**Clinical Complexity and Impact of the ABC (Atrial fibrillation Better Care) Pathway in Patients with Atrial Fibrillation: A report from the ESC-EHRA EURObservational Research Programme in AF General Long-Term Registry**

**Brief Title:** Clinical Complexity in AF Patients

Additional File 1

|  |  |
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**Table S1: Items Included into the Frailty Index**

|  |  |  |
| --- | --- | --- |
| ***1. Biological Parameters Domain*** | **DEFINITION** | **DEFICIT**  **VALUE** |
| Systolic Blood Pressure | ≥140 mmHg | 1 |
| Diastolic Blood Pressure | ≥90 mmHg | 1 |
| Heart Rate | ≥110 bpm | 1 |
| Body Mass Index | <18.5 kg/m2  25.0-29.9 kg/m2  ≥30.0 kg/m2 | 1  0.5  1 |
| ***2. Comorbidities Domain*** |  |  |
| Hypertension | Present | 1 |
| Diabetes Mellitus | Present | 1 |
| Lipid Disorder | Present | 1 |
| Coronary Artery Disease | Present | 1 |
| Heart Failure | Present | 1 |
| Valvular Disease | Present | 1 |
| Cardiomyopathy | Present | 1 |
| Pulmonary Arterial Hypertension | Present | 1 |
| Peripheral Artery Disease | Present | 1 |
| Previous Thromboembolic Events | Present | 1 |
| Previous Hemorrhagic Events | Present | 1 |
| Hyperthyroidism | Present | 1 |
| Hypothyroidism | Present | 1 |
| Chronic Kidney Disease | Present | 1 |
| Liver Disease | Present | 1 |
| Chronic Obstructive Pulmonary Disease | Present | 1 |
| Obstructive Sleep Apnoea Syndrome | Present | 1 |
| Dementia | Present | 1 |
| History of Anaemia | Present | 1 |
| Malignancy | Present | 1 |
| ***3. Symptoms Domain*** |  |  |
| Palpitations | Present | 1 |
| Syncope | Present | 1 |
| Shortness of Breath | Present | 1 |
| Chest Pain | Present | 1 |
| General not-Well Being | Present | 1 |
| Dizziness | Present | 1 |
| Fatigue | Present | 1 |
| Fear | Present | 1 |
| Other Symptoms | Present | 1 |
| ***4. Function/Autonomy Domain***  *(EQ-5D-5L Questionnaire)* |  |  |
| Mobility | No Problems  Slight Problems  Moderate Problems  Severe Problems  Unable to Walk | 0  0.25  0.5  0.75  1 |
| Self-Care | No Problems  Slight Problems  Moderate Problems  Severe Problems  Unable to Wash/Dress | 0  0.25  0.5  0.75  1 |
| Usual Activities | No Problems  Slight Problems  Moderate Problems  Severe Problems  Unable to Usual Activities | 0  0.25  0.5  0.75  1 |
| Pain/Discomfort | No Pain/Discomfort  Slight Pain/Discomfort  Moderate Pain/Discomfort  Severe Pain/Discomfort  Extreme Pain/Discomfort | 0  0.25  0.5  0.75  1 |
| Anxiety/Depression | None  Slight Anxious/Depressed  Moderate Anxious/Depressed  Severely Anxious/Depressed  Extremely Anxious/Depressed | 0  0.25  0.5  0.75  1 |
| ***5. Biomarkers Domain*** |  |  |
| Creatinine Clearance (CKD-EPI) | <60 mL/min | 1 |
| Haemoglobin | <13 mg/dL for males  <12 mg/dL for females | 1 |

