ORIGINAL RESEARCH

Long-Term Medication Adherence Trajectories to Direct Oral Anticoagulants and Clinical Outcomes in Patients With Atrial Fibrillation

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BACKGROUND: Direct oral anticoagulants (DOACs) are widely used in patients with nonvalvular atrial fibrillation for stroke prevention. However, long-term adherence to DOACs and clinical outcomes in real-world clinical practice is not well understood. This study evaluated long-term medication adherence patterns to DOAC therapy and clinical outcomes in a large US integrated health care system.

METHODS AND RESULTS: We included adult patients with nonvalvular atrial fibrillation who newly initiated DOACs between 2012 and 2018 in Kaiser Permanente Southern California. Long-term (3.5 years) adherence trajectories to DOAC were investigated using monthly proportion of days covered and group-based trajectory models. Factors associated with long-term adherence trajectories were investigated. Multivariable Poisson regression analyses were used to investigate thromboembolism and major bleeding events associated with long-term adherence trajectories. Of 18,920 patients newly initiating DOACs, we identified 3 DOAC adherence trajectories: consistently adherent (85.2%), early discontinuation within 6 months (10.6%), and gradually declining adherence (4.2%). Predictors such as lower CHA2DS2-VASc (0–1 versus ≥5) and previous injurious falls were associated with both early discontinuation and gradually declining adherence trajectories. Early discontinuation of DOAC therapy was associated with a higher risk of thromboembolism (rate ratio, 1.40; 95% CI, 1.05–1.86) especially after 12 months from DOAC initiation but a lower risk of major bleed compared with consistent adherence (rate ratio, 0.48; 95% CI, 0.30–0.75), specifically during the first 12 months following DOAC initiation. A gradual decline in adherence to DOACs was not statistically significantly associated with thromboembolism outcomes compared with consistent adherence.

CONCLUSIONS: Although a large proportion of patients with nonvalvular atrial fibrillation were adherent to DOAC therapy over 3.5 years, early discontinuation of DOAC was associated a higher risk of thromboembolic events. Future tailored interventions for early discontinuers may improve clinical outcomes.

Key Words: anticoagulant ■ atrial fibrillation ■ medication adherence

Direct oral anticoagulants (DOACs) are widely used for prevention of ischemic stroke in patients with nonvalvular atrial fibrillation (NVAF).1,2 Once patients with NVAF initiate DOAC therapy, most are expected to continue DOAC medications for their lifetime. Compared with warfarin, DOACs are more convenient because they have fewer interactions with food, less need for routine laboratory monitoring, and a lower risk of bleeding.3–5 However, there is uncertainty whether patients taking DOACs are able to take their medications as directed for a long time without the intensive monitoring and provider follow-up required for...
CLINICAL PERSPECTIVE

What Is New?
- With a systematic direct oral anticoagulants monitoring program in a US integrated health care system, over 85% patients with nonvalvular atrial fibrillation who were on direct oral anticoagulants were consistently adherent to their therapy for 3.5 years.
- Several clinical factors were associated with direct oral anticoagulant adherence trajectories, which can be used for identifying candidates for future adherence interventions.
- Early discontinuation of direct oral anticoagulant therapy was associated with a higher risk of thromboembolism compared with consistent adherence.

What Are the Clinical Implications?
- Future tailored interventions for early discontinuers may improve clinical outcomes.
- Major bleeding events in early treatment periods in those with consistent adherence should be monitored carefully.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| BIC          | Bayesian Information Criterion |
| DOACs        | direct oral anticoagulants |
| KPSC         | Kaiser Permanente Southern California |
| NVAF         | nonvalvular atrial fibrillation |
| PDC          | proportion of days covered |

warfarin. Previous studies in the United States have shown that the mean proportion of days covered (PDC) ranges from 0.67 to 0.86 during the first 6 months and between 0.57 to 0.89 during the first 12 months of DOAC therapy; in other studies, ≈1 in 3 patients were found to be nonadherent, defined as having PDC <0.80. Data on adherence to DOAC therapy beyond 12 months are currently limited.

Medication adherence is typically summarized using PDC during a fixed follow-up time, most frequently 6 or 12 months. More recently, longitudinal adherence patterns have been identified using group-based trajectory modeling. This modeling approach is able to more appropriately categorize complex nonadherence behaviors. Two recent studies identified 4 different adherence patterns of oral anticoagulants using the group-based trajectory modeling among Medicare beneficiaries such as early discontinuers, late initiators, late discontinuers, and continuous adherers.

However, these studies also focused on adherence during the first 12 months after NVAF diagnosis, and therefore, long-term adherence trajectories to DOAC therapy are still largely unknown.

