**Supplementary Material**

**Data source**

Patients with HF were identified through the Swedish HF Registry (SwedeHF). SwedeHF has been previously described(1). Briefly, it is an ongoing voluntary health care quality registry founded in 2000 and implemented on a national basis in 2003. Written consent is not required, but patients are

informed of registration and allowed to opt-out. A majority of Swedish hospitals (~60 out of 75 hospitals) and to a minor extent also primary care centers enroll patients without financial compensation, and collect approximately 80 variables, i.e. data on demographics, comorbidities, clinical parameters, biomarkers, treatments and organizational aspects, from adult in-patient wards and out-patient clinics (www.swedehf.se). The inclusion criterion was clinician-judged HF until April 2017 and after that defined as a diagnosis of HF according to the following ICD-10 codes: I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0 and I13.2. Reported coverage of SwedeHF in 2019 was 30.4% of prevalent HF population in Sweden.

Linkage to Statistics Sweden provided socioeconomic data. The National Patient Registry provided data on additional comorbidities and hospital accesses outcomes. The Cause of Death Registry provided date and cause of death. More details on selection criteria and variable definitions are available at <https://kiheartfailure.github.io/shfdb3/>. Linkage between the registries was allowed by the personal identification number, which all residents in Sweden have.

Establishment of the HF registry and this analysis with linking of the registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki.

**Supplementary Table 1. Guideline recommended drugs and doses for heart failure with reduced ejection fraction.**

|  |  |  |
| --- | --- | --- |
| **RASI** | **Target dose** | **Target dose percentage** |
| **Captopril** |  |  |
|  | 150 mg daily | ≥100% |
|  | 75 – <150 mg | ≥50 - 99% |
|  | <75 mg | <50% |
| **Enalapril** |  |  |
|  | 20 mg daily | ≥100% |
|  | 10 - <20 mg | ≥50 - 99% |
|  | <10 mg | <50% |
| **Lisinopril** |  |  |
|  | 35 mg daily | ≥100% |
|  | 17.5 - <35 mg | ≥50 - 99% |
|  | <17.5 mg | <50% |
| **Ramipril** |  |  |
|  | 10 mg daily | ≥100% |
|  | 5 - <10 mg | ≥50 - 99% |
|  | <5 mg | <50% |
| **Trandolapril** |  |  |
|  | 4 mg daily | ≥100% |
|  | 2 - <4 mg | ≥50 - 99% |
|  | < 2 mg | <50% |
| **Candesartan** |  |  |
|  | 32 mg daily | ≥100% |
|  | 16 - <32 mg | ≥50 - 99% |
|  | < 16 mg | <50% |
| **Valsartan** |  |  |
|  | 320 mg daily | ≥100% |
|  | 160 - <320 mg | ≥50 - 99% |
|  | < 160 mg | <50% |
| **Losartan** |  |  |
|  | 150 mg daily | ≥100% |
|  | 75 - <150 mg | ≥50 - 99% |
|  | < 75 mg | <50% |
|  | | |
| **ARNI** | **Target dose** | **Target dose percentage** |
| **Sacubitril/Valsartan** |  |  |
|  | 194/206 mg daily | ≥100% |
|  | 97/103 - <194/206 mg | ≥50 - 99% |
|  | < 97/103 mg | <50% |
| **Beta-blocker** | **Target dose** | **Target dose percentage** |
| **Metoprolol** |  |  |
|  | 200 mg daily | ≥100% |
|  | 100 – <200 mg | ≥50 - 99% |
|  | <100 mg | <50% |
| **Bisoprolol** |  |  |
|  | 10 mg daily | ≥100% |
|  | 5 – <10 mg | ≥50 - 99% |
|  | <5 mg | <50% |
| **Carvedilol** |  |  |
|  | 50 mg daily (<85 kg)  100 mg 2x daily (>85 kg) | ≥100% |
|  | 25 – <50 mg (<85 kg)  50 – <100 mg (>85 kg) | ≥50 - 99% |
|  | <25 mg (<85 kg)  <50 mg (>85 kg) | <50% |
|  | | |
| **MRA** |  |  |
| **Spironolactone** |  |  |
|  | 50 mg daily | ≥100% |
|  | 25 - <50 mg | ≥50 - 99% |
|  | < 25 mg | <50% |
| **Eplerenone** |  |  |
|  | 50 mg daily | ≥100% |
|  | 25 - <50 mg | ≥50 - 99% |
|  | < 25 mg | <50% |

**Abbreviations.** ARNI = angiotensin-receptor neprilysin inhibitor; MRA = mineralocorticoid receptor; RASI = renin-angiotensin-system inhibitor