**Table S2: Baseline Characteristics of the Cohort**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Total N=9966** | **Non Clinically Complex  N=1677** | **Clinically Complex N=8289** | **Frailty**  **N=2108** | **Multimorbidity  N=7894** | **Polypharmacy N=5366** |
| *Socio-Demographic Characteristics* | |  |  |  |  |  |
| **Age**, *years* median [IQR] | 71 [62-77] | 63 [53-72] | 72 [64-78] | 73 [66-79] | 72 [64-78] | 72 [65-78] |
| **Female**, n (%) | 4004 (40.2) | 549 (32.7) | 3455 (41.7) | 1038 (49.2) | 3301 (41.8) | 2285 (42.6) |
| **European Region**, n (%)  Northern Europe  Western Europe  Eastern Europe  Southern Europe | 1331 (13.4) 3242 (32.5) 1643 (16.5) 3750 (37.6) | 412 (24.6) 553 (33.0) 141 (8.4) 571 (34.0) | 919 (11.1) 2689 (32.4) 1502 (18.1) 3179 (38.4) | 191 (9.1) 481 (22.8) 593 (28.1) 843 (40.0) | 827 (10.5) 2567 (32.5) 1447 (18.3) 3053 (38.7) | 546 (10.2) 1631 (30.4) 1008 (18.8) 2181 (40.6) |
| *Clinical Characteristics and Comorbidities* | |  |  |  |  |  |
| **Site of Inclusion**, n (%)  Outpatient Facility  Hospital | 4785 (48.0) 5181 (52.0) | 935 (55.8) 742 (44.2) | 3850 (46.4) 4439 (53.6) | 632 (30.0) 1476 (70.0) | 3664 (46.4) 4230 (53.6) | 2208 (41.1) 3158 (58.8) |
| **Reason for Admission**, n (%)  Other than AF  AF | 3360 (33.7) 6606 (66.3) | 172 (10.3) 1505 (89.7) | 3188 (38.5) 5101 (61.5) | 1015 (48.1) 1093 (51.9) | 3114 (39.4) 4780 (60.6) | 2356 (43.9) 3010 (56.1) |
| **BMI**, *kg/m2* median [IQR] | 27.5 [24.8-31.1] | 26.7 [24.4-30.1] | 27.7 [24.8-31.2] | 28.8 [25.5-32.7] | 27.7 [24.8-31.2] | 28.0 [25.2-31.6] |
| **SBP**, *mmHg* median [IQR] | 130 [120-142] | 130 [120-140] | 130 [120-144] | 140 [120-150] | 130 [120-144] | 130 [120-145] |
| **DBP**, *mmHg* median [IQR] | 80 [70-87] | 80 [70-86] | 80 [70-88] | 80 [70-90] | 80 [70-87] | 80 [70-87] |
| **LVEF,** *%* median [IQR] | 55 [45-61] | 60 [55-64] | 55 [45-60] | 50 [39-60] | 55 [45-60] | 53 [40-60] |
| **Type of AF**, n (%)  First Diagnosed  Paroxysmal Persistent Long-Standing Persistent Permanent Unknown | 1583 (15.9) 2612 (26.2) 1962 (19.7) 429 (4.3) 3220 (32.3)  157 (1.6) | 379 (22.6)  602 (35.9)  373 (22.2)  49 (2.9)  230 (13.7)  44 (2.6) | 1204 (14.5)  2010 (24.3)  1589 (19.2)  380 (4.6)  2990 (36.1)  113 (1.4) | 315 (15.0)  485 (24.0)  384 (18.2)  110 (5.2)  794 (37.7)  18 (0.9) | 1120 (14.2)  1904 (24.1)  1488 (18.9)  361 (4.6)  2912 (36.9)  107 (1.4) | 749 (14.0)  1254 (23.4)  997 (18.6)  246 (4.6)  2055 (38.3)  65 (1.2) |
| **Heart Failure**, n (%) | 3793 (38.1) | 35 (2.1) | 3758 (45.3) | 1539 (73.0) | 3726 (47.2) | 2721 (50.7) |
