**Supplemental Material**

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Supplemental Figure 1. Study flow diagram for creation of the main cohort of patients with atrial fibrillation and a new prescription for warfarin, apixaban, rivaroxaban, or dabigatran.

**Supplemental Table 1:** Databases used to derive study variables.\*

|  |  |  |
| --- | --- | --- |
| Database | Abbreviation | Data held |
| Canadian Institutes of  Health Information  Discharge Abstract  Database | DAD | Demographic and clinical information  about all hospital admissions and  discharges, including transfers and deaths |
| ICES Physician Database (IPDB) | IPDB | Characteristics of physicians and surgeons licensed to practice in  Ontario |
| National Ambulatory Care  Reporting System | NACRS | Emergency department visits, day surgery  and mandated outpatient clinics |
| Ontario Drug Benefit  database | ODB | Prescription drug information for persons > 65 years |
| Ontario Health Insurance  Plan database | OHIP | Physicians claims for services provided |
| Ontario Laboratory Information System Database | OLIS | Provincial database of laboratory test results |
| Registered Persons  Database | RPDB | Individual health card number, date of  birth, sex, postal code and death date  (where applicable) |
| Canadian Institutes of Health Information Same Day Surgery | SDS | Patient-level demographic, diagnostic, procedural and treatment  information on all day surgeries |

\*Diagnoses in these datasets are recorded using the Canadian Coding Standards for the International Statistical Classification of Diseases and Related Health Problems (hospital) and physician billing claim codes (OHIP).

**Supplemental Table 2:** Codes used to identify baseline conditions.

|  |  |  |
| --- | --- | --- |
| **Comorbid Conditions** | | |
| Hypertension | | |
| CIHI | ICD-10 | "I10", "I11", "I12", "I13", "I15" |
| OHIP | Diagnostic code | "401", "402", 403" |
| Prior Stroke/TIA | | |
| CIHI | ICD-10 | "I62", "I630", "I631", "I632", "I633", "I634", "I635", "I638", "I639", "I64", "H341", "I600", "I601", "I602", "I603", "I604", "I605", "I606", "I607", "I609", "I61", "G450", "G451", "G452", "G453", "G458", "G459", "H340" |
| Heart Failure | | |
| CIHI | ICD-10 | "I500", "I501", "I509", "I255", "J81" |
| CCI | "1HP53","1HP55","1HZ53GRFR","1HZ53LAFR","1HZ53SYFR" |
| OHIP | Diagnostic code | "428" |
| Fee code | "R701", "R702", "Z429" |
| Myocardial Infarction | | |
| CIHI | ICD-10 | "I21", "I22" |
| Diabetes | | |
| CIHI | ICD-10 | "E10", "E11", "E13", "E14" |
| OHIP | Diagnostic code | "250" |
| Fee code | "K045", "K046", "K029", "K030", "Q040" |
| Peptic Ulcer Disease | | |
| CIHI | ICD-10 | "K25", "K26", "K27", "K28" |
| Alcoholism | | |
| CIHI | ICD-10 | "E244", "E512", "E52", "F10", "G312", "G621", "G721", "I426", "K292", "K70", "K860", "T51", "X45", "X65", "Y15", "Y573", "Z502", "Z714", "Z721" |
| Moderate/Severe Liver Disease | | |
| CIHI | ICD-10 | "B16", "B17", "B18", "B19", "I85", "R17", "R18", "R160", "R162", "B942", "Z225", "E831", "E830", "K70", "K713", "K714", "K715", "K717", "K721", "K729", "K73", "K74", "K753", "K754", "K758", "K759", "K76", "K77" |
| OHIP | Diagnostic code | "571", "573", "070" |
| Fee code | "Z551", "Z554" |
| Venous Thromboembolism | | |
| CIHI | ICD-10 | "I801", "I802", "I803", "I822", "I828", "I829", "O871", "O878", "O879", "I26", "O882" |
| CCI | "3KX30DA","3KX30DB","3KX30DC","3KX30DD", "3KR10VA”,"3KR10VC","3KR10VN","3KR12VA", "3KX10VA","3KX10VC","3KX10VN","3KX10VX",  "3KX12VA","3IM10VC","3IM10VX","3IM10VY","3IM12VA", "3GT70CA", "3GT70CC", "3GT70CE","3GT70KC","3GT70KD", "3GT70KE", "3JY10VA", "3JY10VC", "3JY10VN", "3JY10VX", "3JY12VA","3JY20WC","3JY20WE", "3GT20WC", "3GT20WE" |
| OHIP | Diagnostic code | "451", "671", "415", "677" |
| Fee code | "J198", "J498", "J193", "J493", "J202", "J502", "J659", "J660", "J859", "J860", "X406", "X407", "X125" |
| Prior Major Hemorrhage | | |
| CIHI | ICD-10 | "I600", "I601", "I602", "I603", "I604", "I605", "I606", "I607", "I609", "I61", "I62", "I850", "I9820", "I983", "K2210", "K2211", "K2212", "K2214", "K2216", "K226", "K228", "K250", "K252", "K254", "K256", "K260", "K262", "K264", "K266", "K270", "K272", "K274", "K276", "K280", "K282", "K284", "K286", "K290", "K3180", "K6380", "K920", "K921", "K5520", "K625", "K922", "M2509", "M2501", "M2502", "M2503", "M2504", "M2505", "M2506", "M2507", "M2508", "M2500", "M1229", "M1221", "M1222", "M1223", "M1224", "M1225", "M1226", "M1227", "M1228", "M1220", "R58" |
| Major Cancer | | |
| CIHI | ICD-10 | "971", "980", "982", "984", "985", "986", "987", "988", "989", "990", "991", "993", "C15", "C18", "C19", "C20", "C22", "C25", "C34", "C50", "C56", "C61", "C82", "C83", "C85", "C91", "C92", "C93", "C94", "C95", "D00", "D05", "D010", "D011", "D012", "D022", "D075" |
| OHIP | Diagnostic code | "203", "204", "205", "206", "207", "208", "150", "154", "155", "157", "162", "174", "175", "183", "185" |
| Acute Kidney Injury | | |
| CIHI | ICD-10 | "N17" |
| Peripheral Vascular Disease | | |
| CIHI | ICD-10 | "I700", "I702", "I708", "I709", "I731", "I738", "I739", "K551" |
| CCI | "1KA76", "1KA50", "1KE76", "1KG50", "1KG57", "1KG76MI", "1KG87", "1IA87LA", "1IB87LA", "1IC87LA", "1ID87", "1KA87LA", "1KE57" |
| OHIP | Fee code | "R787", "R780", "R797", "R804", "R809", "R875", "R815", "R936", "R783", "R784","R785", "E626", "R814", "R786", "R937", "R860", "R861", "R855", "R856", "R933", "R934", "R791", "E672", "R794", "R813", "R867", "E649" |
| **Baseline Kidney Function** | | |
| Estimated Glomerular Filtration Rate | | |
| OLIS | Observation code | "14682-9" |
| Albumin Creatinine Ratio | | |
| OLIS | Observation code | "14959-1", "30000-4", "32294-1" |

