokalemia | 1860 (4.1%) | 1415 (5.0%) |  | 882 (3.4%) | 612 (4.4%) | 417 (3.9%) | 341 (5.2%) | 561 (6.3%) | 462 (5.8%) |  |
|  | Hyperkalemia | 654 (1.4%) | 1402 (4.9%) |  | 429 (1.7%) | 756 (5.4%) | 131 (1.2%) | 320 (4.9%) | 94 (1.1%) | 326 (4.1%) |  |
| Haemoglobin, median (IQR) |  | 137 (125, 148) | 127 (115, 139) | <0.001 | 139 (127, 149) | 129 (117, 141) | 136 (124, 147) | 126 (114, 138) | 131 (119, 142) | 123 (112, 135) | <0.001 |
| NT-proBNP, median (IQR) |  | 1770 (758, 3730) | 3600 (1672, 7940) | <0.001 | 2110 (924, 4519) | 4548 (2060, 10000) | 1319 (525, 2800) | 3120 (1490, 6720) | 1500 (680, 2900) | 2822 (1347, 5649) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 49163 (90.5%) | 28107 (77.8%) | <0.001 | 29678 (95.6%) | 15246 (84.7%) | 11372 (90.4%) | 6204 (76.1%) | 8113 (75.7%) | 6657 (66.7%) | <0.001 |
| Beta-blockers |  | 48581 (88.7%) | 32047 (87.9%) | <0.001 | 28959 (92.6%) | 16571 (91.1%) | 11016 (86.9%) | 7152 (87.2%) | 8606 (79.8%) | 8324 (82.6%) | <0.001 |
| MRA |  | 19940 (36.5%) | 12135 (33.4%) | <0.001 | 13191 (42.2%) | 6566 (36.2%) | 3470 (27.4%) | 2422 (29.6%) | 3279 (30.5%) | 3147 (31.3%) | <0.001 |
| DIuretics |  | 37058 (67.7%) | 32320 (88.6%) | <0.001 | 21454 (68.7%) | 16071 (88.4%) | 7401 (58.4%) | 7105 (86.6%) | 8203 (76.0%) | 9144 (90.7%) | <0.001 |
| Digoxin |  | 7661 (14.0%) | 4509 (12.4%) | <0.001 | 4474 (14.3%) | 2304 (12.7%) | 1519 (12.0%) | 976 (11.9%) | 1668 (15.4%) | 1229 (12.2%) | <0.001 |
| Antiplatelet therapy |  | 22487 (41.1%) | 15542 (42.7%) | <0.001 | 13473 (43.1%) | 8450 (46.5%) | 5480 (43.3%) | 3415 (41.7%) | 3534 (32.8%) | 3677 (36.5%) | <0.001 |
| Anticoagulant therapy |  | 24778 (45.3%) | 17585 (48.3%) | <0.001 | 13720 (43.9%) | 8372 (46.1%) | 5606 (44.3%) | 4134 (50.4%) | 5452 (50.6%) | 5079 (50.4%) | <0.001 |
| Statins |  | 26696 (48.8%) | 17639 (48.4%) | 0.26 | 15497 (49.6%) | 9331 (51.4%) | 6593 (52.0%) | 4074 (49.7%) | 4606 (42.7%) | 4234 (42.0%) | <0.001 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Nitrates |  | 4858 (8.9%) | 6727 (18.5%) | <0.001 | 2429 (7.8%) | 3311 (18.2%) | 1189 (9.4%) | 1529 (18.7%) | 1240 (11.5%) | 1887 (18.7%) | <0.001 |
| HF devices |  | 2942 (5.4%) | 1996 (5.5%) | 0.45 | 2350 (7.6%) | 1629 (9.0%) | 406 (3.2%) | 255 (3.2%) | 186 (1.8%) | 112 (1.1%) | <0.001 |
| EF categories | HFrEF | 31350 (57.1%) | 18239 (49.9%) | <0.001 | 31350 (100.0%) | 18239 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 12698 (23.1%) | 8223 (22.5%) |  | 0 (0.0%) | 0 (0.0%) | 12698 (100.0%) | 8223 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 10836 (19.7%) | 10117 (27.7%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 10836 (100.0%) | 10117 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 14801 (27.0%) | 9170 (25.1%) | <0.001 | 7838 (25.0%) | 3881 (21.3%) | 3613 (28.5%) | 2209 (26.9%) | 3350 (30.9%) | 3080 (30.4%) | <0.001 |
| Hypertension |  | 32274 (58.8%) | 27109 (74.1%) | <0.001 | 16628 (53.0%) | 12464 (68.3%) | 7831 (61.7%) | 6381 (77.6%) | 7815 (72.1%) | 8264 (81.7%) | <0.001 |
| Diabetes |  | 12224 (22.3%) | 11606 (31.7%) | <0.001 | 6938 (22.1%) | 5690 (31.2%) | 2677 (21.1%) | 2604 (31.7%) | 2609 (24.1%) | 3312 (32.7%) | <0.001 |
| CAD |  | 26075 (47.5%) | 21858 (59.8%) | <0.001 | 14994 (47.8%) | 11685 (64.1%) | 6566 (51.7%) | 5025 (61.1%) | 4515 (41.7%) | 5148 (50.9%) | <0.001 |
| AF |  | 28295 (51.6%) | 22966 (62.8%) | <0.001 | 14758 (47.1%) | 10555 (57.9%) | 6676 (52.6%) | 5451 (66.3%) | 6861 (63.3%) | 6960 (68.8%) | <0.001 |
| VHD |  | 12762 (23.3%) | 11611 (31.7%) | <0.001 | 6272 (20.0%) | 5288 (29.0%) | 2937 (23.1%) | 2643 (32.1%) | 3553 (32.8%) | 3680 (36.4%) | <0.001 |
| CKD |  | 0 (0.0%) | 36579 (100.0%) | <0.001 | 0 (0.0%) | 18239 (100.0%) | 0 (0.0%) | 8223 (100.0%) | 0 (0.0%) | 10117 (100.0%) | <0.001 |
| Anaemia |  | 14501 (26.4%) | 16687 (45.6%) | <0.001 | 7389 (23.6%) | 7729 (42.4%) | 3396 (26.7%) | 3861 (47.0%) | 3716 (34.3%) | 5097 (50.4%) | <0.001 |
| COPD |  | 6433 (11.7%) | 5164 (14.1%) | <0.001 | 3335 (10.6%) | 2289 (12.6%) | 1443 (11.4%) | 1204 (14.6%) | 1655 (15.3%) | 1671 (16.5%) | <0.001 |
| Liver disease |  | 1251 (2.3%) | 665 (1.8%) | <0.001 | 742 (2.4%) | 318 (1.7%) | 236 (1.9%) | 143 (1.7%) | 273 (2.5%) | 204 (2.0%) | <0.001 |
| PAD |  | 3774 (6.9%) | 4142 (11.3%) | <0.001 | 2020 (6.4%) | 2087 (11.4%) | 917 (7.2%) | 937 (11.4%) | 837 (7.7%) | 1118 (11.1%) | <0.001 |
| Stroke or TIA |  | 7324 (13.3%) | 7336 (20.1%) | <0.001 | 3864 (12.3%) | 3538 (19.4%) | 1706 (13.4%) | 1654 (20.1%) | 1754 (16.2%) | 2144 (21.2%) | <0.001 |
| Depression |  | 1986 (3.6%) | 1276 (3.5%) | 0.30 | 1137 (3.6%) | 601 (3.3%) | 424 (3.3%) | 278 (3.4%) | 425 (3.9%) | 397 (3.9%) | 0.012 |
| Dementia |  | 620 (1.1%) | 780 (2.1%) | <0.001 | 298 (1.0%) | 376 (2.1%) | 122 (1.0%) | 170 (2.1%) | 200 (1.8%) | 234 (2.3%) | <0.001 |
| Cancer <3years |  | 6091 (11.1%) | 5273 (14.4%) | <0.001 | 3113 (9.9%) | 2550 (14.0%) | 1552 (12.2%) | 1190 (14.5%) | 1426 (13.2%) | 1533 (15.2%) | <0.001 |
| Muscolo-skeletal <3years |  | 15509 (28.3%) | 12611 (34.5%) | <0.001 | 7803 (24.9%) | 5635 (30.9%) | 3821 (30.1%) | 2931 (35.6%) | 3885 (35.9%) | 4045 (40.0%) | <0.001 |
| Dysthyroidism |  | 3367 (6.1%) | 3494 (9.6%) | <0.001 | 1602 (5.1%) | 1526 (8.4%) | 802 (6.3%) | 776 (9.4%) | 963 (8.9%) | 1192 (11.8%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 20013 (36.5%) | 6850 (18.7%) | <0.001 | 11804 (37.7%) | 3311 (18.2%) | 4513 (35.5%) | 1559 (19.0%) | 3696 (34.1%) | 1980 (19.6%) | <0.001 |
|  | 2-3 | 21979 (40.0%) | 13176 (36.0%) |  | 12666 (40.4%) | 6762 (37.1%) | 5108 (40.2%) | 2904 (35.3%) | 4205 (38.8%) | 3510 (34.7%) |  |
|  | 4-7 | 10689 (19.5%) | 13515 (36.9%) |  | 5755 (18.4%) | 6755 (37.0%) | 2527 (19.9%) | 3059 (37.2%) | 2407 (22.2%) | 3701 (36.6%) |  |
|  | >=8 | 2203 (4.0%) | 3038 (8.3%) |  | 1125 (3.6%) | 1411 (7.7%) | 550 (4.3%) | 701 (8.5%) | 528 (4.9%) | 926 (9.2%) |  |

**Supplementary Table 10. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by anaemia.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 60275 (66%) | 31188 (34%) |  | 34471 (69%) | 15118 (31%) | 13664 (65%) | 7257 (35%) | 12140 (58%) | 8813 (42%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 23022 (38.2%) | 10312 (33.1%) | <0.001 | 10551 (30.6%) | 3818 (25.3%) | 5516 (40.4%) | 2389 (32.9%) | 6955 (57.3%) | 4105 (46.6%) | <0.001 |
|  | Male | 37253 (61.8%) | 20876 (66.9%) |  | 23920 (69.4%) | 11300 (74.7%) | 8148 (59.6%) | 4868 (67.1%) | 5185 (42.7%) | 4708 (53.4%) |  |
| Age, median (IQR) |  | 74 (65, 81) | 79 (71, 84) | <0.001 | 71 (62, 79) | 77 (69, 83) | 74 (66, 81) | 79 (72, 84) | 79 (71, 84) | 81 (74, 86) | <0.001 |
| Family type | Cohabitating | 31908 (53.0%) | 15604 (50.1%) | <0.001 | 18843 (54.8%) | 7942 (52.6%) | 7476 (54.8%) | 3710 (51.1%) | 5589 (46.1%) | 3952 (44.9%) | <0.001 |
|  | Living alone | 28273 (47.0%) | 15550 (49.9%) |  | 15560 (45.2%) | 7151 (47.4%) | 6170 (45.2%) | 3544 (48.9%) | 6543 (53.9%) | 4855 (55.1%) |  |
| Smoking |  | 6244 (12.8%) | 2310 (9.9%) | <0.001 | 4205 (14.7%) | 1433 (12.2%) | 1240 (11.2%) | 469 (8.6%) | 799 (8.7%) | 408 (6.7%) | <0.001 |
| Alcohol user |  | 1973 (5.1%) | 714 (4.1%) | <0.001 | 1326 (5.7%) | 393 (4.4%) | 411 (4.6%) | 156 (3.8%) | 236 (3.5%) | 165 (3.8%) | <0.001 |
| Location of care | Out-patient | 36627 (60.8%) | 13473 (43.2%) | <0.001 | 21388 (62.0%) | 7111 (47.0%) | 8971 (65.7%) | 3438 (47.4%) | 6268 (51.6%) | 2924 (33.2%) | <0.001 |
|  | In-patient | 23648 (39.2%) | 17715 (56.8%) |  | 13083 (38.0%) | 8007 (53.0%) | 4693 (34.3%) | 3819 (52.6%) | 5872 (48.4%) | 5889 (66.8%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 34850 (57.8%) | 22821 (73.2%) | <0.001 | 21218 (61.6%) | 11088 (73.3%) | 6430 (47.1%) | 4838 (66.7%) | 7202 (59.3%) | 6895 (78.2%) | <0.001 |
| Duration of HF | <6mo | 32941 (55.9%) | 14681 (48.3%) | <0.001 | 20211 (59.8%) | 7462 (50.3%) | 7189 (53.9%) | 3329 (47.0%) | 5541 (47.2%) | 3890 (45.9%) | <0.001 |
|  | >=6mo | 25960 (44.1%) | 15700 (51.7%) |  | 13611 (40.2%) | 7359 (49.7%) | 6149 (46.1%) | 3752 (53.0%) | 6200 (52.8%) | 4589 (54.1%) |  |
| Follow-up location | Primary care | 17021 (29.3%) | 11105 (37.5%) | <0.001 | 6578 (19.7%) | 4169 (28.8%) | 4554 (34.5%) | 2714 (39.4%) | 5889 (51.0%) | 4222 (51.2%) | <0.001 |
|  | Hospital | 41100 (70.7%) | 18498 (62.5%) |  | 26782 (80.3%) | 10298 (71.2%) | 8662 (65.5%) | 4179 (60.6%) | 5656 (49.0%) | 4021 (48.8%) |  |
| NYHA functional class | I-II | 29627 (64.5%) | 10452 (51.2%) | <0.001 | 16766 (61.4%) | 4950 (46.4%) | 7646 (72.7%) | 2853 (59.2%) | 5215 (64.6%) | 2649 (53.6%) | <0.001 |
|  | III-IV | 16284 (35.5%) | 9979 (48.8%) |  | 10547 (38.6%) | 5726 (53.6%) | 2878 (27.3%) | 1963 (40.8%) | 2859 (35.4%) | 2290 (46.4%) |  |
| BMI, median (IQR) |  | 27 (24, 31) | 26 (23, 29) | <0.001 | 27 (24, 30) | 25 (22, 29) | 27 (24, 31) | 26 (23, 30) | 27 (24, 32) | 26 (23, 30) | <0.001 |
| SBP, median (IQR) |  | 125 (112, 140) | 125 (110, 140) | <0.001 | 121 (110, 140) | 120 (110, 135) | 130 (117, 140) | 129 (115, 140) | 130 (120, 145) | 130 (118, 145) | <0.001 |
| DBP, median (IQR) |  | 75 (67, 80) | 70 (60, 80) | <0.001 | 75 (67, 80) | 70 (60, 80) | 75 (70, 80) | 70 (62, 80) | 75 (67, 80) | 70 (60, 80) | <0.001 |
| MAP, median (IQR) |  | 92 (83, 100) | 88 (80, 97) | <0.001 | 90 (82, 100) | 87 (79, 97) | 93 (85, 102) | 90 (82, 99) | 93 (85, 103) | 90 (82, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 72 (64, 82) | <0.001 | 72 (63, 84) | 73 (64, 83) | 70 (61, 80) | 71 (63, 81) | 71 (63, 82) | 72 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 71 (54, 88) | 58 (41, 78) | <0.001 | 73 (56, 89) | 59 (42, 80) | 72 (55, 88) | 58 (41, 78) | 65 (49, 83) | 55 (39, 74) | <0.001 |
| Potassium categories | Normakalemia | 46129 (93.9%) | 22564 (90.6%) | <0.001 | 26363 (94.3%) | 10830 (91.0%) | 10702 (94.1%) | 5370 (90.8%) | 9064 (92.6%) | 6364 (89.9%) | <0.001 |
|  | Hypokalemia | 1880 (3.8%) | 1395 (5.6%) |  | 912 (3.3%) | 582 (4.9%) | 435 (3.8%) | 323 (5.5%) | 533 (5.4%) | 490 (6.9%) |  |
|  | Hyperkalemia | 1121 (2.3%) | 935 (3.8%) |  | 696 (2.5%) | 489 (4.1%) | 230 (2.0%) | 221 (3.7%) | 195 (2.0%) | 225 (3.2%) |  |
| Haemoglobin, median (IQR) |  | 141 (133, 150) | 115 (107, 121) | <0.001 | 142 (134, 151) | 116 (109, 123) | 140 (133, 149) | 115 (107, 121) | 137 (130, 146) | 113 (105, 118) | <0.001 |
| NT-proBNP, median (IQR) |  | 1900 (820, 4080) | 3445 (1603, 7520) | <0.001 | 2240 (990, 4930) | 4420 (2029, 9723) | 1440 (584, 3100) | 3000 (1372, 6440) | 1600 (735, 3171) | 2703 (1333, 5434) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 52787 (88.5%) | 24483 (79.4%) | <0.001 | 31970 (93.8%) | 12954 (86.6%) | 11900 (87.9%) | 5676 (79.0%) | 8917 (74.3%) | 5853 (67.3%) | <0.001 |
| Beta-blockers |  | 53828 (89.5%) | 26800 (86.2%) | <0.001 | 31905 (92.7%) | 13625 (90.4%) | 11968 (87.8%) | 6200 (85.7%) | 9955 (82.3%) | 6975 (79.6%) | <0.001 |
| MRA |  | 21444 (35.7%) | 10631 (34.3%) | <0.001 | 14078 (41.0%) | 5679 (37.8%) | 3731 (27.4%) | 2161 (29.9%) | 3635 (30.1%) | 2791 (31.9%) | <0.001 |
| DIuretics |  | 43239 (72.0%) | 26139 (84.1%) | <0.001 | 24975 (72.7%) | 12550 (83.3%) | 8702 (63.8%) | 5804 (80.2%) | 9562 (79.1%) | 7785 (88.6%) | <0.001 |
| Digoxin |  | 8716 (14.5%) | 3454 (11.1%) | <0.001 | 5089 (14.8%) | 1689 (11.2%) | 1733 (12.7%) | 762 (10.5%) | 1894 (15.6%) | 1003 (11.4%) | <0.001 |
| Antiplatelet therapy |  | 23798 (39.6%) | 14231 (45.8%) | <0.001 | 14276 (41.6%) | 7647 (50.8%) | 5597 (41.1%) | 3298 (45.7%) | 3925 (32.5%) | 3286 (37.5%) | <0.001 |
| Anticoagulant therapy |  | 28924 (48.1%) | 13439 (43.3%) | <0.001 | 15965 (46.5%) | 6127 (40.7%) | 6553 (48.1%) | 3187 (44.1%) | 6406 (53.0%) | 4125 (47.0%) | <0.001 |
| Statins |  | 28599 (47.6%) | 15736 (50.6%) | <0.001 | 16668 (48.5%) | 8160 (54.1%) | 6893 (50.6%) | 3774 (52.2%) | 5038 (41.6%) | 3802 (43.3%) | <0.001 |
| Nitrates |  | 6342 (10.6%) | 5243 (16.9%) | <0.001 | 3260 (9.5%) | 2480 (16.5%) | 1518 (11.1%) | 1200 (16.6%) | 1564 (12.9%) | 1563 (17.8%) | <0.001 |
| HF devices |  | 3376 (5.7%) | 1562 (5.1%) | <0.001 | 2727 (8.0%) | 1252 (8.4%) | 443 (3.3%) | 218 (3.1%) | 206 (1.7%) | 92 (1.1%) | <0.001 |
| EF categories | HFrEF | 34471 (57.2%) | 15118 (48.5%) | <0.001 | 34471 (100.0%) | 15118 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 13664 (22.7%) | 7257 (23.3%) |  | 0 (0.0%) | 0 (0.0%) | 13664 (100.0%) | 7257 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 12140 (20.1%) | 8813 (28.3%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 12140 (100.0%) | 8813 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 17211 (28.6%) | 6760 (21.7%) | <0.001 | 9044 (26.2%) | 2675 (17.7%) | 4154 (30.4%) | 1668 (23.0%) | 4013 (33.1%) | 2417 (27.4%) | <0.001 |
| Hypertension |  | 37679 (62.5%) | 21704 (69.6%) | <0.001 | 19545 (56.7%) | 9547 (63.1%) | 8968 (65.6%) | 5244 (72.3%) | 9166 (75.5%) | 6913 (78.4%) | <0.001 |
| Diabetes |  | 13414 (22.3%) | 10416 (33.4%) | <0.001 | 7668 (22.2%) | 4960 (32.8%) | 2866 (21.0%) | 2415 (33.3%) | 2880 (23.7%) | 3041 (34.5%) | <0.001 |
| CAD |  | 28962 (48.0%) | 18971 (60.8%) | <0.001 | 16707 (48.5%) | 9972 (66.0%) | 7061 (51.7%) | 4530 (62.4%) | 5194 (42.8%) | 4469 (50.7%) | <0.001 |
| AF |  | 33134 (55.0%) | 18127 (58.1%) | <0.001 | 17412 (50.5%) | 7901 (52.3%) | 7730 (56.6%) | 4397 (60.6%) | 7992 (65.8%) | 5829 (66.1%) | <0.001 |
| VHD |  | 14002 (23.2%) | 10371 (33.3%) | <0.001 | 7036 (20.4%) | 4524 (29.9%) | 3177 (23.3%) | 2403 (33.1%) | 3789 (31.2%) | 3444 (39.1%) | <0.001 |
| CKD |  | 19892 (33.0%) | 16687 (53.5%) | <0.001 | 10510 (30.5%) | 7729 (51.1%) | 4362 (31.9%) | 3861 (53.2%) | 5020 (41.4%) | 5097 (57.8%) | <0.001 |
| Anaemia |  | 0 (0.0%) | 31188 (100.0%) | <0.001 | 0 (0.0%) | 15118 (100.0%) | 0 (0.0%) | 7257 (100.0%) | 0 (0.0%) | 8813 (100.0%) | <0.001 |
| COPD |  | 7127 (11.8%) | 4470 (14.3%) | <0.001 | 3651 (10.6%) | 1973 (13.1%) | 1599 (11.7%) | 1048 (14.4%) | 1877 (15.5%) | 1449 (16.4%) | <0.001 |
| Liver disease |  | 1030 (1.7%) | 886 (2.8%) | <0.001 | 639 (1.9%) | 421 (2.8%) | 179 (1.3%) | 200 (2.8%) | 212 (1.7%) | 265 (3.0%) | <0.001 |
| PAD |  | 4064 (6.7%) | 3852 (12.4%) | <0.001 | 2184 (6.3%) | 1923 (12.7%) | 951 (7.0%) | 903 (12.4%) | 929 (7.7%) | 1026 (11.6%) | <0.001 |
| Stroke or TIA |  | 8662 (14.4%) | 5998 (19.2%) | <0.001 | 4573 (13.3%) | 2829 (18.7%) | 2030 (14.9%) | 1330 (18.3%) | 2059 (17.0%) | 1839 (20.9%) | <0.001 |
| Depression |  | 1973 (3.3%) | 1289 (4.1%) | <0.001 | 1100 (3.2%) | 638 (4.2%) | 424 (3.1%) | 278 (3.8%) | 449 (3.7%) | 373 (4.2%) | <0.001 |
| Dementia |  | 692 (1.1%) | 708 (2.3%) | <0.001 | 344 (1.0%) | 330 (2.2%) | 150 (1.1%) | 142 (2.0%) | 198 (1.6%) | 236 (2.7%) | <0.001 |
| Cancer <3years |  | 6063 (10.1%) | 5301 (17.0%) | <0.001 | 3186 (9.2%) | 2477 (16.4%) | 1481 (10.8%) | 1261 (17.4%) | 1396 (11.5%) | 1563 (17.7%) | <0.001 |
| Muscolo-skeletal <3years |  | 16710 (27.7%) | 11410 (36.6%) | <0.001 | 8488 (24.6%) | 4950 (32.7%) | 3975 (29.1%) | 2777 (38.3%) | 4247 (35.0%) | 3683 (41.8%) | <0.001 |
| Dysthyroidism |  | 4248 (7.0%) | 2613 (8.4%) | <0.001 | 2053 (6.0%) | 1075 (7.1%) | 980 (7.2%) | 598 (8.2%) | 1215 (10.0%) | 940 (10.7%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 21416 (35.5%) | 5447 (17.5%) | <0.001 | 12579 (36.5%) | 2536 (16.8%) | 4733 (34.6%) | 1339 (18.5%) | 4104 (33.8%) | 1572 (17.8%) | <0.001 |
|  | 2-3 | 23756 (39.4%) | 11399 (36.5%) |  | 13694 (39.7%) | 5734 (37.9%) | 5459 (40.0%) | 2553 (35.2%) | 4603 (37.9%) | 3112 (35.3%) |  |
|  | 4-7 | 12628 (21.0%) | 11576 (37.1%) |  | 6905 (20.0%) | 5605 (37.1%) | 2878 (21.1%) | 2708 (37.3%) | 2845 (23.4%) | 3263 (37.0%) |  |
|  | >=8 | 2475 (4.1%) | 2766 (8.9%) |  | 1293 (3.8%) | 1243 (8.2%) | 594 (4.3%) | 657 (9.1%) | 588 (4.8%) | 866 (9.8%) |  |

**Supplementary Table 11. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by chronic obstructive pulmonary disease (COPD).**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 79866 (87%) | 11597 (13%) |  | 43965 (89%) | 5624 (11%) | 18274 (87%) | 2647 (13%) | 17627 (84%) | 3326 (16%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 28687 (35.9%) | 4647 (40.1%) | <0.001 | 12540 (28.5%) | 1829 (32.5%) | 6851 (37.5%) | 1054 (39.8%) | 9296 (52.7%) | 1764 (53.0%) | <0.001 |
|  | Male | 51179 (64.1%) | 6950 (59.9%) |  | 31425 (71.5%) | 3795 (67.5%) | 11423 (62.5%) | 1593 (60.2%) | 8331 (47.3%) | 1562 (47.0%) |  |
| Age, median (IQR) |  | 75 (66, 83) | 76 (69, 82) | <0.001 | 73 (64, 81) | 74 (67, 80) | 76 (67, 83) | 77 (71, 82) | 80 (73, 85) | 78 (72, 84) | <0.001 |
| Family type | Cohabitating | 42072 (52.8%) | 5440 (46.9%) | <0.001 | 24064 (54.8%) | 2721 (48.4%) | 9895 (54.2%) | 1291 (48.8%) | 8113 (46.1%) | 1428 (43.0%) | <0.001 |
|  | Living alone | 37676 (47.2%) | 6147 (53.1%) |  | 19813 (45.2%) | 2898 (51.6%) | 8359 (45.8%) | 1355 (51.2%) | 9504 (53.9%) | 1894 (57.0%) |  |
| Smoking |  | 6272 (10.0%) | 2282 (23.9%) | <0.001 | 4319 (12.1%) | 1319 (27.7%) | 1221 (8.5%) | 488 (22.2%) | 732 (5.8%) | 475 (18.5%) | <0.001 |
| Alcohol user |  | 2278 (4.6%) | 409 (6.2%) | <0.001 | 1500 (5.2%) | 219 (6.4%) | 478 (4.2%) | 89 (6.0%) | 300 (3.2%) | 101 (6.2%) | <0.001 |
| Location of care | Out-patient | 44731 (56.0%) | 5369 (46.3%) | <0.001 | 25546 (58.1%) | 2953 (52.5%) | 11127 (60.9%) | 1282 (48.4%) | 8058 (45.7%) | 1134 (34.1%) | <0.001 |
|  | In-patient | 35135 (44.0%) | 6228 (53.7%) |  | 18419 (41.9%) | 2671 (47.5%) | 7147 (39.1%) | 1365 (51.6%) | 9569 (54.3%) | 2192 (65.9%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 49354 (61.8%) | 8317 (71.7%) | <0.001 | 28293 (64.4%) | 4013 (71.4%) | 9527 (52.1%) | 1741 (65.8%) | 11534 (65.4%) | 2563 (77.1%) | <0.001 |
| Duration of HF | <6mo | 42723 (54.8%) | 4899 (43.3%) | <0.001 | 25116 (58.3%) | 2557 (46.2%) | 9461 (53.1%) | 1057 (40.8%) | 8146 (47.9%) | 1285 (40.1%) | <0.001 |
|  | >=6mo | 35236 (45.2%) | 6424 (56.7%) |  | 17996 (41.7%) | 2974 (53.8%) | 8369 (46.9%) | 1532 (59.2%) | 8871 (52.1%) | 1918 (59.9%) |  |
| Follow-up location | Primary care | 23910 (31.2%) | 4216 (38.3%) | <0.001 | 9294 (21.9%) | 1453 (27.0%) | 6204 (35.3%) | 1064 (42.4%) | 8412 (50.4%) | 1699 (54.7%) | <0.001 |
|  | Hospital | 52819 (68.8%) | 6779 (61.7%) |  | 33157 (78.1%) | 3923 (73.0%) | 11394 (64.7%) | 1447 (57.6%) | 8268 (49.6%) | 1409 (45.3%) |  |
| NYHA functional class | I-II | 36482 (62.3%) | 3597 (46.0%) | <0.001 | 19949 (59.0%) | 1767 (42.5%) | 9564 (70.6%) | 935 (52.4%) | 6969 (62.6%) | 895 (47.8%) | <0.001 |
|  | III-IV | 22046 (37.7%) | 4217 (54.0%) |  | 13882 (41.0%) | 2391 (57.5%) | 3992 (29.4%) | 849 (47.6%) | 4172 (37.4%) | 977 (52.2%) |  |
| BMI, median (IQR) |  | 26 (23, 30) | 26 (23, 31) | <0.001 | 26 (23, 30) | 26 (22, 30) | 27 (24, 30) | 27 (23, 31) | 27 (24, 31) | 27 (23, 32) | <0.001 |
| SBP, median (IQR) |  | 125 (111, 140) | 124 (110, 140) | <0.001 | 120 (110, 139) | 120 (110, 135) | 130 (115, 141) | 126 (115, 140) | 130 (120, 145) | 130 (115, 142) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (63, 80) | <0.001 | 72 (65, 80) | 70 (62, 80) | 74 (65, 80) | 70 (65, 80) | 72 (65, 80) | 70 (63, 80) | <0.001 |
| MAP, median (IQR) |  | 91 (83, 100) | 90 (80, 98) | <0.001 | 90 (81, 99) | 88 (80, 97) | 93 (83, 100) | 90 (82, 100) | 93 (83, 101) | 90 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 74 (65, 84) | <0.001 | 72 (63, 83) | 74 (65, 85) | 70 (62, 80) | 73 (64, 84) | 71 (63, 81) | 74 (65, 85) | <0.001 |
| eGFR, median (IQR) |  | 67 (50, 86) | 64 (46, 84) | <0.001 | 69 (51, 88) | 67 (49, 86) | 68 (50, 86) | 63 (46, 83) | 61 (45, 80) | 60 (43, 80) | <0.001 |
| Potassium categories | Normakalemia | 60263 (93.0%) | 8430 (91.2%) | <0.001 | 33124 (93.5%) | 4069 (91.6%) | 14105 (93.2%) | 1967 (91.9%) | 13034 (91.7%) | 2394 (90.0%) | <0.001 |
|  | Hypokalemia | 2799 (4.3%) | 476 (5.2%) |  | 1298 (3.7%) | 196 (4.4%) | 651 (4.3%) | 107 (5.0%) | 850 (6.0%) | 173 (6.5%) |  |
|  | Hyperkalemia | 1720 (2.7%) | 336 (3.6%) |  | 1008 (2.8%) | 177 (4.0%) | 384 (2.5%) | 67 (3.1%) | 328 (2.3%) | 92 (3.5%) |  |
| Haemoglobin, median (IQR) |  | 133 (120, 145) | 131 (118, 143) | <0.001 | 136 (123, 147) | 133 (120, 145) | 133 (120, 144) | 130 (118, 142) | 127 (115, 139) | 127 (114, 139) | <0.001 |
| NT-proBNP, median (IQR) |  | 2266 (987, 5027) | 2573 (1130, 5642) | <0.001 | 2682 (1166, 6020) | 3088 (1350, 6930) | 1834 (739, 4001) | 2175 (899, 4831) | 1967 (907, 4009) | 2212 (1016, 4581) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 68038 (86.1%) | 9232 (80.7%) | <0.001 | 39954 (91.9%) | 4970 (89.7%) | 15480 (85.5%) | 2096 (80.1%) | 12604 (72.3%) | 2166 (66.0%) | <0.001 |
| Beta-blockers |  | 70734 (88.8%) | 9894 (85.6%) | <0.001 | 40447 (92.2%) | 5083 (90.6%) | 15921 (87.3%) | 2247 (85.2%) | 14366 (81.8%) | 2564 (77.5%) | <0.001 |
| MRA |  | 27819 (35.0%) | 4256 (36.9%) | <0.001 | 17525 (40.0%) | 2232 (39.9%) | 5069 (27.9%) | 823 (31.2%) | 5225 (29.8%) | 1201 (36.3%) | <0.001 |
| DIuretics |  | 59650 (74.9%) | 9728 (84.3%) | <0.001 | 32891 (75.0%) | 4634 (82.8%) | 12367 (67.8%) | 2139 (81.1%) | 14392 (81.9%) | 2955 (89.2%) | <0.001 |
| Digoxin |  | 10529 (13.2%) | 1641 (14.2%) | 0.004 | 5980 (13.6%) | 798 (14.3%) | 2137 (11.7%) | 358 (13.6%) | 2412 (13.7%) | 485 (14.6%) | <0.001 |
| Antiplatelet therapy |  | 32982 (41.4%) | 5047 (43.7%) | <0.001 | 19228 (43.9%) | 2695 (48.1%) | 7770 (42.7%) | 1125 (42.7%) | 5984 (34.1%) | 1227 (37.2%) | <0.001 |
| Anticoagulant therapy |  | 37168 (46.7%) | 5195 (45.0%) | <0.001 | 19729 (45.0%) | 2363 (42.2%) | 8478 (46.5%) | 1262 (47.8%) | 8961 (51.0%) | 1570 (47.5%) | <0.001 |
| Statins |  | 38505 (48.4%) | 5830 (50.4%) | <0.001 | 21865 (49.9%) | 2963 (52.9%) | 9300 (51.0%) | 1367 (51.8%) | 7340 (41.8%) | 1500 (45.3%) | <0.001 |
| Nitrates |  | 9697 (12.2%) | 1888 (16.4%) | <0.001 | 4881 (11.1%) | 859 (15.3%) | 2257 (12.4%) | 461 (17.5%) | 2559 (14.6%) | 568 (17.2%) | <0.001 |
| HF devices |  | 4396 (5.6%) | 542 (4.7%) | <0.001 | 3549 (8.1%) | 430 (7.7%) | 581 (3.2%) | 80 (3.1%) | 266 (1.5%) | 32 (1.0%) | <0.001 |
| EF categories | HFrEF | 43965 (55.0%) | 5624 (48.5%) | <0.001 | 43965 (100.0%) | 5624 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 18274 (22.9%) | 2647 (22.8%) |  | 0 (0.0%) | 0 (0.0%) | 18274 (100.0%) | 2647 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 17627 (22.1%) | 3326 (28.7%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 17627 (100.0%) | 3326 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 20716 (25.9%) | 3255 (28.1%) | <0.001 | 10364 (23.6%) | 1355 (24.1%) | 5047 (27.6%) | 775 (29.3%) | 5305 (30.1%) | 1125 (33.8%) | <0.001 |
| Hypertension |  | 51389 (64.3%) | 7994 (68.9%) | <0.001 | 25561 (58.1%) | 3531 (62.8%) | 12326 (67.5%) | 1886 (71.3%) | 13502 (76.6%) | 2577 (77.5%) | <0.001 |
| Diabetes |  | 20378 (25.5%) | 3452 (29.8%) | <0.001 | 11022 (25.1%) | 1606 (28.6%) | 4481 (24.5%) | 800 (30.2%) | 4875 (27.7%) | 1046 (31.4%) | <0.001 |
| CAD |  | 41020 (51.4%) | 6913 (59.6%) | <0.001 | 23120 (52.6%) | 3559 (63.3%) | 9977 (54.6%) | 1614 (61.0%) | 7923 (44.9%) | 1740 (52.3%) | <0.001 |
| AF |  | 44610 (55.9%) | 6651 (57.4%) | 0.002 | 22420 (51.0%) | 2893 (51.4%) | 10509 (57.5%) | 1618 (61.1%) | 11681 (66.3%) | 2140 (64.3%) | <0.001 |
| VHD |  | 21224 (26.6%) | 3149 (27.2%) | 0.19 | 10197 (23.2%) | 1363 (24.2%) | 4856 (26.6%) | 724 (27.4%) | 6171 (35.0%) | 1062 (31.9%) | <0.001 |
| CKD |  | 31415 (39.3%) | 5164 (44.5%) | <0.001 | 15950 (36.3%) | 2289 (40.7%) | 7019 (38.4%) | 1204 (45.5%) | 8446 (47.9%) | 1671 (50.2%) | <0.001 |
| Anaemia |  | 26718 (33.5%) | 4470 (38.5%) | <0.001 | 13145 (29.9%) | 1973 (35.1%) | 6209 (34.0%) | 1048 (39.6%) | 7364 (41.8%) | 1449 (43.6%) | <0.001 |
| COPD |  | 0 (0.0%) | 11597 (100.0%) | <0.001 | 0 (0.0%) | 5624 (100.0%) | 0 (0.0%) | 2647 (100.0%) | 0 (0.0%) | 3326 (100.0%) | <0.001 |
| Liver disease |  | 1565 (2.0%) | 351 (3.0%) | <0.001 | 891 (2.0%) | 169 (3.0%) | 315 (1.7%) | 64 (2.4%) | 359 (2.0%) | 118 (3.5%) | <0.001 |
| PAD |  | 6179 (7.7%) | 1737 (15.0%) | <0.001 | 3274 (7.4%) | 833 (14.8%) | 1446 (7.9%) | 408 (15.4%) | 1459 (8.3%) | 496 (14.9%) | <0.001 |
| Stroke or TIA |  | 12524 (15.7%) | 2136 (18.4%) | <0.001 | 6426 (14.6%) | 976 (17.4%) | 2853 (15.6%) | 507 (19.2%) | 3245 (18.4%) | 653 (19.6%) | <0.001 |
| Depression |  | 2695 (3.4%) | 567 (4.9%) | <0.001 | 1490 (3.4%) | 248 (4.4%) | 573 (3.1%) | 129 (4.9%) | 632 (3.6%) | 190 (5.7%) | <0.001 |
| Dementia |  | 1200 (1.5%) | 200 (1.7%) | 0.069 | 580 (1.3%) | 94 (1.7%) | 250 (1.4%) | 42 (1.6%) | 370 (2.1%) | 64 (1.9%) | <0.001 |
| Cancer <3years |  | 9759 (12.2%) | 1605 (13.8%) | <0.001 | 4955 (11.3%) | 708 (12.6%) | 2345 (12.8%) | 397 (15.0%) | 2459 (14.0%) | 500 (15.0%) | <0.001 |
| Muscolo-skeletal <3years |  | 23794 (29.8%) | 4326 (37.3%) | <0.001 | 11531 (26.2%) | 1907 (33.9%) | 5716 (31.3%) | 1036 (39.1%) | 6547 (37.1%) | 1383 (41.6%) | <0.001 |
| Dysthyroidism |  | 5787 (7.2%) | 1074 (9.3%) | <0.001 | 2687 (6.1%) | 441 (7.8%) | 1324 (7.2%) | 254 (9.6%) | 1776 (10.1%) | 379 (11.4%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 26680 (33.4%) | 183 (1.6%) | <0.001 | 15055 (34.2%) | 60 (1.1%) | 6019 (32.9%) | 53 (2.0%) | 5606 (31.8%) | 70 (2.1%) | <0.001 |
|  | 2-3 | 30470 (38.2%) | 4685 (40.4%) |  | 17016 (38.7%) | 2412 (42.9%) | 7005 (38.3%) | 1007 (38.0%) | 6449 (36.6%) | 1266 (38.1%) |  |
|  | 4-7 | 18838 (23.6%) | 5366 (46.3%) |  | 9942 (22.6%) | 2568 (45.7%) | 4346 (23.8%) | 1240 (46.8%) | 4550 (25.8%) | 1558 (46.8%) |  |
|  | >=8 | 3878 (4.9%) | 1363 (11.8%) |  | 1952 (4.4%) | 584 (10.4%) | 904 (4.9%) | 347 (13.1%) | 1022 (5.8%) | 432 (13.0%) |  |

