

Supplemental Table 1. Baseline characteristics of patients with nonvalvular atrial fibrillation newly initiating a DOAC, before and after propensity score matching: characteristics not included in propensity score models due to high missingness assessed in the year prior to and including index date

| | Patient characteristics before propensity score matching | | | | Patient characteristics after propensity score matching | | | | | | | | |
|--|--|----------------------|---------------------------|----------------------|---|----------------------|-------|------------------------|--------------------------|-------|----------------------|---------------------------|-------|
| | Apixaban | Rivaroxaban | Edoxaban | Dabigatran | Apixaban | Rivaroxaban | ASD | Apixaban | Other DOACs | ASD | Rivaroxaban | Other DOACs | ASD |
| Number of patients | 2,801 | 2,221 | 398 | 261 | 1,839 | 1,839 | | 2,276 | 2,276 | | 1,985 | 1,985 | |
| Patient characteristics, evaluated as the last value observed in the one year prior to index date | | | | | | | | | | | | | |
| Marital status | | | | | | | 0.222 | | | 0.128 | | | 0.289 |
| Married; n (%) | 32 (1.1%) | 21 (0.9%) | 8 (2.0%) | 1 (0.4%) | 21 (1.1%) | 18 (1.0%) | | 28 (1.2%) | 28 (1.2%) | | 19 (1.0%) | 26 (1.3%) | |
| Unmarried; n (%) | 13 (0.5%) | 11 (0.5%) | 3 (0.8%) | 0 (0.0%) | 8 (0.4%) | 11 (0.6%) | | 9 (0.4%) | 12 (0.5%) | | 11 (0.6%) | 8 (0.4%) | |
| Missing; n (%) | 2,756 (98.4%) | 2,189 (98.6%) | 387 (97.2%) | 260 (99.6%) | 1,810 (98.4%) | 1,810 (98.4%) | | 2,239 (98.4%) | 2,236 (98.2%) | | 1,955 (98.5%) | 1,951 (98.3%) | |
| Cigarettes per day | | | | | | | 0.216 | | | 0.150 | | | 0.163 |
| mean (sd) | 10.50 (5.98) | 12.22 (8.33) | 12.25 (8.28) | 11.15 (5.98) | 10.51 (6.01) | 12.00 (7.71) | | 10.34 (6.05) | 11.38 (7.72) | | 12.17 (8.10) | 10.99 (6.27) | |
| median [IQR] | 10.00 [5.75, 15.00] | 10.00 [5.00, 16.25] | 10.00 [6.50, 15.00] | 10.00 [6.00, 17.50] | 10.00 [5.50, 15.00] | 10.00 [5.00, 15.00] | | 10.00 [5.75, 15.00] | 10.00 [5.00, 15.00] | | 10.00 [5.00, 20.00] | 10.00 [6.00, 15.00] | |
| Missing; n (%) | 2,695 (96.2%) | 2,127 (95.8%) | 382 (96.0%) | 248 (95.0%) | 1,774 (96.5%) | 1,764 (95.9%) | | 2,190 (96.2%) | 2,181 (95.8%) | | 1,907 (96.1%) | 1,913 (96.4%) | |
| Glasses per day* | | | | | | | 0.076 | | | 0.043 | | | 0.128 |
| mean (sd) | 40,314.49 (901,176.02) | 14.69 (15.77) | 175,469.73 (3,379,675.36) | 20.22 (35.00) | 58,421.88 (1,084,888.39) | 15.00 (16.19) | | 46,984.77 (872,895.01) | 99,476.87 (1,413,606.11) | | 14.70 (15.95) | 162,906.26 (1,806,540.38) | |
| median [IQR] | 10.00 [2.00, 18.00] | 10.00 [4.00, 20.00] | 12.00 [5.00, 20.25] | 10.00 [2.00, 21.50] | 10.00 [2.00, 20.00] | 10.00 [4.00, 20.00] | | 10.00 [2.00, 18.00] | 10.00 [4.00, 21.00] | | 10.00 [4.00, 20.00] | 10.00 [3.00, 20.00] | |
| Missing; n (%) | 2,301 (82.1%) | 1,822 (82.0%) | 328 (82.4%) | 212 (81.2%) | 1,494 (81.2%) | 1,504 (81.8%) | | 1,847 (81.2%) | 1,871 (82.2%) | | 1,626 (81.9%) | 1,614 (81.3%) | |
| BMI (kg/m ²) | | | | | | | 0.083 | | | 0.045 | | | 0.074 |
| mean (sd) | 29.20 (6.24) | 29.86 (6.51) | 28.81 (6.28) | 29.83 (6.34) | 29.23 (6.29) | 29.75 (6.42) | | 29.21 (6.24) | 29.49 (6.43) | | 29.78 (6.48) | 29.30 (6.46) | |
| median [IQR] | 28.30 [24.70, 32.60] | 28.90 [25.30, 33.40] | 27.80 [24.50, 32.23] | 29.20 [25.40, 32.90] | 28.30 [24.70, 32.40] | 28.80 [25.30, 33.40] | | 28.40 [24.78, 32.60] | 28.55 [25.08, 33.00] | | 28.80 [25.20, 33.40] | 28.50 [24.80, 32.60] | |
| Missing; n (%) | 970 (34.6%) | 846 (38.1%) | 104 (26.1%) | 98 (37.5%) | 672 (36.5%) | 702 (38.2%) | | 790 (34.7%) | 830 (36.5%) | | 765 (38.5%) | 708 (35.7%) | |
| HbA1c (mmol/mol) | | | | | | | 0.066 | | | 0.076 | | | 0.075 |
| mean (sd) | 46.53 (15.17) | 48.59 (16.25) | 46.69 (14.76) | 46.92 (13.99) | 46.87 (16.39) | 47.94 (16.05) | | 46.41 (15.13) | 47.58 (16.65) | | 48.34 (16.04) | 47.12 (16.24) | |