In this study, we investigated long-term medication adherence patterns using group-based trajectories to DOAC therapy. We further investigated factors associated with long-term adherence trajectories and clinical outcomes of thromboembolism and major bleeding associated with DOAC medication adherence trajectories.

METHODS

Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions.

Study Cohort

We conducted a retrospective cohort study by identifying new users of DOAC among patients with NVAF. Kaiser Permanente Southern California (KPSC) is a large integrated health care delivery system that provides medical services to its members through its own facilities (15 hospitals, more than 200 outpatient facilities). All clinical care and interactions with the system are captured in comprehensive electronic health records. Over 95% of KPSC members have a pharmacy benefit and, therefore, have an incentive to fill their medication within the system. All dispensed prescriptions and claims outside KPSC are captured in the pharmacy database. This study was approved by the KPSC institutional review board, and patient informed consent was waived.

We included patients ≥18 years of age with a prescription fill for a DOAC (dabigatran, apixaban, edoxaban, or rivaroxaban) between January 2012 and December 2018 in KPSC. The first date of DOAC prescription dispense was defined as the index date. Patients were required to have a diagnosis of atrial fibrillation or atrial flutter (International Classification of Diseases, Ninth Revision [ICD-9] codes of 427.3, 427.31, 427.32; International Classification of Diseases, Tenth Revision [ICD-10] codes of I48.x) within 12 months before the index date. Eligible patients also were members of the health plan (allowing a 45-day gap) and had to have a pharmacy benefit 12 months before the index date. Patients with a mechanical heart valve, mitral
valve stenosis, or severe liver disease and those residing in a nursing home or on hospice in the 12 months before the index date were excluded from the analysis. Women who were pregnant before index or during follow-up were also excluded. Patients were required to have a minimum 30 days follow-up and 2 prescription dispenses to allow adherence calculations. Therefore, patients with <30 days membership or an outcome event within 30 days of index were also excluded. Two separate cohorts (one for thromboembolic events and the other for major bleeding) were created to evaluate efficacy and safety outcomes separately. The cohort diagram is shown in Figure S1.

Patients were followed from the index date until the outcomes of interest (thromboembolic events or major bleeding), death, disenrollment from the health plan, switching from DOAC therapy to warfarin, or study end date (December 31, 2018), whichever occurred first.

**Monthly Medication Adherence**

Adherence to any DOAC medication was calculated using pharmacy dispensing data from electronic health records. DOAC adherence was defined using PDC in monthly intervals (denominator of PDC). If a patient was censored before the next monthly interval, the denominator of PDC in that specific period was up to the censoring date instead of 30 days. The refill date was adjusted for patients who refilled their medications earlier than scheduled by shifting the fill date forward to the day after the end of supply of the previous fill. Patients who switched therapy between DOACs (eg, dabigatran to apixaban) were considered as continuing DOAC therapy.

**Outcomes**

The outcomes of interest were thromboembolism (ischemic stroke and systemic embolism) and major bleeding (intracranial hemorrhage, major gastrointestinal bleeding, and other major bleeding). Hospital discharge diagnoses in the primary position were used to identify these events, which have shown positive predictive values of 77% to 85% (Table S1).

**Patient Demographic and Clinical Characteristics**

Patient demographic characteristics (age, sex, race and ethnicity) and census block-level median household income were identified. We included clinically important medical characteristics using 12 months of data before the index date. Clinical characteristics included presence of congestive heart failure, hypertension, diabetes, stroke, transient ischemic attack, peripheral vascular disease, myocardial infarction, bleeding, chronic obstructive pulmonary disease, alcoholism, cancer, injurious falls, and dementia and were defined by diagnosis and procedure codes. Creatinine clearance was calculated using the Cockcroft-Gault equation recommended by clinical guidelines for DOACs. CHA2DS2-VASc and HAS-BLED scores were calculated to assess stroke and bleeding risk before the index date.

**Statistical Analysis**

Using the monthly PDC, we applied group-based trajectory modeling to detect and define groups of patients with similar adherence patterns following initiation of the DOAC medication. Trajectories were modeled using flexible polynomial models based on significant linear, quadratic, and cubic terms. The optimal number of trajectories was selected by comparing Bayesian information criterion and the mean of posterior probabilities in each class. Because PDC captures the number of days covered each month and frequent zero counts were observed, the zero-inflated Poisson model was used. Long-term adherence trajectories were investigated until 5% of patients remained in the cohort (3.5 years). Patients were assigned to 1 of the trajectory groups based on the estimated probabilities of membership in each trajectory group. Mean (SD) PDC during follow-up was compared by adherence trajectory groups.

