

SUPPLEMENTARY WEB MATERIAL

Web Figure 1(a). Relative effect of date of first prescription on non-adherence (as per Table 2)

Web Figure 1(b). Relative effect of date of first prescription on non-adherence between different OACs (as per Web Table 2(e))

Web Figure 2. Kaplan-Meier analysis of persistence over time, with patients who switch censored at the time they switch

Web Table 1. Clinical trial data for adherence and persistence with direct anticoagulants.

Web Table 2(a) Likelihood of non-adherence by oral anticoagulant with 6-month restriction on prescription period for patients included in the analysis.

Web Table 2(b) Likelihood of non-adherence by oral anticoagulant with 12-month restriction on prescription period for patients included in the analysis.

Web Table 2(c) Likelihood of non-adherence by oral anticoagulant with individual CHA₂DS₂Vasc and HASBLED risk factors and other categorical variables.

Web Table 2(d) Likelihood of non-adherence by oral anticoagulant with apixaban as reference category.

Web Table 2(e). Likelihood of non-adherence by oral anticoagulant with interactions between time (linear) and OAC.

Web Table 3. Persistence and adherence with varying definitions status at 1 year for the first OAC ever prescribed after AF.

Web Table 4. Baseline characteristics according to adherence status at one year after OAC initiation, adopting an 80% threshold for PDC

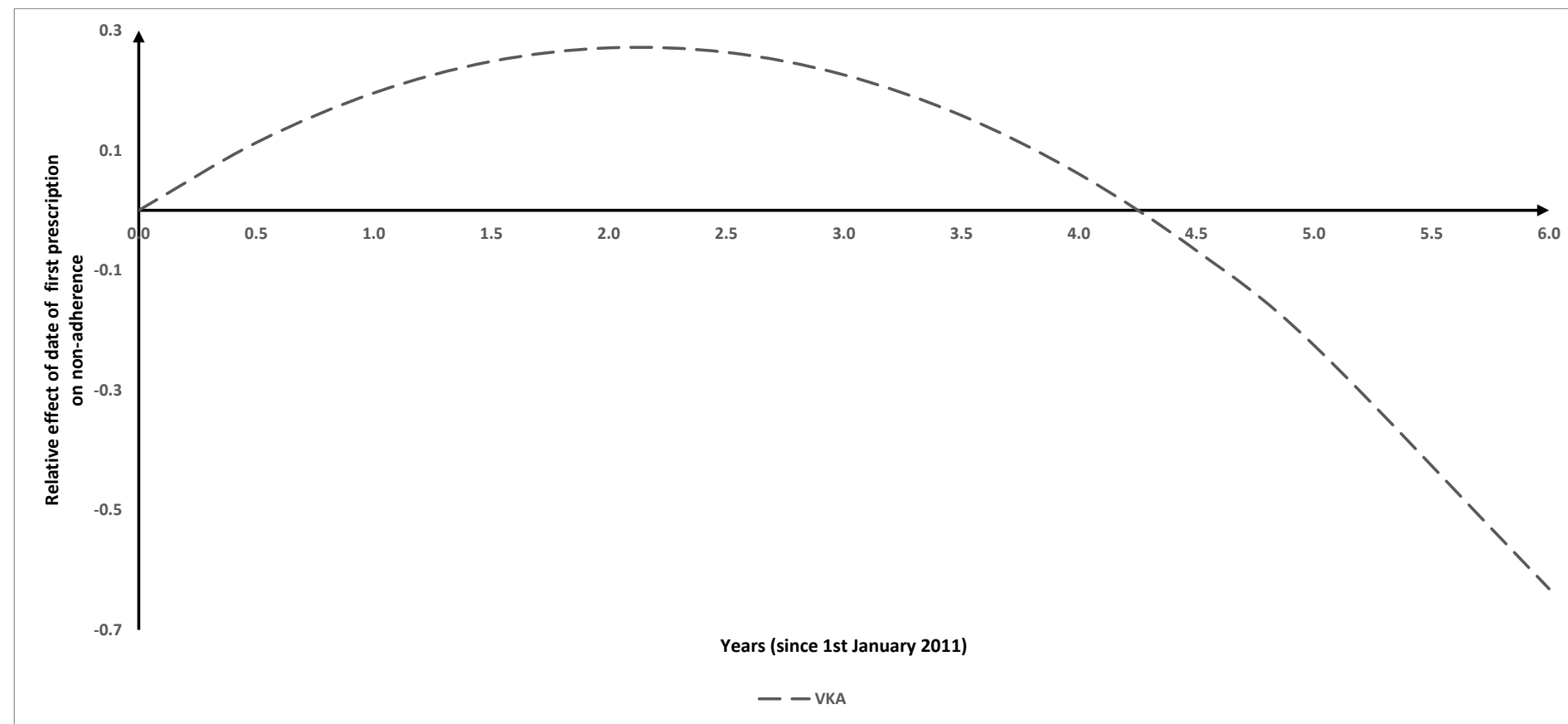
Web Table 5(a). Risk of non-persistence by oral anticoagulant with individual CHA₂DS₂Vasc and HASBLED risk factors and anaemia.

Web Table 5(b) Risk of non-persistence by oral anticoagulant with apixaban as reference category.