| median [IQR] | 44.00 [39.00, 52.00] | 45.00 [39.00, 54.00] | 43.00 [39.00, 52.25] | 44.00 [40.00, 52.00] | 44.00 [39.00, 53.00] | 44.00 [39.00, 53.00] | | 44.00 [39.00, 52.00] | 44.00 [39.00, 53.00] | | 45.00 [39.00, 54.00] | 44.00 [39.00, 53.00] | |
| Missing; n (%) | 1,544 (55.1%) | 1,235 (55.6%) | 252 (63.3%) | 150 (57.5%) | 1,025 (55.7%) | 1,034 (56.2%) | | 1,262 (55.4%) | 1,299 (57.1%) | | 1,104 (55.6%) | 1,110 (55.9%) | |
| INR | | | | | | | 0.036 | | | 0.021 | | | 0.044 |
| mean (sd) | 4.77 (13.57) | 3.77 (8.53) | 8.34 (19.23) | 2.01 (0.81) | 4.33 (12.41) | 3.94 (9.40) | | 4.71 (13.54) | 4.44 (11.17) | | 3.94 (9.07) | 4.42 (12.60) | |
| median [IQR] | 2.40 [1.80, 2.80] | 2.30 [1.80, 2.90] | 2.40 [2.00, 3.20] | 2.00 [1.40, 2.38] | 2.40 [1.80, 2.80] | 2.30 [1.80, 2.90] | | 2.40 [1.80, 2.80] | 2.30 [1.80, 2.90] | | 2.30 [1.80, 2.90] | 2.30 [1.80, 2.75] | |
| Missing; n (%) | 2,464 (88.0%) | 1,880 (84.6%) | 349 (87.7%) | 225 (86.2%) | 1,606 (87.3%) | 1,575 (85.6%) | | 1,982 (87.1%) | 1,952 (85.8%) | | 1,685 (84.9%) | 1,708 (86.0%) | |
| GFR (ml/min/1.73 m ²) | | | | | | | 0.135 | | | 0.131 | | | 0.145 |
| mean (sd) | 61.04 (16.17) | 63.66 (15.95) | 62.25 (15.62) | 64.86 (15.23) | 61.49 (16.24) | 63.67 (16.01) | | 61.21 (16.17) | 63.30 (15.79) | | 63.72 (15.97) | 61.39 (16.30) | |
| median [IQR] | 61.00 [50.00, 73.00] | 64.00 [52.00, 76.00] | 60.00 [52.00, 76.00] | 65.00 [54.00, 79.00] | 61.00 [50.00, 74.00] | 64.00 [52.00, 76.00] | | 61.00 [50.00, 74.00] | 64.00 [52.00, 76.00] | | 64.00 [52.00, 76.00] | 60.40 [50.00, 74.00] | |
| Missing; n (%) | 1,052 (37.6%) | 870 (39.2%) | 190 (47.7%) | 94 (36.0%) | 736 (40.0%) | 714 (38.8%) | | 879 (38.6%) | 909 (39.9%) | | 781 (39.3%) | 786 (39.6%) | |
| CrCl (ml/min) | | | | | | | 0.029 | | | 0.017 | | | 0.066 |
| mean (sd) | 63.93 (22.40) | 65.75 (19.46) | 56.73 (21.52) | 71.84 (4.95) | 66.81 (21.09) | 66.22 (19.78) | | 63.89 (21.95) | 64.24 (20.10) | | 65.75 (19.46) | 67.14 (22.51) | |
| median [IQR] | 63.00 [48.00, 81.50] | 65.00 [52.50, 77.25] | 50.00 [40.00, 65.00] | 71.00 [68.25, 75.84] | 64.50 [49.43, 82.25] | 66.35 [51.50, 77.75] | | 62.50 [48.75, 81.25] | 63.50 [47.50, 77.25] | | 65.00 [52.50, 77.25] | 66.50 [46.50, 85.11] | |
| Missing; n (%) | 2,700 (96.4%) | 2,175 (97.9%) | 383 (96.2%) | 256 (98.1%) | 1,793 (97.5%) | 1,795 (97.6%) | | 2,194 (96.4%) | 2,214 (97.3%) | | 1,939 (97.7%) | 1,943 (97.9%) | |
| Apixaban and rivaroxaban dosage, evaluated on the index date; n (%)** | | | | | | | | | | | | | |
| Apixaban 2.5mg | 761 (27.2%) | - | - | - | 512 (27.8%) | - | - | 622 (27.3%) | - | - | - | 499 (25.1%) | - |
| Apixaban 5mg | 2,063 (73.7%) | - | - | - | 1,342 (73.0%) | - | - | 1,674 (73.6%) | - | - | - | 1,161 (58.5%) | - |
| Rivaroxaban 2.5mg | - | 14 (0.6%) | - | - | - | 9 (0.5%) | - | - | 9 (0.4%) | - | 12 (0.6%) | - | - |
| Rivaroxaban 10mg | - | 18 (0.8%) | - | - | - | 15 (0.8%) | - | - | 11 (0.5%) | - | 14 (0.7%) | - | - |
| Rivaroxaban 15mg | - | 409 (18.4%) | - | - | - | 341 (18.5%) | - | - | 329 (14.5%) | - | 370 (18.6%) | - | - |
| Rivaroxaban 20mg | - | 1,793 (80.7%) | - | - | - | 1,484 (80.7%) | - | - | 1,368 (60.1%) | - | 1,600 (80.6%) | - | - |
| Edoxaban 15mg | - | - | 2 (0.5%) | - | - | - | - | - | - | - | - | 1 (0.1%) | - |
| Edoxaban 30mg | - | - | 108 (27.1%) | - | - | - | - | - | - | - | - | 34 (1.7%) | - |
| Edoxaban 60mg | - | - | 295 (74.1%) | - | - | - | - | - | - | - | - | 91 (4.6%) | - |
| Dabigatran 75mg | - | - | - | 16 (6.1%) | - | - | - | - | - | - | - | 14 (0.6%) | - |
| Dabigatran 110mg | - | - | - | 123 (47.1%) | - | - | - | - | - | - | - | 91 (4.0%) | - |
| Dabigatran 150mg | - | - | - | 125 (47.9%) | - | - | - | - | - | - | - | 88 (3.9%) | - |

