Trends in Uptake and Adherence to Oral Anticoagulation for Patients With Incident Atrial Fibrillation at High Stroke Risk Across Health Care Settings

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BACKGROUND: Oral anticoagulation (OAC) therapy prevents morbidity and mortality in nonvalvular atrial fibrillation; whether location of diagnosis influences OAC uptake or adherence is unknown.

METHODS AND RESULTS: Retrospective cohort study (2008–2019), identifying adults with incident nonvalvular atrial fibrillation across health care settings (emergency department, hospital, outpatient) at high risk of stroke. OAC uptake and adherence via proportion of days covered for direct OACs and time in therapeutic range for warfarin were measured. Proportion of days covered was categorized as low (0–39%), intermediate (40–79%), and high (80–100%). Warfarin control was defined as time in therapeutic range ≥65%. All-cause mortality was examined at a 3-year landmark. Among 75,389 patients with nonvalvular atrial fibrillation (47.0% women, mean 77.4 years), 19.7% were diagnosed in the emergency department, 59.1% in the hospital, and 21.2% in the outpatient setting. Ninety-day OAC uptake was 51.6% in the emergency department, 50.9% in the hospital, and 67.9% in the outpatient setting (P<0.0001). High direct OAC adherence increased from 64.9% to 80.3% in the emergency department, 64.3% to 81.7% in the hospital, and 70.9% to 88.6% in the outpatient setting over time (P values for trend <0.0001). Warfarin control was 40.3% overall and remained unchanged. In multivariable analysis, outpatient diagnosis compared with the hospital was associated with greater OAC uptake (odds ratio [OR], 1.79; [95% CI, 1.72–1.87]) and direct OAC (OR, 1.42; [95% CI, 1.27–1.59]) and warfarin (OR, 1.49; [95% CI, 1.36–1.63]) adherence. Varying or persistently low adherence was associated with a poor prognosis, especially for warfarin.

CONCLUSIONS: Locale of nonvalvular atrial fibrillation diagnosis is associated with varying OAC uptake and adherence. Interventions specific to health care settings are needed to improve stroke prevention.

Key Words: adherence ■ anticoagulation ■ atrial fibrillation ■ health care settings ■ uptake

Atrial fibrillation (AF), the most common cardiac arrhythmia,1 is a leading cause of stroke in older populations.2–5 Stroke caused by AF causes longer-term morbidity, greater health care resource use compared with stroke unrelated to AF, and higher mortality.5–11 Oral anticoagulant (OAC) therapy is highly effective for stroke prevention in AF with a relative risk reduction of ≈60% with warfarin compared with placebo and 20% with direct oral anticoagulants (DOACs) compared with warfarin.12,13 However, treatment adherence is critical to reducing the associated risk of stroke.14 Because of convenience in administration...
CLINICAL PERSPECTIVE

What Is New?
• Driven by greater direct oral anticoagulant use, oral anticoagulant (OAC) uptake and adherence has increased over time but remains poor overall, with a third of eligible patients with nonvalvular atrial fibrillation not being prescribed OAC therapy, primarily in the emergency department and the hospital.
• Patients with OAC adherence that varies or is persistently low have increased mortality, especially with warfarin.

What Are the Clinical Implications?
• Several risk factors, including location of diagnosis, may identify patients at high risk for OAC nonadherence who may have improved mortality with prescription of direct OAC instead of warfarin.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Alberta Health Services at sporab@ualberta.ca.

Study Population

We identified all adult patients discharged from the ED or hospital or who had at least 2 outpatient visits at least 30 days apart within a year with a new primary or secondary diagnosis of NVAF (International Classification of Diseases, Tenth Revision [ICD-10] code I48) and at high risk of stroke (CHA2DS2-VASc >2 in men and >3 in women) in Alberta, Canada, between April 1, 2008, and March 31, 2019. We used a washout period of 5 years to identify incident AF.