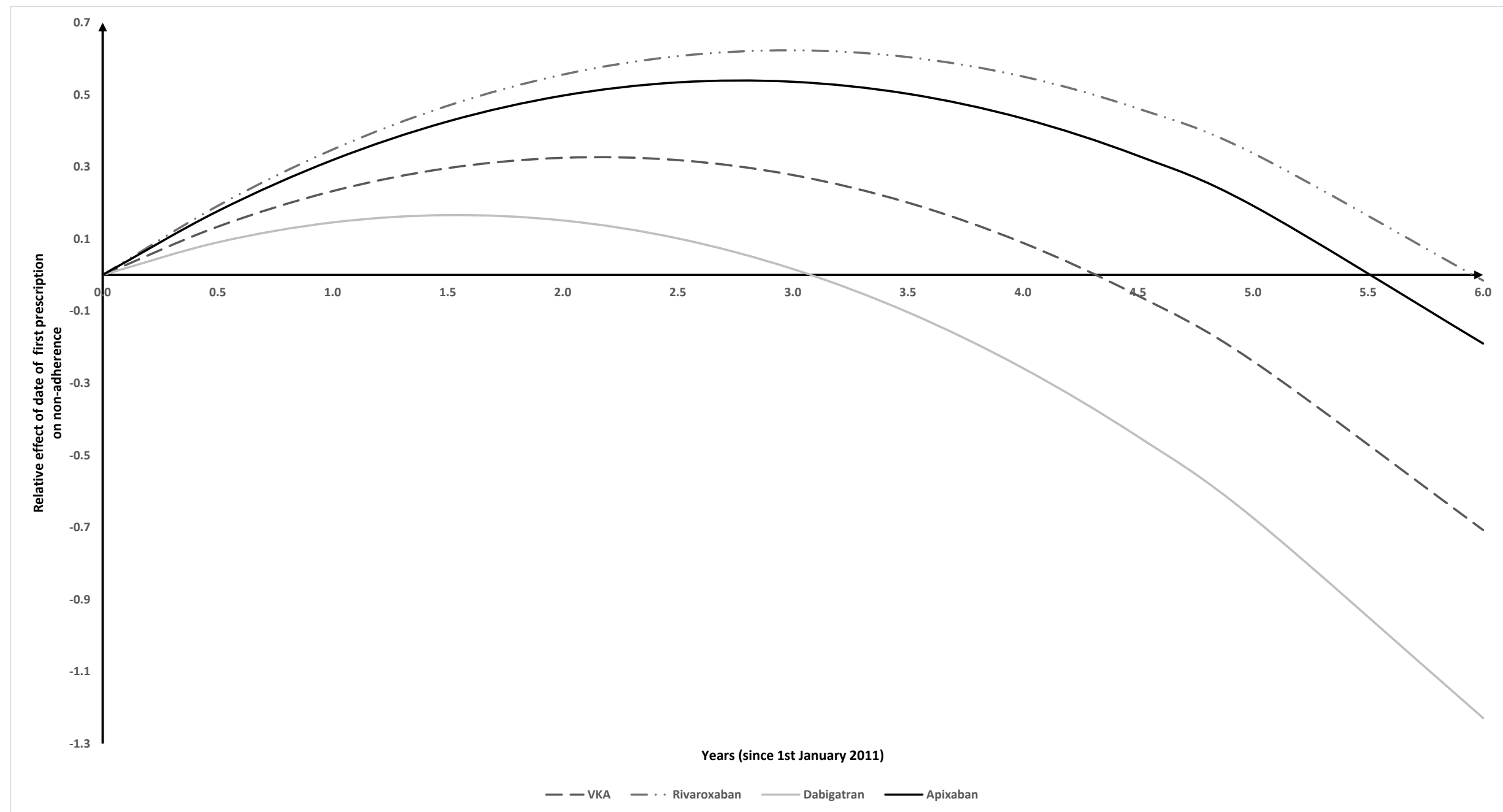
Web Table 6. Baseline characteristics according to persistence status at one year after OAC initiation, adopting a 90-day prescription gap.

Web Table 7. Switching of medication during the whole study period (2011-2016) in non-persistent and primary non-adherent patients with atrial fibrillation

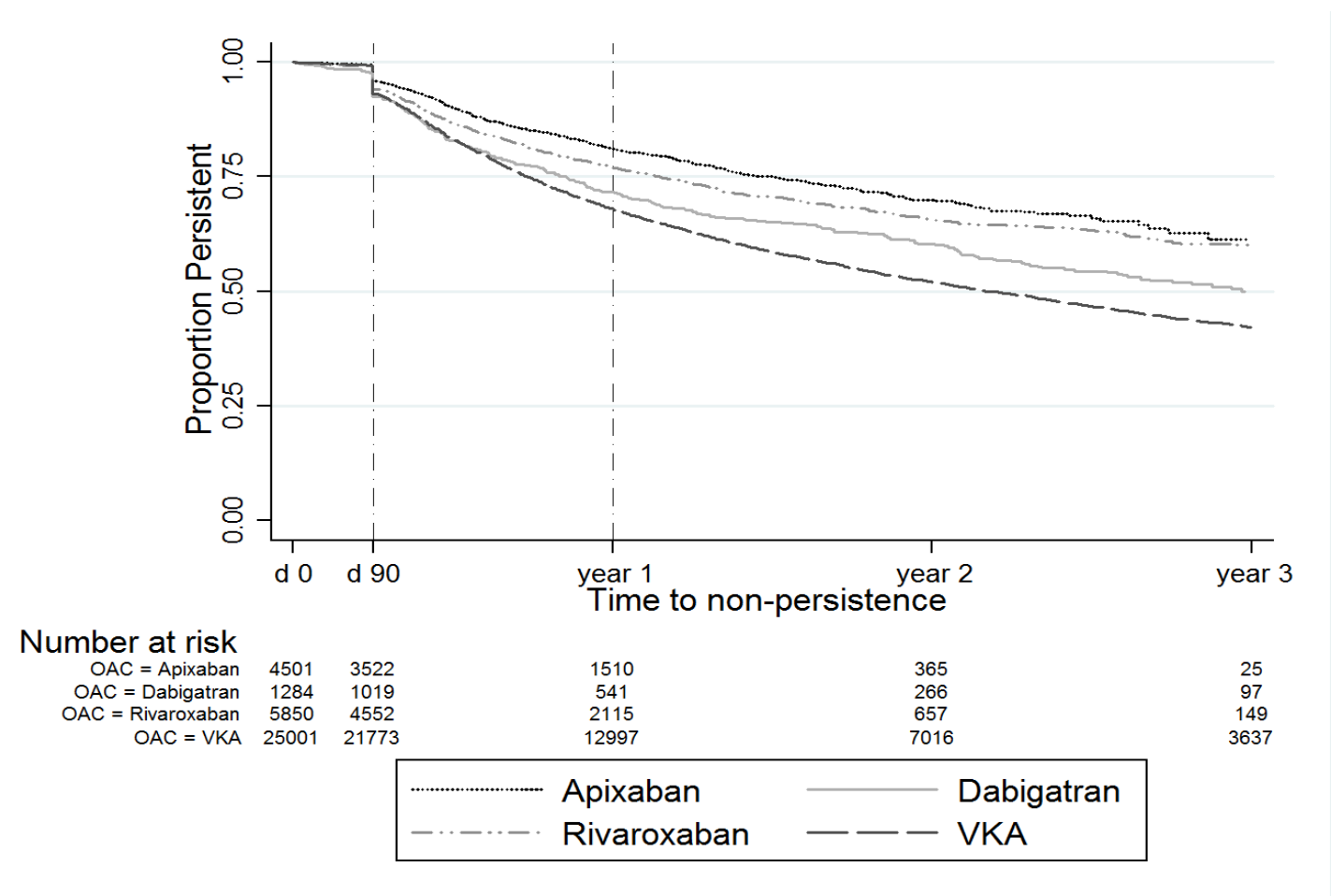
Web Table 8: Risk of non-persistence by oral anticoagulant, with patients who switch censored at the time they switch



Web Figure 1(a). Relative effect of date of first prescription on non-adherence (as per Table 2)



Web Figure 1. Relative effect of date of first prescription on non-adherence between different OACs (as per Web Table 2(e))



Web Figure 2. Kaplan-Meier analysis of persistence over time, with patients who switch censored at the time they switch

Web Table 1. Clinical trial data for adherence and persistence with direct oral anticoagulants.

| Drug | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|-------------------------------------|--------------------|-----------------|-------------------------------------|
| Clinical trial | RE-LY | ROCKET-AF | ARISTOTLE | ENGAGE AF |
| Year of publication | 2009 | 2011 | 2011 | 2013 |
| Date of NICE approval | 15/3/2012 | 23/5/2012 | 27/2/2013 | 23/9/2015 |
| Adherence | - | - | - | - |
| Persistence with DOAC (%) | 78.8 (high dose) 79.3 (low dose) | 76.3 | 74.7 | 65.6 (high dose) 67.0 (low dose) |
| Persistence with warfarin (%) | 83.4 | 77.8 | 72.5 | 65.5 |
| Time in therapeutic range for warfarin | 66% | 68% | 67% | 58% |
| Median duration of treatment (yrs) | 2 | 1.6 | 1.8 | 2.5 |
| Median duration of follow-up (yrs) | 2 | 2.1 | 1.8 | 2.8 |