Descriptive statistics were used to compare patient demographic and clinical characteristics by adherence trajectory groups. To investigate further how these characteristics are associated with each adherence trajectory group, we conducted multinomial logistic regression analyses. Clinically relevant predictors (age, sex, race and ethnicity, CHA2DS2-VASc score, HAS-BLED score) were included in the model. Also, other potential predictors were tested as covariates and statistically significant variables from univariate models were included in the final multivariable model. Odds ratios (ORs) with 95% CI were reported.

To evaluate clinical outcomes associated with long-term adherence trajectories, we calculated thromboembolic and major bleeding events per 100 person-years during follow-up. We also evaluated outcomes by timing of events (during the first 12 months, and after 12 months). We conducted multivariable Poisson regression analyses to investigate associations between clinical outcomes and long-term adherence trajectories. Clinically relevant covariates were tested as covariates and statistically significant variables from
univariate models were included in the final multivariable model. Sensitivity analyses were conducted after excluding previous warfarin users and patients with CHA2DS2-VASc score ≤1. Rate ratios with 95% CIs were reported. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS
We included a total of 18,920 patients with NVAF initiating DOAC therapy for the thromboembolic outcomes analysis, and 18,940 patients for bleeding outcomes analysis (Figure S1). Among the 18,920 patients with NVAF, the mean (SD) age was 72.6 (10.6) years, 42.8% were female, and 64.5% were non-Hispanic White patients, 18.1% Hispanic patients, 8.2% Asian/Pacific Islanders, and 7.2% were non-Hispanic Black patients (Table 1). Most patients (92.5%) initiated treatment with dabigatran and 5.3% initiated with apixaban. Most patients (82.1%) had CHA2DS2-VASc score ≥2.

Long-Term Adherence Trajectories
Models with up to 6 trajectory groups were considered. Cubic terms were nonsignificant in all models; therefore, the second-order polynomial model was selected. After model order was determined, Bayesian information criterion selected 3 distinct trajectories, and the mean of posterior probabilities in each class showed good discrimination between groups. Visual inspection of these trajectories supported 3 distinct adherence patterns over 3.5 years of follow-up. Visual inspection also showed that models allowing up to 6 trajectory groups showed only 3 meaningful trajectory groups, confirming the selection of 3 distinct groups was optimal (consistent adherence [85.2%], early discontinuation [10.6%], and gradual decline [4.2%]) (Figure 1). Among those with 3.5 years of follow-up, 78.0% were consistently adherent. Mean (SD) PDC for consistently adherent patients was 0.91 (0.17) during the first 6 months and PDCs remained consistently high throughout follow-up (Figure 1). The PDC of the early discontinuation group was low in the first 6 months (mean [SD] PDC=0.35 [0.20]). The PDC of the gradual decline group was moderately high in the first 6 months (mean [SD]=0.74 [0.27]) and started to decline between 7 and 12 months (mean [SD]=0.36 [0.32]) and stayed below 0.13 after 12 months (Figure 1).

Patient and Clinical Characteristics Associated With Long-Term Adherence Trajectory Groups
Patients who were consistently adherent to DOACs were older and a greater proportion were female and non-Hispanic White patients compared with the early discontinuation and gradual decline groups (Table 1).

Thromboembolic and Major Bleeding Event by Long-Term Adherence Trajectories
Thromboembolic and major bleeding events are shown stratified by long-term adherence trajectory groups as well as follow-up period (either during the first 12 months or after 12 months from the index date) (Table 2). Thromboembolism event rates were 1.41 per 100 person-years for the consistent adherence group, 1.78 per 100 person-years for the early discontinuation group, and 0.96 per 100 person-years for the gradual decline group. More thromboembolism events occurred during the first 12 months in the consistent adherence group, whereas more thromboembolism events occurred after 12 months from the index date in the early discontinuation and gradual decline groups. Major bleed event rates were 1.46 per 100 person-years for the consistent adherence group, 0.62 per 100 person-years for the early discontinuation group, and 0.53 per 100 person-years for the gradual decline group. More major bleed events occurred during the first 12 months than after 12 months in the consistent adherence group but not in the other 2 groups.

Early discontinuation of DOACs was associated with a higher risk of thromboembolism during follow-up than consistent adherence (rate ratio, 1.40; 95% CI, 1.05–1.86) (Table 3). These differences were mainly from higher event rates after 12 months of follow-up. Early discontinuation of DOACs was associated with a 2-fold higher risk of thromboembolism than consistent adherence (rate ratio, 2.22; 95% CI, 1.41–3.50) after 12 months, but there were no differences in thromboembolism during the first 12 months between early discontinuation and consistent adherence groups (rate ratio, 0.86; 95% CI, 0.52–1.42). Early discontinuation of DOACs was also associated with a lower risk of major bleed compared with consistent adherence, mainly driven by higher bleeding...
### Table 1. Patient and Clinical Characteristics by Long-Term Adherence Trajectories