Characteristics assessed in the year prior to and including index date.

SD = standard deviation; IQR = interquartile range; DOAC = direct oral anticoagulants; ASD = absolute standardized difference.

* Values reported reflect all available data without modification or cleaning.

** Patients with prescriptions for multiple dosages are reported as having all dosages observed

Supplemental table 2. Per-protocol analysis using a 3000 baseline period for all characteristics: Baseline characteristics of patients with nonvalvular atrial fibrillation newly initiating a DOAC, before and after propensity score matching

| | Patient characteristics before propensity score matching | | | | Patient characteristics after propensity score matching | | | | | | | | |
|--|--|---------------|--------------|--------------|---|---------------|-------|---------------|---------------|-------|---------------|---------------|-------|
| | Apixaban | Rivaroxaban | Edoxaban | Dabigatran | Apixaban | Rivaroxaban | ASD | Apixaban | Other DOACs | ASD | Rivaroxaban | Other DOACs | ASD |
| Number of patients | 2,801 | 2,221 | 398 | 261 | 1,840 | 1,840 | | 2,301 | 2,301 | | 2,023 | 2,023 | |
| Year of Cohort Entry Date | | | | | | | 0.034 | | | 0.017 | | | 0.038 |
| 2014 | 76 (2.7%) | 138 (6.2%) | 0 (0.0%) | 32 (12.3%) | 76 (4.1%) | 81 (4.4%) | | 76 (3.3%) | 78 (3.4%) | | 116 (5.7%) | 108 (5.3%) | |
| 2015 | 365 (13.0%) | 548 (24.7%) | 0 (0.0%) | 81 (31.0%) | 357 (19.4%) | 359 (19.5%) | | 362 (15.7%) | 372 (16.2%) | | 441 (21.8%) | 436 (21.6%) | |
| 2016 | 571 (20.4%) | 646 (29.1%) | 11 (2.8%) | 77 (29.5%) | 532 (28.9%) | 523 (28.4%) | | 555 (24.1%) | 550 (23.9%) | | 582 (28.8%) | 596 (29.5%) | |
| 2017 | 546 (19.5%) | 383 (17.2%) | 20 (5.0%) | 42 (16.1%) | 388 (21.1%) | 374 (20.3%) | | 427 (18.6%) | 423 (18.4%) | | 379 (18.7%) | 392 (19.4%) | |
| 2018 | 530 (18.9%) | 257 (11.6%) | 115 (28.9%) | 21 (8.0%) | 242 (13.2%) | 256 (13.9%) | | 393 (17.1%) | 385 (16.7%) | | 257 (12.7%) | 250 (12.4%) | |
| 2019 | 423 (15.1%) | 143 (6.4%) | 129 (32.4%) | 5 (1.9%) | 145 (7.9%) | 142 (7.7%) | | 263 (11.4%) | 268 (11.6%) | | 142 (7.0%) | 146 (7.2%) | |
| 2020 | 290 (10.4%) | 106 (4.8%) | 123 (30.9%) | 3 (1.1%) | 100 (5.4%) | 105 (5.7%) | | 225 (9.8%) | 225 (9.8%) | | 106 (5.2%) | 95 (4.7%) | |
| Age (years) | | | | | | | 0.053 | | | 0.038 | | | 0.038 |
| mean (sd) | 77.35 (8.54) | 76.71 (8.62) | 77.11 (8.35) | 76.23 (8.56) | 77.34 (8.60) | 76.89 (8.26) | | 77.14 (8.63) | 76.82 (8.39) | | 76.84 (8.53) | 77.17 (8.72) | |
| median [IQR] | 78 [72, 83] | 77 [71, 83] | 78 [72, 83] | 77 [70, 82] | 78 [71, 83] | 77 [71, 83] | | 77 [71, 83] | 77 [71, 83] | | 77 [71, 83] | 78 [71, 83] | |
| Age categories (years) | | | | | | | 0.021 | | | 0.003 | | | 0.019 |
| < 55 | 30 (1.1%) | 34 (1.5%) | 5 (1.3%) | 4 (1.5%) | 18 (1.0%) | 17 (0.9%) | | 26 (1.1%) | 26 (1.1%) | | 30 (1.5%) | 26 (1.3%) | |
| 55 - 64 | 131 (4.7%) | 120 (5.4%) | 18 (4.5%) | 13 (5.0%) | 96 (5.2%) | 92 (5.0%) | | 116 (5.0%) | 117 (5.1%) | | 99 (4.9%) | 100 (4.9%) | |