Web Table 2(a) Likelihood of non-adherence by oral anticoagulant with 6-month restriction on prescription period for patients included in the analysis.

| Odds ratios (95% CI) | Multivariable | P-value |
|---|---------------------|---------|
| N | 25,058 | |
| VKA | 1.00 (-) | |
| Dabigatran | 0.52 (0.44 to 0.60) | <0.001 |
| Rivaroxaban | 0.71 (0.66 to 0.78) | |
| Apixaban | 0.70 (0.63 to 0.77) | |
| CHA₂DS₂Vasc | | |
| [0,1] | 1.00 (-) | |
| [2] | 0.97 (0.89 to 1.06) | <0.001 |
| [3,4] | 0.90 (0.83 to 0.97) | |
| [5,9] | 0.78 (0.71 to 0.87) | |
| HASBLED | | |
| [0,2] | 1.00 (-) | |
| [3,9] | 1.01 (0.94 to 1.08) | 0.85 |
| Number of drugs | 0.98 (0.97 to 1.00) | 0.008 |
| Townsend Quintile | | |
| [1] | 1.00 (-) | |
| [2] | 0.94 (0.88 to 1.01) | <0.001 |
| [3] | 0.84 (0.78 to 0.90) | |
| [4] | 0.90 (0.83 to 0.97) | |
| [5] | 0.85 (0.78 to 0.93) | |
| Date of first prescription (years after 1st January 2011) | | |
| Continuous/ Linear | 1.13 (1.06 to 1.21) | <0.001 |
| Continuous/ Quadratic | 0.97 (0.96 to 0.98) | |
| BIC | 34443.03 | |

Web Table 2(b) Likelihood of non-adherence by oral anticoagulant with 12-month restriction on prescription period for patients included in the analysis.

| Odds ratios (95% CI) | Multivariable | P-value |
|----------------------|---------------------|---------|
| N | 14,127 | |
| VKA | 1.00 (-) | |
| Dabigatran | 0.53 (0.43 to 0.66) | <0.001 |

| Odds ratios (95% CI) | Multivariable | P-value |
|---|---------------------|---------|
| N | 14,127 | |
| Rivaroxaban | 0.65 (0.57 to 0.73) | |
| Apixaban | 0.65 (0.56 to 0.75) | |
| CHA₂DS₂Vasc | | |
| [0,1] | 1.00 (-) | |
| [2] | 0.95 (0.84 to 1.07) | |
| [3,4] | 0.88 (0.79 to 0.99) | 0.002 |
| [5,9] | 0.77 (0.66 to 0.88) | |
| HASBLED | | |
| [0,2] | 1.00 (-) | |
| [3,9] | 1.06 (0.96 to 1.16) | 0.24 |
| Number of drugs | 0.99 (0.97 to 1.00) | 0.15 |
| Townsend Quintile | | |
| [1] | 1.00 (-) | |
| [2] | 0.89 (0.81 to 0.98) | |
| [3] | 0.80 (0.73 to 0.89) | <0.001 |
| [4] | 0.85 (0.76 to 0.94) | |
| [5] | 0.83 (0.73 to 0.94) | |
| Date of first prescription (years after 1st January 2011) | | |
| Continuous/ Linear | 1.14 (1.02 to 1.26) | <0.001 |
| Continuous/ Quadratic | 0.97 (0.95 to 0.99) | |
| BIC | 18942.83 | |

Web Table 2(c) Likelihood of non-adherence by oral anticoagulant with individual CHA₂DS₂Vasc and HASBLED risk factors and other categorical variables.

| Odds ratios (95% CI) | Multivariable | P-value |
|----------------------|---------------------|---------|
| N | 31,615 | |
| VKA | 1.00 (-) | |
| Dabigatran | 0.54 (0.47 to 0.61) | <0.001 |
| Rivaroxaban | 0.77 (0.71 to 0.82) | |

| Odds ratios (95% CI) | Multivariable | P-value |
|---|---------------------|---------|
| N | 31,615 | |
| Apixaban | 0.77 (0.71 to 0.84) | |
| Congestive cardiac failure | 1.03 (0.88 to 1.21) | 0.68 |
| Hypertension | 1.10 (1.05 to 1.16) | <0.001 |
| Age (years) | | |
| <65 | 1.00 (-) | |
| 65 to 74 | 1.00 (0.93 to 1.07) | |
| >=75 | 0.83 (0.77 to 0.88) | <0.001 |
| Diabetes | 0.92 (0.87 to 0.98) | 0.009 |
| Stroke/TIA | 0.94 (0.84 to 1.04) | 0.22 |
| Vascular disease | 1.11 (1.03 to 1.19) | 0.006 |
| Female sex | 0.90 (0.86 to 0.95) | <0.001 |
| Chronic kidney disease | 0.98 (0.93 to 1.04) | 0.59 |
| Liver disease | 1.02 (0.64 to 1.60) | 0.95 |
| Stroke | 1.00 (0.88 to 1.14) | 0.99 |
| Bleeding | 0.96 (0.85 to 1.08) | 0.51 |
| Drug use predisposing to bleeding | 1.01 (0.68 to 1.51) | 0.95 |
| Alcohol misuse | 1.05 (0.91 to 1.22) | 0.46 |
| Anaemia | 0.39 (0.18 to 0.87) | 0.022 |
| Number of drugs | 0.98 (0.97 to 0.99) | 0.002 |
| Townsend Quintile | | |
| [1] | 1.00 (-) | |
| [2] | 0.93 (0.87 to 0.99) | |
| [3] | 0.85 (0.80 to 0.91) | |
| [4] | 0.90 (0.84 to 0.97) | <0.001 |
| [5] | 0.85 (0.79 to 0.93) | |
| Date of first prescription (years after 1st January 2011) | | |
| Continuous/Linear | 1.30 (1.22 to 1.37) | |
| Continuous/Quadratic | 0.94 (0.93 to 0.95) | <0.001 |
| BIC | 42896.91 | |

Web Table 2(d) Likelihood of non-adherence by oral anticoagulant with apixaban as reference category.

