

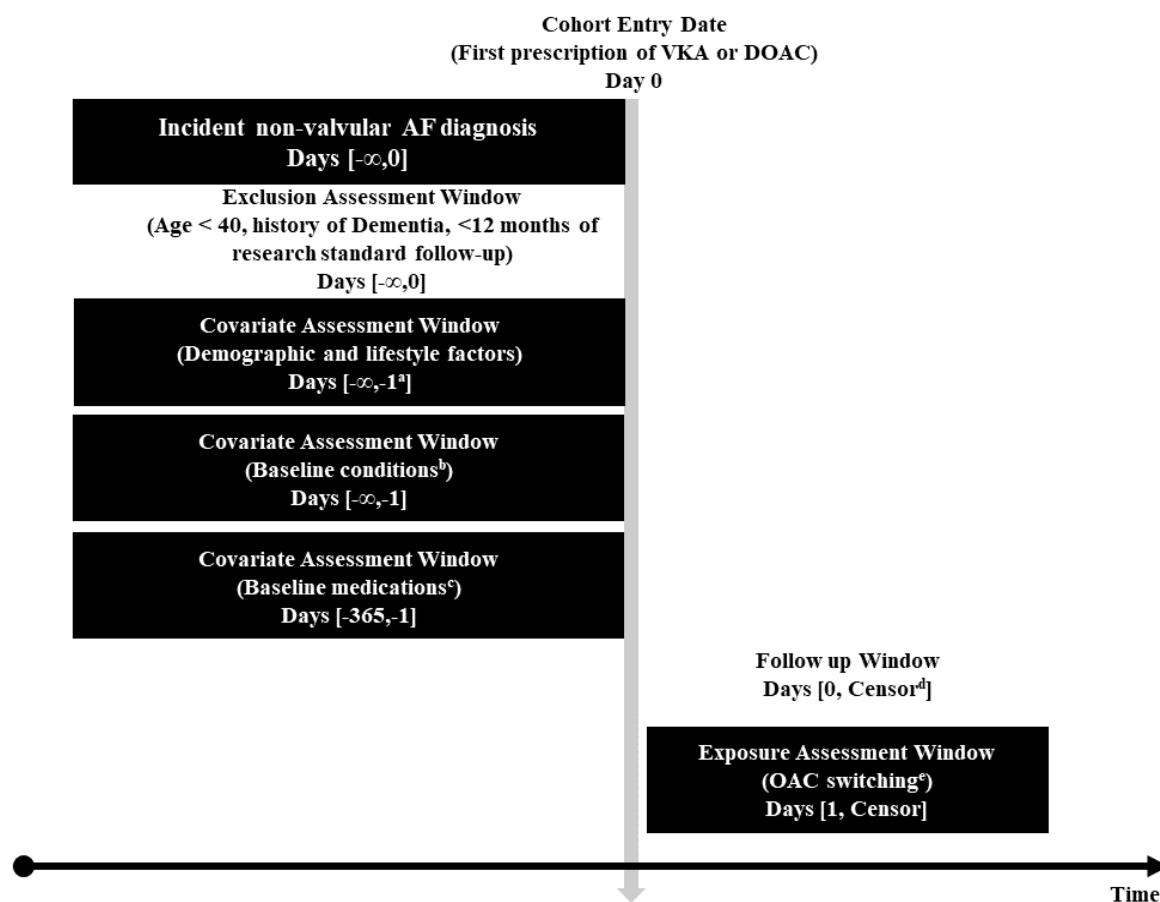
**Supplementary Table 1** Baseline characteristics of the sample, switchers versus non-switchers