**Supplementary Table 12. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by liver disease.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 89547 (98%) | 1916 (2%) |  | 48529 (98%) | 1060 (2%) | 20542 (98%) | 379 (2%) | 20476 (98%) | 477 (2%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 32815 (36.6%) | 519 (27.1%) | <0.001 | 14162 (29.2%) | 207 (19.5%) | 7807 (38.0%) | 98 (25.9%) | 10846 (53.0%) | 214 (44.9%) | <0.001 |
|  | Male | 56732 (63.4%) | 1397 (72.9%) |  | 34367 (70.8%) | 853 (80.5%) | 12735 (62.0%) | 281 (74.1%) | 9630 (47.0%) | 263 (55.1%) |  |
| Age, median (IQR) |  | 76 (67, 83) | 67 (59, 76) | <0.001 | 73 (64, 81) | 65 (56, 74) | 76 (68, 83) | 69 (60, 76) | 80 (73, 85) | 72 (64, 79) | <0.001 |
| Family type | Cohabitating | 46726 (52.3%) | 786 (41.1%) | <0.001 | 26388 (54.5%) | 397 (37.5%) | 11010 (53.7%) | 176 (46.4%) | 9328 (45.6%) | 213 (44.7%) | <0.001 |
|  | Living alone | 42695 (47.7%) | 1128 (58.9%) |  | 22050 (45.5%) | 661 (62.5%) | 9511 (46.3%) | 203 (53.6%) | 11134 (54.4%) | 264 (55.3%) |  |
| Smoking |  | 8109 (11.5%) | 445 (30.3%) | <0.001 | 5329 (13.5%) | 309 (36.9%) | 1638 (10.1%) | 71 (24.8%) | 1142 (7.7%) | 65 (18.7%) | <0.001 |
| Alcohol user |  | 2478 (4.5%) | 209 (16.8%) | <0.001 | 1585 (5.0%) | 134 (18.8%) | 529 (4.1%) | 38 (15.3%) | 364 (3.4%) | 37 (13.2%) | <0.001 |
| Location of care | Out-patient | 49187 (54.9%) | 913 (47.7%) | <0.001 | 27973 (57.6%) | 526 (49.6%) | 12206 (59.4%) | 203 (53.6%) | 9008 (44.0%) | 184 (38.6%) | <0.001 |
|  | In-patient | 40360 (45.1%) | 1003 (52.3%) |  | 20556 (42.4%) | 534 (50.4%) | 8336 (40.6%) | 176 (46.4%) | 11468 (56.0%) | 293 (61.4%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 56260 (62.8%) | 1411 (73.6%) | <0.001 | 31496 (64.9%) | 810 (76.4%) | 11024 (53.7%) | 244 (64.4%) | 13740 (67.1%) | 357 (74.8%) | <0.001 |
| Duration of HF | <6mo | 46712 (53.4%) | 910 (48.6%) | <0.001 | 27130 (57.0%) | 543 (52.3%) | 10353 (51.7%) | 165 (43.7%) | 9229 (46.7%) | 202 (44.3%) | <0.001 |
|  | >=6mo | 40698 (46.6%) | 962 (51.4%) |  | 20475 (43.0%) | 495 (47.7%) | 9688 (48.3%) | 213 (56.3%) | 10535 (53.3%) | 254 (55.7%) |  |
| Follow-up location | Primary care | 27633 (32.2%) | 493 (26.9%) | <0.001 | 10535 (22.5%) | 212 (20.9%) | 7164 (36.3%) | 104 (28.6%) | 9934 (51.4%) | 177 (38.7%) | <0.001 |
|  | Hospital | 58257 (67.8%) | 1341 (73.1%) |  | 36279 (77.5%) | 801 (79.1%) | 12581 (63.7%) | 260 (71.4%) | 9397 (48.6%) | 280 (61.3%) |  |
| NYHA functional class | I-II | 39424 (60.6%) | 655 (50.7%) | <0.001 | 21357 (57.4%) | 359 (47.0%) | 10341 (68.6%) | 158 (61.5%) | 7726 (60.6%) | 138 (50.9%) | <0.001 |
|  | III-IV | 25626 (39.4%) | 637 (49.3%) |  | 15868 (42.6%) | 405 (53.0%) | 4742 (31.4%) | 99 (38.5%) | 5016 (39.4%) | 133 (49.1%) |  |
| BMI, median (IQR) |  | 26 (23, 30) | 26 (23, 30) | 0.14 | 26 (23, 30) | 26 (23, 29) | 27 (24, 30) | 27 (24, 30) | 27 (24, 31) | 28 (24, 32) | <0.001 |
| SBP, median (IQR) |  | 125 (111, 140) | 120 (109, 135) | <0.001 | 120 (110, 138) | 120 (105, 130) | 130 (115, 140) | 125 (110, 140) | 130 (120, 145) | 125 (110, 140) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (65, 80) | 0.015 | 71 (65, 80) | 70 (65, 80) | 74 (65, 80) | 70 (65, 80) | 71 (65, 80) | 70 (62, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (83, 100) | 88 (80, 98) | <0.001 | 90 (81, 99) | 87 (80, 97) | 92 (83, 100) | 90 (81, 100) | 93 (83, 101) | 89 (80, 97) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 74 (65, 85) | <0.001 | 72 (64, 83) | 76 (65, 88) | 70 (62, 80) | 71 (63, 82) | 71 (63, 82) | 74 (66, 84) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 67 (49, 85) | 73 (50, 92) | <0.001 | 69 (51, 87) | 76 (54, 94) | 67 (50, 86) | 70 (50, 92) | 61 (44, 80) | 65 (47, 87) | <0.001 |
| Potassium categories | Normakalemia | 67256 (92.8%) | 1437 (90.7%) | 0.002 | 36402 (93.3%) | 791 (90.7%) | 15790 (93.1%) | 282 (89.5%) | 15064 (91.4%) | 364 (91.7%) | <0.001 |
|  | Hypokalemia | 3192 (4.4%) | 83 (5.2%) |  | 1452 (3.7%) | 42 (4.8%) | 740 (4.4%) | 18 (5.7%) | 1000 (6.1%) | 23 (5.8%) |  |
|  | Hyperkalemia | 1992 (2.7%) | 64 (4.0%) |  | 1146 (2.9%) | 39 (4.5%) | 436 (2.6%) | 15 (4.8%) | 410 (2.5%) | 10 (2.5%) |  |
| Haemoglobin, median (IQR) |  | 133 (120, 145) | 128 (115, 142) | <0.001 | 135 (123, 147) | 133 (119, 145) | 133 (120, 144) | 125 (113, 138) | 127 (115, 139) | 122 (108, 135) | <0.001 |
| NT-proBNP, median (IQR) |  | 2300 (1006, 5101) | 2499 (991, 6062) | 0.057 | 2719 (1181, 6085) | 3363 (1330, 7660) | 1880 (763, 4125) | 1817 (733, 4200) | 2010 (926, 4089) | 1794 (718, 4000) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 75762 (85.5%) | 1508 (80.1%) | <0.001 | 44003 (91.7%) | 921 (89.1%) | 17278 (84.9%) | 298 (79.3%) | 14481 (71.6%) | 289 (61.2%) | <0.001 |
| Beta-blockers |  | 78940 (88.4%) | 1688 (88.4%) | 0.96 | 44563 (92.0%) | 967 (91.7%) | 17828 (87.0%) | 340 (89.7%) | 16549 (81.2%) | 381 (80.0%) | <0.001 |
| MRA |  | 31203 (35.0%) | 872 (45.8%) | <0.001 | 19261 (39.9%) | 496 (47.2%) | 5731 (28.0%) | 161 (42.5%) | 6211 (30.5%) | 215 (45.1%) | <0.001 |
| DIuretics |  | 67834 (76.0%) | 1544 (81.0%) | <0.001 | 36673 (75.8%) | 852 (81.0%) | 14232 (69.5%) | 274 (72.9%) | 16929 (83.0%) | 418 (87.6%) | <0.001 |
| Digoxin |  | 11897 (13.3%) | 273 (14.3%) | 0.22 | 6609 (13.7%) | 169 (16.0%) | 2452 (12.0%) | 43 (11.3%) | 2836 (13.9%) | 61 (12.8%) | <0.001 |
| Antiplatelet therapy |  | 37360 (41.9%) | 669 (35.1%) | <0.001 | 21530 (44.5%) | 393 (37.4%) | 8763 (42.8%) | 132 (35.2%) | 7067 (34.7%) | 144 (30.2%) | <0.001 |
| Anticoagulant therapy |  | 41610 (46.6%) | 753 (39.5%) | <0.001 | 21690 (44.8%) | 402 (38.2%) | 9578 (46.8%) | 162 (42.9%) | 10342 (50.7%) | 189 (39.6%) | <0.001 |
| Statins |  | 43665 (48.9%) | 670 (35.1%) | <0.001 | 24459 (50.6%) | 369 (35.0%) | 10525 (51.4%) | 142 (37.5%) | 8681 (42.5%) | 159 (33.4%) | <0.001 |
| Nitrates |  | 11397 (12.8%) | 188 (9.9%) | <0.001 | 5656 (11.7%) | 84 (8.0%) | 2679 (13.1%) | 39 (10.3%) | 3062 (15.0%) | 65 (13.6%) | <0.001 |
| HF devices |  | 4836 (5.5%) | 102 (5.4%) | 0.84 | 3897 (8.1%) | 82 (7.8%) | 648 (3.2%) | 13 (3.5%) | 291 (1.5%) | 7 (1.5%) | <0.001 |
| EF categories | HFrEF | 48529 (54.2%) | 1060 (55.3%) | 0.002 | 48529 (100.0%) | 1060 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 20542 (22.9%) | 379 (19.8%) |  | 0 (0.0%) | 0 (0.0%) | 20542 (100.0%) | 379 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 20476 (22.9%) | 477 (24.9%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 20476 (100.0%) | 477 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 23476 (26.2%) | 495 (25.8%) | 0.71 | 11492 (23.7%) | 227 (21.4%) | 5727 (27.9%) | 95 (25.1%) | 6257 (30.6%) | 173 (36.3%) | <0.001 |
| Hypertension |  | 58173 (65.0%) | 1210 (63.2%) | 0.10 | 28504 (58.7%) | 588 (55.5%) | 13958 (67.9%) | 254 (67.0%) | 15711 (76.7%) | 368 (77.1%) | <0.001 |
| Diabetes |  | 23200 (25.9%) | 630 (32.9%) | <0.001 | 12311 (25.4%) | 317 (29.9%) | 5150 (25.1%) | 131 (34.6%) | 5739 (28.0%) | 182 (38.2%) | <0.001 |
| CAD |  | 47037 (52.5%) | 896 (46.8%) | <0.001 | 26161 (53.9%) | 518 (48.9%) | 11413 (55.6%) | 178 (47.0%) | 9463 (46.2%) | 200 (41.9%) | <0.001 |
| AF |  | 50196 (56.1%) | 1065 (55.6%) | 0.68 | 24768 (51.0%) | 545 (51.4%) | 11894 (57.9%) | 233 (61.5%) | 13534 (66.1%) | 287 (60.2%) | <0.001 |
| VHD |  | 23787 (26.6%) | 586 (30.6%) | <0.001 | 11290 (23.3%) | 270 (25.5%) | 5446 (26.5%) | 134 (35.4%) | 7051 (34.4%) | 182 (38.2%) | <0.001 |
| CKD |  | 35914 (40.1%) | 665 (34.7%) | <0.001 | 17921 (36.9%) | 318 (30.0%) | 8080 (39.3%) | 143 (37.7%) | 9913 (48.4%) | 204 (42.8%) | <0.001 |
| Anaemia |  | 30302 (33.8%) | 886 (46.2%) | <0.001 | 14697 (30.3%) | 421 (39.7%) | 7057 (34.4%) | 200 (52.8%) | 8548 (41.7%) | 265 (55.6%) | <0.001 |
| COPD |  | 11246 (12.6%) | 351 (18.3%) | <0.001 | 5455 (11.2%) | 169 (15.9%) | 2583 (12.6%) | 64 (16.9%) | 3208 (15.7%) | 118 (24.7%) | <0.001 |
| Liver disease |  | 0 (0.0%) | 1916 (100.0%) | <0.001 | 0 (0.0%) | 1060 (100.0%) | 0 (0.0%) | 379 (100.0%) | 0 (0.0%) | 477 (100.0%) | <0.001 |
| PAD |  | 7724 (8.6%) | 192 (10.0%) | 0.032 | 4014 (8.3%) | 93 (8.8%) | 1809 (8.8%) | 45 (11.9%) | 1901 (9.3%) | 54 (11.3%) | <0.001 |
| Stroke or TIA |  | 14372 (16.0%) | 288 (15.0%) | 0.23 | 7250 (14.9%) | 152 (14.3%) | 3309 (16.1%) | 51 (13.5%) | 3813 (18.6%) | 85 (17.8%) | <0.001 |
| Depression |  | 3129 (3.5%) | 133 (6.9%) | <0.001 | 1666 (3.4%) | 72 (6.8%) | 672 (3.3%) | 30 (7.9%) | 791 (3.9%) | 31 (6.5%) | <0.001 |
| Dementia |  | 1378 (1.5%) | 22 (1.1%) | 0.17 | 662 (1.4%) | 12 (1.1%) | 285 (1.4%) | 7 (1.8%) | 431 (2.1%) | <5 (0.6%) | <0.001 |
| Cancer <3years |  | 11155 (12.5%) | 209 (10.9%) | 0.042 | 5576 (11.5%) | 87 (8.2%) | 2694 (13.1%) | 48 (12.7%) | 2885 (14.1%) | 74 (15.5%) | <0.001 |
| Muscolo-skeletal <3years |  | 27460 (30.7%) | 660 (34.4%) | <0.001 | 13118 (27.0%) | 320 (30.2%) | 6614 (32.2%) | 138 (36.4%) | 7728 (37.7%) | 202 (42.3%) | <0.001 |
| Dysthyroidism |  | 6714 (7.5%) | 147 (7.7%) | 0.77 | 3065 (6.3%) | 63 (5.9%) | 1556 (7.6%) | 22 (5.8%) | 2093 (10.2%) | 62 (13.0%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 26660 (29.8%) | 203 (10.6%) | <0.001 | 14998 (30.9%) | 117 (11.0%) | 6030 (29.4%) | 42 (11.1%) | 5632 (27.5%) | 44 (9.2%) | <0.001 |
|  | 2-3 | 34491 (38.5%) | 664 (34.7%) |  | 19009 (39.2%) | 419 (39.5%) | 7893 (38.4%) | 119 (31.4%) | 7589 (37.1%) | 126 (26.4%) |  |
|  | 4-7 | 23463 (26.2%) | 741 (38.7%) |  | 12128 (25.0%) | 382 (36.0%) | 5428 (26.4%) | 158 (41.7%) | 5907 (28.8%) | 201 (42.1%) |  |
|  | >=8 | 4933 (5.5%) | 308 (16.1%) |  | 2394 (4.9%) | 142 (13.4%) | 1191 (5.8%) | 60 (15.8%) | 1348 (6.6%) | 106 (22.2%) |  |

**Supplementary Table 13. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by peripheral artery disease (PAD).**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 83547 (91%) | 7916 (9%) |  | 45482 (92%) | 4107 (8%) | 19067 (91%) | 1854 (9%) | 18998 (91%) | 1955 (9%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 30842 (36.9%) | 2492 (31.5%) | <0.001 | 13379 (29.4%) | 990 (24.1%) | 7297 (38.3%) | 608 (32.8%) | 10166 (53.5%) | 894 (45.7%) | <0.001 |
|  | Male | 52705 (63.1%) | 5424 (68.5%) |  | 32103 (70.6%) | 3117 (75.9%) | 11770 (61.7%) | 1246 (67.2%) | 8832 (46.5%) | 1061 (54.3%) |  |
| Age, median (IQR) |  | 75 (66, 82) | 77 (70, 83) | <0.001 | 73 (64, 81) | 75 (69, 81) | 76 (67, 83) | 77 (71, 83) | 80 (73, 85) | 79 (73, 85) | <0.001 |
| Family type | Cohabitating | 43398 (52.0%) | 4114 (52.0%) | 0.97 | 24602 (54.2%) | 2183 (53.2%) | 10186 (53.5%) | 1000 (54.0%) | 8610 (45.4%) | 931 (47.6%) | <0.001 |
|  | Living alone | 40025 (48.0%) | 3798 (48.0%) |  | 20789 (45.8%) | 1922 (46.8%) | 8861 (46.5%) | 853 (46.0%) | 10375 (54.6%) | 1023 (52.4%) |  |
| Smoking |  | 7591 (11.5%) | 963 (15.6%) | <0.001 | 5033 (13.6%) | 605 (18.3%) | 1511 (10.0%) | 198 (13.8%) | 1047 (7.6%) | 160 (11.3%) | <0.001 |
| Alcohol user |  | 2488 (4.8%) | 199 (4.4%) | 0.20 | 1605 (5.4%) | 114 (4.5%) | 519 (4.3%) | 48 (4.5%) | 364 (3.6%) | 37 (3.8%) | <0.001 |
| Location of care | Out-patient | 46311 (55.4%) | 3789 (47.9%) | <0.001 | 26404 (58.1%) | 2095 (51.0%) | 11467 (60.1%) | 942 (50.8%) | 8440 (44.4%) | 752 (38.5%) | <0.001 |
|  | In-patient | 37236 (44.6%) | 4127 (52.1%) |  | 19078 (41.9%) | 2012 (49.0%) | 7600 (39.9%) | 912 (49.2%) | 10558 (55.6%) | 1203 (61.5%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 52249 (62.5%) | 5422 (68.5%) | <0.001 | 29475 (64.8%) | 2831 (68.9%) | 10107 (53.0%) | 1161 (62.6%) | 12667 (66.7%) | 1430 (73.1%) | <0.001 |
| Duration of HF | <6mo | 44245 (54.2%) | 3377 (43.7%) | <0.001 | 25895 (58.0%) | 1778 (44.2%) | 9750 (52.4%) | 768 (42.4%) | 8600 (46.9%) | 831 (44.2%) | <0.001 |
|  | >=6mo | 37318 (45.8%) | 4342 (56.3%) |  | 18723 (42.0%) | 2247 (55.8%) | 8857 (47.6%) | 1044 (57.6%) | 9738 (53.1%) | 1051 (55.8%) |  |
| Follow-up location | Primary care | 25552 (31.9%) | 2574 (34.2%) | <0.001 | 9710 (22.1%) | 1037 (26.4%) | 6607 (36.0%) | 661 (37.3%) | 9235 (51.4%) | 876 (47.7%) | <0.001 |
|  | Hospital | 54636 (68.1%) | 4962 (65.8%) |  | 34193 (77.9%) | 2887 (73.6%) | 11728 (64.0%) | 1113 (62.7%) | 8715 (48.6%) | 962 (52.3%) |  |
| NYHA functional class | I-II | 37396 (61.3%) | 2683 (50.2%) | <0.001 | 20379 (58.2%) | 1337 (45.3%) | 9755 (69.3%) | 744 (59.2%) | 7262 (61.1%) | 602 (53.2%) | <0.001 |
|  | III-IV | 23606 (38.7%) | 2657 (49.8%) |  | 14658 (41.8%) | 1615 (54.7%) | 4328 (30.7%) | 513 (40.8%) | 4620 (38.9%) | 529 (46.8%) |  |
| BMI, median (IQR) |  | 27 (23, 30) | 26 (23, 29) | <0.001 | 26 (23, 30) | 25 (23, 29) | 27 (24, 31) | 26 (23, 30) | 27 (24, 31) | 26 (23, 30) | <0.001 |
| SBP, median (IQR) |  | 125 (110, 140) | 127 (114, 140) | <0.001 | 120 (110, 138) | 122 (110, 140) | 130 (115, 140) | 130 (118, 143) | 130 (120, 145) | 130 (120, 150) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (62, 80) | <0.001 | 72 (65, 80) | 70 (62, 80) | 74 (65, 80) | 70 (63, 80) | 71 (65, 80) | 70 (60, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (83, 100) | 90 (82, 99) | <0.001 | 90 (81, 99) | 89 (80, 97) | 92 (83, 100) | 92 (83, 100) | 93 (83, 101) | 92 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 72 (63, 81) | 0.12 | 72 (64, 84) | 72 (64, 82) | 70 (62, 81) | 71 (62, 80) | 72 (63, 82) | 70 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 68 (50, 86) | 58 (41, 78) | <0.001 | 70 (52, 88) | 59 (42, 79) | 68 (50, 86) | 60 (42, 79) | 62 (45, 80) | 55 (39, 74) | <0.001 |
| Potassium categories | Normakalemia | 62844 (93.0%) | 5849 (90.7%) | <0.001 | 34151 (93.4%) | 3042 (91.4%) | 14699 (93.3%) | 1373 (90.2%) | 13994 (91.6%) | 1434 (89.5%) | <0.001 |
|  | Hypokalemia | 2926 (4.3%) | 349 (5.4%) |  | 1346 (3.7%) | 148 (4.4%) | 670 (4.3%) | 88 (5.8%) | 910 (6.0%) | 113 (7.1%) |  |
|  | Hyperkalemia | 1803 (2.7%) | 253 (3.9%) |  | 1048 (2.9%) | 137 (4.1%) | 390 (2.5%) | 61 (4.0%) | 365 (2.4%) | 55 (3.4%) |  |
| Haemoglobin, median (IQR) |  | 133 (121, 145) | 127 (114, 139) | <0.001 | 136 (124, 147) | 128 (116, 141) | 133 (120, 144) | 126 (114, 140) | 128 (116, 140) | 123 (111, 136) | <0.001 |
| NT-proBNP, median (IQR) |  | 2244 (980, 4942) | 3160 (1342, 7420) | <0.001 | 2659 (1157, 5930) | 3795 (1579, 8885) | 1810 (732, 3945) | 2678 (1177, 6260) | 1943 (900, 3956) | 2586 (1173, 5503) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 70911 (85.8%) | 6359 (81.2%) | <0.001 | 41377 (92.0%) | 3547 (87.3%) | 16091 (85.2%) | 1485 (80.6%) | 13443 (71.6%) | 1327 (68.9%) | <0.001 |
| Beta-blockers |  | 73688 (88.4%) | 6940 (88.0%) | 0.25 | 41808 (92.1%) | 3722 (90.8%) | 16550 (87.0%) | 1618 (87.5%) | 15330 (81.0%) | 1600 (82.5%) | <0.001 |
| MRA |  | 29321 (35.3%) | 2754 (35.0%) | 0.65 | 18148 (40.1%) | 1609 (39.4%) | 5352 (28.2%) | 540 (29.3%) | 5821 (30.8%) | 605 (31.2%) | <0.001 |
| DIuretics |  | 62915 (75.5%) | 6463 (81.9%) | <0.001 | 34190 (75.4%) | 3335 (81.4%) | 13026 (68.5%) | 1480 (80.0%) | 15699 (82.9%) | 1648 (84.7%) | <0.001 |
| Digoxin |  | 11271 (13.5%) | 899 (11.4%) | <0.001 | 6307 (13.9%) | 471 (11.5%) | 2304 (12.1%) | 191 (10.3%) | 2660 (14.1%) | 237 (12.2%) | <0.001 |
| Antiplatelet therapy |  | 33936 (40.8%) | 4093 (51.9%) | <0.001 | 19667 (43.4%) | 2256 (55.2%) | 7938 (41.8%) | 957 (51.7%) | 6331 (33.5%) | 880 (45.2%) | <0.001 |
| Anticoagulant therapy |  | 38772 (46.6%) | 3591 (45.5%) | 0.082 | 20284 (44.7%) | 1808 (44.2%) | 8893 (46.8%) | 847 (45.8%) | 9595 (50.7%) | 936 (48.1%) | <0.001 |
| Statins |  | 39316 (47.2%) | 5019 (63.6%) | <0.001 | 22122 (48.8%) | 2706 (66.1%) | 9477 (49.8%) | 1190 (64.3%) | 7717 (40.8%) | 1123 (57.6%) | <0.001 |
| Nitrates |  | 10028 (12.1%) | 1557 (19.8%) | <0.001 | 4966 (11.0%) | 774 (18.9%) | 2336 (12.3%) | 382 (20.7%) | 2726 (14.4%) | 401 (20.6%) | <0.001 |
| HF devices |  | 4443 (5.4%) | 495 (6.3%) | <0.001 | 3579 (7.9%) | 400 (9.8%) | 603 (3.2%) | 58 (3.2%) | 261 (1.4%) | 37 (1.9%) | <0.001 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| EF categories | HFrEF | 45482 (54.4%) | 4107 (51.9%) | <0.001 | 45482 (100.0%) | 4107 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 19067 (22.8%) | 1854 (23.4%) |  | 0 (0.0%) | 0 (0.0%) | 19067 (100.0%) | 1854 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 18998 (22.7%) | 1955 (24.7%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 18998 (100.0%) | 1955 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 22296 (26.7%) | 1675 (21.2%) | <0.001 | 10987 (24.2%) | 732 (17.8%) | 5387 (28.3%) | 435 (23.5%) | 5922 (31.2%) | 508 (26.0%) | <0.001 |
| Hypertension |  | 53179 (63.7%) | 6204 (78.4%) | <0.001 | 26052 (57.3%) | 3040 (74.0%) | 12722 (66.7%) | 1490 (80.4%) | 14405 (75.8%) | 1674 (85.6%) | <0.001 |
| Diabetes |  | 20930 (25.1%) | 2900 (36.6%) | <0.001 | 11091 (24.4%) | 1537 (37.4%) | 4629 (24.3%) | 652 (35.2%) | 5210 (27.4%) | 711 (36.4%) | <0.001 |
| CAD |  | 42344 (50.7%) | 5589 (70.6%) | <0.001 | 23617 (51.9%) | 3062 (74.6%) | 10258 (53.8%) | 1333 (71.9%) | 8469 (44.6%) | 1194 (61.1%) | <0.001 |
| AF |  | 46700 (55.9%) | 4561 (57.6%) | 0.003 | 23089 (50.8%) | 2224 (54.2%) | 11022 (57.8%) | 1105 (59.6%) | 12589 (66.3%) | 1232 (63.0%) | <0.001 |
| VHD |  | 21550 (25.8%) | 2823 (35.7%) | <0.001 | 10191 (22.4%) | 1369 (33.3%) | 4923 (25.8%) | 657 (35.4%) | 6436 (33.9%) | 797 (40.8%) | <0.001 |
| CKD |  | 32437 (38.8%) | 4142 (52.3%) | <0.001 | 16152 (35.5%) | 2087 (50.8%) | 7286 (38.2%) | 937 (50.5%) | 8999 (47.4%) | 1118 (57.2%) | <0.001 |
| Anaemia |  | 27336 (32.7%) | 3852 (48.7%) | <0.001 | 13195 (29.0%) | 1923 (46.8%) | 6354 (33.3%) | 903 (48.7%) | 7787 (41.0%) | 1026 (52.5%) | <0.001 |
| COPD |  | 9860 (11.8%) | 1737 (21.9%) | <0.001 | 4791 (10.5%) | 833 (20.3%) | 2239 (11.7%) | 408 (22.0%) | 2830 (14.9%) | 496 (25.4%) | <0.001 |
| Liver disease |  | 1724 (2.1%) | 192 (2.4%) | 0.032 | 967 (2.1%) | 93 (2.3%) | 334 (1.8%) | 45 (2.4%) | 423 (2.2%) | 54 (2.8%) | 0.002 |
| PAD |  | 0 (0.0%) | 7916 (100.0%) | <0.001 | 0 (0.0%) | 4107 (100.0%) | 0 (0.0%) | 1854 (100.0%) | 0 (0.0%) | 1955 (100.0%) | <0.001 |
| Stroke or TIA |  | 12803 (15.3%) | 1857 (23.5%) | <0.001 | 6446 (14.2%) | 956 (23.3%) | 2927 (15.4%) | 433 (23.4%) | 3430 (18.1%) | 468 (23.9%) | <0.001 |
| Depression |  | 2957 (3.5%) | 305 (3.9%) | 0.15 | 1583 (3.5%) | 155 (3.8%) | 638 (3.3%) | 64 (3.5%) | 736 (3.9%) | 86 (4.4%) | 0.020 |
| Dementia |  | 1255 (1.5%) | 145 (1.8%) | 0.022 | 603 (1.3%) | 71 (1.7%) | 265 (1.4%) | 27 (1.5%) | 387 (2.0%) | 47 (2.4%) | <0.001 |
| Cancer <3years |  | 10255 (12.3%) | 1109 (14.0%) | <0.001 | 5127 (11.3%) | 536 (13.1%) | 2476 (13.0%) | 266 (14.3%) | 2652 (14.0%) | 307 (15.7%) | <0.001 |
| Muscolo-skeletal <3years |  | 24812 (29.7%) | 3308 (41.8%) | <0.001 | 11885 (26.1%) | 1553 (37.8%) | 5951 (31.2%) | 801 (43.2%) | 6976 (36.7%) | 954 (48.8%) | <0.001 |
| Dysthyroidism |  | 6227 (7.5%) | 634 (8.0%) | 0.073 | 2848 (6.3%) | 280 (6.8%) | 1425 (7.5%) | 153 (8.3%) | 1954 (10.3%) | 201 (10.3%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 26701 (32.0%) | 162 (2.0%) | <0.001 | 15062 (33.1%) | 53 (1.3%) | 6024 (31.6%) | 48 (2.6%) | 5615 (29.6%) | 61 (3.1%) | <0.001 |
|  | 2-3 | 32714 (39.2%) | 2441 (30.8%) |  | 18146 (39.9%) | 1282 (31.2%) | 7444 (39.0%) | 568 (30.6%) | 7124 (37.5%) | 591 (30.2%) |  |
|  | 4-7 | 20036 (24.0%) | 4168 (52.7%) |  | 10310 (22.7%) | 2200 (53.6%) | 4595 (24.1%) | 991 (53.5%) | 5131 (27.0%) | 977 (50.0%) |  |
|  | >=8 | 4096 (4.9%) | 1145 (14.5%) |  | 1964 (4.3%) | 572 (13.9%) | 1004 (5.3%) | 247 (13.3%) | 1128 (5.9%) | 326 (16.7%) |  |