| 65 - 74 | 808 (28.8%) | 634 (28.5%) | 120 (30.2%) | 83 (31.8%) | 514 (27.9%) | 530 (28.8%) | | 686 (29.8%) | 683 (29.7%) | | 577 (28.5%) | 585 (28.9%) | |
| >= 75 | 1,832 (65.4%) | 1,433 (64.5%) | 255 (64.1%) | 161 (61.7%) | 1,212 (65.9%) | 1,201 (65.3%) | | 1,473 (64.0%) | 1,475 (64.1%) | | 1,317 (65.1%) | 1,312 (64.9%) | |
| Gender | | | | | | | 0.003 | | | 0.006 | | | 0.013 |
| Female | 1,070 (38.2%) | 785 (35.3%) | 158 (39.7%) | 81 (31.0%) | 661 (35.9%) | 664 (36.1%) | | 864 (37.5%) | 857 (37.2%) | | 730 (36.1%) | 717 (35.4%) | |
| Male | 1,731 (61.8%) | 1,436 (64.7%) | 240 (60.3%) | 180 (69.0%) | 1,179 (64.1%) | 1,176 (63.9%) | | 1,437 (62.5%) | 1,444 (62.8%) | | 1,293 (63.9%) | 1,306 (64.6%) | |
| Non-Major Bleeding Events | | | | | | | 0.010 | | | 0.017 | | | 0.026 |
| Anemia | 79 (2.8%) | 63 (2.8%) | 5 (1.3%) | 9 (3.4%) | 52 (2.8%) | 50 (2.7%) | | 55 (2.4%) | 58 (2.5%) | | 53 (2.6%) | 51 (2.5%) | 0.006 |
| Diabetes Mellitus | 104 (3.7%) | 98 (4.4%) | 7 (1.8%) | 11 (4.2%) | 76 (4.1%) | 69 (3.8%) | 0.020 | 85 (3.7%) | 89 (3.9%) | 0.009 | 83 (4.1%) | 86 (4.3%) | 0.007 |
| Hypertension | 165 (5.9%) | 132 (5.9%) | 22 (5.5%) | 18 (6.9%) | 106 (5.8%) | 99 (5.4%) | 0.017 | 138 (6.0%) | 131 (5.7%) | 0.013 | 117 (5.8%) | 126 (6.2%) | 0.019 |
| Heart Failure | 208 (7.4%) | 161 (7.2%) | 19 (4.8%) | 13 (5.0%) | 126 (6.8%) | 119 (6.5%) | 0.015 | 149 (6.5%) | 155 (6.7%) | 0.010 | 139 (6.9%) | 135 (6.7%) | 0.008 |
| Osteoporosis and Hip Fractures | 32 (1.1%) | 23 (1.0%) | 9 (2.3%) | 5 (1.9%) | 16 (0.9%) | 20 (1.1%) | 0.022 | 30 (1.3%) | 28 (1.2%) | 0.008 | 23 (1.1%) | 18 (0.9%) | 0.025 |
| Malignant Neoplasms | 111 (4.0%) | 77 (3.5%) | 17 (4.3%) | 12 (4.6%) | 73 (4.0%) | 63 (3.4%) | 0.029 | 85 (3.7%) | 86 (3.7%) | 0.002 | 74 (3.7%) | 72 (3.6%) | 0.005 |
| Acute Kidney Injury | 49 (1.7%) | 30 (1.4%) | 3 (0.8%) | 2 (0.8%) | 24 (1.3%) | 25 (1.4%) | 0.005 | 31 (1.3%) | 33 (1.4%) | 0.007 | 28 (1.4%) | 33 (1.6%) | 0.020 |
| Chronic Kidney Disease | 80 (2.9%) | 80 (3.6%) | 9 (2.3%) | 6 (2.3%) | 59 (3.2%) | 59 (3.2%) | 0.000 | 73 (3.2%) | 70 (3.0%) | 0.008 | 69 (3.4%) | 64 (3.2%) | 0.014 |
| Asthma and COPD | 145 (5.2%) | 135 (6.1%) | 17 (4.3%) | 10 (3.8%) | 108 (5.9%) | 109 (5.9%) | 0.002 | 125 (5.4%) | 123 (5.3%) | 0.004 | 110 (5.4%) | 116 (5.7%) | 0.013 |
| Dementia | 34 (1.2%) | 23 (1.0%) | 1 (0.3%) | 2 (0.8%) | 19 (1.0%) | 20 (1.1%) | 0.005 | 23 (1.0%) | 25 (1.1%) | 0.009 | 22 (1.1%) | 21 (1.0%) | 0.005 |
| Aspirin | 824 (29.4%) | 709 (31.9%) | 89 (22.4%) | 93 (35.6%) | 569 (30.9%) | 569 (30.9%) | 0.000 | 653 (28.4%) | 684 (29.7%) | 0.030 | 643 (31.8%) | 628 (31.0%) | 0.016 |
| Antiplatelets (other than aspirin) | 164 (5.9%) | 123 (5.5%) | 18 (4.5%) | 16 (6.1%) | 99 (5.4%) | 110 (6.0%) | 0.026 | 130 (5.6%) | 127 (5.5%) | 0.006 | 115 (5.7%) | 114 (5.6%) | 0.002 |
| Warfarin | 391 (14.0%) | 397 (17.9%) | 53 (13.3%) | 41 (15.7%) | 292 (15.9%) | 294 (16.0%) | 0.003 | 350 (15.2%) | 344 (15.0%) | 0.007 | 328 (16.2%) | 322 (15.9%) | 0.008 |
