**Supplementary Appendix**

**Sex differences in the prognostic role of achieving target doses of heart failure medications: data from the Swedish Heart Failure registry**

Ferrari A et al.

**Supplemental Table S1.** Variables and outcomes definition from the Swedish HF Registry and the National Patient Registry

|  |  |
| --- | --- |
| **Variables** | **Definition** |
| Hypertension | Diagnosis in SwedeHF or in NPR (ICD-10 codes: I10-I15) |
| Diabetes mellitus | Diagnosis in SwedeHF or in NPR (ICD-10 codes: E10-E14) |
| Ischemic heart disease | Diagnosis in SwedeHF or in NPR (ICD-10 codes: 410-1, 120-5). |
| Previous Coronary Revascularization | Diagnosis in Swede-HF |
| Atrial fibrillation | Diagnosis in SwedeHF (history of atrial fibrillation/atrial flutter or ECG showing atrial fibrillation/atrial flutter) or in NPR (ICD-10 code: I48). |
| Valve disease | Diagnosis in SwedeHF or in NPR (ICD-10 codes: A520, I05-I08, I091, I098, I34-I39, Q230-Q233, Z952, Z954) |
| Anaemia | Haemoglobin <120 g/L in females and < 130 g/L in males; ICD: D5; D60-4 |
| Stroke or TIA | Diagnosis in the NPR (ICD-10 codes: 430-4, 438, I60-4, I690-4, G45) |
| Liver disease | Diagnosis in the NPR (ICD-10 codes: B18, I85, I864, I982, K70, K710, K711, K713-7, K72-4, K760, K762-9) |
| COPD | Diagnosis in the NPR (ICD-10 codes: J40-4) |
| Dementia | Diagnosis in the NPR (ICD-10 codes: F00-4) |
| History of cancer within 3 years | Diagnosis in the NPR (ICD-10 codes: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97) |
| History of musculoskeletal disease within 3 years | Diagnosis in the NPR (ICD:M) |
| **Outcomes** |  |
| Cardiovascular mortality | Main diagnosis in Causes of Death register (ICD-10 codes: I00-I99, J81, K761, G45, R57) |
| HF hospitalization | Main diagnosis in NPR (ICD-10 codes: I50, I42, I43, I255, K761, I110, I130, I132, J81, R57) |
| Abbreviations. AF: atrial fibrillation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; HF: heart failure; ICD-10: International Classification of Diseases, Tenth Revision; NPR: National Patient Registry; TIA: transitory ischemic attack; ECG: electrocardiogram; SwedeHF: Swedish HF Registry | |

**Supplemental Table S2.** Target dose definition for the pharmacological therapies considered for the current study according to the 2021 European Society of Cardiology Guidelines on Heart Failure.

|  |  |  |
| --- | --- | --- |
| ***RASI*** | **Dose** | **TD percentage** |
| **Captopril** |  |  |
|  | 150 mg | 100% |
|  | 75 – <150 mg | 50-99% |
|  | <75 mg | 1-49% |
| **Enalapril** |  |  |
|  | 20 mg | 100% |
|  | 10 – <20 mg | 50-99% |
|  | <10 mg | 1-49% |
| **Lisinopril** |  |  |
|  | 35 mg | 100% |
|  | 17.5 – <35 mg | 50-99% |
|  | <17.5 mg | 1-49% |
| **Ramipril** |  |  |
|  | 10 mg | 100% |
|  | 5 – <10 mg | 50-99% |
|  | <5 mg | 1-49% |
| **Trandolapril** |  |  |
|  | 4 mg | 100% |
|  | 2 – <4 mg | 50-99% |
|  | <2 mg | 1-49% |
| **Candesartan** |  |  |
|  | 32 mg | 100% |
|  | 16 – <32 mg | 50-99% |
|  | <16 mg | 1-49% |
| **Valsartan** |  |  |
|  | 320 mg | 100% |
|  | 160 – <320 mg | 50-99% |
|  | <160 mg | 1-49% |
| **Losartan** |  |  |
|  | 150 mg | 100% |
|  | 75 – <150 mg | 50-99% |
|  | <75 mg | 1-49% |
| ***ARNI*** |  | **TD percentage** |
| **Sacubitril/Valsartan** |  |  |
|  | 194/206 mg | 100% |
|  | 97/103 – <194/206 mg | 50-99% |
|  | <97/103 mg | 1-49% |
| ***Beta-blockers*** |  | **TD percentage** |
| **Metoprolol** |  |  |
|  | 200 mg | 100% |
|  | 100 – <200 mg | 50-99% |
|  | <100 mg | 1-49% |
| **Bisoprolol** |  |  |
|  | 10 mg | 100% |
|  | 5 – <10 mg | 50-99% |
|  | <5 mg | 1-49% |
| **Carvedilol** |  |  |
|  | 50 mg (<85 kg)  100 mg x2 (>85 kg) | 100% |
|  | 25 – <50 mg (<85 kg)  50 – <100 mg (>85 kg) | 50-99% |
|  | <25 mg (<85 kg)  <50 mg (>85 kg) | 1-49% |
| ***MRA*** |  | **TD percentage** |
| **Spironolactone** |  |  |
|  | 50 mg | 100% |
|  | 25 mg | 50% |
| **Eplerenone** | 50 mg | 100% |
|  | 25 mg | 50% |
| Abbreviations. ARNI: Angiotensin Receptor Neprilysin Inhibitors; MRA: Mineralocorticoid receptor antagonist; RASI: Renin-Angiotensin System Inhibitors; TD: target dose. | | |

**Supplemental Table S3.** Patient characteristics according to sex and the achieved percentage of target dose category for RASI/ARNI