**Supplementary Table 14. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by stroke or TIA**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 76803 (86%) | 14660 (16%) |  | 42187 (85%) | 7402 (15%) | 17561 (84%) | 3360 (16%) | 17055 (81%) | 3898 (19%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 28094 (36.6%) | 5240 (35.7%) | 0.054 | 12381 (29.3%) | 1988 (26.9%) | 6663 (37.9%) | 1242 (37.0%) | 9050 (53.1%) | 2010 (51.6%) | <0.001 |
|  | Male | 48709 (63.4%) | 9420 (64.3%) |  | 29806 (70.7%) | 5414 (73.1%) | 10898 (62.1%) | 2118 (63.0%) | 8005 (46.9%) | 1888 (48.4%) |  |
| Age, median (IQR) |  | 75 (66, 82) | 79 (72, 84) | <0.001 | 72 (63, 80) | 77 (69, 83) | 75 (67, 82) | 79 (72, 84) | 79 (72, 85) | 81 (76, 86) | <0.001 |
| Family type | Cohabitating | 40104 (52.3%) | 7408 (50.6%) | <0.001 | 22811 (54.2%) | 3974 (53.7%) | 9453 (53.9%) | 1733 (51.6%) | 7840 (46.0%) | 1701 (43.6%) | <0.001 |
|  | Living alone | 36578 (47.7%) | 7245 (49.4%) |  | 19287 (45.8%) | 3424 (46.3%) | 8089 (46.1%) | 1625 (48.4%) | 9202 (54.0%) | 2196 (56.4%) |  |
| Smoking |  | 7484 (12.2%) | 1070 (9.7%) | <0.001 | 4972 (14.4%) | 666 (11.6%) | 1490 (10.6%) | 219 (8.7%) | 1022 (8.2%) | 185 (6.8%) | <0.001 |
| Alcohol user |  | 2380 (4.9%) | 307 (3.7%) | <0.001 | 1539 (5.5%) | 180 (4.0%) | 503 (4.5%) | 64 (3.4%) | 338 (3.7%) | 63 (3.3%) | <0.001 |
| Location of care | Out-patient | 43180 (56.2%) | 6920 (47.2%) | <0.001 | 24698 (58.5%) | 3801 (51.4%) | 10707 (61.0%) | 1702 (50.7%) | 7775 (45.6%) | 1417 (36.4%) | <0.001 |
|  | In-patient | 33623 (43.8%) | 7740 (52.8%) |  | 17489 (41.5%) | 3601 (48.6%) | 6854 (39.0%) | 1658 (49.3%) | 9280 (54.4%) | 2481 (63.6%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 47619 (62.0%) | 10052 (68.6%) | <0.001 | 27225 (64.5%) | 5081 (68.6%) | 9186 (52.3%) | 2082 (62.0%) | 11208 (65.7%) | 2889 (74.1%) | <0.001 |
| Duration of HF | <6mo | 41366 (55.1%) | 6256 (43.9%) | <0.001 | 24416 (59.0%) | 3257 (45.0%) | 9106 (53.1%) | 1412 (43.4%) | 7844 (47.6%) | 1587 (42.4%) | <0.001 |
|  | >=6mo | 33679 (44.9%) | 7981 (56.1%) |  | 16984 (41.0%) | 3986 (55.0%) | 8058 (46.9%) | 1843 (56.6%) | 8637 (52.4%) | 2152 (57.6%) |  |
| Follow-up location | Primary care | 22370 (30.3%) | 5756 (41.4%) | <0.001 | 8545 (21.0%) | 2202 (31.2%) | 5800 (34.3%) | 1468 (45.7%) | 8025 (49.7%) | 2086 (57.5%) | <0.001 |
|  | Hospital | 51446 (69.7%) | 8152 (58.6%) |  | 32213 (79.0%) | 4867 (68.8%) | 11100 (65.7%) | 1741 (54.3%) | 8133 (50.3%) | 1544 (42.5%) |  |
| NYHA functional class | I-II | 34957 (61.9%) | 5122 (51.8%) | <0.001 | 19184 (58.9%) | 2532 (46.9%) | 9127 (69.8%) | 1372 (60.5%) | 6646 (61.6%) | 1218 (54.8%) | <0.001 |
|  | III-IV | 21497 (38.1%) | 4766 (48.2%) |  | 13404 (41.1%) | 2869 (53.1%) | 3947 (30.2%) | 894 (39.5%) | 4146 (38.4%) | 1003 (45.2%) |  |
| BMI, median (IQR) |  | 27 (23, 30) | 26 (23, 30) | <0.001 | 26 (23, 30) | 26 (23, 29) | 27 (24, 31) | 26 (23, 30) | 27 (24, 31) | 27 (23, 30) | <0.001 |
| SBP, median (IQR) |  | 125 (110, 140) | 127 (114, 140) | <0.001 | 120 (110, 138) | 120 (110, 139) | 130 (115, 140) | 130 (117, 143) | 130 (120, 145) | 130 (120, 148) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (65, 80) | <0.001 | 72 (65, 80) | 70 (65, 80) | 74 (65, 80) | 73 (65, 80) | 71 (65, 80) | 70 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (82, 100) | 90 (83, 100) | 1.00 | 90 (81, 99) | 90 (80, 98) | 92 (83, 100) | 93 (83, 100) | 93 (83, 100) | 93 (84, 101) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 83) | 72 (63, 82) | 0.63 | 72 (64, 84) | 72 (64, 82) | 70 (62, 80) | 71 (63, 81) | 72 (63, 82) | 72 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 68 (50, 87) | 60 (44, 78) | <0.001 | 71 (52, 88) | 61 (45, 80) | 69 (51, 87) | 61 (44, 78) | 62 (45, 81) | 57 (42, 74) | <0.001 |
| Potassium categories | Normakalemia | 57964 (92.9%) | 10729 (92.3%) | <0.001 | 31845 (93.4%) | 5348 (92.4%) | 13519 (93.0%) | 2553 (92.8%) | 12600 (91.4%) | 2828 (91.8%) | <0.001 |
|  | Hypokalemia | 2685 (4.3%) | 590 (5.1%) |  | 1226 (3.6%) | 268 (4.6%) | 621 (4.3%) | 137 (5.0%) | 838 (6.1%) | 185 (6.0%) |  |
|  | Hyperkalemia | 1757 (2.8%) | 299 (2.6%) |  | 1012 (3.0%) | 173 (3.0%) | 391 (2.7%) | 60 (2.2%) | 354 (2.6%) | 66 (2.1%) |  |
| Haemoglobin, median (IQR) |  | 133 (121, 145) | 130 (117, 142) | <0.001 | 136 (123, 147) | 132 (120, 144) | 133 (120, 144) | 130 (118, 142) | 128 (116, 140) | 125 (113, 137) | <0.001 |
| NT-proBNP, median (IQR) |  | 2220 (955, 4929) | 2811 (1295, 6134) | <0.001 | 2631 (1130, 5870) | 3464 (1530, 7775) | 1790 (709, 3942) | 2407 (1143, 5232) | 1920 (884, 3980) | 2397 (1116, 4680) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 65515 (86.2%) | 11755 (81.1%) | <0.001 | 38492 (92.2%) | 6432 (88.0%) | 14893 (85.6%) | 2683 (80.4%) | 12130 (71.9%) | 2640 (68.8%) | <0.001 |
| Beta-blockers |  | 67964 (88.7%) | 12664 (86.7%) | <0.001 | 38879 (92.4%) | 6651 (90.1%) | 15267 (87.1%) | 2901 (86.5%) | 13818 (81.3%) | 3112 (80.3%) | <0.001 |
| MRA |  | 27204 (35.6%) | 4871 (33.4%) | <0.001 | 16975 (40.4%) | 2782 (37.7%) | 4914 (28.1%) | 978 (29.3%) | 5315 (31.3%) | 1111 (28.7%) | <0.001 |
| DIuretics |  | 57467 (75.1%) | 11911 (81.5%) | <0.001 | 31631 (75.2%) | 5894 (79.8%) | 11859 (67.7%) | 2647 (79.0%) | 13977 (82.2%) | 3370 (86.7%) | <0.001 |
| Digoxin |  | 10214 (13.3%) | 1956 (13.4%) | 0.87 | 5746 (13.7%) | 1032 (14.0%) | 2063 (11.8%) | 432 (12.9%) | 2405 (14.1%) | 492 (12.7%) | <0.001 |
| Antiplatelet therapy |  | 31526 (41.2%) | 6503 (44.5%) | <0.001 | 18452 (43.9%) | 3471 (47.0%) | 7434 (42.5%) | 1461 (43.6%) | 5640 (33.2%) | 1571 (40.5%) | <0.001 |
| Anticoagulant therapy |  | 34653 (45.3%) | 7710 (52.8%) | <0.001 | 18248 (43.4%) | 3844 (52.1%) | 7950 (45.4%) | 1790 (53.4%) | 8455 (49.8%) | 2076 (53.5%) | <0.001 |
| Statins |  | 35677 (46.6%) | 8658 (59.2%) | <0.001 | 20256 (48.2%) | 4572 (61.9%) | 8664 (49.5%) | 2003 (59.7%) | 6757 (39.8%) | 2083 (53.6%) | <0.001 |
| Nitrates |  | 9063 (11.9%) | 2522 (17.3%) | <0.001 | 4509 (10.7%) | 1231 (16.7%) | 2148 (12.3%) | 570 (17.0%) | 2406 (14.2%) | 721 (18.6%) | <0.001 |
| HF devices |  | 4118 (5.4%) | 820 (5.7%) | 0.23 | 3319 (7.9%) | 660 (9.0%) | 558 (3.2%) | 103 (3.1%) | 241 (1.4%) | 57 (1.5%) | <0.001 |
| EF categories | HFrEF | 42187 (54.9%) | 7402 (50.5%) | <0.001 | 42187 (100.0%) | 7402 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 17561 (22.9%) | 3360 (22.9%) |  | 0 (0.0%) | 0 (0.0%) | 17561 (100.0%) | 3360 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 17055 (22.2%) | 3898 (26.6%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 17055 (100.0%) | 3898 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 20623 (26.9%) | 3348 (22.8%) | <0.001 | 10273 (24.4%) | 1446 (19.5%) | 4991 (28.4%) | 831 (24.7%) | 5359 (31.4%) | 1071 (27.5%) | <0.001 |
| Hypertension |  | 48234 (62.8%) | 11149 (76.1%) | <0.001 | 23833 (56.5%) | 5259 (71.0%) | 11544 (65.7%) | 2668 (79.4%) | 12857 (75.4%) | 3222 (82.7%) | <0.001 |
| Diabetes |  | 19142 (24.9%) | 4688 (32.0%) | <0.001 | 10233 (24.3%) | 2395 (32.4%) | 4245 (24.2%) | 1036 (30.8%) | 4664 (27.3%) | 1257 (32.2%) | <0.001 |
| CAD |  | 38834 (50.6%) | 9099 (62.1%) | <0.001 | 21790 (51.7%) | 4889 (66.0%) | 9515 (54.2%) | 2076 (61.8%) | 7529 (44.1%) | 2134 (54.7%) | <0.001 |
| AF |  | 41689 (54.3%) | 9572 (65.3%) | <0.001 | 20788 (49.3%) | 4525 (61.1%) | 9863 (56.2%) | 2264 (67.4%) | 11038 (64.7%) | 2783 (71.4%) | <0.001 |
| VHD |  | 19917 (25.9%) | 4456 (30.4%) | <0.001 | 9557 (22.7%) | 2003 (27.1%) | 4538 (25.8%) | 1042 (31.0%) | 5822 (34.1%) | 1411 (36.2%) | <0.001 |
| CKD |  | 29243 (38.1%) | 7336 (50.0%) | <0.001 | 14701 (34.8%) | 3538 (47.8%) | 6569 (37.4%) | 1654 (49.2%) | 7973 (46.7%) | 2144 (55.0%) | <0.001 |
| Anaemia |  | 25190 (32.8%) | 5998 (40.9%) | <0.001 | 12289 (29.1%) | 2829 (38.2%) | 5927 (33.8%) | 1330 (39.6%) | 6974 (40.9%) | 1839 (47.2%) | <0.001 |
| COPD |  | 9461 (12.3%) | 2136 (14.6%) | <0.001 | 4648 (11.0%) | 976 (13.2%) | 2140 (12.2%) | 507 (15.1%) | 2673 (15.7%) | 653 (16.8%) | <0.001 |
| Liver disease |  | 1628 (2.1%) | 288 (2.0%) | 0.23 | 908 (2.2%) | 152 (2.1%) | 328 (1.9%) | 51 (1.5%) | 392 (2.3%) | 85 (2.2%) | 0.014 |
| PAD |  | 6059 (7.9%) | 1857 (12.7%) | <0.001 | 3151 (7.5%) | 956 (12.9%) | 1421 (8.1%) | 433 (12.9%) | 1487 (8.7%) | 468 (12.0%) | <0.001 |
| Stroke or TIA |  | 0 (0.0%) | 14660 (100.0%) | <0.001 | 0 (0.0%) | 7402 (100.0%) | 0 (0.0%) | 3360 (100.0%) | 0 (0.0%) | 3898 (100.0%) | <0.001 |
| Depression |  | 2542 (3.3%) | 720 (4.9%) | <0.001 | 1399 (3.3%) | 339 (4.6%) | 545 (3.1%) | 157 (4.7%) | 598 (3.5%) | 224 (5.7%) | <0.001 |
| Dementia |  | 928 (1.2%) | 472 (3.2%) | <0.001 | 450 (1.1%) | 224 (3.0%) | 198 (1.1%) | 94 (2.8%) | 280 (1.6%) | 154 (4.0%) | <0.001 |
| Cancer <3years |  | 9392 (12.2%) | 1972 (13.5%) | <0.001 | 4707 (11.2%) | 956 (12.9%) | 2289 (13.0%) | 453 (13.5%) | 2396 (14.0%) | 563 (14.4%) | <0.001 |
| Muscolo-skeletal <3years |  | 22961 (29.9%) | 5159 (35.2%) | <0.001 | 11097 (26.3%) | 2341 (31.6%) | 5551 (31.6%) | 1201 (35.7%) | 6313 (37.0%) | 1617 (41.5%) | <0.001 |
| Dysthyroidism |  | 5527 (7.2%) | 1334 (9.1%) | <0.001 | 2566 (6.1%) | 562 (7.6%) | 1275 (7.3%) | 303 (9.0%) | 1686 (9.9%) | 469 (12.0%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 26179 (34.1%) | 684 (4.7%) | <0.001 | 14851 (35.2%) | 264 (3.6%) | 5866 (33.4%) | 206 (6.1%) | 5462 (32.0%) | 214 (5.5%) | <0.001 |
|  | 2-3 | 29560 (38.5%) | 5595 (38.2%) |  | 16461 (39.0%) | 2967 (40.1%) | 6764 (38.5%) | 1248 (37.1%) | 6335 (37.1%) | 1380 (35.4%) |  |
|  | 4-7 | 17542 (22.8%) | 6662 (45.4%) |  | 9166 (21.7%) | 3344 (45.2%) | 4092 (23.3%) | 1494 (44.5%) | 4284 (25.1%) | 1824 (46.8%) |  |
|  | >=8 | 3522 (4.6%) | 1719 (11.7%) |  | 1709 (4.1%) | 827 (11.2%) | 839 (4.8%) | 412 (12.3%) | 974 (5.7%) | 480 (12.3%) |  |

**Supplementary Table 15. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by depression**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 88201 (96%) | 3262 (4%) |  | 47851 (96%) | 1738 (4%) | 20219 (97%) | 702 (3%) | 20131 (96%) | 822 (4%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 31819 (36.1%) | 1515 (46.4%) | <0.001 | 13718 (28.7%) | 651 (37.5%) | 7556 (37.4%) | 349 (49.7%) | 10545 (52.4%) | 515 (62.7%) | <0.001 |
|  | Male | 56382 (63.9%) | 1747 (53.6%) |  | 34133 (71.3%) | 1087 (62.5%) | 12663 (62.6%) | 353 (50.3%) | 9586 (47.6%) | 307 (37.3%) |  |
| Age, median (IQR) |  | 76 (67, 82) | 73 (62, 81) | <0.001 | 73 (64, 81) | 70 (59, 79) | 76 (68, 83) | 73 (61, 81) | 80 (73, 85) | 78 (70, 84) | <0.001 |
| Family type | Cohabitating | 46131 (52.4%) | 1381 (42.3%) | <0.001 | 26013 (54.5%) | 772 (44.4%) | 10885 (53.9%) | 301 (42.9%) | 9233 (45.9%) | 308 (37.5%) | <0.001 |
|  | Living alone | 41943 (47.6%) | 1880 (57.7%) |  | 21745 (45.5%) | 966 (55.6%) | 9314 (46.1%) | 400 (57.1%) | 10884 (54.1%) | 514 (62.5%) |  |
| Smoking |  | 8058 (11.6%) | 496 (20.2%) | <0.001 | 5346 (13.7%) | 292 (21.6%) | 1597 (10.0%) | 112 (20.7%) | 1115 (7.6%) | 92 (16.3%) | <0.001 |
| Alcohol user |  | 2548 (4.7%) | 139 (7.5%) | <0.001 | 1640 (5.2%) | 79 (7.4%) | 527 (4.2%) | 40 (9.7%) | 381 (3.6%) | 20 (5.3%) | <0.001 |
| Location of care | Out-patient | 48603 (55.1%) | 1497 (45.9%) | <0.001 | 27614 (57.7%) | 885 (50.9%) | 12063 (59.7%) | 346 (49.3%) | 8926 (44.3%) | 266 (32.4%) | <0.001 |
|  | In-patient | 39598 (44.9%) | 1765 (54.1%) |  | 20237 (42.3%) | 853 (49.1%) | 8156 (40.3%) | 356 (50.7%) | 11205 (55.7%) | 556 (67.6%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 55334 (62.7%) | 2337 (71.6%) | <0.001 | 31039 (64.9%) | 1267 (72.9%) | 10833 (53.6%) | 435 (62.0%) | 13462 (66.9%) | 635 (77.3%) | <0.001 |
| Duration of HF | <6mo | 45954 (53.4%) | 1668 (52.6%) | 0.42 | 26705 (56.9%) | 968 (57.0%) | 10193 (51.7%) | 325 (47.3%) | 9056 (46.6%) | 375 (47.9%) | <0.001 |
|  | >=6mo | 40159 (46.6%) | 1501 (47.4%) |  | 20239 (43.1%) | 731 (43.0%) | 9539 (48.3%) | 362 (52.7%) | 10381 (53.4%) | 408 (52.1%) |  |
| Follow-up location | Primary care | 27055 (32.0%) | 1071 (34.7%) | 0.001 | 10332 (22.4%) | 415 (25.0%) | 7031 (36.2%) | 237 (35.3%) | 9692 (50.9%) | 419 (55.2%) | <0.001 |
|  | Hospital | 57581 (68.0%) | 2017 (65.3%) |  | 35837 (77.6%) | 1243 (75.0%) | 12407 (63.8%) | 434 (64.7%) | 9337 (49.1%) | 340 (44.8%) |  |
| NYHA functional class | I-II | 38992 (60.7%) | 1087 (50.9%) | <0.001 | 21150 (57.5%) | 566 (46.3%) | 10206 (68.7%) | 293 (61.0%) | 7636 (60.7%) | 228 (52.5%) | <0.001 |
|  | III-IV | 25214 (39.3%) | 1049 (49.1%) |  | 15617 (42.5%) | 656 (53.7%) | 4654 (31.3%) | 187 (39.0%) | 4943 (39.3%) | 206 (47.5%) |  |
| BMI, median (IQR) |  | 26 (23, 30) | 27 (24, 31) | 0.001 | 26 (23, 30) | 26 (23, 30) | 27 (24, 30) | 28 (24, 32) | 27 (24, 31) | 27 (24, 32) | <0.001 |
| SBP, median (IQR) |  | 125 (111, 140) | 123 (110, 140) | <0.001 | 120 (110, 139) | 120 (109, 131) | 130 (115, 140) | 126 (113, 140) | 130 (120, 145) | 130 (120, 145) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 72 (65, 80) | 0.82 | 71 (65, 80) | 71 (65, 80) | 74 (65, 80) | 72 (65, 80) | 71 (65, 80) | 73 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (82, 100) | 90 (82, 100) | 0.004 | 90 (81, 99) | 88 (80, 97) | 92 (83, 100) | 91 (83, 100) | 93 (83, 101) | 93 (85, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 72 (64, 84) | <0.001 | 72 (64, 83) | 74 (65, 85) | 70 (62, 80) | 71 (63, 83) | 72 (63, 82) | 72 (64, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 67 (49, 85) | 68 (49, 88) | 0.003 | 69 (51, 87) | 72 (51, 90) | 67 (50, 86) | 67 (48, 89) | 61 (45, 80) | 61 (44, 82) | <0.001 |
| Potassium categories | Normakalemia | 66288 (92.8%) | 2405 (91.7%) | 0.073 | 35896 (93.3%) | 1297 (92.2%) | 15540 (93.1%) | 532 (91.6%) | 14852 (91.5%) | 576 (90.6%) | <0.001 |
|  | Hypokalemia | 3138 (4.4%) | 137 (5.2%) |  | 1435 (3.7%) | 59 (4.2%) | 725 (4.3%) | 33 (5.7%) | 978 (6.0%) | 45 (7.1%) |  |
|  | Hyperkalemia | 1975 (2.8%) | 81 (3.1%) |  | 1135 (3.0%) | 50 (3.6%) | 435 (2.6%) | 16 (2.8%) | 405 (2.5%) | 15 (2.4%) |  |
| Haemoglobin, median (IQR) |  | 133 (120, 145) | 129 (117, 142) | <0.001 | 135 (123, 147) | 132 (120, 145) | 133 (120, 144) | 128 (116, 141) | 127 (115, 139) | 125 (113, 136) | <0.001 |
| NT-proBNP, median (IQR) |  | 2304 (1010, 5117) | 2129 (885, 5172) | 0.085 | 2725 (1190, 6110) | 2810 (1070, 6588) | 1887 (768, 4126) | 1753 (596, 4100) | 2013 (925, 4091) | 1776 (817, 3937) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 74652 (85.6%) | 2618 (81.3%) | <0.001 | 43366 (91.6%) | 1558 (90.8%) | 17030 (85.0%) | 546 (78.6%) | 14256 (71.7%) | 514 (63.5%) | <0.001 |
| Beta-blockers |  | 77802 (88.4%) | 2826 (87.1%) | 0.019 | 43948 (92.0%) | 1582 (91.2%) | 17570 (87.1%) | 598 (85.6%) | 16284 (81.2%) | 646 (79.6%) | <0.001 |
| MRA |  | 30903 (35.2%) | 1172 (36.2%) | 0.27 | 19028 (39.9%) | 729 (42.3%) | 5686 (28.2%) | 206 (29.5%) | 6189 (30.9%) | 237 (29.0%) | <0.001 |
| DIuretics |  | 66841 (76.0%) | 2537 (78.2%) | 0.005 | 36176 (75.8%) | 1349 (78.1%) | 14011 (69.5%) | 495 (70.7%) | 16654 (83.0%) | 693 (84.8%) | <0.001 |
| Digoxin |  | 11785 (13.4%) | 385 (11.8%) | 0.010 | 6572 (13.8%) | 206 (11.9%) | 2410 (12.0%) | 85 (12.1%) | 2803 (14.0%) | 94 (11.5%) | <0.001 |
| Antiplatelet therapy |  | 36555 (41.6%) | 1474 (45.4%) | <0.001 | 21127 (44.3%) | 796 (46.0%) | 8565 (42.5%) | 330 (47.3%) | 6863 (34.2%) | 348 (42.5%) | <0.001 |
| Anticoagulant therapy |  | 41141 (46.8%) | 1222 (37.6%) | <0.001 | 21451 (45.0%) | 641 (37.0%) | 9475 (47.0%) | 265 (37.9%) | 10215 (51.0%) | 316 (38.7%) | <0.001 |
| Statins |  | 42878 (48.8%) | 1457 (44.9%) | <0.001 | 24023 (50.4%) | 805 (46.6%) | 10337 (51.3%) | 330 (47.1%) | 8518 (42.5%) | 322 (39.4%) | <0.001 |
| Nitrates |  | 11113 (12.7%) | 472 (14.5%) | 0.001 | 5534 (11.6%) | 206 (11.9%) | 2615 (13.0%) | 103 (14.7%) | 2964 (14.8%) | 163 (19.9%) | <0.001 |
| HF devices |  | 4771 (5.5%) | 167 (5.2%) | 0.43 | 3854 (8.1%) | 125 (7.3%) | 635 (3.2%) | 26 (3.8%) | 282 (1.4%) | 16 (2.0%) | <0.001 |
| EF categories | HFrEF | 47851 (54.3%) | 1738 (53.3%) | 0.004 | 47851 (100.0%) | 1738 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 20219 (22.9%) | 702 (21.5%) |  | 0 (0.0%) | 0 (0.0%) | 20219 (100.0%) | 702 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 20131 (22.8%) | 822 (25.2%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 20131 (100.0%) | 822 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 22984 (26.1%) | 987 (30.3%) | <0.001 | 11248 (23.5%) | 471 (27.1%) | 5585 (27.6%) | 237 (33.8%) | 6151 (30.6%) | 279 (33.9%) | <0.001 |
| Hypertension |  | 57188 (64.8%) | 2195 (67.3%) | 0.004 | 28024 (58.6%) | 1068 (61.4%) | 13725 (67.9%) | 487 (69.4%) | 15439 (76.7%) | 640 (77.9%) | <0.001 |
| Diabetes |  | 22924 (26.0%) | 906 (27.8%) | 0.023 | 12174 (25.4%) | 454 (26.1%) | 5075 (25.1%) | 206 (29.3%) | 5675 (28.2%) | 246 (29.9%) | <0.001 |
| CAD |  | 46160 (52.3%) | 1773 (54.4%) | 0.023 | 25751 (53.8%) | 928 (53.4%) | 11181 (55.3%) | 410 (58.4%) | 9228 (45.8%) | 435 (52.9%) | <0.001 |
| AF |  | 49634 (56.3%) | 1627 (49.9%) | <0.001 | 24536 (51.3%) | 777 (44.7%) | 11766 (58.2%) | 361 (51.4%) | 13332 (66.2%) | 489 (59.5%) | <0.001 |
| VHD |  | 23527 (26.7%) | 846 (25.9%) | 0.35 | 11145 (23.3%) | 415 (23.9%) | 5403 (26.7%) | 177 (25.2%) | 6979 (34.7%) | 254 (30.9%) | <0.001 |
| CKD |  | 35303 (40.0%) | 1276 (39.1%) | 0.30 | 17638 (36.9%) | 601 (34.6%) | 7945 (39.3%) | 278 (39.6%) | 9720 (48.3%) | 397 (48.3%) | <0.001 |
| Anaemia |  | 29899 (33.9%) | 1289 (39.5%) | <0.001 | 14480 (30.3%) | 638 (36.7%) | 6979 (34.5%) | 278 (39.6%) | 8440 (41.9%) | 373 (45.4%) | <0.001 |
| COPD |  | 11030 (12.5%) | 567 (17.4%) | <0.001 | 5376 (11.2%) | 248 (14.3%) | 2518 (12.5%) | 129 (18.4%) | 3136 (15.6%) | 190 (23.1%) | <0.001 |
| Liver disease |  | 1783 (2.0%) | 133 (4.1%) | <0.001 | 988 (2.1%) | 72 (4.1%) | 349 (1.7%) | 30 (4.3%) | 446 (2.2%) | 31 (3.8%) | <0.001 |
| PAD |  | 7611 (8.6%) | 305 (9.4%) | 0.15 | 3952 (8.3%) | 155 (8.9%) | 1790 (8.9%) | 64 (9.1%) | 1869 (9.3%) | 86 (10.5%) | <0.001 |
| Stroke or TIA |  | 13940 (15.8%) | 720 (22.1%) | <0.001 | 7063 (14.8%) | 339 (19.5%) | 3203 (15.8%) | 157 (22.4%) | 3674 (18.3%) | 224 (27.3%) | <0.001 |
| Depression |  | 0 (0.0%) | 3262 (100.0%) | <0.001 | 0 (0.0%) | 1738 (100.0%) | 0 (0.0%) | 702 (100.0%) | 0 (0.0%) | 822 (100.0%) | <0.001 |
| Dementia |  | 1277 (1.4%) | 123 (3.8%) | <0.001 | 611 (1.3%) | 63 (3.6%) | 267 (1.3%) | 25 (3.6%) | 399 (2.0%) | 35 (4.3%) | <0.001 |
| Cancer <3years |  | 11009 (12.5%) | 355 (10.9%) | 0.007 | 5482 (11.5%) | 181 (10.4%) | 2678 (13.2%) | 64 (9.1%) | 2849 (14.2%) | 110 (13.4%) | <0.001 |
| Muscolo-skeletal <3years |  | 26787 (30.4%) | 1333 (40.9%) | <0.001 | 12812 (26.8%) | 626 (36.0%) | 6468 (32.0%) | 284 (40.5%) | 7507 (37.3%) | 423 (51.5%) | <0.001 |
| Dysthyroidism |  | 6466 (7.3%) | 395 (12.1%) | <0.001 | 2949 (6.2%) | 179 (10.3%) | 1496 (7.4%) | 82 (11.7%) | 2021 (10.0%) | 134 (16.3%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 26175 (29.7%) | 688 (21.1%) | <0.001 | 14701 (30.7%) | 414 (23.8%) | 5930 (29.3%) | 142 (20.2%) | 5544 (27.5%) | 132 (16.1%) | <0.001 |
|  | 2-3 | 33951 (38.5%) | 1204 (36.9%) |  | 18781 (39.2%) | 647 (37.2%) | 7751 (38.3%) | 261 (37.2%) | 7419 (36.9%) | 296 (36.0%) |  |
|  | 4-7 | 23147 (26.2%) | 1057 (32.4%) |  | 11999 (25.1%) | 511 (29.4%) | 5349 (26.5%) | 237 (33.8%) | 5799 (28.8%) | 309 (37.6%) |  |
|  | >=8 | 4928 (5.6%) | 313 (9.6%) |  | 2370 (5.0%) | 166 (9.6%) | 1189 (5.9%) | 62 (8.8%) | 1369 (6.8%) | 85 (10.3%) |  |

**Supplementary Table 16. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by dementia**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 90063 (98%) | 1400 (2%) |  | 48915 (99%) | 674 (1%) | 20629 (99%) | 292 (1%) | 20519 (98%) | 434 (2%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 32714 (36.3%) | 620 (44.3%) | <0.001 | 14117 (28.9%) | 252 (37.4%) | 7782 (37.7%) | 123 (42.1%) | 10815 (52.7%) | 245 (56.5%) | <0.001 |
|  | Male | 57349 (63.7%) | 780 (55.7%) |  | 34798 (71.1%) | 422 (62.6%) | 12847 (62.3%) | 169 (57.9%) | 9704 (47.3%) | 189 (43.5%) |  |
| Age, median (IQR) |  | 75 (66, 82) | 82 (78, 86) | <0.001 | 73 (64, 81) | 81 (76, 85) | 76 (68, 83) | 83 (78, 87) | 80 (73, 85) | 84 (79, 87) | <0.001 |
| Family type | Cohabitating | 46850 (52.1%) | 662 (47.3%) | <0.001 | 26435 (54.1%) | 350 (51.9%) | 11058 (53.7%) | 128 (43.8%) | 9357 (45.6%) | 184 (42.4%) | <0.001 |
|  | Living alone | 43085 (47.9%) | 738 (52.7%) |  | 22387 (45.9%) | 324 (48.1%) | 9550 (46.3%) | 164 (56.2%) | 11148 (54.4%) | 250 (57.6%) |  |
| Smoking |  | 8475 (11.9%) | 79 (9.6%) | 0.048 | 5586 (14.0%) | 52 (12.8%) | 1694 (10.3%) | 15 (8.3%) | 1195 (8.0%) | 12 (5.2%) | <0.001 |
| Alcohol user |  | 2672 (4.8%) | 15 (2.7%) | 0.021 | 1711 (5.3%) | <10 (2.7%) | 565 (4.4%) | <5 (1.6%) | 396 (3.6%) | <10 (3.5%) | <0.001 |
| Location of care | Out-patient | 49713 (55.2%) | 387 (27.6%) | <0.001 | 28300 (57.9%) | 199 (29.5%) | 12305 (59.6%) | 104 (35.6%) | 9108 (44.4%) | 84 (19.4%) | <0.001 |
|  | In-patient | 40350 (44.8%) | 1013 (72.4%) |  | 20615 (42.1%) | 475 (70.5%) | 8324 (40.4%) | 188 (64.4%) | 11411 (55.6%) | 350 (80.6%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 56521 (62.8%) | 1150 (82.1%) | <0.001 | 31742 (64.9%) | 564 (83.7%) | 11052 (53.6%) | 216 (74.0%) | 13727 (66.9%) | 370 (85.3%) | <0.001 |
| Duration of HF | <6mo | 47046 (53.5%) | 576 (42.4%) | <0.001 | 27383 (57.1%) | 290 (43.7%) | 10413 (51.7%) | 105 (36.7%) | 9250 (46.7%) | 181 (44.0%) | <0.001 |
|  | >=6mo | 40876 (46.5%) | 784 (57.6%) |  | 20597 (42.9%) | 373 (56.3%) | 9720 (48.3%) | 181 (63.3%) | 10559 (53.3%) | 230 (56.0%) |  |
| Follow-up location | Primary care | 27259 (31.5%) | 867 (68.6%) | <0.001 | 10366 (22.0%) | 381 (61.9%) | 7081 (35.7%) | 187 (70.8%) | 9812 (50.6%) | 299 (77.9%) | <0.001 |
|  | Hospital | 59201 (68.5%) | 397 (31.4%) |  | 36845 (78.0%) | 235 (38.1%) | 12764 (64.3%) | 77 (29.2%) | 9592 (49.4%) | 85 (22.1%) |  |
| NYHA functional class | I-II | 39706 (60.5%) | 373 (49.1%) | <0.001 | 21553 (57.3%) | 163 (41.0%) | 10401 (68.6%) | 98 (58.0%) | 7752 (60.5%) | 112 (58.0%) | <0.001 |
|  | III-IV | 25876 (39.5%) | 387 (50.9%) |  | 16038 (42.7%) | 235 (59.0%) | 4770 (31.4%) | 71 (42.0%) | 5068 (39.5%) | 81 (42.0%) |  |
| BMI, median (IQR) |  | 26 (23, 30) | 25 (22, 28) | <0.001 | 26 (23, 30) | 25 (22, 28) | 27 (24, 31) | 25 (22, 29) | 27 (24, 31) | 26 (22, 29) | <0.001 |
| SBP, median (IQR) |  | 125 (110, 140) | 125 (112, 140) | 0.30 | 120 (110, 138) | 120 (110, 135) | 130 (115, 140) | 130 (115, 145) | 130 (120, 145) | 130 (120, 150) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (65, 80) | 0.004 | 71 (65, 80) | 70 (64, 80) | 74 (65, 80) | 71 (65, 80) | 71 (65, 80) | 70 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (82, 100) | 90 (82, 100) | 0.19 | 90 (81, 99) | 89 (80, 97) | 92 (83, 100) | 93 (83, 100) | 93 (83, 101) | 93 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 74 (65, 85) | <0.001 | 72 (64, 83) | 75 (65, 85) | 70 (62, 80) | 74 (64, 87) | 71 (63, 82) | 74 (66, 85) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 67 (49, 86) | 57 (42, 73) | <0.001 | 69 (51, 88) | 57 (42, 72) | 68 (50, 86) | 55 (41, 71) | 61 (45, 80) | 59 (42, 73) | <0.001 |
| Potassium categories | Normakalemia | 67738 (92.8%) | 955 (89.7%) | <0.001 | 36716 (93.3%) | 477 (92.6%) | 15870 (93.0%) | 202 (89.8%) | 15152 (91.6%) | 276 (84.9%) | <0.001 |
|  | Hypokalemia | 3185 (4.4%) | 90 (8.5%) |  | 1462 (3.7%) | 32 (6.2%) | 739 (4.3%) | 19 (8.4%) | 984 (5.9%) | 39 (12.0%) |  |
|  | Hyperkalemia | 2036 (2.8%) | 20 (1.9%) |  | 1179 (3.0%) | 6 (1.2%) | 447 (2.6%) | 4 (1.8%) | 410 (2.5%) | 10 (3.1%) |  |
| Haemoglobin, median (IQR) |  | 133 (120, 145) | 124 (113, 137) | <0.001 | 135 (123, 147) | 125 (116, 140) | 133 (120, 144) | 125 (115, 136) | 127 (115, 139) | 122 (111, 134) | <0.001 |
| NT-proBNP, median (IQR) |  | 2290 (1000, 5080) | 3750 (1628, 8450) | <0.001 | 2709 (1176, 6070) | 5200 (2280, 10947) | 1870 (757, 4096) | 3151 (1375, 7950) | 2000 (917, 4067) | 2579 (1103, 5869) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 76278 (85.6%) | 992 (72.3%) | <0.001 | 44389 (91.8%) | 535 (81.2%) | 17370 (85.0%) | 206 (71.3%) | 14519 (71.6%) | 251 (59.1%) | <0.001 |
| Beta-blockers |  | 79502 (88.5%) | 1126 (80.8%) | <0.001 | 44948 (92.1%) | 582 (86.6%) | 17933 (87.1%) | 235 (80.8%) | 16621 (81.3%) | 309 (71.9%) | <0.001 |
| MRA |  | 31680 (35.3%) | 395 (28.3%) | <0.001 | 19536 (40.1%) | 221 (32.9%) | 5826 (28.4%) | 66 (22.7%) | 6318 (31.0%) | 108 (25.0%) | <0.001 |
| DIuretics |  | 68178 (75.9%) | 1200 (86.1%) | <0.001 | 36946 (75.8%) | 579 (86.4%) | 14266 (69.3%) | 240 (82.2%) | 16966 (83.0%) | 381 (88.4%) | <0.001 |
| Digoxin |  | 11997 (13.4%) | 173 (12.4%) | 0.28 | 6700 (13.7%) | 78 (11.6%) | 2458 (11.9%) | 37 (12.7%) | 2839 (13.9%) | 58 (13.4%) | <0.001 |
| Antiplatelet therapy |  | 37327 (41.6%) | 702 (50.3%) | <0.001 | 21574 (44.3%) | 349 (51.9%) | 8739 (42.5%) | 156 (53.6%) | 7014 (34.3%) | 197 (45.6%) | <0.001 |
| Anticoagulant therapy |  | 41883 (46.7%) | 480 (34.4%) | <0.001 | 21863 (44.8%) | 229 (34.1%) | 9644 (46.9%) | 96 (32.9%) | 10376 (50.8%) | 155 (35.8%) | <0.001 |
| Statins |  | 43775 (48.8%) | 560 (40.1%) | <0.001 | 24515 (50.3%) | 313 (46.6%) | 10553 (51.3%) | 114 (39.0%) | 8707 (42.6%) | 133 (30.7%) | <0.001 |
| Nitrates |  | 11327 (12.6%) | 258 (18.5%) | <0.001 | 5619 (11.5%) | 121 (18.1%) | 2657 (12.9%) | 61 (20.9%) | 3051 (14.9%) | 76 (17.6%) | <0.001 |
| HF devices |  | 4901 (5.5%) | 37 (2.7%) | <0.001 | 3948 (8.1%) | 31 (4.7%) | 656 (3.2%) | <10 (1.8%) | 297 (1.5%) | <5 (0.2%) | <0.001 |
| EF categories | HFrEF | 48915 (54.3%) | 674 (48.1%) | <0.001 | 48915 (100.0%) | 674 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 20629 (22.9%) | 292 (20.9%) |  | 0 (0.0%) | 0 (0.0%) | 20629 (100.0%) | 292 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 20519 (22.8%) | 434 (31.0%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 20519 (100.0%) | 434 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 23729 (26.3%) | 242 (17.3%) | <0.001 | 11636 (23.8%) | 83 (12.3%) | 5758 (27.9%) | 64 (21.9%) | 6335 (30.9%) | 95 (21.9%) | <0.001 |
| Hypertension |  | 58357 (64.8%) | 1026 (73.3%) | <0.001 | 28614 (58.5%) | 478 (70.9%) | 13996 (67.8%) | 216 (74.0%) | 15747 (76.7%) | 332 (76.5%) | <0.001 |
| Diabetes |  | 23404 (26.0%) | 426 (30.4%) | <0.001 | 12400 (25.4%) | 228 (33.8%) | 5203 (25.2%) | 78 (26.7%) | 5801 (28.3%) | 120 (27.6%) | <0.001 |
| CAD |  | 47097 (52.3%) | 836 (59.7%) | <0.001 | 26249 (53.7%) | 430 (63.8%) | 11408 (55.3%) | 183 (62.7%) | 9440 (46.0%) | 223 (51.4%) | <0.001 |
| AF |  | 50361 (55.9%) | 900 (64.3%) | <0.001 | 24913 (50.9%) | 400 (59.3%) | 11931 (57.8%) | 196 (67.1%) | 13517 (65.9%) | 304 (70.0%) | <0.001 |
| VHD |  | 23923 (26.6%) | 450 (32.1%) | <0.001 | 11363 (23.2%) | 197 (29.2%) | 5482 (26.6%) | 98 (33.6%) | 7078 (34.5%) | 155 (35.7%) | <0.001 |
| CKD |  | 35799 (39.7%) | 780 (55.7%) | <0.001 | 17863 (36.5%) | 376 (55.8%) | 8053 (39.0%) | 170 (58.2%) | 9883 (48.2%) | 234 (53.9%) | <0.001 |
| Anaemia |  | 30480 (33.8%) | 708 (50.6%) | <0.001 | 14788 (30.2%) | 330 (49.0%) | 7115 (34.5%) | 142 (48.6%) | 8577 (41.8%) | 236 (54.4%) | <0.001 |
| COPD |  | 11397 (12.7%) | 200 (14.3%) | 0.069 | 5530 (11.3%) | 94 (13.9%) | 2605 (12.6%) | 42 (14.4%) | 3262 (15.9%) | 64 (14.7%) | <0.001 |
| Liver disease |  | 1894 (2.1%) | 22 (1.6%) | 0.17 | 1048 (2.1%) | 12 (1.8%) | 372 (1.8%) | <10 (2.4%) | 474 (2.3%) | <5 (0.7%) | 0.003 |
| PAD |  | 7771 (8.6%) | 145 (10.4%) | 0.022 | 4036 (8.3%) | 71 (10.5%) | 1827 (8.9%) | 27 (9.2%) | 1908 (9.3%) | 47 (10.8%) | <0.001 |
| Stroke or TIA |  | 14188 (15.8%) | 472 (33.7%) | <0.001 | 7178 (14.7%) | 224 (33.2%) | 3266 (15.8%) | 94 (32.2%) | 3744 (18.2%) | 154 (35.5%) | <0.001 |
| Depression |  | 3139 (3.5%) | 123 (8.8%) | <0.001 | 1675 (3.4%) | 63 (9.3%) | 677 (3.3%) | 25 (8.6%) | 787 (3.8%) | 35 (8.1%) | <0.001 |
| Dementia |  | 0 (0.0%) | 1400 (100.0%) | <0.001 | 0 (0.0%) | 674 (100.0%) | 0 (0.0%) | 292 (100.0%) | 0 (0.0%) | 434 (100.0%) | <0.001 |
| Cancer <3years |  | 11208 (12.4%) | 156 (11.1%) | 0.14 | 5589 (11.4%) | 74 (11.0%) | 2708 (13.1%) | 34 (11.6%) | 2911 (14.2%) | 48 (11.1%) | <0.001 |
| Muscolo-skeletal <3years |  | 27609 (30.7%) | 511 (36.5%) | <0.001 | 13203 (27.0%) | 235 (34.9%) | 6646 (32.2%) | 106 (36.3%) | 7760 (37.8%) | 170 (39.2%) | <0.001 |
| Dysthyroidism |  | 6702 (7.4%) | 159 (11.4%) | <0.001 | 3053 (6.2%) | 75 (11.1%) | 1549 (7.5%) | 29 (9.9%) | 2100 (10.2%) | 55 (12.7%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 26843 (29.8%) | 20 (1.4%) | <0.001 | 15106 (30.9%) | <10 (1.3%) | 6066 (29.4%) | <10 (2.1%) | 5671 (27.6%) | <10 (1.2%) | <0.001 |
|  | 2-3 | 34658 (38.5%) | 497 (35.5%) |  | 19182 (39.2%) | 246 (36.5%) | 7912 (38.4%) | 100 (34.2%) | 7564 (36.9%) | 151 (34.8%) |  |
|  | 4-7 | 23483 (26.1%) | 721 (51.5%) |  | 12158 (24.9%) | 352 (52.2%) | 5439 (26.4%) | 147 (50.3%) | 5886 (28.7%) | 222 (51.2%) |  |
|  | >=8 | 5079 (5.6%) | 162 (11.6%) |  | 2469 (5.0%) | 67 (9.9%) | 1212 (5.9%) | 39 (13.4%) | 1398 (6.8%) | 56 (12.9%) |  |

