**Supplement SCB EAST-AFNET 4**

**Supplementary table 1**

|   | All patients  | All patients - Model with Interaction |
| --- | --- | --- |
| Predictors | Estimates | CI | p | Estimates | CI | p |
| SCB meds | 0.69 | 0.51 – 0.93 | **0.015** | 1.10 | 0.54 – 2.25 | 0.792 |
| Random group: ERC | 1.19 | 0.98 – 1.45 | 0.075 | 1.23 | 1.01 – 1.50 | **0.040** |
| Age | 1.06 | 1.05 – 1.08 | **<0.001** | 1.07 | 1.05 – 1.08 | **<0.001** |
| Male Gender | 1.11 | 0.92 – 1.35 | 0.267 | 1.12 | 0.92 – 1.36 | 0.245 |
| Interactionterm Meds:Random group |  |  |  | 0.58 | 0.27 – 1.26 | 0.173 |
| CAD | 1.10 | 0.87 – 1.38 | 0.434 | 1.09 | 0.86 – 1.38 | 0.451 |
| LV Hypertrophy on ecg | 1.53 | 1.03 – 2.27 | **0.035** | 1.53 | 1.03 – 2.28 | **0.034** |
| Stable HF | 1.46 | 1.20 – 1.77 | **<0.001** | 1.46 | 1.20 – 1.78 | **<0.001** |

**Supplementary table 2**

Baseline characteristics of patients with or without SCB intake according to randomized groups

