Trajectories of Oral Anticoagulation Adherence Among Medicare Beneficiaries Newly Diagnosed With Atrial Fibrillation

Inmaculada Hernandez, PharmD, PhD; Meiqi He, MS; Nemin Chen, MPH; Maria M. Brooks, PhD; Samir Saba, MD; Walid F. Gellad, MD, MPH

**Background**—Only 50% of atrial fibrillation (AF) patients recommended for oral anticoagulation (OAC) use these medications, and less than half of them adhere to OAC. In a cohort of Medicare beneficiaries newly diagnosed with AF, we identified groups of patients with similar trajectories of OAC use and adherence, and evaluated patient characteristics affecting group membership.

**Methods and Results**—We selected continuously enrolled Medicare Part D beneficiaries with first AF diagnosis in 2014 to 2015 (n=34,898). We calculated the proportion of days covered with OAC over the first 12 months after diagnosis and identified OAC adherence trajectories using group-based trajectory models. We constructed multinomial logistic regression models to evaluate how demographics, system-level factors, and clinical characteristics were associated with group membership. We identified 4 trajectories of OAC adherence: patients who never used OAC (43.8%), late OAC initiators (7.6%), early OAC discontinuers (8.9%), and continuously adherent patients (40.1%). Predictors such as sex, black race, residence in the South, or HAS-BLED score were associated with not only OAC use, but also the timing of initiation and the likelihood of discontinuation. For example, HAS-BLED score ≥4 was associated with a higher likelihood of not using OAC (odds ratio 1.35; 95% CI, 1.14–1.62), of late initiation (1.55; 95% CI, 1.11–2.05), and of early discontinuation (odds ratio 1.35; 95% CI, 1.01–1.84).

**Conclusions**—We identified 4 distinct trajectories of OAC adherence after first AF diagnosis, with <45% of newly diagnosed AF patients belonging to the trajectory group characterized by continuous OAC adherence. Trajectories were associated not only with demographic and clinical characteristics but also with regional factors.

**Key Words**: adherence • anticoagulation • atrial fibrillation

Atrial fibrillation (AF) is associated with a 5-fold increase in stroke risk and is the most common cause of ischemic stroke in the elderly.1–3 Oral anticoagulation (OAC) reduces the risk of stroke associated with AF by 60%; yet, only half of AF patients recommended for OAC actually receive these medications, and less than half of them adhere to OAC over time.5–13 Before 2010, one of the main reasons for OAC underuse was the sole availability of warfarin for stroke prevention in AF.5,14,15 Warfarin has multiple limitations, including a narrow therapeutic index, requirement for routine blood monitoring, significant interactions with diet and other medications used for AF, and a nonnegligible risk of intracranial bleeding.5,16,17 However, recent evidence suggests that underuse and lack of adherence to OAC have barely improved after the approval of direct oral anticoagulants (DOACs),18–22 even though these agents have a more stable pharmacokinetic profile than warfarin, lower risk of intracranial bleeding, and do not require routine blood monitoring.23–26

Previous research evaluating what patient characteristics affect OAC use and adherence found that risk factors for stroke, such as age >75 years, hypertension, or a history of stroke, increase use and adherence to OAC.12,21,22,27–29 However, most prior studies used the proportion of days covered (PDC) with OAC as the single measure of adherence,28,29 and did not examine the longitudinal pattern of OAC adherence.
Clinical Perspective

What Is New?

- Among patients newly diagnosed with atrial fibrillation, we identified 4 trajectories of adherence to oral anticoagulation (OAC): patients who never used OAC (43.8%), late OAC initiators (7.6%), early OAC discontinuers (8.9%), and continuously adherent patients (40.1%).
- Important predictors such as sex, black race, or HAS-BLED score were associated not only with OAC use, but also with the timing of initiation and the likelihood of discontinuation.
- Membership in adherence trajectories was associated not only with demographic and clinical characteristics but also with regional factors.

What Are the Clinical Implications?

- With <45% of newly diagnosed atrial fibrillation patients adhering to OAC, underuse and suboptimal adherence to OAC remain a significant clinical challenge, even after the approval of direct oral anticoagulants.
- Suboptimal use and adherence to OAC is not only a product of intermittent gaps in therapy, but also of lack of OAC initiation, of late initiation, and of discontinuation of therapy among initiators.
- Given the major potential impact associated with stroke prevention, interventions designed to improve OAC use and adherence that address each of these underlying reasons are warranted.

Methods

Data Source and Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because Medicare claims data were obtained under a Data User Agreement that does not allow data sharing. Using 2013 to 2016 medical and pharmacy claims from a 5% random sample of Medicare beneficiaries, we included patients who were newly diagnosed with AF between January 1, 2014 and December 31, 2015 (Figure 1). We used the Centers for Medicare and Medicaid Chronic Condition Warehouse indicator of AF,33 which traces the first AF diagnosis back to January 1999. Index date was defined as the first diagnosis of AF. We excluded patients who had a diagnosis of valvular disease in the year before the index date (definition of valvular disease in Table S1). Because the objective of the study was to describe patterns of OAC adherence in the first year after AF diagnosis, we excluded patients who died within 360 days of diagnosis, or who were not continuously enrolled in Stand-Alone Prescription Drug Plans. The final sample included 34 898 patients. All individuals were followed for 360 days after first AF diagnosis. This study was deemed exempt by the Institutional Review Board at the University of Pittsburgh.