**Supplementary Table 2. Characteristics of the overall study population and divided according to treatments use vs non-use.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total population** | **RASI/ARNI** | | | **Beta-blockers** | | |
| **Variable** |  | **non-use** | **use** | **p-value** | **non-use** | **use** | **p-value** |
| **n** | 12421 | 2002 (16%) | 10419 (84%) |  | 1480 (12%) | 10941 (88%) |  |
| ***Demographic/Organizational characteristics*** | | | | | | | |
| **Sex Male, n (%)\*^** | 7921 (64%) | 1125 (56%) | 6796 (65%) | <0.001 | 972 (66%) | 6949 (64%) | 0.100 |
| **Age (years), mean (SD)** | 74 (12) | 79 (11) | 73 (12) | <0.001 | 77 (12) | 74 (12) | <0.001 |
| **Age category, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| <70 years | 3676 (30%) | 301 (15%) | 3375 (32%) |  | 301 (20%) | 3375 (31%) |  |
| 70-79 years | 4100 (33%) | 526 (26%) | 3574 (34%) |  | 431 (29%) | 3669 (33%) |  |
| ≥80 years | 4645 (37%) | 1175 (59%) | 3470 (33%) |  | 748 (50%) | 3897 (36%) |  |
| **Outpatient, n (%)\*^** | 7987 (64%) | 796 (40%) | 7191 (69%) | <0.001 | 805 (54%) | 7182 (66%) | <0.001 |
| **F-up referral HF nurse clinic, n (%)\*^** | 6148 (52.0%) | 689 (37%) | 5459 (55%) | <0.001 | 634 (46%) | 5514 (53%) | <0.001 |
| **F-up referral specialty, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| Hospital | 7132 (60%) | 838 (45%) | 6294 (62%) |  | 691 (49%) | 6441 (61%) |  |
| Primary care | 4493 (37%) | 931 (50%) | 3562 (35%) |  | 663 (47%) | 3830 (36%) |  |
| Other | 319 (3%) | 88 (5%) | 231 (2%) |  | 52 (4%) | 267 (2%) |  |
| **Year of registration, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| < 2009 | 3207 (26%) | 449 (28) | 2648 (25%) |  | 440 (30%) | 2767 (25%) |  |
| 2010-2013 | 3191 (26%) | 568 (28%) | 2623 (25%) |  | 417 (28%) | 2774 (25%) |  |
| 2014-2016 | 3159 (25%) | 532 (27%) | 2627 (25%) |  | 341 (23%) | 2818 (26%) |  |
| > 2016 | 2864 (23%) | 343 (17%) | 2521 (24%) |  | 281 (19%) | 2582 (24%) |  |
| ***Clinical characteristics*** | | | | | | | |
| **HF duration > 6 months, n (%)\*^** | 9404 (77%) | 1543 (79%) | 7861 (77%) | 0.067 | 1131 (78%) | 8273 (77%) | 0.220 |
| **NYHA class, n (%)\*^** |  |  |  | <0.001 |  |  | 0.070 |
| **I-II** | 5971 (65%) | 634 (53%) | 5337 (67%) |  | 626 (62%) | 5345 (66%) |  |
| **III-IV** | 3164 (35%) | 564 (47%) | 2600 (33%) |  | 371 (37%) | 2793 (34%) |  |
| **SBP, mmHg, mean (SD)** | 128 (20) | 128 (21) | 128 (20) | 0.420 | 129 (20) | 128 (20) | 0.007 |
| **DBP, mmHg, mean (SD)** | 73 (12) | 72 (12) | 73 (12) | 0.004 | 72 (12) | 73 (12) | <0.001 |
| **MAP>90 mmHg, n (%)\*^** | 5982 (49%) | 934 (47%) | 5048 (50%) | 0.098 | 683 (47%) | 5299 (49%) | 0.099 |
| **HR, bpm, mean (SD)** | 72 (14) | 76 (16) | 71 (14) | <0.001 | 72 (15) | 72 (14) | 0.580 |
| **HR >70 bpm, n (%)\*^** | 5583 (47%) | 1097 (58%) | 4486 (45%) | <0.001 | 669 (49%) | 4914 (47%) | 0.290 |
| ***Laboratory measurements*** | | | | | | | |
| **eGFR (mL/min/1.73 m²), n (%)\*^** |  |  |  | <0.001 |  |  | 0.100 |
| eGFR <30 mL/min/1.73 m² | 929 (8%) | 449 (23%) | 480 (5%) |  | 120 (8%) | 809 (8%) |  |
| eGFR 30-59 mL/min/1.73 m² | 4812 (40%) | 922 (47%) | 3890 (38%) |  | 608 (42%) | 4204 (39%) |  |
| eGFR ≥60 mL/min/1.73 m² | 6417 (53%) | 598 (30%) | 5819 (57%) |  | 733 (50%) | 5684 (53%) |  |
| **NT-proBNP (ng/L), median (IQR)\*^** | 1650 (654-3820) | 3479 (1530-8311) | 1460 (584-3306) | <0.001 | 1782 (667-4536) | 1630 (653-3730) | 0.077 |
| NT-proBNP > 1650 ng/L, n (%) | 3289 (50%) | 690 (73%) | 2605 (46%) |  | 353 (48%) | 2936 (50%) |  |
| NT-proBNP ≤ 1650 ng/L, n (%) | 3289 (50%) | 251 (27%) | 3038 (54%) |  | 385 (52%) | 2910 (50%) |  |
| **Potassium, n (%)\*^** |  |  |  | <0.001 |  |  | 0.240 |
| Hyperkalemia (> 5 mEq/L) | 382 (4%) | 64 (4%) | 318 (4%) |  |  |  |  |
| Normokalemia (3.5-5.0 mEq/L) | 9195 (92%) | 1325 (89%) | 7870 (93%) |  |  |  |  |
| Hypokalemia (<3.5 mEq/L) | 370 (4%) | 105 (7%) | 265 (3%) |  |  |  |  |
| ***Medical history/comorbidities*** | | | | | | | |
| **BMI, kg/m², median (IQR)\*^** | 27 (24-31) | 26 (23-30) | 27 (24-31) | <0.001 | 26 (23-30) | 27 (24-31) | <0.001 |
| BMI < 22.5, n (%) | 1120 (16%) | 278 (24%) | 842 (15%) |  | 162 (20%) | 958 (16%) |  |
| BMI 22.5-30, n (%) | 3725 (54%) | 610 (52%) | 3115 (54%) |  | 452 (55%) | 3273 (53%) |  |
| BMI >30, n (%) | 2098 (30%) | 289 (25%) | 1809 (31%) |  | 202 (25%) | 1896 (31%) |  |
| **Smoking, n (%)\*^** |  |  |  | 0.004 |  |  | 0.310 |
| Current | 940 (10%) | 119 (8%) | 821 (10%) |  | 95 (9%) | 845 (10%) |  |
| Former | 4305 (45%) | 638 (44%) | 3667 (46%) |  | 498 (45%) | 3807 (45%) |  |
| Never | 4259 (45%) | 707 (48%) | 3552 (44%) |  | 505 (46%) | 3754 (45%) |  |
| **Diabetes, n (%)\*^** | 3642 (29%) | 626 (31%) | 3016 (29%) | 0.037 | 416 (28%) | 3226 (29%) | 0.270 |
| **AF, n (%)\*^** | 7746 (62.4%) | 1407 (70%) | 6339 (61%) | <0.001 | 919 (62%) | 6827 (62%) | 0.820 |
| **Ischemic heart disease, n (%)\*^** | 7482 (60%) | 1261 (63%) | 6221 (60%) | 0.006 | 860 (58%) | 6622 (60%) | 0.075 |
| **Anemia, n (%)~\*^** | 4349 (37.4%) | 994 (51%) | 3355 (35%) | <0.001 | 622 (44%) | 3727 (36%) | <0.001 |
| **Hypertension, n (%)\*^** | 8555 (69%) | 1418 (71%) | 7137 (68%) | 0.039 | 964 (65%) | 7591 (69%) | <0.001 |
| **Peripheral artery disease, n (%)\*^** | 1294 (10%) | 255 (13%) | 1039 (10%) | <0.001 | 160 (11%) | 1134 (10%) | 0.600 |
| **Revascularization, n (%)\*^** | 4429 (36%) | 619 (31%) | 3810 (37%) | <0.001 | 466 (31%) | 3963 (36%) | <0.001 |
| **Stroke/TIA, n (%)\*^** | 2176 (17%) | 470 (23%) | 1706 (16%) | <0.001 | 286 (19%) | 1890 (17%) | 0.052 |
| **Valve disease, n (%)\*^** | 3906 (32%) | 840 (43%) | 3066 (30%) | <0.001 | 523 (36%) | 3383 (31%) | <0.001 |
| **Malignant cancer <3 years, n (%)\*^** | 1610 (13%) | 267 (13%) | 2493 (24%) | 0.032 | 238 (16%) | 1372 (12%) | <0.001 |
| **COPD, n (%)\*^** | 2092 (17%) | 426 (21%) | 1666 (16%) | <0.001 | 297 (20%) | 1795 (16%) | <0.001 |
| **Liver disease, n (%)\*^** | 270 (2%) | 70 (3%) | 200 (2%) | <0.001 | 28 (2%) | 242 (2%) | 0.430 |
| ***Treatments*** | | | | | | | |
| **RASI/ARNI, n (%)\*^** | 10419 (84%) | - | - | - | 1087 (73%) | 9332 (85%) | <0.001 |
| **Beta-blockers, n (%)\*^** | 10941 (88%) | 1609 (80%) | 9332 (90%) | <0.001 | - | - | - |
| **MRA, n (%)\*^** | 4501 (36%) | 688 (34%) | 3813 (37%) | 0.057 | 464 (31%) | 4037 (37%) | <0.001 |
| **Diuretics, n (%)\*^** | 9643 (78%) | 1731 (87%) | 7912 (76%) | <0.001 | 1144 (77%) | 8499 (78%) | 0.700 |
| **Digoxin, n (%)\*^** | 1765 (14%) | 295 (15%) | 1470 (14%) | 0.44 | 177 (12%) | 1588 (14%) | 0.008 |
| **Antiplatelet therapy, n (%)\*^** | 5062 (41%) | 815 (41%) | 4247 (41%) | 0.99 | 592 (40%) | 4470 (41%) | 0.520 |
| **Anticoagulant therapy, n (%)\*^** | 6054 (49%) | 883 (44%) | 5171 (50%) | <0.001 | 605 (41%) | 5449 (50%) | <0.001 |
| **Statins, n (%)\*^** | 6284 (51%) | 771 (38%) | 5513 (53%) | <0.001 | 551 (37%) | 5733 (52%) | <0.001 |
| **Nitrates, n (%)\*^** | 2042 (16%) | 414 (20%) | 1628 (16%) | <0.001 | 244 (16%) | 1798 (16%) | 0.960 |
| **ICD\*^** | 581 (5%) | 59 (3%) | 522 (5%) | <0.001 | 21 (2%) | 560 (5%) | <0.001 |
| **CRT\*^** | 468 (4%) | 40 (2%) | 428 (4%) | <0.001 | 20 (1%) | 448 (4%) | <0.001 |
| ***Socioeconomic characteristics*** | | | | | | | |
| **Family type Living alone, n (%)\*^** | 5940 (48%) | 1103 (55%) | 4837 (46%) | <0.001 | 746 (50%) | 5194 (47%) | 0.036 |
| **Children, n (%)\*^** | 10444 (84%) | 1706 (85%) | 8738 (84%) | 0.13 | 1246 (84%) | 9198 (84%) | 0.910 |
| **Education, n (%)\*^** |  |  |  | <0.001 |  |  | 0.160 |
| Compulsory school | 5393 (44.3%) | 1004 (51%) | 4389 (43%) |  | 657 (45%) | 4736 (44%) |  |
| Secondary school | 4751 (39.1%) | 662 (34%) | 4089 (40%) |  | 532 (37%) | 4219 (39%) |  |
| University | 2017 (16.6%) | 278 (14%) | 1739 (17%) |  | 255 (18%) | 1762 (16%) |  |
| **Income, n (%)\*^** |  |  |  | <0.001 |  |  | 0.086 |
| Low | 4289 (34%) | 792 (40%) | 3497 (33%) |  | 517 (35%) | 3772 (34%) |  |
| Medium | 4763 (38%) | 810 (40.%) | 3953 (38%) |  | 596 (40%) | 4167 (38%) |  |
| High | 3363 (27%) | 400 (20%) | 2963 (28%) |  | 367 (25%) | 2996 (27%) |  |