| **Characteristics** | **No Sodium Channel Blocker at BL/Discharge at BL/Discharge** | **Sodium Channel Blocker intake at BL/Discharge** |
| --- | --- | --- |
| **ERC**, N = 8411 | **UC**, N = 1,3631 | **ERC**, N = 5541 | **UC**, N = 311 |
|  |
| Age |  |  |  |  |
|     Mean ± SD | 71 ± 8.4 | 70 ± 8.2 | 69 ± 8.5 | 69 ± 7.6 |
|     Median (IQR) | 72 (66.0, 76) | 71 (66.0, 76) | 70 (64.0, 75) | 71 (64.0, 74) |
| Gender |  |  |  |  |
|     Female | 350/841 (42%) | 632/1,363 (46%) | 295/554 (53%) | 16/31 (52%) |
|     Male | 491/841 (58%) | 731/1,363 (54%) | 259/554 (47%) | 15/31 (48%) |
| Body Mass Index (calculated) [kg/m²] |  |  |  |  |
|     Mean ± SD | 29.3 ± 5.4 | 29.3 ± 5.4 | 29.0 ± 5.3 | 27.8 ± 4.2 |
|     Median (IQR) | 28.6 (25.5, 32.2) | 28.7 (25.5, 32.4) | 28.4 (25.5, 31.6) | 27.6 (24.6, 30.0) |
| AF type |  |  |  |  |
| Concomitant cardiovascular conditions |  |  |  |  |
|     First episode | 326/837 (39%) | 511/1,363 (37%) | 202/554 (36%) | 9/31 (29%) |
|     Paroxysmal | 256/837 (31%) | 478/1,363 (35%) | 245/554 (44%) | 15/31 (48%) |
|     Persistent or long-standing persistent | 255/837 (30%) | 374/1,363 (27%) | 107/554 (19%) | 7/31 (23%) |
| Sinus rhythm at baseline | 395/835 (47%) | 729/1,362 (54%) | 367/554 (66%) | 14/31 (45%) |
| Median days since AF diagnosis (IQR) |  |  |  |  |
|     Mean ± SD | 82.9 ± 140.2 | 85.1 ± 186.0 | 79.5 ± 212.3 | 103.0 ± 139.1 |
|     Median (IQR) | 38.0 (6.0, 118.5) | 36.0 (6.0, 108.8) | 33.0 (6.0, 103.0) | 65.0 (8.5, 152.0) |
| Absence of atrial fibrillation symptoms | 243/790 (31%) | 398/1,300 (31%) | 152/515 (30%) | 8/28 (29%) |
| Previous pharmacological or electrical cardioversion | 306/816 (38%) | 524/1,358 (39%) | 240/548 (44%) | 19/31 (61%) |
| Prior AF ablation | 0/841 (0%) | 3/1,363 (0.2%) | 0/554 (0%) | 0/31 (0%) |
| Previous stroke or transient ischemic attack | 112/841 (13%) | 149/1,363 (11%) | 63/554 (11%) | 4/31 (13%) |
| At least mild cognitive impairment | 371/796 (47%) | 575/1,310 (44%) | 211/530 (40%) | 9/31 (29%) |
| Arterial hypertension | 736/841 (88%) | 1,191/1,363 (87%) | 494/554 (89%) | 29/31 (94%) |
| Systolic blood pressure [mmHg] |  |  |  |  |
|     Mean ± SD | 137 ± 20.6 | 137 ± 19.3 | 135 ± 17.3 | 136 ± 21.3 |
|     Median (IQR) | 136 (122.0, 150) | 137 (123.0, 150) | 130 (123.0, 143) | 132 (122.5, 147) |
| Diastolic blood pressure [mmHg] |  |  |  |  |
|     Mean ± SD | 81 ± 12.7 | 81 ± 12.0 | 80 ± 11.0 | 77 ± 11.4 |
|     Median (IQR) | 80 (74.0, 90) | 80 (74.0, 90) | 80 (71.0, 89) | 78 (70.0, 80) |
| Stable heart failure | 249/841 (30%) | 394/1,363 (29%) | 147/554 (27%) | 8/31 (26%) |
| Medication at discharge |  |  |  |  |
| HFrEF | 55/249 (22%) | 74/394 (19%) | 2/147 (1.4%) | 1/8 (12%) |