Covariates

Covariates included patient demographics, social determinants, and clinical characteristics, and were all defined on index date. Demographics included age, sex, and race as indicated in the Medicare Master Beneficiary Summary file. Social determinants included eligibility for Medicaid coverage, low-income subsidy receipt, region of residence (Northeast, Midwest, West, Southeast, or Southwest), socioeconomic score, measured at the zip code level, and index of dissimilarity, measured at the Metropolitan Statistical Area level.34 Data from American Community Survey Data35 obtained from the US Census Bureau were linked to Medicare claims using the zip code, and the socioeconomic score was calculated using a factor analysis approach that identified key census variables and combined them using z-scores into a meaningful score that represents socioeconomic status.36 The index of dissimilarity, which measures the fraction of blacks (or whites) who would have to move from their neighborhoods to other neighborhoods to achieve perfect integration, was also calculated on the basis of American Community Survey data and a previously defined formula.37,38

Clinical characteristics included CHAD2S2-VASc score, HAS-BLED score, history of acute myocardial infarction (AMI), Alzheimer disease or dementia, chronic kidney disease, heart
failure, diabetes mellitus, hypertension, stroke or transient ischemic attack, recent bleeding, and recent use of antiplatelet agents and of NSAIDs. CHA2DS2-VASc and HAS-BLED scores are validated tools that predict the risk of ischemic stroke in AF and the risk of bleeding on OAC, respectively. Because claims data do not contain international normalized ratio levels, we calculated the HAS-BLED score as the sum of all factors except international normalized ratio, as done previously in the literature. In defining each of the factors included in CHAD2S2-VASc and HAS-BLED scores, we used Centers for Medicare and Medicaid Chronic Condition Warehouse definitions when available. When not available, we used 12 months of claims data before AF diagnosis and published definitions of covariates (Data S1 and Table S1).

**Outcomes**

Our primary outcome was the PDC with OAC, and was measured at each 30-day interval after first AF diagnosis. To define PDC with OAC, we extracted all prescriptions for OACs, including warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban filled after the first AF diagnosis, and arrayed them chronologically. Using the date of fill and the days of supply, we created a supply diary for each patient. We then calculated PDC with OAC for each 30-day interval as the ratio of the...
number of days covered with OAC in each 30-day interval (numerator) and 30 (denominator).

Statistical Analysis
We used group-based trajectory models to identify patient groups with similar adherence patterns. Group-based trajectory models assume that the population is composed of heterogeneous groups, each with a distinct trajectory. These models are preferred over methods such as latent class analysis for modeling trajectories that do not vary monotonically, as can be the case for drug adherence (patients can be intermittently adherent to drugs). To implement group-based trajectory models, we first transformed the PDC with OAC using the arcsine transformation so that it followed a censored normal distribution, which is one of the assumptions of this model. The time variable was months since first AF diagnosis (1–12). We used the most flexible functional form of time, allowing up to a fifth-order polynomial, as previously done in the literature. Group-based trajectory analyses were performed using PROC TRAJ (https://www.andrew.cmu.edu/user/bjones/) in SAS statistical software. The final model was selected using Nagin’s criteria. Models with a lower number of groups were favored in order to allow for a robust estimation of the effect of patient characteristics on group membership using multinomial logistic regression. The output of the final model included the estimated average trajectory for each group, and the estimated probabilities of membership in each trajectory group for each patient. Using these estimated probabilities, patients were assigned to the trajectory group for which membership probability was highest, and the assigned groups were used in analyses to determine how patient characteristics were associated with trajectory membership. We compared patient characteristics across trajectory groups using \( \chi^2 \) tests.

Results
Study Cohort Characteristics
The mean age of the study sample was 75.4 years (SD 10.0), 55.5% were female, and 87.3% were white. Among the 34 898 study participants, annual PDC was 40.0% (SD 39.3%), and 21 213 (60.8%) filled at least 1 prescription for OAC in the year after AF diagnosis, including 10 383 who filled at least 1 prescription for warfarin, and 12 579 who filled at least 1 prescription for DOACs. Among the 21 213 patients who filled at least 1 OAC prescription, the mean annual PDC was 65.8% (SD 29.0%). Table S2 compares selected characteristics between patients included in the study and those who

Figure 2. Trajectories of adherence to oral anticoagulation in the first year after atrial fibrillation diagnosis among Medicare beneficiaries. The x-axis represents time in months since the first diagnosis of atrial fibrillation. The y-axis represents the proportion of days covered with oral anticoagulation in each month. The proportions in the legends represent the estimated proportion of participants in each trajectory group among all study participants. Dashed lines represent 95% CIs. AF indicates atrial fibrillation.
### Table 1. Baseline Patient Characteristics of Medicare Beneficiaries With New Atrial Fibrillation Diagnosis, by Oral Anticoagulation Trajectory Group