| Antianemic Preparations | 519 (18.5%) | 334 (15.0%) | 49 (12.3%) | 33 (12.6%) | 276 (15.0%) | 294 (16.0%) | 0.027 | 369 (16.0%) | 365 (15.9%) | 0.005 | 307 (15.2%) | 298 (14.7%) | 0.012 |
| NSAIDs | 340 (12.1%) | 275 (12.4%) | 50 (12.6%) | 42 (16.1%) | 237 (12.9%) | 236 (12.8%) | 0.002 | 288 (12.5%) | 286 (12.4%) | 0.003 | 261 (12.9%) | 250 (12.4%) | 0.016 |
| Opioids | 862 (30.8%) | 640 (28.8%) | 113 (28.4%) | 73 (28.0%) | 532 (28.9%) | 534 (29.0%) | 0.002 | 666 (28.9%) | 670 (29.1%) | 0.004 | 596 (29.5%) | 585 (28.9%) | 0.012 |
| SSRIs | 240 (8.6%) | 181 (8.1%) | 36 (9.0%) | 17 (6.5%) | 147 (8.0%) | 157 (8.5%) | 0.020 | 194 (8.4%) | 195 (8.5%) | 0.002 | 164 (8.1%) | 161 (8.0%) | 0.005 |
| Antidepressants (other than SSRIs) | 301 (10.7%) | 235 (10.6%) | 36 (9.0%) | 26 (10.0%) | 193 (10.5%) | 199 (10.8%) | 0.011 | 238 (10.3%) | 236 (10.3%) | 0.003 | 214 (10.6%) | 207 (10.2%) | 0.011 |
| Antiepileptics | 210 (7.5%) | 150 (6.8%) | 25 (6.3%) | 19 (7.3%) | 124 (6.7%) | 127 (6.9%) | 0.006 | 154 (6.7%) | 163 (7.1%) | 0.015 | 142 (7.0%) | 138 (6.8%) | 0.008 |
| Antipsychotics | 141 (5.0%) | 92 (4.1%) | 20 (5.0%) | 12 (4.6%) | 80 (4.3%) | 82 (4.5%) | 0.005 | 109 (4.7%) | 103 (4.5%) | 0.012 | 91 (4.5%) | 87 (4.3%) | 0.010 |
| Benzodiazepines | 256 (9.1%) | 182 (8.2%) | 43 (10.8%) | 23 (8.8%) | 162 (8.8%) | 154 (8.4%) | 0.016 | 196 (8.5%) | 201 (8.7%) | 0.008 | 170 (8.4%) | 173 (8.6%) | 0.005 |
| Lipid Lowering Drugs | 1,539 (54.9%) | 1,199 (54.0%) | 191 (48.0%) | 138 (52.9%) | 1,012 (55.0%) | 998 (54.2%) | 0.015 | 1,216 (52.8%) | 1,254 (54.5%) | 0.033 | 1,089 (53.8%) | 1,092 (54.0%) | 0.003 |
| Insulin | 91 (3.2%) | 80 (3.6%) | 9 (2.3%) | 5 (1.9%) | 57 (3.1%) | 61 (3.3%) | 0.012 | 70 (3.0%) | 73 (3.2%) | 0.008 | 61 (3.0%) | 67 (3.3%) | 0.017 |
| Antihyperglycemics other than Insulins | 525 (18.7%) | 466 (21.0%) | 51 (12.8%) | 54 (20.7%) | 363 (19.7%) | 372 (20.2%) | 0.012 | 421 (18.3%) | 446 (19.4%) | 0.028 | 406 (20.1%) | 396 (19.6%) | 0.012 |
| Antihypertensives | 2,611 (93.2%) | 2,079 (93.6%) | 366 (92.0%) | 242 (92.7%) | 1,723 (93.6%) | 1,718 (93.4%) | 0.011 | 2,141 (93.0%) | 2,151 (93.5%) | 0.017 | 1,889 (93.4%) | 1,901 (94.0%) | 0.024 |
| Antiarrhythmics | 94 (3.4%) | 91 (4.1%) | 10 (2.5%) | 10 (3.8%) | 67 (3.6%) | 70 (3.8%) | 0.009 | 79 (3.4%) | 80 (3.5%) | 0.002 | 81 (4.0%) | 75 (3.7%) | 0.015 |
| Nitrates Cardiac Vasodilators | 130 (4.6%) | 99 (4.5%) | 21 (5.3%) | 9 (3.4%) | 79 (4.3%) | 81 (4.4%) | 0.005 | 105 (4.6%) | 105 (4.6%) | 0.000 | 95 (4.7%) | 100 (4.9%) | 0.012 |
| Cardiac Stimulants | 347 (12.4%) | 272 (12.2%) | 30 (7.5%) | 17 (6.5%) | 236 (12.8%) | 229 (12.4%) | 0.011 | 271 (11.8%) | 263 (11.4%) | 0.011 | 237 (11.7%) | 235 (11.6%) | 0.003 |
| Gastrointestinal Protective Agents | 1,214 (43.3%) | 893 (40.2%) | 173 (43.5%) | 106 (40.6%) | 752 (40.9%) | 761 (41.4%) | 0.010 | 952 (41.4%) | 955 (41.5%) | 0.003 | 830 (41.0%) | 802 (39.6%) | 0.028 |