| Odds ratios (95% CI) | Multivariable | P-value |
|--|---------------------|---------|
| N | 31,615 | |
| Apixaban | 1.00 (-) | |
| Dabigatran | 0.70 (0.61 to 0.81) | |
| Rivaroxaban | 0.99 (0.90 to 1.08) | <0.001 |
| VKA | 1.29 (1.19 to 1.41) | |
| CHA₂DS₂Vasc | | |
| [0,1] | 1.00 (-) | |
| [2] | 1.00 (0.93 to 1.08) | |
| [3,4] | 0.94 (0.88 to 1.01) | <0.001 |
| [5,9] | 0.81 (0.74 to 0.89) | |
| HASBLED | | |

| Odds ratios (95% CI) | Multivariable | P-value |
|---|---------------------|---------|
| N | 31,615 | |
| [0,2] | 1.00 (-) | |
| [3,9] | 0.98 (0.93 to 1.05) | 0.62 |
| Number of drugs | 0.99 (0.98 to 1.00) | 0.067 |
| Townsend Quintile | | |
| [1] | 1.00 (-) | |
| [2] | 0.93 (0.87 to 0.99) | <0.001 |
| [3] | 0.86 (0.80 to 0.91) | |
| [4] | 0.91 (0.85 to 0.97) | |
| [5] | 0.86 (0.80 to 0.94) | |
| Date of first prescription (years after 1st January 2011) | | |
| Continuous/ Linear | 1.29 (1.22 to 1.37) | <0.001 |
| Continuous/ Quadratic | 0.94 (0.93 to 0.95) | |
| BIC | 42880.41 | |

Web Table 2(e). Likelihood of non-adherence by oral anticoagulant with interactions between time (linear) and OAC.

| Odds ratios (95% CI) | Multivariable | P-value |
|--|---------------------|---------|
| N | 31,615 | |
| OAC (effect on first prescribing) | | |
| Apixaban | 1.00 (-) | <0.001 |
| Dabigatran | 1.36 (0.77 to 2.39) | |
| Rivaroxaban | 0.89 (0.55 to 1.45) | |
| VKA | 1.86 (1.20 to 2.90) | |
| CHA₂DS₂Vasc | | |
| [0,1] | 1.00 (-) | <0.001 |
| [2] | 1.00 (0.93 to 1.08) | |
| [3,4] | 0.94 (0.88 to 1.01) | |
| [5,9] | 0.81 (0.74 to 0.89) | |
| HASBLED | | |
| [0,2] | 1.00 (-) | 0.64 |
| [3,9] | 0.99 (0.93 to 1.05) | |
| Number of drugs | 0.99 (0.98 to 1.00) | 0.069 |
| Townsend Quintile | | |

| Odds ratios (95% CI) | Multivariable | P-value |
|---|---------------------|---------|
| N | 31,615 | |
| OAC (effect on first prescribing) | | |
| [1] | 1.00 (-) | |
| [2] | 0.93 (0.87 to 0.99) | <0.001 |
| [3] | 0.86 (0.80 to 0.91) | |
| [4] | 0.91 (0.85 to 0.97) | |
| [5] | 0.86 (0.80 to 0.94) | |
| Date of first prescription (years after 1st January 2011) | | |
| Continuous/ Linear | 1.48 (1.29 to 1.69) | <0.001 |
| Interacted with Apixaban | 1.00 (-) | |
| Interacted with Dabigatran | 0.84 (0.73 to 0.97) | 0.002 |
| Interacted with Rivaroxaban | 1.03 (0.93 to 1.14) | |
| Interacted with VKA | 0.92 (0.83 to 1.01) | |
| Continuous/ Quadratic | 0.93 (0.92 to 0.94) | <0.001 |
| BIC | 42896.51 | |

Web Table 3. Adherence and persistence with varying definitions status at 1 year for the first OAC ever prescribed after AF.

| | Overall | VKA | Dabigatran | Rivaroxaban | Apixaban |
|--|-----------------------------|-----------------------------|--------------------------|----------------------------|----------------------------|
| Adherence at 1 year [n (%; 95% CI)] | | | | | |
| Allocated to analysis | N=33,960 | N=23,552 | N=1,140 | N=5,191 | N=4,077 |
| PDC threshold | | | | | |
| 70% | 22,870 (67.3; 66.8-67.8) | 15,384 (65.3; 64.7-65.9) | 872 (76.5; 73.9-78.9) | 3,645 (70.2; 69.0-71.4) | 2,969 (72.8; 71.4-74.2) |
| 80% | 18,731 (55.2; 54.6-55.7) | 12,061 (51.2; 50.6-51.8) | 758 (66.5; 63.7-69.2) | 3,276 (63.1; 61.8-64.4) | 2,636 (64.7; 63.2-66.1) |
| 90% | 13,931 (41.0; 40.5-41.5) | 8,357 (35.5; 34.9-36.1) | 606 (53.2; 50.3-56.0) | 2,776 (53.5; 52.1-54.8) | 2,192 (53.8; 52.2-55.3) |
| Persistence at 1 year [n (%; 95% CI)] | | | | | |
| Allocated to analysis | N=36,636 | N=25,001 | N=1,284 | N=5,850 | N=4,501 |
| Prescription gap | | | | | |
| 60-day | 9,874 (38.6; 38.1-39.2) | 7,170 (35.3; 34.7-35.9) | 340 (40.8; 37.8-43.7) | 1,368 (47.0; 45.5-48.6) | 996 (51.5; 49.7-53.3) |

| | | | | | |
|----------------|-----------------------------|-----------------------------|--------------------------|----------------------------|----------------------------|
| 90-day | 16,879 (65.9; 65.4-66.5) | 12,750 (63.4; 62.8-64.0) | 521 (61.4; 58.3-64.2) | 2,098 (72.3; 70.9-73.7) | 1,510 (78.7; 77.1-80.1) |
| 120-day | 19,644 (76.8; 76.3-77.2) | 15,151 (75.7; 75.2-76.3) | 575 (68.1; 65.1-70.8) | 2,280 (79.0; 77.7-80.2) | 1,638 (85.6; 84.3-86.9) |

PDC:Proportion of days covered

Web Table 4. Baseline characteristics according to adherence status at one year after OAC initiation, adopting an 80% threshold for PDC