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RASI/ARNI** | | Males | | | | |  | Females | | | | | |
|  | Variables | No use | 1-49% | 50-99% | 100% | p-value |  | No use | 1-49% | 50-99% | 100% | p-value |
|  | Number | 2051 | 2953 | 3525 | 4231 |  |  | 872 | 1350 | 1423 | 1507 |  |
|  | Age (year), median (IQR) | 80.0 (73.0, 85.0) | 78.0 (71.0, 83.0) | 76.0 (69.0, 82.0) | 74.0 (66.0, 81.0) | <0.001 |  | 83.0 (76.0, 88.0) | 80.0 (73.0, 85.0) | 79.0 (71.0, 84.0) | 77.0 (70.0, 83.0) | <0.001 |
|  | Age class |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | <75 years | 591 (28.8%) | 1105 (37.4%) | 1506 (42.7%) | 2176 (51.4%) |  |  | 186 (21.3%) | 387 (28.7%) | 475 (33.4%) | 606 (40.2%) |  |
|  | ≥75 years | 1460 (71.2%) | 1848 (62.6%) | 2019 (57.3%) | 2055 (48.6%) |  |  | 686 (78.7%) | 963 (71.3%) | 948 (66.6%) | 901 (59.8%) |  |
|  | Year of registration |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | 2000-2005 | 106 (5.2%) | 183 (6.2%) | 98 (2.8%) | 120 (2.8%) |  |  | 48 (5.5%) | 85 (6.3%) | 43 (3.0%) | 65 (4.3%) |  |
|  | 2006-2011 | 790 (38.5%) | 861 (29.2%) | 938 (26.6%) | 1140 (26.9%) |  |  | 344 (39.4%) | 409 (30.3%) | 373 (26.2%) | 456 (30.3%) |  |
|  | 2012-2017 | 834 (40.7%) | 1236 (41.9%) | 1446 (41.0%) | 1592 (37.6%) |  |  | 354 (40.6%) | 558 (41.3%) | 610 (42.9%) | 572 (38.0%) |  |
|  | 2018-2020 | 321 (15.7%) | 673 (22.8%) | 1043 (29.6%) | 1379 (32.6%) |  |  | 126 (14.4%) | 298 (22.1%) | 397 (27.9%) | 414 (27.5%) |  |
|  | Caregiver at registration |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Inpatient | 1215 (59.2%) | 1124 (38.1%) | 1215 (34.5%) | 1174 (27.7%) |  |  | 558 (64.0%) | 600 (44.4%) | 537 (37.7%) | 494 (32.8%) |  |
|  | Outpatient | 836 (40.8%) | 1829 (61.9%) | 2310 (65.5%) | 3057 (72.3%) |  |  | 314 (36.0%) | 750 (55.6%) | 886 (62.3%) | 1013 (67.2%) |  |
|  | Location of follow-up |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Hospital | 1039 (54.8%) | 1939 (68.5%) | 2413 (71.1%) | 2996 (73.2%) |  |  | 329 (41.2%) | 724 (56.1%) | 845 (61.8%) | 911 (62.8%) |  |
|  | Primary care | 766 (40.4%) | 786 (27.8%) | 879 (25.9%) | 986 (24.1%) |  |  | 419 (52.4%) | 513 (39.7%) | 471 (34.4%) | 501 (34.5%) |  |
|  | Other | 92 (4.8%) | 107 (3.8%) | 101 (3.0%) | 112 (2.7%) |  |  | 51 (6.4%) | 54 (4.2%) | 52 (3.8%) | 39 (2.7%) |  |
|  | Follow-up referral to HF clinic | 806 (42.8%) | 1614 (58.0%) | 2140 (63.5%) | 2615 (64.5%) | <0.001 |  | 280 (35.1%) | 649 (50.7%) | 784 (58.2%) | 830 (57.9%) | <0.001 |
|  | Education |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Compulsory school | 1004 (49.9%) | 1254 (43.1%) | 1485 (42.8%) | 1675 (40.3%) |  |  | 485 (57.7%) | 639 (48.5%) | 661 (47.8%) | 692 (47.3%) |  |
|  | Secondary school | 729 (36.2%) | 1148 (39.4%) | 1388 (40.0%) | 1700 (40.9%) |  |  | 262 (31.2%) | 504 (38.2%) | 522 (37.7%) | 551 (37.7%) |  |
|  | University | 281 (14.0%) | 509 (17.5%) | 593 (17.1%) | 778 (18.7%) |  |  | 94 (11.2%) | 175 (13.3%) | 200 (14.5%) | 220 (15.0%) |  |
|  | Family situation |  |  |  |  | 0.21 |  |  |  |  |  | <0.001 |
|  | Cohabitating | 1160 (56.6%) | 1746 (59.2%) | 2054 (58.3%) | 2498 (59.2%) |  |  | 245 (28.1%) | 480 (35.6%) | 533 (37.5%) | 629 (41.8%) |  |
|  | Living alone | 890 (43.4%) | 1203 (40.8%) | 1468 (41.7%) | 1724 (40.8%) |  |  | 627 (71.9%) | 870 (64.4%) | 890 (62.5%) | 877 (58.2%) |  |
|  | Disposable income (euro), median (IQR) | 1526.0 (1261.0, 1893.0) | 1579.0 (1299.0, 1988.0) | 1611.0 (1321.0, 2114.0) | 1653.5 (1323.0, 2260.0) | <0.001 |  | 1282.5 (1064.0, 1531.5) | 1338.0 (1092.0, 1596.0) | 1347.0 (1099.0, 1647.0) | 1323.0 (1085.0, 1618.0) | <0.001 |
|  | Children | 1722 (84.0%) | 2477 (83.9%) | 2881 (81.7%) | 3496 (82.6%) | 0.065 |  | 726 (83.3%) | 1216 (90.1%) | 1227 (86.2%) | 1310 (86.9%) | <0.001 |
|  | NYHA class |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | I-II | 414 (29.4%) | 904 (39.4%) | 1220 (44.1%) | 1831 (53.5%) |  |  | 193 (33.6%) | 380 (39.5%) | 476 (44.3%) | 599 (48.9%) |  |
|  | III-IV | 994 (70.6%) | 1393 (60.6%) | 1548 (55.9%) | 1589 (46.5%) |  |  | 381 (66.4%) | 582 (60.5%) | 598 (55.7%) | 625 (51.1%) |  |
|  | Ejection fraction |  |  |  |  | <0.001 |  |  |  |  |  | 0.76 |
|  | 30-39% | 1054 (51.4%) | 1456 (49.3%) | 1720 (48.8%) | 2279 (53.9%) |  |  | 520 (59.6%) | 784 (58.1%) | 840 (59.0%) | 904 (60.0%) |  |
|  | <30% | 997 (48.6%) | 1497 (50.7%) | 1805 (51.2%) | 1952 (46.1%) |  |  | 352 (40.4%) | 566 (41.9%) | 583 (41.0%) | 603 (40.0%) |  |
|  | Heart rate (bpm), median (IQR) | 72.0 (65.0, 83.0) | 71.0 (63.0, 80.0) | 71.0 (63.0, 80.0) | 70.0 (62.0, 80.0) | <0.001 |  | 75.0 (66.0, 87.0) | 72.0 (64.0, 82.0) | 72.0 (64.0, 82.0) | 71.0 (63.0, 80.0) | <0.001 |
|  | MAP (mmHg), median (IQR) | 86.7 (77.7, 94.0) | 85.0 (76.7, 93.3) | 86.3 (76.7, 95.0) | 86.8 (80.0, 96.7) | <0.001 |  | 86.7 (80.0, 96.7) | 86.7 (77.3, 95.0) | 86.7 (79.2, 96.7) | 88.3 (80.0, 97.3) | <0.001 |
|  | BMI (kg/m2), median (IQR) | 25.2 (22.4, 28.7) | 25.7 (23.1, 28.8) | 26.0 (23.2, 29.4) | 26.6 (23.7, 30.2) | <0.001 |  | 24.6 (21.1, 28.8) | 25.3 (22.0, 29.3) | 25.5 (22.1, 29.8) | 25.9 (22.3, 30.1) | <0.001 |
|  | Body surface area (m2), median (IQR) | 1.9 (1.8, 2.1) | 2.0 (1.9, 2.1) | 2.0 (1.9, 2.1) | 2.0 (1.9, 2.2) | <0.001 |  | 1.7 (1.6, 1.8) | 1.7 (1.6, 1.8) | 1.7 (1.6, 1.9) | 1.7 (1.6, 1.9) | <0.001 |
|  | NT-proBNP (pg/ml), median (IQR) | 6813.0 (2695.0, 15933.0) | 3742.5 (1471.5, 8721.0) | 2815.0 (1167.0, 6409.0) | 2009.0 (808.0, 4751.0) | <0.001 |  | 5726.5 (2357.0, 15449.0) | 3837.0 (1730.0, 8898.0) | 3146.0 (1260.0, 7210.0) | 2330.0 (864.0, 5652.0) | <0.001 |
|  | NT-proBNP |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | <median (3039 pg/ml) | 282 (29.8%) | 762 (47.0%) | 1165 (55.7%) | 1632 (64.5%) |  |  | 125 (33.8%) | 330 (45.3%) | 449 (52.8%) | 510 (60.2%) |  |
|  | ≥ median (3039 pg/ml) | 664 (70.2%) | 858 (53.0%) | 926 (44.3%) | 899 (35.5%) |  |  | 245 (66.2%) | 399 (54.7%) | 402 (47.2%) | 337 (39.8%) |  |
|  | eGFR (ml/min/1.73 m2), median (IQR) | 40.2 (27.9, 57.4) | 50.7 (36.8, 69.9) | 57.5 (43.5, 77.6) | 64.3 (48.8, 83.7) | <0.001 |  | 41.3 (27.6, 57.1) | 46.8 (33.1, 63.0) | 53.9 (39.5, 71.6) | 57.1 (42.7, 74.8) | <0.001 |
|  | eGFR |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | ≥60 ml/min/1.73 m2 | 460 (22.7%) | 1058 (36.6%) | 1593 (46.3%) | 2350 (57.1%) |  |  | 194 (22.5%) | 394 (29.7%) | 560 (40.3%) | 654 (44.6%) |  |
|  | 30-59 ml/min/1.73 m2 | 979 (48.3%) | 1420 (49.1%) | 1586 (46.1%) | 1612 (39.1%) |  |  | 408 (47.3%) | 673 (50.8%) | 687 (49.5%) | 716 (48.9%) |  |
|  | <30 ml/min/1.73 m2 | 587 (29.0%) | 414 (14.3%) | 261 (7.6%) | 157 (3.8%) |  |  | 261 (30.2%) | 258 (19.5%) | 141 (10.2%) | 95 (6.5%) |  |
|  | Potassium (mmol/l), median (IQR) | 4.1 (3.8, 4.5) | 4.2 (4.0, 4.6) | 4.3 (4.0, 4.6) | 4.3 (4.0, 4.6) | <0.001 |  | 4.1 (3.8, 4.5) | 4.2 (3.9, 4.5) | 4.2 (3.9, 4.5) | 4.3 (4.0, 4.5) | <0.001 |