|   | <b>Switchers</b> | <b>Non-switchers</b> |
|---|------------------|----------------------|
|   | 4,485<br>(11.4%) | 34,715<br>(88.6%)    |
| <b>Gender</b>                                       |                  |                      |
| Male  | 2,320 (51.7)     | 19,391 (55.9)        |
| Female  | 2,165 (48.3)     | 15,324 (44.1)        |
| <b>Age category</b>                                 |                  |                      |
| 40-49   | 85 (1.9)         | 630 (1.8)            |
| 50-59   | 317 (7.1)        | 2,366 (6.8)          |
| 60-69   | 998 (22.3)       | 6,919 (19.9)         |
| 70-79   | 1,647 (36.7)     | 12,541 (36.1)        |
| >80   | 1,438 (32.1)     | 12,259 (35.3)        |
| <b>Ethnicity</b>                                    |                  |                      |
| White   | 2,034 (45.4)     | 16,513 (47.6)        |
| South Asian   | 22 (0.5)         | 182 (0.5)            |
| Black   | 5 (0.1)          | 103 (0.3)            |
| Mixed/Other   | 22 (0.5)         | 135 (0.4)            |
| Missing   | 2,404 (53.6)     | 17,782 (51.2)        |
| <b>Socio-economic status (IMD - patient level)</b>  |                  |                      |
| 1   | 514 (11.5)       | 4,396 (12.7)         |
| 2   | 450 (10.0)       | 3,904 (11.2)         |
| 3   | 429 (9.6)        | 3,571 (10.3)         |
| 4   | 329 (7.3)        | 2,714 (7.8)          |
| 5   | 228 (5.1)        | 2,166 (6.2)          |
| Missing   | 2,535 (56.5)     | 17,964 (51.8)        |
| <b>Socio-economic status (IMD - practice level)</b> |                  |                      |
| 1   | 903 (20.1)       | 6,543 (18.8)         |
| 2   | 641 (14.3)       | 5,679 (16.4)         |
| 3   | 1,013 (22.6)     | 7,664 (22.1)         |
| 4   | 898 (20.0)       | 6,772 (19.5)         |
| 5   | 1,030 (23.0)     | 8,057 (23.2)         |
| <b>BMI category</b>                                 |                  |                      |
| Underweight   | 99 (2.2)         | 733 (2.1)            |
| Normal  | 1,129 (25.2)     | 8,654 (24.9)         |
| Overweight  | 1,778 (39.6)     | 13,990 (40.3)        |
| Obese   | 1,479 (33.0)     | 11,338 (32.7)        |
| <b>Hazardous alcohol status</b>                     |                  |                      |
| Yes   | 4,109 (91.6)     | 32,360 (93.2)        |
| No  | 376 (8.4)        | 2,355 (6.8)          |
| <b>Smoking status</b>                               |                  |                      |
| Non/ex-smoker                                       | 4,032 (89.9)     | 31,066 (89.5)        |
| Current   | 451 (10.1)       | 3,564 (10.3)         |
| Missing   | 2 (0.04)         | 85 (0.2)             |
| <b>Consultation frequency/year<sup>^</sup></b>      |                  |                      |
| 1 to 10   | 476 (10.6)       | 4,941 (14.2)         |
| 11 to 20  | 1,321 (29.5)     | 10,962 (31.6)        |
| 21 to 30  | 1,145 (25.5)     | 8,516 (24.5)         |
| 31 to 40  | 723 (16.1)       | 4,790 (13.8)         |
| 41 to 50  | 377 (8.4)        | 2,498 (7.2)          |
| 51 to 60  | 171 (3.8)        | 1,255 (3.6)          |
| Over 60   | 240 (5.4)        | 1,653 (4.8)          |