| **Coronary Artery Disease**, n (%) | 2773 (27.8) | 31 (1.8) | 2742 (33.1) | 992 (47.1) | 2709 (34.3) | 2093 (39.0) |
| **Hypertension**, n (%) | 6168 (61.9) | 349 (20.8) | 5819 (70.2) | 1701 (80.7) | 5684 (72.0) | 3870 (72.1) |
| **Diabetes Mellitus**, n (%) | 2277 (22.8) | 34 (2.0) | 2243 (27.1) | 914 (43.4) | 2225 (28.2) | 1858 (34.6) |
| **Lipid Disorder**, n (%) | 3970 (39.8) | 132 (7.9) | 3838 (46.3) | 1212 (57.5) | 3804 (48.2) | 2679 (49.9) |
| **Previous TE Events**, n (%) | 1150 (11.5) | 83 (4.9) | 1067 (12.9) | 398 (18.9) | 1041 (13.2) | 714 (13.3) |
| **Previous Hemorrhagic Events**, n (%) | 527 (5.3) | 48 (2.9) | 479 (5.8) | 214 (10.2) | 466 (5.9) | 333 (6.2) |
| **PAD**, n (%) | 792 (7.9) | 11 (0.7) | 781 (9.4) | 378 (17.9) | 780 (9.9) | 570 (10.6) |
| **CKD**, n (%) | 1194 (12.0) | 11 (0.7) | 1183 (14.4) | 649 (30.9) | 1179 (15.0) | 889 (16.7) |
| **COPD**, n (%) | 889 (8.9) | 21 (1.3) | 868 (10.5) | 395 (18.7) | 865 (11.0) | 655 (12.2) |
| **Anaemia**, n (%) | 521 (5.2) | 4 (0.2) | 517 (6.2) | 327 (15.5) | 515 (6.5) | 350 (6.5) |
| **Dementia**, n (%) | 110 (1.1) | 1 (0.1) | 109 (1.3) | 68 (3.2) | 109 (1.4) | 66 (1.2) |
| **Malignancy**, n (%) | 741 (7.4) | 36 (2.2) | 705 (8.5) | 230 (10.9) | 700 (8.8) | 405 (7.6) |
| **CHA2DS2-VASc**, median [IQR] | 3 [2-4] | 1 [0-2] | 3 [2-5] | 4 [3-5] | 4 [2-5] | 4 [3-5] |
| **High TE Risk**, n (%) | 7490 (75.2) | 514 (30.7) | 6976 (84.2) | 1994 (94.6) | 6777 (85.9) | 4713 (87.9) |
| **HAS-BLED**, Median [IQR] | 1 [1-2] | 1 [0-1] | 2 [1-2] | 2 [1-3] | 2 [1-2] | 2 [1-2] |
| **High Bleeding Risk**, n (%) | 1723 (17.3) | 53 (3.2) | 1670 (20.1) | 750 (35.6) | 1637 (20.7) | 1210 (22.5) |
| *ABC Criteria (n=6091)* |  |  |  |  |  |  |
| **ABC compliant,** n (%) | 1856 (30.5) | 461 (35.3) | 1395 (29.2) | 143 (12.2) | 1299 (28.6) | 931 (31.7) |
| **Number of ABC criteria fulfilled**, n (%)  0 1 2 3 | 133 (2.2) 1139 (18.7) 2963 (48.6) 1856 (30.5) | 18 (1.4) 210 (16.1) 617 (47.2) 461 (35.3) | 115 (2.4) 929 (19.4) 2346 (49.0) 1395 (29.2) | 80 (6.8) 394 (33.5) 558 (47.5) 143 (12.2) | 108 (2.4) 880 (19.4) 2248 (49.6) 1299 (28.7) | 50 (1.7) 497 (16.9) 1456 (49.6) 931 (31.7) |
| **‘A’ criterion adherent,** n (%) | 4624 (75.9) | 808 (61.9) | 3816 (79.7) | 890 (75.7) | 3634 (80.1) | 2500 (85.2) |
| **‘B’ criterion adherent,** n (%) | 4890 (80.3) | 1100 (84.2) | 3790 (79.2) | 681 (58.0) | 3600 (79.4) | 2283 (77.8) |
| **‘C’ criterion adherent,** n (%) | 3119 (51.2) | 919 (70.4) | 2200 (46.0) | 368 (31.3) | 2039 (45.0) | 1419 (48.4) |