| Characteristics                          | Total (n=18,920) | Consistent adherence (n=16,111) | Early discontinuation (n=2,008) | Gradual decline (n=801) |
|-----------------------------------------|------------------|---------------------------------|---------------------------------|-------------------------|
| Age, y                                  |                  |                                 |                                 |                         |
| <65                                     | 3,889 (20.6%)    | 2,960 (18.4%)                  | 650 (32.4%)                     | 279 (34.8%)             |
| 65–74                                   | 6,740 (35.6%)    | 5,898 (36.6%)                  | 598 (29.8%)                     | 244 (30.5%)             |
| 75–84                                   | 6,275 (33.2%)    | 5,519 (34.3%)                  | 537 (26.7%)                     | 219 (27.3%)             |
| ≥85                                     | 2,016 (10.7%)    | 1,734 (10.8%)                  | 223 (11.1%)                     | 59 (7.4%)               |
| Female sex                              | 8,107 (42.8%)    | 7,056 (43.8%)                  | 748 (37.3%)                     | 303 (37.8%)             |
| Age category, y                         |                  |                                 |                                 |                         |
| <65                                     | 3,421 (18.1%)    | 2,860 (17.8%)                  | 415 (20.7%)                     | 146 (18.2%)             |
| 65–74                                   | 15,586 (82.8%)   | 13,433 (83.3%)                 | 1,414 (7.0%)                    | 72 (9.0%)               |
| 75–84                                   | 6,361 (33.6%)    | 5,409 (33.6%)                  | 690 (34.4%)                     | 262 (32.7%)             |
| ≥85                                     | 1,206 (64.5%)    | 1,0481 (65.1%)                 | 1,239 (61.7%)                   | 486 (60.7%)             |
| Multi-race/Native American/Unknown      | 376 (2.0%)       | 310 (1.9%)                     | 47 (2.3%)                       | 19 (2.4%)               |
| Neighborhood household income           |                  |                                 |                                 |                         |
| ≤$25,000                                | 184 (1.0%)       | 153 (0.9%)                     | 20 (1.0%)                       | 11 (1.4%)               |
| $25,001–$50,000                         | 4,143 (21.9%)    | 3,505 (21.8%)                  | 465 (23.2%)                     | 173 (21.6%)             |
| $50,001–$80,000                         | 7,943 (42.0%)    | 6,810 (42.3%)                  | 798 (39.7%)                     | 335 (41.8%)             |
| >$80,000                                | 6,361 (33.6%)    | 5,409 (33.6%)                  | 690 (34.4%)                     | 262 (32.7%)             |
| Unknown                                 | 289 (1.5%)       | 234 (1.5%)                     | 35 (1.7%)                       | 20 (2.5%)               |
| Clinical characteristics                |                  |                                 |                                 |                         |
| Congestive heart failure                | 3,012 (15.9%)    | 2,614 (16.2%)                  | 267 (13.3%)                     | 131 (16.4%)             |
| Hypertension                            | 11,582 (61.2%)   | 10,061 (62.4%)                 | 1,053 (52.4%)                   | 468 (58.4%)             |
| Diabetes                                | 5,202 (27.5%)    | 4,549 (28.2%)                  | 456 (22.7%)                     | 197 (24.6%)             |
| Stroke/transient ischemic attack        | 1,332 (7.0%)     | 1,195 (7.4%)                   | 96 (4.8%)                       | 41 (5.1%)               |
| Peripheral vascular disease             | 4,082 (2.2%)     | 3,505 (2.2%)                   | 42 (2.1%)                       | 16 (2.0%)               |
| Intracranial hemorrhage                 | 66 (0.3%)        | 58 (0.4%)                      | 6 (0.3%)                        | 2 (0.2%)                |
| Gastrointestinal bleed                  | 1,134 (6.0%)     | 988 (6.1%)                     | 103 (5.1%)                      | 43 (5.4%)               |
| Other bleed                             | 1,158 (6.1%)     | 999 (6.2%)                     | 111 (5.5%)                      | 48 (6.0%)               |
| Creatinine clearance (CrCl), mL/min     |                  |                                 |                                 |                         |
| CrCl ≥60                                | 13,128 (69.4%)   | 11,140 (69.1%)                 | 1,391 (69.3%)                   | 597 (74.5%)             |
| CrCl 30–59                              | 4,912 (26.0%)    | 4,264 (26.5%)                  | 480 (23.9%)                     | 168 (21.0%)             |
| CrCl 15–29                              | 308 (1.6%)       | 258 (1.6%)                     | 41 (2.0%)                       | 9 (1.1%)                |
| CrCl <15                                | 26 (0.1%)        | 21 (0.1%)                      | 5 (0.2%)                        | 0 (0%)                  |
| Missing                                 | 546 (2.9%)       | 426 (2.7%)                     | 91 (4.5%)                       | 27 (3.4%)               |
| Alcoholism                              | 822 (4.3%)       | 706 (4.4%)                     | 80 (4.0%)                       | 36 (4.5%)               |
| Dementia                                | 932 (4.9%)       | 795 (4.9%)                     | 101 (5.0%)                      | 36 (4.5%)               |
| Injurious fall                          | 1,620 (8.6%)     | 1,325 (8.2%)                   | 181 (9.0%)                      | 114 (14.2%)             |
| Chronic obstructive pulmonary disease   | 2,331 (12.3%)    | 2,048 (12.7%)                  | 204 (10.2%)                     | 79 (9.9%)               |
| Cancer                                  | 1,686 (8.9%)     | 1,467 (8.9%)                   | 162 (8.1%)                      | 57 (7.1%)               |
| Myocardial infarction                   | 772 (4.1%)       | 655 (4.1%)                     | 93 (4.6%)                       | 24 (3.0%)               |
| Charlson Comorbidity Index              | 2.4 (1.9)        | 2.4 (1.9)                      | 2.1 (1.9)                       | 2.0 (1.8)               |
| CHA₂DS₂-VASc score                     | 2.9 (1.5)        | 2.9 (1.4)                      | 2.4 (1.6)                       | 2.5 (1.6)               |
| CHA₂DS₂-VASc score category             |                  |                                 |                                 |                         |
| 0–1                                     | 3,392 (17.9%)    | 2,518 (15.6%)                  | 632 (31.5%)                     | 242 (30.2%)             |