| | | | | | | | | | | | | | |
|---|---------------|---------------|-------------|-------------|-------------|-------------|-------|---------------|---------------|-------|-------------|-------------|-------|
| Bisphosphonates and Other Agents Affecting Bone Structure | 228 (8.1%) | 171 (7.7%) | 32 (8.0%) | 15 (5.7%) | 135 (7.3%) | 138 (7.5%) | 0.006 | 192 (8.3%) | 188 (8.2%) | 0.006 | 166 (8.2%) | 151 (7.5%) | 0.028 |
| Systemic Corticosteroids | 442 (15.8%) | 345 (15.5%) | 53 (13.3%) | 37 (14.2%) | 272 (14.8%) | 271 (14.7%) | 0.002 | 353 (15.3%) | 358 (15.6%) | 0.006 | 308 (15.2%) | 307 (15.2%) | 0.001 |
| Antineoplastics | 140 (5.0%) | 99 (4.5%) | 21 (5.3%) | 13 (5.0%) | 81 (4.4%) | 88 (4.8%) | 0.018 | 111 (4.8%) | 113 (4.9%) | 0.004 | 93 (4.6%) | 90 (4.4%) | 0.007 |
| Systemic Antibiotics | 1,357 (48.4%) | 1,075 (48.4%) | 177 (44.5%) | 119 (45.6%) | 872 (47.4%) | 867 (47.1%) | 0.005 | 1,084 (47.1%) | 1,097 (47.7%) | 0.011 | 969 (47.9%) | 961 (47.5%) | 0.008 |
| Systemic Antivirals | 31 (1.1%) | 32 (1.4%) | 3 (0.8%) | 3 (1.1%) | 22 (1.2%) | 22 (1.2%) | 0.000 | 29 (1.3%) | 26 (1.1%) | 0.012 | 26 (1.3%) | 26 (1.3%) | 0.000 |
| Vaccines and Immunoglobulins | 137 (4.9%) | 204 (9.2%) | 11 (2.8%) | 24 (9.2%) | 119 (6.5%) | 131 (7.1%) | 0.026 | 133 (5.8%) | 134 (5.8%) | 0.002 | 157 (7.8%) | 138 (6.8%) | 0.036 |
| CHA2DS2 VASc score | | | | | | | | | | 0.013 | | | 0.045 |
| 0 | 93 (3.3%) | 79 (3.6%) | 16 (4.0%) | 13 (5.0%) | 64 (3.5%) | 64 (3.5%) | 0.047 | 83 (3.6%) | 80 (3.5%) | | 74 (3.7%) | 73 (3.6%) | |
| 1 | 518 (18.5%) | 442 (19.9%) | 79 (19.8%) | 57 (21.8%) | 347 (18.9%) | 354 (19.2%) | | 452 (19.6%) | 459 (19.9%) | | 392 (19.4%) | 379 (18.7%) | |
| 2 | 1,174 (41.9%) | 949 (42.7%) | 165 (41.5%) | 112 (42.9%) | 794 (43.2%) | 802 (43.6%) | | 962 (41.8%) | 964 (41.9%) | | 861 (42.6%) | 892 (44.1%) | |
| 3 | 868 (31.0%) | 631 (28.4%) | 119 (29.9%) | 63 (24.1%) | 542 (29.5%) | 529 (28.7%) | | 684 (29.7%) | 682 (29.6%) | | 587 (29.0%) | 572 (28.3%) | |
| 4 | 133 (4.7%) | 99 (4.5%) | 18 (4.5%) | 14 (5.4%) | 79 (4.3%) | 82 (4.5%) | | 108 (4.7%) | 104 (4.5%) | | 95 (4.7%) | 93 (4.6%) | |
| 5 | 14 (0.5%) | 20 (0.9%) | 1 (0.3%) | 2 (0.8%) | 13 (0.7%) | 9 (0.5%) | | 12 (0.5%) | 12 (0.5%) | | 13 (0.6%) | 14 (0.7%) | |
| 6 | 1 (0.0%) | 1 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.1%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | | 1 (0.0%) | 0 (0.0%) | |
| 7 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | |
| 8 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | |
| 9 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | | 0 (0.0%) | 0 (0.0%) | |

