Supplementary files

**Figure S1.** Absolute standardised difference of rate vs rhythm control strategies for the variables included in the weighting scheme before and after propensity score weighting



#

# **Figure S2.** Propensity score distribution for rhythm strategy in patients with rhythm and rate strategy, total and overlap population



# **Figure S3.** Distribution of treatmentstrategy initiated at diagnosis by cohort of enrolment

# **Figure S4.** Cumulative incidence and adjusted hazard ratios1 for a) all-cause mortality, b) non-haemorrhagic stroke/SE and c) major bleeding within two-year follow-up by treatment strategy initiated at diagnosis

1. ***All-cause mortality***



1. ***Non-haemorrhagic stroke/SE***



1. ***Major bleeding***



**Table S1**. List of variables in the propensity model

Variables in the propensity model were as following: cohort of enrolment, country, care setting speciality and location, sex, age, ethnicity, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe chronic kidney disease, dementia, hyperthyroidism, hypothyroidism, HF, vascular disease, acute coronary syndromes, carotid occlusive disease, prior stroke/TIA/SE, venous thromboembolism, prior bleeding, current smoking, heavy alcohol consumption, type of AF, baseline anticoagulation and antiplatelet use.

# **Table S2.** Distribution of treatment strategy initiated at diagnosis by country of enrolment

|  |  |
| --- | --- |
| **Country** | **Treatment strategy** |
| **Rate control****N (row %)** | **Rhythm control****N (row %)** |
| Argentina | 363 (42.1) | 500 (57.9) |
| Australia | 474 (54.3) | 399 (45.7) |
| Austria | 300 (71.6) | 119 (28.4) |
| Belgium | 357 (21.5) | 1304 (78.5) |
| Brazil | 423 (43.3) | 553 (56.7) |
| Canada | 585 (67.9) | 277 (32.1) |
| Chile | 473 (53.3) | 414 (46.7) |
| China | 1338 (58.6) | 945 (41.4) |
| Czech Republic | 630 (36.1) | 1116 (63.9) |
| Denmark | 241 (48.2) | 259 (51.8) |
| Egypt | 97 (24.7) | 296 (75.3) |
| Finland | 85 (23.7) | 273 (76.3) |
| France | 1565 (54.2) | 1325 (45.9) |
| Germany | 1565 (54.2) | 1325 (45.8) |
| Hungary | 597 (50.3) | 590 (49.7) |
| India | 569 (44.7) | 703 (55.3) |
| Italy | 766 (50.1) | 762 (49.9) |
| Japan | 2290 (52.5) | 2069 (47.8) |
| South Korea | 1337 (44.5) | 1668 (55.5) |
| Mexico | 309 (36.1) | 546 (63.9) |
| Netherlands | 650 (56.4) | 502 (43.6) |
| Norway | 91 (37.9) | 149 (62.1) |
| Poland | 624 (27.4) | 1653 (72.6) |
| Russia | 534 (26.4) | 1491 (73.6) |
| Singapore | 196 (66.2) | 100 (33.8) |
| South Africa | 266 (47.4) | 295 (52.6) |
| Spain | 1226 (59.9) | 822 (40.1) |
| Sweden | 629 (58.6) | 445 (41.4) |
| Switzerland | 37 (43.5) | 48 (56.5) |
| Thailand | 1188 (79.4) | 309 (20.6) |
| Turkey | 206 (37.9) | 337 (62.1) |
| Ukraine | 175 (11.3) | 1374 (88.7) |
| United Arab Emirates | 143 (36.3) | 251 (63.7) |
| United Kingdom | 1840 (78.7) | 497 (21.3) |
| United States | 340 (47.2) | 380 (52.8) |

# **Table S3.** Distribution of selected medications by treatment strategy

|  |  |
| --- | --- |
| **Baseline medications** | **Treatment strategy** |
| **Rate control****N (%)** | **Rhythm control****N (%)** |
|  |  |  |
| ACEi/ARB | 11173 (51.9) | 12810 (53.7) |
| β-blockers | 11883 (55.2) | 13230 (55.4) |
| Aldosterone blockade | 1409 (6.6) | 1576 (6.6) |
| Antihypertensive therapy1 | 18211 (84.6) | 20056 (84.1) |
| Statins | 8422 (39.1) | 9506 (39.8) |
|  |  |  |