Patients with a prior AF diagnosis in any diagnostic position were excluded. Patients with <5 years of lead data were not excluded but represent only 4.7% of the cohort. The cohort consisted of 75,389 patients with NVAF (Figure S1). The uptake analysis examined 64,373 patients with at least a 90-day follow-up to ascertain OAC uptake. The adherence analysis examined the 24,876 patients with OAC uptake within 90 days and diagnosis after April 1, 2012, to have international normalized ratio laboratory data available. Mortality analysis was performed at a 3-year landmark in the 64,822 patients who had at least 3 years’ completed follow-up to establish a pattern of adherence, and then a time-to-event mortality analysis was performed with additional subsequent follow-up of up to 3 years. The median follow-up time was 1.5 years in the time-to-event analysis.

Data Sources

We conducted a retrospective population-based study linking the following administrative databases: (1) the Discharge Abstract Database, which records the most responsible and up to 24 other diagnoses for all acute-care hospitalizations; (2) the National Ambulatory Care Reporting System, which captures all visits to any ED and hospital-based specialist outpatient visits and includes up to 10 diagnosis fields per visit; (3) the Practitioner Claims Database, which captures nonhospital-based physician office visits; (4) the Population together with comparable or greater effectiveness and safety, DOACs have emerged as a preferred choice to warfarin for stroke prevention. Notwithstanding these advantages, warfarin represents anywhere from a quarter to a third of all OAC prescriptions.

Many studies have assessed whether the advantages of DOACs over warfarin for stroke prevention have translated into increased uptake in clinical practice and found DOAC uptake increased over time. However, uptake trends vary significantly between studies, which may be attributable to differences in study periods and locations of diagnoses. Although adherence to DOACs has been shown to be higher than warfarin, studies were limited by warfarin prescription use rather than the more accurate measure of time in therapeutic range (TTR).

Importantly, there is a paucity of data characterizing patterns in uptake and adherence over time, especially after widespread availability of DOACs. In addition, these studies were limited by lack of stratification by location of diagnosis. There are data to suggest that AF epidemiology is changing, with fewer patients with incident AF being managed in the hospital; therefore, evaluating uptake and adherence patterns across health care settings may help to identify care gaps and opportunities to address them.

Accordingly, we evaluated uptake and adherence patterns to DOACs and warfarin (including laboratory data) for patients with incident nonvalvular AF (NVAF) at high risk for stroke across various health care settings (hospital, emergency department [ED], and outpatient setting) over a 10-year period. We also examined predictors of uptake and adherence and the effect of adherence patterns on mortality.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description                  |
|--------------|------------------------------|
| DOAC         | direct oral anticoagulant    |
| NVAF         | nonvalvular atrial fibrillation |
| OAC          | oral anticoagulation         |
| TTR          | time in therapeutic range    |
Registry (demographic and geographic information); (5) the Pharmaceutical Information Network (PIN) (drug codes in Table S2) from outpatient pharmacies for patients of all ages (DOACs were introduced to the provincial formulary in 2012); and (6) the Alberta Vital Statistics Database, which records all deaths in the province.

**Data Elements and Variables**
We identified comorbidities (heart failure, hypertension, diabetes, stroke/transient ischemic attack, peripheral artery disease, coronary artery disease, major bleeding, anemia, thrombocytopenia, excess alcohol, falls, and chronic kidney disease) as present using validated ICD codes, if they were documented in any of the aforementioned databases during the 5 years before incident AF diagnosis (definition in Data S1 and codes in Table S1). The urban/rural location of patient residence was established using the Alberta Health Postal Code Translation File and was linked to postal codes of residence from Statistics Canada dissemination areas. Socioeconomic effects were estimated using the Pampalon Material Deprivation Index based on census dissemination areas. The Pampalon Material Deprivation Index considers education, employment, solitary living, marital separation, and single-parent family rates, in addition to average income, to assign quintiles of material deprivation.

**Uptake and Adherence**
Uptake of warfarin and DOACs was identified as the first dispensation within 90 days after discharge. Adherence was measured as the proportion of days covered for DOACs. Warfarin control was based on TTR. Proportion of days covered was calculated for DOACs adherence starting at the first dispensation within 90 days of discharge and followed for 365 days unless censored by death, switching OACs, out-migration, or the study end date. Proportion of days covered for DOAC was categorized as low (0–39%), intermediate (40–79%), and high (80–100%). An international normalized ratio between 2.0 and 3.0 was used to define the therapeutic range for TTR. TTR was calculated for warfarin control starting at the first warfarin dispensation within 90 days of discharge and followed for 365 days unless censored by death, switching OACs, out-migration, or the study end date. International normalized ratio values between lab tests, up to 56 days apart, were linearly interpolated using Rosendaal’s method. Warfarin control was defined as TTR of ≥65% in those days with a measured or interpolated international normalized ratio value.