| Adherence threshold for PDC: >80% | Overall | | VKA | | Dabigatran | | Rivaroxaban | | Apixaban | |
|-----------------------------------|----------------------------|--------------------------------|----------------------------|--------------------------------|-------------------------|-----------------------------|---------------------------|-------------------------------|---------------------------|-------------------------------|
| | 1-year Adherent (n=18,731) | 1-year Non-adherent (n=15,229) | 1-year Adherent (n=12,061) | 1-year Non-adherent (n=11,491) | 1-year Adherent (n=758) | 1-year Non-adherent (n=382) | 1-year Adherent (n=3,276) | 1-year Non-adherent (n=1,915) | 1-year Adherent (n=2,636) | 1-year Non-adherent (n=1,441) |
| Characteristic | | | | | | | | | | |
| Age Mean(SD) | 74.9(10.5) | 73.8(10.1) | 74.5(10.2) | 74.1(9.9) | 73.6(11.2) | 72.3(10.9) | 75.7(10.9) | 73.0(10.9) | 76.1(10.4) | 72.5(10.9) |
| Female n(%) | 8,695(46.4) | 6,542(43.0) | 5,488(45.5) | 5,015(43.6) | 312(41.2) | 143(37.4) | 1,580(48.2) | 772(40.3) | 1,315(49.9) | 612(42.5) |
| Townsend Quintile (Median; IQR) | (3; 2-4) | (2; 1-4) | (3; 1-4) | (2; 1-4) | (2; 1-3) | (2; 1-3) | (3; 2-4) | (2; 1-3) | (3; 2-4) | (3; 1-4) |
| Level 1 n(%) | 4,261(22.8) | 3,915(25.7) | 2,803(23.2) | 2,951(25.7) | 184(24.3) | 114(29.8) | 667(20.4) | 509(26.6) | 607(23.0) | 341(23.7) |
| Level 2 n(%) | 4,169(22.3) | 3,510(23.1) | 2,717(22.5) | 2,662(23.2) | 185(24.4) | 107(28.0) | 711(21.7) | 439(22.9) | 556(21.1) | 302(21.0) |
| Level 3 n(%) | 3,836(20.5) | 2,967(19.5) | 2,469(20.5) | 2,220(19.3) | 175(23.1) | 64(16.8) | 672(20.5) | 415(21.7) | 520(19.7) | 268(18.6) |
| Level 4 n(%) | 3,013(16.1) | 2,444(16.1) | 1,955(16.2) | 1,882(16.4) | 112(14.8) | 53(13.9) | 545(16.6) | 266(13.9) | 401(15.2) | 243(16.9) |
| Level 5 n(%) | 1,984(10.6) | 1,516(10.0) | 1,200(10.0) | 1,166(10.2) | 62(8.2) | 27(7.1) | 373(11.4) | 140(7.3) | 349(13.2) | 183(12.7) |
| Missing n(%) | 1,468(7.8) | 877(5.8) | 917(7.6) | 610(5.3) | 40(5.3) | 17(4.5) | 308(9.4) | 146(7.6) | 203(7.7) | 104(7.2) |
| COMORBIDITIES [n(%)] | | | | | | | | | | |
| Heart failure | 1,422(7.6) | 1,076(7.1) | 921(7.6) | 868(7.6) | 48(6.3) | 19(5.0) | 244(7.5) | 100(5.2) | 209(7.9) | 89(6.2) |
| Hypertension | 11,738(62.7) | 9,596(63.0) | 7,599(63.0) | 7,320(63.7) | 448(59.1) | 215(56.3) | 2,015(61.5) | 1,196(62.5) | 1,676(63.6) | 865(60.0) |
| Diabetes mellitus | 3,514(18.8) | 2,673(17.6) | 2,253(18.7) | 2,053(17.9) | 133(17.6) | 62(16.2) | 621(19.0) | 317(16.6) | 507(19.2) | 241(16.7) |
| Stroke/TIA | 2,464(13.2) | 1,812(11.9) | 1,516(12.6) | 1,378(12.0) | 99(13.1) | 48(12.6) | 430(13.1) | 228(11.9) | 419(15.9) | 158(11.0) |
| Vascular disease | 2,379(12.7) | 2,033(13.4) | 1,532(12.7) | 1,567(13.6) | 88(11.6) | 41(10.7) | 236(12.3) | 392(12.0) | 367(13.9) | 189(13.1) |
| Alcohol misuse | 476(2.5) | 423(2.8) | 269(2.2) | 282(2.5) | 23(3.0) | 10(2.6) | 92(2.8) | 62(3.2) | 92(3.5) | 69(4.8) |
| CKD | 4,079(21.8) | 3,145(20.7) | 2,566(21.3) | 2,501(21.8) | 135(17.8) | 61(16.0) | 751(22.9) | 331(17.3) | 627(23.8) | 252(17.5) |
| Liver disease | 48(0.3) | 41(0.3) | 35(0.3) | 26(0.2) | 2(0.3) | 2(0.5) | 4(0.1) | 7(0.4) | 7(0.3) | 6(0.4) |
| Hypercholesterolaemia | 13,538(72.3) | 10,961(71.2) | 8,717(72.3) | 8,259(71.9) | 542(71.5) | 280(73.3) | 2,337(71.3) | 1,380(72.1) | 1,942(73.7) | 1,042(72.3) |
| Smoking Status | | | | | | | | | | |
| Smoker | 1,714(9.2) | 1,388(9.1) | 1,124(9.3) | 991(8.6) | 56(7.4) | 30(7.9) | 313(9.6) | 208(10.9) | 221(8.4) | 159(11.0) |

| | | | | | | | | | | |
|--|--------------|--------------|-------------|-------------|-----------|-----------|-------------|-------------|-------------|-------------|
| Ex-smoker | 7,119(38.0) | 5,836(38.3) | 4,663(38.7) | 4,514(39.3) | 291(38.4) | 143(37.4) | 1,208(36.9) | 664(34.7) | 957(36.3) | 515(35.7) |
| Never smoked | 9,485(50.6) | 7,619(50.0) | 6,021(49.9) | 5,714(49.7) | 393(51.9) | 198(51.8) | 1,685(51.4) | 980(51.2) | 1,386(52.6) | 727(50.5) |
| Not indicated | 413(2.2) | 386(2.5) | 253(2.1) | 272(2.4) | 18(2.4) | 11(2.9) | 70(2.1) | 63(3.3) | 72(2.7) | 40(2.8) |
| RISK SCORES [n(%)] | | | | | | | | | | |
| CHA ₂ DS ₂ -VASC | | | | | | | | | | |
| [0,1] | 2,893(15.4) | 2,517(16.5) | 1,866(15.6) | 1,774(15.4) | 142(18.7) | 92(24.1) | 516(15.8) | 367(19.2) | 349(13.2) | 284(19.7) |
| [2] | 3,569(19.1) | 3,136(20.6) | 2,371(19.7) | 2,304(20.1) | 158(20.8) | 92(24.1) | 572(17.5) | 406(21.2) | 468(17.8) | 334(23.2) |
| [3,4] | 9,154(48.9) | 7,450(48.9) | 5,889(48.8) | 5,745(50.0) | 353(46.6) | 154(40.3) | 1,615(49.3) | 900(47.0) | 1,297(49.2) | 651(45.2) |
| [5,9] | 3,115(16.6) | 2,126(14.0) | 1,915(15.9) | 1,668(14.5) | 105(13.9) | 44(11.5) | 573(17.5) | 242(12.6) | 522(19.8) | 172(11.9) |
| HASBLED-1 | | | | | | | | | | |
| [0,2] | 14,337(76.5) | 11,897(78.1) | 9,334(77.4) | 8,873(77.2) | 614(81.0) | 317(83.0) | 2,463(75.2) | 1,538(80.3) | 1,926(73.1) | 1,169(81.1) |
| [3,9] | 4,394(23.5) | 3,332(21.9) | 2,727(22.6) | 2,618(22.8) | 144(19.0) | 65(17.0) | 813(24.8) | 377(19.7) | 710(26.9) | 272(18.9) |
| DRUGS [n(%)] | | | | | | | | | | |
| Aspirin | 10,599(56.6) | 8,450(55.5) | 6,860(56.9) | 6,485(56.4) | 428(56.5) | 179(46.9) | 1,792(54.7) | 986(51.5) | 1,519(57.6) | 800(55.5) |
| Statin | 8,900(47.5) | 7,175(47.1) | 5,729(47.5) | 5,455(47.5) | 349(46.0) | 151(39.5) | 1,493(45.6) | 888(46.4) | 1,329(50.4) | 681(47.3) |
| BP-lowering drugs | 14,882(79.5) | 12,145(79.8) | 9,610(79.7) | 9,234(80.4) | 572(75.5) | 280(73.3) | 2,556(78.0) | 1,486(77.6) | 2,144(81.3) | 1,145(79.5) |
| Number of Drugs Mean(SD) | 5.6(2.2) | 5.5(2.2) | 5.5(2.2) | 5.5(2.2) | 5.5(2.2) | 5.0(2.2) | 5.6(2.2) | 5.3(2.2) | 5.8(2.2) | 5.5(2.2) |