**Supplemental Table 3:** Variables Included in the Propensity Score Model.

|  |  |
| --- | --- |
| **Category** | **Variable** |
| *Demographics* | Age, sex, neighbourhood income quintile, long-term residence, rural locale |
| *Healthcare Utilization* | Emergency department visits, family physician visits, hospitalization, cardiologist visits, nephrologist visits |
| *Comorbidities* | ATRIA bleeding score, CHADS2VaSc score, Charlson Index, hypertension,  prior Stroke/TIA, Heart failure, myocardial infarction, diabetes, peptic ulcer disease, alcoholism, moderate/Severe liver disease, venous thromboembolism, prior major hemorrhage, peripheral vascular disease, major cancer, Prior acute kidney injury |
| *Laboratory Data* | Baseline eGFR (ml/min), Albuminuria |
| *Medications* | Antiplatelet agents (non-ASA), anti-inflammatories (i.e. NSAIDs), antibiotics, antifungals, anticonvulsants, corticosteroids, gastroprotective medications, other anticoagulants, ACEi, ARBs, beta-blockers, calcium channel blockers, non-potassium sparing diuretics, potassium sparing diuretics, oral hypoglycemic agents and insulin, protease inhibitors, P-glycoprotein Inhibitors, P-glycoprotein & Cytochrome 3A4 inducers, P-glycoprotein & Cytochrome 3A4 inhibitors, SSRIs, statins |

**Supplemental Table 4:** Kidney Disease: Improving Global Outcomes (KDIGO) AKI Staging criteria thresholds.

|  |  |
| --- | --- |
|  | **Definition** |
| Stage 1 | 1.5-<2.0 times baseline OR ≥26.5 µmol/L increase AND does not meet definition for stage 2 or 3. |
| Stage 2 | 2.0-<3.0 times baseline AND does not meet definition for stage 3. |
| Stage 3 | ≥3.0x baseline OR increase to ≥353.6 µmol/L with a minimum rise of 26.5 µmol/L OR acute dialysis. |