**Supplementary Table 17. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by cancer**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 80099 (88%) | 11364 (12%) |  | 43926 (89%) | 5663 (11%) | 18179 (87%) | 2742 (13%) | 17994 (86%) | 2959 (14%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 29805 (37.2%) | 3529 (31.1%) | <0.001 | 12953 (29.5%) | 1416 (25.0%) | 7036 (38.7%) | 869 (31.7%) | 9816 (54.6%) | 1244 (42.0%) | <0.001 |
|  | Male | 50294 (62.8%) | 7835 (68.9%) |  | 30973 (70.5%) | 4247 (75.0%) | 11143 (61.3%) | 1873 (68.3%) | 8178 (45.4%) | 1715 (58.0%) |  |
| Age, median (IQR) |  | 75 (66, 82) | 78 (72, 84) | <0.001 | 73 (63, 80) | 77 (70, 83) | 76 (67, 82) | 78 (72, 83) | 79 (72, 85) | 81 (75, 86) | <0.001 |
| Family type | Cohabitating | 41049 (51.3%) | 6463 (56.9%) | <0.001 | 23437 (53.5%) | 3348 (59.2%) | 9594 (52.8%) | 1592 (58.1%) | 8018 (44.6%) | 1523 (51.5%) | <0.001 |
|  | Living alone | 38925 (48.7%) | 4898 (43.1%) |  | 20399 (46.5%) | 2312 (40.8%) | 8564 (47.2%) | 1150 (41.9%) | 9962 (55.4%) | 1436 (48.5%) |  |
| Smoking |  | 7790 (12.3%) | 764 (8.7%) | <0.001 | 5173 (14.4%) | 465 (10.3%) | 1537 (10.7%) | 172 (8.0%) | 1080 (8.2%) | 127 (5.9%) | <0.001 |
| Alcohol user |  | 2458 (5.0%) | 229 (3.3%) | <0.001 | 1606 (5.6%) | 113 (3.1%) | 498 (4.4%) | 69 (4.0%) | 354 (3.7%) | 47 (3.0%) | <0.001 |
| Location of care | Out-patient | 43889 (54.8%) | 6211 (54.7%) | 0.78 | 25217 (57.4%) | 3282 (58.0%) | 10753 (59.2%) | 1656 (60.4%) | 7919 (44.0%) | 1273 (43.0%) | <0.001 |
|  | In-patient | 36210 (45.2%) | 5153 (45.3%) |  | 18709 (42.6%) | 2381 (42.0%) | 7426 (40.8%) | 1086 (39.6%) | 10075 (56.0%) | 1686 (57.0%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 50590 (63.2%) | 7081 (62.3%) | 0.079 | 28715 (65.4%) | 3591 (63.4%) | 9798 (53.9%) | 1470 (53.6%) | 12077 (67.1%) | 2020 (68.3%) | <0.001 |
| Duration of HF | <6mo | 42034 (53.7%) | 5588 (50.5%) | <0.001 | 24716 (57.3%) | 2957 (53.3%) | 9228 (52.0%) | 1290 (48.5%) | 8090 (46.6%) | 1341 (46.9%) | <0.001 |
|  | >=6mo | 36189 (46.3%) | 5471 (49.5%) |  | 18383 (42.7%) | 2587 (46.7%) | 8533 (48.0%) | 1368 (51.5%) | 9273 (53.4%) | 1516 (53.1%) |  |
| Follow-up location | Primary care | 24364 (31.7%) | 3762 (34.7%) | <0.001 | 9361 (22.1%) | 1386 (25.5%) | 6301 (36.0%) | 967 (36.8%) | 8702 (51.2%) | 1409 (50.3%) | <0.001 |
|  | Hospital | 52505 (68.3%) | 7093 (65.3%) |  | 33040 (77.9%) | 4040 (74.5%) | 11180 (64.0%) | 1661 (63.2%) | 8285 (48.8%) | 1392 (49.7%) |  |
| NYHA functional class | I-II | 35465 (60.9%) | 4614 (56.7%) | <0.001 | 19466 (57.8%) | 2250 (52.1%) | 9199 (69.0%) | 1300 (64.8%) | 6800 (60.8%) | 1064 (58.4%) | <0.001 |
|  | III-IV | 22733 (39.1%) | 3530 (43.3%) |  | 14207 (42.2%) | 2066 (47.9%) | 4135 (31.0%) | 706 (35.2%) | 4391 (39.2%) | 758 (41.6%) |  |
| BMI, median (IQR) |  | 27 (23, 30) | 26 (23, 29) | <0.001 | 26 (23, 30) | 25 (23, 29) | 27 (24, 31) | 26 (23, 29) | 27 (24, 31) | 26 (23, 30) | <0.001 |
| SBP, median (IQR) |  | 125 (111, 140) | 125 (110, 140) | <0.001 | 120 (110, 139) | 120 (110, 135) | 130 (116, 140) | 127 (115, 140) | 130 (120, 145) | 130 (118, 145) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (64, 80) | <0.001 | 72 (65, 80) | 70 (63, 80) | 74 (65, 80) | 70 (65, 80) | 71 (65, 80) | 70 (64, 80) | <0.001 |
| MAP, median (IQR) |  | 91 (83, 100) | 90 (81, 99) | <0.001 | 90 (81, 99) | 88 (80, 97) | 93 (83, 100) | 90 (83, 100) | 93 (83, 101) | 92 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 72 (63, 83) | 0.026 | 72 (64, 83) | 72 (64, 84) | 70 (62, 80) | 72 (63, 83) | 72 (63, 82) | 71 (62, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 68 (50, 86) | 62 (45, 81) | <0.001 | 70 (52, 88) | 63 (46, 82) | 68 (50, 86) | 64 (47, 83) | 62 (45, 80) | 59 (43, 76) | <0.001 |
| Potassium categories | Normakalemia | 60123 (93.0%) | 8570 (91.6%) | <0.001 | 32971 (93.4%) | 4222 (92.1%) | 13946 (93.2%) | 2126 (91.9%) | 13206 (91.7%) | 2222 (90.2%) | <0.001 |
|  | Hypokalemia | 2774 (4.3%) | 501 (5.4%) |  | 1285 (3.6%) | 209 (4.6%) | 636 (4.2%) | 122 (5.3%) | 853 (5.9%) | 170 (6.9%) |  |
|  | Hyperkalemia | 1766 (2.7%) | 290 (3.1%) |  | 1031 (2.9%) | 154 (3.4%) | 386 (2.6%) | 65 (2.8%) | 349 (2.4%) | 71 (2.9%) |  |
| Haemoglobin, median (IQR) |  | 134 (121, 145) | 127 (115, 140) | <0.001 | 136 (124, 148) | 130 (117, 142) | 133 (120, 145) | 127 (115, 140) | 128 (116, 140) | 124 (112, 135) | <0.001 |
| NT-proBNP, median (IQR) |  | 2259 (980, 5005) | 2620 (1194, 5819) | <0.001 | 2670 (1150, 5990) | 3196 (1479, 7270) | 1834 (742, 4040) | 2160 (904, 4622) | 1946 (898, 4000) | 2290 (1058, 4600) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 68068 (85.9%) | 9202 (81.8%) | <0.001 | 39928 (91.9%) | 4996 (89.2%) | 15345 (85.2%) | 2231 (82.3%) | 12795 (72.0%) | 1975 (67.3%) | <0.001 |
| Beta-blockers |  | 70882 (88.7%) | 9746 (86.0%) | <0.001 | 40451 (92.3%) | 5079 (89.9%) | 15864 (87.5%) | 2304 (84.1%) | 14567 (81.3%) | 588 (2363 (80.1%)19.9%) | <0.001 |
| MRA |  | 28382 (35.6%) | 3693 (32.6%) | <0.001 | 17690 (40.5%) | 2067 (36.7%) | 5133 (28.4%) | 759 (27.8%) | 5559 (31.1%) | 867 (29.5%) | <0.001 |
| DIuretics |  | 60523 (75.8%) | 8855 (78.2%) | <0.001 | 33116 (75.6%) | 4409 (78.1%) | 12559 (69.3%) | 1947 (71.2%) | 14848 (82.8%) | 2499 (84.7%) | <0.001 |
| Digoxin |  | 10763 (13.5%) | 1407 (12.4%) | 0.002 | 6022 (13.8%) | 756 (13.4%) | 2198 (12.1%) | 297 (10.9%) | 2543 (14.2%) | 354 (12.0%) | <0.001 |
| Antiplatelet therapy |  | 33685 (42.2%) | 4344 (38.4%) | <0.001 | 19564 (44.7%) | 2359 (41.8%) | 7900 (43.6%) | 995 (36.4%) | 6221 (34.7%) | 990 (33.6%) | <0.001 |
| Anticoagulant therapy |  | 37080 (46.4%) | 5283 (46.7%) | 0.62 | 19567 (44.7%) | 2525 (44.8%) | 8445 (46.6%) | 1295 (47.5%) | 9068 (50.6%) | 1463 (49.7%) | <0.001 |
| Statins |  | 39229 (49.1%) | 5106 (45.1%) | <0.001 | 22145 (50.6%) | 2683 (47.5%) | 9427 (52.0%) | 1240 (45.4%) | 7657 (42.7%) | 1183 (40.1%) | <0.001 |
| Nitrates |  | 10038 (12.6%) | 1547 (13.7%) | 0.001 | 4994 (11.4%) | 746 (13.2%) | 2368 (13.1%) | 350 (12.8%) | 2676 (14.9%) | 451 (15.3%) | <0.001 |
| HF devices |  | 4468 (5.7%) | 470 (4.2%) | <0.001 | 3606 (8.3%) | 373 (6.7%) | 587 (3.3%) | 74 (2.7%) | 275 (1.6%) | 23 (0.8%) | <0.001 |
| EF categories |  | 43926 (54.8%) | 5663 (49.8%) | <0.001 | 43926 (100.0%) | 5663 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 18179 (22.7%) | 2742 (24.1%) |  | 0 (0.0%) | 0 (0.0%) | 18179 (100.0%) | 2742 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 17994 (22.5%) | 2959 (26.0%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 17994 (100.0%) | 2959 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 21698 (27.1%) | 2273 (20.0%) | <0.001 | 10715 (24.4%) | 1004 (17.7%) | 5239 (28.8%) | 583 (21.3%) | 5744 (31.9%) | 686 (23.2%) | <0.001 |
| Hypertension |  | 51644 (64.5%) | 7739 (68.1%) | <0.001 | 25532 (58.1%) | 3560 (62.9%) | 12319 (67.8%) | 1893 (69.0%) | 13793 (76.7%) | 2286 (77.3%) | <0.001 |
| Diabetes |  | 20975 (26.2%) | 2855 (25.1%) | 0.016 | 11259 (25.6%) | 1369 (24.2%) | 4616 (25.4%) | 665 (24.3%) | 5100 (28.3%) | 821 (27.7%) | <0.001 |
| CAD |  | 41929 (52.3%) | 6004 (52.8%) | 0.33 | 23512 (53.5%) | 3167 (55.9%) | 10152 (55.8%) | 1439 (52.5%) | 8265 (45.9%) | 1398 (47.2%) | <0.001 |
| AF |  | 44424 (55.5%) | 6837 (60.2%) | <0.001 | 22179 (50.5%) | 3134 (55.3%) | 10453 (57.5%) | 1674 (61.1%) | 11792 (65.5%) | 2029 (68.6%) | <0.001 |
| VHD |  | 21247 (26.5%) | 3126 (27.5%) | 0.027 | 10143 (23.1%) | 1417 (25.0%) | 4845 (26.7%) | 735 (26.8%) | 6259 (34.8%) | 974 (32.9%) | <0.001 |
| CKD |  | 31306 (39.1%) | 5273 (46.4%) | <0.001 | 15689 (35.7%) | 2550 (45.0%) | 7033 (38.7%) | 1190 (43.4%) | 8584 (47.7%) | 1533 (51.8%) | <0.001 |
| Anaemia |  | 25887 (32.3%) | 5301 (46.6%) | <0.001 | 12641 (28.8%) | 2477 (43.7%) | 5996 (33.0%) | 1261 (46.0%) | 7250 (40.3%) | 1563 (52.8%) | <0.001 |
| COPD |  | 9992 (12.5%) | 1605 (14.1%) | <0.001 | 4916 (11.2%) | 708 (12.5%) | 2250 (12.4%) | 397 (14.5%) | 2826 (15.7%) | 500 (16.9%) | <0.001 |
| Liver disease |  | 1707 (2.1%) | 209 (1.8%) | 0.042 | 973 (2.2%) | 87 (1.5%) | 331 (1.8%) | 48 (1.8%) | 403 (2.2%) | 74 (2.5%) | <0.001 |
| PAD |  | 6807 (8.5%) | 1109 (9.8%) | <0.001 | 3571 (8.1%) | 536 (9.5%) | 1588 (8.7%) | 266 (9.7%) | 1648 (9.2%) | 307 (10.4%) | <0.001 |
| Stroke or TIA |  | 12688 (15.8%) | 1972 (17.4%) | <0.001 | 6446 (14.7%) | 956 (16.9%) | 2907 (16.0%) | 453 (16.5%) | 3335 (18.5%) | 563 (19.0%) | <0.001 |
| Depression |  | 2907 (3.6%) | 355 (3.1%) | 0.007 | 1557 (3.5%) | 181 (3.2%) | 638 (3.5%) | 64 (2.3%) | 712 (4.0%) | 110 (3.7%) | <0.001 |
| Dementia |  | 1244 (1.6%) | 156 (1.4%) | 0.14 | 600 (1.4%) | 74 (1.3%) | 258 (1.4%) | 34 (1.2%) | 386 (2.1%) | 48 (1.6%) | <0.001 |
| Cancer <3years |  | 0 (0.0%) | 11364 (100.0%) | <0.001 | 0 (0.0%) | 5663 (100.0%) | 0 (0.0%) | 2742 (100.0%) | 0 (0.0%) | 2959 (100.0%) | <0.001 |
| Muscolo-skeletal <3years |  | 24067 (30.0%) | 4053 (35.7%) | <0.001 | 11612 (26.4%) | 1826 (32.2%) | 5748 (31.6%) | 1004 (36.6%) | 6707 (37.3%) | 1223 (41.3%) | <0.001 |
| Dysthyroidism |  | 5942 (7.4%) | 919 (8.1%) | 0.011 | 2736 (6.2%) | 392 (6.9%) | 1380 (7.6%) | 198 (7.2%) | 1826 (10.1%) | 329 (11.1%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 26863 (33.5%) | 0 (0.0%) | <0.001 | 15115 (34.4%) | 0 (0.0%) | 6072 (33.4%) | 0 (0.0%) | 5676 (31.5%) | 0 (0.0%) | <0.001 |
|  | 2-3 | 32010 (40.0%) | 3145 (27.7%) |  | 17909 (40.8%) | 1519 (26.8%) | 7211 (39.7%) | 801 (29.2%) | 6890 (38.3%) | 825 (27.9%) |  |
|  | 4-7 | 17941 (22.4%) | 6263 (55.1%) |  | 9305 (21.2%) | 3205 (56.6%) | 4111 (22.6%) | 1475 (53.8%) | 4525 (25.1%) | 1583 (53.5%) |  |
|  | >=8 | 3285 (4.1%) | 1956 (17.2%) |  | 1597 (3.6%) | 939 (16.6%) | 785 (4.3%) | 466 (17.0%) | 903 (5.0%) | 551 (18.6%) |  |

**Supplementary Table 18. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by muscolo-skeletal disease**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 63343 (69%) | 28120 (31%) |  | 36151 (73%) | 13438 (27%) | 14169 (68%) | 6752 (32%) | 13023 (62%) | 7930 (38%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 21126 (33.4%) | 12208 (43.4%) | <0.001 | 9640 (26.7%) | 4729 (35.2%) | 5021 (35.4%) | 2884 (42.7%) | 6465 (49.6%) | 4595 (57.9%) | <0.001 |
|  | Male | 42217 (66.6%) | 15912 (56.6%) |  | 26511 (73.3%) | 8709 (64.8%) | 9148 (64.6%) | 3868 (57.3%) | 6558 (50.4%) | 3335 (42.1%) |  |
| Age, median (IQR) |  | 75 (65, 82) | 77 (69, 83) | <0.001 | 72 (63, 80) | 75 (67, 81) | 76 (67, 82) | 77 (70, 83) | 80 (72, 85) | 80 (73, 85) | <0.001 |
| Family type | Cohabitating | 33264 (52.6%) | 14248 (50.7%) | <0.001 | 19623 (54.4%) | 7162 (53.3%) | 7648 (54.1%) | 3538 (52.4%) | 5993 (46.1%) | 3548 (44.8%) | <0.001 |
|  | Living alone | 29961 (47.4%) | 13862 (49.3%) |  | 16441 (45.6%) | 6270 (46.7%) | 6500 (45.9%) | 3214 (47.6%) | 7020 (53.9%) | 4378 (55.2%) |  |
| Smoking |  | 6398 (12.7%) | 2156 (10.0%) | <0.001 | 4337 (14.6%) | 1301 (12.1%) | 1245 (11.0%) | 464 (8.8%) | 816 (8.5%) | 391 (6.9%) | <0.001 |
| Alcohol user |  | 1987 (5.0%) | 700 (4.2%) | <0.001 | 1322 (5.5%) | 397 (4.7%) | 400 (4.5%) | 167 (4.1%) | 265 (3.8%) | 136 (3.3%) | <0.001 |
| Location of care | Out-patient | 35446 (56.0%) | 14654 (52.1%) | <0.001 | 20962 (58.0%) | 7537 (56.1%) | 8613 (60.8%) | 3796 (56.2%) | 5871 (45.1%) | 3321 (41.9%) | <0.001 |
|  | In-patient | 27897 (44.0%) | 13466 (47.9%) |  | 15189 (42.0%) | 5901 (43.9%) | 5556 (39.2%) | 2956 (43.8%) | 7152 (54.9%) | 4609 (58.1%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 39178 (61.9%) | 18493 (65.8%) | <0.001 | 23328 (64.5%) | 8978 (66.8%) | 7323 (51.7%) | 3945 (58.4%) | 8527 (65.5%) | 5570 (70.2%) | <0.001 |
| Duration of HF | <6mo | 34300 (55.4%) | 13322 (48.6%) | <0.001 | 20893 (58.9%) | 6780 (51.5%) | 7343 (53.1%) | 3175 (48.2%) | 6064 (48.2%) | 3367 (44.1%) | <0.001 |
|  | >=6mo | 27587 (44.6%) | 14073 (51.4%) |  | 14588 (41.1%) | 6382 (48.5%) | 6486 (46.9%) | 3415 (51.8%) | 6513 (51.8%) | 4276 (55.9%) |  |
| Follow-up location | Primary care | 18554 (30.5%) | 9572 (35.6%) | <0.001 | 7526 (21.6%) | 3221 (24.9%) | 4819 (35.3%) | 2449 (37.8%) | 6209 (50.5%) | 3902 (52.1%) | <0.001 |
|  | Hospital | 42245 (69.5%) | 17353 (64.4%) |  | 27344 (78.4%) | 9736 (75.1%) | 8815 (64.7%) | 4026 (62.2%) | 6086 (49.5%) | 3591 (47.9%) |  |
| NYHA functional class | I-II | 29522 (62.8%) | 10557 (54.7%) | <0.001 | 16646 (59.4%) | 5070 (50.9%) | 7590 (71.3%) | 2909 (62.0%) | 5286 (63.2%) | 2578 (55.4%) | <0.001 |
|  | III-IV | 17505 (37.2%) | 8758 (45.3%) |  | 11378 (40.6%) | 4895 (49.1%) | 3055 (28.7%) | 1786 (38.0%) | 3072 (36.8%) | 2077 (44.6%) |  |
| BMI, median (IQR) |  | 26 (23, 30) | 27 (24, 31) | <0.001 | 26 (23, 30) | 26 (23, 30) | 27 (24, 30) | 27 (24, 31) | 27 (24, 31) | 27 (24, 32) | <0.001 |
| SBP, median (IQR) |  | 125 (110, 140) | 125 (112, 140) | 0.063 | 120 (110, 139) | 120 (110, 137) | 130 (116, 141) | 130 (115, 140) | 130 (120, 145) | 130 (119, 145) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (65, 80) | <0.001 | 72 (65, 80) | 70 (65, 80) | 74 (65, 80) | 72 (65, 80) | 71 (65, 80) | 70 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 91 (83, 100) | 90 (82, 100) | <0.001 | 90 (81, 99) | 90 (80, 98) | 93 (83, 101) | 92 (83, 100) | 93 (83, 101) | 92 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 72 (64, 83) | 0.002 | 72 (63, 83) | 72 (64, 84) | 70 (62, 80) | 71 (63, 82) | 71 (63, 82) | 72 (63, 82) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 68 (50, 86) | 64 (46, 83) | <0.001 | 70 (52, 88) | 66 (48, 86) | 69 (51, 87) | 64 (47, 84) | 62 (46, 81) | 59 (43, 78) | <0.001 |
| Potassium categories | Normakalemia | 47145 (93.1%) | 21548 (92.2%) | <0.001 | 26890 (93.5%) | 10303 (92.7%) | 10786 (93.2%) | 5286 (92.7%) | 9469 (91.8%) | 5959 (90.9%) | <0.001 |
|  | Hypokalemia | 2160 (4.3%) | 1115 (4.8%) |  | 1054 (3.7%) | 440 (4.0%) | 495 (4.3%) | 263 (4.6%) | 611 (5.9%) | 412 (6.3%) |  |
|  | Hyperkalemia | 1353 (2.7%) | 703 (3.0%) |  | 817 (2.8%) | 368 (3.3%) | 298 (2.6%) | 153 (2.7%) | 238 (2.3%) | 182 (2.8%) |  |
| Haemoglobin, median (IQR) |  | 135 (122, 146) | 129 (117, 141) | <0.001 | 137 (124, 148) | 131 (119, 143) | 134 (121, 146) | 129 (116, 141) | 129 (116, 141) | 124 (113, 136) | <0.001 |
| NT-proBNP, median (IQR) |  | 2250 (973, 5020) | 2430 (1077, 5312) | <0.001 | 2650 (1150, 5951) | 2950 (1270, 6647) | 1780 (710, 3891) | 2101 (889, 4460) | 1935 (890, 4015) | 2100 (980, 4198) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 54474 (87.0%) | 22796 (81.9%) | <0.001 | 33007 (92.3%) | 11917 (89.7%) | 12078 (86.1%) | 5498 (82.2%) | 9389 (73.0%) | 5381 (68.6%) | <0.001 |
| Beta-blockers |  | 56218 (89.0%) | 24410 (87.1%) | <0.001 | 33381 (92.5%) | 12149 (90.7%) | 12311 (87.1%) | 5857 (87.0%) | 10526 (81.1%) | 6404 (81.1%) | <0.001 |
| MRA |  | 22436 (35.6%) | 9639 (34.4%) | <0.001 | 14498 (40.3%) | 5259 (39.3%) | 3954 (28.0%) | 1938 (28.8%) | 3984 (30.8%) | 2442 (31.0%) | <0.001 |
| DIuretics |  | 47100 (74.6%) | 22278 (79.5%) | <0.001 | 26980 (74.9%) | 10545 (78.8%) | 9538 (67.5%) | 4968 (73.7%) | 10582 (81.5%) | 6765 (85.6%) | <0.001 |
| Digoxin |  | 8573 (13.6%) | 3597 (12.8%) | 0.002 | 5038 (14.0%) | 1740 (13.0%) | 1652 (11.7%) | 843 (12.5%) | 1883 (14.5%) | 1014 (12.8%) | <0.001 |
| Antiplatelet therapy |  | 26642 (42.2%) | 11387 (40.7%) | <0.001 | 15962 (44.3%) | 5961 (44.5%) | 6148 (43.5%) | 2747 (40.8%) | 4532 (34.9%) | 2679 (34.0%) | <0.001 |
| Anticoagulant therapy |  | 28901 (45.8%) | 13462 (48.1%) | <0.001 | 16006 (44.4%) | 6086 (45.5%) | 6440 (45.6%) | 3300 (49.0%) | 6455 (49.8%) | 4076 (51.6%) | <0.001 |
| Statins |  | 30813 (48.8%) | 13522 (48.2%) | 0.12 | 18036 (50.0%) | 6792 (50.7%) | 7280 (51.5%) | 3387 (50.2%) | 5497 (42.3%) | 3343 (42.3%) | <0.001 |
| Nitrates |  | 7409 (11.7%) | 4176 (14.9%) | <0.001 | 3887 (10.8%) | 1853 (13.9%) | 1689 (12.0%) | 1029 (15.3%) | 1833 (14.1%) | 1294 (16.4%) | <0.001 |
| HF devices |  | 3514 (5.6%) | 1424 (5.1%) | 0.003 | 2870 (8.0%) | 1109 (8.3%) | 442 (3.2%) | 219 (3.3%) | 202 (1.6%) | 96 (1.2%) | <0.001 |
| EF categories | HFrEF | 36151 (57.1%) | 13438 (47.8%) | <0.001 | 36151 (100.0%) | 13438 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 14169 (22.4%) | 6752 (24.0%) |  | 0 (0.0%) | 0 (0.0%) | 14169 (100.0%) | 6752 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 13023 (20.6%) | 7930 (28.2%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 13023 (100.0%) | 7930 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 15838 (25.0%) | 8133 (28.9%) | <0.001 | 8286 (22.9%) | 3433 (25.5%) | 3791 (26.8%) | 2031 (30.1%) | 3761 (28.9%) | 2669 (33.7%) | <0.001 |
| Hypertension |  | 39342 (62.1%) | 20041 (71.3%) | <0.001 | 20311 (56.2%) | 8781 (65.3%) | 9288 (65.6%) | 4924 (72.9%) | 9743 (74.8%) | 6336 (79.9%) | <0.001 |
| Diabetes |  | 15623 (24.7%) | 8207 (29.2%) | <0.001 | 8669 (24.0%) | 3959 (29.5%) | 3419 (24.1%) | 1862 (27.6%) | 3535 (27.1%) | 2386 (30.1%) | <0.001 |
| CAD |  | 32228 (50.9%) | 15705 (55.8%) | <0.001 | 18794 (52.0%) | 7885 (58.7%) | 7673 (54.2%) | 3918 (58.0%) | 5761 (44.2%) | 3902 (49.2%) | <0.001 |
| AF |  | 34584 (54.6%) | 16677 (59.3%) | <0.001 | 18091 (50.0%) | 7222 (53.7%) | 8020 (56.6%) | 4107 (60.8%) | 8473 (65.1%) | 5348 (67.4%) | <0.001 |
| VHD |  | 16329 (25.8%) | 8044 (28.6%) | <0.001 | 8176 (22.6%) | 3384 (25.2%) | 3667 (25.9%) | 1913 (28.3%) | 4486 (34.4%) | 2747 (34.6%) | <0.001 |
| CKD |  | 23968 (37.8%) | 12611 (44.8%) | <0.001 | 12604 (34.9%) | 5635 (41.9%) | 5292 (37.3%) | 2931 (43.4%) | 6072 (46.6%) | 4045 (51.0%) | <0.001 |
| Anaemia |  | 19778 (31.2%) | 11410 (40.6%) | <0.001 | 10168 (28.1%) | 4950 (36.8%) | 4480 (31.6%) | 2777 (41.1%) | 5130 (39.4%) | 3683 (46.4%) | <0.001 |
| COPD |  | 7271 (11.5%) | 4326 (15.4%) | <0.001 | 3717 (10.3%) | 1907 (14.2%) | 1611 (11.4%) | 1036 (15.3%) | 1943 (14.9%) | 1383 (17.4%) | <0.001 |
| Liver disease |  | 1256 (2.0%) | 660 (2.3%) | <0.001 | 740 (2.0%) | 320 (2.4%) | 241 (1.7%) | 138 (2.0%) | 275 (2.1%) | 202 (2.5%) | <0.001 |
| PAD |  | 4608 (7.3%) | 3308 (11.8%) | <0.001 | 2554 (7.1%) | 1553 (11.6%) | 1053 (7.4%) | 801 (11.9%) | 1001 (7.7%) | 954 (12.0%) | <0.001 |
| Stroke or TIA |  | 9501 (15.0%) | 5159 (18.3%) | <0.001 | 5061 (14.0%) | 2341 (17.4%) | 2159 (15.2%) | 1201 (17.8%) | 2281 (17.5%) | 1617 (20.4%) | <0.001 |
| Depression |  | 1929 (3.0%) | 1333 (4.7%) | <0.001 | 1112 (3.1%) | 626 (4.7%) | 418 (3.0%) | 284 (4.2%) | 399 (3.1%) | 423 (5.3%) | <0.001 |
| Dementia |  | 889 (1.4%) | 511 (1.8%) | <0.001 | 439 (1.2%) | 235 (1.7%) | 186 (1.3%) | 106 (1.6%) | 264 (2.0%) | 170 (2.1%) | <0.001 |
| Cancer <3years |  | 7311 (11.5%) | 4053 (14.4%) | <0.001 | 3837 (10.6%) | 1826 (13.6%) | 1738 (12.3%) | 1004 (14.9%) | 1736 (13.3%) | 1223 (15.4%) | <0.001 |
| Muscolo-skeletal <3years |  | 0 (0.0%) | 28120 (100.0%) | <0.001 | 0 (0.0%) | 13438 (100.0%) | 0 (0.0%) | 6752 (100.0%) | 0 (0.0%) | 7930 (100.0%) | <0.001 |
| Dysthyroidism |  | 3997 (6.3%) | 2864 (10.2%) | <0.001 | 1964 (5.4%) | 1164 (8.7%) | 916 (6.5%) | 662 (9.8%) | 1117 (8.6%) | 1038 (13.1%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 21387 (33.8%) | 5476 (19.5%) | <0.001 | 12497 (34.6%) | 2618 (19.5%) | 4739 (33.4%) | 1333 (19.7%) | 4151 (31.9%) | 1525 (19.2%) | <0.001 |
|  | 2-3 | 24655 (38.9%) | 10500 (37.3%) |  | 14305 (39.6%) | 5123 (38.1%) | 5501 (38.8%) | 2511 (37.2%) | 4849 (37.2%) | 2866 (36.1%) |  |
|  | 4-7 | 14579 (23.0%) | 9625 (34.2%) |  | 7939 (22.0%) | 4571 (34.0%) | 3284 (23.2%) | 2302 (34.1%) | 3356 (25.8%) | 2752 (34.7%) |  |
|  | >=8 | 2722 (4.3%) | 2519 (9.0%) |  | 1410 (3.9%) | 1126 (8.4%) | 645 (4.6%) | 606 (9.0%) | 667 (5.1%) | 787 (9.9%) |  |