Web Table 5(a) Risk of non-persistence by oral anticoagulant with individual CHA₂DS₂Vasc and HASBLED risk factors and other factors.

| Hazard ratios (95% CI) | Multivariable |
|--|---------------------|
| N | 34,109 |
| OAC (effect on first prescribing) | |
| VKA | 1.00 (-) |
| Dabigatran | 1.24 (1.09 to 1.42) |
| Rivaroxaban | 0.84 (0.77 to 0.93) |
| Apixaban | 0.52 (0.46 to 0.59) |
| Time-dependent effect of OAC (per year of prescriptions) | |
| VKA | 1.00 (-) |
| Dabigatran | 0.75 (0.65 to 0.86) |
| Rivaroxaban | 0.69 (0.62 to 0.77) |
| Apixaban | 0.91 (0.79 to 1.06) |
| Congestive cardiac failure | 1.17 (1.05 to 1.31) |
| Hypertension | 0.87 (0.83 to 0.91) |
| Time-dependent effect of Hypertension (per year of prescriptions) | 1.05 (1.01 to 1.09) |
| Age (years) (effect on first prescribing) | |
| <65 | 1.00 (-) |
| 65 to 74 | 0.68 (0.64 to 0.73) |
| ≥75 | 0.68 (0.63 to 0.72) |
| Time-dependent effect of Age (per year of prescriptions) | |
| <65 | 1.00 (-) |
| 65 to 74 | 1.07 (1.01 to 1.13) |
| ≥75 | 1.13 (1.08 to 1.19) |
| Diabetes | 0.99 (0.94 to 1.03) |
| Stroke/TIA | 0.92 (0.86 to 1.00) |
| Vascular disease | 1.09 (1.03 to 1.14) |
| Female sex | 1.01 (0.97 to 1.04) |
| Chronic kidney disease | 1.07 (1.03 to 1.11) |
| Liver disease | 1.29 (0.95 to 1.76) |
| Stroke | 1.05 (0.96 to 1.16) |
| Prior bleeding | 1.13 (1.04 to 1.23) |
| Drug use predisposing to bleeding | 1.23 (0.94 to 1.63) |
| Alcohol misuse | 1.17 (1.07 to 1.30) |
| Anaemia | 1.15 (0.73 to 1.83) |
| Number of drugs | 1.00 (0.99 to 1.01) |
| Townsend Quintile | |
| [1] | 1.00 (-) |
| [2] | 0.99 (0.94 to 1.03) |
| [3] | 0.94 (0.90 to 0.99) |
| [4] | 0.95 (0.91 to 1.00) |
| [5] | 0.95 (0.89 to 1.00) |
| Date of first prescription^a (years after 1st January 2011) | 1.04 (1.02 to 1.05) |

^a Time difference (in years) between the date of the first ever OAC prescription for each patient and the start date of the study (1st January 2011).

^b Time-dependent covariates are interacted with survival analysis time (e.g. time on a specific OAC), i.e. (end date of persistence or exit from/end of study - date of first ever OAC prescription)/365.25.

Web Table 5(b) Risk of non-persistence by oral anticoagulant with the same model specification as in Table 3 but with apixaban as reference category.

| Hazard ratios (95% CI) | Multivariable |
|---|---------------------|
| N | 34,109 |
| OAC (effect on first prescribing) | |
| Apixaban | 1.00 (-) |
| Dabigatran | 2.36 (1.97 to 2.82) |
| Rivaroxaban | 1.61 (1.39 to 1.86) |
| VKA | 1.90 (1.68 to 2.16) |
| Time-dependent effect of OAC (per year of prescriptions) | |
| Apixaban | 1.00 (-) |
| Dabigatran | 0.82 (0.68 to 1.00) |
| Rivaroxaban | 0.76 (0.64 to 0.91) |
| VKA | 1.10 (0.95 to 1.28) |
| CHA₂DS₂Vasc (effect on first prescribing) | |
| [0,1] | 1.00 (-) |
| [2] | 0.71 (0.66 to 0.76) |
| [3,4] | 0.66 (0.62 to 0.71) |
| [5,9] | 0.69 (0.63 to 0.76) |
| Time-dependent effect of CHA₂DS₂Vasc (per year of prescriptions) | |
| [0,1] | 1.00 (-) |
| [2] | 1.05 (0.99 to 1.12) |
| [3,4] | 1.12 (1.07 to 1.18) |
| [5,9] | 1.13 (1.06 to 1.20) |
| HASBLED | |
| [0,2] | 1.00 (-) |
| [3,9] | 1.04 (0.99 to 1.08) |
| Number of drugs | 1.00 (0.99 to 1.01) |
| Townsend Quintile | |
| [1] | 1.00 (-) |
| [2] | 0.99 (0.95 to 1.03) |
| [3] | 0.95 (0.91 to 1.00) |
| [4] | 0.97 (0.93 to 1.02) |
| [5] | 0.97 (0.92 to 1.03) |
| Date of first prescription^a (years after 1st January 2011) | 1.03 (1.02 to 1.05) |

^a Time difference (in years) between the date of the first ever OAC prescription for each patient and the start date of the study (1st January 2011).

^b Time-dependent covariates are interacted with survival analysis time (e.g. time on a specific OAC), i.e. (end date of persistence or exit from/end of study - date of first ever OAC prescription)/365.25.