**Outcomes**
The primary outcomes were temporal trends in OAC uptake and adherence for incident NVAF patients at high risk of stroke across health care settings. The secondary outcomes were predictors of uptake and adherence and 3-year all-cause mortality.

**Statistical Analysis**
Descriptive statistics are presented as means and SD for continuous variables and count with percentages for categorical variables, as appropriate, unless otherwise specified. Chi-square tests were used to compare between locations. Tests for trends used the Cochran-Armitage or Jonckheere-Terpstra test, as appropriate. All-cause mortality after a 3-year landmark was described using Kaplan-Meier curves, and comparisons used the log-rank statistic. Logistic regression models for OAC uptake and high adherence were adjusted for locale of diagnosis, age category (18–64, 65–74, and ≥75 years), sex, urban/rural location, material deprivation, history of major bleeding, anemia, thrombocytopenia, history of falls, and chronic kidney disease. Cox proportional hazards models for all-cause mortality after the 3-year landmark adjusted for the same covariates above and the previous 3-year adherence category censoring occurred at the earliest of the end of follow-up or out-migration. For the 3-year landmark mortality model, the 3 annual adherence categories were aggregated to always high, always low, and varies. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

**Ethics**
This study was approved by the University of Alberta Health Research Ethics Board (Pro00083729), including waiving the need for individual patient informed consent.

**RESULTS**

**Baseline Characteristics**
Of the total 75,389 adults with incident NVAF at high risk of stroke, 14,816 (19.7%) were first diagnosed in the ED, 44,564 (59.1%) in the hospital, and 16,009 (21.2%) in the outpatient setting (Table). Overall, the mean age was 77.4 (SD, 10.7) years old and 47.0% were women. Patients diagnosed in the hospital were older and had higher comorbidity burden; patients diagnosed in the ED were more likely to be women who live in a rural setting; and patients diagnosed in the outpatient setting were less likely to be materially deprived. The risk factors contributing most often to the CHA2DS2-VASc score were hypertension and coronary artery disease in the hospital, while in the ED and outpatient setting, it was hypertension and diabetes.

**Uptake of OAC**
The overall 90-day OAC uptake was 55.2% and varied significantly by locations with 51.7% in the ED, 50.9%
in the hospital, and 67.9% in the outpatient setting (P<0.0001; Figure 1). Over the 10-year study period, OAC uptake increased from 44.3% to 67.0% overall, 39.3% to 67.8% in the ED, 39.6% to 64.5% in the hospital, and 60.0% to 71.1% in the outpatient setting (Figure 1; P value for trend <0.0001, respectively). During this time, DOAC uptake increased from 0% to 51.6%, and warfarin decreased from 44.3% to 15.4%. Overall, 17.7% of patients initially prescribed warfarin switched over to a DOAC within 1 year, while 5.6% of patients prescribed a DOAC changed to warfarin (Figure S2).

Predictors of OAC uptake are shown in Figure S3. In multivariable analysis, the strongest predictor of OAC uptake was diagnosis in the outpatient setting (odds ratio [OR], 1.79, [95% CI, 1.72–1.87]) (P<0.0001). Age categories 65 to 74 (OR, 1.20; [95% CI, 1.14–1.27]) and ≥75 (OR, 1.21; [95% CI, 1.15–1.28]), and quintiles of material deprivation were independent predictors of OAC uptake. Female sex and comorbidities including prior major bleed, history of thrombocytopenia, cancer, liver disease, excess alcohol, prior falls, and chronic kidney disease were associated with a lower odds of OAC uptake.