| Variable, n (%) | Nonusers (Group 1, n = 15,273) | Late Initiators (Group 2, n = 2639) | Early Discontinuers (Group 3, n = 3,010) | Continuously Adherent Patients (Group 4, n = 13,976) | P Value |
|-----------------|---------------------------------|-------------------------------------|--------------------------------------|-------------------------------------------------|---------|
| **Initiation of OAC** |                                 |                                     |                                      |                                                 |         |
| Filled ≥1 Rx for warfarin* | 632 (4.1)                      | 1118 (42.4)                          | 1461 (48.5)                           | 7172 (51.3)                                      | <0.001  |
| Filled ≥1 Rx for DOACs* | 979 (6.4)                      | 1716 (65.0)                          | 1781 (59.2)                           | 8103 (58.0)                                      | <0.001  |
| **Demographics** |                                 |                                     |                                      |                                                 |         |
| Age (y) |                                     |                                       |                                       |                                                 |         |
| <65 | 1330 (8.7)                          | 231 (8.8)                            | 231 (7.7)                             | 1029 (7.4)                                       | <0.001  |
| 65–74 | 5692 (37.3)                         | 1089 (41.3)                          | 1283 (42.6)                           | 5753 (41.2)                                      |         |
| ≥75  | 8251 (54.0)                         | 1319 (50.0)                          | 1496 (49.7)                           | 7194 (51.5)                                      |         |
| Female sex | 8801 (57.6)                  | 1505 (57.0)                          | 1533 (50.9)                           | 7537 (53.9)                                      | <0.001  |
| Race |                                 |                                       |                                       |                                                 |         |
| White | 13,069 (85.6)                      | 2288 (86.7)                          | 2596 (86.2)                           | 12,507 (89.5)                                    |         |
| Black | 1222 (8.0)                         | 221 (8.4)                            | 255 (8.5)                             | 774 (5.5)                                        |         |
| Hispanic | 281 (1.8)                    | 39 (1.5)                             | 42 (1.4)                              | 161 (1.2)                                        |         |
| Other | 701 (4.6)                          | 91 (3.4)                             | 117 (3.9)                             | 534 (3.8)                                        |         |
| **Social determinants** |                                       |                                       |                                       |                                                 | <0.001  |
| Eligibility for Medicaid | 4319 (28.3)                      | 653 (24.7)                           | 704 (23.4)                             | 2958 (21.2)                                      |         |
| Eligibility for low-income subsidy | 4960 (32.5)                  | 769 (29.1)                           | 832 (27.6)                             | 3465 (24.8)                                      |         |
| Quartiles Socioeconomic Score† |                            |                                       |                                       |                                                 | <0.001  |
| Q1 | 3866 (26.1)                         | 675 (26.6)                           | 763 (26.2)                             | 3145 (23.2)                                      |         |
| Q2 | 3639 (24.6)                         | 679 (26.7)                           | 690 (23.7)                             | 3389 (25.0)                                      |         |
| Q3 | 3511 (23.7)                         | 585 (23.0)                           | 730 (25.1)                             | 3488 (25.7)                                      |         |
| Q4 | 3779 (25.5)                         | 600 (23.6)                           | 724 (24.9)                             | 3556 (26.2)                                      |         |
| Quartiles index of dissimilarity‡ |                                 |                                       |                                       | 0.1871                                           |         |
| Q1 | 3816 (25.0)                         | 660 (25.0)                           | 797 (26.6)                             | 3404 (24.4)                                      |         |
| Q2 | 3672 (24.1)                         | 635 (24.1)                           | 665 (22.2)                             | 3378 (24.2)                                      |         |
| Q3 | 3797 (24.9)                         | 648 (24.6)                           | 727 (24.2)                             | 3429 (24.6)                                      |         |
| Q4 | 3971 (26.0)                         | 692 (26.3)                           | 812 (27.1)                             | 3754 (26.9)                                      |         |
| **Region** |                                       |                                       |                                       |                                                 | <0.001  |
| Midwest | 3449 (22.6)                       | 595 (22.6)                           | 742 (24.7)                             | 3716 (26.6)                                      |         |
| Northeast | 3504 (23.0)                        | 623 (23.6)                           | 640 (21.3)                             | 3492 (25.0)                                      |         |
| Southeast | 4436 (29.1)                       | 824 (31.3)                           | 886 (29.5)                             | 3736 (26.8)                                      |         |
| Southwest | 1500 (9.8)                        | 261 (9.9)                            | 283 (9.4)                              | 1122 (8.0)                                       |         |
| West | 2364 (15.5)                         | 333 (12.6)                           | 451 (15.0)                             | 1892 (13.6)                                      |         |
| **Clinical characteristics** |                                       |                                       |                                       |                                                 |         |
| CHA2DS2-VASc score |                                 |                                       |                                       |                                                 | <0.001  |
| 0–2 | 2439 (16.0)                         | 451 (17.1)                           | 454 (15.1)                             | 2264 (16.2)                                      |         |
| 3–4 | 5387 (35.3)                         | 942 (35.7)                           | 1140 (37.9)                            | 5530 (39.6)                                      |         |
| ≥5  | 7447 (48.8)                         | 1246 (47.2)                          | 1416 (47.0)                            | 6182 (44.2)                                      |         |
| HAS-BLED score§ |                                 |                                       |                                       |                                                 | <0.001  |
| 0–1 | 1498 (9.8)                          | 314 (11.9)                           | 264 (8.8)                              | 1599 (11.4)                                      |         |
| 2–3 | 9341 (61.2)                         | 1589 (60.2)                          | 1993 (66.2)                            | 9325 (66.7)                                      |         |

Continued
were excluded because they died within 12 months of AF diagnosis. Excluded patients were generally older and more likely to have CHA2DS2-VASc ≥ 5.