**Supplementary Table 19. Baseline characteristics of the whole study population, HFrEF, HFmrEF and HFpEF sub-populations stratified by dysthyroidism**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **All** | | | **EF categories** | | | | | | |
|  |  |  |  |  | **HFrEF** | | **HFmrEF** | | **HFpEF** | |  |
| **Variable** | **Level** | **No** | **Yes** | **p-value** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **p-value** |
| N |  | 84602 (92%) | 6861 (8%) |  | 46461 (94%) | 3128 (6%) | 19343 (92%) | 1578 (8%) | 18798 (90%) | 2155 (10%) |  |
| **Demographics and organisational/socioeconomics** |  |  |  |  |  |  |  |  |  |  |  |
| Sex | Female | 28565 (33.8%) | 4769 (69.5%) | <0.001 | 12425 (26.7%) | 1944 (62.1%) | 6807 (35.2%) | 1098 (69.6%) | 9333 (49.6%) | 1727 (80.1%) | <0.001 |
|  | Male | 56037 (66.2%) | 2092 (30.5%) |  | 34036 (73.3%) | 1184 (37.9%) | 12536 (64.8%) | 480 (30.4%) | 9465 (50.4%) | 428 (19.9%) |  |
| Age, median (IQR) |  | 75 (66, 82) | 79 (71, 84) | <0.001 | 73 (64, 80) | 77 (68, 83) | 76 (68, 83) | 78 (71, 84) | 79 (72, 85) | 81 (75, 86) | <0.001 |
| Family type | Cohabitating | 44489 (52.7%) | 3023 (44.1%) | <0.001 | 25278 (54.5%) | 1507 (48.3%) | 10472 (54.2%) | 714 (45.2%) | 8739 (46.5%) | 802 (37.3%) | <0.001 |
|  | Living alone | 39992 (47.3%) | 3831 (55.9%) |  | 21095 (45.5%) | 1616 (51.7%) | 8850 (45.8%) | 864 (54.8%) | 10047 (53.5%) | 1351 (62.7%) |  |
| Smoking |  | 8104 (12.1%) | 450 (8.7%) | <0.001 | 5384 (14.2%) | 254 (10.5%) | 1608 (10.5%) | 101 (8.4%) | 1112 (8.1%) | 95 (6.2%) | <0.001 |
| Alcohol user |  | 2595 (4.9%) | 92 (2.3%) | <0.001 | 1673 (5.5%) | 46 (2.4%) | 539 (4.5%) | 28 (3.1%) | 383 (3.8%) | 18 (1.7%) | <0.001 |
| Location of care | Out-patient | 46782 (55.3%) | 3318 (48.4%) | <0.001 | 26824 (57.7%) | 1675 (53.5%) | 11575 (59.8%) | 834 (52.9%) | 8383 (44.6%) | 809 (37.5%) | <0.001 |
|  | In-patient | 37820 (44.7%) | 3543 (51.6%) |  | 19637 (42.3%) | 1453 (46.5%) | 7768 (40.2%) | 744 (47.1%) | 10415 (55.4%) | 1346 (62.5%) |  |
| **Clinical variables** |  |  |  |  |  |  |  |  |  |  |  |
| Recent HF hospitalization <12months |  | 52951 (62.6%) | 4720 (68.8%) | <0.001 | 30181 (65.0%) | 2125 (67.9%) | 10286 (53.2%) | 982 (62.2%) | 12484 (66.4%) | 1613 (74.8%) | <0.001 |
| Duration of HF | <6mo | 44371 (53.7%) | 3251 (48.6%) | <0.001 | 26099 (57.3%) | 1574 (51.5%) | 9762 (51.7%) | 756 (48.8%) | 8510 (46.9%) | 921 (44.1%) | <0.001 |
|  | >=6mo | 38216 (46.3%) | 3444 (51.4%) |  | 19485 (42.7%) | 1485 (48.5%) | 9109 (48.3%) | 792 (51.2%) | 9622 (53.1%) | 1167 (55.9%) |  |
| Follow-up location | Primary care | 25655 (31.6%) | 2471 (38.0%) | <0.001 | 9937 (22.2%) | 810 (27.1%) | 6690 (36.0%) | 578 (38.5%) | 9028 (50.8%) | 1083 (53.6%) | <0.001 |
|  | Hospital | 55561 (68.4%) | 4037 (62.0%) |  | 34904 (77.8%) | 2176 (72.9%) | 11918 (64.0%) | 923 (61.5%) | 8739 (49.2%) | 938 (46.4%) |  |
| NYHA functional class | I-II | 37602 (60.9%) | 2477 (54.0%) | <0.001 | 20600 (57.7%) | 1116 (49.0%) | 9814 (68.9%) | 685 (62.8%) | 7188 (60.9%) | 676 (55.6%) | <0.001 |
|  | III-IV | 24157 (39.1%) | 2106 (46.0%) |  | 15113 (42.3%) | 1160 (51.0%) | 4435 (31.1%) | 406 (37.2%) | 4609 (39.1%) | 540 (44.4%) |  |
| BMI, median (IQR) |  | 26 (23, 30) | 27 (23, 31) | 0.74 | 26 (23, 30) | 26 (23, 30) | 27 (24, 30) | 27 (24, 31) | 27 (24, 31) | 27 (23, 31) | <0.001 |
| SBP, median (IQR) |  | 125 (111, 140) | 125 (110, 140) | 0.76 | 120 (110, 138) | 120 (110, 135) | 130 (115, 140) | 128 (113, 140) | 130 (120, 145) | 130 (120, 145) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 70 (64, 80) | <0.001 | 72 (65, 80) | 70 (63, 80) | 74 (65, 80) | 70 (65, 80) | 71 (65, 80) | 70 (65, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (83, 100) | 90 (82, 100) | <0.001 | 90 (81, 99) | 88 (80, 97) | 92 (83, 100) | 90 (82, 100) | 93 (83, 101) | 93 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 72 (63, 82) | 72 (64, 84) | <0.001 | 72 (64, 83) | 73 (64, 84) | 70 (62, 80) | 72 (64, 84) | 71 (63, 82) | 72 (64, 84) | <0.001 |
| **Laboratory** |  |  |  |  |  |  |  |  |  |  |  |
| eGFR, median (IQR) |  | 68 (50, 86) | 59 (43, 78) | <0.001 | 70 (52, 88) | 61 (44, 80) | 68 (50, 86) | 61 (44, 79) | 62 (45, 80) | 57 (42, 75) | <0.001 |
| Potassium categories | Normakalemia | 63472 (92.9%) | 5221 (91.6%) | <0.001 | 34803 (93.4%) | 2390 (92.0%) | 14864 (93.1%) | 1208 (92.3%) | 13805 (91.6%) | 1623 (90.6%) | <0.001 |
|  | Hypokalemia | 2957 (4.3%) | 318 (5.6%) |  | 1368 (3.7%) | 126 (4.8%) | 693 (4.3%) | 65 (5.0%) | 896 (5.9%) | 127 (7.1%) |  |
|  | Hyperkalemia | 1896 (2.8%) | 160 (2.8%) |  | 1103 (3.0%) | 82 (3.2%) | 415 (2.6%) | 36 (2.8%) | 378 (2.5%) | 42 (2.3%) |  |
| Haemoglobin, median (IQR) |  | 133 (121, 145) | 127 (116, 140) | <0.001 | 136 (123, 147) | 130 (118, 143) | 133 (120, 144) | 127 (116, 139) | 128 (115, 140) | 124 (113, 135) | <0.001 |
| NT-proBNP, median (IQR) |  | 2281 (991, 5071) | 2586 (1180, 5624) | <0.001 | 2690 (1167, 6027) | 3400 (1453, 7538) | 1868 (746, 4120) | 2090 (985, 4208) | 1985 (910, 4034) | 2200 (1023, 4470) | <0.001 |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
| ACEi/ARB/ARNI |  | 71914 (85.9%) | 5356 (79.2%) | <0.001 | 42210 (91.8%) | 2714 (88.1%) | 16341 (85.2%) | 1235 (79.5%) | 13363 (71.9%) | 1407 (66.2%) | <0.001 |
| Beta-blockers |  | 74670 (88.5%) | 5958 (87.2%) | 0.001 | 42697 (92.1%) | 2833 (90.9%) | 16801 (87.1%) | 1367 (86.8%) | 15172 (81.0%) | 1758 (81.9%) | <0.001 |
| MRA |  | 29676 (35.2%) | 2399 (35.2%) | 0.94 | 18513 (40.0%) | 1244 (40.0%) | 5430 (28.2%) | 462 (29.4%) | 5733 (30.7%) | 693 (32.5%) | <0.001 |
| DIuretics |  | 63841 (75.7%) | 5537 (81.0%) | <0.001 | 35039 (75.7%) | 2486 (79.8%) | 13319 (69.0%) | 1187 (75.4%) | 15483 (82.7%) | 1864 (86.8%) | <0.001 |
| Digoxin |  | 11128 (13.2%) | 1042 (15.3%) | <0.001 | 6296 (13.6%) | 482 (15.5%) | 2272 (11.8%) | 223 (14.1%) | 2560 (13.7%) | 337 (15.7%) | <0.001 |
| Antiplatelet therapy |  | 35455 (42.1%) | 2574 (37.7%) | <0.001 | 20653 (44.6%) | 1270 (40.8%) | 8287 (43.0%) | 608 (38.7%) | 6515 (34.8%) | 696 (32.5%) | <0.001 |
| Anticoagulant therapy |  | 38946 (46.2%) | 3417 (50.0%) | <0.001 | 20602 (44.5%) | 1490 (47.8%) | 8952 (46.4%) | 788 (50.1%) | 9392 (50.2%) | 1139 (53.1%) | <0.001 |
| Statins |  | 41270 (48.9%) | 3065 (44.8%) | <0.001 | 23315 (50.3%) | 1513 (48.6%) | 9953 (51.6%) | 714 (45.3%) | 8002 (42.7%) | 838 (39.1%) | <0.001 |
| Nitrates |  | 10538 (12.5%) | 1047 (15.3%) | <0.001 | 5308 (11.5%) | 432 (13.9%) | 2481 (12.9%) | 237 (15.1%) | 2749 (14.7%) | 378 (17.6%) | <0.001 |
| HF devices |  | 4571 (5.5%) | 367 (5.4%) | 0.86 | 3675 (8.0%) | 304 (9.8%) | 621 (3.3%) | 40 (2.6%) | 275 (1.5%) | 23 (1.1%) | <0.001 |
| EF categories | HFrEF | 46461 (54.9%) | 3128 (45.6%) | <0.001 | 46461 (100.0%) | 3128 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | <0.001 |
|  | HFmrEF | 19343 (22.9%) | 1578 (23.0%) |  | 0 (0.0%) | 0 (0.0%) | 19343 (100.0%) | 1578 (100.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | HFpEF | 18798 (22.2%) | 2155 (31.4%) |  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 18798 (100.0%) | 2155 (100.0%) |  |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |  |
| Obesity |  | 22077 (26.1%) | 1894 (27.6%) | 0.006 | 10988 (23.6%) | 731 (23.4%) | 5347 (27.6%) | 475 (30.1%) | 5742 (30.5%) | 688 (31.9%) | <0.001 |
| Hypertension |  | 54395 (64.3%) | 4988 (72.7%) | <0.001 | 27005 (58.1%) | 2087 (66.7%) | 13052 (67.5%) | 1160 (73.5%) | 14338 (76.3%) | 1741 (80.8%) | <0.001 |
| Diabetes |  | 21811 (25.8%) | 2019 (29.4%) | <0.001 | 11747 (25.3%) | 881 (28.2%) | 4809 (24.9%) | 472 (29.9%) | 5255 (28.0%) | 666 (30.9%) | <0.001 |
| CAD |  | 44249 (52.3%) | 3684 (53.7%) | 0.026 | 24936 (53.7%) | 1743 (55.7%) | 10698 (55.3%) | 893 (56.6%) | 8615 (45.8%) | 1048 (48.6%) | <0.001 |
| AF |  | 46975 (55.5%) | 4286 (62.5%) | <0.001 | 23523 (50.6%) | 1790 (57.2%) | 11138 (57.6%) | 989 (62.7%) | 12314 (65.5%) | 1507 (69.9%) | <0.001 |
| VHD |  | 22301 (26.4%) | 2072 (30.2%) | <0.001 | 10709 (23.0%) | 851 (27.2%) | 5139 (26.6%) | 441 (27.9%) | 6453 (34.3%) | 780 (36.2%) | <0.001 |
| CKD |  | 33085 (39.1%) | 3494 (50.9%) | <0.001 | 16713 (36.0%) | 1526 (48.8%) | 7447 (38.5%) | 776 (49.2%) | 8925 (47.5%) | 1192 (55.3%) | <0.001 |
| Anaemia |  | 28575 (33.8%) | 2613 (38.1%) | <0.001 | 14043 (30.2%) | 1075 (34.4%) | 6659 (34.4%) | 598 (37.9%) | 7873 (41.9%) | 940 (43.6%) | <0.001 |
| COPD |  | 10523 (12.4%) | 1074 (15.7%) | <0.001 | 5183 (11.2%) | 441 (14.1%) | 2393 (12.4%) | 254 (16.1%) | 2947 (15.7%) | 379 (17.6%) | <0.001 |
| Liver disease |  | 1769 (2.1%) | 147 (2.1%) | 0.77 | 997 (2.1%) | 63 (2.0%) | 357 (1.8%) | 22 (1.4%) | 415 (2.2%) | 62 (2.9%) | 0.003 |
| PAD |  | 7282 (8.6%) | 634 (9.2%) | 0.073 | 3827 (8.2%) | 280 (9.0%) | 1701 (8.8%) | 153 (9.7%) | 1754 (9.3%) | 201 (9.3%) | <0.001 |
| Stroke or TIA |  | 13326 (15.8%) | 1334 (19.4%) | <0.001 | 6840 (14.7%) | 562 (18.0%) | 3057 (15.8%) | 303 (19.2%) | 3429 (18.2%) | 469 (21.8%) | <0.001 |
| Depression |  | 2867 (3.4%) | 395 (5.8%) | <0.001 | 1559 (3.4%) | 179 (5.7%) | 620 (3.2%) | 82 (5.2%) | 688 (3.7%) | 134 (6.2%) | <0.001 |
| Dementia |  | 1241 (1.5%) | 159 (2.3%) | <0.001 | 599 (1.3%) | 75 (2.4%) | 263 (1.4%) | 29 (1.8%) | 379 (2.0%) | 55 (2.6%) | <0.001 |
| Cancer <3years |  | 10445 (12.3%) | 919 (13.4%) | 0.011 | 5271 (11.3%) | 392 (12.5%) | 2544 (13.2%) | 198 (12.5%) | 2630 (14.0%) | 329 (15.3%) | <0.001 |
| Muscolo-skeletal <3years |  | 25256 (29.9%) | 2864 (41.7%) | <0.001 | 12274 (26.4%) | 1164 (37.2%) | 6090 (31.5%) | 662 (42.0%) | 6892 (36.7%) | 1038 (48.2%) | <0.001 |
| Dysthyroidism |  | 0 (0.0%) | 6861 (100.0%) | <0.001 | 0 (0.0%) | 3128 (100.0%) | 0 (0.0%) | 1578 (100.0%) | 0 (0.0%) | 2155 (100.0%) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 25368 (30.0%) | 1495 (21.8%) | <0.001 | 14424 (31.0%) | 691 (22.1%) | 5709 (29.5%) | 363 (23.0%) | 5235 (27.8%) | 441 (20.5%) | <0.001 |
|  | 2-3 | 32577 (38.5%) | 2578 (37.6%) |  | 18219 (39.2%) | 1209 (38.7%) | 7423 (38.4%) | 589 (37.3%) | 6935 (36.9%) | 780 (36.2%) |  |
|  | 4-7 | 22033 (26.0%) | 2171 (31.6%) |  | 11542 (24.8%) | 968 (30.9%) | 5098 (26.4%) | 488 (30.9%) | 5393 (28.7%) | 715 (33.2%) |  |
|  | >=8 | 4624 (5.5%) | 617 (9.0%) |  | 2276 (4.9%) | 260 (8.3%) | 1113 (5.8%) | 138 (8.7%) | 1235 (6.6%) | 219 (10.2%) |  |

**Supplementary table 20. Cross-tabulation of comorbidities in patients with HFrEF**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All**  **(**49589**)** | **Obesity**  **(23971)** | **Hypert.**  **(**29092**)** | **Diabetes**  **(**12628**)** | **CAD**  **(**26679**)** | **AF**  **(**25313**)** | **VHD**  **(**11560**)** | **CKD**  **(**18239**)** | **Anaemia**  **(**15118**)** | **COPD**  **(**5624**)** | **Liver**  **(**1060**)** | **PAD**  **(**4107**)** | **Stroke**  **(**7402**)** | **Depres.**  **(**1738**)** | **Dement**  **(**674**)** | **Cancer**  **(**5663**)** | **Muscolo**  **(**13438**)** | **Dist.**  **(**3128**)** |
| **Obesity** | 11719 (23.6%) | - | 7870 (27.1%) | 4426 (35.0%) | 5764 (21.6%) | 6074 (24.0%) | 2034 (17.6%) | 3881 (21.3%) | 2675 (17.7%) | 1355 (24.1%) | 227 (21.4%) | 732 (17.8%) | 1446 (19.5%) | 471 (27.1%) | 83 (12.3%) | 1004 (17.7%) | 3433 (25.5%) | 731 (23.4%) |
| **Hypert.** | 29092 (58.7%) | 7870 (67.2%) | - | 9616 (76.1%) | 17199 (64.5%) | 15625 (61.7%) | 6875 (59.5%) | 12464 (68.3%) | 9547 (63.1%) | 3531 (62.8%) | 588 (55.5%) | 3040 (74.0%) | 5259 (71.0%) | 1068 (61.4%) | 478 (70.9%) | 3560 (62.9%) | 8781 (65.3%) | 2087 (66.7%) |
| **Diabetes** | 12628 (25.5%) | 4426 (37.8%) | 9616 (33.1%) | - | 8610 (32.3%) | 6337 (25.0%) | 2785 (24.1%) | 5690 (31.2%) | 4960 (32.8%) | 1606 (28.6%) | 317 (29.9%) | 1537 (37.4%) | 2395 (32.4%) | 454 (26.1%) | 228 (33.8%) | 1369 (24.2%) | 3959 (29.5%) | 881 (28.2%) |
| **CAD** | 26679 (53.8%) | 5764 (49.2%) | 17199 (59.1%) | 8610 (68.2%) | - | 12911 (51.0%) | 6665 (57.7%) | 11685 (64.1%) | 9972 (66.0%) | 3559 (63.3%) | 518 (48.9%) | 3062 (74.6%) | 4889 (66.0%) | 928 (53.4%) | 430 (63.8%) | 3167 (55.9%) | 7885 (58.7%) | 1743 (55.7%) |
| **AF** | 25313 (51.0%) | 6074 (51.8%) | 15625 (53.7%) | 6337 (50.2%) | 12911 (48.4%) | - | 6842 (59.2%) | 10555 (57.9%) | 7901 (52.3%) | 2893 (51.4%) | 545 (51.4%) | 2224 (54.2%) | 4525 (61.1%) | 777 (44.7%) | 400 (59.3%) | 3134 (55.3%) | 7222 (53.7%) | 1790 (57.2%) |
| **VHD** | 11560 (23.3%) | 2034 (17.4%) | 6875 (23.6%) | 2785 (22.1%) | 6665 (25.0%) | 6842 (27.0%) | - | 5288 (29.0%) | 4524 (29.9%) | 1363 (24.2%) | 270 (25.5%) | 1369 (33.3%) | 2003 (27.1%) | 415 (23.9%) | 197 (29.2%) | 1417 (25.0%) | 3384 (25.2%) | 851 (27.2%) |
| **CKD** | 18239 (36.8%) | 3881 (33.1%) | 12464 (42.8%) | 5690 (45.1%) | 11685 (43.8%) | 10555 (41.7%) | 5288 (45.7%) | - | 7729 (51.1%) | 2289 (40.7%) | 318 (30.0%) | 2087 (50.8%) | 3538 (47.8%) | 601 (34.6%) | 376 (55.8%) | 2550 (45.0%) | 5635 (41.9%) | 1526 (48.8%) |
| **Anaemia** | 15118 (30.5%) | 2675 (22.8%) | 9547 (32.8%) | 4960 (39.3%) | 9972 (37.4%) | 7901 (31.2%) | 4524 (39.1%) | 7729 (42.4%) | - | 1973 (35.1%) | 421 (39.7%) | 1923 (46.8%) | 2829 (38.2%) | 638 (36.7%) | 330 (49.0%) | 2477 (43.7%) | 4950 (36.8%) | 1075 (34.4%) |
| **COPD** | 5624 (11.3%) | 1355 (11.6%) | 3531 (12.1%) | 1606 (12.7%) | 3559 (13.3%) | 2893 (11.4%) | 1363 (11.8%) | 2289 (12.6%) | 1973 (13.1%) | - | 169 (15.9%) | 833 (20.3%) | 976 (13.2%) | 248 (14.3%) | 94 (13.9%) | 708 (12.5%) | 1907 (14.2%) | 441 (14.1%) |
| **Liver** | 1060 (2.1%) | 227 (1.9%) | 588 (2.0%) | 317 (2.5%) | 518 (1.9%) | 545 (2.2%) | 270 (2.3%) | 318 (1.7%) | 421 (2.8%) | 169 (3.0%) | - | 93 (2.3%) | 152 (2.1%) | 72 (4.1%) | 12 (1.8%) | 87 (1.5%) | 320 (2.4%) | 63 (2.0%) |
| **PAD** | 4107 (8.3%) | 732 (6.2%) | 3040 (10.4%) | 1537 (12.2%) | 3062 (11.5%) | 2224 (8.8%) | 1369 (11.8%) | 2087 (11.4%) | 1923 (12.7%) | 833 (14.8%) | 93 (8.8%) | - | 956 (12.9%) | 155 (8.9%) | 71 (10.5%) | 536 (9.5%) | 1553 (11.6%) | 280 (9.0%) |
| **Stroke** | 7402 (14.9%) | 1446 (12.3%) | 5259 (18.1%) | 2395 (19.0%) | 4889 (18.3%) | 4525 (17.9%) | 2003 (17.3%) | 3538 (19.4%) | 2829 (18.7%) | 976 (17.4%) | 152 (14.3%) | 956 (23.3%) | - | 339 (19.5%) | 224 (33.2%) | 956 (16.9%) | 2341 (17.4%) | 562 (18.0%) |
| **Depres.** | 1738 (3.5%) | 471 (4.0%) | 1068 (3.7%) | 454 (3.6%) | 928 (3.5%) | 777 (3.1%) | 415 (3.6%) | 601 (3.3%) | 638 (4.2%) | 248 (4.4%) | 72 (6.8%) | 155 (3.8%) | 339 (4.6%) | - | 63 (9.3%) | 181 (3.2%) | 626 (4.7%) | 179 (5.7%) |
| **Dementia** | 674 (1.4%) | 83 (0.7%) | 478 (1.6%) | 228 (1.8%) | 430 (1.6%) | 400 (1.6%) | 197 (1.7%) | 376 (2.1%) | 330 (2.2%) | 94 (1.7%) | 12 (1.1%) | 71 (1.7%) | 224 (3.0%) | 63 (3.6%) | - | 74 (1.3%) | 235 (1.7%) | 75 (2.4%) |
| **Cancer <3years** | 5663 (11.4%) | 1004 (8.6%) | 3560 (12.2%) | 1369 (10.8%) | 3167 (11.9%) | 3134 (12.4%) | 1417 (12.3%) | 2550 (14.0%) | 2477 (16.4%) | 708 (12.6%) | 87 (8.2%) | 536 (13.1%) | 956 (12.9%) | 181 (10.4%) | 74 (11.0%) | - | 1826 (13.6%) | 392 (12.5%) |
| **Muscolo**  **skeletal <3years** | 13438 (27.1%) | 3433 (29.3%) | 8781 (30.2%) | 3959 (31.4%) | 7885 (29.6%) | 7222 (28.5%) | 3384 (29.3%) | 5635 (30.9%) | 4950 (32.7%) | 1907 (33.9%) | 320 (30.2%) | 1553 (37.8%) | 2341 (31.6%) | 626 (36.0%) | 235 (34.9%) | 1826 (32.2%) | - | 1164 (37.2%) |
| **Dist.** | 3128 (6.3%) | 731 (6.2%) | 2087 (7.2%) | 881 (7.0%) | 1743 (6.5%) | 1790 (7.1%) | 851 (7.4%) | 1526 (8.4%) | 1075 (7.1%) | 441 (7.8%) | 63 (5.9%) | 280 (6.8%) | 562 (7.6%) | 179 (10.3%) | 75 (11.1%) | 392 (6.9%) | 1164 (8.7%) | - |

**Supplementary Table 21. Cross-tabulation of comorbidities in patients with HFmrEF**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All**  **(**20921**)** | **Obesity**  **(**5822**)** | **Hypert.**  **(**14212**)** | **Diabetes**  **(**5281**)** | **CAD**  **(**11591**)** | **AF**  **(**12127**)** | **VHD**  **(**5580**)** | **CKD**  **(**8223**)** | **Anaemia**  **(**7257**)** | **COPD**  **(**2647**)** | **Liver**  **(**379**)** | **PAD**  **(**1854**)** | **Stroke**  **(**3360**)** | **Depres.**  **(**702**)** | **Dement**  **(**292**)** | **Cancer**  **(2742)** | **Muscolo**  **(**6752**)** | **Dist.**  **(**1578**)** |
| **Obesity** | 5822 (27.8%) | - | 4468 (31.4%) | 2218 (42.0%) | 3126 (27.0%) | 3420 (28.2%) | 1198 (21.5%) | 2209 (26.9%) | 1668 (23.0%) | 775 (29.3%) | 95 (25.1%) | 435 (23.5%) | 831 (24.7%) | 237 (33.8%) | 64 (21.9%) | 583 (21.3%) | 2031 (30.1%) | 475 (30.1%) |
| **Hypert.** | 14212 (67.9%) | 4468 (76.7%) | - | 4465 (84.5%) | 8326 (71.8%) | 8611 (71.0%) | 3823 (68.5%) | 6381 (77.6%) | 5244 (72.3%) | 1886 (71.3%) | 254 (67.0%) | 1490 (80.4%) | 2668 (79.4%) | 487 (69.4%) | 216 (74.0%) | 1893 (69.0%) | 4924 (72.9%) | 1160 (73.5%) |
| **Diabetes** | 5281 (25.2%) | 2218 (38.1%) | 4465 (31.4%) | - | 3584 (30.9%) | 3005 (24.8%) | 1268 (22.7%) | 2604 (31.7%) | 2415 (33.3%) | 800 (30.2%) | 131 (34.6%) | 652 (35.2%) | 1036 (30.8%) | 206 (29.3%) | 78 (26.7%) | 665 (24.3%) | 1862 (27.6%) | 472 (29.9%) |
| **CAD** | 11591 (55.4%) | 3126 (53.7%) | 8326 (58.6%) | 3584 (67.9%) | - | 6028 (49.7%) | 3032 (54.3%) | 5025 (61.1%) | 4530 (62.4%) | 1614 (61.0%) | 178 (47.0%) | 1333 (71.9%) | 2076 (61.8%) | 410 (58.4%) | 183 (62.7%) | 1439 (52.5%) | 3918 (58.0%) | 893 (56.6%) |
| **AF** | 12127 (58.0%) | 3420 (58.7%) | 8611 (60.6%) | 3005 (56.9%) | 6028 (52.0%) | - | 3819 (68.4%) | 5451 (66.3%) | 4397 (60.6%) | 1618 (61.1%) | 233 (61.5%) | 1105 (59.6%) | 2264 (67.4%) | 361 (51.4%) | 196 (67.1%) | 1674 (61.1%) | 4107 (60.8%) | 989 (62.7%) |
| **VHD** | 5580 (26.7%) | 1198 (20.6%) | 3823 (26.9%) | 1268 (24.0%) | 3032 (26.2%) | 3819 (31.5%) | - | 2643 (32.1%) | 2403 (33.1%) | 724 (27.4%) | 134 (35.4%) | 657 (35.4%) | 1042 (31.0%) | 177 (25.2%) | 98 (33.6%) | 735 (26.8%) | 1913 (28.3%) | 441 (27.9%) |
| **CKD** | 8223 (39.3%) | 2209 (37.9%) | 6381 (44.9%) | 2604 (49.3%) | 5025 (43.4%) | 5451 (44.9%) | 2643 (47.4%) | - | 3861 (53.2%) | 1204 (45.5%) | 143 (37.7%) | 937 (50.5%) | 1654 (49.2%) | 278 (39.6%) | 170 (58.2%) | 1190 (43.4%) | 2931 (43.4%) | 776 (49.2%) |
| **Anaemia** | 7257 (34.7%) | 1668 (28.6%) | 5244 (36.9%) | 2415 (45.7%) | 4530 (39.1%) | 4397 (36.3%) | 2403 (43.1%) | 3861 (47.0%) | - | 1048 (39.6%) | 200 (52.8%) | 903 (48.7%) | 1330 (39.6%) | 278 (39.6%) | 142 (48.6%) | 1261 (46.0%) | 2777 (41.1%) | 598 (37.9%) |
| **COPD** | 2647 (12.7%) | 775 (13.3%) | 1886 (13.3%) | 800 (15.1%) | 1614 (13.9%) | 1618 (13.3%) | 724 (13.0%) | 1204 (14.6%) | 1048 (14.4%) | - | 64 (16.9%) | 408 (22.0%) | 507 (15.1%) | 129 (18.4%) | 42 (14.4%) | 397 (14.5%) | 1036 (15.3%) | 254 (16.1%) |
| **Liver** | 379 (1.8%) | 95 (1.6%) | 254 (1.8%) | 131 (2.5%) | 178 (1.5%) | 233 (1.9%) | 134 (2.4%) | 143 (1.7%) | 200 (2.8%) | 64 (2.4%) | - | 45 (2.4%) | 51 (1.5%) | 30 (4.3%) | <10 (2.4%) | 48 (1.8%) | 138 (2.0%) | 22 (1.4%) |
| **PAD** | 1854 (8.9%) | 435 (7.5%) | 1490 (10.5%) | 652 (12.3%) | 1333 (11.5%) | 1105 (9.1%) | 657 (11.8%) | 937 (11.4%) | 903 (12.4%) | 408 (15.4%) | 45 (11.9%) | - | 433 (12.9%) | 64 (9.1%) | 27 (9.2%) | 266 (9.7%) | 801 (11.9%) | 153 (9.7%) |
| **Stroke** | 3360 (16.1%) | 831 (14.3%) | 2668 (18.8%) | 1036 (19.6%) | 2076 (17.9%) | 2264 (18.7%) | 1042 (18.7%) | 1654 (20.1%) | 1330 (18.3%) | 507 (19.2%) | 51 (13.5%) | 433 (23.4%) | - | 157 (22.4%) | 94 (32.2%) | 453 (16.5%) | 1201 (17.8%) | 303 (19.2%) |
| **Depres.** | 702 (3.4%) | 237 (4.1%) | 487 (3.4%) | 206 (3.9%) | 410 (3.5%) | 361 (3.0%) | 177 (3.2%) | 278 (3.4%) | 278 (3.8%) | 129 (4.9%) | 30 (7.9%) | 64 (3.5%) | 157 (4.7%) | - | 25 (8.6%) | 64 (2.3%) | 284 (4.2%) | 82 (5.2%) |
| **Dementia** | 292 (1.4%) | 64 (1.1%) | 216 (1.5%) | 78 (1.5%) | 183 (1.6%) | 196 (1.6%) | 98 (1.8%) | 170 (2.1%) | 142 (2.0%) | 42 (1.6%) | 7 (1.8%) | 27 (1.5%) | 94 (2.8%) | 25 (3.6%) | - | 34 (1.2%) | 106 (1.6%) | 29 (1.8%) |
| **Cancer <3years** | 2742 (13.1%) | 583 (10.0%) | 1893 (13.3%) | 665 (12.6%) | 1439 (12.4%) | 1674 (13.8%) | 735 (13.2%) | 1190 (14.5%) | 1261 (17.4%) | 397 (15.0%) | 48 (12.7%) | 266 (14.3%) | 453 (13.5%) | 64 (9.1%) | 34 (11.6%) | - | 1004 (14.9%) | 198 (12.5%) |
| **Muscolo**  **skeletal <3years** | 6752 (32.3%) | 2031 (34.9%) | 4924 (34.6%) | 1862 (35.3%) | 3918 (33.8%) | 4107 (33.9%) | 1913 (34.3%) | 2931 (35.6%) | 2777 (38.3%) | 1036 (39.1%) | 138 (36.4%) | 801 (43.2%) | 1201 (35.7%) | 284 (40.5%) | 106 (36.3%) | 1004 (36.6%) | - | 662 (42.0%) |
| **Dist.** | 1578 (7.5%) | 475 (8.2%) | 1160 (8.2%) | 472 (8.9%) | 893 (7.7%) | 989 (8.2%) | 441 (7.9%) | 776 (9.4%) | 598 (8.2%) | 254 (9.6%) | 22 (5.8%) | 153 (8.3%) | 303 (9.0%) | 82 (11.7%) | 29 (9.9%) | 198 (7.2%) | 662 (9.8%) | - |

**Supplementary Table 22. Cross-tabulation of comorbidities in patients with HFpEF**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All**  **(**20953**)** | **Obesity**  **(**6430**)** | **Hypert.**  **(**16079**)** | **Diabetes**  **(**5921**)** | **CAD**  **(**9663**)** | **AF**  **(**13821**)** | **VHD**  **(**7233**)** | **CKD**  **(**10117**)** | **Anaemia**  **(**8813**)** | **COPD**  **(**3326**)** | **Liver**  **(**477**)** | **PAD**  **(**1955**)** | **Stroke**  **(**3898**)** | **Depres.**  **(**822**)** | **Dement**  **(**434**)** | **Cancer**  **(**2959**)** | **Muscolo**  **(**7930**)** | **Dist.**  **(**2155**)** |
| **Obesity** | 6430 (30.7%) | - | 5441 (33.8%) | 2756 (46.5%) | 2853 (29.5%) | 4151 (30.0%) | 1648 (22.8%) | 3080 (30.4%) | 2417 (27.4%) | 1125 (33.8%) | 173 (36.3%) | 508 (26.0%) | 1071 (27.5%) | 279 (33.9%) | 95 (21.9%) | 686 (23.2%) | 2669 (33.7%) | 688 (31.9%) |
| **Hypert.** | 16079 (76.7%) | 5441 (84.6%) | - | 5250 (88.7%) | 7760 (80.3%) | 10719 (77.6%) | 5314 (73.5%) | 8264 (81.7%) | 6913 (78.4%) | 2577 (77.5%) | 368 (77.1%) | 1674 (85.6%) | 3222 (82.7%) | 640 (77.9%) | 332 (76.5%) | 2286 (77.3%) | 6336 (79.9%) | 1741 (80.8%) |
| **Diabetes** | 5921 (28.3%) | 2756 (42.9%) | 5250 (32.7%) | - | 3348 (34.6%) | 3731 (27.0%) | 1760 (24.3%) | 3312 (32.7%) | 3041 (34.5%) | 1046 (31.4%) | 182 (38.2%) | 711 (36.4%) | 1257 (32.2%) | 246 (29.9%) | 120 (27.6%) | 821 (27.7%) | 2386 (30.1%) | 666 (30.9%) |
| **CAD** | 9663 (46.1%) | 2853 (44.4%) | 7760 (48.3%) | 3348 (56.5%) | - | 6070 (43.9%) | 3406 (47.1%) | 5148 (50.9%) | 4469 (50.7%) | 1740 (52.3%) | 200 (41.9%) | 1194 (61.1%) | 2134 (54.7%) | 435 (52.9%) | 223 (51.4%) | 1398 (47.2%) | 3902 (49.2%) | 1048 (48.6%) |
| **AF** | 13821 (66.0%) | 4151 (64.6%) | 10719 (66.7%) | 3731 (63.0%) | 6070 (62.8%) | - | 5144 (71.1%) | 6960 (68.8%) | 5829 (66.1%) | 2140 (64.3%) | 287 (60.2%) | 1232 (63.0%) | 2783 (71.4%) | 489 (59.5%) | 304 (70.0%) | 2029 (68.6%) | 5348 (67.4%) | 1507 (69.9%) |
| **VHD** | 7233 (34.5%) | 1648 (25.6%) | 5314 (33.0%) | 1760 (29.7%) | 3406 (35.2%) | 5144 (37.2%) | - | 3680 (36.4%) | 3444 (39.1%) | 1062 (31.9%) | 182 (38.2%) | 797 (40.8%) | 1411 (36.2%) | 254 (30.9%) | 155 (35.7%) | 974 (32.9%) | 2747 (34.6%) | 780 (36.2%) |
| **CKD** | 10117 (48.3%) | 3080 (47.9%) | 8264 (51.4%) | 3312 (55.9%) | 5148 (53.3%) | 6960 (50.4%) | 3680 (50.9%) | - | 5097 (57.8%) | 1671 (50.2%) | 204 (42.8%) | 1118 (57.2%) | 2144 (55.0%) | 397 (48.3%) | 234 (53.9%) | 1533 (51.8%) | 4045 (51.0%) | 1192 (55.3%) |
| **Anaemia** | 8813 (42.1%) | 2417 (37.6%) | 6913 (43.0%) | 3041 (51.4%) | 4469 (46.2%) | 5829 (42.2%) | 3444 (47.6%) | 5097 (50.4%) | - | 1449 (43.6%) | 265 (55.6%) | 1026 (52.5%) | 1839 (47.2%) | 373 (45.4%) | 236 (54.4%) | 1563 (52.8%) | 3683 (46.4%) | 940 (43.6%) |
| **COPD** | 3326 (15.9%) | 1125 (17.5%) | 2577 (16.0%) | 1046 (17.7%) | 1740 (18.0%) | 2140 (15.5%) | 1062 (14.7%) | 1671 (16.5%) | 1449 (16.4%) | - | 118 (24.7%) | 496 (25.4%) | 653 (16.8%) | 190 (23.1%) | 64 (14.7%) | 500 (16.9%) | 1383 (17.4%) | 379 (17.6%) |
| **Liver** | 477 (2.3%) | 173 (2.7%) | 368 (2.3%) | 182 (3.1%) | 200 (2.1%) | 287 (2.1%) | 182 (2.5%) | 204 (2.0%) | 265 (3.0%) | 118 (3.5%) | - | 54 (2.8%) | 85 (2.2%) | 31 (3.8%)5 | (0.7%) | 74 (2.5%) | 202 (2.5%) | 62 (2.9%) |
| **PAD** | 1955 (9.3%) | 508 (7.9%) | 1674 (10.4%) | 711 (12.0%) | 1194 (12.4%) | 1232 (8.9%) | 797 (11.0%) | 1118 (11.1%) | 1026 (11.6%) | 496 (14.9%) | 54 (11.3%) | - | 468 (12.0%) | 86 (10.5%) | 47 (10.8%) | 307 (10.4%) | 954 (12.0%) | 201 (9.3%) |
| **Stroke** | 3898 (18.6%) | 1071 (16.7%) | 3222 (20.0%) | 1257 (21.2%) | 2134 (22.1%) | 2783 (20.1%) | 1411 (19.5%) | 2144 (21.2%) | 1839 (20.9%) | 653 (19.6%) | 85 (17.8%) | 468 (23.9%) | - | 224 (27.3%) | 154 (35.5%) | 563 (19.0%) | 1617 (20.4%) | 469 (21.8%) |
| **Depres.** | 822 (3.9%) | 279 (4.3%) | 640 (4.0%) | 246 (4.2%) | 435 (4.5%) | 489 (3.5%) | 254 (3.5%) | 397 (3.9%) | 373 (4.2%) | 190 (5.7%) | 31 (6.5%) | 86 (4.4%) | 224 (5.7%) | - | 35 (8.1%) | 110 (3.7%) | 423 (5.3%) | 134 (6.2%) |
| **Dementia** | 434 (2.1%) | 95 (1.5%) | 332 (2.1%) | 120 (2.0%) | 223 (2.3%) | 304 (2.2%) | 155 (2.1%) | 234 (2.3%) | 236 (2.7%) | 64 (1.9%) | 3 (0.6%) | 47 (2.4%) | 154 (4.0%) | 35 (4.3%) | - | 48 (1.6%) | 170 (2.1%) | 55 (2.6%) |
| **Cancer <3years** | 2959 (14.1%) | 686 (10.7%) | 2286 (14.2%) | 821 (13.9%) | 1398 (14.5%) | 2029 (14.7%) | 974 (13.5%) | 1533 (15.2%) | 1563 (17.7%) | 500 (15.0%) | 74 (15.5%) | 307 (15.7%) | 563 (14.4%) | 110 (13.4%) | 48 (11.1%) | - | 1223 (15.4%) | 329 (15.3%) |
| **Muscolo**  **skeletal <3years** | 7930 (37.8%) | 2669 (41.5%) | 6336 (39.4%) | 2386 (40.3%) | 3902 (40.4%) | 5348 (38.7%) | 2747 (38.0%) | 4045 (40.0%) | 3683 (41.8%) | 1383 (41.6%) | 202 (42.3%) | 954 (48.8%) | 1617 (41.5%) | 423 (51.5%) | 170 (39.2%) | 1223 (41.3%) | - | 1038 (48.2%) |
| **Dist.** | 2155 (10.3%) | 688 (10.7%) | 1741 (10.8%) | 666 (11.2%) | 1048 (10.8%) | 1507 (10.9%) | 780 (10.8%) | 1192 (11.8%) | 940 (10.7%) | 379 (11.4%) | 62 (13.0%) | 201 (10.3%) | 469 (12.0%) | 134 (16.3%) | 55 (12.7%) | 329 (11.1%) | 1038 (13.1%) | - |