**Table. Baseline Demographics, Stratified by Setting Where NVAF Was First Diagnosed**

| Total, n (%) | Setting | ED, n (%) | Hospital, n (%) | Outpatient, n (%) | P value |
|-------------|---------|-----------|----------------|------------------|---------|
| Sample      | 75,389 (100.0) | 14,816 (19.7) | 44,564 (59.1) | 16,009 (21.2) |         |
| Female      | 35,457 (47.0) | 7,371 (49.8) | 20,957 (47.0) | 7,129 (44.5) | <0.0001 |

**Age, y**

| Mean±SD | 18–64 | 65–74 | ≥75 | Rural |
|---------|------|------|-----|------|
| 77.4 (10.7) | 76.4 (10.7) | 78.0 (11.0) | 76.3 (9.9) | 77.4 (10.7) |
| P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

**Material deprivation quintiles**

| Quintile | 1—least deprived | 2 | 3 | 4 | 5—most deprived* |
|----------|------------------|---|---|---|------------------|
|          | 11,335 (15.0) | 2238 (15.1) | 6356 (14.3) | 2741 (17.1) | 15,959 (21.2) |
|          | 11,081 (14.7) | 2090 (14.1) | 6388 (14.3) | 2623 (16.4) | 16,131 (36.2) |
|          | 12,779 (17.0) | 2556 (17.3) | 7414 (16.6) | 2869 (17.5) | 2559 (17.3) |
|          | 16,806 (21.0) | 3159 (21.3) | 9395 (21.1) | 2522 (20.3) | 2236 (14.0) |

ED indicates emergency department; and NVAF, nonvalvular atrial fibrillation.

*Deprivation could not be determined in 8429 (11.2%) patients.
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the outpatient setting (P<0.0001). Over the study period, there was a significant increase in high adherence to DOAC therapy across all health care settings. High adherence to DOACs increased from 64.9% to 80.3% in the ED, 64.3% to 81.7% in the hospital, and 70.9% to 88.6% in the outpatient setting (P<0.001, respectively).

Changes in adherence categories over a 3-year period following the first DOAC prescription are shown in Figure S4 and Table S3. Between consecutive years, for patients with NVAF who had high or low adherence after the first year of DOAC initiation, the vast majority (87–92%) remained in the same adherence category in the next year.

Predictors of DOAC adherence are shown in Figure 3. After adjusting for confounders, there was a 42% higher odds of high DOAC adherence when NVAF was diagnosed in the outpatient setting (95% CI, 1.27–1.58) compared with the hospital setting and 16% higher odds for female sex (95% CI, 1.06–1.27). There was a 10% decreased odds of DOAC adherence if diagnosed in the ED (95% CI, 0.81–0.99) and a 41% and 38% increased odds for those aged 65 to 74 and ≥75, respectively, compared with age 18 to 64.

Warfarin Control Patterns Across Health Care Settings

Warfarin control was ≥65% in 40.3% of patients taking warfarin. Trends in warfarin control across health care settings are shown in Figure 2. When NVAF was diagnosed in the ED, warfarin control was 38.2%, 36.1% in the hospital, and 47.5% in the outpatient setting. Over time, warfarin control decreased in ED-diagnosed patients, while it remained unchanged in the hospital and outpatient setting (P value for trends <0.0003, 0.12, and 0.24, respectively).

Changes in control categories over a 3-year period following first warfarin prescription are shown in Figure S5 and Table S3. For patients with TTR ≥65% in the first year, ≈25% had suboptimal warfarin control in the subsequent year. While those who were suboptimal in the first year, 47.8% had TTR ≥65% in the subsequent year.
second year and 41.1% in the third year. Trends were similar across different locations of diagnosis.

Predictors of warfarin control are shown in Figure 3. Diagnosis in the outpatient setting was associated with a 49% greater odds of warfarin control (95% CI, 1.37–1.63) compared with the hospital setting and a 22% lower odds for the most materially deprived patients (95% CI, 0.68–0.89) compared with the least.

**Mortality**

Overall, 935 (14.4%) patients with OAC update died in the 3 years after the landmark period. Kaplan-Meier curves for 3-year mortality according to OAC adherence/control categories (always high, always low, varies) are shown in Figure 4. For DOACs, patients with NVAF with both variable and low adherence had a worse prognosis. For warfarin, patients with variable control had fewer deaths than those with persistently low TTR. Predictors associated with all-cause mortality are shown in Figure S6.