**Supplemental Table 5:** Baseline characteristics included in propensity scores, but not shown in Table 1, after inverse probability of treatment weighting.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Warfarin N=2,269** | **Dabigatran N=2,277** | **Std Diffa (%)** | **Warfarin N=5,363** | **Rivaroxaban N=5,263** | **Std Diffa (%)** | **Warfarin N=8,383** | **Apixaban N=8,217** | **Std Diffa (%)** |
|  |  |  |  |  |  |  |  |  |  |
| **Demographic** |  |  |  |  |  |  |  |  |  |
| Long-term care status, n (%) | 81 (4) | 75 (3) | 2 | 349 (7) | 289 (6) | 4 | 618 (7) | 514 (6) | 4 |
| SES - n (%) |  |  |  |  |  |  |  |  |  |
| 1 (lowest quintile) | 456 (20) | 450 (20) | 1 | 1188 (22) | 1134 (22) | 2 | 1802 (22) | 1735 (21) | 1 |
| 2 (second lowest) | 452 (20) | 468 (21) | 2 | 991 (19) | 992 (19) | 1 | 1809 (2) | 1772 (22) | 0 |
| 3 (middle) | 437 (19) | 429 (19) | 1 | 1111 (21) | 1051 (20) | 1 | 1598 (19) | 1536 (19) | 1 |
| 4 (second highest) | 453 (20) | 455 (20) | 0 | 979 (18) | 955 (18) | 1 | 1569 (19) | 1511 (18) | 1 |
| 5 (highest) | 471 (21) | 473 (21) | 0 | 1094 (20) | 1125 (21) | 2 | 1606 (19) | 1649 (20) | 2 |
| Rural locale b, n (%) | 276 (12) | 268 (12) | 1 | 599 (11) | 593 (11) | 0 | 727 (9) | 681 (8) | 1 |
|  |  |  |  |  |  |  |  |  |  |
| **Healthcare Utilization c** |  |  |  |  |  |  |  |  |  |
| Mean No. of hospitalizations (SD) | 0.5 (0.6) | 0.5 (0.9) | 4 | 0.7 (1.1) | 0.7 (1.0) | 5 | 0.9 (1.5) | 0.8 (1.1) | 5 |
| Mean No. of ED visits (SD) | 1.5 (1.3) | 1.4 (1.9) | 5 | 1.9 (2.3) | 1.8 (2.3) | 4 | 2.1 (2.9) | 2.0 (2.2) | 3 |
| Mean No. of FP/GP visits (SD) | 11.3 (8.0) | 11.3 (13.0) | 0 | 12.9 (15.0) | 13 (15.6) | 0 | 14.2 (19.5) | 14.3 (15.9) | 1 |
| Mean No. Cardiologist visit (SD) | 3.5 (2.8) | 3.4 (4.2) | 4 | 3.9 (4.7) | 3.8 (4.6) | 4 | 4.7 (6.6) | 4.6 (5.1) | 2 |
| Mean No. Nephrologist visit (SD) | 0.2 (0.5) | 0.2 (0.8) | 0 | 0.2 (1.1) | 0.2 (1.5) | 0 | 0.3 (1.6) | 0.3 (1.3) | 1 |
|  |  |  |  |  |  |  |  |  |  |
| **Comorbidities d, n (%)** |  |  |  |  |  |  |  |  |  |
| Peripheral vascular disease | 44 (2) | 44 (2) | 0 | 97 (2) | 101 (2) | 1 | 209 (3) | 188 (2) | 1 |
|  |  |  |  |  |  |  |  |  |  |
| **Concomitant Drug Use e, n (%)** |  |  |  |  |  |  |  |  |  |
| ACEi | 685 (30) | 675 (30) | 1 | 1559 (29) | 1522 (29) | 0 | 2534 (30) | 2468 (30) | 0 |
| ARBs | 473 (21) | 484 (21) | 1 | 1091 (20) | 1103 (21) | 2 | 1864 (22) | 1864 (23) | 1 |
| Beta-blockers | 1079 (48) | 1082 (48) | 0 | 2336 (44) | 2337 (44) | 2 | 4022 (48) | 3974 (48) | 1 |
| Calcium channel blockers | 713 (31) | 712 (31) | 0 | 1766 (33) | 1704 (32) | 1 | 2962 (35) | 2895 (35) | 0 |
| Non-potassium sparing diuretics | 676 (30) | 663 (29) | 2 | 1547 (29) | 1502 (29) | 1 | 2779 (33) | 2701 (33) | 1 |
| Oral hypoglycemic agents and insulin | 390 (17) | 403 (18) | 1 | 924 (17) | 876 (17) | 2 | 1652 (20) | 1554 (19) | 2 |
| P-glycoprotein Inhibitors | 615 (27) | 622 (27) | 0 | NR | NR | NR | NR | NR | NR |
| P-glycoprotein & Cytochrome 3A4 Inducer | NR | NR | NR | NR | NR | NR | 12 (0) | 12 (0) | 0 |
| P-glycoprotein & Cytochrome 3A4 Inhibitor | NR | NR | NR | NR | NR | NR | 2290 (27) | 2270 (28) | 1 |
| SSRI | 186 (8) | 195 (9) | 1 | 580 (11) | 525 (10) | 3 | 942 (11) | 880 (11) | 2 |
| Statins | 1085 (48) | 1083 (48) | 0 | 2520 (47) | 2465 (47) | 0 | 4200 (50) | 4083 (50) | 1 |

Abbreviations: ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin II receptor blocker; eGFR = estimated glomerular filtration rate; ED = emergency department; FP= family physician; GP= general practitioner; SES= socioeconomic status; SSRI= selective serotonin reuptake inhibitor; SD= standard deviation; Std Diff = standardized difference; TIA = transient ischemic attack.

a Standardized differences were used to compare warfarin and DOAC users. Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of difference between groups with respect to a pooled standard deviation. A standardized difference > 10% is considered a meaningful difference between groups. In this study, standardized differences were calculated using warfarin as the referent.

b Rural defined as residing in a location with a population of ≤ 10 000 individuals.

c Health care utilization in the 365 days prior to index date were considered.

d Comorbidities in the 5 years prior to the index date were considered.

e Concurrent medication use in the 120 days prior to index date were considered.