|  | Hemoglobin (g/l), median (IQR) | 126.0 (113.0, 139.0) | 130.0 (118.0, 143.0) | 132.0 (120.0, 145.0) | 136.0 (123.0, 147.0) | <0.001 |  | 124.0 (113.0, 136.0) | 125.0 (115.0, 135.0) | 126.0 (117.0, 137.0) | 128.0 (118.0, 138.0) | <0.001 |
|  | Anemia | 1207 (58.8%) | 1531 (51.8%) | 1688 (47.9%) | 1800 (42.5%) | <0.001 |  | 358 (41.1%) | 539 (39.9%) | 518 (36.4%) | 519 (34.4%) | 0.002 |
|  | Atrial fibrillation | 1406 (68.6%) | 1927 (65.3%) | 2251 (63.9%) | 2531 (59.8%) | <0.001 |  | 548 (62.8%) | 813 (60.2%) | 813 (57.1%) | 771 (51.2%) | <0.001 |
|  | Hypertension | 1412 (68.8%) | 1945 (65.9%) | 2317 (65.7%) | 2769 (65.4%) | 0.047 |  | 629 (72.1%) | 951 (70.4%) | 973 (68.4%) | 1012 (67.2%) | 0.048 |
|  | Diabetes | 771 (37.6%) | 1041 (35.3%) | 1135 (32.2%) | 1397 (33.0%) | <0.001 |  | 290 (33.3%) | 419 (31.0%) | 439 (30.9%) | 395 (26.2%) | 0.001 |
|  | COPD | 386 (18.8%) | 495 (16.8%) | 576 (16.3%) | 629 (14.9%) | <0.001 |  | 147 (16.9%) | 226 (16.7%) | 225 (15.8%) | 244 (16.2%) | 0.89 |
|  | Ischemic heart disease | 1554 (75.8%) | 2129 (72.1%) | 2470 (70.1%) | 2819 (66.6%) | <0.001 |  | 600 (68.8%) | 855 (63.3%) | 856 (60.2%) | 829 (55.0%) | <0.001 |
|  | Peripheral artery disease | 368 (17.9%) | 418 (14.2%) | 470 (13.3%) | 480 (11.3%) | <0.001 |  | 93 (10.7%) | 132 (9.8%) | 153 (10.8%) | 115 (7.6%) | 0.018 |
|  | Stroke or TIA | 538 (26.2%) | 674 (22.8%) | 678 (19.2%) | 806 (19.0%) | <0.001 |  | 198 (22.7%) | 247 (18.3%) | 273 (19.2%) | 218 (14.5%) | <0.001 |
|  | Kidney disease | 1015 (49.5%) | 1026 (34.7%) | 857 (24.3%) | 715 (16.9%) | <0.001 |  | 325 (37.3%) | 362 (26.8%) | 255 (17.9%) | 185 (12.3%) | <0.001 |
|  | Liver disease | 76 (3.7%) | 105 (3.6%) | 121 (3.4%) | 103 (2.4%) | 0.009 |  | 22 (2.5%) | 34 (2.5%) | 32 (2.2%) | 15 (1.0%) | 0.010 |
|  | Major bleeding | 609 (29.7%) | 739 (25.0%) | 791 (22.4%) | 802 (19.0%) | <0.001 |  | 253 (29.0%) | 306 (22.7%) | 325 (22.8%) | 275 (18.2%) | <0.001 |
|  | Dementia | 68 (3.3%) | 67 (2.3%) | 76 (2.2%) | 75 (1.8%) | 0.002 |  | 45 (5.2%) | 39 (2.9%) | 46 (3.2%) | 25 (1.7%) | <0.001 |
|  | Depression | 81 (3.9%) | 97 (3.3%) | 141 (4.0%) | 147 (3.5%) | 0.36 |  | 47 (5.4%) | 68 (5.0%) | 84 (5.9%) | 74 (4.9%) | 0.64 |
|  | Cancer history in the last 3 years | 379 (18.5%) | 475 (16.1%) | 535 (15.2%) | 562 (13.3%) | <0.001 |  | 81 (9.3%) | 152 (11.3%) | 152 (10.7%) | 142 (9.4%) | 0.29 |
|  | Musculoskeletal disease in the last 3 years | 769 (37.5%) | 1013 (34.3%) | 1139 (32.3%) | 1256 (29.7%) | <0.001 |  | 349 (40.0%) | 591 (43.8%) | 557 (39.1%) | 559 (37.1%) | 0.003 |
|  | Smoking |  |  |  |  | <0.001 |  |  |  |  |  | 0.020 |
|  | Current | 136 (8.8%) | 218 (9.2%) | 306 (11.2%) | 428 (12.8%) |  |  | 49 (8.2%) | 78 (7.8%) | 102 (9.6%) | 124 (10.7%) |  |
|  | Former | 819 (52.8%) | 1222 (51.8%) | 1424 (52.0%) | 1684 (50.4%) |  |  | 189 (31.7%) | 364 (36.3%) | 362 (34.0%) | 432 (37.3%) |  |
|  | Never | 595 (38.4%) | 918 (38.9%) | 1008 (36.8%) | 1228 (36.8%) |  |  | 358 (60.1%) | 561 (55.9%) | 601 (56.4%) | 603 (52.0%) |  |
|  | Myocardial infarction | 1261 (61.5%) | 1675 (56.7%) | 1980 (56.2%) | 2200 (52.0%) | <0.001 |  | 464 (53.2%) | 664 (49.2%) | 636 (44.7%) | 629 (41.7%) | <0.001 |
|  | Revascularization | 1575 (76.8%) | 2178 (73.8%) | 2508 (71.1%) | 2876 (68.0%) | <0.001 |  | 605 (69.4%) | 864 (64.0%) | 866 (60.9%) | 843 (55.9%) | <0.001 |
|  | Valve disease | 820 (40.0%) | 978 (33.1%) | 1047 (29.7%) | 1166 (27.6%) | <0.001 |  | 399 (45.8%) | 482 (35.7%) | 486 (34.2%) | 466 (30.9%) | <0.001 |
|  | MRA | 707 (34.6%) | 1105 (37.6%) | 1463 (41.6%) | 2153 (51.0%) | <0.001 |  | 314 (36.2%) | 499 (37.2%) | 596 (42.0%) | 697 (46.4%) | <0.001 |
|  | Diuretic | 1849 (90.5%) | 2570 (87.2%) | 2909 (82.8%) | 3282 (77.7%) | <0.001 |  | 781 (90.0%) | 1168 (86.8%) | 1212 (85.5%) | 1213 (80.7%) | <0.001 |
|  | Digoxin | 262 (12.8%) | 414 (14.1%) | 485 (13.8%) | 565 (13.4%) | 0.61 |  | 146 (16.8%) | 225 (16.7%) | 202 (14.2%) | 212 (14.1%) | 0.086 |
|  | Statin | 978 (47.8%) | 1607 (54.5%) | 2008 (57.1%) | 2530 (59.9%) | <0.001 |  | 287 (33.0%) | 557 (41.3%) | 631 (44.4%) | 726 (48.3%) | <0.001 |
|  | Device | 97 (5.4%) | 190 (7.6%) | 287 (9.4%) | 374 (10.2%) | <0.001 |  | 25 (3.1%) | 44 (3.7%) | 79 (6.2%) | 74 (5.6%) | 0.002 |
|  | Antiplatelet therapy | 952 (46.7%) | 1223 (41.5%) | 1457 (41.4%) | 1719 (40.7%) | <0.001 |  | 412 (47.4%) | 561 (41.7%) | 587 (41.4%) | 655 (43.6%) | 0.026 |
|  | Anticoagulant therapy | 920 (45.0%) | 1554 (52.7%) | 1893 (53.8%) | 2282 (54.1%) | <0.001 |  | 339 (39.1%) | 631 (46.9%) | 641 (45.2%) | 638 (42.4%) | 0.001 |
|  | Nitrates | 474 (23.2%) | 534 (18.1%) | 534 (15.2%) | 588 (13.9%) | <0.001 |  | 223 (25.6%) | 278 (20.6%) | 274 (19.3%) | 235 (15.7%) | <0.001 |
|  | ACE inhibitors |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Captopril | 0 (0.0%) | 8 (0.3%) | 9 (0.3%) | 17 (0.4%) |  |  | 0 (0.0%) | 0 (0.0%) | 5 (0.4%) | 5 (0.3%) |  |
|  | Enalapril | 0 (0.0%) | 334 (11.3%) | 790 (22.4%) | 962 (22.7%) |  |  | 0 (0.0%) | 144 (10.7%) | 298 (20.9%) | 386 (25.6%) |  |
|  | Lisinopril | 0 (0.0%) | 11 (0.4%) | 31 (0.9%) | 57 (1.3%) |  |  | 0 (0.0%) | 8 (0.6%) | 12 (0.8%) | 7 (0.5%) |  |
|  | Ramipril | 0 (0.0%) | 251 (8.5%) | 801 (22.7%) | 1152 (27.2%) |  |  | 0 (0.0%) | 91 (6.7%) | 302 (21.2%) | 406 (26.9%) |  |
|  | No ACEi | 2051 (100.0%) | 2349 (79.5%) | 1894 (53.7%) | 2043 (48.3%) |  |  | 872 (100.0%) | 1107 (82.0%) | 806 (56.6%) | 703 (46.6%) |  |
|  | ARB |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Candesartan | 0 (0.0%) | 1249 (42.3%) | 924 (26.2%) | 1199 (28.3%) |  |  | 0 (0.0%) | 563 (41.7%) | 430 (30.2%) | 494 (32.8%) |  |
|  | Losartan | 0 (0.0%) | 1035 (35.0%) | 518 (14.7%) | 89 (2.1%) |  |  | 0 (0.0%) | 525 (38.9%) | 244 (17.1%) | 42 (2.8%) |  |
|  | Valsartan | 0 (0.0%) | 32 (1.1%) | 42 (1.2%) | 60 (1.4%) |  |  | 0 (0.0%) | 12 (0.9%) | 26 (1.8%) | 18 (1.2%) |  |
|  | No ARB | 2051 (100.0%) | 637 (21.6%) | 2041 (57.9%) | 2883 (68.1%) |  |  | 872 (100.0%) | 250 (18.5%) | 723 (50.8%) | 953 (63.2%) |  |
|  | ARNI | 0 (0.0%) | 33 (1.1%) | 410 (11.6%) | 695 (16.4%) | <0.001 |  | 0 (0.0%) | 7 (0.5%) | 106 (7.4%) | 149 (9.9%) | <0.001 |
|  | eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula; anemia was defined as hemoglobin <120 g/L in females and <130 in males; body surface area was computed with the Du Bois and Du Bois formula.  **Legend.** BMI = body mass index, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range, MAP = mean arterial pressure, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association, NT-proBNP = N-terminal-pro brain natriuretic peptide, TIA = transient ischemic attack, HF = heart failure, n = number. | | | | | | | | | | | | |