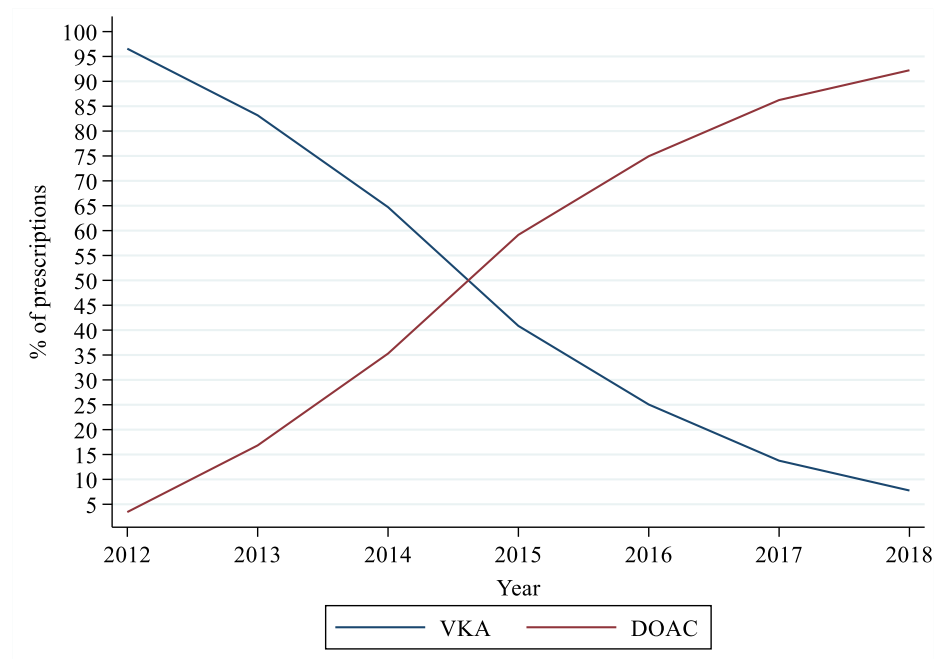
|   |              |               |
|---|--------------|---------------|
| None                                      | 32 (0.7)     | 100 (0.3)     |
| <b>Calendar year of OAC prescription*</b> |              |               |
| 2012                                      | 811 (18.1)   | 4,103 (11.8)  |
| 2013                                      | 1,094 (16.1) | 5,234 (15.1)  |
| 2014                                      | 1,036 (23.1) | 5,767 (16.6)  |
| 2015                                      | 807 (18.0)   | 6,058 (17.5)  |
| 2016                                      | 466 (10.4)   | 5,064 (14.6)  |
| 2017                                      | 206 (4.6)    | 4,550 (13.1)  |
| 2018                                      | 65 (1.5)     | 3,939 (11.4)  |
| <b>Conditions at baseline</b>             |              |               |
| Diabetes                                  | 1,165 (26.0) | 8,921(25.7)   |
| Hypertension history                      | 3,176 (70.8) | 23,544(67.8)  |
| Myocardial infarction history             | 544 (12.1)   | 4,068 (11.7)  |
| Heart failure history                     | 1,221 (27.2) | 7,847 (22.6)  |
| Stroke/TIA/thromboembolism history        | 955 (21.3)   | 6,259 (18.0)  |
| Vascular disease history                  | 1,371 (30.6) | 9,406 (27.1)  |
| Renal disease history                     | 1,485 (33.1) | 10,422 (30.0) |
| Liver disease history                     | 117 (2.6)    | 723 (2.1)     |
| <b>Medications at baseline</b>            |              |               |
| Statin use                                | 3,233 (72.1) | 23,796 (68.6) |
| Antiplatelet drugs/NSAIDs                 | 3,024 (67.4) | 22,054 (63.5) |
| ACE inhibitor or ARB                      | 1,826 (40.7) | 13,980 (40.3) |
| Beta blockers                             | 2,817 (62.8) | 23,649 (68.1) |
| Class I or III antiarrhythmics            | 4,103 (91.5) | 32,571 (93.8) |
| Digoxin                                   | 572 (12.8)   | 3,866 (11.1)  |
| Diuretics                                 | 2,142 (47.8) | 16,133 (46.5) |
| Antidepressants                           | 945 (21.1)   | 6,256 (18.0)  |
| Antipsychotics                            | 33 (0.7)     | 230 (0.7)     |
| Proton pump inhibitors                    | 2,091 (46.6) | 15,779 (45.5) |

^Primary care consultations in the year prior to first oral anticoagulant prescription