**Supplemental Table 6:** Baseline characteristics of the cohort (unweighted).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Warfarin**  **N=4, 926** | **Dabigatran**  **N=2, 277** | **Std Diff (%)a** | **Warfarin**  **N=4, 926** | **Rivaroxaban**  **N=5, 623** | **Std Diff (%)a** | **Warfarin**  **N=4, 926** | **Apixaban**  **N=8, 217** | **Std Diff (%)a** |
| **Demographic** |  |  |  |  |  |  |  |  |  |
| Age, Mean (SD) | 80 (8) | 78 (7) | 29 | 80 (8) | 77.8 (8) | 31 | 80.1 (8) | 79.9 (8) | 2 |
| Women, n (%) | 2436 (50) | 1003 (44) | 11 | 2436 (50) | 2652 (50) | 2 | 2436 (50) | 4408 (54) | 8 |
| Long-term care status, n (%) | 281 (6) | 75 (3) | 12 | 281 (6) | 289 (6) | 1 | 281 (6) | 514 (6) | 3 |
| SES - n (%) |  |  |  |  |  |  |  |  |  |
| 1 (lowest quintile) | 1085 (22) | 450 (20) | 5 | 1085 (22) | 1134 (22) | 1 | 1085 (22) | 1735 (21) | 2 |
| 2 (second lowest) | 979 (20) | 468 (21) | 2 | 979 (20) | 992 (19) | 3 | 979 (20) | 1772 (22) | 4 |
| 3 (middle) | 947 (19) | 429 (19) | 1 | 947 (19) | 1051 (20) | 2 | 947 (19) | 1536 (19) | 1 |
| 4 (second highest) | 917 (19) | 455 (20) | 4 | 917 (19) | 955 (18) | 1 | 917 (19) | 1511 (18) | 1 |
| 5 (highest) | 984 (20) | 473 (21) | 2 | 984 (20) | 1125 (21) | 3 | 984 (20) | 1649 (20) | 0 |
| Rural locale b, n (%) | 569 (12) | 268 (12) | 1 | 569 (12) | 593 (11) | 1 | 569 (12) | 681 (8) | 11 |
|  |  |  |  |  |  |  |  |  |  |
| **Healthcare Utilization c** |  |  |  |  |  |  |  |  |  |
| Mean No. of hospitalizations (SD) | 0.8 (1.1) | 0.5 (0.9) | 26 | 0.8 (1.1) | 0.7 (1.00) | 8 | 0.8 (1.1) | 0.8 (1.1) | 5 |
| Mean No. of ED visits (SD) | 1.9 (2.3) | 1.4 (1.9) | 22 | 1.9 (2.3) | 1.1 (2.3) | 3 | 1.9 (2.3) | 2.0 (2.2) | 7 |
| Mean No. of FP/GP visits (SD) | 17.4 (17.2) | 11.3 (13.0) | 40 | 17.4 (17.2) | 13.0 (15.6) | 27 | 17.4 (17.2) | 14.3 (15.9) | 19 |
| Mean No. Cardiologist visit (SD) | 4.8 (6.3) | 3.4 (4.2) | 27 | 4.8 (6.3) | 3.8 (4.6) | 20 | 4.8 (6.3) | 4.6 (5.1) | 3 |
| Mean No. Nephrologist visit (SD) | 0.6 (2.1) | 0.2 (0.8) | 30 | 0.6 (2.1) | 0.2 (1.5) | 23 | 0.6 (2.1) | 0.3 (1.3) | 19 |
|  |  |  |  |  |  |  |  |  |  |
| **Comorbidities d n (%)** |  |  |  |  |  |  |  |  |  |
| ATRIA bleeding score, Median (IQR) | 3.7 (2.2) | 2.8 (1.8) | 47 | 3.7 (2.2) | 2.8 (1.9) | 44 | 3.7 (2.2) | 3.0 (1.9) | 33 |
| CHADS2VaSc, Median (IQR) | 4.1 (1.3) | 3.7 (1.3) | 29 | 4.1 (1.3) | 3.7 (1.4) | 30 | 4.1 (1.3) | 4.0 (1.4) | 4 |
| Charlson Index, Mean (SD) | 1.4 (1.8) | 0.9 (1.5) | 31 | 1.4 (1.8) | 1.0 (1.5) | 25 | 1.4 (1.8) | 1.2 (1.7) | 10 |
| Hypertension | 3766 (77) | 1728 (76) | 1 | 3766 (77) | 3867 (74) | 7 | 3766 (77) | 6285 (77) | 0 |
| Prior Stroke/TIA | 382 (8) | 139 (6) | 7 | 382 (8) | 342 (7) | 5 | 382 (8) | 912 (11) | 11 |
| Heart failure | 2174 (44) | 695 (31) | 28 | 2174 (44) | 1452 (28) | 35 | 2174 (44) | 2873 (35) | 19 |
| Myocardial infarction | 360 (7) | 99 (4) | 13 | 360 (7) | 293 (6) | 7 | 360 (7) | 526 (6) | 4 |
| Diabetes | 1708 (35) | 751 (33) | 4 | 1708 (35) | 1606 (31) | 9 | 1708 (35) | 2641 (32) | 6 |
| Peptic ulcer disease | 14 (3) | 25 (1) | 13 | 14 (3) | 105 (2) | 6 | 14 (3) | 174 (2) | 5 |
| Alcoholism | 63 (1) | 44 (2) | 5 | 63 (1) | 85 (2) | 3 | 63 (1) | 150 (2) | 4 |
| Moderate/Severe liver disease | 224 (5) | 84 (4) | 4 | 224 (5) | 190 (4) | 5 | 224 (5) | 376 (5) | 0 |
| Venous thromboembolism | 298 (6) | 57 (3) | 17 | 298 (6) | 281 (5) | 3 | 298 (6) | 249 (3) | 15 |