**Supplementary Table 23.** **Baseline characteristics stratified by the number of comorbidities in patients with HFrEF**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Level** | **No Comorbidities** | **1 to 3 Comorbidities** | **4 to 6 Comorbidities** | **>6 Comorbidities** | **p-value** |
| N |  | 1283 (2.6%) | 21138 (42.6%) | 21659 (43.7%) | 5509 (11.1%) |  |
| **Demographics and organisational/socioeconomics** | | | | | | |
| Sex | Female | 381 (29.7%) | 5911 (28.0%) | 6431 (29.7%) | 1646 (29.9%) | <0.001 |
|  | Male | 902 (70.3%) | 15227 (72.0%) | 15228 (70.3%) | 3863 (70.1%) |  |
| Age, median (IQR) |  | 60 (51, 69) | 69 (59, 77) | 76 (68, 82) | 78 (72, 83) | <0.001 |
| Smoking |  | 226 (20.0%) | 2890 (16.2%) | 2078 (12.1%) | 444 (10.6%) | <0.001 |
| Alcohol user |  | 75 (7.5%) | 971 (6.6%) | 572 (4.2%) | 101 (3.2%) | <0.001 |
| Location of care | Out-patient | 873 (68.0%) | 13445 (63.6%) | 11754 (54.3%) | 2427 (44.1%) | <0.001 |
|  | In-patient | 410 (32.0%) | 7693 (36.4%) | 9905 (45.7%) | 3082 (55.9%) |  |
| Follow-up location | Primarycare | 84 (6.7%) | 3442 (16.7%) | 5467 (26.3%) | 1754 (33.4%) | <0.001 |
|  | Hospital | 1172 (93.3%) | 17119 (83.3%) | 15298 (73.7%) | 3491 (66.6%) |  |
| Family type | Cohabitating | 773 (60.5%) | 11706 (55.5%) | 11427 (52.8%) | 2879 (52.3%) | <0.001 |
|  | Living alone | 504 (39.5%) | 9370 (44.5%) | 10207 (47.2%) | 2630 (47.7%) |  |
| **Clinical variables and comorbidities** | | | | | | |
| Duration of HF | <6months | 1041 (82.4%) | 14568 (70.1%) | 10226 (48.2%) | 1838 (34.1%) | <0.001 |
|  | >=6months | 223 (17.6%) | 6208 (29.9%) | 10981 (51.8%) | 3558 (65.9%) |  |
| Previous HF hospitalization (within 12 months) |  | 879 (68.5%) | 12683 (60.0%) | 14505 (67.0%) | 4239 (76.9%) | <0.001 |
| NYHA | I-II | 828 (75.6%) | 11633 (68.3%) | 7979 (49.6%) | 1276 (33.9%) | <0.001 |
|  | III-IV | 267 (24.4%) | 5405 (31.7%) | 8118 (50.4%) | 2483 (66.1%) |  |
| BMI, median (IQR) |  | 25 (22, 27) | 26 (23, 29) | 26 (23, 30) | 28 (24, 32) | <0.001 |
| SBP, median (IQR) |  | 120 (106, 130) | 120 (110, 138) | 121 (110, 140) | 120 (110, 138) | <0.001 |
| DBP, median (IQR) |  | 70 (65, 80) | 75 (66, 80) | 70 (65, 80) | 70 (60, 80) | <0.001 |
| MAP, median (IQR) |  | 88 (80, 97) | 90 (82, 100) | 90 (80, 98) | 88 (80, 97) | <0.001 |
| Heart rate, median (IQR) |  | 70 (60, 80) | 72 (62, 84) | 73 (64, 84) | 73 (65, 83) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 1086 (84.6%) | 10382 (49.1%) | 3514 (16.2%) | 133 (2.4%) | <0.001 |
|  | 2-3 | 147 (11.5%) | 8494 (40.2%) | 9673 (44.7%) | 1114 (20.2%) |  |
|  | 4-7 | 44 (3.4%) | 1908 (9.0%) | 7329 (33.8%) | 3229 (58.6%) |  |
|  | >=8 | <10 (0.5%) | 354 (1.7%) | 1143 (5.3%) | 1033 (18.8%) |  |
| **Laboratory** | | | | | | |
| eGFR, median (IQR) |  | 89 (77, 99) | 79 (66, 93) | 60 (46, 80) | 47 (35, 59) | <0.001 |
| Potassium categories | Normakalemia | 1027 (96.2%) | 16307 (95.0%) | 15866 (92.2%) | 3993 (90.0%) | <0.001 |
|  | Hypokalemia | 21 (2.0%) | 500 (2.9%) | 751 (4.4%) | 222 (5.0%) |  |
|  | Hyperkalemia | 20 (1.9%) | 360 (2.1%) | 582 (3.4%) | 223 (5.0%) |  |
| Haemoglobin, median (IQR) |  | 144 (136, 153) | 141 (132, 151) | 131 (119, 143) | 120 (111, 131) | <0.001 |
| NT-proBNP, median (IQR) |  | 1860 (786, 4200) | 2130 (904, 4640) | 3210 (1440, 7170) | 4352 (1996, 9598) | <0.001 |
| **Treatments** | | | | | | |
| ACEi/ARB/ARNI |  | 1247 (98.3%) | 19971 (95.5%) | 19209 (89.7%) | 4497 (82.7%) | <0.001 |
| Beta-blockers |  | 1166 (91.2%) | 19580 (92.8%) | 19800 (91.6%) | 4984 (90.8%) | <0.001 |
| MRA |  | 495 (38.6%) | 8251 (39.2%) | 8898 (41.3%) | 2113 (38.6%) | <0.001 |
| Diuretics |  | 776 (60.8%) | 14052 (66.7%) | 17729 (82.1%) | 4968 (90.5%) | <0.001 |
| Digoxin |  | 34 (2.7%) | 2845 (13.5%) | 3169 (14.7%) | 730 (13.3%) | <0.001 |
| Antiplatelet therapy |  | 329 (25.7%) | 8872 (42.1%) | 10237 (47.4%) | 2485 (45.3%) | <0.001 |
| Anticoagulant therapy |  | 224 (17.5%) | 8272 (39.3%) | 10550 (48.9%) | 3046 (55.5%) | <0.001 |
| Statins |  | 264 (20.6%) | 8722 (41.4%) | 12318 (57.1%) | 3524 (64.2%) | <0.001 |
| Nitrate |  | <10 (0.7%) | 1184 (5.6%) | 3247 (15.1%) | 1300 (23.7%) | <0.001 |
| HF Devices |  | 96 (7.5%) | 1375 (6.6%) | 1963 (9.2%) | 545 (10.0%) | <0.001 |

**Supplemtnary Table 24.** **Baseline characteristics stratified by the number of comorbidities in patients with HFmrEF**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Level** | **No Comorbidities** | **1 to 3 Comorbidities** | **4 to 6 Comorbidities** | **>6 Comorbidities** | **p-value** |
| N |  | 282 (1.3%) | 7419 (35.5%) | 10053 (48.1%) | 3167 (15.1%) |  |
| **Demographics and organisational/socioeconomics** | | | | | | |
| Sex | Female | 108 (38.3%) | 2639 (35.6%) | 3932 (39.1%) | 1226 (38.7%) | <0.001 |
|  | Male | 174 (61.7%) | 4780 (64.4%) | 6121 (60.9%) | 1941 (61.3%) |  |
| Age, median (IQR) |  | 57 (44, 67) | 71 (62, 79) | 78 (71, 84) | 79 (73, 84) | <0.001 |
| Smoking |  | 45 (19.4%) | 775 (12.5%) | 703 (9.0%) | 186 (7.9%) | <0.001 |
| Alcohol user |  | 14 (6.7%) | 259 (5.1%) | 230 (3.8%) | 64 (3.7%) | 0.002 |
| Location of care | Out-patient | 239 (84.8%) | 5249 (70.8%) | 5547 (55.2%) | 1374 (43.4%) | <0.001 |
|  | In-patient | 43 (15.2%) | 2170 (29.2%) | 4506 (44.8%) | 1793 (56.6%) |  |
| Follow-up location | Primary-care | 38 (13.7%) | 2087 (29.0%) | 3853 (40.0%) | 1290 (42.9%) | <0.001 |
|  | Hospital | 240 (86.3%) | 5115 (71.0%) | 5769 (60.0%) | 1717 (57.1%) |  |
| Family type | Cohabitating | 179 (63.5%) | 4246 (57.3%) | 5177 (51.5%) | 1584 (50.0%) | <0.001 |
|  | Living alone | 103 (36.5%) | 3158 (42.7%) | 4870 (48.5%) | 1583 (50.0%) |  |
| **Clinical variables and comorbidities** | | | | | | |
| Duration of HF | <6mo | 186 (68.1%) | 4647 (63.9%) | 4637 (47.3%) | 1048 (34.0%) | <0.001 |
|  | >=6mo | 87 (31.9%) | 2623 (36.1%) | 5157 (52.7%) | 2034 (66.0%) |  |
| Previous HF hospitalization (within 12 months) |  | 88 (31.2%) | 2989 (40.3%) | 5878 (58.5%) | 2313 (73.0%) | <0.001 |
| NYHA | I-II | 219 (91.6%) | 4864 (80.9%) | 4474 (63.1%) | 942 (47.0%) | <0.001 |
|  | III-IV | 20 (8.4%) | 1147 (19.1%) | 2611 (36.9%) | 1063 (53.0%) |  |
| BMI, median (IQR) |  | 25 (23, 27) | 26 (23, 29) | 27 (24, 31) | 29 (25, 33) | <0.001 |
| SBP, median (IQR) |  | 120 (110, 134) | 130 (115, 140) | 130 (117, 142) | 130 (115, 140) | <0.001 |
| DBP, median (IQR) |  | 72 (65, 80) | 75 (69, 80) | 73 (65, 80) | 70 (63, 80) | <0.001 |
| MAP, median (IQR) |  | 90 (80, 97) | 93 (84, 102) | 93 (83, 100) | 90 (82, 100) | <0.001 |
| Heart rate, median (IQR) |  | 65 (58, 76) | 70 (60, 80) | 72 (63, 82) | 72 (64, 83) | <0.001 |
| Charlson Comorbidity index | 0-1 | 236 (83.7%) | 3731 (50.3%) | 1992 (19.8%) | 113 (3.6%) | <0.001 |
|  | 2-3 | 36 (12.8%) | 2890 (39.0%) | 4359 (43.4%) | 727 (23.0%) |  |
|  | 4-7 | <10 (3.2%) | 653 (8.8%) | 3147 (31.3%) | 1777 (56.1%) |  |
|  | >=8 | <5 (0.4%) | 145 (2.0%) | 555 (5.5%) | 550 (17.4%) |  |
| **Laboratory** | | | | | | |
| eGFR, median (IQR) |  | 94 (82, 105) | 80 (67, 93) | 61 (46, 80) | 48 (35, 60) | <0.001 |
| Potassium categories | Normakalemia | 232 (95.9%) | 5893 (95.7%) | 7590 (91.8%) | 2357 (90.2%) | <0.001 |
|  | Hypokalemia | <10 (3.7%) | 173 (2.8%) | 433 (5.2%) | 143 (5.5%) |  |
|  | Hyperkalemia | <5 (0.4%) | 94 (1.5%) | 243 (2.9%) | 113 (4.3%) |  |
| Haemoglobin, median (IQR) |  | 144 (136, 152) | 140 (130, 149) | 129 (118, 141) | 118 (109, 129) | <0.001 |
| NT-proBNP, median (IQR) |  | 270 (94, 693) | 1140 (414, 2620) | 2216 (1025, 4600) | 3031 (1455, 6692) | <0.001 |
| **Treatments** | | | | | | |
| ACEi/ARB/ARNI |  | 258 (92.1%) | 6669 (90.7%) | 8298 (83.3%) | 2351 (75.1%) | <0.001 |
| Beta-blockers |  | 204 (72.6%) | 6390 (86.3%) | 8810 (87.8%) | 2764 (87.6%) | <0.001 |
| MRA |  | 38 (13.5%) | 1705 (23.1%) | 3115 (31.1%) | 1034 (32.8%) | <0.001 |
| Diuretics |  | 57 (20.2%) | 3823 (51.6%) | 7784 (77.6%) | 2842 (90.1%) | <0.001 |
| Digoxin |  | <5 (0.7%) | 766 (10.4%) | 1330 (13.3%) | 397 (12.6%) | <0.001 |
| Antiplatelet therapy |  | 65 (23.0%) | 3259 (44.0%) | 4282 (42.7%) | 1289 (40.9%) | <0.001 |
| Anticoagulant therpy |  | 14 (5.0%) | 2735 (37.0%) | 5180 (51.7%) | 1811 (57.5%) | <0.001 |
| Statins |  | 54 (19.1%) | 3317 (44.8%) | 5375 (53.6%) | 1921 (60.9%) | <0.001 |
| Nitrates |  | <5 (1.1%) | 439 (5.9%) | 1534 (15.3%) | 742 (23.5%) | <0.001 |
| HF devices |  | 13 (4.6%) | 242 (3.3%) | 311 (3.2%) | 95 (3.1%) | 0.48 |

**Supplementary Table 25.** **Baseline characteristics stratified by the number of comorbidities in patients with HFpEF**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Level** | **No Comorbidities** | **1 to 3 Comorbidities** | **4 to 6 Comorbidities** | **>6 Comorbidities** | **p-value** |
| N |  | 125 (0.6%) | 5251 (25.1%) | 11259 (53.7%) | 4318 (20.6%) |  |
| **Demographics and organisational/socioeconomics** | | | | | | |
| Sex | Female | 61 (48.8%) | 2640 (50.3%) | 6136 (54.5%) | 2223 (51.5%) | <0.001 |
|  | Male | 64 (51.2%) | 2611 (49.7%) | 5123 (45.5%) | 2095 (48.5%) |  |
| Age, median (IQR) |  | 60 (36, 75) | 77 (67, 84) | 81 (74, 86) | 80 (75, 85) | <0.001 |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Smoking |  | 11 (11.1%) | 405 (10.1%) | 580 (7.1%) | 211 (7.0%) | <0.001 |
| Alcohol user |  | <5 (5.1%) | 118 (3.8%) | 212 (3.6%) | 67 (3.1%) | 0.51 |
| Location of care | Out-patient | 98 (78.4%) | 2984 (56.8%) | 4669 (41.5%) | 1441 (33.4%) | <0.001 |
|  | In-patient | 27 (21.6%) | 2267 (43.2%) | 6590 (58.5%) | 2877 (66.6%) |  |
| Follow-up location | Primary-care | 36 (30.3%) | 2422 (48.2%) | 5569 (52.5%) | 2084 (51.5%) | <0.001 |
|  | Hospital | 83 (69.7%) | 2599 (51.8%) | 5032 (47.5%) | 1963 (48.5%) |  |
| Family type | Cohabitating | 69 (55.2%) | 2561 (48.8%) | 4957 (44.1%) | 1954 (45.3%) | <0.001 |
|  | Living alone | 56 (44.8%) | 2683 (51.2%) | 6295 (55.9%) | 2364 (54.7%) |  |
| **Clinical variables and comorbidities** | | | | | | |
|  |  |  |  |  |  |  |
| Previous HF hospitalization (within 12 months) |  | 40 (32.0%) | 2728 (52.0%) | 7881 (70.0%) | 3448 (79.9%) | <0.001 |
| Duration of HF | <6mo | 66 (54.5%) | 2819 (55.4%) | 5035 (46.4%) | 1511 (36.3%) | <0.001 |
|  | >=6mo | 55 (45.5%) | 2266 (44.6%) | 5817 (53.6%) | 2651 (63.7%) |  |
| NYHA | I-II | 85 (89.5%) | 2736 (74.3%) | 3973 (57.8%) | 1070 (45.3%) | <0.001 |
|  | III-IV | 10 (10.5%) | 948 (25.7%) | 2900 (42.2%) | 1291 (54.7%) |  |
| BMI, median (IQR) |  | 25 (23, 27) | 26 (23, 29) | 27 (23, 31) | 30 (25, 34) | <0.001 |
| SBP, median (IQR) |  | 120 (110, 137) | 130 (120, 145) | 130 (120, 145) | 130 (120, 147) | <0.001 |
| DBP, median (IQR) |  | 70 (65, 80) | 75 (68, 80) | 70 (65, 80) | 70 (60, 80) | <0.001 |
| MAP, median (IQR) |  | 88 (80, 97) | 93 (85, 102) | 93 (83, 100) | 91 (83, 100) | <0.001 |
| Heart rate, median (IQR) |  | 67 (57, 76) | 70 (62, 80) | 72 (63, 82) | 72 (64, 82) | <0.001 |
| Charlson Comorbidity Index | 0-1 | 99 (79.2%) | 2898 (55.2%) | 2495 (22.2%) | 184 (4.3%) | <0.001 |
|  | 2-3 | 19 (15.2%) | 1801 (34.3%) | 4843 (43.0%) | 1052 (24.4%) |  |
|  | 4-7 | <10 (4.0%) | 466 (8.9%) | 3316 (29.5%) | 2321 (53.8%) |  |
|  | >=8 | <5 (1.6%) | 86 (1.6%) | 605 (5.4%) | 761 (17.6%) |  |
| **Laboratory** | | | | | | |
| eGFR, median (IQR) |  | 91 (81, 101) | 76 (63, 89) | 59 (44, 77) | 47 (35, 59) | <0.001 |
| Potassium categories | Normakalemia | 103 (96.3%) | 3911 (93.5%) | 8197 (91.1%) | 3217 (89.8%) | <0.001 |
|  | Hypokalemia | <5 (2.8%) | 209 (5.0%) | 587 (6.5%) | 224 (6.3%) |  |
|  | Hyperkalemia | <5 (0.9%) | 61 (1.5%) | 216 (2.4%) | 142 (4.0%) |  |
| Haemoglobin, median (IQR) |  | 139 (133, 146) | 136 (127, 146) | 126 (115, 138) | 117 (107, 127) | <0.001 |
| NT-proBNP, median (IQR) |  | 306 (110, 1030) | 1340 (514, 2876) | 2130 (1020, 4200) | 2680 (1332, 5438) | <0.001 |
| **Treatments** | | | | | | |
| ACEi/ARB/ARNI |  | 84 (68.3%) | 3834 (73.9%) | 8040 (72.2%) | 2812 (66.0%) | <0.001 |
| Beta-blockers |  | 76 (60.8%) | 4049 (77.5%) | 9182 (81.8%) | 3623 (84.3%) | <0.001 |
| MRA |  | 24 (19.4%) | 1375 (26.4%) | 3612 (32.3%) | 1415 (33.0%) | <0.001 |
| Diuretics |  | 43 (34.4%) | 3637 (69.5%) | 9673 (86.2%) | 3994 (92.9%) | <0.001 |
| Digoxin |  | <5 (3.2%) | 723 (13.8%) | 1660 (14.8%) | 510 (11.9%) | <0.001 |
| Antiplatelet therapy |  | 17 (13.7%) | 1669 (31.9%) | 3962 (35.4%) | 1563 (36.4%) | <0.001 |
| Anticoagulant therpy |  | <10 (4.0%) | 2107 (40.3%) | 5979 (53.3%) | 2440 (56.7%) | <0.001 |
| Statins |  | 16 (12.8%) | 1585 (30.3%) | 4850 (43.2%) | 2389 (55.5%) | <0.001 |
| Nitrates |  | <5 (1.6%) | 369 (7.1%) | 1687 (15.1%) | 1069 (24.9%) | <0.001 |
| HF devices |  | <10 (7.4%) | 101 (2.0%) | 143 (1.3%) | 45 (1.1%) | <0.001 |

**Supplementary Table 26: Adjusted HR for all cause mortality and interaction by EF categories**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-interaction** |
| **Variable** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** |  |
| **Demographics and organisational/socioeconomics** | | | | |  |
| Sex (male vs female) | 1.19 (1.17-1.22), <0.001 | 1.22 (1.18-1.26), <0.001 | 1.19 (1.13-1.24), <0.001 | 1.17 (1.12-1.23), <0.001 | 0.2321 |
| Age (>= 75 vs < 75) | 1.80 (1.75-1.85), <0.001 | 1.86 (1.80-1.93), <0.001 | 1.75 (1.66-1.85), <0.001 | 1.69 (1.60-1.78), <0.001 | 0.0036 |
| Smoking | 1.15 (1.10-1.21), <0.001 | 1.13 (1.08-1.19), <0.001 | 1.15 (1.05-1.27), 0.002 | 1.20 (1.09-1.33), <0.001 | 0.5070 |
| In-patient vs out-patient | 1.20 (1.16-1.24), <0.001 | 1.17 (1.13-1.21), <0.001 | 1.21 (1.15-1.28), <0.001 | 1.27 (1.21-1.33), <0.001 | 0.0133 |
| Follow-up (hospital vs primary care/other) | 0.75 (0.73-0.76), <0.001 | 0.71 (0.69-0.74), <0.001 | 0.78 (0.75-0.82), <0.001 | 0.78 (0.75-0.82), <0.001 | 0.0003 |
| Family type (living alone vs cohabiting) | 1.14 (1.12-1.17), <0.001 | 1.16 (1.12-1.19), <0.001 | 1.09 (1.04-1.14), <0.001 | 1.16 (1.11-1.21), <0.001 | 0.0797 |
| Secondary school vs compulsory | 0.92 (0.90-0.95), <0.001 | 0.92 (0.89-0.95), <0.001 | 0.95 (0.91-1.00), 0.045 | 0.91 (0.87-0.96), <0.001 | 0.3698 |
| University vs compulsory | 0.88 (0.85-0.91), <0.001 | 0.87 (0.83-0.91), <0.001 | 0.87 (0.81-0.93), <0.001 | 0.92 (0.86-0.98), 0.009 |  |
| Index year <2014 vs >= 2014 | 1.04 (1.01-1.06), 0.002 | 1.00 (0.97-1.03), 0.992 | 1.04 (0.99-1.09), 0.086 | 1.10 (1.06-1.15), <0.001 | 0.0007 |
| Income categories >=median vs < median | 0.92 (0.90-0.94), <0.001 | 0.89 (0.86-0.92), <0.001 | 0.93 (0.89-0.97), 0.002 | 0.97 (0.93-1.02), 0.207 | 0.0035 |
| **Clinical variables** | | | | |  |
| Duration HF >= 6 months vs <6 months | 1.31 (1.28-1.34), <0.001 | 1.43 (1.39-1.48), <0.001 | 1.22 (1.16-1.28), <0.001 | 1.19 (1.14-1.24), <0.001 | <0.001 |
| Previous hospitalizations (within 1 year) | 1.23 (1.19-1.28), <0.001 | 1.17 (1.13-1.23), <0.001 | 1.33 (1.26-1.41), <0.001 | 1.36 (1.28-1.44), <0.001 | <0.001 |
| HFmrEF vs HFrEF | 1.02 (0.99-1.05), 0.134 |  |  |  |  |
| HFpEF vs HFrEF | 1.01 (0.98-1.04), 0.418 |  |  |  |  |
| NYHA class III/IV vs I/II | 1.39 (1.35-1.43), <0.001 | 1.40(1.35-1.45), <0.001 | 1.42 (1.34-1.50), <0.001 | 1.36 (1.29-1.44), <0.001 | 0.6361 |
| MAP >90 vs <= 90 mmHg | 0.82 (0.81-0.84), <0.001 | 0.81 (0.79-0.84), <0.001 | 0.86 (0.82-0.90), <0.001 | 0.82 (0.79-0.85), <0.001 | 0.0745 |
| HR >70 vs <=70 beats/min | 1.12 (1.10-1.15), <0.001 | 1.06 (1.03-1.10), <0.001 | 1.18 (1.13-1.24), <0.001 | 1.19 (1.14-1.24), <0.001 | <0.001 |
| **Laboratory** | | | | |  |
| Hypokalemia vs normokalemia | 1.17 (1.10-1.24), <0.001 | 1.19 (1.11-1.29), <0.001 | 1.22 (1.11-1.35), <0.001 | 1.09 (0.99-1.21), 0.089 | 0.4897 |
| Hyperkalemia vs normokalemia | 1.16 (1.08-1.25), <0.001 | 1.19 (1.07-1.31), 0.001 . | 1.09 (0.96-1.25), 0.189 | 1.18 (1.04-1.33), 0.010 |  |
| NT-proBNP (>= median vs < median) | 1.46 (1.41-1.51), <0.001 | 1.43 (1.37-1.50), <0.001 | 1.48 (1.39-1.58), <0.001 | 1.48 (1.41-1.55), <0.001 | 0.4619 |
| **Treatments** | | | | |  |
| ACE-i/ARB/ARNI | 0.73 (0.71-0.75), <0.001 | 0.68 (0.65-0.71), <0.001 | 0.72 (0.68-0.76), <0.001 | 0.78 (0.75-0.83), <0.001 | <0.001 |
| Beta-blockers | 0.84 (0.82-0.87), <0.001 | 0.82 (0.78-0.86), <0.001 | 0.84 (0.79-0.89), <0.001 | 0.86 (0.82-0.91), <0.001 | 0.4550 |
| MRA | 1.02 (0.99-1.04), 0.103 | 0.98 (0.95-1.01), 0.152 | 1.04 (0.99-1.09), 0.147 | 1.08 (1.03-1.12), 0.001 | 0.0012 |
| Diuretics | 1.36 (1.32-1.41), <0.001 | 1.35 (1.29-1.42), <0.001 | 1.43 (1.34-1.52), <0.001 | 1.31 (1.22-1.40), <0.001 | 0.1842 |
| Digoxin | 1.00 (0.97-1.03), 0.659 | 1.01 (0.97-1.06), 0.541 | 0.94 (0.88-1.00), 0.056 | 1.01 (0.96-1.07), 0.631 | 0.1184 |
| Antiplatelet therapy | 0.94 (0.92-0.97), <0.001 | 0.98 (0.95-1.02), 0.354 | 0.90 (0.85-0.94), <0.001 | 0.91 (0.87-0.95), <0.001 | 0.0003 |
| Anticoagulant therapy | 0.76 (0.74-0.79), <0.001 | 0.78 (0.75-0.81), <0.001 | 0.76 (0.72-0.80), <0.001 | 0.75 (0.72-0.79), <0.001 | 0.3774 |
| Statins | 0.80 (0.78-0.82), <0.001 | 0.86 (0.83-0.89), <0.001 | 0.76 (0.72-0.79), <0.001 | 0.74 (0.71-0.78), <0.001 | <0.001 |
| Nitrates | 1.06 (1.03-1.09), <0.001 | 1.13 (1.09-1.18), <0.001 | 1.05 (0.99-1.11), 0.126 | 0.95 (0.90-1.01), 0.094 | <0.001 |
| CRT/ICD | 1.07 (1.01-1.12), 0.049 | 1.08 (1.02-1.15), 0.006 | 1.06 (0.91-1.22), 0.449 | 0.89 (0.71-1.10), 0.282 | 0.2234 |
| **Comorbidities** |  |  |  |  |  |
| Obesity | 0.81 (0.79-0.84), <0.001 | 0.85 (0.82-0.89), <0.001 | 0.80 (0.76-0.85), <0.001 | 0.77 (0.74-0.81), <0.001 | 0.0050 |
| Hypertension | 1.01 (0.98-1.03), 0.557 | 1.03 (1.00-1.06), 0.095 | 1.05 (1.00-1.10), 0.068 | 0.93 (0.88-0.97), 0.002 | 0.0004 |
| Diabetes | 1.25 (1.22-1.28), <0.001 | 1.29 (1.25-1.34), <0.001 | 1.30 (1.23-1.36), <0.001 | 1.14 (1.09-1.20), 0.001 | <0.001 |
| CAD | 1.18 (1.15-1.21), <0.001 | 1.35 (1.31-1.40), <0.001 | 1.09 (1.04-1.14), 0.001 | 1.02 (0.98-1.06), 0.340 | <0.001 |
| Atrial fibrillation | 1.17 (1.14-1.21), <0.001 | 1.21 (1.16-1.25), <0.001 | 1.17 (1.12-1.23), <0.001 | 1.11 (1.06-1.17), <0.001 | 0.0108 |
| Valvular heart disease | 1.20 (1.17-1.23), <0.001 | 1.22 (1.18-1.26), <0.001 | 1.19 (1.13-1.24), <0.001 | 1.18 (1.13-1.23), <0.001 | 0.4929 |
| CKD | 1.37 (1.34-1.41), <0.001 | 1.45 (1.41-1.50), <0.001 | 1.35 (1.29-1.41), <0.001 | 1.36 (1.31-1.42), <0.001 | <0.001 |
| Anaemia | 1.29 (1.26-1.32), <0.001 | 1.33 (1.29-1.37), <0.001 | 1.28 (1.22-1.34), <0.001 | 1.22 (1.17-1.28), <0.001 | 0.0041 |
| COPD | 1.32 (1.28-1.35), <0.001 | 1.29 (1.24-1.34), <0.001 | 1.32 (1.24-1.40), <0.001 | 1.35 (1.29-1.42), <0.001 | 0.3431 |
| Liver disease | 1.30 (1.22-1.40), <0.001 | 1.27 (1.16-1.40), <0.001 | 1.46 (1.26-1.70), <0.001 | 1.26 (1.11-1.44), 0.001 | 0.2560 |
| PAD | 1.28 (1.24-1.32), <0.001 | 1.36 (1.30-1.42), <0.001 | 1.33 (1.25-1.43), <0.001 | 1.10 (1.05-1.19), <0.001 | <0.001 |
| Stroke/TIA | 1.20 (1.17-1.23), <0.001 | 1.24 (1.20-1.29), <0.001 | 1.22 (1.16-1.29), <0.001 | 1.12 (1.06-1.17), <0.001 | 0.0019 |
| Depression | 1.02 (0.96-1.07), 0.587 | 0.99 (0.91-1.07), 0.755 | 1.07 (0.95-1.20), 0.247 | 1.02 (0.93-1.13), 0.650 | 0.5112 |
| Dementia | 1.55 (1.45-1.65), <0.001 | 1.57 (1.43-1.72), <0.001 | 1.52 (1.32-1.74), <0.001 | 1.54 (1.38-1.72), <0.001 | 0.9022 |
| Cancer (<3years) | 1.31 (1.28-1.35), <0.001 | 1.35 (1.30-1.41), <0.001 | 1.37 (1.29-1.46), <0.001 | 1.21 (1.14-1.27), <0.001 | 0.0011 |
| MuscoloSkeletal disease | 1.02 (1.00-1.04), 0.107 | 1.05 (1.01-1.08), 0.005 | 1.00 (0.95-1.04), 0.877 | 0.99 (0.95-1.03), 0.656 | 0.0601 |
| Dysthyroidism | 1.00 (0.96-1.04), 0.936 | 1.01 (0.96-1.07), 0.676 | 0.92 (0.85-1.00), 0.061 | 1.03 (0.97-1.10), 0.377 | 0.1003 |