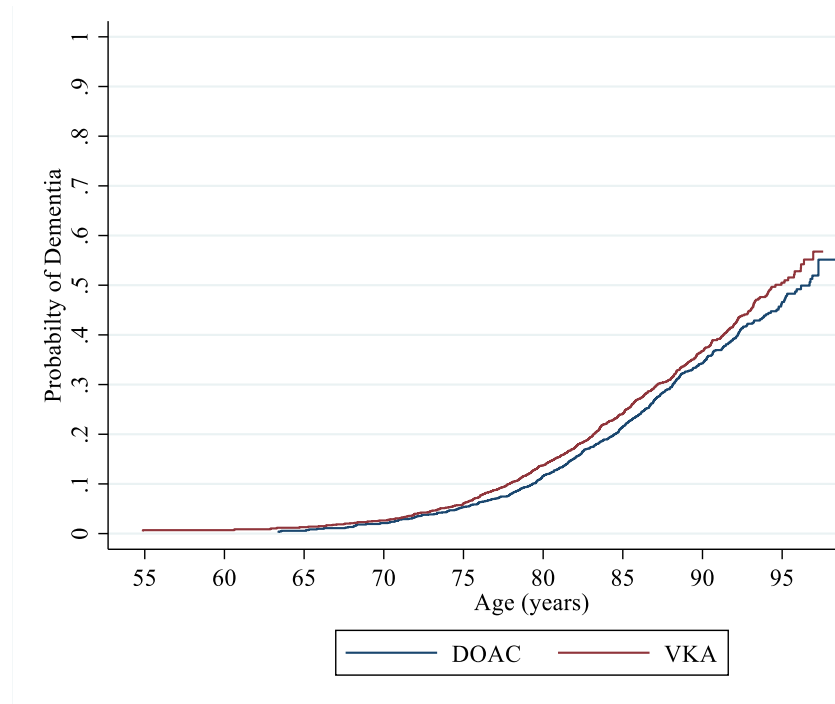
\*Year prescribed first oral anti-coagulant

**Supplementary Figure 1:** Graphical presentation of study design for primary analysis

- a. Demographic and lifestyle variables recording closest to first OAC prescription, where appropriate. Primary care consultation frequency in the year prior to first oral anticoagulant prescription.
- b. Baseline conditions recorded at any time prior to OAC prescription: diabetes, hypertension, myocardial infarction, heart failure, stroke/ thromboembolism, vascular disease, chronic renal disease and chronic liver disease.
- c. Medications recorded within one year prior to OAC prescription: statin use, antiplatelet drugs or non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitor or ARB, beta blockers, class 1 or 3 antiarrhythmics, digoxin, antipsychotics, antidepressants, and proton pump inhibitors.
- d. Censored at earliest of: dementia diagnosis, death, transfer out of the general practice, last data collection date from the practice, end of OAC prescription, or the end of study period (31 Dec 2018).
- e. Patients initially prescribed one class of OAC, who then switched to the other class contributed exposure time initially to one class and then subsequently to the other.

**Supplementary Figure 2: OAC treatment initiation among AF patients**

**Caption:** This figure illustrates the percentage of prescriptions for vitamin k antagonists (VKAs) versus direct oral anti-coagulants (DOACs), by year of prescription. Prescriptions represent the first prescription of DOAC and/or VKA per participant, to allow for switching.

**Supplementary Figure 3:** Cumulative incidence curves of dementia, by age

**Caption:** This figure shows the cumulative incidence of dementia (by age) in people with incident atrial fibrillation, treated with direct oral anti-coagulants versus vitamin k antagonists. The graph is censored at age 100 due to one outlier in the data.

**Supplementary Table 2** Association between oral anticoagulant use and incident dementia defined using clinical codes – partially and fully adjusted primary analysis models