| Peripheral vascular disease | 157 (3) | 44 (2) | 8 | 157 (3) | 101 (2) | 8 | 157 (3) | 188 (2) | 6 |
| Prior major hemorrhage | 429 (10) | 141 (6) | 10 | 429 (10) | 344 (7) | 8 | 429 (10) | 606 (7) | 5 |
| Major Cancer | 849 (17) | 344 (15) | 6 | 849 (17) | 835 (16) | 3 | 849 (17) | 1360 (17) | 2 |
| Prior Acute Kidney Injury | 620 (13) | 97 (4) | 30 | 620 (13) | 318 (6) | 23 | 620 (13) | 737 (9) | 12 |
|  |  |  |  |  |  |  |  |  |  |
| **Laboratory Data e** |  |  |  |  |  |  |  |  |  |
| Baseline eGFR (ml/min), Mean (SD) | 59 (21) | 69 (16) | 54 | 58.6 (21) | 70 (16) | 58 | 59 (21) | 65 (18) | 34 |
| *eGFR category, n (%)* |  |  |  |  |  |  |  |  |  |
| <30 ml/min/1.73m2 | 519 (11) | 15 (1) | 44 | 519 (11) | 47 (1) | 42 | 519 (11) | 185 (2) | 34 |
| 30-<60 ml/min/1.73m2 | 2004 (41) | 727 (32) | 18 | 2004 (41) | 1439 (27) | 29 | 2004 (41) | 3025 (37) | 8 |
| ≥60 ml/min/1.73m2 | 2403 (49) | 1535 (67) | 38 | 2403 (49) | 3777 (72) | 48 | 2403 (49) | 5007 (61) | 24 |
| *Albuminuria, n (%)* |  |  |  |  |  |  |  |  |  |
| Undetectable/Normal(<30 mg/g) | 728 (15) | 443 (20) |  | 728 (15) | 275 (5) |  | 836 (16) | 1222 (15) |  |
| Mild (30-300 mg/g) | 513 (10) | 179 (8) | 9 | 513 (10) | 359 (7) | 13 | 513 (10) | 635 (8) | 9 |
| Heavy (>300 mg/g) | 167 (3) | 34 (2) | 12 | 167 (3) | 90 (2) | 11 | 167 (3) | 187 (2) | 7 |
| Not measured | 3518 (71) | 1621 (71) | 0 | 3518 (71) | 3878 (76) | 10 | 3518 (71) | 6173 (75) | 8 |
|  |  |  |  |  |  |  |  |  |  |
| **Concomitant Drug Use f, n (%)** |  |  |  |  |  |  |  |  |  |
| ACE inhibitors | 1656 (34) | 675 (30) | 9 | 1656 (34) | 1522 (29) | 10 | 1656 (34) | 2468 (30) | 8 |
| ARBs | 1073 (22) | 484 (21) | 1 | 1073 (22) | 1103 (21) | 2 | 1073 (22) | 1864 (23) | 2 |
| Antiplatelet agents (non-ASA) | 406 (8) | 147 (6) | 7 | 406 (8) | 447 (9) | 1 | 406 (8) | 970 (12) | 12 |
| Anti-inflammatories (i.e. NSAIDs) | 310 (6) | 206 (9) | 10 | 310 (6) | 543 (10) | 15 | 310 (6) | 721 (9) | 9 |
| Antibiotics | 1521 (31) | 617 (27) | 8 | 1521 (31) | 1520 (29) | 4 | 1521 (31) | 2526 (31) | 0 |
| Antifungals | 59 (1) | 21 (1) | 3 | 59 (1) | 59 (1) | 1 | 59 (1) | 87 (1) | 1 |
| Anticonvulsants | 359 (7) | 132 (6) | 6 | 359 (7) | 418 (8) | 2 | 359 (7) | 633 (8) | 2 |
| Beta-blockers | 2649 (54) | 1082 (48) | 13 | 2649 (54) | 2337 (44) | 19 | 2649 (54) | 3974 (48) | 11 |
| Calcium channel blockers | 1757 (36) | 712 (31) | 9 | 1757 (36) | 1704 (32) | 7 | 1757 (36) | 2895 (35) | 1 |
| Corticosteroids | 1327 (27) | 552 (24) | 6 | 1327 (27) | 1319 (25) | 4 | 1327 (27) | 2235 (27) | 1 |
| Gastroprotective medications | 1968 (40) | 712 (31) | 18 | 1968 (40) | 1782 (34) | 13 | 1968 (40) | 3227 (40) | 1 |
| Non-potassium sparing diuretics | 2130 (43) | 663 (29) | 30 | 2130 (43) | 1502 (29) | 31 | 2130 (43) | 2701 (33) | 21 |
| Oral hypoglycemic agents and | 942 (19) | 403 (18) | 4 | 942 (19) | 876 (17) | 7 | 942 (19) | 1554 (19) | 1 |
| insulin |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| P-glycoprotein Inhibitors | 1653 (34) | 622 (27) | 14 | 1653 (34) | NR | NR | 1653 (34) | NR | NR |
| P-glycoprotein & Cytochrome 3A4  Inducer | 10 (0) | NR | NR | 10 (0) | NR | NR | 10 (0) | NR | NR |
| P-glycoprotein & Cytochrome 3A4  Inhibitor | 1653 (34) | NR | NR | 1653 (34) | NR | NR | 1653 (34) | NR | NR |
| SSRI | 478 (10) | 195 | 4 | 478 (10) | 525 (10) | 1 | 478 (10) | 880 (11) | 3 |
| Statins | 2720 (55) | 1083 | 15 | 2720 (55) | 2465 (47) | 17 | 2720 (55) | 4083(50) | 11 |
|  |  |  |  |  |  |  |  |  |  |