*Description of Supplemental Table S3*

Compared with males, females **not using** RASI/ARNI were older, less often outpatients at registration and referred less to specialty care or HF nurse led clinics, had lower education, more likely lived alone, had lower income, and had children in a similar proportion. Females were less likely to have NYHA class III-IV, showed higher EF and heart rate, while similar arterial pressure. Their body surface area and NT-proBNP levels were more likely lower, while their renal function and potassium levels were similar to males. Females less likely had a history of anemia, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, peripheral artery disease, stroke, kidney or liver disease, major bleeding, previous cancer, smoking, but more likely had hypertension, dementia, depression, musculoskeletal disease, and valve disease. Females were similarly receiving diuretics and antiplatelet therapy, were less likely receiving statins and anticoagulant therapy, but more likely took mineralocorticoid receptor antagonists, digoxin, nitrates.

In patients achieving **100% of TD** for RASI/ARNI, as compared with males, females were older, less often outpatients at registration and referred less to specialty care or HF nurse led clinics, had lower education, more likely lived alone, had lower income, and more likely had children. They were more likely to have NYHA class III-IV, but higher EF, heart rate and arterial pressure. Their body surface area, renal function, and potassium levels were more likely lower, while NT-proBNP levels higher. Females less likely had a history of anemia, atrial fibrillation, diabetes, ischemic heart disease, kidney or liver disease, major bleeding, dementia, previous cancer, smoking, but more likely had hypertension, chronic obstructive pulmonary disease, depression, musculoskeletal disease, and valve disease. Females were less likely receiving mineralocorticoid receptor antagonists, statins, and anticoagulant therapy, but more likely diuretics, digoxin, antiplatelet therapy, and nitrates.

**Supplemental Table S4.** Patient characteristics according to sex and the achieved percentage of target dose category for beta-blockers