Adherence Trajectories

Group-based trajectory analyses identified 4 distinct trajectories of OAC adherence: patients who never used OAC ("non-users," group 1, 43.8%), patients who initiated OAC in months 3 to 8 post AF diagnosis ("late initiators," group 2, 7.6%), patients who initiated OAC early after AF diagnosis but who discontinued treatment in months 3 to 8 ("early discontinuers," group 3, 8.6%), and patients who were continuously adherent to OAC ("continuously adherent patients," group 4, 40.1%) (Figure 2). This 4-group model met all of Nagin’s criteria (average posterior probability > 70%, narrow CIs for estimated probability, and odds of correct classification > 5 for all 4 groups, Table S3). The model diagnostics indicate that the 4 group model performs exceptionally well for this sample.

Association Between Patient Characteristics and Group Trajectory Membership

Unadjusted results

Table 1 compares the observed characteristics of patients in each of the 4 trajectory groups. Approximately half of the study participants were 75 years or older, and the proportion of patients older than 75 was higher for the nonusers group (54.0%), followed by the continuously adherent group (51.5%), the late initiator group (50.0%), and finally the early discontinuers group (49.7%), with P < 0.001. Female sex was most prevalent in the nonusers (57.6%) and late initiators (57.0%) groups than in the continuously adherent (53.9%) and early discontinuers (50.9%) groups. The proportion of black patients and of those eligible for Medicaid and for low-income subsidy was significantly lower in the continuously adherent group than in the remainder of the groups. The proportion of patients with CHA2DS2-VASc score ≥ 5, HAS-BLED ≥ 4, Alzheimer disease or other dementia, and chronic kidney disease was highest in the nonusers group.

Adjusted results

Table 2 shows the results of multivariable multinomial logistic regression models. Specifically, it presents the odds ratio (OR) for each covariate selected in the stepwise selection procedure of belonging to a given adherence trajectory group compared with belonging to the continuously adherent trajectory group. The reference trajectory group for all ORs listed in the text below is the continuously adherent trajectory group; this is often omitted from the writing for the sake of simplicity.

Demographic Characteristics. Age > 65 years was associated with a lower likelihood of not using OAC (OR of not using OAC versus continuous adherence 0.85; 95% CI, 0.76–0.97 for 65–74 years, and 0.85; 95% CI, 0.77–0.98 for ≥ 75, both compared with < 65). Female sex was associated with higher odds of not using OAC (OR 1.15; 95% CI 1.09–1.22), and of
late initiation (OR 1.15; 95% CI, 1.06–1.30), but with lower odds of early discontinuation (OR 0.85; 95% CI, 0.78–0.94). Additionally, black race was associated with a higher likelihood of not using OAC (OR 1.35; 95% CI, 1.17–1.44), of late initiation (OR 1.35; 95% CI, 1.14–1.59), and of early discontinuation (OR 1.45; 95% CI, 1.25–1.72), compared with white race.

**Social Determinants.** Eligibility for low-income subsidy was associated with higher odds of not using OAC (OR 1.15; 95% CI, 1.11–1.25). Region of residence was also significantly associated with trajectory group membership: Compared with residence in the Northeast, residence in the Southeast or the Southwest increased the likelihood of not using OAC (OR 1.15; 95%, CI 1.08–1.23 for Southeast; 1.35; 95% CI, 1.21–1.47 for Southwest), of late initiation (OR 1.25; 95% CI, 1.09–1.37 for Southeast; 1.35; 95% CI 1.13–1.56 for Southwest), and of early discontinuation (OR 1.25; 95% CI, 1.13–1.43 for Southeast; 1.35; 95% CI, 1.17–1.62 for Southwest).