1Defined as at least one of the following: ACEI or ARB (only if CKD stage lower than IV or V), Calcium Channel Blocker, β-blocker, diuretics, clonidine, α-blockers

**Table S4.** Distribution of rhythm control treatment options (non-mutually exclusive categories) among the 23,858 patients included in the “Rhythm control” strategy

|  |  |
| --- | --- |
| **Treatment strategy/Treatment options** | **N (%)** |
| Reported rhythm strategy initiated | 19637 (82.3) |
| Anti-arrhythmics (with or without rate modifiers) | 4561 (19.1) |
| Ablation | 157 (0.7) |
| Cardioversion | 6621 (27.8) |
| Class 1a | 769 (3.2) |
| Class 1c | 3971 (16.6) |
| Class 3 | 8962 (37.6) |
| Propaphenone | 0 (0.0) |

# **Table S5.** Distribution of atrial fibrillation symptoms1 at diagnosis by treatment strategy initiated at diagnosis

|  |  |
| --- | --- |
| **Symptoms** | **Treatment strategy** |
| **Rate control****N (%)** | **Rhythm control****N (%)** |
|  |  |  |
| Palpitations | 6875 (31.9) | 11102 (46.5) |
| Shortness of breath | 6339 (29.5) | 7540 (31.6) |
| Chest pain/discomfort | 3672 (17.1) | 5395 (22.6) |
| Dizziness | 2381 (11.1) | 3104 (13.0) |
| Tiredness | 2614 (12.1) | 3790 (15.9) |
| Sweating | 727 (3.4) | 1213 (5.1) |
| Fainting | 810 (3.8) | 992 (4.2) |
| Other unspecified symptoms | 1582 (7.4) | 1598 (6.7) |
|  |  |  |
| Any symptom | 15039 (69.9) | 19292 (80.9) |
|  |  |  |

# **Table S6.** Event rates (per 100 person-years) within two-year follow-up by treatment strategy initiated at diagnosis

|  |  |
| --- | --- |
| Outcome | Treatment strategy |
| **Rate control** | **Rhythm control** |
| **Events** | **Rate (95% CI)** | **Events** | **Rate (95% CI)** |
|  |  |  |  |  |
| All-cause mortality | 1758 | 4.43 (4.22-4.64) | 1321 | 2.94 (2.78-3.10) |
| Cardiovascular mortality | 606 | 1.53 (1.41-1.65) | 477 | 1.06 (0.97-1.16) |
| Non-cardiovascular mortality | 684 | 1.72 (1.60-1.86) | 514 | 1.14 (1.05-1.25) |
| Non-haemorrhagic stroke/SE | 455 | 1.16 (1.05-1.27) | 373 | 0.84 (0.75-0.92) |
| Major bleeding | 456 | 1.16 (1.06-1.27) | 374 | 0.84 (0.76-0.93) |
| New/worsening heart failure | 364 | 0.93 (0.84-1.03) | 328 | 0.74 (0.66-0.82) |

**Table S7.** Sensitivity analysis: exclusion of patients with new onset (unclassified) AF. Study population: N = 22057; rate control: N = 9513 (43.1%); rhythm control: N = 12544 (56.9%). Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis after the exclusion of patients with new onset (unclassified) AF.

|  |  |
| --- | --- |
| **Outcome** | **Rhythm vs Rate (ref.)** |
| **Unadjusted** | **,** | **Adjusted** |
| **HR (95% CI)** | **p-value** |  | **HR (95% CI)** | **p-value** |
|  |  |  |  |  |  |
| All-cause mortality | 0.72 (0.64-0.81) | <.0001 |  | 0.88 (0.78-0.99) | 0.0446 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.87 (0.71-1.07) | 0.1802 |  | 0.99 (0.79-1.24) | 0.9284 |
|  |  |  |  |  |  |
| Major bleeding | 0.82 (0.67-1.01) | 0.0631 |  | 0.95 (0.76-1.19) | 0.2211 |
|  |  |  |  |  |  |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use.