**Supplementary Table 27: Adjusted HR for CV mortality and interaction by EF categories**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-interaction** |
| **Variable** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** |  |
| **Demographics and organisational/socioeconomics** | | | | |  |
| Sex (male vs female) | 1.24 (1.20-1.28), <0.001 | 1.29 (1.23-1.34), <0.001 | 1.21 (1.15-1.30), <0.001 | 1.16 (1.10-1.23), <0.001 | 0.0010 |
| Age (>= 75 vs < 75) | 1.98 (1.91-2.05), <0.001 | 1.96 (1.87-2.05), <0.001 | 1.99 (1.85-2.15), <0.001 | 2.04 (1.88-2.20), <0.001 | 0.6468 |
| Smoking | 1.14 (1.07-1.21), <0.001 | 1.15 (1.08-1.23), <0.001 | 1.10 (0.96-1.26), 0.156 | 1.13 (0.99-1.30), 0.076 | 0.8508 |
| In-patient vs out-patient | 1.21 (1.17-1.26), <0.001 | 1.19 (1.13-1.24), <0.001 | 1.22 (1.14-1.31), <0.001 | 1.30 (1.21-1.39),<0.001 | 0.0468 |
| Follow-up (hospital vs primary care/other) | 0.72 (0.70-0.75), <0.001 | 0.71 (0.68-0.74), <0.001 | 0.76 (0.71-0.80), <0.001 | 0.72 (0.68-0.77), <0.001 | 0.2809 |
| Family type (living alone vs cohabiting) | 1.20 (1.16-1.23). <0.001 | 1.19 (1.15-1.24), <0.001 | 1.15 (1.08-1.22), <0.001 | 1.25 (1.18-1.32), <0.001 | 0.1182 |
| Secondary school vs compulsory | 0.92 (0.89-0.94), <0.001 | 0.91 (0.87-0.95), <0.001 | 0.96 (0.90-1.02), 0.180 | 0.88 (0.84-0.94), <0.001 | 0.1890992 |
| University vs compulsory | 0.87 (0.83-0.91), <0.001 | 0.85 (0.80-0.91), <0.001 | 0.85 (0.77-0.93), <0.001 | 0.91 (0.84-1.00), 0.040 |  |
| Index year <2014 vs >= 2014 | 0.95 (0.92-0.98), <0.001 | 0.92 (0.88-0.96), <0.001 | 0.97 (0.91-1.03), 0.285 | 0.99 (0.94-1.05), 0.833 | 0.0484 |
| Income categories >=median vs < median | 0.90 (0.87-0.93), <0.001 | 0.89 (0.85-0.93), <0.001 | 0.88 (0.83-0.94), <0.001 | 0.94 (0.89-0.99), 0.030 | 0.2310 |
| **Clinical variables** | | | | |  |
| Duration HF >= 6 months vs <6 months | 1.40 (1.36-1.44), <0.001 | 1.50 (1.44-1.56), <0.001 | 1.32 (1.25-1.41), <0.001 | 1.27 (1.21-1.35), <0.001 | <0.001 |
| Previous hospitalizations (within 1 year) | 1.35 (1-29-1.42), <0.001 | 1.27 (1.20-1.34), <0.001 | 1.47 (1.36-1.58), <0.001 | 1.47 (1.36-1.59), 0.001 | 0.0001 |
| HFmrEF vs HFrEF | 0.93 (0.90-0.97), <0.001 |  |  |  |  |
| HFpEF vs HFrEF | 0.89 (0.86-0.93), <0.001 |  |  |  |  |
| NYHA class III/IV vs I/II | 1.42 (1.38 -1.47), <0.001 | 1.43 (1.37-1.50), <0.001 | 1.45 (1.35-1.56), <0.001 | 1.39 (1.30-1.48), <0.001 | 0.6503 |
| MAP >90 vs <= 90 mmHg | 0.80 (0.78-0.82), <0.001 | 0.78 (0.75-0.81), <0.001 | 0.85 (0.80-0.90), <0.001 | 0.81 (0.77-0.85), <0.001 | 0.0340 |
| HR >70 vs <=70 beats/min | 1.11 (1.08-1.14), <0.001 | 1.06 (1.02-1.10), 0.004 | 1.16 (1.09-1.24), <0.001 | 1.16 (1.10-1.23), <0.001 | 0.0070 |
| **Laboratory** | | | | |  |
| Hypokalemia vs normokalemia | 1.20 (1.12-1.28), <0.001 | 1.23 (1.12-1.35), <0.001 | 1.21 (1.08-1.36), 0.002 | 1.13 (1.00-1.29), 0.054 | 0.6471 |
| Hyperkalemia vs normokalemia | 1.14 (1.04-1.23), 0.011 | 1.18 (1.04-1.33), 0.008 | 1.05 (0.88-1.25), 0.619 | 1.09 (0.92-1.30), 0.312 |  |
| NT-proBNP (>= median vs < median) | 1.52 (1.46-1.58), <0.001 | 1.47 (1.40-1.55), <0.001 | 1.56 (1.43-1.70), <0.001 | 1.56 (1.46-1.67), <0.001 | 0.2395 |
| **Treatments** | | | | |  |
| ACE-i/ARB/ARNI | 0.74 (0.72-0.77), <0.001 | 0.69 (0.66-0.73), <0.001 | 0.74 (0.69-0.80), <0.001 | 0.81 (0.76-0.86), <0.001 | 0.0003 |
| Beta-blockers | 0.82 (0.79-0.86), <0.001 | 0.81 (0.76-0.86), <0.001 | 0.81 (0.75-0.88), <0.001 | 0.84 (0.79-0.90), <0.001 | 0.6945 |
| MRA | 1.04 (1.01-1.07), 0.002 | 1.00 (0.96-1.04), 0.942 | 1.04 (0.98-1.11), 0.209 | 1.15 (1.09-1.22), <0.001 | 0.0002 |
| Diuretics | 1.44 (1.38-1.51), <0.001 | 1.41 (1.33-1.50), <0.001 | 1.67 (1.52-1.83), <0.001 | 1.31 (1.19-1.44), <0.001 | 0.0010 |
| Digoxin | 1.02 (0.98-1.06), 0.264 | 1.01 (0.96-1.06), 0.674 | 0.96 (0.88-1.04), 0.323 | 1.07 (1.00-1.15), 0.064 | 0.1404 |
| Antiplatelet therapy | 1.00 (0.96-1.04), 0.912 | 1.06 (1.01-1.10), 0.030 | 0.95 (0.89-1.01), 0.093 | 0.92 (0.86-0.98), 0.006 | <0.001 |
| Anticoagulant therapy | 0.80 (0.77-0.83) <0.001 | 0.80 (0.76-0.84), <0.001 | 0.80 (0.75-0.85), <0.001 | 0.80 (0.76-0.85), <0.001 | 0.9848 |
| Statins | 0.81 (0.79-0.84), <0.001 | 0.89 (0.86-0.93), <0.001 | 0.75 (0.71-0.80), <0.001 | 0.71 (0.67-0.75), <0.001 | <0.001 |
| Nitrates | 1.10 (1.06-1.14), <0.001 | 1.18 (1.13-1.24), <0.001 | 1.08 (1.00-1.16), 0.044 | 0.98 (0.91-1.05), 0.586 | <0.001 |
| CRT/ICD | 1.18 (1.11-1.26), <0.001 | 1.22 (1.14-1.30), <0.001 | 1.03 (0.85-1.26), 0.753 | 0.92 (0.69-1.23), 0.566 | 0.0619 |
| **Comorbidities** |  |  |  |  |  |
| Obesity | 0.82 (0.79-0.84), <0.001 | 0.87 (0.83-0.92), <0.001 | 0.79 (0.73-0.85), <0.001 | 0.75 (0.70-0.80), <0.001 | 0.0005 |
| Hypertension | 1.03 (1.00-1.06), 0.068 | 1.04 (1.00-1.08), 0.050 | 1.10 (1.03-1.18), 0.005 | 0.94 (0.88-1.00), 0.063 | 0.0025 |
| Diabetes | 1.13 (1.09-1.16), <0.001 | 1.17 (1.12-1.22), <0.001 | 1.18 (1.11-1.26), <0.001 | 1.00 (0.94-1.06), 0.950 | <0.001 |
| CAD | 1.29 (1.25-1.3), <0.001 | 1.51 (1.44-1.58), <0.001 | 1.17 (1.10-1.25), <0.001 | 1.07 (1.01-1.13), 0.016 | <0.001 |
| Atrial fibrillation | 1.25 (1.21-1.30), <0.001 | 1.23 (1.18-1.29), <0.001 | 1.25 (1.17-1.33), <0.001 | 1.29 (1.22-1.38), <0.001 | 0.4122 |
| Valvular heart disease | 1.33 (1.29-1.37), <0.001 | 1.31 (1.25-1.36), <0.001 | 1.32 (1.24-1.40), <0.001 | 1.38 (1.31-1.46), <0.001 | 0.2124 |
| CKD | 1.44 (1.40-1.49), <0.001 | 1.50 (1.44-1.56), <0.001 | 1.43 (1.35-1.52), <0.001 | 1.34 (1.27-1.42), <0.001 | 0.0031 |
| Anaemia | 1.21 (1.17-1.24), <0.001 | 1.24 (1.19-1.29), <0.001 | 1.20 (1.13-1.28), <0.001 | 1.15 (1.09-1.22), <0.001 | 0.0904 |
| COPD | 1.08 (1.04-1.12), <0.001 | 1.10 (1.04-1.16), 0.001 | 1.10 (1.01-1.19), 0.026 | 1.03 (0.96-1.11), 0.453 | 0.3103 |
| Liver disease | 1.20 (1.09-1.31), 0.007 | 1.22(1.08-1.37), 0.002 | 1.17 (0.93-1.46), 0.177 | 1.17 (0.97-1.41), 0.106 | 0.9180 |
| PAD | 1.29 (1.24-1.35), <0.001 | 1.3 (1.28-1.43), <0.001 | 1.37 (1.26-1.50), <0.001 | 1.12 (1.03-1.22), 0.006 | 0.0005 |
| Stroke/TIA | 1.23 (1.19-1.28), <0.001 | 1.26 (1.21-1.32), <0.001 | 1.25 (1.17-1.34), <0.001 | 1.17 (1.10-1.24), 0.001 | 0.1197 |
| Depression | 0.98 (0.91-1.05), 0.584 | 0.93 (0.85-1.03), 0.173 | 1.06 (0.91-1.24), 0.452 | 1.00 (0.89-1.15), 0.854 | 0.3326 |
| Dementia | 1.40 (1.29-1.52), <0.001 | 1.39 (1.24-1.57), <0.001 | 1.36 (1.14-1.63), 0.001 | 1.44 (1.24-1.66), <0.001 | 0.8980 |
| Cancer (<3years) | 0.99 (0.95-1.03), 0.664 | 0.96 (0.91-1.01), 0.147 | 1.09 (1.00-1.18), 0.051 | 0.98 (0.91-1.06), 0.579 | 0.0477 |
| MuscoloSkeletal disease | 0.98 (0.95-1.00), 0.210 | 1.00 (0.96-1.04), 0.878 | 0.95 (0.89-1.01), 0.092 | 0.97 (0.92-1.02), 0.262 | 0.2777 |
| Dysthyroidism | 1.02 (0.97-1.07), 0.479 | 1.02 (0.95-1.09), 0..612 | 0.96 (0.86-1.07), 0.424 | 1.06 (0.97-1.15), 0.198 | 0.3530 |

**Supplementary Table 28: Adjusted HR for Non-CV mortality and interaction by EF categories**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-interaction** |
| **Variable** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** |  |
| **Demographics and organisational/socioeconomics** | | | | |  |
| Sex (male vs female) | 1.14 (1.10-1.19), <0.001 | 1.13 (1.07-1.19), <0.001 | 1.14 (1.06-1.23), <0.001 | 1.16 (1.09-1.23), <0.001 | 0.8447 |
| Age (>= 75 vs < 75) | 1.59 (1.53-1.66), <0.001 | 1.69 (1.60-1.79), <0.001 | 1.54 (1.43-1.67), <0.001 | 1.45 (1.35-1.56), <0.001 | 0.0015 |
| Smoking | 1.18 (1.11-1.26), <0.001 | 1.14 (1.06-1.23), <0.001 | 1.21 (1.07-1.36), 0.002 | 1.25 (1.10-1.42), 0.001 | 0.3638 |
| In-patient vs out-patient | 1.18 (1.12-1.24), <0.001 | 1.12 (1.06-1.19), <0.001 | 1.23(1.13-1.33), <0.001 | 1.25 (1.16-1.35), <0.001 | 0.0143 |
| Follow-up (hospital vs primary care/other) | 0.79 (0.76-0.83), <0.001 | 0.73 (0.69-0.78), <0.001 | 0.82 (0.76-0.88), <0.001 | 0.86 (0.80-0.92), <0.001 | 0.0006 |
| Family type (living alone vs cohabiting) | 1.07 (1.03-1.11), <0.001 | 1.10 (1.05-1.16), <0.001 | 1.02 (0.95-1.09), 0.659 | 1.06 (1.00-1.13), 0.045 | 0.1900 |
| Secondary school vs compulsory | 0.94 (0.91-0.97), <0.001 | 0.95 (0.90-1.00), 0.043 | 0.93 (0.86-1.00), 0.045 | 0.93 (0.87-0.99), 0.026 | 0.9823 |
| University vs compulsory | 0.90 (0.865-0.95), <0.001 | 0.91 (0.84-0.98), 0.012 | 0.88 (0.79-0.98), 0.018 | 0.89 (0.81-0.98), 0.021 |  |
| Index year <2014 vs >= 2014 | 1.16 (1.12-1.20), <0.001 | 1.14 (1.09-1.21), <0.001 | 1.11 (1.03-1.19), 0.004 | 1.22 (1.15-1.30), <0.001 | 0.1001 |
| Income categories >=median vs < median | 0.95 (0.92-0.99), 0.013 | 0.91 (0.87-0.96), 0.001 | * 1. (0.91-1.05), 0.529 | 1.00 (0.94-1.06), 0.971 | 0.0621 |
| **Clinical variables** | | | | |  |
| Duration HF >= 6 months vs <6 months | 1.16 (1.12-1.20), <0.001 | 1.31 (1.24-1.38), <0.001 | 1.10 (1.02-1.18), 0.010 | 1.09 (1.02-1.16), 0.008 | <0.0001 |
| Previous hospitalizations (within 1 year) | 1.13 (1.07-1.19), <0.001 | 1.03 (0.96-1.10), 0.3 | 1.21 (1.11-1.32), <0.001 | 1.26 (1.16-1.37), <0.001 | <0.0001 |
| HFmrEF vs HFrEF | 1.18 (1.13-1.23), <0.001 |  |  |  |  |
| HFpEF vs HFrEF | 1.23 (1.17-1.28), <0.001 |  |  |  |  |
| NYHA class III/IV vs I/II | 1.34 (1.28-1.40), <0.001 | 1.32 (1.25-1.40), <0.001 | 1.37 (1.26-1.50), <0.001 | 1.33 (1.23-1.45), <0.001 | 0.7696 |
| MAP >90 vs <= 90 mmHg | 0.86 (0.83-0.89), <0.001 | 0.88 (0.84-0.92), <0.001 | 0.88 (0.82-0.94), <0.001 | 0.83 (0.78-0.88), <0.001 | 0.2540 |
| HR >70 vs <=70 beats/min | 1.15 (1.11-1.19), <0.001 | 1.08 (1.02-1.13), 0.005 | 1.21 (1.12-1.30), <0.001 | 1.22 (1.14-1.29), <0.001 | 0.0056 |
| **Laboratory** | | | | |  |
| Hypokalemia vs normokalemia | 1.12 (1.04-1.22),0.004 | 1.12 (1.00-1.26), 0.058 | 1.25 (1.06-1.47), 0.007 | 1.05 (0.91-1.21), 0.518 | 0.3870 |
| Hyperkalemia vs normokalemia | 1.21 (1.10-1.33), <0.001 | 1.19 (1.04-1.37), 0.013 | 1.16 (0.96-1.40), 0.127 | 1.28 (1.08-1.51), 0.005 |  |
| NT-proBNP (>= median vs < median) | 1.38 (1.31-1.46), <0.001 | 1.34 (1.23-1.46), <0.001 | 1.42 (1.30-1.54), <0.001 | 1.40 (1.30-1.51), <0.001 | 0.6059 |
| **Treatments** | | | | |  |
| ACE-i/ARB/ARNI | 0.70 (0.68-0.73), <0.001 | 0.66 (0.62-0.71), <0.001 | 0.69 (0.63-0.74), <0.001 | 0.75 (0.70-0.80), <0.001 | 0.0277 |
| Beta-blockers | 0.88 (0.84-0.92), <0.001 | 0.85 (0.78-0.92), <0.001 | 0.88 (0.80-0.97), 0.008 | 0.90 (0.83-0.97), 0.005 | 0.60426 |
| MRA | 0.97 (0.94-1.01),0.274 | 0.94 (0.89-0.99), 0.021 | 1.04 (0.96-1.12), 0.328 | 0.98 (0.92-1.05), 0.569 | 0.1003 |
| Diuretics | 1.26 (1.20-1.32), <0.001 | 1.26 (1.17-1.34), <0.001 | 1.25 (1.14-1.37), <0.001 | 1.33 (1.20-1.47), <0.001 | 0.6314 |
| Digoxin | 0.96 (0.92-1.02), 0.169 | 1.01 (0.94-1.08), 0.664 | 0.91 (0.82-1.01), 0.075 | 0.94 (0.86-1.03), 0.204 | 0.2297 |
| Antiplatelet therapy | 0.88 (0.84-0.92), <0.001 | 0.88 (0.83-0.93), <0.001 | 0.84 (0.78-0.91), <0.001 | 0.91 (0.85-0.97), 0.003 | 0.2602 |
| Anticoagulant therapy | 0.73 (0.69-0.76), <0.001 | 0.75 (0.71-0.80), <0.001 | 0.72 (0.66-0.78), <0.001 | 0.70 (0.65-0.75), <0.001 | 0.1918 |
| Statins | 0.79 (0.76-0.82), <0.001 | 0.80 (0.76-0.84), <0.001 | 0.77 (0.72-0.83), <0.001 | 0.79 (0.74-0.84), <0.001 | 0.6196 |
| Nitrates | 0.98 (0.93-1.03), 0.391 | 1.00 (0.93-1.07), 0.938 | 1,00 (0.91-1.10), 0.951 | 0.94 (0.87-1.02), 0.136 | 0.4611 |
| CRT/ICD | 0.88 (0.81-0.97), 0.007 | 0.85 (0.77-0.94), <0.001 | 1.09 (0.88-1.36), 0.418 | 0.85 (0.61-1.19), 0.350 | 0.1101 |
| **Comorbidities** |  |  |  |  |  |
| Obesity | 0.82 (0.78-0.85), <0.001 | 0.83 (0.78-0.89), <0.001 | 0.83 (0.76-0.90). <0.001 | 0.79 (0.74-0.85), <0.001 | 0.5093 |
| Hypertension | 0.98 (0.94-1.02), 0.248 | 1.01 (0.96-1.06), 0.682 | 0.99 (0.92-1.07), 0.802 | 0.90 (0.84-0.97), 0.005 | 0.0329 |
| Diabetes | 1.46 (1.41-1.52), <0.001 | 1.54 (1.46-1.63), <0.001 | 1.48 (1.37-1.59), <0.001 | 1.35 (1.26-1.44), <0.001 | 0.0352 |
| CAD | 1.03 (0.99-1.07), 0.123 | 1.11 (1.05-1.17, <0.001 | 0.98 (0.92-1.06), 0.665 | 0.97 (0.91-1.03), 0.301 | 0.0006 |
| Atrial fibrillation | 1.07 (1.02-1.11), 0.004 | 1.14 (1.08-1.20), <0.001 | 1.09 (1.01-1.18), 0.027 | 0.94 (0.88-1.01), 0.075 | <0.001 |
| Valvular heart disease | 1.01 (0.97-1.05), 0.554 | 1.05 (0.99-1.11), 0.095 | 1.02 (0.95-1.10), 0.574 | 0.96 (0.90-1.02), 0.189 | 0.1026 |
| CKD | 1.27 (1.22-1.32), <0.001 | 1.34 (1.27-1.41), <0.001 | 1.25 (1.17-1.35), <0.001 | 1.18 (1.11-1.26), <0.001 | 0.0052 |
| Anaemia | 1.42 (1.37-1.48), <0.001 | 1.50 (1.42-1.58); <0.001 | 1.40 (1.31-1.50), <0.001 | 1.33 (1.26-1.42), <0.001 | 0.0113 |
| COPD | 1.72 (1.65-1.80), <0.001 | 1.67 (1.56-1.77), <0.001 | 1.67 (1.54-1.82), <0.001 | 1.842 (1.71-1.97), <0.001 | 0.0827 |
| Liver disease | 1.45 (1.31-1.60), <0.001 | 1.37 (1.19-1.59), <0.001 | 1.82 (1.48-2.22), <0.001 | 1.34 (1.12-1.60), 0.001 | 0.0481 |
| PAD | 1.27 (1.20-1.33), <0.001 | 1.37 (1.27-1.48), <0.001 | 1.29 (1.16-1.44); <0.001 | 1.11(1.01-1.22), 0.037 | 0.0018 |
| Stroke/TIA | 1.14 (1.09-1.19), <0.001 | 1.18 (1.11-1.26), <0.001 | 1.18 (1.09-1.29), <0.001 | 1.06 (0.99-1.14), 0.190 | 0.0593 |
| Depression | 1.06 (0.98-1.15), 0.155 | 1.08 (0.95-1.21), 0.229 | 1.08 (0.91-1.29), 0.378 | 1.03 (0.89-1.18), 0.700 | 0.8592 |
| Dementia | 1.82 (1.65-2.00), <0.001 | 1.92 (1.660-2.22), <0.001 | 1.77 (1.44-2.17), <0.001 | 1.73 (1.47-2.04), <0.001 | 0.6095 |
| Cancer (<3years) | 1.86 (1.79-1.94), <0.001 | 2.17 (2.05-2.30), <0.001 | 1.80 (1.65-1.96), <0.001 | 1.52 (1.41-1.64), <0.001 | <0.001 |
| MuscoloSkeletal disease | 1.08 (1.04-1.12), <0.001 | 1.13 (1.07-1.19), <0.001 | 1.07 (1.00-1.15), 0.060 | 1.02 (0.96-1.08), 0.553 | 0.0370 |
| Dysthyroidism | 0.97 (0.91-1.03), 0.352 | 1.00 (0.91-1.10), 0.954 | 0.88 (0.77-1.00), 0.042 | 1.00 (0.91-1.10), 0.992 | 0.1855 |

**Supplementary Table 29: Adjusted HR for any hospitalization and interaction by EF categories**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-interaction** |
| **Variable** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** |  |
| **Demographics and organisational/socioeconomics** | | | | |  |
| Sex (male vs female) | 1.03 (1.01-1.05), 0.002 | 1.04 (1.01-1.07), 0.001 | 1.02 (0.98-1.05), 0.310 | 1.01 (0.98-1.04), 0.530 | 0.2093 |
| Age (>= 75 vs < 75) | 1.11 (1.09-1.13), <0.001 | 1.12 (1.09-1.14), <0.001 | 1.15 (1.11-1.19), <0.001 | 1.06 (1.02-1.10), 0.002 | 0.0017 |
| Smoking | 1.03 (1.01-1.06), 0.020 | 1.02 (0.99-1.06), 0.256 | 1.03 (0.96-1.09), 0.422 | 1.08 (1.02-1.15), 0.009 | 0.2347 |
| In-patient vs out-patient | 1.21 (1.19-1.24), <0.001 | 1.17 (1.14-1.20), <0.001 | 1.28 (1.23-1.33), <0.001 | 1.29 (1.25-1.33), <0.001 | <0.001 |
| Follow-up (hospital vs primary care/other) | 1.00 (0.98-1.02), 0.980 | 1.00 (0.98-1.03), 0.800 | 0.98 (0.95-1.02), 0.439 | 1.02 (0.98-1.05), 0.344 | 0.4614 |
| Family type (living alone vs cohabiting) | 1.03 (1.01-1.05), <0.001 | 1.02 (0.99-1.04), 0.168 | 1.04 (1.00-1.07), 0.025 | 1.06 (1.03-1.09), <0.001 | 0.0847 |
| Secondary school vs compulsory | 0.99 (0.97-1.00),  0.132 | 0.99 (0.97-1.02), 0.629 | 0.97 (0.94-1.00), 0.083 | 0.98 (0.95-1.01), 0.234 | 0.7438 |
| University vs compulsory | 0.95 (0.93-0.98), <0.001 | 0.96 (0.93-0.99), 0.005 | 0.93 (0.89-0.98), 0.003 | 0.95 (0.91-1.00), 0.051 |  |
| Index year <2014 vs >= 2014 | 0.88 (0.87-0.90), <0.001 | 0.89 (0.87-0.91), <0.001 | 0.87 (0.85-0.90), <0.001 | 0.88 (0.85-0.91), <0.001 | 0.6819 |
| Income categories >=median vs < median | 0.96 (0.94-0.97), <0.001 | 0.96 (0.94-0.98), <0.001 | 0.94 (0.91-0.97), <0.001 | 0.96 (0.93-0.99), 0.006 | 0.7112 |
| **Clinical variables** | | | | |  |
| Duration HF >= 6 months vs <6 months | 1.11 (1.10-1.14), <0.001 | 1.17 (1.14-1.20), <0.001 | 1.09 (1.06-1.13), <0.001 | 1.05 (1.01-1.08), 0.005 | <0.001 |
| Previous hospitalizations (within 1 year) | 1.20 (1.17-1.23), <0.001 | 1.13 (1.10-1.16), <0.001 | 1.29 (1.24-1.34), <0.001 | 1.32 (1.27-1.37), <0.001 | <0.001 |
| HFmrEF vs HFrEF | 1.01 (0.99-1.03), 0.366 |  |  |  |  |
| HFpEF vs HFrEF | 1.05 (1.02-1.07), <0.001 |  |  |  |  |
| NYHA class III/IV vs I/II | 1.22 (1.20-1.24), <0.001 | 1.23 (1.20-1.26), <0.001 | 1.25 (1.21-1.29), <0.001 | 1.18 (1.13-1.23), <0.001 | 0.0891 |
| MAP >90 vs <= 90 mmHg | 0.91 (0.89-0.92), <0.001 | 0.90 (0.88-0.92), <0.001 | 0.93 (0.90-0.96), <0.001 | 0.91 (0.88-0.93), <0.001 | 0.4065 |
| HR >70 vs <=70 beats/min | 1.04 (1.03-1.06), <0.001 | 1.02 (1.00-1.04), 0.069 | 1.07 (1.04-1.11), <0.001 | 1.06 (1.03-1.10), <0.001 | 0.0197 |
| **Laboratory** | | | | |  |
| Hypokalemia vs normokalemia | 1.10 (1.05-1.14), <0.001 | 1.09 (1.03-1.16), 0.006 | 1.13 (1.05-1.22), 0.002 | 1.08 (1.01-1.16), 0.034 | 0.7853 |
| Hyperkalemia vs normokalemia | 1.09 (1.04-1.15), 0.001 | 1.09 (1.02-1.16), 0.012 | 1.06 (0.96-1.18), 0.243 | 1.14 (1.02-1.27), 0.025 |  |
| NT-proBNP (>= median vs < median) | 1.14 (1.12-1.16), <0.001 | 1.10 (1.08-1.13), <0.001 | 1.19 (1.15-1.24), <0.001 | 1.16 (1.12-1.20), <0.001 | 0.0030 |
| **Treatments** | | | | |  |
| ACE-i/ARB/ARNI | 0.87 (0.85-0.89), <0.001 | 0.85 (0.82-0.88), <0.001 | 0.85 (0.82-0.89), <0.001 | 0.91 (0.87-0.94), <0.001 | 0.0190 |
| Beta-blockers | 0.90 (0.88-0.92), <0.001 | 0.87 (0.84-0.90), <0.001 | 0.87 (0.83-0.92), <0.001 | 0.95 (0.92-0.99), 0.020 | 0.0011 |
| MRA | 0.96 (0.94-0.97), <0.001 | 0.94 (0.92-0.96), <0.001 | 0.98 (0.94-1.01), 0.216 | 0.97 (0.94-1.00), 0.079 | 0.1420 |
| Diuretics | 1.13 (1.10-1.15), <0.001 | 1.07 (1.05-1.10), <0.001 | 1.23 (1.18-1.27), <0.001 | 1.18 (1.13-1.23), <0.001 | <0.001 |
| Digoxin | 0.94 (0.92-0.96), <0.001 | 0.93 (0.90-0.96), <0.001 | 0.92 (0.87-0.96), 0.001 | 0.97 (0.93-1.02), 0.229 | 0.1566 |
| Antiplatelet therapy | 1.02 (1.00-1.04), 0.101 | 1.04 (1.01-1.07), 0.002 | 0.97 (0.94-1.01), 0.110 | * 1. (0.98-1.05), 0.587 | 0.0022 |
| Anticoagulant therapy | 0.96 (0.94-0.98), 0.001 | 0.97 (0.94-1.00), 0.021 | 0.97 (0.94-1.01), 0.156 | 0.93 (0.90-0.97), <0.001 | 0.0835 |
| Statins | 0.94 (0.92-0.96), <0.001 | 0.98 (0.95-1.00), 0.046 | 0.90 (0.87-0.93), <0.001 | 0.90 (0.87-0.93), <0.001 | <0.001 |
| Nitrates | 1.13 (1.10-1.15), <0.001 | 1.13 (1.10-1.17), <0.001 | 1.19 (1.14-1.24), <0.001 | 1.07 (1.03-1.12), 0.002 | 0.0031 |
| CRT/ICD | 1.08 (1.05-1.12), <0.001 | 1.11 (1.07-1.16), <0.001 | 1.01 (0.92-1.11), 0.783 | 0.89 (0.77-1.02), 0.088 | 0.0022 |
| **Comorbidities** |  |  |  |  |  |
| Obesity | 0.96 (0.94-0.98), <0.001 | 0.95 (0.93-0.98), 0.001 | 0.96 (0.92-0.99), 0.020 | 0.97 (0.94-1.01), 0.117 | 0.5751 |
| Hypertension | 1.06 (1.04-1.08), <0.001 | 1.07 (1.05-1.09), <0.001 | 1.09 (1.06-1.13), <0.001 | 1.00 (0.96-1.03), 0.834 | 0.0006 |
| Diabetes | 1.17 (1.15-1.20), <0.001 | 1.18 (1.15-1.21), <0.001 | 1.21 (1.17-1.26), <0.001 | 1.13 (1.09-1.17), <0.001 | 0.0142 |
| CAD | 1.14 (1.12-1.16), <0.001 | 1.20 (1.17-1.23), <0.001 | 1.09 (1.05-1.12), <0.001 | 1.09 (1.05-1.12), <0.001 | <0.001 |
| Atrial fibrillation | 1.13 (1.10-1.15), <0.001 | 1.13 (1.10-1.16), <0.001 | 1.17 (1.13-1.21), <0.001 | 1.09 (1.05-1.13), <0.001 | 0.0121 |
| Valvular heart disease | 1.13 (1.11-1.15), <0.001 | 1.12 (1.10-1.15), <0.001 | 1.14 (1.10-1.18), <0.001 | 1.12 (1.09-1.16), <0.001 | 0.7057 |
| CKD | 1.14 (1.12-1.16), 0.001 | 1.15 (1.12-1.18), <0.001 | 1.17 (1.13-1.21), <0.001 | 1.12 (1.08-1.15), <0.001 | 0.1330 |
| Anaemia | 1.22 (1.20-1.24), <0.001 | 1.22 (1.20-1.25), <0.001 | 1.25 (1.21-1.30), <0.001 | 1.18 (1.14-1.22), <0.001 | 0.0265 |
| COPD | 1.26 (1.23-1.29), <0.001 | 1.23 (1.19-1.27), <0.001 | 1.30 (1.23-1.36), <0.001 | 1.28 (1.23-1.33), <0.001 | 0.1002 |
| Liver disease | 1.23 (1.17-1.29), <0.001 | 1.18 (1.1-1.27), 0.002 | 1.40 (1.25-1.57), <0.001 | 1.21 (1.10-1.34), <0.001 | 0.0466 |
| PAD | 1.19 (1.16-1.23), <0.001 | 1.24 (1.19-1.28), <0.001 | 1.24 (1.17-1.30), <0.001 | 1.08 (1.03-1.14), 0.003 | <0.001 |
| Stroke/TIA | 1.13 (1.10-1.15), <0.001 | 1.13 (1.09-1.16), <0.001 | 1.17 (1.12-1.22), <0.001 | 1.08 (1.04-1.13); <0.001 | 0.0322 |
| Depression | 1.22 (1.17-1.27), <0.001 | 1.21 (1.15-1.28), <0.001 | 1.25 (1.15-1.36); <0.001 | 1.21 (1.12-1.30), <0.001 | 0.8310 |
| Dementia | 1.02 (0.96-1.09), 0.494 | 1.03 (0.94-1.12), 0.517 | 0.98 (0.86-1.12), 0.801 | 1.03 (0.93-1.15), 0.528 | 0.8168 |
| Cancer (<3years) | 1.18 (1.16-1.21), <0.001 | 1.20 (1.17-1.24); <0.001 | 1.23 (1.17-1.29), <0.001 | 1.12 (1.07-1.16)<0.001 | 0.0045 |
| MuscoloSkeletal disease | 1.20 (1.18-1.22), <0.001 | 1.22 (1.20-1.25), <0.001 | 1.19 (1.15-1.23), <0.001 | 1.16 (1.13-1.20), <0.001 | 0.0269 |
| Dysthyroidism | 1.08 (1.05-1.11), <0.001 | 1.11 (1.06-1.15), <0.001 | 1.05 (0.99-1.11), 0.126 | 1.07 (1.02-1.12), 0.009 | 0.2871 |

**Supplementary Table 30: Adjusted HR for CV hospitalization and interaction by EF categories**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-interaction** |
| **Variable** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** |  |
| **Demographics and organisational/socioeconomics** | | | | |  |
| Sex (male vs female) | 1.08 (1.06-1.10), <0.001 | 1.13 (1.10-1.16), <0.001 | 1.06 (1.01-1.10), 0.008 | 1.01 (0.97-1.05), 0.615 | <0.001 |
| Age (>= 75 vs < 75) | 1.07 (1.05-1.10), <0.001 | 1.05 (1.03-1.08), <0.001 | 1.15 (1.10-1.20), <0.001 | 1.06 (1.02-1.11), 0.008 | 0.0013 |
| Smoking | 1.00 (0.96-1.03), 0.948 | 0.99 (0.95-1.04), 0.712 | 0.97 (0.90-1.05), 0.497 | 1.06 (0.98-1.14), 0.134 | 0.2470 |
| In-patient vs out-patient | 1.20 (1.17-1.24), <0.001 | 1.16 (1.13-1.20), <0.001 | 1.27 (1.22-1.33), <0.001 | 1.27 (1.22-1.33), <0.001 | <0.001 |
| Follow-up (hospital vs primary care/other) | 1.06 (1.04-1.09), <0.001 | 1.06 (1.03-1.09), <0.001 | 1.02 (0.98-1.07), 0.276 | 1.10 (1.06-1.15), <0.001 | 0.0256 |
| Family type (living alone vs cohabiting) | 1.02 (1.00-1.04), 0.020 | 1.00 (0.98-1.03), 0.858 | 1.03 (0.99-1.07), 0.186 | 1.07 (1.03-1.11), 0.001 | 0.0183 |
| Secondary school vs compulsory | 1.01 (0.99-1.03), 0.317 | 1.03 (1.00-1.06), 0.032 | 0.98 (0.94-1.02), 0.381 | 0.99 (0.95-1.03), 0.607 | 0.2954 |
| University vs compulsory | 0.98 (0.95-1.01), 0.150 | 0.99 (0.95-1.03), 0.547 | 0.96 (0.91-1.02), 0.162 | 0.98 (0.93-1.04), 0.461 |  |
| Index year <2014 vs >= 2014 | 0.83 (0.81-0.84), <0.001 | 0.83 (0.81-0.86), <0.001 | 0.81 (0.78-0.84), <0.001 | 0.80 (0.77-0.83), <0.001 | 0.1614 |
| Income categories >=median vs < median | 0.95 (0.93-0.97), <0.001 | 0.96 (0.94-0.99), 0.006 | 0.92 (0.88-0.95), <0.001 | 0.96 (0.92-1.00), 0.051 | 0.0756 |
| **Clinical variables** | | | | |  |
| Duration HF >= 6 months vs <6 months | 1.17 (1.15-1.19), <0.001 | 1.24 (1.21-1.27), <0.001 | 1.15 (1.11-1.20), <0.001 | 1.05 (1.01-1.10), 0.007 | <0.001 |
| Previous hospitalizations (within 1 year) | 1.28 (1.24-1.32), <0.001 | 1.20 (1.16-1.23), <0.001 | 1.42 (1.35-1.48), <0.001 | 1.43 (1.36-1.50), <0.001 | <0.001 |
| HFmrEF vs HFrEF | 0.93 (0.91-0.95), <0.001 |  |  |  |  |
| HFpEF vs HFrEF | 0.94 (0.92-0.96), <0.001 |  |  |  |  |
| NYHA class III/IV vs I/II | 1.24 (1.21-1.26), <0.001 | 1.24 (1.21-1.28), <0.001 | 1.28 (1.23-1.34), <0.001 | 1.18 (1.13-1.24), <0.001 | 0.0046 |
| MAP >90 vs <= 90 mmHg | 0.89 (0.88-0.91), <0.001 | 0.88 (0.86-0.90), <0.001 | 0.93 (0.89-0.96), <0.001 | 0.91 (0.87-0.94), <0.001 | 0.0410 |
| HR >70 vs <=70 beats/min | 1.02 (1.00-1.04), 0.019 | 1.03 (1.00-1.06), 0.023 | 1.04 (1.00-1.09), 0.046 | 0.99 (0.95-1.03), 0.586 | 0.1325 |
| **Laboratory** | | | | |  |
| Hypokalemia vs normokalemia | 1.08 (1.03-1.13), 0.002 | 1.09 (1.01-1.17), 0.018 | 1.08 (0.98-1.19), 0.1002 | 1.07 (0.97-1.16), 0.162 | 0.9337 |
| Hyperkalemia vs normokalemia | 1.08 (1.02-1.15), 0.010 | 1.07 (0.99-1.15), 0.112 | 1.08 (0.95-1.22), 0.244 | 1.14 (0.99-1.30), 0.060 |  |
| NT-proBNP (>= median vs < median) | 1.19 (1.16-1.22), <0.001 | 1.14 (1.11-1.18), <0.001 | 1.25 (1.19-1.31), <0.001 | 1.22 (1.16-1.28), <0.001 | 0.0031 |
| **Treatments** | | | | |  |
| ACE-i/ARB/ARNI | 0.89 (0.87-0.91), <0.001 | 0.86 (0.82-0.90), <0.001 | 0.85 (0.81-0.90), <0.001 | 0.94 (0.91-0.98), 0.007 | 0.0015 |
| Beta-blockers | 0.90 (0.88-0.93), <0.001 | 0.85 (0.81-0.88), <0.001 | 0.90 (0.85-0.95), <0.001 | 0.98 (0.93-1.03), 0.368 | 0.0001 |
| MRA | 0.99 (0.97-1.01), 0.487 | 0.99 (0.96-1.01), 0.387 | 1.01 (0.96-1.05), 0.764 | 0.99 (0.95-1.03), 0.712 | 0.7792 |
| Diuretics | 1.19 (1.16-1.22), <0.001 | 1.12 (1.08-1.16), <0.001 | 1.34 (1.28-1.41),<0.001 | 1.21 (1.14-1.28), <0.001 | <0.0001 |
| Digoxin | 0.97 (0.94-1.00), 0.023 | 0.94 (0.91-0.98), 0.001 | 0.97 (0.91-1.03), 0.281 | 1.03 (0.98-1.09), 0.276 | 0.0217 |
| Antiplatelet therapy | 1.05 (1.03-1.08), <0.001 | 1.08 (1.05-1.11), <0.001 | 1.01 (0.96-1.05), 0.706 | 1.03 (0.99-1.07), 0.176 | 0.0064 |
| Anticoagulant therapy | 0.99 (0.96-1.02), 0.470 | 0.99 (0.96-1.02), 0.454 | 1.02 (0.98-1.07), 0.363 | 0.98 (0.94-1.02), 0.246 | 0.2236 |
| Statins | 0.96 (0.94-0.98), 0.001 | 1.02 (0.99-1.04), 0.248 | 0.92 (0.89-0.96), <0.001 | 0.89 (0.86-0.93), <0.001 | <0.001 |
| Nitrates | 1.21 (1.18-1.25), <0.001 | 1.20 (1.16-1.25), <0.001 | 1.32 (1.25-1.39), <0.001 | 1.15 (1.10-1.21), <0.001 | 0.0005 |
| CRT/ICD | 1.16 (1.12-1.21), <0.001 | 1.19 (1.14-1.24), <0.001 | 1.12 (1.00-1.25), 0.053 | 0.98 (0.83-1.15), 0.767 | 0.0550 |
| **Comorbidities** |  |  |  |  |  |
| Obesity | 0.96 (0.94-0.99), 0.001 | 0.95 (0.93-0.98), 0.002 | 0.96 (0.92-1.01), 0.095 | 0.99 (0.95-1.03), 0.511 | 0.4001 |
| Hypertension | 1.08 (1.06-1.10), <0.001 | 1.07 (1.04-1.10), <0.001 | 1.16 (1.11-1.21), <0.001 | 1.02 (0.98-1.07), 0.375 | 0.0003 |
| Diabetes | 1.17 (1.15-1.20), <0.001 | 1.18 (1.15-1.21), <0.001 | 1.24 (1.18-1.29), <0.001 | 1.10 (1.06-1.15), <0.001 | 0.0003 |
| CAD | 1.21 (1.18-1.23), <0.001 | 1.28 (1.24-1.32), <0.001 | 1.15 (1.10-1.20), <0.001 | 1.13 (1.07-1.16), <0.001 | <0.001 |
| Atrial fibrillation | 1.16 (1.14-1.19), <0.001 | 1.14 (1.10-1.17), <0.001 | 1.25 (1.20-1.31), <0.001 | 1.16 (1.12-1.22), <0.001 | 0.0006 |
| Valvular heart disease | 1.24 (1.21-1.26), <0.001 | 1.20 (1.16-1.23), <0.001 | 1.27 (1.22-1.33), <0.001 | 1.29 (1.24-1.34), <0.001 | 0.0016 |
| CKD | 1.18 (1.15-1.20), <0.001 | 1.17 (1.14-1.20), <0.001 | 1.21 (1.17-1.26), <0.001 | 1.16 (1.12-1.20), <0.001 | 0.2013 |
| Anaemia | 1.10 (1.08-1.12), <0.001 | 1.09 (1.06-1.12), <0.001 | 1.14 (1.10- 1.19), <0.001 | 1.07 (1.03-1.11), 0.001 | 0.0448 |
| COPD | 1.08 (1.05-1.10), <0.001 | 1.08 (1.04-1.12), <0.001 | 1.10 (1.04-1.16), 0.001 | 1.05 (1.00-1.10), 0.054 | 0.4782 |
| Liver disease | 1.22 (1.15-1.30), <0.001 | 1.17 (1.08-1.27), <0.001 | 1.37 (1.19-1.56), <0.001 | 1.24 (1.10-1.40), <0.001 | 0.1539 |
| PAD | 1.24 (1.21-1.28), <0.001 | 1.27 (1.22-1.32), <0.001 | 1.30 (1.22-1.38), <0.001 | 1.14 (1.09-1.22), <0.001 | 0.0059 |
| Stroke/TIA | 1.10 (1.07-1.13), <0.001 | 1.11 (1.07-1.14), <0.001 | 1.13 (1.07-1.18),< 0.001 | 1.06 (1.01-1.11), 0.013 | 0.1767 |
| Depression | 1.06 (1.01-1.11), 0.023 | 1.07 (1.00-1.14), 0.041 | 1.05 (0.95-1.17), 0.358 | 1.03 (0.94-1.13), 0.529 | 0.8431 |
| Dementia | 0 .89 (0.80-0.94), <0.001 | 0.90 (0.81-1.00), 0.053 | 0.88 (0.74-1.04), 0.138 | 0.81 (0.70-0.93), 0.003 | 0.4750 |
| Cancer (<3years) | 1.03 (1.00-1.06), 0.056 | 1.02 (0.98-1.06), 0.323 | 1.08 (1.02-1.14), 0.012 | 1.00 (0.95-1.06), 0.927 | 0.1685 |
| MuscoloSkeletal disease | 1.09 (1.07-1.11), <0.001 | 1.10 (1.07-1.13), <0.001 | 1.08 (1.03-1.12), <0.001 | 1.08 (1.04-1.12), <0.001 | 0.7002 |
| Dysthyroidism | 1.06 (1.03-1.10), 0.001 | 1.09 (1.04-1.14), 0.001 | 1.02 (0.94-1.09); 0.678 | 1.06 (1.00-1.13), 0.043 | 0.2839 |

