**Supplementary table 1. Baseline clinical characteristics according to age, diabetes, heart failure, and renal function.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total (n=1,43; 100%)** | **Age <75 years (n=742; 51.8%)** | **Age ≥75 years (n=691; 48.2%)** | **P** | **Diabetes (n=388; 27.1%)** | **P\*** | **Heart failure (n=326; 22.7)** | **P\*\*** | **<60 ml/min\*\*\* (n=498; 35.1%)** | **≥60 ml/min\*\*\* (n=919; 64.9%)** | **P** |
| **Age, years** | 74.2±9.7 | -- | -- |  | 74.1±9.0 | 0.759 | 75.3±9.9 | 0.011 | 81.2±7.0 | 70.4±8.8 | <0.001 |
| **Sex (male)**,n (%) | 795 (55.5) | 474 (63.9) | 321 (46.5) | <0.001 | 244 (62.9) | 0.001 | 193 (59.2) | 0.124 | 204 (41.0) | 587 (63.9) | <0.001 |
| **Hypertension**, n (%) | 1,137 (79.3) | 580 (78.2) | 557 (80.6) | 0.254 | 339 (87.4) | <0.001 | 261 (80.1) | 0.716 | 411 (82.5) | 712 (77.5) | 0.025 |
| **Diabetes**, n (%) | 388 (27.1) | 206 (27.8) | 182 (26.3) | 0.544 | 388 (100) | <0.001 | 119 (36.5) | <0.001 | 117 (23.5) | 269 (29.3) | 0.020 |
| **Heart failure,** n (%) | 326 (22.7) | 153 (20.6) | 173 (25.0) | 0.046 | 119 (30.7) | <0.001 | 326 (100) | <0.001 | 133 (26.7) | 192 (20.9) | 0.013 |
| **PAD,** n (%) | 58 (4.0) | 29 (3.9) | 29 (4.2) | 0.782 | 27 (7.0) | 0.001 | 22 (6.7) | 0.005 | 22 (4.4) | 36 (3.9) | 0.650 |
| **Permanent AF**,n (%) | 535 (37.5) | 232 (31.3) | 303 (43.8) | <0.001 | 158 (40.7) | 0.106 | 166 (50.9) | <0.001 | 205 (41.2) | 327 (35.6) | 0.038 |
| **CHA2DS2-VASc score** | 3.5±1.5 | 2.7 ±1.2 | 4.4±1.3 | <0.001 | 4.4±1.6 | <0.001 | 4.5±1.6 | <0.001 | 4.2±1.4 | 3.1±1.5 | <0.001 |
| **HAS-BLED score** | 1.6±1.0 | 1.2±1.0 | 1.9±1.0 | <0.001 | 1.7±1.0 | 0.001 | 1.8±1.1 | <0.001 | 2.0±1.0 | 1.3±0.9 | <0.001 |
| **2MACE** ≥3**,** n (%) | 385 (26.9) | 85 (11.5) | 300 (43.4) | <0.001 | 157 (40.5) | <0.001 | 150 (46.0) | <0.001 | 191 (38.4) | 191 (20.8) | <0.001 |

BMI: body mass index; PAD: peripheral artery disease; AF: atrial fibrillation; \*vs no diabetes; \*\*vs no heart failure; \*\*\* Cockcroft-Gault.

Supplementary table 2. Incidence of events at 2,5 years and annual rates categorized by age, diabetes, heart failure, and renal function.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Age <75 years** | **Age ≥75 years** | **P** | **Diabetes**  | **P\*\*** | **Heart failure**  | **P\*\*\*** | **<60 ml/min**  | **≥60 ml/min**  | **P** |
| **Stroke + SE + TIA** n (%) Annual rate |  6 (0.8) 0.36 |  17 (2.5) 1.13 |  0.013 0.017 |  12 (3.1) 1.43 |  0.006 0.015 |  8 (2.5) 1.15 |  0.165 0.217 |  9 (1.8) 0.84 |  14 (1.5) 0.67 |  0.686 0.742 |
| **Major bleeding** n (%) Annual rate |  6 (0.8) 0.36 |  23 (3.3) 1.80 |  0.001 <0.001 |  12 (3.1) 1.55 |  0.080 0.143 |  8 (2.5) 1.44 |  0.530 0.330 |  16 (3.2) 1.87 |  13 (1.4) 0.62 |  0.022 0.003 |
| **MACE** n (%) Annual rate |  14 (1.9) 1.01 |  16 (2.3) 1.13 |  0.586 0.875 |  11 (2.8) 1.55 |  0.232 0.113 |  17 (5.2) 3.02 |  <0.001 <0.001 |  19 (3.8) 1.97 |  11 (1.2) 0.62 |  0.001 0.002 |
| **Myocardial infarction** n (%) Annual rate |  4 (0.5) 0.24 |  1 (0.1) 0.07 |  0.376 0.449 |  2 (0.5) 0.24 |  0.617 0.793 |  3 (0.9) 0.43 |  0.081 0.146 |  1 (0.2) 0.09 |  4 (0.4) 0.19 |  0.662 0.899 |
| **Revascularization** n (%) Annual rate |  6 (0.8) 0.36 |  3 (0.4) 0.20 |  0.509 0.624 |  2 (0.5) 0.24 |  >0.999 >0.999 |  4 (1.2) 0.58 |  0.126 0.223 |  4 (0.8) 0.37 |  5 (0.5) 0.24 |  0.728 0.728 |
| **Cardiovascular death** n (%) Annual rate |  7 (0.9) 0.42 |  13 (1.9) 0.86 |  0.130 0.170 |  9 (2.3) 1.07 |  0.069 0.055 |  14 (4.3) 2.01 |  <0.001 <0.001 |  16 (3.2) 1.50 |  4 (0.4) 0.19 |  <0.001 <0.001 |