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Beta-blockers** | | Males | | | | |  | Females | | | | |
|  | Variables | No use | 1-49% | 50-99% | 100% | p-value |  | No use | 1-49% | 50-99% | 100% | p-value |
|  | Number | 1173 | 4181 | 4161 | 3245 |  |  | 467 | 1673 | 1757 | 1255 |  |
|  | Age (year), median (IQR) | 79.0 (71.0, 84.0) | 79.0 (71.0, 84.0) | 76.0 (69.0, 82.0) | 74.0 (66.0, 80.0) | <0.001 |  | 81.0 (72.0, 86.0) | 81.0 (73.0, 86.0) | 79.0 (72.0, 85.0) | 77.0 (71.0, 83.0) | <0.001 |
|  | Age class |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | <75 years | 392 (33.4%) | 1468 (35.1%) | 1757 (42.2%) | 1761 (54.3%) |  |  | 140 (30.0%) | 477 (28.5%) | 569 (32.4%) | 468 (37.3%) |  |
|  | ≥75 years | 781 (66.6%) | 2713 (64.9%) | 2404 (57.8%) | 1484 (45.7%) |  |  | 327 (70.0%) | 1196 (71.5%) | 1188 (67.6%) | 787 (62.7%) |  |
|  | Year of registration |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | 2000-2005 | 89 (7.6%) | 184 (4.4%) | 150 (3.6%) | 84 (2.6%) |  |  | 46 (9.9%) | 97 (5.8%) | 61 (3.5%) | 37 (2.9%) |  |
|  | 2006-2011 | 426 (36.3%) | 1317 (31.5%) | 1166 (28.0%) | 820 (25.3%) |  |  | 176 (37.7%) | 550 (32.9%) | 563 (32.0%) | 293 (23.3%) |  |
|  | 2012-2017 | 394 (33.6%) | 1658 (39.7%) | 1748 (42.0%) | 1308 (40.3%) |  |  | 162 (34.7%) | 668 (39.9%) | 706 (40.2%) | 558 (44.5%) |  |
|  | 2018-2020 | 264 (22.5%) | 1022 (24.4%) | 1097 (26.4%) | 1033 (31.8%) |  |  | 83 (17.8%) | 358 (21.4%) | 427 (24.3%) | 367 (29.2%) |  |
|  | Caregiver at registration |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Inpatient | 462 (39.4%) | 1850 (44.2%) | 1509 (36.3%) | 907 (28.0%) |  |  | 230 (49.3%) | 805 (48.1%) | 749 (42.6%) | 405 (32.3%) |  |
|  | Outpatient | 711 (60.6%) | 2331 (55.8%) | 2652 (63.7%) | 2338 (72.0%) |  |  | 237 (50.7%) | 868 (51.9%) | 1008 (57.4%) | 850 (67.7%) |  |
|  | Location of follow-up |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Hospital | 652 (57.8%) | 2542 (64.2%) | 2788 (70.1%) | 2405 (76.4%) |  |  | 213 (47.0%) | 850 (53.5%) | 945 (56.8%) | 801 (66.5%) |  |
|  | Primary care | 432 (38.3%) | 1250 (31.6%) | 1063 (26.7%) | 672 (21.3%) |  |  | 218 (48.1%) | 663 (41.7%) | 655 (39.4%) | 368 (30.6%) |  |
|  | Other | 44 (3.9%) | 168 (4.2%) | 129 (3.2%) | 71 (2.3%) |  |  | 22 (4.9%) | 76 (4.8%) | 63 (3.8%) | 35 (2.9%) |  |
|  | Follow-up referral to HF clinic | 563 (50.4%) | 2181 (55.6%) | 2411 (61.0%) | 2020 (65.0%) | <0.001 |  | 192 (43.0%) | 783 (49.6%) | 861 (52.4%) | 707 (59.4%) | <0.001 |
|  | Education |  |  |  |  | 0.018 |  |  |  |  |  | 0.81 |
|  | Compulsory school | 512 (44.3%) | 1854 (45.3%) | 1713 (41.9%) | 1339 (41.8%) |  |  | 237 (51.7%) | 807 (50.0%) | 849 (49.6%) | 584 (47.8%) |  |
|  | Secondary school | 457 (39.6%) | 1537 (37.5%) | 1664 (40.7%) | 1307 (40.8%) |  |  | 165 (36.0%) | 587 (36.4%) | 625 (36.5%) | 462 (37.8%) |  |
|  | University | 186 (16.1%) | 706 (17.2%) | 711 (17.4%) | 558 (17.4%) |  |  | 56 (12.2%) | 220 (13.6%) | 237 (13.9%) | 176 (14.4%) |  |
|  | Family situation |  |  |  |  | 0.11 |  |  |  |  |  | <0.001 |
|  | Cohabitating | 667 (57.0%) | 2396 (57.4%) | 2473 (59.5%) | 1922 (59.3%) |  |  | 164 (35.1%) | 564 (33.7%) | 630 (35.9%) | 529 (42.2%) |  |
|  | Living alone | 504 (43.0%) | 1781 (42.6%) | 1682 (40.5%) | 1318 (40.7%) |  |  | 303 (64.9%) | 1109 (66.3%) | 1126 (64.1%) | 726 (57.8%) |  |
|  | Disposable income (euro), median (IQR) | 1567.0 (1270.0, 1994.0) | 1575.0 (1293.0, 2031.0) | 1587.0 (1303.0, 2081.0) | 1662.5 (1347.5, 2217.5) | <0.001 |  | 1267.0 (1039.0, 1541.0) | 1320.0 (1073.0, 1576.0) | 1326.0 (1085.0, 1605.0) | 1374.0 (1129.0, 1654.0) | <0.001 |
|  | Children | 995 (84.8%) | 3453 (82.6%) | 3453 (83.0%) | 2675 (82.4%) | 0.28 |  | 407 (87.2%) | 1448 (86.6%) | 1524 (86.7%) | 1100 (87.6%) | 0.84 |
|  | NYHA class |  |  |  |  | 0.089 |  |  |  |  |  | 0.51 |
|  | I-II | 398 (45.6%) | 1344 (42.6%) | 1416 (44.1%) | 1211 (45.7%) |  |  | 139 (41.5%) | 509 (41.9%) | 555 (43.0%) | 445 (44.9%) |  |
|  | III-IV | 475 (54.4%) | 1813 (57.4%) | 1797 (55.9%) | 1439 (54.3%) |  |  | 196 (58.5%) | 706 (58.1%) | 737 (57.0%) | 547 (55.1%) |  |
|  | Ejection fraction |  |  |  |  | 0.012 |  |  |  |  |  | <0.001 |
|  | 30-39% | 648 (55.2%) | 2086 (49.9%) | 2108 (50.7%) | 1667 (51.4%) |  |  | 273 (58.5%) | 926 (55.3%) | 1097 (62.4%) | 752 (59.9%) |  |
|  | <30% | 525 (44.8%) | 2095 (50.1%) | 2053 (49.3%) | 1578 (48.6%) |  |  | 194 (41.5%) | 747 (44.7%) | 660 (37.6%) | 503 (40.1%) |  |
|  | Heart rate (bpm), median (IQR) | 70.0 (62.0, 80.0) | 70.0 (62.0, 80.0) | 70.0 (62.0, 80.0) | 72.0 (64.0, 82.0) | <0.001 |  | 74.0 (64.0, 83.0) | 72.0 (64.0, 82.0) | 72.0 (64.0, 81.0) | 74.0 (65.0, 84.0) | 0.001 |
|  | MAP (mmHg), median (IQR) | 86.7 (76.7, 96.7) | 85.0 (76.7, 93.3) | 86.7 (78.3, 95.0) | 87.0 (80.0, 96.7) | <0.001 |  | 90.0 (80.0, 96.7) | 86.0 (77.5, 95.0) | 86.7 (80.0, 96.7) | 89.7 (80.0, 97.7) | <0.001 |
|  | BMI (kg/m2), median (IQR) | 25.2 (22.5, 28.4) | 25.1 (22.6, 28.4) | 26.1 (23.4, 29.5) | 27.1 (24.2, 30.9) | <0.001 |  | 24.4 (21.2, 29.2) | 24.5 (21.4, 28.7) | 25.7 (22.4, 30.0) | 26.5 (22.7, 30.6) | <0.001 |
|  | Body surface area (m2), median (IQR) | 2.0 (1.8, 2.1) | 2.0 (1.8, 2.1) | 2.0 (1.9, 2.1) | 2.0 (1.9, 2.2) | <0.001 |  | 1.7 (1.6, 1.8) | 1.7 (1.6, 1.8) | 1.7 (1.6, 1.9) | 1.8 (1.6, 1.9) | <0.001 |
|  | NT-proBNP (pg/ml), median (IQR) | 2532.0 (1062.0, 5999.0) | 3478.0 (1285.0, 8190.0) | 3000.0 (1196.0, 7449.0) | 2553.0 (1049.0, 6090.0) | <0.001 |  | 3137.5 (1035.0, 8521.0) | 3585.0 (1297.5, 9025.5) | 3111.5 (1225.0, 7778.5) | 3254.0 (1490.0, 7108.0) | 0.53 |
|  | NT-proBNP |  |  |  |  | <0.001 |  |  |  |  |  | 0.13 |
|  | <median (3039 pg/ml) | 362 (59.2%) | 1133 (48.9%) | 1232 (52.8%) | 1114 (57.9%) |  |  | 109 (50.9%) | 421 (47.4%) | 511 (52.8%) | 373 (51.3%) |  |
|  | ≥ median (3039 pg/ml) | 249 (40.8%) | 1185 (51.1%) | 1102 (47.2%) | 811 (42.1%) |  |  | 105 (49.1%) | 467 (52.6%) | 457 (47.2%) | 354 (48.7%) |  |
|  | eGFR (ml/min/1.73 m2), median (IQR) | 59.2 (42.6, 78.6) | 54.4 (39.6, 74.7) | 55.1 (39.3, 74.8) | 57.3 (41.5, 77.6) | <0.001 |  | 53.0 (38.9, 71.1) | 50.0 (35.9, 68.8) | 51.0 (36.6, 68.9) | 50.4 (36.2, 68.1) | 0.100 |
|  | eGFR |  |  |  |  | <0.001 |  |  |  |  |  | 0.092 |
|  | ≥60 ml/min/1.73 m2 | 554 (48.4%) | 1722 (42.1%) | 1730 (42.5%) | 1455 (45.9%) |  |  | 181 (39.5%) | 576 (35.0%) | 624 (36.4%) | 421 (34.4%) |  |
|  | 30-59 ml/min/1.73 m2 | 490 (42.8%) | 1882 (46.0%) | 1840 (45.2%) | 1385 (43.7%) |  |  | 229 (50.0%) | 805 (49.0%) | 832 (48.5%) | 618 (50.5%) |  |
|  | <30 ml/min/1.73 m2 | 100 (8.7%) | 487 (11.9%) | 504 (12.4%) | 328 (10.4%) |  |  | 48 (10.5%) | 263 (16.0%) | 260 (15.2%) | 184 (15.0%) |  |
|  | Potassium (mmol/l), median (IQR) | 4.2 (4.0, 4.5) | 4.2 (3.9, 4.5) | 4.3 (4.0, 4.6) | 4.3 (4.0, 4.6) | <0.001 |  | 4.2 (3.9, 4.4) | 4.2 (3.9, 4.5) | 4.2 (3.9, 4.5) | 4.2 (4.0, 4.5) | 0.033 |
|  | Hemoglobin (g/l), median (IQR) | 133.0 (120.0, 145.0) | 130.0 (118.0, 142.0) | 132.0 (119.0, 144.0) | 135.0 (122.0, 147.0) | <0.001 |  | 126.0 (116.0, 137.0) | 126.0 (115.0, 135.0) | 125.0 (115.0, 137.0) | 128.0 (117.0, 139.0) | <0.001 |
|  | Anemia | 545 (46.5%) | 2196 (52.5%) | 2023 (48.6%) | 1462 (45.1%) | <0.001 |  | 166 (35.5%) | 632 (37.8%) | 683 (38.9%) | 453 (36.1%) | 0.35 |
|  | Atrial fibrillation | 753 (64.2%) | 2432 (58.2%) | 2653 (63.8%) | 2277 (70.2%) | <0.001 |  | 234 (50.1%) | 838 (50.1%) | 1037 (59.0%) | 836 (66.6%) | <0.001 |
|  | Hypertension | 714 (60.9%) | 2643 (63.2%) | 2787 (67.0%) | 2299 (70.8%) | <0.001 |  | 286 (61.2%) | 1076 (64.3%) | 1231 (70.1%) | 972 (77.5%) | <0.001 |
|  | Diabetes | 329 (28.0%) | 1263 (30.2%) | 1476 (35.5%) | 1276 (39.3%) | <0.001 |  | 129 (27.6%) | 467 (27.9%) | 529 (30.1%) | 418 (33.3%) | 0.010 |
|  | COPD | 182 (15.5%) | 635 (15.2%) | 717 (17.2%) | 552 (17.0%) | 0.043 |  | 77 (16.5%) | 239 (14.3%) | 310 (17.6%) | 216 (17.2%) | 0.045 |
|  | Ischemic heart disease | 776 (66.2%) | 3027 (72.4%) | 3019 (72.6%) | 2150 (66.3%) | <0.001 |  | 261 (55.9%) | 1087 (65.0%) | 1080 (61.5%) | 712 (56.7%) | <0.001 |
|  | Peripheral artery disease | 151 (12.9%) | 620 (14.8%) | 578 (13.9%) | 387 (11.9%) | 0.003 |  | 42 (9.0%) | 160 (9.6%) | 172 (9.8%) | 119 (9.5%) | 0.96 |
|  | Stroke or TIA | 277 (23.6%) | 944 (22.6%) | 847 (20.4%) | 628 (19.4%) | <0.001 |  | 87 (18.6%) | 320 (19.1%) | 333 (19.0%) | 196 (15.6%) | 0.062 |
|  | Kidney disease | 274 (23.4%) | 1202 (28.7%) | 1240 (29.8%) | 897 (27.6%) | <0.001 |  | 67 (14.3%) | 354 (21.2%) | 393 (22.4%) | 313 (24.9%) | <0.001 |
|  | Liver disease | 33 (2.8%) | 139 (3.3%) | 136 (3.3%) | 97 (3.0%) | 0.73 |  | 8 (1.7%) | 41 (2.5%) | 30 (1.7%) | 24 (1.9%) | 0.43 |
|  | Major bleeding | 280 (23.9%) | 1008 (24.1%) | 955 (23.0%) | 698 (21.5%) | 0.059 |  | 99 (21.2%) | 358 (21.4%) | 421 (24.0%) | 281 (22.4%) | 0.29 |
|  | Dementia | 29 (2.5%) | 133 (3.2%) | 85 (2.0%) | 39 (1.2%) | <0.001 |  | 15 (3.2%) | 57 (3.4%) | 62 (3.5%) | 21 (1.7%) | 0.016 |
|  | Depression | 41 (3.5%) | 163 (3.9%) | 147 (3.5%) | 115 (3.5%) | 0.78 |  | 30 (6.4%) | 85 (5.1%) | 104 (5.9%) | 54 (4.3%) | 0.16 |
|  | Cancer history in the last 3 years | 183 (15.6%) | 664 (15.9%) | 655 (15.7%) | 449 (13.8%) | 0.067 |  | 50 (10.7%) | 186 (11.1%) | 156 (8.9%) | 135 (10.8%) | 0.14 |
|  | Musculoskeletal disease in the last 3 years | 391 (33.3%) | 1378 (33.0%) | 1367 (32.9%) | 1041 (32.1%) | 0.81 |  | 190 (40.7%) | 642 (38.4%) | 718 (40.9%) | 506 (40.3%) | 0.47 |
|  | Smoking |  |  |  |  | 0.13 |  |  |  |  |  | 0.21 |
|  | Current | 86 (9.5%) | 330 (10.2%) | 389 (11.8%) | 283 (11.1%) |  |  | 33 (9.5%) | 106 (8.7%) | 129 (10.0%) | 85 (8.9%) |  |
|  | Former | 457 (50.6%) | 1651 (51.1%) | 1712 (51.9%) | 1329 (52.1%) |  |  | 105 (30.3%) | 421 (34.4%) | 462 (35.6%) | 359 (37.6%) |  |
|  | Never | 361 (39.9%) | 1248 (38.6%) | 1199 (36.3%) | 941 (36.9%) |  |  | 209 (60.2%) | 698 (57.0%) | 705 (54.4%) | 511 (53.5%) |  |
|  | Myocardial infarction | 591 (50.4%) | 2455 (58.7%) | 2400 (57.7%) | 1670 (51.5%) | <0.001 |  | 200 (42.8%) | 855 (51.1%) | 823 (46.8%) | 515 (41.0%) | <0.001 |
|  | Yes |  |  |  |  |  |  |  |  |  |  |  |
|  | Revascularization | 789 (67.3%) | 3081 (73.7%) | 3070 (73.8%) | 2197 (67.7%) | <0.001 |  | 266 (57.0%) | 1092 (65.3%) | 1092 (62.2%) | 728 (58.0%) | <0.001 |
|  | Valve disease | 405 (34.5%) | 1391 (33.3%) | 1303 (31.3%) | 912 (28.1%) | <0.001 |  | 167 (35.8%) | 643 (38.4%) | 619 (35.2%) | 404 (32.2%) | 0.006 |
|  | MRA | 423 (36.2%) | 1637 (39.3%) | 1776 (42.8%) | 1592 (49.2%) | <0.001 |  | 172 (36.9%) | 636 (38.1%) | 740 (42.3%) | 558 (44.7%) | <0.001 |
|  | Diuretic | 974 (83.3%) | 3459 (82.9%) | 3466 (83.6%) | 2711 (83.6%) | 0.82 |  | 396 (84.8%) | 1432 (85.9%) | 1485 (84.9%) | 1061 (84.9%) | 0.84 |
|  | Digoxin | 141 (12.1%) | 410 (9.8%) | 542 (13.1%) | 633 (19.5%) | <0.001 |  | 78 (16.7%) | 198 (11.9%) | 232 (13.2%) | 277 (22.1%) | <0.001 |
|  | Statin | 538 (46.0%) | 2228 (53.4%) | 2404 (58.0%) | 1953 (60.2%) | <0.001 |  | 148 (31.7%) | 657 (39.3%) | 798 (45.4%) | 598 (47.9%) | <0.001 |
|  | Device | 36 (3.3%) | 211 (5.6%) | 351 (9.8%) | 350 (13.4%) | <0.001 |  | 11 (2.5%) | 66 (4.3%) | 77 (4.9%) | 68 (6.3%) | 0.012 |
|  | Antiplatelet therapy | 485 (41.6%) | 1987 (47.7%) | 1736 (41.8%) | 1143 (35.3%) | <0.001 |  | 203 (43.5%) | 826 (49.6%) | 761 (43.5%) | 425 (33.9%) | <0.001 |
|  | Anticoagulant therapy | 550 (47.0%) | 1890 (45.3%) | 2200 (53.0%) | 2009 (61.9%) | <0.001 |  | 171 (36.6%) | 586 (35.2%) | 787 (44.9%) | 705 (56.4%) | <0.001 |
|  | Nitrates | 188 (16.1%) | 668 (16.0%) | 753 (18.2%) | 521 (16.1%) | 0.031 |  | 93 (19.9%) | 323 (19.3%) | 367 (21.0%) | 227 (18.2%) | 0.28 |
|  | Drug |  |  |  |  | <0.001 |  |  |  |  |  | <0.001 |
|  | Bisoprolol | 0 (0.0%) | 1576 (37.7%) | 1904 (45.8%) | 1728 (53.3%) |  |  | 0 (0.0%) | 669 (40.0%) | 826 (47.0%) | 688 (54.8%) |  |
|  | Carvedilol | 0 (0.0%) | 112 (2.7%) | 129 (3.1%) | 181 (5.6%) |  |  | 0 (0.0%) | 31 (1.9%) | 48 (2.7%) | 43 (3.4%) |  |
|  | Metoprolol | 0 (0.0%) | 2493 (59.6%) | 2128 (51.1%) | 1336 (41.2%) |  |  | 0 (0.0%) | 973 (58.2%) | 883 (50.3%) | 524 (41.8%) |  |
|  | No beta-blocker | 1173 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |  |  | 467 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |  |
|  | eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula; anemia was defined as hemoglobin <120 g/L in females and <130 in males; body surface area was computed with the Du Bois and Du Bois formula.  **Legend.** BMI = body mass index, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range, MAP = mean arterial pressure, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association, NT-proBNP = N-terminal-pro brain natriuretic peptide, TIA = transient ischemic attack, HF = heart failure, n = number. | | | | | | | | | | | |