Abbreviations: ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin II receptor blocker; ATRIA= anticoagulation and risk factors in atrial fibrillation; eGFR = estimated glomerular filtration rate; ED = emergency department; FP= family physician; GP= general practitioner; SES= socioeconomic status; SSRI= selective serotonin reuptake inhibitor; SD= standard deviation; Std Diff = standardized difference; TIA = transient ischemic attack.

a Standardized differences were used to compare warfarin and DOAC users. Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of difference between groups with respect to a pooled standard deviation. A standardized difference > 10% is considered a meaningful difference between groups. In this study, standardized differences were calculated using warfarin as the referent.

b Rural defined as residing in a location with a population of ≤ 10 000 individuals.

c Health care utilization in the 365 days prior to index date were considered.

d Comorbidities in the 5 years prior to the index date were considered.

e Concurrent medication use in the 120 days prior to index date were considered.

f Laboratory measurements in the 365 days prior to index date were considered.

**Supplemental Table 7:** Reasons for end of follow-up by oral anticoagulant.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Drug** | | | |  |
| **Outcome** | **Apixaban** | **Dabigatran** | **Rivaroxaban** | **Warfarin** | **Total** |
| Death, N(%) | 790 (9.6%) | 109 (4.8%) | 389 (7.4%) | 458 (9.3%) | -- |
| End of data availability, N( %) | 3557 (43.3%) | 682 (30.0%) | 1971 (37.5%) | 546 (11.1%) | -- |
| Discontinuation, N(%) | 3387 (41.2%) | 1039 (45.6%) | 2344 (44.5%) | 3017 (61.3%) | -- |
| Switched to different anticoagulant, N(%) | 483 (5.9%) | 447 (19.6%) | 559 (10.6%) | 905 (18.4%) | -- |
| Median follow-up, in days (IQR) | 432 (97-725) | 330 (90-743) | 375 (60-730) | 100 (35-404) | 308 (61-682) |