|   | Adjusted for age, calendar year and time-on-treatment (as time-scales) and gender |             |             |             | Additionally, adjusted for demographic/lifestyle factors |             |             |                   | Additionally, adjusted for demographic/lifestyle factors + clinical conditions |             |             |             | Additionally, adjusted for demographic/lifestyle factors + clinical conditions + medications |             |             |                   |
|---|---|-------------|-------------|-------------|--|-------------|-------------|-------------------|--|-------------|-------------|-------------|--|-------------|-------------|-------------------|
|   | HR  | 95% CI      |             | p-value     | 95% CI   |             | p-value     | HR                | 95% CI   |             | p-value     | HR          | 95% CI   |             | p-value     |                   |
| <b>OAC type</b>                                   |   |             |             |             |  |             |             |                   |  |             |             |             |  |             |             |                   |
| VKA   |   |             |             |             | 1.00   |             |             |                   | 1.00   |             |             |             | 1.00   |             |             |                   |
| DOAC  | <b>0.92</b>   | <b>0.79</b> | <b>1.06</b> | <b>0.25</b> | <b>0.90</b>  | <b>0.78</b> | <b>1.04</b> | <b>0.14</b>       | <b>0.87</b>  | <b>0.75</b> | <b>1.00</b> | <b>0.05</b> | <b>0.84</b>  | <b>0.73</b> | <b>0.98</b> | <b>0.02</b>       |
| <b>Gender</b>                                     |   |             |             |             |  |             |             |                   |  |             |             |             |  |             |             |                   |
| Male  | 1.00  |             |             |             | 1.00   |             |             |                   | 1.00   |             |             |             |  |             |             |                   |
| Female  | 1.02  | 0.91        | 1.14        | 0.76        | 1.04   | 0.92        | 1.16        | 0.55              | 1.03   | 0.92        | 1.16        | 0.56        | 1.01   | 0.90        | 1.14        | 0.89              |
| <b>BMI category</b>                               |   |             |             |             |  |             |             |                   |  |             |             |             |  |             |             |                   |
| normal  |   |             |             |             | 1.00   |             |             |                   | 1.00   |             |             |             | 1.00   |             |             |                   |
| underweight                                       |   |             |             |             | 0.86   | 0.57        | 1.30        | 0.46              | 0.83   | 0.55        | 1.26        | 0.38        | 0.82   | 0.54        | 1.14        | 0.36              |
| overweight  |   |             |             |             | 1.01   | 0.88        | 1.15        | 0.94              | 1.00   | 0.87        | 1.15        | 0.97        | 1.02   | 0.88        | 1.17        | 0.82              |
| obese   |   |             |             |             | 1.00   | 0.86        | 1.16        | 0.97              | 0.99   | 0.85        | 1.15        | 0.89        | 1.02   | 0.87        | 1.19        | 0.83              |
| <b>Smoking status</b>                             |   |             |             |             |  |             |             |                   |  |             |             |             |  |             |             |                   |
| Non/ex-smoker                                     |   |             |             |             | 1.00   |             |             |                   | 1.00   |             |             |             | 1.00   |             |             |                   |
| Current   |   |             |             |             | 1.48   | 1.22        | 1.80        | 0.00 <sup>1</sup> | 1.46   | 1.19        | 1.78        | 0.00        | 1.43   | 1.17        | 1.74        | 0.00 <sup>^</sup> |
| <b>Hazardous alcohol consumption</b>              |   |             |             |             |  |             |             |                   |  |             |             |             |  |             |             |                   |
| No  |   |             |             |             | 1.00   |             |             |                   | 1.00   |             |             |             | 1.00   |             |             |                   |
| Yes   |   |             |             |             | 1.23   | 0.97        | 1.57        | 0.08              | 1.23   | 0.97        | 1.57        | 0.09        | 1.20   | 0.94        | 1.54        | 0.14              |
| <b>Socio-economic status - practice level IMD</b> |   |             |             |             |  |             |             |                   |  |             |             |             |  |             |             |                   |
| 1   |   |             |             |             | 1.00   |             |             |                   | 1.00   |             |             |             | 1.00   |             |             |                   |
| 2   |   |             |             |             | 1.14   | 0.95        | 1.38        | 0.17              | 1.15   | 0.95        | 1.39        | 0.15        | 1.16   | 0.96        | 1.40        | 0.14              |
| 3   |   |             |             |             | 1.10   | 0.92        | 1.31        | 0.30              | 1.10   | 0.92        | 1.31        | 0.32        | 1.08   | 0.90        | 1.29        | 0.39              |
| 4   |   |             |             |             | 1.17   | 0.97        | 1.40        | 0.09              | 1.16   | 0.97        | 1.39        | 0.10        | 1.13   | 0.95        | 1.37        | 0.16              |
| 5   |   |             |             |             | 1.12   | 0.94        | 1.33        | 0.21              | 1.11   | 0.93        | 1.33        | 0.23        | 1.09   | 0.92        | 1.30        | 0.32              |
| <b>Consultation frequency/year<sup>^</sup></b>    |   |             |             |             |  |             |             |                   |  |             |             |             |  |             |             |                   |
| 1 to 10   |   |             |             |             | 1.00   |             |             |                   | 1.00   |             |             |             | 1.00   |             |             |                   |