*Description of Supplemental Table S4*

Compared with males, females **not using** beta-blockers were older, less often outpatients at registration and referred less to specialty care or HF nurse led clinics, had lower education, more likely lived alone, had lower income, and more likely had children. Females were more likely to have NYHA class III-IV, and showed higher EF, heart rate, and arterial pressure. Their body surface area and renal function were more likely lower, their NT-proBNP levels were higher, and their potassium levels were similar to males. Females less likely had a history of anemia, atrial fibrillation, diabetes, ischemic heart disease, peripheral artery disease, stroke, kidney or liver disease, major bleeding, previous cancer, smoking, while more frequently had hypertension, chronic obstructive pulmonary disease, dementia, depression, musculoskeletal disease, and valve disease. Females were more likely receiving mineralocorticoid receptor antagonists, diuretics, digoxin, antiplatelet therapy, nitrates, while less likely used anticoagulant therapy and statins.

In patients achieving **100% of TD** for beta-blockers, as compared with males, females were older, less often outpatients at registration and referred to specialty care or HF nurse led clinics, had lower education, more likely lived alone, had lower income, and more likely had children. They were more likely to have NYHA class III-IV, but higher EF, heart rate and arterial pressure. Their body surface area, renal function, and potassium levels were more likely lower, while NT-proBNP levels higher. Females less likely had a history of anemia, atrial fibrillation, diabetes, ischemic heart disease, kidney or liver disease, previous cancer, smoking, but more likely had hypertension, chronic obstructive pulmonary disease, depression, musculoskeletal disease, major bleeding, dementia, and valve disease. Females were less likely receiving mineralocorticoid receptor antagonists, statins, anticoagulant and antiplatelet therapy, but more likely diuretics, digoxin, and nitrates.

**Supplemental Table S5.** Adjusted associations of the achieved percentage of target dose category for RASI/ARNI, ARNI, and beta-blockers with the risk of the study outcomes in the overall cohort

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Overall cohort (n=17,912) | | | | |
|  |  | No use vs 100% | 1-49% vs 100% | 50-99% vs 100% |
| Adjusted HR for HHF or CV Mortality | | |  |  |
|  |  |  |  |  |
|  | RASI/ARNI | 1.22 (1.14-1.30) | 1.11 (1.05-1.17) | 1.03 (0.97-1.09) |
|  |  |  |  |  |
|  | ARNI | — | 1.04 (0.66-1.64) | 0.98 (0.81-1.18) |
|  |  |  |  |  |
|  | Beta-blockers | 1.26 (1.16-1.36) | 1.11 (1.05-1.18) | 1.08 (1.02-1.15) |
|  |  |  |  |  |
| Adjusted HR for all-cause mortality | | |  |  |
|  |  |  |  |  |
|  | RASI/ARNI | 1.36 (1.28-1.45) | 1.11 (1.05-1.18) | 1.07 (1.01-1.13) |
|  |  |  |  |  |
|  | ARNI | — | 1.19 (0.69-2.05) | 1.26 (0.99-1.61) |
|  |  |  |  |  |
|  | Beta-blockers | 1.28 (1.18-1.38) | 1.16 (1.09-1.23) | 1.10 (1.04-1.17) |
|  |  |  |  |  |
| Adjusted HR for CV Mortality | |  |  |  |
|  |  |  |  |  |
|  | RASI/ARNI | 1.40 (1.30-1.51) | 1.14 (1.06-1.22) | 1.09 (1.01-1.17) |
|  |  |  |  |  |
|  | ARNI | — | 1.57 (0.84-2.92) | 1.26 (0.94-1.70) |
|  |  |  |  |  |
|  | Beta-blockers | 1.29 (1.17-1.42) | 1.17 (1.09-1.26) | 1.13 (1.06-1.22) |
|  |  |  |  |  |
| Adjusted HR for HHF | | |  |  |
|  |  |  |  |  |
|  | RASI/ARNI | 1.11 (1.03-1.20) | 1.15 (1.07-1.22) | 1.03 (0.97-1.10) |
|  |  |  |  |  |
|  | ARNI | — | 0.93 (0.56-1.53) | 0.96 (0.79-1.18) |
|  |  |  |  |  |
|  | Beta-blockers | 1.24 (1.13-1.36) | 1.07 (1.00-1.14) | 1.05 (0.99-1.12) |
| Legend. HR = hazard ratio; RASI/ARNI = renin angiotensin system inhibitor/angiotensin receptor neprilysin inhibitor; HHF = hospitalization for heart failure; CV = cardiovascular. *Note: 100% target dose used as reference. The analysis on ARNI involves only the subpopulation of users* | | | | |