| HFmrEF | 82/249 (33%) | 101/394 (26%) | 28/147 (19%) | 0/8 (0%) |
| HFpEF | 108/249 (43%) | 212/394 (54%) | 116/147 (79%) | 6/8 (75%) |
| CHA2DS2-VASc score |  |  |  |  |
|     Mean ± SD | 3.5 ± 1.3 | 3.3 ± 1.3 | 3.2 ± 1.3 | 3.1 ± 1.3 |
|     Median (IQR) | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) |
| Chronic kidney disease of MDRF stage 3 or 4 | 104/841 (12%) | 173/1,363 (13%) | 68/554 (12%) | 6/31 (19%) |
| Severe coronary atery diseases (prev. MI, CABG or PCI) | 211/841 (25%) | 233/1,363 (17%) | 32/554 (5.8%) | 3/31 (9.7%) |
| Left ventricular hypertrophy on echocardiography | 44/841 (5.2%) | 66/1,363 (4.8%) | 21/554 (3.8%) | 1/31 (3.2%) |
|  |  |  |  |  |
| LVEF at BL |  |  |  |  |
|     Abnormal | 137/818 (17%) | 175/1,327 (13%) | 30/546 (5.5%) | 1/30 (3.3%) |
|     Normal | 681/818 (83%) | 1,152/1,327 (87%) | 516/546 (95%) | 29/30 (97%) |
| Oral anticoagulation with NOAC or VKA | 772/835 (92%) | 1,226/1,362 (90%) | 495/554 (89%) | 24/31 (77%) |
| Digoxin or digitoxin | 39/835 (4.7%) | 84/1,362 (6.2%) | 7/554 (1.3%) | 1/31 (3.2%) |
| Beta blockers | 623/835 (75%) | 1,165/1,362 (86%) | 435/554 (79%) | 26/31 (84%) |
| ACE inhibitors or angiotensin II receptor blocker | 580/835 (69%) | 955/1,362 (70%) | 373/554 (67%) | 24/31 (77%) |
| Mineralocorticoid receptor antagonist | 69/835 (8.3%) | 91/1,362 (6.7%) | 21/554 (3.8%) | 1/31 (3.2%) |
| Diuretic | 369/835 (44%) | 550/1,362 (40%) | 190/554 (34%) | 11/31 (35%) |
| Statin | 404/835 (48%) | 555/1,362 (41%) | 224/554 (40%) | 13/31 (42%) |
| Platelet inhibitor | 180/835 (22%) | 218/1,362 (16%) | 49/554 (8.8%) | 8/31 (26%) |
| Oral antidiabetics | 142/835 (17%) | 229/1,362 (17%) | 86/554 (16%) | 2/31 (6.5%) |
| Planned therapy for rhythm control at baseline |  |  |  |  |
|     AAD | 665/841 (79%) | 33/1,363 (2.4%) | 546/554 (99%) | 24/31 (77%) |
|     Ablation | 104/841 (12%) | 2/1,363 (0.1%) | 8/554 (1.4%) | 0/31 (0%) |
|     None | 72/841 (8.6%) | 1,328/1,363 (97%) | 0/554 (0%) | 7/31 (23%) |
| 1 Mean (SD) or Frequency with no./total no. (%) |

**Supplementary table 3**

Follow-Up Ablation stratified by treatment group and SCB Intake

|  | Early rhythm control | Usual care |
| --- | --- | --- |
|  | Baseline | Later | Never | p-value | Baseline | Later | Never | p-value |
| n | 554 | 135 | 706 |  | 31 | 118 | 1245 |  |
| Ablation overall | 95 (17.1) | 49 (36.3) | 196 (27.8) | 0.002 | 4 (12.9) | 41 (34.7) | 123 (9.9) | <0.001 |
| Ablation before FU12 | 53 (9.6) | 27 (20.0) | 145 (20.5) | 0.018 | 2 (6.5) | 13 (11.0) | 48 (3.9) | 0.003 |
| Ablation before FU24 | 70 (12.6) | 37 (27.4) | 163 (23.1) | 0.012 | 2 (6.5) | 26 (22.0) | 69 (5.5) | <0.001 |

