**Supplement**

**Supplementary Table 1:** Primary safety endpoint of patients with (EVER) or without (NEVER) potassium channel blocker (PCB) intake in patients with early rhythm control (ERC) or usual care (UC).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ERC ONLY** |  |  |  |  |  | **UC** |  |  |
|  | **AmioEVER** | **DroneEVER** | **PCBNEVER** | **p-value\*** | **p-value adj\*\*** | **AmioEVER** | **DroneEVER** | **PCBNEVER** |
| *n* | 398 | 255 | 742 |  |  | 176 | 18 | 1200 |
| *Primary composite safety outcome* | 98 (24.6) | 43 (16.9) | 90 (12.1) | < 0.001 | <0.001 | 37 (21.0) | 2 (11.1) | 184 (15.3) |
| *Stroke* | 17 (4.3) | 4 (1.6) | 19 (2.6) | 0.194 | 0.173 | 4 (2.3) | 0 (0.0) | 58 (4.8) |
| *Death* | 64 (16.1) | 30 (11.8) | 44 (5.9) | < 0.001 | <0.001 | 24 (13.6) | 1 (5.6) | 139 (11.6) |
| *Serious adverse event of special interest related to rhythm control therapy* | 26 (6.5) | 15 (5.9) | 27 (3.6) | 0.097 | 0.125 | 11 (6.2) | 1 (5.6) | 7 (0.6) |
| **Serious adverse event related to antiarrhythmic drug therapy** | | | | | | | | |
| *Nonfatal cardiac arrest* | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 | 1 | 1 (0.6) | 0 (0.0) | 0 (0.0) |
| *Drug toxicity of AF related drug therapy* | 6 (1.5) | 2 (0.8) | 2 (0.3) | 0.102 | 0.09 | 0 (0.0) | 0 (0.0) | 3 (0.2) |
| *Drug induced bradycardia* | 4 (1.0) | 4 (1.6) | 6 (0.8) | 0.585 | 0.524 | 3 (1.7) | 0 (0.0) | 2 (0.2) |
| *Atrioventricular block* | 2 (0.5) | 0 (0.0) | 0 (0.0) | 1 | 1 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| *Torsade de pointes tachycardia* | 1 (0.3) | 0 (0.0) | 0 (0.0) | 1 |  | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Serious adverse event related to AF ablation** | | | | | | | | |
| *Pericardial tamponade* | 0 ( 0.0) | 0 ( 0.0) | 3 ( 0.4) | 1 | 1 | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| *Major bleeding related to AF ablation* | 1 ( 0.3) | 3 ( 1.2) | 2 ( 0.3) | 0.967 | 0.871 | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| *Nonmajor bleeding related to AF ablation* | 1 ( 0.3) | 0 ( 0.0) | 0 ( 0.0) | 1 | 1 | 2 ( 1.1) | 0 ( 0.0) | 0 ( 0.0) |
| **Serious adverse event of special interest related to RC therapy** | | | | | | | | |
| *Blood pressure related event* | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.1) | 1 | 0.998 | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| *Hospitalization for AF* | 7 ( 1.8) | 3 ( 1.2) | 1 ( 0.1) | <0.001 | 0.098 | 2 ( 1.1) | 0 ( 0.0) | 1 ( 0.1) |
| *Other cardiovascular event* | 1 ( 0.3) | 0 ( 0.0) | 4 ( 0.5) | 0.485 | 0.427 | 1 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) |
| *Other event* | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.1) | 1 | 1 | 3 ( 1.7) | 0 ( 0.0) | 0 ( 0.0) |
| *Syncope* | 2 ( 0.5) | 0 ( 0.0) | 2 ( 0.3) | 0.568 | 0.961 | 0 ( 0.0) | 1 ( 5.6) | 0 ( 0.0) |
| *Hospitalization for worsening of HF with decomp HF* | 2 ( 0.5) | 1 ( 0.4) | 0 ( 0.0) | <0.001 |  | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| *Implantation of a pacemaker defi or other* | 0 ( 0.0) | 2 ( 0.8) | 6 ( 0.8) | 0.989 | 0.984 | 2 ( 1.1) | 1 ( 5.6) | 1 ( 0.1) |