(Continued)
event rates during the first 12 months from the consistent adherence group. Gradual decline of adherence to DOACs was not statistically significantly associated with thromboembolism outcomes compared with consistent adherence. Sensitivity analyses for those with CHA2DS2-VASc score ≥2 and no previous use of warfarin showed consistent results.

**DISCUSSION**

This study identified 3 distinct long-term adherence trajectories to DOACs. A large proportion of patients with NVAF were adherent to DOAC therapy over 3.5 years. Other identified adherence patterns were early discontinuation within 6 months and gradual decline; patients comprising these 2 groups may be important candidates for future DOAC adherence interventions. To the best of our knowledge, this study is the first to provide information on long-term adherence trajectories to DOAC therapy and associated outcomes over 3.5 years.

Adherence trajectory modeling has been suggested as a better way to summarize complex longitudinal adherence patterns compared with traditional methods dichotomizing patients as adherent or nonadherent. The trajectory approach may help identifying the timing of interventions as well as the patients most likely to benefit from the intervention by more appropriately categorizing complex nonadherence behaviors. A recent study evaluated an adherence intervention designed to address past adherence trajectories in statin users and was found to be effective. The 3 long-term adherence trajectories found in our study can be used to identify groups for tailored adherence interventions.

Our study identified early discontinuation as an important subgroup to address because of increased risk of thromboembolism. Patient and clinical factors associated with early discontinuation identified from this study such as race or ethnicity of non-Hispanic Black or Hispanic, lower creatinine clearance, previous injurious falls, no prior use of warfarin, or having

| Characteristics | Total (n=18 920) | Consistent adherence (n=16 111) | Early discontinuation (n=2008) | Gradual decline (n=801) |
|-----------------|-----------------|-------------------------------|-------------------------------|------------------------|
| 2               | 4239 (22.4%)    | 3676 (22.8%)                  | 399 (19.9%)                  | 164 (20.5%)            |
| 3               | 4945 (26.1%)    | 4320 (26.8%)                  | 447 (22.3%)                  | 178 (22.2%)            |
| 4               | 4000 (21.1%)    | 3535 (21.9%)                  | 331 (16.5%)                  | 134 (16.7%)            |
| 5 or more       | 2344 (12.4%)    | 2062 (12.8%)                  | 199 (9.9%)                   | 83 (10.4%)             |

**HAS-BLED score**

| HAS-BLED score | Total (n=18 920) |
|----------------|-----------------|
| 0–1            | 10 073 (53.2%) |
| 2              | 6138 (32.4%)   |
| 3              | 2203 (11.6%)   |
| 4 or more      | 506 (2.7%)     |

**Medication use at baseline**

| Medication use at baseline | Total (n=18 920) |
|----------------------------|-----------------|
| Warfarin                   | 5511 (29.1%)    |
| Antihypertensive medications | 18 067 (86.5%) |
| Antiarrhythmic medications | 1724 (8.3%)     |
| Antiplatelet agents        | 5795 (27.8%)    |
| First DOAC                | Total (n=18 920) |
| Dabigatran                | 17 496 (92.5%)  |
| Apixaban                   | 996 (5.3%)      |
| Rivaroxaban                | 423 (2.2%)      |
| Edoxaban                   | 3 (0%)          |
| First DOAC prescriber specialty | Total (n=18 920) |
| Cardiology                | 5276 (27.9%)    |
| Internal medicine/family medicine | 7964 (42.1%) |
| Others                     | 5680 (30.0%)    |