**Supplementary table 4**

**Duration of SCB intake in patients according to different timepoints during the study**

|  | **Early rhythm control** | **Usual care** | **All patients** |  |
| --- | --- | --- | --- | --- |
| **Baseline**N = 554 | **Later**N = 135 | **Baseline** N = 31 | **Later**N = 118 | **Baseline****N = 585** | **Later****N = 253** |
| Total duration of intake (days) |
| Mean (SD) | 1,156 (861) | 951 (862) | 813 (895) | 837 (791) | 1,138 (866) | 898 (830) |
| Median [IQR] | 1,254 [308, 1,840] | 730 [140, 1,743] | 406 [83, 1,444] | 569 [122, 1,275] | 1,214 [290, 1,826] | 690 [131, 1,565] |
| Range | 1 to 2,985 | 1 to 2,657 | 1 to 2,942 | 3 to 2,902 | 1 to 2,985 | 1 to 2,902 |

**Supplementary table 5**

Rate of Sinus rhythm at 12 and 24 months

|  | **ERC** | **UC** |
| --- | --- | --- |
| **Characteristic** | **Baseline**N = 554 | **Later**, N = 135 | **Never**, N = 706 | **Baseline**N = 31 | **Later**N = 118 | **Never**N = 1,245 |
| Sinus rhythm at baseline | 367 (66%) | 61 (45%) | 334 (48%) | 14 (45%) | 78 (66%) | 651 (52%) |
|  Unknown | 0 | 0 | 6 | 0 | 0 | 1 |
| Sinus rhythm at FU12 | 426 (88%) | 111 (87%) | 472 (82%) | 20 (77%) | 96 (88%) | 672 (63%) |
|  Unknown | 71 | 8 | 127 | 5 | 9 | 177 |
| Sinus rhythm at FU24 | 382 (85%) | 108 (86%) | 431 (79%) | 17 (71%) | 83 (78%) | 587 (58%) |
|  Unknown | 105 | 10 | 158 | 7 | 12 | 240 |
| Sinus rhythm at FU12 detailed |
| Dec/Withdr. | 22 (4.4%) | 2 (1.6%) | 54 (8.5%) | 2 (7.1%) | 2 (1.8%) | 65 (5.7%) |
| No Sinus rhythm | 57 (11%) | 16 (12%) | 107 (17%) | 6 (21%) | 13 (12%) | 396 (35%) |
| Sinus rhythm | 426 (84%) | 111 (86%) | 472 (75%) | 20 (71%) | 96 (86%) | 672 (59%) |
|  Unknown | 49 | 6 | 73 | 3 | 7 | 112 |
| Sinus rhythm at FU24 detailed |
| Dec/Withdr. | 35 (7.2%) | 2 (1.6%) | 77 (12%) | 4 (14%) | 2 (1.9%) | 105 (9.5%) |
| No Sinus rhythm | 67 (14%) | 17 (13%) | 117 (19%) | 7 (25%) | 23 (21%) | 418 (38%) |
| Sinus rhythm | 381 (79%) | 108 (85%) | 431 (69%) | 17 (61%) | 83 (77%) | 587 (53%) |
|  Unknown | 71 | 8 | 81 | 3 | 10 | 135 |
|  |

**Supplementary table 6**

Supplementary table 6a

Primary efficacy endpoints according to SCB intake at different time points

|  | Early rhythm control | Usual care |
| --- | --- | --- |
|  | Baseline | Later | Never | Baseline | Later | Never |
| First primary outcome - events/person-yr (incidence/100 person-yr) | 75/2628 (2.9) | 24/688 (3.5) | 150/3083 (4.9) | 4/169 (2.4) | 21/596 (3.5) | 291/5567 (5.2) |
| **Components of first primary outcome - events/person-yr (incidence/100 person-yr)** |
| Death from cardiovascular causes | 18/2784 (0.6) | 6/734 (0.8) | 43/3398 (1.3) | 2/174 (1.1) | 3/651 (0.5) | 89/6163 (1.4) |
| Stroke | 14/2742 (0.5) | 3/725 (0.4) | 23/3345 (0.7) | 1/171 (0.6) | 6/635 (0.9) | 55/6049 (0.9) |
| Hospitalization with worsening of HF | 44/2699 (1.6) | 13/708 (1.8) | 82/3213 (2.6) | 0/174 (0) | 12/614 (2) | 157/5769 (2.7) |
| Hospitalization with acs | 16/2738 (0.6) | 5/720 (0.7) | 32/3304 (1) | 2/172 (1.2) | 3/641 (0.5) | 60/6003 (1) |
| Second primary outcome - Nights spent in hospital/yr | 4.01±12.1 | 4.01±8.6 | 7.62±28.7 | 6.11±20.1 | 4.32±11.5 | 5.11±15.8 |