### Table 2. Estimated Odds Ratios for the Association Between Patient Characteristics and Trajectory Group Membership

| Variable                  | Reference Group           | Odds Ratio of Group Membership (95% CI) |
|---------------------------|---------------------------|----------------------------------------|
|                           | Nonusers vs Continuously Adherent Patients (Group 1 [n=15,273] vs Group 4 [n=13,976]) | Late Initiators vs Continuously Adherent Patients (Group 2 [n=2,639] vs Group 4 [n=13,976]) | Early Discontinuers vs Continuously Adherent Patients (Group 3 [n=3,010] vs Group 4 [n=13,976]) |
| Age (y)                   | 65–74                     | <65                                    | 0.85 (0.76, 0.94)* | 0.85 (0.73, 1.07) | 1.05 (0.85, 1.23) |
|                           | 74                        | >74                                    | 0.85 (0.77, 0.98)* | 0.85 (0.69, 1.04) | 0.95 (0.73, 1.10) |
| Sex                       | Female                    | Male                                   | 1.15 (1.09, 1.22)* | 1.15 (1.06, 1.30)* | 0.85 (0.78, 0.94)* |
| Race                      | Black                     | White                                  | 1.35 (1.17, 1.44)* | 1.35 (1.14, 1.59)* | 1.45 (1.25, 1.72)* |
|                           | Hispanic                  | 1.25 (0.99, 1.49)                      | 1.05 (0.73, 1.55) | 1.05 (0.74, 1.51) |
|                           | Other                     | 1.15 (1.05, 1.34)*                     | 0.95 (0.73, 1.18) | 0.95 (0.79, 1.21) |
| Socioeconomic status      | Low-income subsidy        | No low-income subsidy                  | 1.15 (1.11, 1.25)* | 1.05 (0.96, 1.20) | 1.05 (0.95, 1.17) |
| Region                    | Midwest                   | Northeast                              | 0.95 (0.88, 1.01) | 0.95 (0.81, 1.04) | 1.15 (1.00, 1.26) |
|                           | Southeast                 | 1.15 (1.08, 1.23)*                     | 1.25 (1.09, 1.37)* | 1.25 (1.13, 1.42)* |
|                           | SouthWest                 | 1.35 (1.21, 1.47)*                     | 1.35 (1.13, 1.56)* | 1.35 (1.17, 1.62)* |
|                           | West                      | 1.25 (1.15, 1.35)*                     | 1.05 (0.88, 1.18) | 1.35 (1.18, 1.55)* |
| CHADS2-VASc Score         | 3–4                       | 0–2                                    | 0.75 (0.71, 0.86)* | 0.85 (0.71, 1.01) | 0.95 (0.81, 1.12) |
|                           | ≥5                        |                                        | 0.85 (0.74, 0.98)* | 0.85 (0.67, 1.12) | 1.15 (0.87, 1.41) |
| HAS-BLED Score            | 2–3                       | 0–1                                    | 1.15 (0.99, 1.29) | 1.15 (0.88, 1.39) | 1.35 (1.03, 1.64)* |
|                           | ≥4                        |                                        | 1.35 (1.14, 1.62)* | 1.55 (1.11, 2.05)* | 1.35 (1.01, 1.84)* |
| History of               | AMI                       | No history of the disease               | 1.25 (1.15, 1.40)* | 1.25 (1.05, 1.48)* | 1.25 (1.06, 1.46)* |
|                           | Alzheimer disease or dementia |                                      | 1.95 (1.82, 2.10)* | 1.15 (1.00, 1.32) | 1.15 (1.02, 1.33)* |
|                           | Chronic kidney disease    | 1.15 (1.09, 1.24)*                     | 1.15 (0.98, 1.23) | 1.05 (0.94, 1.17) |
|                           | Heart failure             | 0.95 (0.86, 0.97)*                     | 1.05 (0.93, 1.15) | 1.05 (0.94, 1.15) |
|                           | Diabetes mellitus         | 0.85 (0.82, 0.93)*                     | 1.05 (0.98, 1.21) | 1.05 (0.95, 1.16) |
|                           | Hypertension              | 1.05 (0.89, 1.14)                      | 0.75 (0.61, 0.93)* | 0.97 (0.79, 1.20) |
|                           | Stroke or TIA             | 0.75 (0.68, 0.80)*                     | 0.85 (0.73, 0.98)* | 0.75 (0.65, 0.87)* |
|                           | Recent bleeding           | 1.25 (1.14, 1.32)*                     | 1.05 (0.96, 1.24) | 1.15 (1.03, 1.32)* |
|                           | Recent antiplatelet use    | 1.25 (1.17, 1.37)*                     | 0.95 (0.84, 1.12) | 1.05 (0.89, 1.18) |

Results from a multinomial logistic regression model whose outcome was trajectory group (group 4 set as reference) and predictors included all covariates listed in Table 1. Stepwise procedure was used to select predictors, using P value for entry=0.3 and P value for removal=0.1. The reference for each selected covariate is presented on the first column of the table. AMI indicates acute myocardial infarction; TIA, transient ischemic attack.
*Indicates statistically significant results.
Clinical Characteristics. Higher risk of stroke, as measured by CHA2DS2-VASc score, was associated with lower odds of not using OAC (OR 0.75; 95% CI, 0.71–0.69 for CHA2DS2-VASc 3–4, and 0.85; 95% CI, 0.74–0.98 for CHA2DS2-VASc ≥5, both compared with CHA2DS2-VASc ≤2). However, CHA2DS2-VASc was not significantly associated with early discontinuation or late initiation. In contrast, higher risk of bleeding, as measured by HAS-BLED score ≥4, was associated with a higher likelihood of not using OAC (OR 1.35; 95% CI, 1.14–1.62), of late initiation (OR 1.55; 95% CI, 1.11–2.05), and of early discontinuation (OR 1.35; 95% CI, 1.01–1.84), compared with HAS-BLED ≤1.

A history of AMI was associated with a higher likelihood of not using OAC (OR 1.25; 95% CI, 1.15–1.40), of late initiation (OR 1.25; 95% CI, 1.05–1.48), and of early discontinuation (1.25; 95% CI, 1.06–1.46). In addition, Alzheimer disease or other dementia, chronic kidney disease, a history of recent bleeding and antiplatelet use were all associated with increased odds of not using OAC. The magnitude of the association was particularly strong for Alzheimer disease or other dementia (OR 1.95; 95% CI, 1.82–2.10). Additionally, Alzheimer disease or other dementia was also associated with an increased likelihood of early discontinuation (OR 1.15; 95% CI, 1.02–1.33). Finally, a history of stroke or transient ischemic attack decreased the likelihood of not using OAC (OR 0.75; 95% CI, 0.68–0.80), of late initiation (OR 0.85, 95% CI, 0.73–0.98), and of early discontinuation (OR 0.75; 95% CI, 0.65–0.87).