**Supplemental Table S6.** Unadjusted and adjusted associations of the achieved percentage of target dose category for RASI/ARNI, ARNI, and beta-blockers with the risk of the study outcomes in males and females**.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Males (n=12,760) | | | |  | Females (n=5,152) | | | |  |  |
|  |  | No use | 1-49% | 50-99% | 100% |  | No use | 1-49% | 50-99% | 100% |  |  |
| RASI/ARNI (n) | | 2,051 (16.1%) | 2,953 (23.1%) | 3,525 (27.6%) | 4,231 (33.2%) |  | 872 (16.9%) | 1,350 (26.2%) | 1,423 (27.6%) | 1,507 (29.3%) |  |  |
| ARNI (n) | | — | 33 (2.9%) | 410 (36.0%) | 695 (61.1%) |  | — | 7 (2.7%) | 106 (40.4%) | 149 (56.9%) |  |  |
| Beta-blockers (n) | | 1,173 (9.2%) | 4,181 (32.8%) | 4,161 (32.6%) | 3,245 (25.4%) |  | 467 (9.1%) | 1,673 (32.5%) | 1,757 (34.1%) | 1,255 (24.3%) |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| HF Hospitalization or CV Mortality | | |  |  |  |  |  |  |  |  |  | p-value *ⴕ* |
| RASI/ARNI | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 2.31 (2.16-2.47) | 1.58 (1.48-1.68) | 1.30 (1.22-1.40) | ref. |  | 2.13 (1.91-2.37) | 1.46 (1.32-1.62) | 1.11 (1.01-1.23) | ref. |  | 0.089 |
|  | HR adjusted | 1.20 (1.12-1.29) | 1.12 (1.04-1.19) | 1.07 (1.00-1.14) | ref. |  | 1.26 (1.12-1.42) | 1.08 (0.97-1.19) | 0.92 (0.83-1.03) | ref. |  | 0.030 |
| ARNI |  |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | — | 1.70 (1.08-2.68) | 1.36 (1.13-1.64) | ref. |  | — | 3.33 (1.33-8.34) | 0.99 (0.65-1.49) | ref. |  | 0.110 |
|  | HR adjusted | — | 1.06 (0.64-1.77) | 1.06 (0.86-1.29) | ref. |  | — | 0.89 (0.33-2.39) | 0.68 (0.44-1.05) | ref. |  | 0.191 |
| Beta-blockers | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 1.26 (1.16-1.38) | 1.27 (1.19-1.35) | 1.18 (1.11-1.25) | ref. |  | 1.36 (1.19-1.56) | 1.38 (1.25-1.53) | 1.22 (1.10-1.35) | ref. |  | 0.572 |
|  | HR adjusted | 1.27 (1.15-1.39) | 1.10 (1.03-1.18) | 1.07 (1.00-1.14) | ref. |  | 1.23 (1.06-1.44) | 1.15 (1.03-1.27) | 1.12 (1.01-1.25) | ref. |  | 0.762 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| All-cause mortality | |  |  |  |  |  |  |  |  |  |  | p-value *ⴕ* |
| RASI/ARNI | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 2.82 (2.64-3.01) | 1.67 (1.57-1.78) | 1.36 (1.28-1.44) | ref. |  | 2.56 (2.30-2.85) | 1.51 (1.37-1.67) | 1.15 (1.04-1,28) | ref. |  | 0.070 |
|  | HR adjusted | 1.36 (1.26-1.46) | 1.13 (1.06-1.21) | 1.11 (1.04-1.19) | ref. |  | 1.37 (1.22-1.53) | 1.06 (0.96-1.18) | 0.97 (0.87-1.08) | ref. |  | 0.090 |
| ARNI |  |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | — | 1.96 (1.13-3.39) | 1.86 (1.47-2.35) | ref. |  | — | 11.0 (4.18-28.81) | 1.29 (0.73-2.28) | ref. |  | 0.001 |
|  | HR adjusted | — | 1.01 (0.54-1.88) | 1.36 (1.05-1.76) | ref. |  | — | 2.24 (0.77-6.56) | 0.90 (0.49-1.64) | ref. |  | 0.129 |
| Beta-blockers | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 1.45 (1.33-1.58) | 1.44 (1.36-1.53) | 1.26 (1.19-1.34) | ref. |  | 1.53 (1.33-1.76) | 1.57 (1.42-1.74) | 1.28 (1.15-1.42) | ref. |  | 0.534 |
|  | HR adjusted | 1.30 (1.18-1.43) | 1.14 (1.07-1.23) | 1.11 (1.03-1.19) | ref. |  | 1.23 (1.06-1.43) | 1.19 (1.07-1.33) | 1.09 (0.98-1.22) | ref. |  | 0.622 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| CV Mortality | |  |  |  |  |  |  |  |  |  |  | p-value *ⴕ* |
| RASI/ARNI | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 2.99 (2.76-3.24) | 1.75 (1.62-1.89) | 1.40 (1.30-1.51) | ref. |  | 2.65 (2.33-3.02) | 1.54 (1.36-1.74) | 1.14 (1.00-1.30) | ref. |  | 0.061 |
|  | HR adjusted | 1.40 (1.29-1.53) | 1.16 (1.07-1.26) | 1.13 (1.04-1.23) | ref. |  | 1.37 (1.20-1.57) | 1.07 (0.94-1.22) | 0.97 (0.84-1.11) | ref. |  | 0.191 |
| ARNI |  |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | — | 2.25 (1.20-4.21) | 1.82 (1.37-2.43) | ref. |  | — | 17.50 (6.37-48.09) | 1.23 (0.60-2.51) | ref. |  | 0.001 |
|  | HR adjusted | — | 1.23 (0.59-2.56) | 1.39 (1.01-1.91) | ref. |  | — | 3.54 (1.10-11.33) | 0.85 (0.40-1.81) | ref. |  | 0.082 |
| Beta-blockers | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 1.50 (1.35-1.66) | 1.52 (1.41-1.64) | 1.31 (1.22-1.42) | ref. |  | 1.60 (1.35-1.90) | 1.64 (1.45-1.86) | 1.38 (1.21-1.56) | ref. |  | 0.834 |
|  | HR adjusted | 1.31 (1.16-1.47) | 1.17 (1.07-1.27) | 1.12 (1.03-1.22) | ref. |  | 1.24 (1.03-1.50) | 1.19 (1.04-1.36) | 1.16 (1.01-1.33) | ref. |  | 0.873 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| HF Hospitalization | |  |  |  |  |  |  |  |  |  |  | p-value *ⴕ* |
| RASI/ARNI | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 1.93 (1.78-2.09) | 1.58 (1.47-1.69) | 1.26 (1.17-1.35) | ref. |  | 1.72 (1.51-1.97) | 1.46 (1.30-1.64) | 1.15 (1.02-1.30) | ref. |  | 0.518 |
|  | HR adjusted | 1.10 (1.01-1.20) | 1.16 (1.07-1.25) | 1.05 (0.98-1.14) | ref. |  | 1.13 (0.98-1.31) | 1.12 (0.99-1.26) | 0.96 (0.85-1.09) | ref. |  | 0.516 |
| ARNI |  |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | — | 1.54 (0.92-2.55) | 1.30 (1.06-1.59) | ref. |  | — | 2.83 (1.02-7.86) | 1.01 (0.66-1.55) | ref. |  | 0.262 |
|  | HR adjusted | — | 0.98 (0.56-1.70) | 1.03 (0.83-1.28) | ref. |  | — | 0.72 (0.24-2.17) | 0.72 (0.46-1.13) | ref. |  | 0.352 |
| Beta-blockers | |  |  |  |  |  |  |  |  |  |  |  |
|  | HR unadjusted | 1.13 (1.02-1.25) | 1.12 (1.05-1.21) | 1.10 (1.02-1.18) | ref. |  | 1.17 (0.99-1.38) | 1.19 (1.05-1.33) | 1.09 (0.97-1.22) | ref. |  | 0.931 |
|  | HR adjusted | 1.25 (1.12-1.39) | 1.07 (0.99-1.15) | 1.04 (0.97-1.13) | ref. |  | 1.21 (1.01-1.44) | 1.08 (0.95-1.22) | 1.07 (0.95-1.21) | ref. |  | 0.949 |
| Legend. HR = hazard ratio; RASI/ARNI = renin angiotensin system inhibitor/angiotensin receptor neprilysin inhibitor; HHF = hospitalization for heart failure; CV = cardiovascular; ref. = reference. *Note: 100% target dose used as reference. P-values for interactions between sex and target dose class are reported (ⴕ). The analysis on ARNI involves only the subpopulation of users* | | | | | | | | | | |  |  |