**Supplemental Table 8:** Association between oral anticoagulant and all-cause mortality stratified by eGFR.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **eGFR Strata**  (ml/min per 1.73m2) | **Exposure** | **No.** | **No. (%) with all-cause mortality outcome** | **Incidence rate per 100 person years** | **Weighted Hazard Ratio (95% CI)** |
|  |  |  |  |  |  |  | |
| Apixaban  vs. Warfarin | ≥60 | Warfarin | 5128 | 336 (6.6) | 8.2 | 1.00 (ref.) | |
| Apixaban | 5007 | 414 (8.3) | 6.8 | 0.88 (0.69-1.12) | |
|  |  |  |  |  |  | |
| 30-<60 | Warfarin | 3065 | 324 (10.6) | 14.0 | 1.00 (ref.) | |
| Apixaban | 3025 | 289 (9.6) | 8.6 | 0.64 (0.52-0.88) | |
|  |  |  |  |  |  | |
| <30 | Warfarin | 189 | 44 (23.9) | 32.4 | 1.00 (ref.) | |
| Apixaban | 185 | 26 (14.1) | 17.2 | 0.52 (0.33-0.83) | |
|  |  |  |  |  |  |  | |
|  |  |  |  |  |  |  | |
| Rivaroxaban vs. Warfarin | ≥60 | Warfarin | 3898 | 213 (5.5) | 6.7 | 1.00 (ref.) | |
| Rivaroxaban | 3777 | 242 (6.4) | 5.5 | 0.87 (0.68-1.11) | |
|  |  |  |  |  |  | |
| 30-<60 | Warfarin | 1418 | 124 (8.7) | 11.2 | 1.00 (ref.) | |
| Rivaroxaban | 1439 | 109 (7.6) | 6.9 | 0.63 (0.49-0.82) | |
|  |  |  |  |  |  | |
| <30 | Warfarin | 47 | 9 (19.1) | 27.1 | 1.00 (ref.) | |
| Rivaroxaban | 47 | 9 (19.1) | 28.4 | 1.0 (0.46-2.2) | |
|  |  |  |  |  |  |  | |
|  |  |  |  |  |  |  | |
| Dabigatran vs. Warfarin | ≥60 | Warfarin | 1543 | 76 (4.9) | 6.1 | 1.00 (ref.) | |
| Dabigatran | 1535 | 59 (3.8) | 2.9 | 0.49 (0.35-0.70) | |
|  |  |  |  |  |  | |
| 30-<60 | Warfarin | 712 | 52 (7.3) | 9.8 | 1.00 (ref.) | |
| Dabigatran | 727 | 43(5.9) | 5.1 | 0.56 (0.38-0.8) | |
|  |  |  |  |  |  | |
| <30 | Warfarin | NR | NR | NR | NR | |
| Dabigatran | NR | NR | NR | NR | |

**Abbreviations:** *eGFR* estimated glomerular filtration rate; *ml/min per 1.73m2:* milliliters per minute;

*NR:* not reported due to small cell size (<6 patients)

\*All values are for the weighted cohort.

**Supplemental Table 9:** Association between oral anticoagulants and Kidney Disease: Improving Global Outcomes (KDIGO) AKI Stage thresholds.\*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **AKI Stage** | **Exposure** | **No.** | **Person-years** | **No. (%) with Acute Kidney Injury** | **Incidence rate per 100 person years** | **Weighted Hazard Ratio (95% CI)** |
|  |  |  |  |  |  |  |  | |
| Apixaban  vs. Warfarin | Stage 1 | Warfarin | 8383 | 6394 | 716 (8.5) | 11.6 | 1.00 (ref.) | |
|  | Apixaban | 8217 | 10016 | 840 (10.2) | 9.1 | 0.82 (0.71-0.95) | |
|  |  |  |  |  |  |  | |
| Stage 2 | Warfarin | 8383 | 6394 | 103 (1.2) | 1.7 | 1.00 (ref.) | |
|  | Apixaban | 8217 | 10016 | 119 (1.4) | 1.3 | 0.82 (0.53-1.27) | |
|  |  |  |  |  |  |  | |
| Stage 3 | Warfarin | 8383 | 6394 | 55 (0.7) | 0.9 | 1.00 (ref.) | |
|  | Apixaban | 8217 | 10016 | 58 (0.7) | 0.6 | 0.69 (0.38-1.28) | |
|  |  |  |  |  |  |  |  | |
|  |  |  |  |  |  |  |  | |
| Rivaroxaban  vs. Warfarin | Stage 1 | Warfarin | 5363 | 4229 | 369 (6.9) | 9.0 | 1.00 (ref.) | |
|  | Rivaroxaban | 5263 | 6256 | 437 (8.3) | 7.9 | 0.87 (0.73-1.01) | |
|  |  |  |  |  |  |  | |
| Stage 2 | Warfarin | 5363 | 4229 | 54 (1.0) | 1.3 | 1.00 (ref.) | |
|  | Rivaroxaban | 5263 | 6256 | 57 (1.1) | 1.0 | 0.78 (0.47-1.29) | |
|  |  |  |  |  |  |  | |
| Stage 3 | Warfarin | 5363 | 4229 | 30 (0.6) | 0.7 | 1.00 (ref.) | |
|  | Rivaroxaban | 5263 | 6256 | 31 (0.6) | 0.5 | 0.73 (0.38-1.43) | |
|  |  |  |  |  |  |  | |
|  |  |  |  |  |  |  |  | |
| Dabigatran  vs. Warfarin | Stage 1 | Warfarin | 2269 | 1772 | 138 (6.1) | 9.1 | 1.00 (ref.) | |
|  | Dabigatran | 2277 | 2967 | 146 (6.4) | 5.2 | 0.67 (0.54-0.82) | |
|  |  |  |  |  |  |  | |
| Stage 2 | Warfarin | 2269 | 1772 | 24 (1.1) | 1.4 | 1.00 (ref.) | |
|  | Dabigatran | 2277 | 2967 | 18 (0.8) | 0.6 | 0.51 (0.27-0.96) | |
|  |  |  |  |  |  |  | |
| Stage 3 | Warfarin | 2269 | 1772 | 12 (0.5) | 0.7 | 1.00 (ref.) | |
|  | Dabigatran | 2277 | 2967 | 14 (0.7) | 0.51 | 0.78 (0.34-1.78) | |
|  |  |  |  |  |  |  |  | |

\*All values are for the weighted cohort.