Characteristics reported as N (%) unless otherwise specified.

SD = standard deviation; IQR = interquartile range; DOAC = direct oral anticoagulants; ASD = absolute standardized difference.

Supplemental Table 3. Per-protocol analysis using a 365d baseline period for all characteristics: Hazard ratio of stroke and secondary outcomes among patients with nonvalvular atrial fibrillation newly initiating DOACs after propensity score matching

| | Patients | Events | Rate per 1,000 PY | Patients | Events | Rate per 1,000 PY | Hazard Ratio |
|---|-------------|--------|-------------------|------------------------------|--------|-------------------|-----------------------|
| Apixaban vs rivaroxaban: primary and secondary outcomes | | | | | | | |
| Outcome | Apixaban | | | Rivaroxaban | | | aHR (95% CI) |
| Stroke, ITT | 1,840 | 53 | 11.77 | 1,840 | 56 | 13.00 | 0.89 (0.61, 1.30) |
| Stroke, AT | 1,840 | 30 | 9.26 | 1,840 | 32 | 11.00 | 0.87 (0.53, 1.43) |
| All-cause mortality, ITT* | 1,846 | 276 | 59.46 | 1,846 | 264 | 61.37 | 0.96 (0.81, 1.14) |
| Myocardial infarction (MI), ITT | 1,840 | 22 | 4.84 | 1,840 | 25 | 6.00 | 0.84 (0.47, 1.48) |
| Transient ischemic attack | 1,840 | 32 | 7.08 | 1,840 | 29 | 7.00 | 1.06 (0.64, 1.76) |
| Major bleeding event, ITT | 1,840 | 117 | 26.70 | 1,840 | 189 | 48.00 | 0.57 (0.46, 0.72) |
| Composite angina/MI/stroke | 1,840 | 92 | 20.82 | 1,840 | 98 | 24.00 | 0.89 (0.67, 1.18) |
| Apixaban vs rivaroxaban: primary outcome (stroke) among subgroups, ITT | | | | | | | |
| Subgroup | Apixaban | | | Rivaroxaban | | | aHR (95% CI) |
| Age <75 years | 631 | 12 | 7.17 | 631 | 12 | 8.00 | 0.93 (0.42, 2.06) |
| Age ≥75 years | 1,195 | 37 | 13.29 | 1,195 | 39 | 15.00 | 0.89 (0.57, 1.40) |
| Concomitant aspirin use | 400 | 12 | 11.54 | 400 | 9 | 9.00 | 1.24 (0.52, 2.94) |
| No concomitant aspirin use | 1,416 | 41 | 12.09 | 1,416 | 36 | 11.00 | 1.08 (0.69, 1.69) |
| Prior warfarin use | 271 | 8 | 12.79 | 271 | 10 | 17.00 | 0.73 (0.29, 1.86) |
| No prior warfarin use | 1,528 | 43 | 11.48 | 1,528 | 37 | 11.00 | 1.09 (0.70, 1.69) |
| With diabetes | 44 | 0 | 0.00 | 44 | 2 | 20.00 | <0.001 (<0.001, >999) |
| Without diabetes | 1,771 | 55 | 12.70 | 1,771 | 50 | 12.00 | 1.02 (0.70, 1.50) |
| With heart failure | 83 | 1 | 5.72 | 83 | 2 | 11.00 | 0.49 (0.04, 5.38) |
| Without heart failure | 1,740 | 47 | 10.81 | 1,740 | 50 | 13.00 | 0.87 (0.58, 1.30) |
| CHA2DS2 VASc 0-1 | 403 | 12 | 11.05 | 403 | 7 | 7.00 | 1.54 (0.61, 3.93) |
| CHA2DS2 VASc 2-3 | 1,334 | 38 | 11.74 | 1,334 | 36 | 12.00 | 0.99 (0.62, 1.56) |
| CHA2DS2 VASc 4+ | 61 | 2 | 15.19 | 61 | 0 | 0.00 | >999 (<0.001, >999) |
| Analysis of secondary comparisons: primary outcome (stroke), ITT | | | | | | | |
| Outcome | Apixaban | | | DOACs other than apixaban | | | aHR (95% CI) |
| Stroke | 2,301 | 64 | 12.41 | 2,301 | 65 | 13.00 | 0.95 (0.67, 1.34) |
| Outcome | Rivaroxaban | | | DOACs other than rivaroxaban | | | aHR (95% CI) |
| Stroke | 2,023 | 54 | 11.47 | 2,023 | 58 | 12.00 | 0.99 (0.68, 1.43) |