**Legend.** AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac resynchronization therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); F-up; follow-up, HF: Heart failure; HR: Heart rate; ICD: Implantable cardioverter defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NT-proBNP; N terminal pro- brain natriuretic peptide, NYHA: New York heart association; RAS-inhibitor: Renin-angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack.

~ defined as Hb < 130 g/dl in men and 120 g/dl in women

**\*** = variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no);

**^** = variables included to estimate the propensity score together with index year and duration of HF

**Supplementary Table 3. Missing data.**

|  |  |
| --- | --- |
| **Variable** | **Missing rate (%)** |
| **Sex** | **0** |
| **Age** | **0** |
| **Outpatient** | **5** |
| **F-up referral HF nurse clinic** | **0** |
| **F-up referral speciality** | **4** |
| **Year of registration** | **0** |
| **HF duration > 6 months** | **2** |
| **NYHA class** | **26** |
| **SBP, mmHg** | **2** |
| **DBP, mmHg** | **2** |
| **HR** | **5** |
| **eGFR** | **2** |
| **NT-proBNP** | **46** |
| **Dyskalemia** | **19** |
| **BMI** | **44** |
| **Smoking** | **23** |
| **Diabetes** | **0** |
| **AF** | **0** |
| **Ischemic heart disease** | **0** |
| **Anemia** | **6** |
| **Hypertension** | **0** |
| **Peripheral artery disease** | **0** |
| **Revascularization** | **0** |
| **Stroke/TIA** | **0** |
| **Valve disease** | **2** |
| **Malignant cancer <3 years** | **0** |
| **COPD** | **0** |
| **Liver disease** | **0** |
| **MRA** | **0** |
| **Diuretics** | **0** |
| **Digoxin** | **0** |
| **Antiplatelet therapy** | **0** |
| **Anticoagulant therapy** | **0** |
| **Statins** | **0** |
| **Nitrates** | **0** |
| **ICD** | **2** |
| **CRT** | **2** |
| **Family type Living alone** | **0** |
| **Children** | **0** |
| **Education** | **2** |
| **Income** | **0** |