**DISCUSSION**

In this population-based study of patients with incident NVAF at increased risk of stroke and recommended to be anticoagulated in current guidelines, we found OAC adherence.
uptake has increased over time across all health care settings and is driven by higher DOAC use. Three-quarters of patients were found to have a high adherence to DOAC therapy, and this increased over time and across health care settings. Patients first diagnosed in the outpatient setting were more likely to have OAC uptake and to have high adherence to DOACs compared with the hospital setting after adjusting for confounders. In patients managed with warfarin, control was suboptimal and declined over time in the ED setting but was unchanged in other settings. Variable or persistently low adherence had a poor prognosis, particularly for warfarin.

Observational studies comparing OAC uptake in the pre- and post-DOAC eras using administrative data have shown increased uptake (by \( \approx 50\% \)) in both incident and prevalent NVAF across a variety of health care settings.\(^{18,20,21}\) We observed a similar increase in OAC uptake from 44.3% in 2008 to 67.0% in 2019, corresponding to a relative increase of 51%. Our study builds on this work by demonstrating that OAC uptake increased over time across all locales of diagnosis with a 51% relative increase overall; 72% in the ED, 63% in the hospital, and 19% in the outpatient setting. This finding is in the context of a narrowing difference in uptake between ED and hospital diagnoses compared with patients diagnosed in outpatient clinics over time.\(^{39}\) Patients in the hospital were more likely to have coronary artery disease and may have been prescribed antiplatelet agents, which may cause providers to be less likely to prescribe OAC therapy because of greater bleeding risk. These differences by location of diagnosis are becoming increasingly important as the epidemiology of NVAF changes over time and patients with newly diagnosed AF are seen in health care settings other than the hospital.\(^{29}\) This first point of contact provides an important opportunity to evaluate eligibility for stroke prevention therapy. Regardless of location, one-third of patients were not started on OACs, even in 2018, the final year of the study. Efforts targeted to further understand this care gap are needed.

Comparative studies of incident and prevalent AF across all locations of diagnosis found an \( \approx 20\% \) relative greater adherence to DOACs than warfarin.\(^{25–28}\) Although these previous studies did not report OAC adherence by location and did not use TTR for warfarin,\(^{25–28,40,41}\) our data demonstrate OAC adherence, both for DOACs and warfarin, was overall highest in patients diagnosed in the outpatient setting. Importantly, warfarin control was poor regardless of setting. One possible explanation for the difference with respect to location may be limited follow-up for patients diagnosed in the ED or the hospital. Prior work has demonstrated that patients who are diagnosed with AF in the ED are more likely to receive follow-up if an established family physician is identified.\(^{42}\) A major factor in adherence is physician communication and patient understanding of OACs.\(^{43}\) More research is needed to better understand how both may serve as potential barriers to

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**Figure 4.** All-cause mortality by 3-year adherence category. Kaplan–Meier curves of all-cause mortality by adherence category is shown for DOACs and warfarin on the left and right, respectively. DOAC indicates direct oral anticoagulants; PDC, proportion of days covered; and TTR, time in therapeutic range.
adherence and to help develop mitigating strategies.\textsuperscript{42} Patient health literacy, which is associated with medication adherence, disease status, and outcomes,\textsuperscript{44,45} should be assessed in each patient.\textsuperscript{48} Further studies, including randomized controlled trials, are needed to determine whether provision of educational material on the importance of OAC adherence tailored to patient-specific health literacy can improve adherence. In addition, recommending and tracking OAC adherence discussions as part of AF quality measures may further reduce this care gap.