**Mean (SD) follow-up time in days**

| Mean (SD) follow-up time in days | Total (n=18 920) |
|---------------------------------|-----------------|
| 510.0 (415.0)                  | 481.6 (411.6)   |

The data reported either mean (SD) or N (%). DOAC indicates direct oral anticoagulants.
other prescriber specialty would be useful in identifying patients most likely to benefit from an adherence intervention. Interestingly, many predictors associated with early discontinuation were identified as predictors for the gradual decline adherence trajectory. Moreover, some of these predictors such as Black race, use of

| Follow-up | Total | Consistent Adherence | Early Discontinuation | Gradual Decline | P value |
|-----------|-------|----------------------|-----------------------|----------------|---------|
|           | N (row %) | PDC | Mean (SD) | N (row %) | PDC | Mean (SD) | N (row %) | PDC | Mean (SD) | PDC |
| 0-6 months | 18,920 | 0.84 | 16.111 | 0.91 | 2,038 | 0.35 | 801 | 0.74 | <0.001 |
| (100%) | (0.25) | (85.2%) | (0.17) | (10.0%) | (0.20) | (4.2%) | (0.27) |       |         |
| 7-12 months | 13,715 | 0.73 | 11,065 | 0.86 | 1,829 | 0.00 | 801 | 0.36 | <0.001 |
| (100%) | (0.37) | (80.8%) | (0.21) | (13.3%) | (0.03) | (5.8%) | (0.32) |       |         |
| 13-24 months | 9,767 | 0.72 | 7,733 | 0.89 | 1,258 | 0.00 | 776 | 0.13 | <0.001 |
| (100%) | (0.36) | (79.2%) | (0.16) | (12.9%) | (0.03) | (7.9%) | (0.19) |       |         |
| 25-36 months | 4,418 | 0.70 | 3,432 | 0.89 | 559 | 0.00 | 427 | 0.10 | <0.001 |
| (100%) | (0.40) | (77.7%) | (0.20) | (12.7%) | (0.01) | (8.7%) | (0.20) |       |         |
| 37-42 months | 1,983 | 0.70 | 1,235 | 0.86 | 194 | 0.00 | 154 | 0.12 | <0.001 |
| (100%) | (0.41) | (78.0%) | (0.24) | (12.3%) | (0.02) | (9.7%) | (0.27) |       |         |

**Figure 1.** Long-term adherence trajectories to direct oral anticoagulants. Mean PDC over time by adherence trajectory groups (consistent adherence, early discontinuation, and gradual decline). PDC indicates proportion of days covered.

**Figure 2.** Factors associated with long-term adherence trajectories. **A**, Odds ratio (95% CI) of early discontinuation trajectory compared with consistent adherence trajectory. **B**, Odds ratio (95% CI) of gradually declining adherence trajectory compared with consistent adherence trajectory.
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antiarrhythmic agents, and dementia were identified as predictors associated with decreasing adherence trajectories within 12 months of DOAC initiation in a previous study. However, the current analysis found that the HAS-BLED score is not associated with early discontinuation adherence trajectories, which is different from other study findings. Only a few studies from Europe and Canada investigated long-term DOAC adherence over 3 years. These studies reported around 54% to 78% of DOAC initiators were persistent to DOACs after 3 years. Although the methods to define adherence are different, the results from the current analysis show a relatively higher percentage of patients were adherent to DOAC therapy after 3.5 years (85.2% overall, and 78.0% for those with 3.5 years of follow-up). The mean PDCs during the first 6 months or 7 to 12 months after DOAC initiation was also higher in our study (0.84 and 0.73, respectively) than previous reported ranges. Interestingly, adherence (mean PDC over 12 months) was higher among patients from the Veterans Affairs health care system (0.84–0.89) and relatively lower in a commercially insured population (0.64–0.80) in the United States. The current study results may be more comparable with the results from Veterans Affairs where a DOAC adherence monitoring program has been implemented.

Our study supports the clinical importance of medication adherence. Thromboembolic event rates were similar during the 12 months of DOAC initiation between early discontinuers and consistently adherent patients; however, these rates among early discontinuers during follow-up after the first 12 months were almost double those of consistent adherers. Consistent with previous studies, the current analysis showed that early discontinuation within 6 months from DOAC initiation was associated with a 2-fold higher risk of thromboembolic events while maintaining a similar risk of bleeds after 12 months of follow-up. However, major bleeding events in the first 12 months were significantly higher.