Discussion

To our knowledge, our study is the first to use a nationally representative sample of Medicare beneficiaries to study longitudinal patterns of OAC adherence after first AF diagnosis. Our study yielded 3 main findings: First, we identified 4 main trajectories of OAC adherence in the first year after AF diagnosis. Only 44% of patients were continuously adherent to therapy in the first year, with 40% never initiating therapy, 9% discontinuing early, and 8% initiating late. Second, in addition to clinical characteristics, demographics, socioeconomic factors, and region of residence were important predictors of membership into adherence trajectories. Third, important predictors such as sex, race, region, or risk of bleeding not only affected the odds of OAC use, but were also associated with the timing of OAC initiation and the likelihood of discontinuation.

Our estimates for the rates of OAC initiation are in line with a prior body of literature that showed that only around 50% to 60% of newly diagnosed AF patients initiate OAC in the United States.19–22 In addition, our findings for the association between patient characteristics and membership in adherence trajectory groups are consistent with a prior study from the Veterans Health Administration that found that older age, male sex, white race, and higher CHA2DS2-VASc score all increased the odds of OAC adherence.28 Our results are consistent as well with prior observations that Medicare patients with AF living in the Southern United States are less likely to initiate OAC.20

Nevertheless, our study is an important contribution to the existing literature because instead of capturing adherence using a single measure of PDC, it leveraged advanced models to identify longitudinal patterns of OAC adherence over time. In doing so, we demonstrated that some important predictors of OAC use such as sex, black race, region of residence, HAS-BLED score, and a history of stroke or transient ischemic attack not only affect the initiation of OAC, but also the timing of the initiation and the likelihood of discontinuation. This is important because, in our study, late initiators and early discontinuers accounted for a nonnegligible fraction of newly diagnosed AF patients, and because continuous adherence to OAC is crucial in stroke prevention.5,14 In fact, recent evidence has shown that thromboembolic risk is significantly higher in the first month after AF diagnosis than subsequently,51 and prior research associated a gap in OAC therapy of 1 to 3 months with 96% increased risk of stroke in AF patients at high risk of stroke, which would characterize the majority of our study sample.28

Because our findings demonstrate that suboptimal OAC adherence is not only a product of intermittent gaps in therapy, but also a product of lack of OAC initiation, of late initiation, and of discontinuation of therapy among initiators, interventions designed to improve OAC use and adherence should address each of these underlying reasons. Given the lack of success of most prior interventions attempting to mitigate OAC underuse and suboptimal adherence, and because of the cost-saving potential of OAC in the prevention of stroke, the implementation of payment models that incentivize OAC use has recently been proposed as one of the strategies most likely to mitigate OAC underuse.52,53 In fact, the Pharmacy Quality Alliance recently endorsed the inclusion of adherence to DOACs in the calculation of Medicare star ratings.54 This measure, however, would unlikely mitigate the lack of initiation of OAC or suboptimal adherence to warfarin therapy. The development of more comprehensive quality measures that not only capture adherence among patients using OAC, but also the proportion of nontreated patients, would be more powerful in mitigating OAC underuse. For example, a quality measure to be included in calculations of payments to both payers and providers could reflect the proportion of patients who have ≥80% PDC with OAC among all AF patients with CHA2DS2-VASC ≥2 and no contraindications for OAC therapy.

Additionally, our study explored the association between OAC adherence and a comprehensive list of patient characteristics, demographics, socioeconomic factors, and region of residence. We found associations with all of these factors. For example, older patients were more likely to initiate OAC,20 and patients with a history of AMI were more likely to initiate OAC.20 Our estimates for the rates of OAC initiation are in line with a prior body of literature that showed that only around 50% to 60% of newly diagnosed AF patients initiate OAC in the United States.19–22 In addition, our findings for the association between patient characteristics and membership in adherence trajectory groups are consistent with a prior study from the Veterans Health Administration that found that older age, male sex, white race, and higher CHA2DS2-VASc score all increased the odds of OAC adherence.28 Our results are consistent as well with prior observations that Medicare patients with AF living in the Southern United States are less likely to initiate OAC.20

Nevertheless, our study is an important contribution to the existing literature because instead of capturing adherence using a single measure of PDC, it leveraged advanced models to identify longitudinal patterns of OAC adherence over time. In doing so, we demonstrated that some important predictors of OAC use such as sex, black race, region of residence, HAS-BLED score, and a history of stroke or transient ischemic attack not only affect the initiation of OAC, but also the timing of the initiation and the likelihood of discontinuation. This is important because, in our study, late initiators and early discontinuers accounted for a nonnegligible fraction of newly diagnosed AF patients, and because continuous adherence to OAC is crucial in stroke prevention.5,14 In fact, recent evidence has shown that thromboembolic risk is significantly higher in the first month after AF diagnosis than subsequently,51 and prior research associated a gap in OAC therapy of 1 to 3 months with 96% increased risk of stroke in AF patients at high risk of stroke, which would characterize the majority of our study sample.28

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characteristics, which included factors not captured in prior research, such as socioeconomic score, measures of segregation, and region of residence. We found that adherence trajectory group membership was impacted by receipt of subsidies and region of residence, but not by socioeconomic score or measures of segregation. The lack of significant association between adherence and measures of segregation is interesting, because of the strong impact of black race on trajectory group membership.