**Supplementary Table 31: Adjusted HR for HF hospitalization and interaction by EF categories**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-interaction** |
| **Variable** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** |  |
| **Demographics and organisational/socioeconomics** | | | | |  |
| Sex (male vs female) | 1.12 (1.09-1.15), <0.001 | 1.19 (1.15-1.24), <0.001 | 1.07 (1.02-1.13), 0.010 | 1.02 (0.97-1.07), 0.381 | <0.001 |
| Age (>= 75 vs < 75) | 1.15 (1.12-1.19), <0.001 | 1.05 (1.02-1.09), 0.002 | 1.39 (1.32-1.48), <0.001 | 1.28 (1.21-1.35), <0.001 | <0.001 |
| Smoking | 0.98 (0.93-1.02), 0.286 | 0.99 (0.94-1.05); 0.797 | 0.90 (0.81-1.00), 0.047 | 0.98 (0.89-1.09), 0.748 | 0.2123 |
| In-patient vs out-patient | 1.12 (1.08-1.15), <0.001 | 1.06 (1.03-1.10), 0.001 | 1.21 (1.14-1.28), <0.001 | 1.25 (1.18-1.32), <0.001 | <0.001 |
| Follow-up (hospital vs primary care/other) | 1.01 (0.98-1.04), 0.600 | 1.07 (1.04-1.11), <0.001 | 0.90 (0.86-0.95), <0.001 | 0.98 (0.93-1.03), 0.330 | <0.001 |
| Family type (living alone vs cohabiting) | 1.05 (1.03-1.08), <0.001 | 1.01 (0.98-1.04), 0.492 | 1.09 (1.03-1.14), 0.002 | 1.14 (1.09-1.20), <0.001 | 0.0001 |
| Secondary school vs compulsory | * 1. (0.98-1.03), 0.545 | 1.04 (1.01-1.08), 0.008 | 0.94 (0.89—1.00), 0.038 | 0.97 (0.92-1.03), 0.339 | 0.0032 |
| University vs compulsory | 0.96 (0.92-0.99), 0.013 | 0.99 (0.95-1.05), 0.698 | 0.87 (0.80-0.43), <0.001 | 0.95 (0.88-1.02), 0.180 |  |
| Index year <2014 vs >= 2014 | 0.85 (0.83-0.87), <0.001 | 0.85 (0.82-0.87), <0.001 | 0.84 (0.80-0.89), <0.001 | 0.88 (0.83-0.92), <0.001 | 0.5182 |
| Income categories >=median vs < median | 0.94 (0.92-0.96), <0.001 | 0.96 (0.93-0.99), 0.011 | 0.88 (0.83-0.93), <0.001 | 0.95 (0.90-0.99), 0.030 | 0.0160 |
| **Clinical variables** | | | | |  |
| Duration HF >= 6 months vs <6 months | 1.41 (1.38-1.45), <0.001 | 1.48 (1.44-1.53), <0.001 | 1.45 (1.37-1.53), <0.001 | 1.24 (1.18-1.30), <0.001 | <0.001 |
| Previous hospitalizations (within 1 year) | 1.58 (1.53-1.64), <0.001 | 1.41 (1.35-1.46); <0.001 | 1.85 (1.74-1.97), <0.001 | 1.96 (1.83-2.09), <0.001 | <0.001 |
| HFmrEF vs HFrEF | 0.84 (0.81-0.86), <0.001 |  |  |  |  |
| HFpEF vs HFrEF | 0.82 (0.79-0.85), <0.001 |  |  |  |  |
| NYHA class III/IV vs I/II | 1.31 (1.28-1.35), <0.001 | 1.30 (1.26-1.35), <0.001 | 1.39 (1.31-1.48); <0.001 | 1.28 (1.20-1.35), <0.001 | 0.0787 |
| MAP >90 vs <= 90 mmHg | 0.83 (0.81-0.85), <0.001 | 0.81 (0.78-0.83), <0.001 | 0.86 (0.81-0.90), <0.001 | 0.85 (0.81-0.89), <0.001 | 0.0786 |
| HR >70 vs <=70 beats/min | 1.07 (1.04-1.09), <0.001 | 1.05 (1.01-1.08), 0.004 | 1.11 (1.05-1.17), <0.001 | 1.08 (1.03-1.13), 0.003 | 0.1622 |
| **Laboratory** | | | | |  |
| Hypokalemia vs normokalemia | 1.09 (1.03-1.16), 0.004 | 1.05 (0.97-1.14), 0.232 | 1.15 (1.02-1.30), 0.018 | 1.12 (1.00-1.26), 0.047 | 0.2226 |
| Hyperkalemia vs normokalemia | 1.08 (1.02-1.16), 0.016 | 1.04 (0.95-1.14), 0.361 | 1.07 (0.91-1.26), 0.398 | 1.24 (1.06-1.45), 0.008 |  |
| NT-proBNP (>= median vs < median) | 1.28 (1.24-1.33), <0.001 | 1.18 (1.14-1.23), <0.001 | 1.42 (1.33-1.50), <0.001 | 1.41 (1.33-1.50); <0.001 | <0.001 |
| **Treatments** | | | | |  |
| ACE-i/ARB/ARNI | 0.94 (0.91-0.98), 0.003 | 0.92 (0.87-0.97), 0.001 | 0.89 (0.83-0.95), 0.001 | 1.01 (0.96-1.06), 0.747 | 0.0053 |
| Beta-blockers | 0.90 (0.87-0.93), <0.001 | 0. 84 (0.80-0.89), <0.001 | 0.89 (0.83-0.96); 0.003 | 0.97 (0.91-1.04), 0.402 | 0.0027 |
| MRA | 1.09 (1.07-1.12), <0.001 | 1.08 (1.04-1.11), <0.001 | 1.09 (1.04-1.15), 0.001 | 1.13 (1.08-1.19), <0.001 | 0.2040 |
| Diuretics | 1.48 (1.43-1.53), <0.001 | 1.31 (1.26-1.37), <0.001 | 1.85 (1.71-1.9), <0.001 | 1.78 (1.63-1.94), <0.001 | <0.001 |
| Digoxin | 0.93 (0.90-0.97), <0.001 | 0.88 (0.84-0.92), <0.001 | 0.93 (0.86-1.00), 0.045 | 1.07 (1.00-1.14); 0.049 | <0.001 |
| Antiplatelet therapy | 0.96 (0.93-0.99), 0.004 | 1.01 (0.97-1.04); 0.688 | 0.87 (0.83-0.92), <0.001 | 0.89 (0.84-0.94), <0.001 | <0.001 |
| Anticoagulant therapy | 1.00 (0.96-1.03), 0.861 | 0.95 (0.92-0.99), 0.013 | 1.05 (0.99-1.11); 0.078 | 1.07 (1.01-1.13), 0.012 | <0.001 |
| Statins | 0.95 (0.92-0.97), <0.001 | 1.03 (0.99-1.06), 0.106 | 0.85 (0.80-0.89), <0.001 | 0.86 (0.82-0.90), <0.001 | <0.001 |
| Nitrates | 1.13 (1.10-1.17), <0.001 | 1.12 (1.07-1.16); <0.001 | 1.22 (1.14-1.30), <0.001 | 1.10 (1.03-1.17), 0.003 | 0.0395 |
| CRT/ICD | 1.29 (1.23-1.35), <0.001 | 1.31 (1.24-1.37), <0.001 | 1.25 (1.09-1.43), 0.001 | 1.03 (0.83-1.27), 0.804 | 0.0819 |
| **Comorbidities** |  |  |  |  |  |
| Obesity | 1.04 (1.01-1.07), 0.005 | 1.02 (0.98-1.06), 0.291 | 1.04 (0.98-1.10), 0.163 | 1.08 (1.03-1.14), 0.002 | 0.1489 |
| Hypertension | 1.06 (1.03-1.08), <0.001 | 1.02 (0.99-1.05), 0.193 | 1.20 (1.13-1.27), <0.001 | 1.04 (0.99-1.11); 0.142 | <0.001 |
| Diabetes | 1.23 (1.20-1.26), <0.001 | 1.22 (1.18-1.26), <0.001 | 1.29 (1.22-1.36); <0.001 | 1.21 (1.15-1.28), <0.001 | 0.1931 |
| CAD | 1.16 (1.12-1.19), <0.001 | 1.23 (1.19-1.28), <0.001 | 1.09 (1.04-1.15), 0.001 | 1.05 (1.00-1.10), 0.045 | <0.001 |
| Atrial fibrillation | 1.11 (1.08-1.14), <0.001 | 1.01 (0.98-1.05), 0.462 | 1.31 (1.23-1.38), <0.001 | 1.27 (1.20-1.34), <0.001 | <0.001 |
| Valvular heart disease | 1.21 (1.18-1.24), <0.001 | 1.16 (1.12-1.20); <0.001 | 1.27 (1.21-1.34); <0.001 | 1.27 (1.21-1.34), <0.001 | 0.0006 |
| CKD | 1.28 (1.25-1.32), <0.001 | 1.22 (1.18-1.26), <0.001 | 1.42 (1.35-1.50); <0.001 | 1.35 (1.29-1.42), <0.001 | <0.001 |
| Anaemia | 1.17 (1.14-1.20), <0.001 | 1.12 (1.09-1.16), <0.001 | 1.28 (1.21- 1.35), <0.001 | 1.18 (1.13-1.24); <0.001 | 0.0001 |
| COPD | 1.13 (1.09-1.17), <0.001 | 1.09 (1.05-1.14), <0.001 | 1.18 (1.10-1.27), <0.001 | 1.16 (1.10-1.24); <0.001 | 0.0914 |
| Liver disease | 1.28 (1.19-1.38), <0.001 | 1.28 (1.17-1.41), <0.001 | 1.39 (1.17-1.64), <0.001 | 1.22 (1.05-1.41), 0.033 | 0.5364 |
| PAD | 1.08 (1.04-1.12), 0.034 | 1.08 (1.03-1.13), 0.003 | 1.14 (1.06-1.24), 0.001 | 1.03 (0.95-1.11), 0.445 | 0.1788 |
| Stroke/TIA | 1.04 (1.01-1.07), 0.006 | 1.04 (1.00-1.08), 0.974 | 1.08 (1.01-1.15); 0.017 | 1.02 (0.96-1.08), 0.610 | 0.3543 |
| Depression | 1.09 (1.03-1.15), 0.005 | 1.12 (1.04-1.21), 0.003 | 1.00 (0.87-1.15), 0.990 | 1.08 (0.96-1.21); 0.220 | 0.3498 |
| Dementia | 0.85 (0.78-0.94), 0.001 | 0.84 (0.73-0.95), 0.008 | 0.86 (0.69-1.07); 0.184 | 0.88 (0.74-1.05), 0.170 | 0.8844 |
| Cancer (<3years) | 1.04 (1.01-1.08), 0.014 | 1.03 (0.98-1.08), 0.222 | 1.12 (1.04-1.21), 0.002 | 1.01 (0.95-1.08); 0.680 | 0.0870 |
| MuscoloSkeletal disease | 1.08 (1.06-1.11), <0.001 | 1.08 (1.04-1.12); <0.001 | 1.08 (1.03-1.14), 0.003 | 1.08 (1.03-1.14); 0.001 | 0.9996 |
| Dysthyroidism | 1.05 (1.01-1.09), 0.028 | 1.04 (0.98-1.10); 0.215 | 0.98 (0.89-1.08), 0.707 | 1.11 (1.03-1.19), 0.006 | 0.1175 |

**Supplementary Table 32: Adjusted HR for non-CV hospitalization and interaction by EF categories**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **HFrEF** | **HFmrEF** | **HFpEF** | **p-interaction** |
| **Variable** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** | **HR (95%CI), p-value** |  |
| **Demographics and organisational/socioeconomics** | | | | |  |
| Sex (male vs female) | 1.01 (0.99-1.03), 0.171 | 1.00 (0.97-1.02), 0.735 | 1.02 (0.98-1.06), 0.323 | 1.04 (1.00-1.07), 0.044 | 0.1645 |
| Age (>= 75 vs < 75) | 1.23 (1.21-1.26), <0.001 | 1.29 (1.25-1.33); <0.001 | 1.23 (1.18-1.28), <0.001 | 1.12 (1.08-1.16), <0.001 | <0.001 |
| Smoking | 1.06 (1.03-1.10), <0.001 | 1.06 (1.02-1.10); 0.004 | 1.04 (0.98-1.11), 0.207 | 1.09 (1.02-1.16), 0.013 | 0.6786 |
| In-patient vs out-patient | 1.10 (1.07-1.13), <0.001 | 1.05 (1.02-1.08), 0.001 | 1.15 (1.10-1.20), <0.001 | 1.17 (1.12-1.21), <0.001 | <0.001 |
| Follow-up (hospital vs primary care/other) | 0.93 (0.91-0.95), <0.001 | 0.91 (0.88-0.94); <0.001 | 0.93 (0.90-0.97); <0.001 | 0.94 (0.91-0.98), <0.001 | 0.3291 |
| Family type (living alone vs cohabiting) | * 1. 1.03-1.07), <0.001 | 1.06 (1.03-1.08), <0.001 | 1.04 (1.00-1.07), 0.052 | 1.03 (1.00-1.07), 0.057 | 0.4873 |
| Secondary school vs compulsory | 0.97 (0.95-0.99), 0.002 | 0.96 (0.94-0.99), 0.004 | 0.97 (0.94-1.01), 0.207 | 0.99 (0.95-1.03), 0.577 | 0.6588 |
| University vs compulsory | 0.93 (0.91-0.96), <0.001 | 0.92 (0.89-0.96); <0.001 | 0.93 (0.88-0.98), 0.006 | 0.96 (0.91-1.01); 0.109 |  |
| Index year <2014 vs >= 2014 | 0.91 (0.90-0.93), <0.001 | 0.92 (0.90-0.95), <0.001 | 0.92 (0.88-0.95), <0.001 | 0.95 (0.91-0.98), <0.001 | 0.3886 |
| Income categories >=median vs < median | 0 .94 (0.92-0.96), <0.001 | 0.92 (0.90-0.95), <0.001 | 0.96 (0.92-0.99), 0.022 | 0.96 (0.93-0.99), 0.021 | 0.1117 |
| **Clinical variables** | | | | |  |
| Duration HF >= 6 months vs <6 months | 1.13 (1.11-1.16), <0.001 | 1.17 (1.14-1.20), <0.001 | 1.06 (1.02-1.10), 0.001 | 1.05 (1.01-1.09),0.010 | <0.0001 |
| Previous hospitalizations (within 1 year) | 1.17 (1.13-1.20), <0.001 | 1.09 (1.06-1.13), <0.001 | 1.24 (1.19-1.29); <0.001 | 1.27 (1.21-1.32), <0.001 | <0.001 |
| HFmrEF vs HFrEF | 1.13 (1.11-1.16), <0.001 |  |  |  |  |
| HFpEF vs HFrEF | 1.21 (1.18-1.24), <0.001 |  |  |  |  |
| NYHA class III/IV vs I/II | 1.18 (1.15-1.21), <0.001 | 1.18 (1.14-1.21); <0.001 | 1.20 (1.15-1.25), <0.001 | 1.16 (1.11-1.21), <0.001 | 0.5774 |
| MAP >90 vs <= 90 mmHg | 0.95 (0.93-0.96), <0.001 | 0.95 (0.93-0.98), <0.001 | 0.94 (0.91-0.98), 0.001 | 0.94 (0.91-0.97), <0.001 | 0.7101 |
| HR >70 vs <=70 beats/min | 1.03 (1.01-1.05), <0.001 | 0.98 (0.96-1.01); 0.153 | 1.09 (1.05-1.13), <0.001 | 1.08 (1.04-1.12), <0.001 | <0.001 |
| **Laboratory** | | | | |  |
| Hypokalemia vs normokalemia | 1.10 (1.06-1.15), <0.001 | 1.07 (1.00-1.15); 0.042 | 1.15 (1.05-1.27), 0.003 | 1.11 (1.02-1.20), 0.011 | 0.7993 |
| Hyperkalemia vs normokalemia | 1.09 (1.03-1.15), 0.003 | 1.09 (1.01-1.17), 0.022 | 1.07 (0.96-1.20), 0.224 | 1.09 (0.96-1.23); 0.169 |  |
| NT-proBNP (>= median vs < median) | 1.10 (1.07-1.13), <0.001 | 1.07 (1.04-1.10), <0.001 | 1.15 (1.10-1.20); <0.001 | 1.11 (1.06-1.16); <0.001 | 0.0097 |
| **Treatments** | | | | |  |
| ACE-i/ARB/ARNI | 0.88 (0.86-0.90), <0.001 | 0.85 (0.81-0.88) <0.001 | 0.87 (0.83-0.91); <0.001 | 0.91 (0.88-0.95); <0.001 | 0.0345 |
| Beta-blockers | 0.91 (0.88-0.93), <0.001 | 0.89 (0.85-0.93), <0.001 | 0.86 (0.82-0.91), <0.001 | 0.95 (0.91-1.00); 0.032 | 0.0079 |
| MRA | 0.96 (0.95-0.98), <0.001 | 0.93 (0.90-0.95); <0.001 | 0.98 (0.94-1.02); 0.405 | 1.03 (0.99-1.07), 0.118 | <0.0001 |
| Diuretics | 1.12 (1.09-1.15), <0.001 | 1.07 (1.04-1.10), <0.001 | 1.19 (1.14-1.24); <0.001 | 1.17 (1.12-1.23), <0.001 | <0.0001 |
| Digoxin | 0.94 (0.91-0.96), <0.001 | 0.95 (0.91-0.98), 0.003 | 0.91(0.86-0.96), 0.001 | 0.95 (0.90-1.00), 0.037 | 0.3862 |
| Antiplatelet therapy | 0.98 (0.96-1.01), 0.220 | 1.01 (0.98-1.04), 0.702 | 0.94(0.90-0.98), 0.002 | 0.98 (0.95-1.02), 0.416 | 0.0078 |
| Anticoagulant therapy | 0.93 (0.91-0.96), <0.001 | 0.94 (0.91-0.97), <0.001 | 0.93 (0.89-0.97), 0.001 | 0.92 (0.89-0.96); <0.001 | 0.6709 |
| Statins | 0.91 (0.89-0.93), <0.001 | 0.92 (0.90-0.95), <0.001 | 0.88 (0.85-0.92), <0.001 | 0.91 (0.88-0.95), <0.001 | 0.1217 |
| Nitrates | 1.06 (1.04-1.09), <0.001 | 1.08 (1.04-1.12); <0.001 | 1.06 (1.00-1.12); 0.016 | 1.03 (0.98-1.08), 0.19 | 0.2369 |
| CRT/ICD | 1.00 (0.96-1.04), 0.918 | 1.02 (0.97-1.07), 0.473 | 0.97 (0.87-1.08), 0.539 | 0.86 (0.73-1.00), 0.055 | 0.1000 |
| **Comorbidities** |  |  |  |  |  |
| Obesity | 0.96 (0.94-0.98), 0.001 | 0.95 (0.92-0.989); 0.002 | 0.96 (0.92-1.00), 0.058 | 0.98 (0.94-1.01); 0.203 | 0.5915 |
| Hypertension | 1.06 (1.04-1.08), <0.001 | 1.08 (1.05-1.11), <0.001 | 1.07 (1.03-1.12), 0.001 | 0.99 (0.95-1.03); 0.778 | 0.0030 |
| Diabetes | 1.21 (1.19-1.24), <0.001 | 1.24 (1.20-1.27); <0.001 | 1.21 (1.16-1.26); <0.001 | 1.18 (1.13-1.22); <0.001 | 0.1008 |
| CAD | 1.10 (1.07-1.12), <0.001 | 1.14 (1.11-1.17); <0.001 | 1.04 (1.00-1.08), 0.060 | * 1. (1.04-1.12), <0.001 | 0.0001 |
| Atrial fibrillation | 1.12 (1.09-1.14), <0.001 | 1.15 (1.11-1.18); <0.001 | 1.12 (1.07-1.16), <0.001 | 1.05 (1.01-1.09), 0.011 | 0.0004 |
| Valvular heart disease | 1.01 (0.99-1.03), 0.188 | 1.03 (1.00-1.06), 0.055 | 1.04 (1.00-1.08), 0.063 | 0. 97 (0.94-1.01), 0.125 | 0.0208 |
| CKD | 1.13 (1.11-1.15), <0.001 | 1.15 (1.12-1.18); <0.001 | 1.14 (1.10-1.18), <0.001 | 1.09(1.05-1.12); <0.001 | 0.0271 |
| Anaemia | 1.33 (1.30-1.35), <0.001 | 1.35 (1.31-1.38); <0.001 | 1.35 (1.30-1.40); <0.001 | 1.28 (1.23-1.32); <0.001 | 0.0301 |
| COPD | 1.47 (1.44-1.51), <0.001 | 1.46 (1.41-1.51); <0.001 | 1.48 (1.41-1.56); <0.001 | 1.49 (1.42-1.56); <0.001 | 0.7855 |
| Liver disease | 1.33 (1.26-1.41),<0.001 | 1.28 (1.18-1.39), <0.001 | 1.45(1.28-1.64); <0.001 | 1.34 (1.20-1.49); <0.001 | 0.2844 |
| PAD | 1.18 (1.14-1.21), <0.001 | 1.23 (1.18-1.29); <0.001 | 1.17 (1.10-1.24), <0.001 | 1.08 (1.02-1.15), 0.005 | 0.0013 |
| Stroke/TIA | 1.16 (1.13-1.19), <0.001 | 1.17 (1.13-1.21), <0.001 | 1.19 (1.13-1.24); <0.001 | 1.12(1.08-1.17); <0.0011 | 0.1996 |
| Depression | 1.32 (1.27-1.38), <0.001 | 1.34 (1.26-1.42); <0.001 | 1.34 (1.23-1.47); <0.001 | 1.28 (1.18-1.39); <0.001 | 0.6456 |
| Dementia | 1.13 (1.06-1.21), <0.001 | 1.14 (1.03-1.26); 0.013 | 1.04 (0.90-1.21), 0.594 | 1.19 (1.06-1.34); 0.003 | 0.3559 |
| Cancer (<3years) | 1.32 (1.29-1.35), <0.001 | 1.36 (1.31-1.41); <0.001 | 1.35 (1.28-1.42); <0.001 | 1.22 (1.17—1.28); <0.001 | 0.0012 |
| MuscoloSkeletal disease | 1.32 (1.30-1.35), <0.001 | 1.38 (1.35-1.42); <0.001 | 1.31 (1.26-1.36); <0.001 | 1.24 (1.20-1.29); <0.001 | <0.001 |
| Dysthyroidism | 1.10 (1.07-1.14), <0.001 | 1.13 (1.08-1.19), <0.001 | 1.06 (0.99-1.13); 0.088 | 1.10 (1.04-1.16); 0.001 | 0.2909 |

**Supplemental Table 33: Outcome according to the number of comorbidities**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **No Comorbidities** | **1 to 3 Comorbidities** | **4 to 6 Comorbidities** | **>6 Comorbidities** | **p-interaction** |
| **All-cause mortality** |  |  |  |  |  |
| Event rate/100pts/y (95%CI) | 2.54 (2.18-2.97) | 6.62 (6.48-6.77) | 15.97 (15.75-16.19) | 27.16 (26.58-27.75) |  |
| Crude HR (95% CI), p-value | ref | 2.59 (2.22-3.03), <0.001 | 6.20 (5.31-7.22), <0.001 | 10.40 (8.91-12.14), <0.001 |  |
| Adjusted HR (95% CI), p-value | ref | 1.99 (1.71-2.33), <0.001 | 3.25 (2.78-3.79), <0.001 | 4.41 (3.77-5.16), <0.001 | <0.001 |
| HFrEF | ref | 2.02 (1.69-2.41), <0.001 | 3.47 (2.91-4.15), <0.001 | 4.97 (4.15-5.95), <0.001 |  |
| HFmrEF | ref | 1.57 (1.06-2.34), 0.025 | 2.54 (1.71-3.78), <0.001 | 3.50 (2.35-5.21), <0.001 |  |
| HFpEF | ref | 1.97 (1.16-3.35), 0.012 | 2.75 (1.62-4.65), <0.001 | 3.48 (2.05-5.90), <0.001 |  |
| **CV mortality** |  |  |  |  |  |
| Event rate/100pts/y (95%CI) | 1.49 (1.22-1.82) | 3.91 (3.80-4.02) | 9.82 (9.64-9.99) | 16.26 (15.81-16.72) |  |
| Crude HR (95% CI), p-value | ref | 2.61 (2.13-3.19), <0.001 | 6.45 (5.28-7.89), <0.001 | 10.48 (8.56-12.82), <0.001 |  |
| Adjusted HR (95% CI), p-value | Ref | 1.80 (1.47-2.02), <0.001 | 2.81 (2.30-3.45), <0.001 | 3.62 (2.95-4.44), <0.001 | <0.001 |
| HFrEF | Ref | 1.75 (1.40-2.19), <0.001 | 2.86 (2.29-3.58), <0.001 | 3.83 (3.05-4.80), <0.001 |  |
| HFmrEF | Ref | 1.51 (0.86-2.69), 0.155 | 2.37 (1.34-4.19), 0.003 | 3.13 (1.77-5.54), <0.001 |  |
| HFpEF | Ref | 2.51 (1.04-6.05), 0.040 | 3.40 (1.41-8.20), 0.006 | 4.08 (1.69-9.83), 0.002 |  |
| **Non CV mortality** |  |  |  |  |  |
| Event rate/100pts/y (95%CI) | 1.06 (0.83-1.34) | 2.71 (2.62-2.81) | 6.15 (6.02-6.29) | 10.90 (10.54-11.28) |  |
| Crude HR (95% CI), p-value | Ref | 2.57 (2.02-3.27), <0.001 | 5.83 (4.59-7.40), <0.001 | 10.31 (8.11-13.11), <0.001 |  |
| Adjusted HR (95% CI), p-value | Ref | 2.30 (1.80-2.92), <0.001 | 3.96 (3.11-5.05), <0.001 | 5.88 (4.50-7.50), <0.001 | <0.001 |
| HFrEF | Ref | 2.46 (1.83-3.30), <0.001 | 4.52 (3.37-6.06), <0.001 | 7.29 (5.41-9.81), <0.001 |  |
| HFmrEF | Ref | 1.74 (1.01-3.02), 0.048 | 3.01 (1.73-5.20), <0.001 | 4.42 (2.55-7.67), <0.001 |  |
| HFpEF | Ref | 1.80 (0.93-3.49), 0.079 | 2.66 (1.38-5.14), 0.003 | 3.66 (1.89-7.07), <0.001 |  |
| **Any hospitalization** |  |  |  |  |  |
| Event rate/100pts/y (95%CI) | 21.10 (19.73-22.57) | 34.13 (33.68-34.58) | 66.96 (65.96-67.37) | 119.85 (117.65-122.09) |  |
| Crude HR (95% CI), p-value | Ref | 1.52 (1.42-1.63), <0.001 | 2.59 (2.42-2.77), <0.001 | 3.97 (3.70-4.26), <0.001 |  |
| Adjusted HR (95% CI), p-value | Ref | 1.43 (1.33-1.53), <0.001 | 2.04 (1.90-2.19), <0.001 | 2.74 (2.55-2.95), <0.001 | <0.001 |
| HFrEF | Ref | 1.33 (1.23-1.44), <0.001 | 1.93 (1.79-2.09), <0.001 | 2.63 (2.42-2.86), <0.001 |  |
| HFmrEF | Ref | 1.72 (1.42-2.08), <0.001 | 2.50 (2.07-3.03), <0.001 | 3.41 (2.81-4.14), <0.001 |  |
| HFpEF | Ref | 2.01 (1.52-2.64), <0.001 | 2.68 (2.04-3.53), <0.001 | 3.50 (2.66-4.61), <0.001 |  |
| **CV hospitalization** |  |  |  |  |  |
| Event rate/100pts/y (95%CI) | 11.74 (10.80-12.75) | 17.49 (17.20-17.77) | 32.46 (32.06-32.87) | 54.86 (53.72-56.04) |  |
| Crude HR (95% CI), p-value | Ref | 1.43 (1.32-1.56), <0.001 | 2.40 (2.20-2.60), <0.001 | 3.57 (3.28-3.89), <0.001 |  |
| Adjusted HR (95% CI), p-value | Ref | 1.29 (1.19-1.41), <0.001 | 1.76 (1.62-1.92), <0.001 | 2.26 (2.07-2.47), <0.001 | <0.001 |
| HFrEF | Ref | 1.19 (1.09-1.31), <0.001 | 1.64 (1.49-1.79), <0.001 | 2.10 (1.91-2.32), <0.001 |  |
| HFmrEF | Ref | 1.74 (1.34-2.27)(, <0.001 | 2.45 (1.88-3.19), <0.001 | 3.28 (2.51-4.29), <0.001 |  |
| HFpEF | Ref | 2.12 (1.44-3.13), <0.001 | 2.69 (1.83-3.96), <0.001 | 3.36 (2.28-4.95), <0.001 |  |
| **HF hospitalization** |  |  |  |  |  |
| Event rate/100pts/y (95%CI) | 8.04 (7.31-8.86) | 8.07 (7.89-8.24) | 16.70 (16.44-16.96) | 29.96 (29.22-30.71) |  |
| Crude HR (95% CI), p-value | Ref | 0.99 (0.90-1.10), 0.919 | 1.89 (1.71-2.08), <0.001 | 3.02 (2.74-3.34), <0.001 |  |
| Adjusted HR (95% CI), p-value | Ref | 0.89 (0.81-0.98), 0.023 | 1.27 (1.15-1.40), <0.001 | 1.68 (1.52-1.87), <0.001 | <0.001 |
| HFrEF | Ref | 0.84 (0.76-0.94), 0.002 | 1.17 (1.05-1.30), 0.005 | 1.51 (1.35-1.69), <0.001 |  |
| HFmrEF | Ref | 1.24 (0.86-1.79), 0.255 | 1.96 (1.36-2.83), <0.001 | 2.73 (1.89-3.95), <0.001 |  |
| HFpEF | Ref | 1.92 (1.06-3.48), 0.032 | 2.77 (1.53-5.02), 0.001 | 3.67 (2.03-6.65), <0.001 |  |
| **Non CV hospitalization** |  |  |  |  |  |
| Event rate/100pts/y (95%CI) | 10.39 (9.55-11.31) | 18.46 (18.18-18.75) | 36.56(36.12-37.00) | 64.41 (63.10-65.74) |  |
| Crude HR (95% CI), p-value | Ref | 1.72 (1.58-1.87), <0.001 | 3.17 (2.91-3.45), <0.001 | 5.10 (4.68-5.57), <0.001 |  |
| Adjusted HR (95% CI), p-value | Ref | 1.61 (1.48-1.76), <0.001 | 2.50 (2.29-2.73), <0.001 | 3.58 (3.27-3.92), <0.001 | 0.0002 |
| HFrEF | Ref | 1.57 (1.42-1.74), <0.001 | 2.50 (2.26-2.77), <0.001 | 3.66 (3.29-4.06), <0.001 |  |
| HFmrEF | Ref | 1.70 (1.36-2.11), <0.001 | 2.62 (2.10-3.25), <0.001 | 3.77 (3.02-4.71), <0.001 |  |
| HFpEF | Ref | 1.69 (1.26-2.27), <0.001 | 2.43 (1.81-3.27), <0.001 | 3.41 (2.53-4.58), <0.001 |  |