*For abbreviations see Table 1 in the main text.*

**Supplementary Table 4. Characteristics of the study population matched according to treatments use vs non-use.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **RASI/ARNI** | | | **Beta-blockers** | | |
| **Variable** | **non-use** | **use** | **absolute**  **standardized difference** | **non-use** | **use** | **absolute**  **standardized difference** |
| **n** | 1915 | 1915 |  | 1468 | 1468 |  |
| ***Demographic/Organizational characteristics*** | | | | | | |
| **Sex Male, n (%)** | 1081 (56%) | 1079 (56%) | 0% | 960 (65%) | 943 (64%) | 2% |
| **Age (years), mean (SD)** | 79 (11) | 79 (10) | 5% | 77 (12) | 76 (11) | 5% |
| **Age category, n (%)** |  |  | 3% |  |  | 7% |
| <70 years | 294 (15%) | 284 (15%) |  | 301 (20%) | 321 (22%) |  |
| 70-79 years | 515 (27%) | 540 (28%) |  | 429 (29%) | 458 (31%) |  |
| ≥80 years | 1106 (58%) | 1091 (57%) |  | 738 (50%) | 689 (47%) |  |
| **Outpatient, n (%)** | 788 (41%) | 795 (42%) | 1% | 804 (55%) | 841 (57%) | 5% |
| **F-up referral HF nurse clinic, n (%)** | 677 (38%) | 714 (40%) | 3% | 633 (46%) | 638 (46%) | 0% |
| **F-up referral speciality, n (%)** |  |  | 2% |  |  | 6% |
| Hospital | 815 (46%) | 843 (46%) |  | 691 (49%) | 707 (50%) |  |
| Primary care | 881 (50%) | 894 (49%) |  | 656 (47%) | 638 (45%) |  |
| Other | 80 (5%) | 89 (5%) |  | 48 (3%) | 64 (4%) |  |
| **Year of registration, n (%)** |  |  | 9% |  |  | 8% |
| < 2009 | 538 (28%) | 583 (30%) |  | 432 (29%) | 406 (28%) |  |
| 2010-2013 | 539 (28%) | 494 (26%) |  | 414 (28%) | 384 (26%) |  |
| 2014-2016 | 506 (26%) | 463 (24%) |  | 340 (23%) | 368 (25%) |  |
| > 2016 | 332 (17%) | 375 (20%) |  | 282 (19%) | 310 (21%) |  |
| ***Clinical characteristics*** | | | | | | |
| **HF duration > 6 months, n (%)** | 1476 (78%) | 1495 (79%) | 2% | 1121 (78%) | 1126 (78%) | 1% |
| **NYHA class, n (%)** |  |  | 1% |  |  | 2% |
| **I-II** | 618 (53%) | 648 (53%) |  | 621 (63%) | 651 (63%) |  |
| **III-IV** | 548 (47%) | 584 (47%) |  | 370 (37%) | 374 (36%) |  |
| **SBP, mmHg, mean (SD)** | 128 (21) | 129 (21) | 1% | 130 (20) | 128 (20) | 7% |
| **DBP, mmHg, mean (SD)** | 72 (12) | 72 (12) | 1% | 72 (12) | 72 (11) | 4% |
| **MAP>90 mmHg, n (%)** | 891 (47%) | 901 (48%) | 1% | 677 (47%) | 695 (48%) | 2% |
| **HR, bpm, mean (SD)** | 76 (16) | 75 (15) | 8% | 72 (15) | 72 (14) | 2% |
| **HR >70 bpm, n (%)** | 1033 (57%) | 1033 (57%) | 0% | 665 (49%) | 686 (49%) | 0% |
| ***Laboratory measurements*** | | | | | | |
| **eGFR (mL/min/1.73 m²), n (%)** |  |  | 7% |  |  | 5% |
| eGFR <30 mL/min/1.73 m² | 372 (20%) | 335 (18%) |  | 119 (8%) | 99 (7%) |  |
| eGFR 30-60 mL/min/1.73 m² | 912 (49%) | 907 (48%) |  | 601 (41%) | 606 (42%) |  |
| eGFR >60 mL/min/1.73 m² | 598 (32%) | 656 (35%) |  | 729 (50%) | 730 (51%) |  |
| **NT-proBNP (ng/L), median (IQR)** |  |  | 2% |  |  | 5% |
| NT-proBNP > 1650 ng/L, n (%) | 251 (28%) | 258 (27%) |  | 352 (48%) | 376 (50%) |  |
| NT-proBNP ≤ 1650 ng/L, n (%) | 652 (72%) | 694 (73%) |  | 385 (52%) | 372 (50%) |  |
| **Potassium, n (%)** |  |  | 6% |  |  | 4% |
| Hyperkalemia (> 5 mEq/L) | 61 (4%) | 54 (4%) |  | 370 (37%) | 374 (36%) |  |
| Normokalemia (3.5-5.0 mEq/L) | 1274 (89%) | 1331 (91%) |  | 1038 (92%) | 1054 (91%) |  |
| Hypokalemia (<3.5 mEq/L) | 95 (7%) | 54 (4%) |  | 37 (3%) | 46 (4%) |  |
| ***Medical history/comorbidities*** | | | | | | |
| **BMI, kg/m², median (IQR)** |  |  | 8% |  |  | 1 |
| BMI < 22.5, n (%) | 263 (24%) | 229 (20%) |  | 159 (20%) | 160 (20%) |  |
| BMI 22.5-30, n (%) | 576 (51%) | 590 (53%) |  | 446 (55%) | 449 (55%) |  |
| BMI >30, n (%) | 280 (25%) | 302 (27%) |  | 201 (25%) | 207 (25%) |  |
| **Smoking, n (%)** |  |  | 2% |  |  | 8% |
| Current | 114 (8%) | 119 (8%) |  | 95 (9%) | 100 (9%) |  |
| Former | 606 (43%) | 620 (44%) |  | 491 (45%) | 450 (41%) |  |
| Never | 680 (49%) | 678 (48%) |  | 503 (46%) | 551 (50%) |  |
| **Diabetes, n (%)** | 598 (31%) | 594 (31%) | 1% | 410 (28%) | 440 (30%) | 5% |
| **AF, n (%)** | 1346 (70%) | 1346 (70%) | 0% | 911 (62%) | 905 (62%) | 1% |
| **Ischemic heart disease, n (%)** | 1203 (63%) | 1245 (65%) | 5% | 854 (58%) | 885 (60%) | 4% |
| **Anemia, n (%)~** | 932 (50%) | 911 (49%) | 2% | 612 (44%) | 590 (42%) | 3% |
| **Hypertension, n (%)** | 1353 (71%) | 1365 (71%) | 0% | 959 (65%) | 993 (68%) | 5% |
| **Peripheral artery disease, n (%)** | 244 (13%) | 251 (13%) | 1% | 159 (11%) | 182 (12%) | 5% |
| **Revascularization, n (%)** | 589 (31%) | 662 (34%) | 8% | 466 (32%) | 468 (32%) | 0% |
| **Stroke/TIA, n (%)** | 244 (13%) | 251 (13%) | 0% | 282 (19%) | 274 (19%) | 1% |
| **Valve disease, n (%)** | 1353 (71%) | 1365 (71%) | 1% | 515 (36%) | 511 (36%) | 1% |
| **Malignant cancer <3 years, n (%)** | 273 (14%) | 257 (13%) | 2% | 233 (16%) | 208 (14%) | 5% |
| **COPD, n (%)** | 244 (13%) | 251 (13%) | 2% | 294 (20%) | 299 (20%) | 1% |
| **Liver disease, n (%)** | 64 (3%) | 69 (4%) | 1% | 28 (2%) | 20 (1%) | 4% |
| ***Treatments*** | | | | | | |
| **RASI/ARNI, n (%)** | 0 (0%) | 1927 (100%) | - | 1087 (74%) | 1144 (78%) | 9% |
| **Beta-blockers, n (%)** | 1550 (81%) | 1552 (81%) | 0% | 0 (0%) | 1468 (100%) | - |
| **MRA, n (%)** | 663 (35%) | 675 (35%) | 1% | 463 (31%) | 466 (32%) | 0% |
| **Diuretics, n (%)** | 1655 (87%) | 1656 (87%) | 0% | 1136 (77%) | 1133 (77%) | 0% |
| **Digoxin, n (%)** | 289 (15%) | 296 (16%) | 1% | 177 (12%) | 179 (12%) | 0% |
| **Antiplatelet therapy, n (%)** | 778 (41%) | 771 (40%) | 1% | 591 (40%) | 608 (41%) | 2% |
| **Anticoagulant therapy, n (%)** | 867 (46%) | 895 (47%) | 3% | 604 (41%) | 631 (43%) | 4% |
| **Statins, n (%)** | 754 (39%) | 784 (41%) | 3% | 551 (38%) | 604 (41%) | 7% |
| **Nitrates, n (%)** | 396 (21%) | 425 (22%) | 4% | 243 (17%) | 263 (18%) | 4% |
| **ICD** | 57 (3%) | 54 (3%) | 2% | 21 (1%) | 30 (2%) | 4% |
| **CRT** | 40 (2%) | 45 (2%) | 1% | 20 (1%) | 27 (2%) | 4% |
| ***Socio-economic characteristics*** | | | | | | |
| **Family type Living alone, n (%)** | 1046 (55%) | 1011 (53%) | 4% | 741 (50%) | 742 (51%) | 0% |
| **Children, n (%)** | 1629 (85%) | 1657 (87%) | 4% | 1236 (84%) | 1243 (85%) | 1% |
| **Education, n (%)** |  |  | 1% |  |  | 5% |
| Compulsory school | 948 (51%) | 953 (51%) |  | 649 (45%) | 639 (45%) |  |
| Secondary school | 642 (35%) | 650 (35%) |  | 530 (37%) | 562 (39%) |  |
| University | 269 (15%) | 265 (14%) |  | 253 (18%) | 231 (16%) |  |
| **Income, n (%)** |  |  | 6% |  |  | 3% |
| Low | 760 (40%) | 813 (43%) |  | 514 (35%) | 534 (36%) |  |
| Medium | 765 (40%) | 744 (39%) |  | 590 (40%) | 569 (39%) |  |
| High | 390 (20%) | 358 (19%) |  | 364 (25%) | 364 (25%) |  |

AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac resynchronization therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); HF: Heart failure; HR: Heart rate; ICD: Implantable cardioverter defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NYHA: New York heart association; RAS-inhibitor: Renin-angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack.