Supplementary table 6b

Primary efficacy endpoints according to SCB intake

|  | Early rhythm control | Usual care |
| --- | --- | --- |
|  | Ever | Never | Ever | Never |
| First primary outcome - events/person-yr (incidence/100 person-yr) | 99/3316 (3) | 150/3083 (4.9) | 25/765 (3.3) | 291/5567 (5.2) |
| **Components of first primary outcome - events/person-yr (incidence/100 person-yr)** |
| Death from cardiovascular causes | 24/3517 (0.7) | 43/3398 (1.3) | 5/825 (0.6) | 89/6163 (1.4) |
| Stroke | 17/3468 (0.5) | 23/3345 (0.7) | 7/807 (0.9) | 55/6049 (0.9) |
| Hospitalization with worsening of HF | 57/3407 (1.7) | 82/3213 (2.6) | 12/788 (1.5) | 157/5769 (2.7) |
| Hospitalization with acs | 21/3458 (0.6) | 32/3304 (1) | 5/813 (0.6) | 60/6003 (1) |
| Second primary outcome - Nights spent in hospital/yr | 4.01±11.5 | 7.62±28.7 | 4.69±13.7 | 5.11±15.8 |
| **Key secondary outcomes at 2 years** |
| Change in LVEF | 0.32±8.7 | 2.77±10.6 | 1.94±10.4 | 0.61±9.7 |
| Change in EQ-5D score | 1.63±16.7 | 1.09±18.4 | 4.66±16.7 | 0.25±16.7 |
| Change in SF-12 Mental Score | 0.21±10.7 | 1.26±10.6 | 1.89±10.1 | 1.53±10.1 |
| Change in SF-12 Physical Score | -0.02±8 | 0.63±9 | 2.77±7 | -0.29±8.2 |
| Change in MoCA score | 0.29±3.4 | -0.08±3.2 | 0.11±3.2 | 0.1±3.2 |
| Sinus rhythm | 490/574 (85.4) | 431/548 (78.6) | 100/130 (76.9) | 587/1005 (58.4) |
| Asymptomatic | 436/596 (73.2) | 425/563 (75.5) | 88/132 (66.7) | 762/1039 (73.3) |
| **Other** |
| CASTLE | 92/3407 (2.7) | 146/3213 (4.5) | 19/788 (2.4) | 273/5769 (4.7) |
| CABANA | 57/3473 (1.6) | 105/3349 (3.1) | 14/812 (1.7) | 177/6100 (2.9) |
| Sinus rhythm 12 | 537/610 (88) | 472/579 (81.5) | 116/135 (85.9) | 672/1068 (62.9) |
| At least one reccurent AF | 255/2397 (10.6) | 282/2075 (13.6) | 71/473 (15) | 594/3597 (16.5) |

**Supplementary table 7**

Second primary outcome nights spent in hospital for patients with and without SCB intake

| **Characteristic** | **Early rythm control** | **Usual care** |
| --- | --- | --- |
| **BL**N = 554 (20%) | **Later (before/no endpoint)**N = 61 (2.2%) | **Later (after endpoint)**N = 74 (2.7%) | **Never**N = 706 (25%) | **BL**N = 31 (1.1%) | **Later (before/no endpoint)**N = 44 (1.6%) | **Later (after endpoint)**N = 74 (2.7%) | **Never**N = 1245 (45%) |
| Nights spent in hospital per year |  |  |  |  |  |  |  |  |
| Mean (SD) | 4.0 (12.1) | 1.9 (4.9) | 5.7 (10.5) | 7.6 (28.7) | 6.1 (20.1) | 1.2 (2.0) | 6.2 (14.2) | 5.1 (15.8) |
| Median (IQR) | 1.0 (0.0, 3.4) | 0.5 (0.0, 1.4) | 2.4 (1.1, 5.1) | 1.5 (0.3, 4.8) | 1.4 (0.0, 2.7) | 0.5 (0.0, 1.7) | 3.5 (1.1, 6.4) | 1.2 (0.0, 4.3) |
| Range | 0.0 to 175.0 | 0.0 to 28.3 | 0.2 to 63.9 | 0.0 to 365.0 | 0.0 to 112.3 | 0.0 to 12.0 | 0.1 to 114.8 | 0.0 to 292.0 |

| **Characteristic** | **ERC** | **UC** |
| --- | --- | --- |
| **Ever**N = 615 (22%) | **Never**N = 780 (28%) | **Ever**N = 75 (2.7%) | **Never**N = 1319 (47%) |
| Nights spent in hospital per year |  |  |  |  |
| Mean (SD) | 3.8 (11.6) | 7.4 (27.5) | 3.2 (13.1) | 5.2 (15.7) |
| Median (IQR) | 1.0 (0.0, 3.2) | 1.6 (0.4, 4.9) | 0.7 (0.0, 2.3) | 1.3 (0.1, 4.5) |
| Range | 0.0 to 175.0 | 0.0 to 365.0 | 0.0 to 112.3 | 0.0 to 292.0 |
|  |  |  |  |  |

| **Characteristic** | **Early rhythm control group:****Total nights spent in hospital** |
| --- | --- |
| **Incidence Rate Ratios**1 | **95% CI**2 | **p-value** |
| SCB intake timepoint |  |  |  |
| Never | 1.00 | — |  |
| Ever  | 0.64 | 0.53, 0.78 | <0.001 |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Usual care group:Total nights spent in hospital****Incidence Rate Ratios1** | **95% CI2** | **p-value** |
| SCB intake timepoint |  |  |  |
| Never | 1.00 | — |  |
| Ever | 0.56 | 0.37, 0.86 | 0.008 |

*1* Calculated with mixed negative binomial model with intake timepoint as fixed factor, the log follow-up time as the offset and site as a random effect.