Legend: AF: Atrial Fibrillation; BMI: Body Mass Index; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; DBP: Diastolic Blood Pressure; LVEF: Left Ventricular Ejection Fraction; IQR: Interquartile Range; PAD: Peripheral Artery Disease; SBP: Systolic Blood Pressure; TE: Thromboembolism

**Table S3 - Cox Regression for the risk of major outcomes according to clinical complexity and subgroups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Clinically Complex**  **N=8289** | **Frailty N=2108** | **Multimorbidity N=7894** | **Polypharmacy N=5366** |
| **All-Cause Death, n (%)** | 848 (10.2) | 350 (16.6) | 829 (10.5) | 592 (11.0) |
| *aHR [95% CI]\** | **1.97 [1.40-2.76]** | **3.10 [2.23-4.29]**† | **1.69 [1.26-2.27]** | **1.23 [1.05-1.44]** |
| **MACEs, n (%)** | 840 (10.1) | 348 (16.5) | 824 (10.4) | 637 (11.9) |
| *aHR [95% CI]\** | **1.49 [1.07-2.06]** | **2.49 [1.77-3.50]**† | **1.53 [1.13-2.08]** | **1.42 [1.18-1.70]** |
| **Composite Outcome, n (%)** | 1311 (15.8) | 522 (24.8) | 1278 (16.2) | 939 (17.5) |
| *aHR [95% CI]\** | **1.76 [1.36-2.28]** | **2.95 [2.27-3.83]**† | **1.60 [1.27-2.02]** | **1.25 [1.10-1.44]** |

**Legend:** aHR= Adjusted Hazard Ratio. CI= Confidence Intervals. MACEs= Major Adverse Cardiovascular Events. \*adjusted for: age, sex, hypertension, congestive heart failure, coronary artery disease, previous thromboembolism, peripheral artery disease, type of AF, use of anticoagulant. †As compared with robust.