There are limited real-world, population-level data on warfarin control using TTR for incident NVAF.\textsuperscript{47} We found that the proportion of patients who exhibited adequate warfarin control (TTR $\geq 65\%$) in our study was low, at 40\%. Similarly, a previous study in the same geographic location as our study reported only 41\% of patients exhibited adequate control with warfarin.\textsuperscript{48} while another study in Sweden found a 57\% control rate (TTR $\geq 70\%$). The Swedish study did not restrict its patients to incident NVAF and included only patients $>65$ years old, which may explain the higher adherence in their cohort. Indeed, younger patients are more likely to have poor adherence to warfarin.\textsuperscript{49} The increased adherence observed in the Swedish study may also be attributable to improved continuity of primary care.\textsuperscript{48} Nevertheless, we found that low warfarin control persisted over time and across location of diagnosis. Although definitions of adherence to warfarin and DOAC differed, the most adherent warfarin group had higher all-cause mortality compared with the most adherent DOAC group. Further research is needed to better understand this finding.

Although patients diagnosed in the outpatient setting had greater rates of warfarin control, the overall level was still quite low, suggesting that there may be factors unrelated to physician follow-up. The reasons for poor warfarin control (ie, lack of defined follow-up, labile dietary, interacting medications, alternating dosing regimens, transportation barriers, and unstable living conditions) have been previously described.\textsuperscript{49–51} Identification of modifiable factors that portend poor warfarin control is important to recognize patients who may not be optimal candidates for warfarin therapy. In those that are prescribed warfarin, integrated AF care teams and quality improvement programs can improve OAC use.\textsuperscript{52,53} These findings further reinforce guideline recommendations for first-line DOACs over warfarin.\textsuperscript{15–17}

Previous studies of real-world OAC adherence and outcomes found that low adherence was associated with higher rates of all-cause mortality.\textsuperscript{25,54–56} We found similar results in our cohort, with an increase in mortality in patients with low adherence. Our study also presents novel findings with respect to how adherence patterns change over time. We demonstrate the importance of having high adherence whether it is DOACs or warfarin during the first year after NVAF diagnosis and its relationship to mortality.

Our study has some limitations that warrant discussion. Diagnoses were based on administrative data, and misclassification or underdiagnosis may exist. However, the ICD codes used to identify AF have been previously validated with reasonable accuracy.\textsuperscript{57} Other patient factors, for example, cognitive issues, lack of social supports, and transportation difficulties, may have influenced uptake and adherence but were not available in administrative databases. We assumed a TTR of $\geq 65\%$ as controlled on the basis of prior clinical thresholds.\textsuperscript{36,37} but higher benchmarks may be warranted. Adherence to DOAC therapy in our study was not directly assessed but was inferred from patients’ filled prescriptions via PIN profile. We used proportion of days covered as a measure of DOAC adherence, as this has been previously published when using administrative claims data.\textsuperscript{36} Our data did not include prescription of antiplatelet agents; more research is needed to determine whether the use of antiplatelet agents may affect OAC prescription across all health care settings. Our data did not separate general practitioner from specialist outpatient visits. Further work is needed to better understand practice patterns for OAC uptake and adherence according to urban/rural location and practitioner type. Our study only included patients in the province of Alberta and may not be generalizable to other health care systems.

In this population-based study, we found OAC uptake and adherence increased over time, while warfarin control remained suboptimal across all health care settings. AF diagnosis in outpatient settings is associated with higher OAC uptake and adherence. Poor OAC adherence is associated with a higher mortality, especially for warfarin. These data support guideline recommendations for first-line DOAC therapy. Strategies aimed at improving OAC uptake and adherence across all health care settings where AF diagnosis occurs are needed.

\textbf{ARTICLE INFORMATION}

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SUPPLEMENTAL MATERIAL
Data S1. Supplemental Methods