*2* CI = Confidence Interval

**Supplementary table 8**

Baseline ECG characteristics of patients with and without SCB intake at baseline.

| **Characteristic** | **Overall**, N = 1,3951 | **SCB Intake: ERC group** | **p-value**2 |
| --- | --- | --- | --- |
| **Yes**N = 689 (49%)1 | **No**N = 706 (51%)1 |
| Baseline |
| QRS duration [ms] |  |  |  | <0.001 |
|     Mean ± SD | 96 ± 19 | 95 ± 17 | 97 ± 21 |  |
|     Median (IQR) | 92 (84, 102) | 92 (84, 101) | 92 (84, 102) |  |
|     Missing | 35 | 9 | 26 |  |
| QRS duration [ms] > 120 | 111 (8.2%) | 44 (6.5%) | 67 (9.9%) | 0.022 |
|     Missing | 35 | 9 | 26 |  |
| PR interval |  |  |  | 0.7 |
|     Mean ± SD | 176 ± 32 | 175 ± 33 | 176 ± 31 |  |
|     Median (IQR) | 172 (156, 190) | 172 (154, 190) | 172 (158, 192) |  |
|     Missing | 663 | 275 | 388 |  |
| QT duration [ms] |  |  |  | 0.5 |
|     Mean ± SD | 386 ± 54 | 387 ± 53 | 384 ± 56 |  |
|     Median (IQR) | 390 (358, 420) | 394 (360, 420) | 388 (354, 419) |  |
|     Missing | 40 | 13 | 27 |  |
| QTc [ms] |  |  |  | 0.073 |
|     Mean ± SD | 429 ± 50 | 426 ± 49 | 432 ± 50 |  |
|     Median (IQR) | 429 (407, 451) | 427 (405, 448) | 431 (410, 453) |  |
|     Missing | 40 | 13 | 27 |  |
| Heart rate [beats/minute] |  |  |  | 0.7 |
|     Mean ± SD | 66 ± 13 | 65 ± 12 | 66 ± 14 |  |
|     Median (IQR) | 64 (57, 72) | 64 (56, 72) | 64 (57, 72) |  |
|     Missing | 617 | 254 | 363 |  |
| FU 12 |  |  |  |  |
| Deceased/withdrawal before 12FU | 78 (5.6%) | 24 (3.5%) | 54 (7.6%) |  |
| N at 12FU | 1,317 (94%) | 665 (97%) | 652 (92%) |  |
| QRS duration [ms] |  |  |  | 0.4 |
|     Mean ± SD | 101 ± 20 | 100 ± 18 | 101 ± 21 |  |
|     Median (IQR) | 98 (88, 108) | 98 (90, 109) | 96 (88, 108) |  |
|     Missing | 250 | 100 | 150 |  |
| QRS duration [ms] > 120 | 130 (11%) | 57 (9.7%) | 73 (13%) | 0.074 |
|     Missing | 250 | 100 | 150 |  |
| PR interval |  |  |  | 0.8 |
|     Mean ± SD | 186 ± 37 | 185 ± 35 | 186 ± 39 |  |
|     Median (IQR) | 182 (162, 201) | 182 (162, 200) | 180 (160, 203) |  |
|     Missing | 441 | 179 | 262 |  |
| QT duration [ms] |  |  |  | 0.001 |
|     Mean ± SD | 413 ± 48 | 408 ± 48 | 418 ± 47 |  |
|     Median (IQR) | 413 (389, 440) | 410 (386, 436) | 418 (392, 446) |  |
|     Missing | 255 | 105 | 150 |  |
| QTc [ms] |  |  |  | 0.015 |
|     Mean ± SD | 430 ± 42 | 427 ± 45 | 433 ± 39 |  |
|     Median (IQR) | 430 (410, 450) | 427 (409, 448) | 432 (412, 454) |  |
|     Missing | 255 | 105 | 150 |  |
| Heart rate [beats/minute] |  |  |  | <0.001 |
|     Mean ± SD | 65 ± 12 | 66 ± 12 | 63 ± 12 |  |
|     Median (IQR) | 62 (57, 71) | 64 (57, 73) | 61 (56, 69) |  |
|     Missing | 354 | 137 | 217 |  |
| FU 24 |  |  |  |  |
| Deceased/withdrawal before 24FU | 113 (8.1%) | 36 (5.2%) | 77 (11%) |  |
| N at 24FU | 1,282 (92%) | 653 (95%) | 629 (89%) |  |
| QRS duration [ms] |  |  |  | 0.4 |
|     Mean ± SD | 101 ± 21 | 101 ± 20 | 102 ± 23 |  |
|     Median (IQR) | 97 (88, 108) | 98 (88, 107) | 96 (88, 110) |  |
|     Missing | 322 | 136 | 186 |  |
| QRS duration [ms] > 120 | 141 (13%) | 66 (12%) | 75 (14%) | 0.2 |
|     Missing | 322 | 136 | 186 |  |
| PR interval |  |  |  | 0.3 |
|     Mean ± SD | 184 ± 36 | 185 ± 37 | 182 ± 34 |  |
|     Median (IQR) | 180 (160, 200) | 182 (160, 204) | 180 (160, 200) |  |
|     Missing | 536 | 227 | 309 |  |
| QT duration [ms] |  |  |  | 0.3 |
|     Mean ± SD | 410 ± 49 | 409 ± 49 | 412 ± 49 |  |
|     Median (IQR) | 410 (384, 440) | 410 (383, 438) | 410 (384, 441) |  |
|     Missing | 323 | 139 | 184 |  |
| QTc [ms] |  |  |  | 0.015 |
|     Mean ± SD | 430 ± 44 | 428 ± 43 | 433 ± 44 |  |
|     Median (IQR) | 431 (410, 451) | 429 (408, 447) | 433 (411, 455) |  |
|     Missing | 323 | 139 | 184 |  |
| Heart rate [beats/minute] |  |  |  | 0.7 |
|     Mean ± SD | 65 ± 11 | 65 ± 11 | 65 ± 12 |  |
|     Median (IQR) | 64 (57, 72) | 64 (57, 72) | 64 (57, 72) |  |
|     Missing | 455 | 189 | 266 |  |
| 1 n (%) |
| 2 p-values resulting from mixed linear regression models and Analysis of Deviance Table (Type II Wald chisquare tests). |