~ defined as Hb < 130 g/dl in men and 120 g/dl in women

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Overall population** | | | | | | **Matched population** | | | | | | |
| **RASI/ARNI** | | | | | | | | | | | | |
|  | **use n=10419 events/1000 pts-yr (95%CI)** | **non-use n=2002**  **events/1000 pts-yr (95%CI)** | **IRR (95%CI)** | **Crude HR (95% CI)** | **PS adjusted HR**  **(95% CI)** | **use n=10419 events/1000 pt-yr (95%CI)** | **non-use n=2002**  **events/1000 pts-yr (95%CI)** | | **IRR**  **(95%CI)** | | **Matched HR**  **(95%CI)** | |
| **Cancer related hospitalization** | 20 (18-21) | 26 (22-32) | 0.77^  (0.63-0.93) | 0.81\*  (0.67-0.98) | 0.93  (0.75-1.13) | 21  (18-26) | 25  (21-30) | | 0.84  (0.65-1.09) | | 0.86  (0.66-1.11) | |
| **Beta-blockers** | | | | | | | | | | | | |
|  | **use n=10419 events/1000 pt-yr (95% CI)** | **non-use n=2002**  **events/1000 pts-yr (95%CI)** | **IRR (95%CI)** | **Crude HR (95%CI)** | **PS adjusted HR**  **(95% CI)** | **use n=10419 events/1000 pt-yr (95%CI)** | | **non-use n=2002**  **events/1000 pts-yr (95%CI)** | | **IRR**  **(95%CI)** | | **Matched HR**  **(95%CI)** |
| **Cancer related hospitalization** | 20  (19-21) | 24  (20-29) | 0.83  (0.68-1.01) | 0.85  (0.69-1.04) | 0.96  (0.78-1.18) | 22  (18-27) | | 24  (20-29) | | 0.91  (0.70-1.19) | | 0.91  (0.65-1.26) |

**Supplementary Table 5. Negative control analysis (cancer related hospitalizations).**

**Legend.** CI=confidence interval; CV=cardiovascular; HFH=heart failure hospitalization; HR=hazard ratio; IRR=incidence rate ratio; RASI/ARNI=renin angiotensin system inhibitors/angiotensin receptor neprilyisin inhibitor.