Not surprisingly, patients with risk factors for stroke were more likely to initiate and adhere to OAC. However, we observed that patients with a history of AMI were less likely to initiate OAC, which is consistent with prior literature. Patients with a history of AMI may be less likely to use OAC because of the perceived risk of bleeding with concurrent anticoagulant and antiplatelet therapy. Although we captured prescription claims for antiplatelets, claims data do not contain information on prescriptions filled over-the-counter, including aspirin. In light of the recent evidence supporting that the risk of stroke post-AMI may be higher than originally thought, future research should evaluate patterns of OAC and antiplatelet use in AF patients with a history of AMI, particularly in the first months after AMI.

Our study is subject to several limitations. First, our analyses did not explore reasons behind OAC discontinuation or the consequences of discontinuation. With group-based trajectory models, it was not possible to model whether having a bleeding event after OAC initiation increased the odds of discontinuation. This could have certainly been the case, since we observed that 23.8% of the patients who discontinue OAC treatment had a bleeding event around the time of discontinuation. In future analyses, we intend to simultaneously model OAC adherence trajectories and outcomes, using advanced techniques such as joint latent class mixed models. Second, claims data do not contain certain pieces of information about prescriptions that are relevant for adherence measurement. For example, they do not contain information on whether patients take the medications they fill, and they cannot differentiate whether behaviors such as discontinuation reflect prescriber or patient decision making. Additionally, claims data do not capture prescriptions paid with cash, and thus our estimates could underestimate the proportion of OAC initiators, particularly because of the possibility to purchase warfarin through $4 generic programs. In addition, we have no information on free samples, and some individuals who appear as late initiators may in fact be continuous adherers who start therapy using free samples for a few weeks’ worth supply and thus not show up in claims until later. Third, we did not limit the analyses to patients with CHA2DS2-VASc ≥2, who are recommended for OAC under the American College of Cardiology/American Heart Association/American Heart Rhythm Society, because patients with CHA2DS2-VASc <2 represented only 4% of the study sample. Fourth, in our analyses, we grouped warfarin and DOAC use together. Whereas adherence patterns to DOACs and warfarin may vary, it is reasonable to group them for the study of suboptimal OAC use and adherence, given that the differences in the comparative effectiveness of these agents are of a considerably smaller magnitude than the difference in stroke risk with and without OAC. Finally, our results are not generalizable to patients who died soon after AF diagnosis or to those enrolled in Medicare Advantage prescription drug plans or intermittently enrolled in stand-alone plans, because they were excluded from analyses, since group-based trajectory models cannot handle data not missing at random. Excluded patients were generally older and more likely to have CHA2DS2-VASc ≥5. As a result, our included sample is overrepresentative of healthier and younger patients.

In conclusion, applying group-based trajectory models to Medicare claims data on newly diagnosed AF patients, we described 4 trajectories of adherence to OAC, and observed that <45% of newly diagnosed AF patients belonged to the trajectory group characterized by continuous OAC adherence. Trajectories of OAC adherence were associated not only with demographics and clinical characteristics, but also with regional factors. Some predictors of OAC use were also associated with the timing of the OAC initiation and the likelihood of discontinuation.

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Supplemental Material
Data S1.

Supplemental Methods

Definition of Covariates

To calculate the CHA2DS2-VASc score, female sex, age between 65 and 74, congestive heart failure, hypertension history, vascular disease history and diabetes mellitus are assigned one point, and age of 75 or older and a history of previous stroke, transient ischemic attack or thromboembolism are assigned two points. Congestive heart failure, hypertension, diabetes, and a history of stroke or transient ischemic attack were defined using the CMS Chronic Condition Warehouse definitions. Vascular disease was defined using the CMS Chronic Condition Warehouse definition of acute myocardial infarction, and the diagnosis codes listed in Table S1 for peripheral vascular disease.

In calculating the HAS-BLED score, age of 65 or greater, labile INR, renal disease, liver disease, use of antiplatelet agents or of nonsteroidal anti-inflammatory drugs (NSAIDs), and a history of hypertension, of stroke, of major bleeding and of alcohol or drug use disorder are all assigned one point. Because claims data does not contain information on INR, the HAS-BLED score was calculated as the sum of all previous factors except labile INR. Renal disease, hypertension, and a history of stroke were defined using the CMS Chronic Condition Warehouse definitions. Liver disease and alcohol or drug use disorder were defined using the diagnosis codes listed in Table S1.