Based upon ICD-10 codes, patients were classified as having PAD if they had previously documented PAD and/or graft procedures; CKD for estimated glomerular filtration rates of <90 mL per minute per 1.73 m² or those with albuminuria; falls if documented on an inpatient or outpatient visit; excess alcohol if diagnosed with alcohol withdrawal, alcohol-related end-organ damage, or rehabilitation for excess alcohol use; major bleeding if a major hemorrhage event and/or a blood transfusion in combination with a clinically-relevant nonmajor bleeding code were documented on an inpatient or outpatient visit.
| Clinical Diagnosis          | ICD-10-CA Codes | CCI Procedure Codes |
|----------------------------|----------------|---------------------|
| Valvular disease           | I05 I06 I34 I35 I08.0 I08.1 I08.2 I08.3 | 1.HS.80 1.HS.90 1.HT.80 1.HT.89 1.HT.90 1.HU.80 1.HU.90 1.HV.80 1.HV.90 |
| Heart Failure              | I25.5 I42.0 I42.6 I42.7 I42.8 I42.9 I43 I50 |                   |
| Hypertension               | I10-I13 I15   |                     |
| Diabetes                   | E10-E14       |                     |
| Stroke/TIA                 | I63 I64 H34.1 I61 G45 |                   |
| PAD                        | I70 I71 I73.1 I73.8 I73.9 I77.1 I79.0 I79.2 K55.1 K55.8 K55.9 Z95.8 Z95.9 |                   |
| CAD                        | I25.0 I25.1 I25.2 I25.5 I25.8 I25.9 |                   |
| MI                         | I21 I22       |                     |
| Chronic Kidney Disease     | N18           |                     |
| Anemia                     | D50-D89 D60-D64 |                   |
| Thrombocytopenia           | D69           |                     |
| Falls                      | W00-W19       |                     |
| Excess Alcohol             | E52 F10 G62.1 I42.6 K29.2 K70.0 K70.3 K70.9 T51 Z50.2 Z71.4 Z72.1 |                   |
| Major Bleeding             | H35.6 H43.1 H45.0 I60 I61 I62 M25.0 J94.2 I31.2 |                   |
|                            | or Transfusion with CRNMB |                   |
| Transfusion                | T80.3 T80.4 Y65.0 Z51.3 | 1.LZ.19 |
| CRNMB                      | I85.01 I85.11 I85.21 I85.31 I85.41 I85.51 I85.61 I85.71 I85.81 I85.91 K22.11 K22.6 K25.0 K25.2 K25.4 K25.6 K26.0 K26.2 K26.4 K26.6 K27.0 K27.2 K27.4 K27.6 K28.0 K28.2 K28.4 K28.6 K29.01 K29.11 K29.21 K29.31 K29.41 K29.51 K29.61 K29.71 K29.81 K29.91 K31.80 K55.21 K62.5 K66.1 K92.0 K92.1 K92.2 N02 S06.4 S06.5 S06.6 R04 R31 R58 |                   |

CAD, coronary artery disease; CCI, Canadian Classification of Health Interventions; CRNMB, clinically relevant nonmajor bleeding; CVD, cerebrovascular disease; ICD, International Classification of Disease; PAD, peripheral artery disease; TIA, transient ischemic attack.
Table S2. Oral anticoagulation ATC codes using the PIN profile

| Drug Name (generic) | ATC Code   |
|---------------------|------------|
| Warfarin            | B01AA03    |
| Rivaroxaban         | B01AF01, B01AX06 |
| Apixaban            | B01AF02    |
| Dabigatran          | B01AE07    |
| Edoxaban            | B01AF03    |

ATC, Anatomical Therapeutic Chemical classification system; PIN, Pharmaceutical Information Network.
Table S3. Changes in oral anticoagulation adherence categories over a 3-year period following initiation of therapy

| Starting Adherence | Ending Adherence | NOAC Uptake Transition | Warfarin Uptake Transition |
|--------------------|------------------|-------------------------|---------------------------|
|                    |                  | Year 1 → 2 | Year 2 → 3 | Year 1 → 2 | Year 2 → 3 |
|                    |                  | n (%)      | n (%)      | n (%)      | n (%)      |
| High               | High             | 2,250 (86.7%) | 2,163 (87.7%) | 1,348 (76.7%) | 1,472 (74.5%) |
|                    | Moderate         | 259 (10.0%)  | 226 (9.2%)  | 409 (23.3%)  | 504 (25.5%)  |
|                    | Low              | 87 (3.4%)    | 77 (3.1%)   |            |            |
| Moderate           | High             | 203 (43.2%)  | 213 (49.3%) | 409 (23.3%)  | 504 (25.5%)  |
|                    | Moderate         | 141 (30.0%)  | 121 (28.0%) |            |            |
|                    | Low              | 126 (26.8%)  | 98 (22.7%)  |            |            |
| Low                | High             | 13 (3.8%)    | 20 (3.9%)   | 628 (47.8%) | 450 (41.1%) |
|                    | Moderate         | 32 (9.2%)    | 21 (4.1%)   | 685 (52.2%) | 644 (58.9%) |
|                    | Low              | 301 (87.0%)  | 473 (92.0%) |            |            |
| Total              |                  | 3,412       |            | 3,070       |            |
Figure S1. CONSORT diagram