*\* p value <0.05*

*^ p value <0.01*

**Supplementary Table 6. Characteristics of the overall positive control cohort and divided according to treatments use vs non-use.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total population** | **RASI/ARNI** | | | **Beta-blockers** | | |
| **Variable** |  | **non-use** | **use** | **p-value** | **non-use** | **use** | **p-value** |
| **n** | 26143 | 2691 (10%) | 23452 (90%) |  | 2246 (9%) | 23897 (11%) |  |
| ***Demographic/Organizational characteristics*** | | | | | | | |
| **Sex Male, n (%)\*^** | 19083 (73%) | 1866 (69%) | 17217 (73%) | <0.001 | 1619 (72%) | 17464 (73%) | 0.310 |
| **Age (years), mean (SD)** | 73 (12) | 79 (10) | 72 (12) | <0.001 | 77 (11) | 73 (12) | <0.001 |
| **Age category, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| <70 years | 8802 (34%) | 391 (15%) | 8411 (36%) |  | 477 (21%) | 8325 (35%) |  |
| 70-79 years | 8922 (34%) | 729 (27%) | 8193 (35%) |  | 666 (30%) | 8256 (34%) |  |
| ≥80 years | 8419 (32%) | 1571 (58%) | 6848 (29%) |  | 1103 (49%) | 7316 (31%) |  |
| **Outpatient, n (%)\*^** | 15899 (61%) | 919 (34%) | 14980 (64%) | <0.001 | 1141 (51%) | 14758 (62%) | <0.001 |
| **F-up referral HF nurse clinic, n (%)\*^** | 13829 (56%) | 911 (37%) | 12918 (58%) | <0.001 | 919 (44%) | 12910 (57%) | <0.001 |
| **F-up referral specialty, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| Hospital | 17818 (71%) | 1222 (50%) | 16596 (73%) |  | 1177 (56%) | 16641 (72%) |  |
| Primary care | 6505 (26%) | 1105 (45%) | 5400 (24%) |  | 843 (40%) | 5662 (25%) |  |
| Other | 689 (3%) | 116 (5%) | 573 (3%) |  | 81 (4%) | 608 (3%) |  |
| **Year of registration, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| < 2009 | 8474 (32%) | 937 (35) | 7537 (32%) |  | 944 (42%) | 7530 (31%) |  |
| 2010-2013 | 7257 (28%) | 756 (28%) | 6501 (28%) |  | 564 (25%) | 6693 (28%) |  |
| 2014-2016 | 5668 (22%) | 628 (23%) | 5040 (21%) |  | 425 (19%) | 5243 (22%) |  |
| > 2016 | 4744 (18%) | 370 (14%) | 4374 (19%) |  | 313 (14%) | 4431 (19%) |  |
| ***Clinical characteristics*** | | | | | | | |
| **HF duration > 6 months, n (%)\*^** | 19393 (75%) | 2117 (80%) | 17276 (75%) | <0.001 | 1743 (79%) | 17650 (75%) | <0.001 |
| **NYHA class, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| **I-II** | 10540 (52%) | 578 (35%) | 9962 (54%) |  | 725 (46%) | 9815 (53%) |  |
| **III-IV** | 9569 (48%) | 1085 (65%) | 8484 (46%) |  | 856 (54%) | 8713 (47%) |  |
| **SBP, mmHg, mean (SD)** | 123 (20) | 123 (20) | 123 (20) | 0.80 | 124 (21) | 123 (20) | 0.013 |
| **DBP, mmHg, mean (SD)** | 72 (12) | 71 (12) | 72 (12) | <0.001 | 71 (12) | 72 (12) | <0.001 |
| **MAP>90 mmHg, n (%)\*^** | 10766 (42%) | 1042 (40%) | 9724 (42%) | 0.015 | 910 (41%) | 9856 (42%) | 0.480 |
| **HR, bpm, mean (SD)** | 73 (15) | 77 (16) | 72 (15) | <0.001 | 74 (15) | 73 (15) | <0.001 |
| **HR >70 bpm, n (%)\*^** | 12107 (49%) | 1517 (60%) | 10590 (47%) | <0.001 | 1131 (54%) | 10976 (48%) | <0.001 |
| ***Laboratory measurements*** | | | | | | | |
| **eGFR (mL/min/1.73 m²), n (%)#\*^** |  |  |  | <0.001 |  |  | <0.001 |
| eGFR <30 mL/min/1.73 m² | 1994 (8%) | 731 (27%) | 1263 (5%) |  | 221 (10%) | 1773 (8%) |  |
| eGFR 30-59 mL/min/1.73 m² | 10192 (40%) | 1301 (49%) | 8891 (38%) |  | 970 (44%) | 9222 (39%) |  |
| eGFR ≥60 mL/min/1.73 m² | 13572 (52%) | 622 (23%) | 12950 (56%) |  | 1028 (46%) | 12544 (53%) |  |
| **NT-proBNP (ng/L), median (IQR)\*^** | 2623 (1070-6165) | 6211 (2690-15881) | 2406 (1004-5600) | <0.001 | 2892 (1158-6797) | 2600 (1063-6130) | 0.280 |
| NT-proBNP > 2623 ng/L, n (%) | 6383 (50%) | 851 (76%) | 5532 (48%) |  | 502 (53%) | 5881 (50%) |  |
| NT-proBNP ≤ 2623 ng/L, n (%) | 6383 (50%) | 274 (24%) | 6109 (52%) |  | 447 (47%) | 5936 (50%) |  |
| **Potassium, n (%)\*^** |  |  |  | <0.001 |  |  | 0.068 |
| Hyperkalemia (> 5 mEq/L) | 673 (3%) | 146 (7%) | 527 (3%) |  | 68 (4%) | 605 (3%) |  |
| Normokalemia (3.5-5.0 mEq/L) | 18538 (93%) | 1717 (88%) | 16821 (93%) |  | 1427 (92%) | 17111 (93%) |  |
| Hypokalemia (<3.5 mEq/L) | 821 (4%) | 92 (5%) | 729 (4%) |  | 61 (4%) | 760 (4%) |  |
| ***Medical history/comorbidities*** | | | | | | | |
| **BMI, kg/m², median (IQR)\*^** | 26 (23-30) | 25 (22-29) | 26 (24-30) | <0.001 | 25 (22-28) | 26 (23-30) | <0.001 |
| BMI < 22.5, n (%) | 2829 (19%) | 427 (28%) | 2402 (18%) |  | 320 (27%) | 2509 (18%) |  |
| BMI 22.5-30, n (%) | 8591 (57%) | 810 (53%) | 7781 (57%) |  | 660 (55%) | 7931 (57%) |  |
| BMI >30, n (%) | 3654 (24%) | 284 (19%) | 3370 (25%) |  | 219 (18%) | 3435 (25%) |  |
| **Smoking, n (%)\*^** |  |  |  | 0.004 |  |  | <0.001 |
| Current | 2551 (12%) | 162 (9%) | 2389 (13%) |  | 170 (10%) | 2381 (13%) |  |
| Former | 9674 (47%) | 900 (47%) | 8774 (47%) |  | 762 (46%) | 8912 (47%) |  |
| Never | 8293 (40%) | 845 (44%) | 7448 (40%) |  | 744 (44%) | 7549 (40%) |  |
| **Diabetes, n (%)\*^** | 8188 (31%) | 888 (33%) | 7300 (31%) | 0.047 | 588 (26%) | 7600 (32%) | <0.001 |
| **AF, n (%)\*^** | 14897 (57%) | 1741 (65%) | 13156 (56%) | <0.001 | 1285 (57%) | 13612 (57%) | 0.820 |
| **Ischemic heart disease, n (%)\*^** | 17174 (66%) | 1954 (73%) | 15220 (65%) | <0.001 | 1455 (65%) | 15719 (66%) | 0.340 |
| **Anemia, n (%)~\*^** | 8738 (35%) | 1364 (52%) | 7374 (33%) | <0.001 | 916 (42%) | 7822 (34%) | <0.001 |
| **Hypertension, n (%)\*^** | 16173 (62%) | 1776 (66%) | 14397 (61%) | <0.001 | 1274 (57%) | 14899 (62%) | <0.001 |
| **Peripheral artery disease, n (%)\*^** | 2787 (11%) | 431 (16%) | 2356 (10%) | <0.001 | 268 (12%) | 2519 (10%) | 0.041 |
| **Revascularization, n (%)\*^** | 10753 (41%) | 1053 (39%) | 9700 (41%) | 0.026 | 805 (36%) | 9948 (42%) | <0.001 |
| **Stroke/TIA, n (%)\*^** | 4748 (18%) | 673 (25%) | 4075 (17%) | <0.001 | 490 (22%) | 4258 (18%) | <0.001 |
| **Valve disease, n (%)\*^** | 7609 (29%) | 1154 (44%) | 6455 (28%) | <0.001 | 805 (37%) | 6804 (29%) | <0.001 |
| **Malignant cancer <3 years, n (%)\*^** | 1610 (13%) | 404 (15%) | 2753 (12%) | <0.001 | 329 (15%) | 2828 (12%) | <0.001 |
| **COPD, n (%)\*^** | 3792 (14%) | 464 (17%) | 3328 (14%) | <0.001 | 395 (18%) | 3397 (14%) | <0.001 |
| **Liver disease, n (%)\*^** | 627 (2%) | 92 (3%) | 535 (2%) | <0.001 | 62 (3%) | 565 (2%) | 0.240 |
| ***Treatments*** | | | | | | | |
| **RASI/ARNI, n (%)\*^** | 23452 (90%) | - | - | - | 1764 (79%) | 21688 (91%) | <0.001 |
| **Beta-blockers, n (%)\*^** | 23897 (91%) | 2209 (82%) | 21688 (92%) | <0.001 | - | - | - |
| **MRA, n (%)\*^** | 11405 (44%) | 896 (33%) | 10509 (45%) | <0.001 | 833 (37%) | 10572 (44%) | <0.001 |
| **Diuretics, n (%)\*^** | 21339 (82%) | 2403 (89%) | 18936 (81%) | <0.001 | 1848 (82%) | 19491 (82%) | 0.420 |
| **Digoxin, n (%)\*^** | 4008 (15%) | 367 (14%) | 3641 (15%) | 0.010 | 313 (14%) | 3695 (15%) | 0.055 |
| **Antiplatelet therapy, n (%)\*^** | 11842 (45%) | 1317 (49%) | 10525 (45%) | <0.001 | 1024 (46%) | 10818 (45%) | 0.077 |
| **Anticoagulant therapy, n (%)\*^** | 12377 (47%) | 1037 (39%) | 11340 (48%) | <0.001 | 877 (39%) | 11500 (48%) | <0.001 |
| **Statins, n (%)\*^** | 14065 (54%) | 1090 (40%) | 12975 (55%) | <0.001 | 886 (39%) | 13179 (55%) | <0.001 |
| **Nitrates, n (%)\*^** | 4301 (16%) | 647 (24%) | 3654 (16%) | <0.001 | 392 (17%) | 3909 (16%) | 0.170 |
| **ICD\*^** | 2819 (11%) | 136 (5%) | 2683 (12%) | <0.001 | 90 (4%) | 2729 (12%) | <0.001 |
| **CRT\*^** | 2201 (8%) | 142 (5%) | 2059 (9%) | <0.001 | 114 (5%) | 2087 (9%) | <0.001 |
| ***Socioeconomic characteristics*** | | | | | | | |
| **Family type Living alone, n (%)\*^** | 12033 (46%) | 1399 (52%) | 10634 (45%) | <0.001 | 1096 (49%) | 10937 (46%) | 0.006 |
| **Children, n (%)\*^** | 21756 (83%) | 2258 (84%) | 19498 (83%) | 0.31 | 1896 (84%) | 19860 (83%) | 0.110 |
| **Education, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| Compulsory school | 11543 (45%) | 1409 (54%) | 10134 (44%) |  | 1103 (50%) | 10440 (45%) |  |
| Secondary school | 10040 (39%) | 886 (34%) | 9154 (40%) |  | 770 (35%) | 9270 (40%) |  |
| University | 4001 (16%) | 328 (12%) | 3673 (16%) |  | 325 (15%) | 3676 (16%) |  |
| **Income, n (%)\*^** |  |  |  | <0.001 |  |  | <0.001 |
| Low | 8839 (34%) | 1019 (38%) | 7820 (33%) |  | 806 (36%) | 8033 (34%) |  |
| Medium | 9870 (38%) | 1092 (41%) | 8778 (38%) |  | 908 (40%) | 8962 (38%) |  |
| High | 7394 (28%) | 577 (21%) | 6817 (29%) |  | 529 (24%) | 6865 (29%) |  |

AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac resynchronization therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); HF: Heart failure; HR: Heart rate; ICD: Implantable cardioverter defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NYHA: New York heart association; RAS-inhibitor: Renin-angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack.