**Supplementary table 9**

ECG characteristics of patients with SCB intake at BL, SCB intake later or no SCB intake at baseline and at 12 and 24 months.

| **Characteristic** | **Overall**, N = 1,3951 | **SCB Intake: ERC group** | **p-value**2 |
| --- | --- | --- | --- |
| **Baseline**N = 554 (40%)1 | **Later**N = 135 (9.7%)1 | **Never**N = 706 (51%)1 |
| Baseline |
| QRS duration [ms] |  |  |  |  | <0.001 |
|     Mean ± SD | 96 ± 19 | 96 ± 17 | 91 ± 14 | 97 ± 21 |  |
|     Median (IQR) | 92 (84, 102) | 94 (84, 102) | 90 (80, 98) | 92 (84, 102) |  |
|     Missing | 35 | 9 | 0 | 26 |  |
| QRS duration [ms] > 120 | 111 (8.2%) | 40 (7.3%) | 4 (3.0%) | 67 (9.9%) | 0.025 |
|     Missing | 35 | 9 | 0 | 26 |  |
| PR interval |  |  |  |  | 0.8 |
|     Mean ± SD | 176 ± 32 | 176 ± 33 | 173 ± 31 | 176 ± 31 |  |
|     Median (IQR) | 172 (156, 190) | 172 (156, 190) | 174 (150, 190) | 172 (158, 192) |  |
|     Missing | 663 | 201 | 74 | 388 |  |
| QT duration [ms] |  |  |  |  | 0.5 |
|     Mean ± SD | 386 ± 54 | 389 ± 53 | 380 ± 52 | 384 ± 56 |  |
|     Median (IQR) | 390 (358, 420) | 394 (360, 422) | 388 (356, 412) | 388 (354, 419) |  |
|     Missing | 40 | 12 | 1 | 27 |  |
| QTc [ms] |  |  |  |  | 0.2 |
|     Mean ± SD | 429 ± 50 | 427 ± 50 | 424 ± 48 | 432 ± 50 |  |
|     Median (IQR) | 429 (407, 451) | 428 (406, 448) | 425 (402, 447) | 431 (410, 453) |  |
|     Missing | 40 | 12 | 1 | 27 |  |
| Heart rate [beats/minute] |  |  |  |  | 0.7 |
|     Mean ± SD | 66 ± 13 | 65 ± 11 | 65 ± 17 | 66 ± 14 |  |
|     Median (IQR) | 64 (57, 72) | 64 (57, 72) | 63 (56, 70) | 64 (57, 72) |  |
|     Missing | 617 | 184 | 70 | 363 |  |
| FU 12 |  |  |  |  |  |
| Deceased/withdrawal before 12FU | 78 (5.6%) | 22 (4.0%) | 2 (1.5%) | 54 (7.6%) |  |
| N at 12FU | 1,317 (94%) | 532 (96%) | 133 (99%) | 652 (92%) |  |
| QRS duration [ms] |  |  |  |  | 0.6 |
|     Mean ± SD | 101 ± 20 | 100 ± 18 | 99 ± 18 | 101 ± 21 |  |
|     Median (IQR) | 98 (88, 108) | 98 (90, 108) | 98 (88, 110) | 96 (88, 108) |  |
|     Missing | 250 | 90 | 10 | 150 |  |
| QRS duration [ms] > 120 | 130 (11%) | 45 (9.7%) | 12 (9.6%) | 73 (13%) | 0.2 |
|     Missing | 250 | 90 | 10 | 150 |  |
| PR interval |  |  |  |  | 0.8 |
|     Mean ± SD | 186 ± 37 | 185 ± 34 | 188 ± 36 | 186 ± 39 |  |
|     Median (IQR) | 182 (162, 201) | 181 (162, 200) | 188 (165, 205) | 180 (160, 203) |  |
|     Missing | 441 | 148 | 31 | 262 |  |
| QT duration [ms] |  |  |  |  | 0.004 |
|     Mean ± SD | 413 ± 48 | 407 ± 43 | 412 ± 62 | 418 ± 47 |  |
|     Median (IQR) | 413 (389, 440) | 408 (384, 433) | 414 (397, 444) | 418 (392, 446) |  |
|     Missing | 255 | 95 | 10 | 150 |  |
| QTc [ms] |  |  |  |  | 0.047 |
|     Mean ± SD | 430 ± 42 | 428 ± 40 | 426 ± 59 | 433 ± 39 |  |
|     Median (IQR) | 430 (410, 450) | 426 (409, 447) | 430 (408, 448) | 432 (412, 454) |  |
|     Missing | 255 | 95 | 10 | 150 |  |
| Heart rate [beats/minute] |  |  |  |  | <0.001 |
|     Mean ± SD | 65 ± 12 | 66 ± 12 | 64 ± 12 | 63 ± 12 |  |
|     Median (IQR) | 62 (57, 71) | 65 (58, 73) | 62 (56, 72) | 61 (56, 69) |  |
|     Missing | 354 | 116 | 21 | 217 |  |
| FU 24 |  |  |  |  |  |
| Deceased/withdrawal before 24FU | 113 (8.1%) | 34 (6.1%) | 2 (1.5%) | 77 (11%) |  |
| N at 24FU | 1,282 (92%) | 520 (94%) | 133 (99%) | 629 (89%) |  |
| QRS duration [ms] |  |  |  |  | 0.6 |
|     Mean ± SD | 101 ± 21 | 101 ± 20 | 99 ± 19 | 102 ± 23 |  |
|     Median (IQR) | 97 (88, 108) | 99 (90, 108) | 96 (88, 106) | 96 (88, 110) |  |
|     Missing | 322 | 123 | 13 | 186 |  |
| QRS duration [ms] > 120 | 141 (13%) | 55 (13%) | 11 (9.0%) | 75 (14%) | 0.3 |
|     Missing | 322 | 123 | 13 | 186 |  |
| PR interval |  |  |  |  | 0.2 |
|     Mean ± SD | 184 ± 36 | 184 ± 36 | 190 ± 39 | 182 ± 34 |  |
|     Median (IQR) | 180 (160, 200) | 180 (160, 202) | 190 (161, 208) | 180 (160, 200) |  |
|     Missing | 536 | 191 | 36 | 309 |  |
| QT duration [ms] |  |  |  |  | 0.6 |
|     Mean ± SD | 410 ± 49 | 409 ± 44 | 409 ± 62 | 412 ± 49 |  |
|     Median (IQR) | 410 (384, 440) | 406 (382, 435) | 417 (388, 441) | 410 (384, 441) |  |
|     Missing | 323 | 126 | 13 | 184 |  |
| QTc [ms] |  |  |  |  | 0.037 |
|     Mean ± SD | 430 ± 44 | 429 ± 39 | 424 ± 57 | 433 ± 44 |  |
|     Median (IQR) | 431 (410, 451) | 429 (408, 447) | 430 (409, 449) | 433 (411, 455) |  |
|     Missing | 323 | 126 | 13 | 184 |  |
| Heart rate [beats/minute] |  |  |  |  | 0.6 |
|     Mean ± SD | 65 ± 11 | 66 ± 11 | 65 ± 11 | 65 ± 12 |  |
|     Median (IQR) | 64 (57, 72) | 64 (58, 72) | 64 (56, 70) | 64 (57, 72) |  |
|     Missing | 455 | 166 | 23 | 266 |  |
| 1 n (%) |
| 2 p-values resulting from mixed linear regression models and Analysis of Deviance Table (Type II Wald chisquare tests). |