|                                   |      |      |      |      |      |      |      |      |      |      |      |      |
|-----------------------------------|------|------|------|------|------|------|------|------|------|------|------|------|
| 11 to 20                          | 0.99 | 0.81 | 1.21 | 0.94 | 0.98 | 0.80 | 1.20 | 0.85 | 0.96 | 0.78 | 1.18 | 0.70 |
| 21 to 30                          | 1.06 | 0.86 | 1.30 | 0.59 | 1.04 | 0.85 | 1.28 | 0.71 | 1.02 | 0.82 | 1.25 | 0.89 |
| 31 to 40                          | 1.19 | 0.95 | 1.48 | 0.13 | 1.17 | 0.93 | 1.46 | 0.18 | 1.13 | 0.90 | 1.42 | 0.31 |
| 41 to 50                          | 1.47 | 1.14 | 1.88 | 0.00 | 1.41 | 1.10 | 1.81 | 0.01 | 1.32 | 1.02 | 1.71 | 0.04 |
| 51 to 60                          | 1.15 | 0.83 | 1.61 | 0.40 | 1.11 | 0.80 | 1.55 | 0.54 | 1.03 | 0.73 | 1.45 | 0.85 |
| over 60                           | 1.51 | 1.14 | 2.02 | 0.00 | 1.46 | 1.09 | 1.95 | 0.01 | 1.37 | 1.02 | 1.86 | 0.04 |
| <b>Clinical conditions</b>        |      |      |      |      |      |      |      |      |      |      |      |      |
| Diabetes                          |      |      |      |      | 1.15 | 1.01 | 1.31 | 0.03 | 1.12 | 0.99 | 1.28 | 0.08 |
| Hypertension                      |      |      |      |      | 0.90 | 0.79 | 1.02 | 0.11 | 0.94 | 0.82 | 1.08 | 0.41 |
| Myocardial<br>Infarction          |      |      |      |      | 0.91 | 0.77 | 1.08 | 0.28 | 0.89 | 0.74 | 1.07 | 0.21 |
| Heart failure                     |      |      |      |      | 0.96 | 0.84 | 1.09 | 0.49 | 0.99 | 0.87 | 1.13 | 0.86 |
| Stroke/TIA/thromb<br>oembolism    |      |      |      |      | 1.61 | 1.42 | 1.81 | 0.00 | 1.56 | 1.38 | 1.79 | 0.00 |
| Vascular disease                  |      |      |      |      | 1.09 | 0.97 | 1.22 | 0.16 | 1.08 | 0.96 | 1.22 | 0.18 |
| Renal disease                     |      |      |      |      | 1.04 | 0.92 | 1.17 | 0.56 | 1.05 | 0.93 | 1.19 | 0.41 |
| Liver disease                     |      |      |      |      | 0.92 | 0.57 | 1.49 | 0.73 | 0.90 | 0.54 | 1.43 | 0.60 |
| <b>Medications</b>                |      |      |      |      |      |      |      |      |      |      |      |      |
| Antiplatelet/<br>NSAIDs           |      |      |      |      |      |      |      |      | 1.14 | 0.99 | 1.32 | 0.08 |
| ACE<br>inhibitors/ARB             |      |      |      |      |      |      |      |      | 1.10 | 0.97 | 1.24 | 0.13 |
| Beta-blockers                     |      |      |      |      |      |      |      |      | 1.04 | 0.92 | 1.17 | 0.51 |
| Class I or III<br>Antiarrhythmics |      |      |      |      |      |      |      |      | 0.97 | 0.74 | 1.28 | 0.85 |
| Digoxin                           |      |      |      |      |      |      |      |      | 1.25 | 1.06 | 1.48 | 0.01 |
| Diuretics                         |      |      |      |      |      |      |      |      | 0.75 | 0.67 | 0.85 | 0.00 |
| Antipsychotics                    |      |      |      |      |      |      |      |      | 3.06 | 1.94 | 4.81 | 0.00 |
| Antidepressants                   |      |      |      |      |      |      |      |      | 1.53 | 1.33 | 1.75 | 0.00 |
| Proton Pump Inhibitors            |      |      |      |      |      |      |      |      | 0.89 | 0.79 | 1.00 | 0.05 |
| Statin use                        |      |      |      |      |      |      |      |      | 0.97 | 0.87 | 1.13 | 0.62 |

^Primary care consultations in the year prior to first oral anticoagulant prescription. Note: ethnicity was not included in the final model due to the proportion of missing data.