~ defined as Hb < 130 g/dl in men and 120 g/dl in women

**\*** = variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no);

**^** = variables included to estimate the propensity score together with index year and duration of HF

**Supplementary Table 7. Characteristics of the positive control cohort matched according to treatments use vs non-use.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **RASI/ARNI** | | | **Beta-blockers** | | |
| **Variable** | **non-use** | **use** | **absolute**  **standardized difference** | **non-use** | **use** | **absolute**  **standardized difference** |
| **n** | 2630 | 2630 |  | 2244 | 2244 |  |
| ***Demographic/Organizational characteristics*** | | | | | | |
| **Sex Male, n (%)** | 1822 (69%) | 1791 (68%) | 2% | 960 (65%) | 943 (64%) | 2% |
| **Age (years), mean (SD)** | 79 (10) | 79 (10) | - | 77 (12) | 76 (11) | - |
| **Age category, n (%)** |  |  | 3% |  |  | 7% |
| <70 years | 390 (15%) | 415 (16%) |  | 301 (21%) | 321 (22%) |  |
| 70-79 years | 724 (27%) | 733 (28%) |  | 429 (29%) | 458 (31%) |  |
| ≥80 years | 1516 (58%) | 1482 (56%) |  | 738 (50%) | 689 (47%) |  |
| **Outpatient, n (%)** | 917 (35%) | 972 (37%) | 4% | 804 (55%) | 841 (57%) | 5% |
| **F-up referral HF nurse clinic, n (%)** | 909 (38%) | 972 (40%) | 3% | 633 (46%) | 638 (46%) | 0% |
| **F-up referral speciality, n (%)** |  |  | 6% |  |  | 6% |
| Hospital | 1212 (51%) | 1285 (52%) |  | 691 (50%) | 707 (50%) |  |
| Primary care | 1070 (45%) | 1065 (43%) |  | 656 (47%) | 638 (45%) |  |
| Other | 108 (5%) | 141 (6%) |  | 48 (3%) | 64 (5%) |  |
| **Year of registration, n (%)** |  |  | 9% |  |  | 7% |
| < 2009 | 921 (35%) | 958 (36%) |  | 432 (29%) | 406 (28%) |  |
| 2010-2013 | 737 (28%) | 744 (28%) |  | 414 (28%) | 384 (26%) |  |
| 2014-2016 | 609 (23%) | 513 (19%) |  | 340 (23%) | 368 (25%) |  |
| > 2016 | 363 (14%) | 415 (16%) |  | 282 (19%) | 310 (21%) |  |
| ***Clinical characteristics*** | | | | | | |
| **HF duration > 6 months, n (%)** | 2070 (80%) | 2058 (79%) | 2% | 1121 (78%) | 1126 (78%) | 1% |
| **NYHA class, n (%)** |  |  | 1% |  |  | 2% |
| **I-II** | 577 (35%) | 643 (35%) |  | 621 (63%) | 651 (63%) |  |
| **III-IV** | 1063 (65%) | 1169 (64%) |  | 370 (37%) | 374 (37%) |  |
| **SBP, mmHg, mean (SD)** | 123 (20) | 124 (20) | - | 129 (20) | 128 (20) | - |
| **DBP, mmHg, mean (SD)** | 71 (12) | 71 (12) | - | 72 (12) | 72 (11) | - |
| **MAP>90 mmHg, n (%)** | 1022 (40%) | 1028 (40%) | 1% | 677 (47%) | 695 (48%) | 2% |
| **HR, bpm, mean (SD)** | 77 (16) | 75 (15) | - | 72 (15) | 72 (14) | - |
| **HR >70 bpm, n (%)** | 1470 (60%) | 1431 (58%) | 3% | 665 (49%) | 686 (49%) | 0% |
| ***Laboratory measurements*** | | | | | | |
| **eGFR (mL/min/1.73 m²), n (%)** |  |  | 6% |  |  | 5% |
| eGFR <30 mL/min/1.73 m² | 673 (26%) | 645 (25%) |  | 119 (8%) | 99 (7%) |  |
| eGFR 30-60 mL/min/1.73 m² | 1298 (50%) | 1267 (49%) |  | 601 (42%) | 606 (42%) |  |
| eGFR >60 mL/min/1.73 m² | 622 (24%) | 694 (27%) |  | 729 (50%) | 730 (51%) |  |
| **NT-proBNP (ng/L), median (IQR)** | 6034 (2627-15449) | 4884 (2260-11539) | - | 1785 (667-4536) | 1638 (686-4310) | - |
| NT-proBNP > 2623 ng/L, n (%) | 825 (75%) | 821 (71%) | 9% | 294 (40%) | 280 (37%) | 5% |
| NT-proBNP ≤ 2623 ng/L, n (%) | 273 (25%) | 340 (29%) |  | 443 (60%) | 468 (63%) |  |
| **Potassium, n (%)** |  |  | 5% |  |  | 4% |
| Hyperkalemia (> 5 mEq/L) | 136 (7%) | 118 (6%) |  | 51 (5%) | 54 (5%) |  |
| Normokalemia (3.5-5.0 mEq/L) | 1676 (88%) | 1702 (90%) |  | 1038 (92%) | 1054 (91%) |  |
| Hypokalemia (<3.5 mEq/L) | 90 (5%) | 78 (4%) |  | 37 (3%) | 46 (4%) |  |
| ***Medical history/comorbidities*** | | | | | | |
| **BMI, kg/m², median (IQR)** | 25 (22-29) | 25 (22-28) |  | 26 (23-30) | 26 (23-30) | 1% |
| BMI < 22.5, n (%) | 411 (28%) | 388 (28%) | 9% | 159 (20%) | 160 (20%) |  |
| BMI 22.5-30, n (%) | 788 (53%) | 906 (58%) |  | 446 (55%) | 449 (55.0%) |  |
| BMI >30, n (%) | 281 (19%) | 273 (17%) |  | 201 (25%) | 207 (25%) |  |
| **Smoking, n (%)** |  |  | 4% |  |  | 8% |
| Current | 159 (9%) | 184 (10%) |  | 95 (9%) | 100 (9%) |  |
| Former | 885 (47%) | 891 (46%) |  | 491 (45%) | 450 (41%) |  |
| Never | 828 (44%) | 866 (44%) |  | 503 (46%) | 551 (50.0%) |  |
| **Diabetes, n (%)** | 871 (33%) | 905 (34%) | 3% | 410 (28%) | 440 (30%) | 4% |
| **AF, n (%)** | 1698 (65%) | 1697 (65%) | 0% | 911 (62%) | 905 (62%) | 1% |
| **Ischemic heart disease, n (%)** | 1910 (73%) | 1912 (73%) | 0% | 854 (58%) | 885 (60%) | 4% |
| **Anemia, n (%)~** | 1314 (51%) | 1268 (50%) | 3% | 612 (44%) | 590 (42%) | 3% |
| **Hypertension, n (%)** | 1732 (66%) | 1723 (66%) | 1% | 959 (65%) | 993 (68%) | 5% |
| **Peripheral artery disease, n (%)** | 410 (16%) | 422 (16%) | 1% | 159 (11%) | 182 (12%) | 5% |
| **Revascularization, n (%)** | 1028 (39%) | 1094 (42%) | 5% | 466 (32%) | 468 (32%) | 0% |
| **Stroke/TIA, n (%)** | 653 (25%) | 627 (24%) | 2% | 282 (19%) | 274 (19%) | 1% |
| **Valve disease, n (%)** | 1117 (43%) | 1105 (42%) | 2% | 515 (36%) | 511 (36%) | 1% |
| **Malignant cancer <3 years, n (%)** | 397 (15%) | 382 (15%) | 2% | 233 (16%) | 208 (14%) | 4% |
| **COPD, n (%)** | 457 (17%) | 473 (18%) | 2% | 294 (20%) | 299 (20%) | 1% |
| **Liver disease, n (%)** | 86 (3%) | 79 (3%) | 2% | 28 (2%) | 20 (1%) | 4% |
| ***Treatments*** | | | | | | |
| **RASI/ARNI, n (%)** | 0 (0%) | 2630 (100%) | - | 1087 (74%) | 1144 (78%) |  |
| **Beta-blockers, n (%)** | 2180 (83%) | 2198 (84%) | 2% | 0 (0%) | 1468 (100%) | - |
| **MRA, n (%)** | 888 (34%) | 898 (34%) | 1% | 463 (32%) | 466 (32%) | 0% |
| **Diuretics, n (%)** | 2352 (90%) | 2362 (90%) | 2% | 1136 (77%) | 1133 (77%) | 0% |
| **Digoxin, n (%)** | 366 (14%) | 386 (15%) | 2% | 177 (12%) | 179 (12%) | 0% |
| **Antiplatelet therapy, n (%)** | 1292 (49%) | 1300 (49%) | 0% | 591 (40%) | 608 (41%) | 2% |
| **Anticoagulant therapy, n (%)** | 1027 (39%) | 1044 (40%) | 1% | 604 (41%) | 631 (43%) | 4% |
| **Statins, n (%)** | 1085 (41%) | 1123 (43%) | 3% | 551 (38%) | 604 (41%) | 7% |
| **Nitrates, n (%)** | 630 (24%) | 615 (23%) | 1% | 243 (17%) | 263 (18%) | 4% |
| **ICD** | 134 (5%) | 141 (5%) | 1% | 21 (1%) | 30 (2%) | 5% |
| **CRT** | 140 (5%) | 151 (6%) | 2% | 20 (1%) | 27 (2%) | 4% |
| ***Socio-economic characteristics*** | | | | | | |
| **Family type Living alone, n (%)** | 1370 (52%) | 1364 (52%) | 0% | 741 (50%) | 742 (51%) | 0% |
| **Children, n (%)** | 2211 (84%) | 2206 (84%) | 1% | 1236 (84%) | 1243 (85%) | 1% |
| **Education, n (%)** |  |  | 2% |  |  | 5% |
| Compulsory school | 1372 (53%) | 1342 (53%) |  | 649 (45%) | 639 (45%) |  |
| Secondary school | 871 (34%) | 885 (34%) |  | 530 (37%) | 562 (39%) |  |
| University | 321 (13%) | 323 (13%) |  | 253 (18%) | 231 (16%) |  |
| **Income, n (%)** |  |  | 4% |  |  | 3% |
| Low | 997 (38%) | 991 (38%) |  | 514 (35%) | 534 (36%) |  |
| Medium | 1059 (40%) | 1101 (42%) |  | 590 (40%) | 569 (39%) |  |
| High | 571 (22%) | 535 (20%) |  | 364 (25%) | 364 (25%) |  |

AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac resynchronization therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); HF: Heart failure; HR: Heart rate; ICD: Implantable cardioverter defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NYHA: New York heart association; RAS-inhibitor: Renin-angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack.

~ defined as Hb < 130 g/dl in men and 120 g/dl in women

**Supplementary Table 8. Primary and secondary study outcomes in the positive control population (HFrEF, n=26143).**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Overall population** | | | | | **Matched population** | | | | | |
| **RASI/ARNI** | | | | | | | | | | |
|  | **use n=23452 events/1000 pt-yr (95% CI)** | **non-use n=2691**  **events/1000 pts-yr (95%CI)** | **IRR (95%CI)** | **HR**  **(95% CI)** | | **PS adjusted HR**  **(95% CI)** | **use n=2630 events/1000 pt-yr (95%CI)** | **non-use n=2630**  **events/1000 pts-yr (95%CI)** | **IRR**  **(95%CI)** | **HR**  **(95%CI)** |
| **CV mortality/HFH** | 223  (219-226) | 562  (538-587) | 0.40^  (0.38-0.42) | 0.50^  (0.47-0.52) | | 0.91^  (0.85-0.97) | 437  (418-456) | 552  (528-577) | 0.79^  (0.74-0.84) | 0.82^  (0.77-0.87) |
| **All-cause mortality** | 134  (132-137) | 397  (381-314) | 0.34^  (0.32-0.35) | 0.36^  (0.34-0.37) | | 0.72^  (0.69-0.76) | 279  (267-292) | 389  (373-406) | 0.72^  (0.68-0.76) | 0.68^  (0.64-0.73) |
| **CV mortality** | 89  (88-91) | 269  (256-283) | 0.33^  (0.31-0.35) | 0.36^  (0.34-0.38) | | 0.75^  (0.70-0.79) | 193  (183-203) | 263  (250-276) | 0.73^  (0.68-0.79) | 0.73^  (0.67-0.78) |
| **HFH** | 179  (176-183) | 388  (368-408) | 0.46^  (0.44-0.49) | 0.59^  (0.56-0.63) | | 0.88^  (0.82-0.93) | 320  (304-337) | 384  (365-405) | 0.83^  (0.77-0.90) | 0.88^  (0.82-0.95) |
| **Beta-blockers** | | | | | | | | | | |
|  | **use n=23897 events/1000 pt-yr (95% CI)** | **non-use n=2246**  **events/1000 pts-yr (95%CI)** | **IRR (95%CI)** | **HR**  **(95%CI)** | | **PS adjusted HR**  **(95% CI)** | **use n=2244 events/1000 pt-yr (95%CI)** | **non-use n=2244**  **events/1000 pts-yr (95%CI)** | **IRR**  **(95%CI)** | **HR**  **(95%CI)** |
| **CV mortality/HFH** | 233  (229-237) | 347  (331-365) | 0.67^  (0.64-0.71) | 0.73^  (0.69-0.77) | | 0.87^  (0.83-0.92) | 273  (260-287) | 347  (330-364) | 0.79^  (0.73-0.84) | 0.85^  (0.79-0.91) |
| **All-cause mortality** | 142  (140-145) | 236  (225-248) | 0.60^  (0.57-0.63) | 0.62^  (0.59-0.65) | | 0.87^  (0.82-0.91) | 182  (173-192) | 236  (225-247) | 0.77^  (0.72-0.83) | 0.77^  (0.72-0.83) |
| **CV mortality** | 95  (93-96) | 163  (154-173) | 0.58^  (0.55-0.62) | 0.60^  (0.56-0.63) | | 0.84^  (0.79-0.89) | 123  (115-131) | 163  (154-173) | 0.75^  (0.69-0.82) | 0.76^  (0.70-0.83) |
| **HFH** | 186  (182-189) | 255  (241-270) | 0.73^  (0.69-0.77) | 0.80^  (0.75-0.85) | | 0.88^  (0.83-0.94) | 206  (195-218) | 255  (240-270) | 0.81^  (0.75-0.88) | 0.88^  (0.81-0.96) |

**Legend.** CI=confidence interval; CV=cardiovascular; HFH=heart failure hospitalization; HR=hazard ratio; IRR=incidence rate ratio; PS=propensity score; RASI/ARNI=renin angiotensin system inhibitors/angiotensin receptor neprilyisin inhibitor.

*\* p value <0.05*

*^ p value <0.01*

**Supplementary Figure 1. Kernel density plot reporting the propensity score distribution in the overall (n = 12421) and matched (n = 1915 for RASI/ARNI, left panel and n = 1468 for beta-blockers, right panel) cohort of patients with HFmrEF of age by treatment arm.**

**Legend.** RASI/ARNI=renin angiotensin system inhibitors/angiotensin receptor neprilyisin inhibitor



**Supplementary Figure 2. Kernel density plot reporting the propensity score distribution in the overall (n = 26143) and matched (n = 2630 for RASI/ARNI, left panel and n = 2244 for beta-blockers, right panel) positive control cohort of patients with HFrEF by treatment arm.**

**Legend.** RASI/ARNI=renin angiotensin system inhibitors/angiotensin receptor neprilyisin inhibitor

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**References**

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