**Table S8**. Sensitivity analysis: exclusion of patients diagnosed in primary care/GP care setting.

Study population: N = 39468; rate control: N = 18059 (45.8%); rhythm control: N = 21409 (54.2%). Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis after the exclusion of patients diagnosed in primary care/GP care setting.

|  |  |
| --- | --- |
| **Outcome** | **Rhythm vs Rate (ref.)** |
| **Unadjusted** |  | **Adjusted** |
| **HR (95% CI)** | **p-value** |  | **HR (95% CI)** | **p-value** |
|  |  |  |  |  |  |
| All-cause mortality | 0.67 (0.62-0.72) | <.0001 |  | 0.85 (0.78-0.92) | <.0001 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.72 (0.62-0.83) | <.0001 |  | 0.82 (0.70-0.96) | 0.0155 |
|  |  |  |  |  |  |
| Major bleeding | 0.75 (0.65-0.87) | 0.0001 |  | 0.94 (0.81-1.11) | 0.4731 |
|  |  |  |  |  |  |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use.

**Table S9.** Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis in patients with heart failure at baseline

|  |  |
| --- | --- |
| **Outcome** | **Rhythm vs Rate (ref.)** |
| **Unadjusted** |  | **Adjusted** |
| **HR (95% CI)** | **p-value** |  | **HR (95% CI)** | **p-value** |
|  |  |  |  |  |  |
| All-cause mortality | 0.62 (0.55-0.70) | <.0001 |  | 0.73 (0.65-0.83) | <.0001 |
|  |  |  |  |  |  |
| Cardiovascular mortality | 0.78 (0.66-0.93) | 0.0046 |  | 0.83 (0.69-1.00) | 0.0480 |
|  |  |  |  |  |  |
| Non-cardiovascular mortality | 0.49 (0.39-0.60) | <.0001 |  | 0.64 (0.51-0.80) | 0.0001 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.96 (0.75-1.24) | 0.7580 |  | 0.97 (0.74-1.28) | 0.8488 |
|  |  |  |  |  |  |
| Major bleeding | 0.69 (0.52-0.93) | 0.0129 |  | 0.88 (0.64-1.20) | 0.4109 |
|  |  |  |  |  |  |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use.

**Table S10.** Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis in patients without heart failure at baseline

|  |  |
| --- | --- |
| **Outcome** | **Rhythm vs Rate (ref.)** |
| **Unadjusted** |  | **Adjusted** |
| **HR (95% CI)** | **p-value** |  | **HR (95% CI)** | **p-value** |
|  |  |  |  |  |  |
| All-cause mortality | 0.68 (0.62-0.74) | <.0001 |  | 0.91 (0.82-1.00) | 0.0530 |
|  |  |  |  |  |  |
| Cardiovascular mortality | 0.59 (0.50-0.70) | <.0001 |  | 0.73 (0.61-0.88) | 0.0007 |
|  |  |  |  |  |  |
| Non-cardiovascular mortality | 0.75 (0.66-0.86) | <.0001 |  | 1.08 (0.94-1.26) | 0.2765 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.64 (0.54-0.75) | <.0001 |  | 0.80 (0.67-0.96) | 0.0136 |
|  |  |  |  |  |  |
| Major bleeding | 0.73 (0.63-0.86) | 0.0001 |  | 0.92 (0.77-1.08) | 0.3011 |
|  |  |  |  |  |  |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use

**Table S11.** Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis in patients with CHA2DS2-VASc >4 (N = 9185)

|  |  |
| --- | --- |
| Outcome | Rhythm vs Rate (ref.) |
| Unadjusted |  | Adjusted |
| HR (95% CI) | p-value |  | HR (95% CI) | p-value |
|  |  |  |  |  |  |
| All-cause mortality | 0.72 (0.64-0.81) | <.0001 |  | 0.84 (0.74-0.95) | 0.0068 |
|  |  |  |  |  |  |
| Cardiovascular mortality | 0.77 (0.64-0.92) | 0.0048 |  | 0.78 (0.64-0.95) | 0.0130 |
|  |  |  |  |  |  |
| Non-cardiovascular mortality | 0.70 (0.57-0.85) | 0.0003 |  | 0.92 (0.74-1.13) | 0.4160 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.80 (0.64-1.00) | 0.0501 |  | 0.84 (0.65-1.08) | 0.1743 |
|  |  |  |  |  |  |
| Major bleeding | 0.69 (0.54-0.88) | 0.0029 |  | 0.86 (0.66-1.12) | 0.2533 |
|  |  |  |  |  |  |
| New/worsening heart failure | 0.92 (0.71-1.19) | 0.5347 |  | 0.99 (0.75-1.32) | 0.9713 |
|  |  |  |  |  |  |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use.