| n(%) | Overall | | | VKA | | | Dabigatran | | | Rivaroxaban | | | Apixaban | | |
|--|----------------------|-------------------------|---------------------------------|----------------------|-------------------------|--------------------------------|--------------------|------------------------|-------------------------------|---------------------|------------------------|--------------------------------|---------------------|------------------------|---------------------------------|
| | Persistent (n=16862) | Non-persistent (n=8401) | Censored ^a (n=11373) | Persistent (n=12736) | Non-persistent (n=6958) | Censored ^a (n=5307) | Persistent (n=521) | Non-persistent (n=322) | Censored ^a (n=441) | Persistent (n=2098) | Non-persistent (n=738) | Censored ^a (n=3014) | Persistent (n=1507) | Non-persistent (n=383) | Censored ^a (n=2,611) |
| Characteristic | | | | | | | | | | | | | | | |
| Age Mean(SD) | 74.5(9.6) | 72.6(11.4) | 75.7(10.7) | 74.5(9.4) | 72.7(11.2) | 76.1(10.2) | 73.8(10.0) | 71.4(12.9) | 74.3(11.0) | 74.6(10.1) | 72.6(12.1) | 75.5(11.1) | 74.6(10.4) | 71.7(13.1) | 75.4(11.0) |
| Female | 7602(45.1) | 3634(43.3) | 5249(46.2) | 5738(45.1) | 3006(43.2) | 2439(46.0) | 204(39.2) | 131(40.7) | 182(41.3) | 949(45.2) | 331(44.9) | 1387(46.0) | 711(47.2) | 166(43.3) | 1,241(47.5) |
| Townsend Quintile (Median; IQR) | (3; 1-4) | (2; 1-4) | (2; 1-4) | (2; 1-4) | (2; 1-4) | (2; 2-4) | (2; 1-4) | (2; 1-3) | (2; 1-3) | (3; 2-4) | (2; 1-3) | (2; 1-4) | (3; 2-4) | (3; 1-4) | (3; 1-4) |
| Level 1 | 4039(24.0) | 2116(25.2) | 2702(23.8) | 3113(24.4) | 1767(25.4) | 1242(23.4) | 131(25.1) | 85(26.4) | 129(29.3) | 456(21.7) | 168(22.8) | 722(24.0) | 339(22.5) | 96(25.1) | 609(23.3) |
| Level 2 | 3752(22.3) | 1907(22.7) | 2605(22.9) | 2850(22.4) | 1577(22.7) | 1277(24.1) | 123(23.6) | 83(25.8) | 114(25.9) | 460(21.9) | 177(24.0) | 662(22.0) | 319(21.2) | 70(18.3) | 552(21.1) |
| Level 3 | 3445(20.4) | 1660(19.8) | 2222(19.5) | 2582(20.3) | 1345(19.3) | 1037(19.5) | 112(21.5) | 74(23.0) | 84(19.1) | 432(20.6) | 165(22.4) | 631(20.9) | 319(21.2) | 76(19.8) | 470(18.0) |
| Level 4 | 2718(16.1) | 1310(15.6) | 1833(16.1) | 2062(16.2) | 1119(16.1) | 881(16.6) | 86(16.5) | 39(12.1) | 60(13.6) | 343(16.4) | 90(12.2) | 464(15.4) | 227(15.1) | 62(16.2) | 428(16.4) |
| Level 5 | 1725(10.2) | 846(10.1) | 1229(10.8) | 1263(9.9) | 707(10.2) | 570(10.7) | 39(7.5) | 28(8.7) | 31(7.0) | 226(10.8) | 63(8.5) | 285(9.5) | 197(13.1) | 48(12.5) | 343(13.1) |
| Missing | 1183(7.0) | 562(6.7) | 782(6.9) | 866(6.8) | 443(6.4) | 300(5.7) | 30(5.8) | 13(4.0) | 23(5.2) | 181(8.6) | 75(10.2) | 250(8.3) | 106(7.0) | 31(8.1) | 209(8.0) |
| COMORBIDITIES | | | | | | | | | | | | | | | |
| Heart failure | 1154(6.8) | 582(6.9) | 963(8.5) | 894(7.0) | 496(7.1) | 518(9.8) | 33(6.3) | 20(6.2) | 26(5.9) | 129(6.2) | 47(6.4) | 210(7.0) | 98(6.5) | 19(5.0) | 209(8.0) |
| Hypertension | 10800(64.1) | 4963(59.1) | 7182(63.2) | 8194(64.3) | 4169(59.9) | 3457(65.1) | 317(60.8) | 175(54.4) | 258(58.5) | 1339(63.8) | 403(54.6) | 1866(61.9) | 950(63.0) | 216(56.4) | 1,601(61.3) |
| Diabetes mellitus | 3066(18.2) | 1443(17.2) | 2178(19.2) | 2294(18.0) | 1210(17.4) | 1089(20.5) | 96(18.4) | 52(16.2) | 61(13.8) | 384(18.3) | 133(18.0) | 539(17.9) | 292(19.4) | 48(12.5) | 489(18.7) |
| Stroke/TIA | 2186(13.0) | 940(11.2) | 1495(13.2) | 1611(12.7) | 783(11.3) | 702(13.2) | 66(12.7) | 37(11.5) | 57(12.9) | 295(14.1) | 82(11.1) | 358(11.9) | 214(14.2) | 38(9.9) | 378(14.5) |
| Vascular disease | 2160(12.8) | 1088(13.0) | 1543(13.6) | 1638(12.9) | 924(13.3) | 753(14.2) | 69(13.2) | 31(9.6) | 49(11.1) | 256(12.2) | 87(11.8) | 373(12.4) | 197(13.1) | 46(12.0) | 368(14.1) |
| Alcohol misuse | 400(2.4) | 242(2.9) | 335(3.0) | 284(2.2) | 182(2.6) | 123(2.3) | 15(2.9) | 14(4.4) | 7(1.6) | 61(2.9) | 26(3.5) | 88(2.9) | 40(2.7) | 20(5.2) | 117(4.5) |
| CKD | 3549(21.1) | 1697(20.2) | 2592(22.8) | 2709(21.3) | 1417(20.4) | 1298(24.5) | 94(18.0) | 58(18.0) | 68(15.4) | 426(20.3) | 150(20.3) | 651(21.6) | 320(21.2) | 72(18.8) | 575(22.0) |
| Liver disease | 33(0.2) | 27(0.3) | 40(0.4) | 24(0.2) | 21(0.3) | 22(0.4) | 1(0.2) | 2(0.6) | 1(0.2) | 3(0.1) | 3(0.4) | 9(0.3) | 5(0.3) | 1(0.3) | 8(0.3) |
| Hyper-cholesterolaemia | 12391(73.5) | 5868(69.9) | 8056(70.8) | 9323(73.2) | 4886(70.2) | 3766(71.0) | 385(73.9) | 227(70.5) | 302(68.5) | 1546(73.7) | 504(68.3) | 2117(70.2) | 1137(75.5) | 251(65.5) | 1871(71.7) |
| Smoking Status | | | | | | | | | | | | | | | |
| Smoker | 1516(9.0) | 798(9.5) | 1060(9.3) | 1117(8.8) | 654(9.4) | 501(9.4) | 44(8.5) | 24(7.5) | 35(7.9) | 216(10.3) | 81(11.0) | 288(9.6) | 139(9.2) | 39(10.2) | 236(9.0) |
| Ex-smoker | 6361(37.7) | 3179(37.8) | 4383(38.5) | 4882(38.3) | 2674(38.4) | 2153(40.6) | 191(36.7) | 123(38.2) | 169(38.3) | 741(35.3) | 256(34.7) | 1127(37.4) | 547(36.3) | 126(32.9) | 934(35.8) |
| Never smoked | 8621(51.1) | 4209(50.1) | 5643(49.6) | 6464(50.8) | 3461(49.7) | 2542(47.9) | 277(53.2) | 165(51.2) | 224(50.8) | 1096(52.2) | 377(51.1) | 1516(50.3) | 784(52.0) | 206(53.8) | 1361(52.1) |
| Not indicated | 364(2.2) | 215(2.6) | 287(2.5) | 273(2.1) | 169(2.4) | 111(2.1) | 9(1.7) | 10(3.1) | 13(3.0) | 45(2.1) | 24(3.3) | 83(2.8) | 37(2.5) | 12(3.1) | 80(3.1) |
| RISK SCORES | | | | | | | | | | | | | | | |
| CHA ₂ DS ₂ -VASc | | | | | | | | | | | | | | | |
| [0-1] | 2414(14.3) | 1797(21.4) | 1644(14.5) | 1767(13.9) | 1451(20.9) | 669(12.6) | 88(16.9) | 92(28.6) | 83(18.8) | 336(16.0) | 162(22.0) | 486(16.1) | 223(14.8) | 92(24.0) | 406(15.6) |
| [2] | 3442(20.4) | 1642(19.6) | 2104(18.5) | 2630(20.7) | 1349(19.4) | 958(18.1) | 115(22.1) | 61(18.9) | 102(23.1) | 413(19.7) | 145(19.7) | 547(18.2) | 284(18.9) | 87(22.7) | 497(19.0) |
| [3-4] | 8481(50.3) | 3767(44.8) | 5637(49.6) | 6461(50.7) | 3150(45.3) | 2708(51.0) | 256(49.1) | 127(39.4) | 188(42.6) | 1002(47.8) | 325(44.0) | 1520(50.4) | 762(50.6) | 165(43.1) | 1221(46.8) |
| [5-9] | 2525(15.0) | 1195(14.2) | 1988(17.5) | 1878(14.8) | 1008(14.5) | 972(18.3) | 62(11.9) | 42(13.0) | 68(15.4) | 347(16.5) | 106(14.3) | 461(15.3) | 238(15.8) | 39(10.2) | 487(18.7) |
| HASBLED-1 | | | | | | | | | | | | | | | |
| [0-2] | 13084(77.6) | 6638(79.0) | 8545(75.1) | 9872(77.5) | 5490(78.9) | 3931(74.1) | 427(82.0) | 255(79.2) | 364(82.5) | 1618(77.1) | 581(78.7) | 2306(76.5) | 1167(77.4) | 312(81.5) | 1,944(74.5) |
| [3-8] | 3778(22.4) | 1763(21.0) | 2828(24.9) | 2864(22.5) | 1468(21.1) | 1376(25.9) | 94(18.0) | 67(20.8) | 77(17.5) | 480(22.9) | 157(21.3) | 708(23.5) | 340(22.6) | 71(18.5) | 667(25.6) |
| DRUGS | | | | | | | | | | | | | | | |
| Aspirin | 9647(57.2) | 4545(54.1) | 6309(55.5) | 7305(57.4) | 3822(54.9) | 3044(57.4) | 291(55.9) | 162(50.3) | 229(51.9) | 1167(55.6) | 372(50.4) | 1574(52.2) | 884(58.7) | 189(49.4) | 1462(56.0) |
| Statin | 8245(48.9) | 3639(43.3) | 5292(46.5) | 6187(48.6) | 3100(44.6) | 2513(47.4) | 240(46.1) | 123(38.2) | 187(42.4) | 1026(48.9) | 275(37.3) | 1346(44.7) | 792(52.6) | 141(36.8) | 1246(47.7) |
| BP-lowering drugs | 13519(80.2) | 6457(76.9) | 9147(80.4) | 10235(80.4) | 5400(77.6) | 4367(82.3) | 404(77.5) | 225(69.9) | 331(75.1) | 1649(78.6) | 553(74.9) | 2356(78.2) | 1231(81.7) | 279(72.9) | 2093(80.2) |
| Number of Drugs Mean(SD) | 5.5(2.2) | 5.4(2.3) | 5.6(2.2) | 5.5(2.2) | 5.4(2.3) | 5.6(2.2) | 5.5(2.2) | 5.2(2.3) | 5.3(2.2) | 5.5(2.3) | 5.3(2.3) | 5.4(2.2) | 5.8(2.2) | 5.3(2.3) | 5.7(2.2) |