PY = person-years; aHR = adjusted hazard ratio; CI = confidence interval; PS = propensity score; ITT = intent-to-treat; AT = as-treated

PS model accounts for age, gender, CHA2DS2 VASc score, year of treatment initiation, and the following diagnoses and treatments in baseline: non-major bleeding events, anemia, diabetes, hypertension, heart failure, osteoporosis/hip fracture, malignant neoplasm, acute kidney injury, chronic kidney disease, asthma/copd, dementia, aspirin, antiplatelets other than aspirin, warfarin, antiemeric preparations, NSAIDs, opioids, SSRIs, antidepressants other than SSRIs, antiepileptics, antipsychotics, benzodiazepines, lipid

In analysis of stroke, MI, TIA, major bleeding events, and AMS, patients were followed until occurrence of outcome, death, end of patient registration, or end of study period (12/2020).

* In analysis of all cause mortality, patients were followed until occurrence of outcome (death), end of study period (12/2020), or the later date of end of patient registration and any recorded death within 90 days of end of patient registration. Propensity score matched sample size for analysis of all cause mortality differs from sample size in analysis of other outcomes because of differences in censoring criteria which impact a small number of patients' eligibility for inclusion in analysis at the start of follow-up. DOACs comprised apixaban, rivaroxaban, edoxaban, dabigatran

Supplemental Table 4: Length of follow-up and censoring reasons for the primary comparison (stroke, ITT and AT analyses) and secondary comparisons (stroke, ITT analyses) after PS-matching

| Exposure group | Apixaban vs rivaroxaban (ITT) | | Apixaban vs rivaroxaban (AT) | | Apixaban vs other DOACs (ITT) | | Rivaroxaban vs other DOACs (ITT) | |
|--|-------------------------------|------------------|------------------------------|-----------------|-------------------------------|------------------|----------------------------------|------------------|
| | Apixaban | Rivaroxaban | Apixaban | Rivaroxaban | Apixaban | Other DOACs | Rivaroxaban | Other DOACs |
| Numer of patients | 1,839 | 1,839 | 1,839 | 1,839 | 2,276 | 2,276 | 1,985 | 1,985 |
| Follow-up time, days | | | | | | | | |
| mean (sd) | 891.39 (604.23) | 839.10 (580.42) | 647.66 (535.75) | 574.74 (510.77) | 829.15 (586.35) | 770.05 (553.42) | 844.22 (588.55) | 894.75 (611.26) |
| median [IQR] | 845 [340, 1,368] | 779 [322, 1,284] | 506 [197, 1,001] | 412 [170, 855] | 742 [298, 1,259] | 681 [296, 1,170] | 784 [318, 1,296] | 828 [343, 1,399] |
| Censor reason | | | | | | | | |
| Death | 40 (2.2%) | 26 (1.4%) | 24 (1.3%) | 18 (1.0%) | 44 (1.9%) | 28 (1.2%) | 29 (1.5%) | 42 (2.1%) |
| End of patient registration | 943 (51%) | 1,074 (58%) | 630 (34%) | 662 (36%) | 1,081 (47%) | 1,227 (54%) | 1,187 (60%) | 1,066 (54%) |
| End of study period (12/2020) | 800 (44%) | 682 (37%) | 448 (24%) | 367 (20%) | 1,086 (48%) | 953 (42%) | 710 (36%) | 812 (41%) |
| Outcome (stroke) | 56 (3.0%) | 57 (3.1%) | 33 (1.8%) | 32 (1.7%) | 65 (2.9%) | 68 (3.0%) | 59 (3.0%) | 65 (3.3%) |
| End of index DOAC | - | - | 615 (33%) | 562 (31%) | - | - | - | - |
| Start of DOAC from other comparator group | - | - | 43 (2.3%) | 119 (6.5%) | - | - | - | - |
| Start of another DOAC (dabigatran, edoxaban) | - | - | 46 (2.5%) | 79 (4.3%) | - | - | - | - |

DOAC = direct oral anticoagulant; ITT = intent-to-treat; AT = as-treated; PS = propensity score.

Apixaban was compared with other DOACs which included rivaroxaban, edoxaban, and dabigatran; rivaroxaban was compared with other DOACs which included apixaban, edoxaban, and dabigatran.