**Supplemental Table S7.** Variables with missing data included in the multiple imputation

|  |  |  |
| --- | --- | --- |
| **Variables** | **Number of missing data** | **% of the total** |
| Hemoglobin | 1,295 | 7,2 |
| Follow-up referral to HF clinic | 958 | 5,3 |
| Location of follow-up | 787 | 4,4 |
| Education | 363 | 2,0 |
| Family situation | 18 | 0,1 |
| Disposable income | 18 | 0,1 |
| NYHA | 4,185 | 23,4 |
| Heart rate | 952 | 5,3 |
| MAP | 485 | 2,7 |
| BMI | 1,837 | 10,3 |
| BSA | 5,936 | 33,1 |
| NT-proBNP | 7,927 | 44,3 |
| eGFR | 394 | 2,2 |
| Potassium | 3,551 | 19,8 |
| Smoking | 4,103 | 22,9 |
| MRA | 60 | 0,3 |
| Diuretic | 54 | 0,3 |
| Digoxin | 41 | 0,2 |
| Statin | 37 | 0,2 |
| Antiplatelet therapy | 52 | 0,3 |
| Anticoagulant therapy | 45 | 0,3 |
| Nitrates | 50 | 0,3 |
| Device | 2,293 | 12,8 |

**Supplemental Figure S1.** Flow-chart summarizing the study cohort selection process.

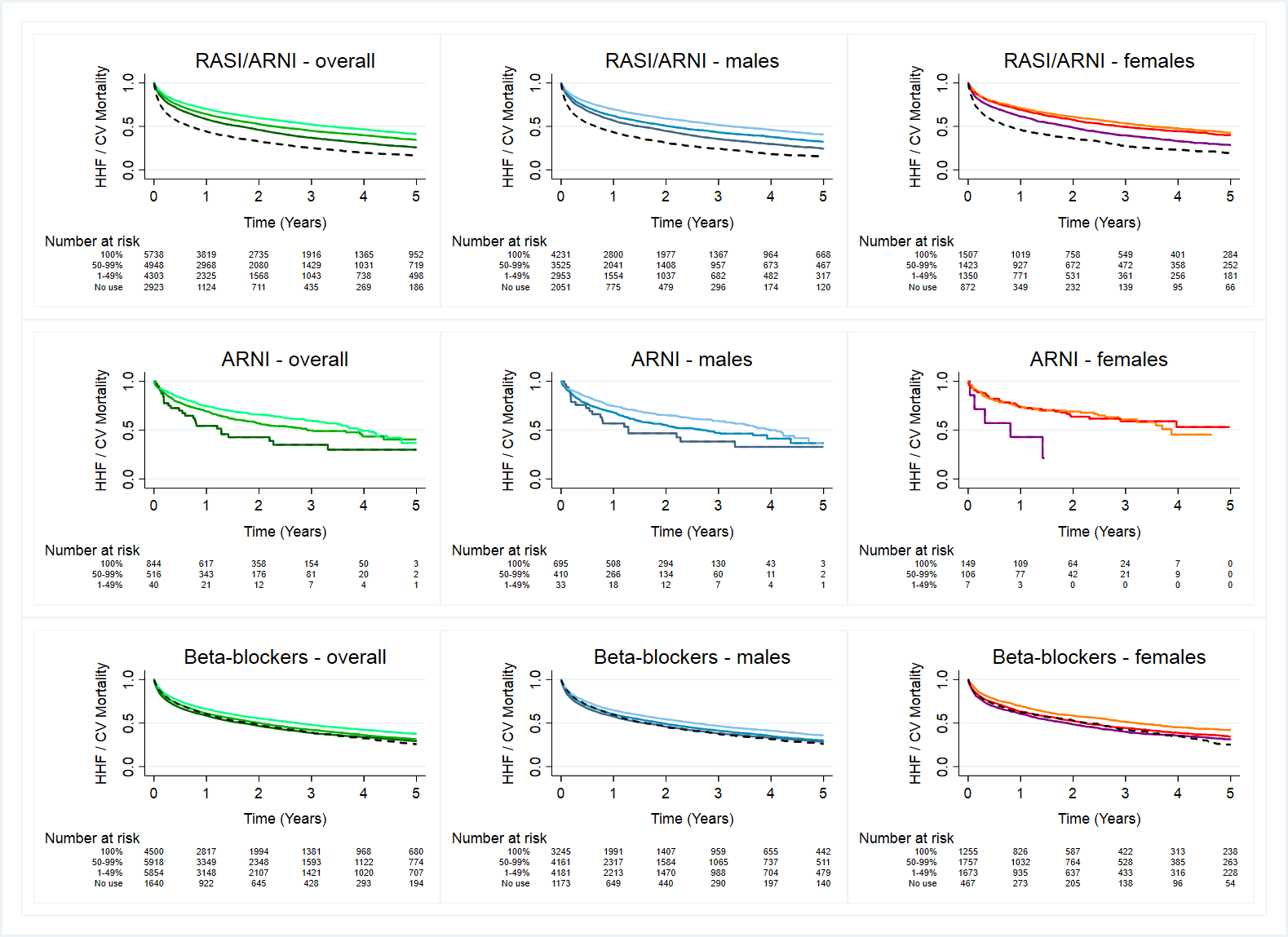
****

**Immagine che contiene testo, schermata, Diagramma, diagramma

Descrizione generata automaticamenteSupplemental Figure S2.** Kernel density function of the distribution of men (blue) and women (red) taking specific percentages of target doses for RASI/ARNI (top) and beta-blockers (bottom)

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

**Supplemental Figure S3.** Kaplan-Meier curves for the primary composite outcome (i.e., cardiovascular mortality/heart failure hospitalization) in the overall population (green) and separately in males and females (blue and red, respectively) across target dose categories of RASI/ARNI, ARNI alone, and beta-blockers (the lower the color intensity, the higher the target dose category). *Note: the analysis on ARNI involves only the subpopulation of users*.



**Legend.** RASI/ARNI = renin-angiotensin-system inhibitor/angiotensin-receptor-neprilysin inhibitor; HHF = hospitalization for heart failure; CV = cardiovascular

**Supplemental Figure S4.** Kaplan-Meier curves for the secondary outcome all-cause mortality in the overall population (green) and separately in males and females (blue and red, respectively) across target dose categories of RASI/ARNI, ARNI alone, and beta-blockers (the lower the color intensity, the higher the target dose category). *Note: the analysis on ARNI involves only the subpopulation of users*.

**Immagine che contiene testo, diagramma, schermata, Parallelo

Descrizione generata automaticamente**

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

**Supplemental Figure S5.** Kaplan-Meier curves for the secondary outcome cardiovascular mortality in the overall population (green) and separately in males and females (blue and red, respectively) across target dose categories of RASI/ARNI, ARNI alone, and beta-blockers (the lower the color intensity, the higher the target dose category). *Note: the analysis on ARNI involves only the subpopulation of users*.

**Immagine che contiene testo, schermata, diagramma, Carattere

Descrizione generata automaticamente**

**Legend.** RASI/ARNI = renin angiotensin system inhibitor/angiotensin receptor neprilysin inhibitor; CV = cardiovascular

**Immagine che contiene testo, schermata, numero, diagramma

Descrizione generata automaticamenteSupplemental Figure S6.** Adjusted hazard ratios for the secondary outcomes all-cause mortality (top), cardiovascular mortality (middle), and hospitalization for heart failure (bottom) in the overall population (green) and separately in males (blue) vs. females (red) according to the achieved percentage of target dose category for RASI/ARNI (left), ARNI (center), and beta-blockers (right). *Note: 100% of target dose used as reference. P-values for interactions between sex and target dose class are reported (ⴕ). The analysis on ARNI involves only the subpopulation of users*

**Legend.** RASI/ARNI = renin angiotensin system inhibitor/angiotensin receptor neprilysin inhibitor; HR = hazard ratio; TD = target dose; CV = cardiovascular; HHF = hospitalization for heart failure

**Supplemental Figure S7.** Kaplan-Meier curves for the secondary outcome hospitalization for heart failure in the overall population (green) and separately in males and females (blue and red, respectively) across target dose categories of RASI/ARNI, ARNI alone, and beta-blockers (the lower the color intensity, the higher the target dose category). *Note: the analysis on ARNI involves only the subpopulation of users*.

**Immagine che contiene testo, schermata, diagramma, Diagramma

Descrizione generata automaticamente**

**Legend.** RASI/ARNI = renin angiotensin system inhibitor/angiotensin receptor neprilysin inhibitor; HHF= heart failure hospitalization

**Supplemental Figure S8.** Sensitivity analysis on RASI alone. The plots represent the adjusted hazard ratios for the primary composite outcome (top left) and the secondary outcomes all-cause mortality (top right), cardiovascular mortality (bottom left), and hospitalization for heart failure (bottom right) in the overall population (green) and separately in males (blue) vs. females (red) according to the achieved percentage of target dose category for RASI. The results are overall consistent with those obtained for RASI/ARNI. *Note: 100% of target dose used as reference. P-values for interactions between sex and target dose class are reported (ⴕ).*

*Immagine che contiene testo, diagramma, schermata, Parallelo

Descrizione generata automaticamente*

**Legend.** RASI = renin angiotensin system inhibitor (angiotensin-converting-enzyme-inhibitors or angiotensin-receptor-blockers); HR = hazard ratio; TD = target dose; CV = cardiovascular; HHF = hospitalization for heart failure