**Supplementary Table 2:** Cox models with time-dependent potassium channel blocker (PCB) intake for ERC patients – First primary outcome and its components

|  | First primary outcome | | Death from cardiovascular causes | | Stroke | | Hospitalization Worsening HF | | Hospitalization with acute coronary syndrome | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Predictors | HR (CI) | p | HR (CI) | p | HR (CI) | p | HR (CI) | p | HR (CI) | p |
| Amiodarone Intake | 1.33 (0.99 – 1.80) | 0.069 | 1.80 (1.05 – 3.10) | **0.039** | 0.12 (0.02 – 0.89) | **0.037** | 1.84 (1.27 – 2.68) | **0.002** | 1.00 (0.49 – 2.04) | 0.994 |
| Dronedarone Intake | 0.50 (0.28 – 0.91) | **0.024** | 0.40 (0.10 – 1.64) | 0.207 | 0.42 (0.10 – 1.74) | 0.242 | 0.45 (0.18 – 1.11) | 0.084 | 0.48 (0.15 – 1.57) | 0.230 |
| Age | 1.05 (1.03 – 1.07) | **<0.001** | 1.08 (1.05 – 1.12) | **<0.001** | 1.06 (1.02 – 1.11) | **0.002** | 1.06 (1.03 – 1.08) | **<0.001** | 1.01 (0.97 – 1.04) | 0.639 |
| Male Gender | 1.19 (0.91 – 1.54) | 0.201 | 1.09 (0.66 – 1.81) | 0.735 | 1.39 (0.72 – 2.66) | 0.337 | 0.99 (0.70 – 1.40) | 0.939 | 1.27 (0.70 – 2.29) | 0.430 |
| CAD | 1.84 (1.38 – 2.46) | **<0.001** | 1.34 (0.75 – 2.39) | 0.304 | 1.20 (0.54 – 2.66) | 0.666 | 1.51 (1.02 – 2.24) | 0.050 | 3.91 (2.21 – 6.93) | **<0.001** |
| LV Hypertrophy on ECG | 1.54 (0.87 – 2.72) | 0.148 | 2.44 (0.95 – 6.25) | 0.070 | 1.57 (0.37 – 6.69) | 0.578 | 1.12 (0.45 – 2.77) | 0.803 | 1.94 (0.68 – 5.53) | 0.223 |
| Stable HF | 1.66 (1.28 – 2.16) | **<0.001** | 1.67 (1.01 – 2.78) | **0.042** | 0.79 (0.36 – 1.72) | 0.561 | 2.42 (1.72 – 3.41) | **<0.001** | 0.97 (0.53 – 1.78) | 0.918 |

**Supplementary Table 3:** Cox models with time-dependent sodium channel blocker (SCB) intake for ERC patients – Safety outcomes.

|  | Primary composite safety outcome | | Death | | SAE of special interest related to RC therapy | |
| --- | --- | --- | --- | --- | --- | --- |
| Predictors | HR (CI) | p | HR (CI) | p | HR (CI) | p |
| Amiodarone Intake | 1.22 (0.88 – 1.69) | 0.255 | 1.42 (0.95 – 2.12) | 0.098 | 1.91 (1.08 – 3.38) | **0.031** |
| Dronedarone Intake | 0.81  (0.49 – 1.35) | 0.435 | 0.59  (0.26 – 1.36) | 0.226 | 1.65  (0.82 – 3.33) | 0.171 |
| Age | 1.07 (1.05 – 1.09) | **<0.001** | 1.09 (1.07 – 1.12) | **<0.001** | 1.03 (1.00 – 1.06) | 0.073 |
| Male Gender | 1.11 (0.85 – 1.45) | 0.462 | 1.38 (0.97 – 1.97) | 0.080 | 0.74 (0.45 – 1.21) | 0.233 |
| CAD | 1.17 (0.84 – 1.62) | 0.352 | 1.15 (0.76 – 1.73) | 0.512 | 1.09 (0.58 – 2.04) | 0.803 |
| LV Hypertrophy on ECG | 1.94 (1.13 – 3.32) | **0.014** | 2.32 (1.19 – 4.51) | **0.014** | 1.42 (0.51 – 3.98) | 0.510 |
| Stable HF | 1.24 (0.93 – 1.65) | 0.135 | 1.48 (1.03 – 2.12) | **0.036** | 1.08 (0.63 – 1.85) | 0.759 |

**Supplementary Figure 1:** Choice of initial drug therapy by centers.