A history of recent bleeding was defined as having a claim with ICD-9 or ICD-10 codes for bleeding events in the year before index date (list of codes for bleeding events in Table S1).
Recent antiplatelet use was defined as filling a prescription for aspirin, clopidogrel, prasugrel, dipyridamol, ticlopidine or ticagrelor in the six months before index date.4-10

Recent NSAID use was defined as filling a prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid or indomethacin in the six months before index date.4-10
| Covariate                  | ICD-9 Codes                      | ICD-10 Codes                      |
|---------------------------|----------------------------------|-----------------------------------|
| Valvular Disease          | 394.0, V43.3                     | I05.0, Z95.2                      |
|                           | 440.0x, 440.2x, 440.9x, 441.3x,  | I70.0, I70.2, I70.9, I71.3, I71.4,|
|                           | 441.4x, 441.5x, 441.9x, 443.9x,  | I71.8, I71.9, I73.9, I74.3, I74.5,|
|                           | 444.22, 444.81, 447.1x, 443.81,  | I77.1, I79.8, E11.51, I65.2, I63.03,|
|                           | 250.70, 433.10, 433.11, 433.30   | I63.13, I63.23, I65.8             |
| Peripheral Vascular Disease | 571.xx                           | K70, K71, K72, K73, K74, K75, K76,|
| Liver Disease             | 303.xx, 304.xx, 305.xx            | F10, F11, F12, F13, F14, F15, F16,|
|                           |                                  | F17, F18, F19                      |
| Alcohol or Drug Use Disorder |                                 | F10, F11, F12, F13, F14, F15, F16,|
|                           |                                  | F17, F18, F19                      |
| Bleeding events           |                                  |                                   |
| Intracranial Bleeding     | 430, 431, 432                    | I60, I61, I62                     |
| Hemoperitoneum            | 568.81                           | K66.1                             |
| Hematuria                 | 599.7                            | R31                               |
|                           | 530.7, 531.0, 531.2, 531.4, 531.6, | K22.6, K25.0, K25.2, K25.4, K25.6,|
|                           | 532.0, 532.2, 532.4, 533.0, 533.2, | K26.0, K26.2, K26.4, K26.6, K27.0,|
|                           | 533.6, 534.0, 534.2, 534.4, 534.6, | K27.2, K28.0, K28.2, K28.4, K28.6,|
|                           | 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.85, 578 | K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K55.21, K92.0, K92.1, K92.2 |
| Gastrointestinal Hemorrhage |                                 |                                   |
| Epistaxis                 | 784.7                            | R04.0                             |
| Hemoptysis                | 786.3                            | R04.2                             |
| Vaginal Hemorrhage        | 626.2                            | N92.0                             |
| Hemarthrosis              | 719.1                            | M25.0, M12.2                      |
| Conjunctival Hemorrhage   | 372.72                           | H11.33                            |
| Not Otherwise Specified Hemorrhage | 459                       | R58                                |

ICD-9=International Classification of Diseases, Ninth Revision Codes; ICD-10=International Classification of Diseases, Tenth Revision Codes.
Table S2. Comparison of Selected Baseline Characteristics between the Study Participants and Beneficiaries Excluded from the Study Because of Death within 12 months of Atrial Fibrillation Diagnosis.

| Variable-n(%)         | Included in the Sample (n=24,898) | Excluded Due to Death (n=9,116) | P-value |
|-----------------------|-----------------------------------|---------------------------------|---------|
| Age                   |                                    |                                 | <0.001  |
| <65                   | 2821 (8.1)                        | 629 (6.9)                       |         |
| 65-74                 | 13817 (39.6)                      | 1978 (21.7)                     |         |
| >=75                  | 18260 (52.3)                      | 6509 (71.4)                     |         |
| Female sex            | 19376 (55.5)                      | 5494 (60.3)                     | <0.001  |
| Race                  |                                    |                                 | <0.001  |
| White                 | 30460 (87.3)                      | 7730 (84.8)                     |         |
| Black                 | 2472 (7.1)                        | 919 (10.1)                      |         |
| Hispanic              | 523 (1.5)                         | 152 (1.7)                       |         |
| Other                 | 1443 (4.1)                        | 315 (3.5)                       |         |
| Eligibility for Medicaid | 8634 (24.7)                      | 3523 (38.6)                     | <0.001  |
| CHA2DS2-VASc score    |                                    |                                 | <0.001  |
| 0-2                   | 5608 (16.1)                       | 457 (5.0)                       |         |
| 3-4                   | 12999 (37.2)                      | 2316 (25.4)                     |         |
| ≥5                    | 16291 (46.7)                      | 6343 (69.6)                     |         |
| HAS-BLED score        |                                    |                                 | <0.001  |
| 0-1                   | 3675 (10.5)                       | 349 (3.8)                       |         |
| 2-3                   | 22248 (63.8)                      | 4691 (51.5)                     |         |
| ≥4                    | 8975 (25.7)                       | 4076 (44.7)                     |         |
| Stroke or TIA         | 7131 (20.4)                       | 2719 (29.8)                     | <0.001  |

TIA= Transient Ischemic Attack.

The table compares selected baseline characteristics between patients included in the study and those that were excluded because they died within 12 months of atrial fibrillation diagnosis. Excluded patients were generally older and more likely to have CHA2DS2-VASc≥5. Consequently, our sample is over representative of healthier and younger patients.
Table S3. Group-based Trajectory Model Diagnostics.

| Group   | Average Posterior Probability | Odds of Correct Classification | Estimated Probability of Group Membership | Proportion Classified in Group |
|---------|-------------------------------|--------------------------------|-------------------------------------------|------------------------------|
| Group 1 | 0.9953                        | 634                            | 0.4368                                    | 0.4376                       |
| Group 2 | 0.9495                        | 56                             | 0.0763                                    | 0.0756                       |
| Group 3 | 0.9706                        | 99                             | 0.0869                                    | 0.0863                       |
| Group 4 | 0.9888                        | 265                            | 0.4000                                    | 0.4005                       |
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