### Table 2. Thromboembolism and Major Bleeding Stratified by Long-Term Adherence Trajectories

|                      | Consistent adherence | Early discontinuation | Gradual decline |
|----------------------|----------------------|-----------------------|-----------------|
|                      | Total | First 12 mo | After 12 mo | Total | First 12 mo | After 12 mo | Total | First 12 mo | After 12 mo |
| Thromboembolic events* |       |             |             |       |             |             |       |             |             |
| Total patient, N     | 1611  | 1611        | 8077       | 2008  | 2008        | 1339        | 801   | 801         | 793         |
| Total person-years (PY) | 21259 | 11943       | 9316       | 3305  | 1809        | 1496        | 1874  | 801         | 1073        |
| Total events, N      | 299   | 136         | 83         | 59    | 18          | 25          | 18    | 13          |
| Total event rates per 100 PY | 1.41  | 1.14        | 0.89       | 1.78  | 1.00        | 1.67        | 0.96  | ...         | 1.21        |
| Ischemic stroke, N   | 279   | 130         | 77         | 55    | 18          | 21          | 17    | ...         | 12          |
| Ischemic stroke, rates | 1.31  | 1.10        | 0.83       | 1.66  | 1.00        | 1.40        | 0.91  | ...         | 1.12        |
| Systemic embolism, N | 24    | 9           | 6          | 4     | ...         | 2           | 2     | ...         | 2           |
| Systemic embolism, rates | 0.11  | 0.08        | 0.06       | 0.12  | ...         | 0.27        | 0.11  | ...         | 0.19        |
| Major bleed events†  |       |             |             |       |             |             |       |             |             |
| Total patient, N     | 16167 | 16167       | 8102       | 1957  | 1957        | 1309        | 816   | 816         | 806         |
| Total PY             | 21323 | 11983       | 9340       | 3212  | 1764        | 1448        | 1904  | 816         | 1088        |
| Total events, N      | 312   | 142         | 80         | 20    | 7           | 9           | 10    | 1           |
| Total event rates per 100 PY | 1.46  | 1.19        | 0.86       | 0.62  | 0.40        | 0.62        | 0.53  | 0.12        | 0.64        |
| ICH, N               | 23    | 11          | 7          | 3     | ...         | 2           | 2     | 1           |
| ICH, rates           | 0.11  | 0.09        | 0.07       | 0.09  | ...         | 0.14        | 0.11  | 0.12        | 0.09        |
| GI bleed, N          | 271   | 119         | 72         | 16    | 6           | 7           | 8     | ...         | 6           |
| GI bleed, rates      | 1.27  | 0.99        | 0.77       | 0.50  | 0.34        | 0.48        | 0.42  | ...         | 0.55        |
| Other bleed, N       | 29    | 17          | 3          | 1     | 1           | ...         | ...   | ...         | ...         |
| Other bleed, rates   | 0.14  | 0.14        | 0.03       | 0.03  | 0.06        | ...         | ...   | ...         | ...         |

*Patients were followed from the index date (first DOAC prescription) until the thromboembolic event, death, disenrollment from the health plan, switching from DOAC therapy to warfarin, or study end date (December 31, 2018), whichever occurred first. The percentages of switch to warfarin were 8.6%, 6.3%, and 3.8% for consistent adherence, early discontinuation, and gradual decline groups, respectively.

†Major bleeding event was used as a censoring event instead of thromboembolic event.

... no observation. GI indicates gastrointestinal; and ICH, intracranial hemorrhage.
in the consistent adherent group than the early discontinuation group, which suggests careful monitoring is needed in consistent adherers.

Interestingly, patients in our study with a gradually declining adherence pattern had no thromboembolic events during the first 12 months of follow-up but had a higher rate of thromboembolic events compared with consistently adherent patients after 12 months. The lower event rates during the first 12 months may be because of baseline differences between the 2 groups, where patients in the gradual decline group were younger and had lower CHA2DS2-VASc scores. No thromboembolic events in the first 12 months for gradual decliners may have affected later medication adherence behaviors; most patients in the gradual decline group were adherent to DOACs in the first 6 months of follow-up; however, these patients became nonadherent later and had more thromboembolic events later.