**Table S12.** Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis in patients with CHA2DS2-VASc ≤4 (N = 36197)

|  |  |
| --- | --- |
| Outcome | Rhythm vs Rate (ref.) |
| Unadjusted |  | Adjusted |
| HR (95% CI) | p-value |  | HR (95% CI) | p-value |
|  |  |  |  |  |  |
| All-cause mortality | 0.69 (0.63-0.75) | <.0001 |  | 0.85 (0.77-0.94) | 0.0013 |
|  |  |  |  |  |  |
| Cardiovascular mortality | 0.72 (0.62-0.85) | <.0001 |  | 0.78 (0.66-0.93) | 0.0049 |
|  |  |  |  |  |  |
| Non-cardiovascular mortality | 0.69 (0.60-0.80) | <.0001 |  | 0.96 (0.82-1.12) | 0.5770 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.73 (0.62-0.87) | 0.0004 |  | 0.83 (0.69-1.00) | 0.0512 |
|  |  |  |  |  |  |
| Major bleeding | 0.78 (0.66-0.92) | 0.0036 |  | 0.93 (0.77-1.11) | 0.4175 |
|  |  |  |  |  |  |
| New/worsening heart failure | 0.79 (0.66-0.94) | 0.0101 |  | 0.84 (0.69-1.02) | 0.0863 |
|  |  |  |  |  |  |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use.

**Table S13.** Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis in patients who were enrolled within 2 days of AF diagnosis (n = 18022)

|  |  |
| --- | --- |
| **Outcome** | **Rhythm vs Rate (ref.)** |
| **Unadjusted** |  | **Adjusted** |
| **HR (95% CI)** | **p-value** |  | **HR (95% CI)** | **p-value** |
|  |  |  |  |  |  |
| All-cause mortality | 0.70 (0.63-0.78) | <.0001 |  | 0.86 (0.77-0.98) | 0.0190 |
|  |  |  |  |  |  |
| Cardiovascular mortality | 0.73 (0.60-0.89) | 0.0016 |  | 0.80 (0.65-0.99) | 0.0421 |
|  |  |  |  |  |  |
| Non-cardiovascular mortality | 0.71 (0.60-0.85) | 0.0001 |  | 0.93 (0.77-1.13) | 0.4572 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.60 (0.47-0.75) | <.0001 |  | 0.69 (0.53-0.89) | 0.0045 |
|  |  |  |  |  |  |
| Major bleeding | 0.82 (0.65-1.02) | 0.0783 |  | 0.98 (0.77-1.25) | 0.8912 |
|  |  |  |  |  |  |
| New/worsening heart failure | 0.71 (0.54-0.92) | 0.0109 |  | 0.72 (0.54-0.96) | 0.0238 |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use.

**Table S14.** Unadjusted and adjusted hazard ratios1 for selected outcomes within two-year follow-up by treatment strategy initiated at diagnosis in patients who were enrolled between 3 and 42 days of AF diagnosis (n = 27360)

|  |  |
| --- | --- |
| **Outcome** | **Rhythm vs Rate (ref.)** |
| **Unadjusted** |  | **Adjusted** |
| **HR (95% CI)** | **p-value** |  | **HR (95% CI)** | **p-value** |
|  |  |  |  |  |  |
| All-cause mortality | 0.64 (0.59-0.71) | <.0001 |  | 0.84 (0.76-0.93) | 0.0006 |
|  |  |  |  |  |  |
| Cardiovascular mortality | 0.68 (0.59-0.79) | <.0001 |  | 0.77 (0.65-0.90) | 0.0014 |
|  |  |  |  |  |  |
| Non-cardiovascular mortality | 0.64 (0.55-0.74) | <.0001 |  | 0.95 (0.81-1.12) | 0.5585 |
|  |  |  |  |  |  |
| Non-haemorrhagic stroke/SE | 0.80 (0.68-0.95) | 0.0116 |  | 0.93 (0.77-1.12) | 0.4438 |
|  |  |  |  |  |  |
| Major bleeding | 0.68 (0.57-0.80) | <.0001 |  | 0.85 (0.71-1.03) | 0.1002 |
|  |  |  |  |  |  |
| New/worsening heart failure | 0.84 (0.71-1.01) | 0.0664 |  | 0.95 (0.78-1.17) | 0.6515 |

1Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, baseline antiplatelet and anticoagulant use.

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