Web Table 6. Baseline characteristics according to persistence status at one year after OAC initiation, adopting a 90-day prescription gap.

Web Table 7: Non-persistent and primary non-adherent patients with atrial fibrillation who became non-persistent by switching during the whole study period (2011-2016)

| | Overall | VKA | Dabigatran | Rivaroxaban | Apixaban |
|------------------------------|----------------|--------------|-------------------|--------------------|-----------------|
| Non-persistent | | | | | |
| Total (n) | 16,302 | 13,411 | 553 | 1,510 | 828 |
| Switched; n (%) | 3,302 (20.3) | 2,518 (18.8) | 223 (40.3) | 408 (27.0) | 153 (18.5) |
| Primary non-adherence | | | | | |
| Total (n) | 1,453 | 920 | 97 | 295 | 141 |
| Switched; n (%) | 657 (45.2) | 376 (40.9) | 67 (69.1) | 151 (51.2) | 63 (44.7) |

Web Table 8: Risk of non-persistence by oral anticoagulant, with patients who switch censored at the time they switch.

| Hazard ratios (95% CI) | Multivariable |
|---|---------------------|
| N | 34,109 |
| OAC (effect on first prescribing) | |
| VKA | 1.00 (-) |
| Dabigatran | 0.93 (0.79 to 1.10) |
| Rivaroxaban | 0.81 (0.73 to 0.91) |
| Apixaban | 0.57 (0.50 to 0.66) |
| Time-dependent effect of OAC (per year of prescriptions) | |
| VKA | 1.00 (-) |
| Dabigatran | 0.90 (0.78 to 1.04) |
| Rivaroxaban | 0.80 (0.71 to 0.90) |
| Apixaban | 1.01 (0.86 to 1.18) |
| CHA₂DS₂Vasc (effect on first prescribing) | |
| [0,1] | 1.00 (-) |
| [2] | 0.69 (0.63 to 0.75) |
| [3,4] | 0.62 (0.57 to 0.66) |
| [5,9] | 0.63 (0.57 to 0.70) |
| Time-dependent effect of CHA₂DS₂Vasc (per year of prescriptions) | |
| [0,1] | 1.00 (-) |
| [2] | 1.08 (1.01 to 1.15) |
| [3,4] | 1.19 (1.12 to 1.25) |
| [5,9] | 1.19 (1.11 to 1.28) |
| HASBLED-1 | |
| [0,2] | 1.00 (-) |
| [3,9] | 1.05 (1.00 to 1.10) |
| Number of drugs | 1.00 (0.99 to 1.00) |
| Townsend Quintile | |
| [1] | 1.00 (-) |
| [2] | 0.99 (0.95 to 1.04) |
| [3] | 0.95 (0.90 to 1.00) |
| [4] | 0.98 (0.93 to 1.04) |
| [5] | 0.97 (0.91 to 1.04) |
| Date of first prescription^a (years after 1st January 2011) | 0.97 (0.95 to 0.98) |

^a Time difference (in years) between the date of the first ever OAC prescription for each patient and the start date of the study (1st January 2011).

^b Time-dependent covariates are interacted with survival analysis time (e.g. time on a specific OAC), i.e. (end date of persistence or exit from/end of study - date of first ever OAC prescription)/365.25.