This study has several strengths and limitations. We evaluated long-term adherence trajectories up to 3.5 years in a relatively large population who received DOACs. However, a relatively small number of patients were available for the entire 3.5 years. With an increasing trend of DOAC use, future studies will be able to investigate long-term adherence in a larger population. Moreover, this study did not evaluate medication adherence by type of DOAC, primarily because most patients received dabigatran. In addition, 18% of the study population had CHA2DS2-VASc scores of 0 or 1. It is possible that for some patients, DOAC therapy may not be appropriate. Because of the retrospective nature of the study design, we were not able to confirm the appropriateness of DOAC therapy; however when we conducted sensitivity analyses for those with CHA2DS2-VASc scores ≥2, patients recommended for DOAC therapy, the results were the same. Adherence calculation was based on filled prescription data; therefore, early discontinuation may include both a prescriber’s decision to discontinue the DOAC and patients’ behavior of not filling their DOAC. Also, we required 2 prescription fills for PDC calculation to make sure patients had sufficient data to make a valid estimate of medication adherence. However, this may have inflated DOAC adherence. Although switching from DOAC therapy to warfarin is an appropriate therapeutic option, this study focused on medication adherence to DOACs only. However, a small portion (4%–6%) of early discontinuers and gradual decliners were censored because of the switch to warfarin therapy; therefore, the impact of warfarin switch may be minimal. Lastly, this study was conducted in a single health care system. The study findings may not be generalizable to other settings.

**CONCLUSIONS**

This study showed that a large portion of patients with NVAF were adherent to DOAC therapy over 3.5 years from a large US integrated health care system. Early discontinuation of DOAC therapy within 6 months was associated with a higher risk of thromboembolic outcomes. Future interventions identifying early discontinuers of DOAC therapy may be warranted to improve medication adherence and ultimately improve clinical outcomes.

**ARTICLE INFORMATION**

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SUPPLEMENTAL MATERIAL
Table S1. Definition of Outcomes

| Outcomes                  | ICD-9 or ICD-10 codes |
|---------------------------|-----------------------|
| **Thromboembolism**       |                       |
| - Ischemic stroke         | Principal hospital discharge diagnoses |
|                           | ICD-9 codes 433.x1, 434.x1, 436.x |
|                           | ICD-10 codes I63.x, I67.89 |
|                           | Positive Predictive Values (PPV) for the algorithm = 85% or higher |
| - Systemic embolism       | Principal hospital discharge diagnoses |
|                           | ICD-9 codes 444.2, 444.8 - 444.9, 593.81 |
|                           | ICD-10 codes I74.2 – I74.9, N28.0 |
| **Major Bleed**           |                       |
| - Intracranial hemorrhage | Principal hospital discharge diagnosis |
|                           | ICD-9 codes 430 – 432, 852.2, 852.4x, 853.0x |
|                           | ICD-10 codes I60 - I62, S06.34 - S06.36, S06.4 – S06.5 |
|                           | PPV = 77%¹⁹            |
| - Gastrointestinal bleeds | Principal hospital discharge diagnosis |
|                           | ICD-9 codes 455.2, 455.5, 455.8, 456, 456.0, 456.2, 530.7, 530.82, 531.0 – 531.6, 532.0 – 532.6, 533.0 – 533.6, 534.0 – 534.6, 535.1, 535.3.x1, 537.83, 562.x2, 562.x3, 568.81, 569.3, 569.85, 578 |
|                           | ICD-10 codes I85.01, I85.1, I86, K22.6, K22.8, K25.0 – K25.6, K26.0 – K26.6, K27.0 – K27.6, K28.0 – K28.6, K29.01, K29.21, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K52.81, K55.21, K57.11, K57.13, K57.31, K57.33, K62.5, K64.4, K64.8, K66.1, K92.0 – K92.2 |
| - Other major bleeds      | Principal hospital discharge diagnosis |
|                           | ICD-9 codes 423.0, 459.0, 599.7, 719.11, 784.7, 784.8, 786.3 |
|                           | ICD-10 codes I31.2, M25.01, R04.0 – R04.2, R31, R31.0, R31.9, R58 |
PPV for major bleeds = 85%\textsuperscript{20}
Figure S1. Cohort Flow

38,498 patients with ≥1 DOAC prescription between 2012-2018
(first DOAC date = index date)

27,564 patients diagnosed with AF within 1 year prior to index date and were ≥18 years of age on index date

22,260 patients enrolled at KPSC and had pharmacy benefit within 1 year prior to index date

20,981 patients were not in a skilled nursing facility or in hospice care at any time within 1 year prior to or on the index date

20,168 patients had no mechanical heart valve, mitral valve stenosis, or severe liver disease at baseline and were not pregnant at any time during the study period

1,248 patients had <30 days of follow-up
• 100 patients passed away within 30 days of index
• 602 patients were enrolled for <30 days
• 472 patients switched to warfarin within 30 days

18,994 patients

74 patients experienced thromboembolism within 30 days of the index date

18,920 patients were eligible for analysis for thromboembolism

54 patients experienced major bleeding within 30 days of the index date

18,940 patients were eligible for analysis for bleeding

*Abbreviations: DOAC = direct oral anticoagulants; AF = atrial fibrillation; KPSC = Kaiser Permanente Southern California