AF patients presenting 2008/9-2018/19 n=139,739

- Previous AF n=28,150
  - Valvular n=12,386
  - Not Alberta Residents n=801
  - Age <18 n=12
  - Low Stroke Risk n=23,001

Incident AF at high stroke risk cohort n=75,389

- Deaths within 90 days n=9,612
- Out migration within 90 days n=24
- Less than 90 days follow-up prior to end of study period n=1,380

Uptake analysis n=64,373

- No Uptake within 90 days n=28,824
- Dx Prior to April 2012 no lab data n=10,673

Adherence analysis n=24,876

- Less than 3 years follow-up n=18,394

Mortality analysis n=6,482

AF, atrial fibrillation; Dx, diagnosis.
Figure S2. Change in OAC class prescription within 1 year
Figure S3. Predictors associated with OAC uptake

- **Locale (ref=Hospital)**
  - ED
  - Physician Office

- **Age Group (ref=18-64)**
  - Age 65-74
  - Age 75+

- **Sex (ref=male)**
  - Female

- **Urban/Rural (ref=urban)**
  - Rural

- **Material Deprivation (ref=least deprived)**
  - Quintile 2
  - Quintile 3
  - Quintile 4
  - Quintile 5 - most deprived

- **Comorbidities**
  - Major Bleed
  - Anemia
  - Thrombocytopenia
  - Cancer
  - Liver Disease
  - Excess Alcohol
  - Falls
  - Chronic Kidney Disease

Odds ratios (OR) and 95% confidence intervals (CI) for factors affecting OAC uptake
Figure S4. Change in categories of adherence to DOAC over time

DOAC, direct oral anticoagulant; PDC, proportion of days covered.
Figure S5. Change in categories of adherence to warfarin over time

TTR, time in therapeutic range.
Figure S6. Predictors associated with all-cause mortality

| Category                        | All Cause Mortality HR (95% CI) in DOAC patients | All Cause Mortality HR (95% CI) in Warfarin patients |
|--------------------------------|--------------------------------------------------|-----------------------------------------------------|
| Locale (ref=Hospital)           |                                                  |                                                     |
| ED                             |                                                  |                                                     |
| Physician Office                |                                                  |                                                     |
| 3-year Adherence (ref=AlwaysHigh) |                                                  |                                                     |
| Varies                         |                                                  |                                                     |
| Always Low                     |                                                  |                                                     |
| Age Group (ref>64)              |                                                  |                                                     |
| Age 65-74                       |                                                  |                                                     |
| Age 75+                         |                                                  |                                                     |
| Sex (ref=Male)                  |                                                  |                                                     |
| Female                         |                                                  |                                                     |
| Urban/Rural (ref=urban)         |                                                  |                                                     |
| Rural                          |                                                  |                                                     |
| Material Deprivation (ref=least deprived) |                                                  |                                                     |
| Quintile 2                      |                                                  |                                                     |
| Quintile 3                      |                                                  |                                                     |
| Quintile 4                      |                                                  |                                                     |
| Quintile 5 - most deprived     |                                                  |                                                     |
| Comorbidities                   |                                                  |                                                     |
| Major bleed                     |                                                  |                                                     |
| Anemia                          |                                                  |                                                     |
| Thrombocytopenia                |                                                  |                                                     |
| Cancer                          |                                                  |                                                     |
| Liver Disease                   |                                                  |                                                     |
| Excess Alcohol                  |                                                  |                                                     |
| Falls                           |                                                  |                                                     |
| Chronic Kidney Disease          |                                                  |                                                     |

Hazard ratios (OR) and 95% confidence intervals (CI) for factors affecting all cause mortality. Follow up for all cause mortality begins at 3 years after the first OAC dispense.