MACE: major adverse cardiovascular events; TIA: transient ischemic attack; SE: systemic embolism. \*\*vs no diabetes \*\*\* vs no heart failure.

### Supplementary table 3. Impact of new cardiovascular risk factors on the potentially increased accuracy of 2MACE.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Univariate analysis** | **Multivariate analysis1** | **Multivariate analysis2** |
| **Independent variables** | **Dependent variable “MACE events”** | **Dependent variable “MACE events”** | **Dependent variable “MACE events”** |
| **P** | **Odds Ratio** | **95% CI** | **P** | **Odds Ratio** | **95% CI** | **P** | **Odds Ratio** | **95% CI** |
| Sex | 0.018 | 0.334 | 1.134 -0.828 |  |  |  |  |  |  |
| Diabetes  | 0.147 | 1.764 | 0.819-3.801 |  |  |  |  |  |  |
| Ischemic heart disease  | 0.000 | 4.618 | 2.168-9.840 | 0.002 | 3.411 | 1.599-7.275 | 0.000 | 9.067 | 3.842-21.397 |
| Antiplatelet agents  | 0.000 | 13.629 | 6.281-29.576 |  |  |  |
| Coronary revascularization  | 0.000 | 4.639 | 2.137-10.068 |  |  |  |  |  |  |
| Kidney failure  | 0.007 | 2.976 | 1.356-6.534 | 0.019 | 2.530 | 1.165-5.492 | 0.020 | 2.561 | 1.163-5.640 |
| Peripheral artery disease  | 0.085 | 2.945 | 0.863-10.052 |  |  |  |  |  |  |
| Heart failure  | 0.000 | 4.710 | 2.205-10.061 | 0.002 | 3.402 | 1.593-7.266 | 0.000 | 3.842 | 1.807-8.170 |
| CHA2DS2-VASC  | 0.050 | 1.255 | 1.000-1.577 |  |  |  |  |  |  |
| HAS-BLED  | 0.022 | 1.471 | 1.056-2.049 |  |  |  |  |  |  |
| 2MACE ≥3  | 0.002 | 3.228 | 1.521-6.847 |  |  |  |  |  |  |

1Model including sex, diabetes, ischemic heart disease, kidney failure, peripheral artery disease, heart failure, CHA2DS2-VASc, HAS-BLED, and 2MACE.

2Model including sex, diabetes, ischemic heart disease, antiplatelet agents, kidney failure, peripheral artery disease, heart failure, CHA2DS2-VASc, HAS-BLED, and 2MACE.

CI: confidence interval.

### Supplementary table 4. 2MACE vs 2MACER to predict MACE events. Comparison. IDI, NRI index.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MACE** | **C index** | **95%CI (C index)** | **p value (C index)** | **IDI (%)** | **95%CI (IDI (%))** | **p value (IDI)** | **NRI (%)** | **95%CI (NRI (%))** | **p value (NRI)** |
| **2MACE** | 0.638 | 0.535;0.742 |  |  |  |  |  |  |  |
| **2MACER** | 0.651 | 0.548;0.754 | 0.361 | 0.1 | 0.0;0.3 | 0.126 | 23.9 | -6.6;54.3 | 0.125 |

Note that there have been 30 patients with the event “MACE” (34 events) in 1433 patients.

There is no statistically significant difference between the global areas under the two ROC curves. P-value = 0.361.

IDI (%) = 0.1%; p-value = 0.126. There is no statistically significant improvement in discrimination.

NRI (%) = 23.9%; p-value= 0.125. There is no statistically significant net improvement in event classification.

### Supplementary Figure 1. Survival curves of cardiovascular death (A), myocardial infarction (B), revascularization (C), and MACE (D), according to 2MACE score (<3 vs ≥3).

### Cardiovascular death (n=20 patients, 9/1,042 vs 11/383).





### Log Rank p=0.003

### Myocardial infarction (n=5 patients; 3/1,042 vs 2/383).





### Log Rank p=0.938

### Revascularization (n=9 patients; 4/1,042 vs 5/383).





### Log Rank p=0.120

### MACE (n=30 patients; 14/1,042 vs 16/383).





### Log Rank p<0.001

### Supplementary Figure 2. ROC curves of 2MACE and 2MACER to predict MACE outcomes.



Area Under the Curve of 2MACE: 0.638 (95% CI 0.534-0.742; P =0.01. Area Under the Curve of 2MACER: 0.651 (95% CI 0.547-0.755; P =0.005).

There is no statistically significant difference between the global areas under the two ROC curves. P-value = 0.361.