**Table S4: Baseline characteristics according to cluster allocation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **High Clinical Complexity Cluster**  **N= 4437** | **Moderate Clinical Complexity Cluster  N= 5529** | **P** |
| *Cluster Variables* |  |  |  |
| **Frailty Status**, n (%)  Robust Pre-Frail Frail | 2 (0.0) 2428 (54.7) 2007 (45.2) | 1905 (34.5) 3523 (63.7) 101 (1.8) | <0.001 |
| **Frailty Index**, median [IQR] | 0.24 [0.20-0.29] | 0.12 [0.09-0.16] | <0.001 |
| **Multimorbidity**, n (%) | 4417 (99.5) | 3477 (62.9) | <0.001 |
| **Number of comorbidities,** median [IQR] | 5 [4-6] | 2 [1-3] |  |
| **Polypharmacy**, n (%) | 3693 (83.2) | 1673 (30.3) | <0.001 |
| **Number of drugs**, median [IQR] | 6 [5-7] | 4 [3-5] | <0.001 |
| *Socio-Demographic Characteristics* |  |  |  |
| **Age**, *years* median [IQR] | 74 [67-79] | 67 [59-75] | <0.001 |
| **Female**, n (%) | 1979 (44.6) | 2025 (36.6) | <0.001 |
| **European Region**, n (%)  Northern Europe  Western Europe  Eastern Europe  Southern Europe | 373 (8.4) 1337 (30.1) 985 (22.2) 1742 (39.3) | 958 (17.3) 1905 (34.5) 658 (11.9) 2008 (36.3) | <0.001 |
| *Clinical Characteristics and Comorbidities* | |  |  |
| **Site of Inclusion**, n (%)  Outpatient Facility  Hospital | 1708 (38.5) 2729 (61.5) | 3077 (55.7) 2452 (44.3) | <0.001 |
| **Reason for Admission**, n (%)  Other than AF  AF | 2184 (49.2) 2253 (50.8) | 1176 (21.3) 4353 (78.7) | <0.001 |
| **BMI**, *kg/m2* median [IQR] | 28.1 [25.2-31.8] | 27.1 [24.5-30.4] | <0.001 |
| **SBP**, *mmHg* median [IQR] | 130 [120-145] | 130 [120-140] | <0.001 |
| **DBP**, *mmHg* median [IQR] | 80 [70-89] | 80 [70-86] | 0.051 |
| **LVEF,** *%* median [IQR] | 51 [40-60] | 59 [50-63] | <0.001 |
| **Type of AF**, n (%)  First Diagnosed  Paroxysmal Persistent Long-Standing Persistent Permanent Unknown | 576 (13.0)  974 (22.0)  736 (16.6)  211 (4.8)  1888 (42.6)  51 (1.1) | 1007 (18.2)  1638 (29.6)  1226 (22.2)  218 (3.9)  1332 (24.1)  106 (1.9) | <0.001 |
| **Heart Failure**, n (%) | 2833 (63.8) | 960 (17.4) | <0.001 |
| **Coronary Artery Disease**, n (%) | 2048 (46.2) | 725 (13.1) | <0.001 |
| **Hypertension**, n (%) | 3492 (78.7) | 2676 (48.4) | <0.001 |
| **Diabetes Mellitus**, n (%) | 1766 (39.8) | 511 (9.2) | <0.001 |
| **Lipid Disorder**, n (%) | 2525 (56.9) | 1445 (26.1) | <0.001 |
| **Previous TE Events**, n (%) | 698 (15.7) | 452 (8.2) | <0.001 |
| **Previous Hemorrhagic Events**, n (%) | 352 (7.9) | 175 (3.2) | <0.001 |
| **PAD**, n (%) | 661 (14.9) | 131 (2.4) | <0.001 |
| **CKD**, n (%) | 1017 (23.1) | 177 (3.0) | <0.001 |
| **COPD**, n (%) | 679 (15.3) | 210 (3.8) | <0.001 |
| **Anaemia**, n (%) | 460 (10.4) | 61 (1.1) | <0.001 |
| **Dementia**, n (%) | 97 (2.2) | 13 (0.2) | <0.001 |
| **Malignancy**, n (%) | 469 (10.6) | 272 (4.9) | <0.001 |
| **CHA2DS2-VASc**, median [IQR] | 4 [3-5] | 2 [1-3] | <0.001 |
| **High TE Risk**, n (%) | 4246 (95.8) | 3244 (58.7) | <0.001 |
| **HAS-BLED**, Median [IQR] | 2 [1-3] | 1 [1-2] | <0.001 |
| **High Bleeding Risk**, n (%) | 1304 (29.4) | 419 (7.6) | <0.001 |
| *ABC Criteria (n=6091)* |  |  |  |
| **ABC compliant,** n (%) | 560 (23.4) | 1296 (35.1) | <0.001 |
| **Number of ABC criteria fulfilled**, n (%)  0 1 2 3 | 76 (3.2) 558 (23.3) 1204 (50.2) 560 (23.4) | 57 (1.5) 581 (15.7) 1759 (47.6) 1296 (35.1) | <0.001 |
| **‘A’ criterion adherent,** n (%) | 1928 (80.4) | 2696 (73.0) | <0.001 |
| **‘B’ criterion adherent,** n (%) | 1774 (74.0) | 3116 (84.4) | <0.001 |
| **‘C’ criterion adherent,** n (%) | 944 (39.4) | 2175 (58.9) | <0.001 |

Legend: AF: Atrial Fibrillation; BMI: Body Mass Index; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; DBP: Diastolic Blood Pressure; IQR: Interquartile Range; PAD: Peripheral Artery Disease; SBP: Systolic Blood Pressure; TE: Thromboembolism

**Figure S1 - Kaplan Meier Curves for the risk of MACE according to cluster analysis.**

Legend: p-value for log-rank test



**Figure S2 - Kaplan Meier Curves for the risk of composite outcome according to cluster analysis.**

Legend: p-value for log-rank test



**Figure S3 – Delay of Event analysis for MACE, ABC adherent vs. non-adherent in cluster 1 subgroup**

Legend: DoE=Delay of Event. Figures reported are estimates [95% Confidence Intervals].



**Figure S4 – Delay of Event analysis for Composite Outcome, ABC adherent vs. non-adherent in cluster 1 subgroup**

Legend: DoE=Delay of Event. Figures reported are estimates [95% Confidence Intervals].