**Supplemental Table 10:** Association between oral anticoagulants and a hospital encounter with acute kidney injury, adjusted for study year.\*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Unweighted** | | | | **Weighted** | | | | |
| **Exposure** | **No.** | **No. (%) with AKI** | **Incidence rate**  **(per 100py)** | | **No.** | **No. (%) with AKI** | **Incidence rate**  **(per 100py)** | **Hazard Ratio**  **(95% CI)** |
| Warfarin | 4926 | 551 (11.2) | | 15.6 | 8383 | 874 (10.4) | 14.2 | 1.00 (ref.) |
| Apixaban | 8217 | 1017 (12.4) | | 11.1 | 8217 | 1017 (12.4) | 11.1 | 0.74 (0.64-0.85) |
| Warfarin | 4926 | 551 (11.2) | | 15.6 | 5363 | 453 (8.4) | 11.1 | 1.00 (ref.) |
| Rivaroxaban | 5263 | 525 (10.0) | | 9.1 | 5263 | 525 (10.0) | 9.1 | 0.82 (0.70-0.96) |
| Warfarin | 4926 | 551 (11.2) | | 15.6 | 2269 | 174 (7.7) | 10.2 | 1.00 (ref.) |
| Dabigatran | 2277 | 178 (7.8) | | 6.4 | 2277 | 178 (7.8) | 6.4 | 0.65 (0.53-0.79) |

\*All values are for the weighted cohort.

**Supplemental Table 11:** Association between oral anticoagulants and a hospital encounter with acute kidney injury (intention to treat analysis).\*

|  |
| --- |
|  |
| **Exposure** | **No.** | **No. (%) with AKI** | **Incidence rate**  **(per 100py)** | **Hazard Ratio**  **(95% CI)** |
| Warfarin | 8383 | 2200 (26.2) | 12.3 | 1.00 (ref.) |
| Apixaban | 8217 | 1550 (18.9) | 11.7 | 0.90 (0.82-0.99) |
| Warfarin | 5363 | 1219 (22.7) | 9.9 | 1.00 (ref.) |
| Rivaroxaban | 5263 | 926 (17.6) | 9.4 | 0.94 (0.85-1.04) |
| Warfarin | 2269 | 499 (22.0) | 9.5 | 1.00 (ref.) |
| Dabigatran | 2277 | 415 (18.2) | 8.1 | 0.85 (0.74-0.97) |

\*all values are for the weighted cohort.

**Supplemental Table 12:** Association between oral anticoagulants and a pneumonia (intention to treat analysis)

(all values are for the weighted cohort)

|  |
| --- |
|  |
| **Exposure** | **No.** | **No. (%) with AKI** | **Incidence rate**  **(per 100py)** | **Hazard Ratio**  **(95% CI)** |
| Warfarin | 8383 | 633(7.6) | 10.2 | 1.00 (ref.) |
| Apixaban | 8217 | 830 (10.1) | 9.1 | 0.95 (0.82-1.13) |
| Warfarin | 5363 | 378 (7.1) | 9.2 | 1.00 (ref.) |
| Rivaroxaban | 5263 | 426 (8.1) | 7.4 | 0.85 (0.71-1.01) |
| Warfarin | 2269 | 144 (6.4) | 8.5 | 1.00 (ref.) |
| Dabigatran | 2277 | 188 (8.3) | 6.8 | 0.86 (0.74-0.99) |

**Supplemental Figure 1.** Study flow diagram for creation of the main cohort of patients with atrial fibrillation and a new prescription for warfarin, apixaban, rivaroxaban, or dabigatran.

**210,474** Patients with a new prescription for warfarin, apixaban, rivaroxaban or dabigatran (index date) and a diagnosis of atrial fibrillation/flutter 5 years prior to the prescription January 1, 2009 and March 31, 2017

**2,277** dabigatran users

**4,926** warfarin users

**8,217** apixaban users

**5,263** rivaroxaban users

**20,683** Patients included in the main cohort

**189,791 Patients excluded from the main cohort:**

Incomplete data, non-Ontario resident, death prior to the index date (343)

Age <66 y at the index date (3289)

Chronic dialysis or a kidney transplant 3 y prior to the index date (8287)

Valvular surgery 3 y prior to index date (4006)

No outpatient serum creatinine on or within 1 y of the index date (17,325)

OLIS catchment ineligibility (100,391)

>1 study drug on index date (1253)

Prescription for a study drug 180 days prior to the index date (54897)