**Supplementary table 10**

Cox models with time-dependent SCB for all patients – First primary otucome and its components

|   | First primary outcome | Death from cv causes | Stroke | Hospitalization Worsening HF | Hospitalization Acute coronary syndrome |
| --- | --- | --- | --- | --- | --- |
| Predictors | HR (CI) | p | HR (CI) | p | HR (CI) | p | HR (CI) | p | HR (CI) | p |
| time-dependent SCB intake | 0.56(0.42 – 0.76) | **<0.001** | 0.54(0.29 – 1.00) | 0.056 | 0.63(0.32 – 1.26) | 0.181 | 0.35(0.22 – 0.57) | **<0.001** | 0.92(0.50 – 1.68) | 0.782 |
| Random group: ERC | 0.89(0.75 – 1.06) | 0.202 | 0.84(0.61 – 1.17) | 0.320 | 0.73(0.48 – 1.11) | 0.135 | 1.00(0.79 – 1.26) | 0.997 | 0.84(0.57 – 1.23) | 0.371 |
| Age | 1.05(1.04 – 1.06) | **<0.001** | 1.07(1.05 – 1.10) | **<0.001** | 1.07(1.04 – 1.10) | **<0.001** | 1.06(1.04 – 1.07) | **<0.001** | 1.01(0.99 – 1.03) | 0.400 |
| Male Gender | 1.08(0.91 – 1.28) | 0.403 | 1.17(0.85 – 1.63) | 0.344 | 1.08(0.73 – 1.61) | 0.703 | 0.93(0.74 – 1.18) | 0.557 | 1.16(0.78 – 1.73) | 0.473 |
| CAD | 1.58(1.30 – 1.92) | **<0.001** | 1.32(0.91 – 1.90) | 0.132 | 0.75(0.43 – 1.31) | 0.310 | 1.30(0.99 – 1.70) | 0.063 | 3.60(2.44 – 5.31) | **<0.001** |
| LV Hypertrophy on ecg | 1.42(0.99 – 2.03) | 0.058 | 1.85(0.99 – 3.44) | 0.059 | 1.16(0.47 – 2.88) | 0.758 | 1.37(0.82 – 2.28) | 0.223 | 2.07(1.10 – 3.89) | **0.029** |
| Stable HF | 1.84(1.55 – 2.18) | **<0.001** | 2.30(1.68 – 3.15) | **<0.001** | 0.94(0.60 – 1.47) | 0.776 | 2.63(2.10 – 3.30) | **<0.001** | 0.89(0.59 – 1.34) | 0.578 |

**Supplementary table 11**

Cox models with time dependent SCB intale for all patients – Safety outcomes

|   | Primary composite safety outcome | Death | SAE of special interest related to RC therapy | SAE of special interest related to RC therapyWith Interaction term |
| --- | --- | --- | --- | --- |
| Predictors | HR (95CI) | p | HR (95CI) | p | HR (95CI) | p | HR (95CI) | p |
| Time-dependent SCB intake | 0.69(0.51 – 0.93) | **0.015** | 0.47(0.30 – 0.75) | **0.001** | 1.04(0.62 – 1.72) | 0.893 | 4.98(1.43 – 17.35) | **0.011** |
| Random group: ERC | 1.19(0.98 – 1.45) | 0.075 | 1.00(0.79 – 1.27) | 0.982 | 3.69(2.17 – 6.27) | **<0.001** | 4.43(2.51 – 7.83) | **<0.001** |
| Age | 1.06(1.05 – 1.08) | **<0.001** | 1.08(1.06 – 1.10) | **<0.001** | 1.02(0.99 – 1.05) | 0.102 | 1.02(0.99 – 1.05) | 0.082 |
| Male Gender | 1.11(0.92 – 1.35) | 0.267 | 1.34(1.05 – 1.70) | **0.018** | 0.81(0.52 – 1.25) | 0.332 | 0.82(0.53 – 1.27) | 0.372 |
| CAD | 1.10(0.87 – 1.38) | 0.434 | 1.15(0.87 – 1.51) | 0.315 | 1.02(0.57 – 1.82) | 0.952 | 1.00(0.56 – 1.80) | 0.989 |
| LV Hypertrophy on ecg | 1.53(1.03 – 2.27) | **0.035** | 1.59(0.99 – 2.55) | 0.057 | 1.77(0.76 – 4.12) | 0.186 | 1.78(0.76 – 4.14) | 0.185 |
| Stable HF | 1.46(1.20 – 1.77) | **<0.001** | 1.57(1.24 – 1.99) | **<0.001** | 1.46(0.94 – 2.28) | 0.090 | 1.48(0.94 – 2.31) | 0.082 |
| Interaction SCB\*Random group |  |  |  |  |  |  | 0.18(0.05 – 0.68) | **0.013** |

**Supplementary figures**

**Supplementary figure 1**

The effect on the primary efficacy endpoint as composed by cardiovascular death, stroke or hospitalization due to worsening of heart failure or acute coronary syndrome in patients with and without SCB intake



**Supplementary figure 2**

Nights spent in hospital of patients with SCB intake at baseline, later SCB intake or no SCB intake

