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Joint Latent Class Analysis of Oral Anticoagulation Use and Risk of Stroke or Systemic Thromboembolism in Patients with Atrial Fibrillation

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Abstract

Background—Oral anticoagulation (OAC) is recommended to reduce the risk of stroke or systemic thromboembolism (TE) in atrial fibrillation (AF). In this study, we applied novel joint latent class mixed models to identify heterogeneous patterns of trajectories of OAC use and to determine how these trajectories are associated with risks of thromboembolic outcomes.

Methods and Results—We used 2013–2016 claims data from a 5% random sample of Medicare beneficiaries obtained from the Centers for Medicare and Medicaid Services. Our study sample included 16,399 patients newly diagnosed with AF in 2014–2015 and who were followed for 12 months after first AF diagnosis and filled at least one OAC prescription in this time period. OAC use was defined as number of days covered with OAC every 30-day interval after first AF diagnosis. We used a joint latent class mixed model to simultaneously evaluate the longitudinal patterns of OAC use and time to stroke or TE while adjusting for age, race, CHAD2S2-VASc and HAS-BLED score.

Five classes of OAC use patterns were identified: late users (17.8%); late initiators (12.5%); early discontinuers (18.6%); late discontinuers (15.4%); and continuous users (35.6%). Compared to continuous users, risk of stroke or TE was higher for participants in late initiators (HR=1.73, 95%CI: 1.49, 2.01) and late discontinuers (HR=1.23, 95%CI: 1.04, 1.45).

Conclusion—Late initiators and late discontinuers had higher risk of stroke or TE than continuous users. Early initiation and continuous OAC use is important in preventing stroke and TE among patients diagnosed with AF.

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Code Availability: Code can be made available upon request to the corresponding author.

Keywords

Oral Anticoagulation; Stroke; ischemic; Thromboembolism

Subject terms

Atrial Fibrillation; Ischemic Stroke; Anticoagulants; Epidemiology

Background

Atrial fibrillation (AF) is associated with a 5-fold increase in the risk of stroke or systemic thromboembolism (TE).⁽¹⁾ Oral anticoagulants (OAC) are recommended for stroke or TE prevention in patients with atrial fibrillation (AF) and a moderate or high risk of stroke or TE, which is defined by professional society guidelines as CHA₂DS₂-VASc ≥ 2 for men and CHA₂DS₂-VASc ≥ 3 for women.^(2, 3) However, approximately 50% of patients who have atrial fibrillation and meet guideline requirements for OAC use do not receive this therapy.^(4–6) A multitude of studies have tested the association between OAC use and risk of stroke or TE, finding that OAC use is highly effective, reducing the risk of stroke by 64–83%.⁽⁷⁾ However, most prior studies defined OAC use as a binary variable—whether OAC use was used or not at some point of the study period. This binary definition masks important differences in the underlying patterns of OAC use over time. This definition is important because continuous OAC use is crucial in stroke and TE prevention—a single missed DOAC use is associated with increased risk of stroke and TE.^(8–10) To overcome this limitation, we previously examined the association between OAC use and risk of stroke or TE using time-dependent variables, which captured OAC use in a 30-day time window.⁽⁴⁾ However, this approach is not able to differentiate between underuse of OAC due to lack of initiation, due to early discontinuation, or to low adherence while on therapy.

To fill this evidence gap, we identified trajectories of OAC use over time among OAC users and tested the association between these trajectories and thromboembolic outcomes using novel joint latent class mixed models. We hypothesized that different longitudinal patterns of OAC use would be identified, and they would be associated with time to stroke or TE.

Methods

Study population

We used 2013–2016 claims data from a 5% random sample of US Medicare beneficiaries obtained from the Centers for Medicare and Medicaid Services (CMS). Inclusion in the random sample is based on the last two digits of their Medicare Claim Account Numbers. Claims data included demographics, Chronic Conditions Data Warehouse (CCW) indicators and dates of first occurrence of chronic conditions, generic name, days of supply, and date of fill of pharmacy claims, and International Classification of Diseases (ICD)-9 and -10 diagnosis codes and dates of service for medical claims. This study was approved by the Institutional Review Board of the University of Pittsburgh as exempt.

Inclusion criteria is a diagnosis with AF in 2014–2015, based on the Centers for Medicare and Medicaid Services (CMS) CCW definition of AF as having one inpatient claim or two outpatient claims with ICD-9 diagnosis code 427.31.(11) This CCW indicator of AF tracks the first diagnosis of AF to 1999. We applied seven exclusion criteria (Supplemental Figure S1). First, we excluded patients with a diagnosis of valvular disease in the year before index date. Second, we excluded patients with CHA₂DS₂-VASc score < 2, because they were not recommended for OAC at the time of the study.(12) Third, to be able to define OAC use in the first 30-day period for the totality of the study sample, we excluded patients with follow-up shorter than 30 days. Fourth, we excluded patients who were not continuously enrolled in Medicare Part D Stand Alone Prescription Drug Plans for at least 12 months before AF diagnosis, because we would not have complete prescription information for them. Fifth, to make sure that our sample was representative of patients who ever used OAC, we excluded those who did not fill any prescription for OAC in the year after first AF diagnosis before death or disenrollment from Stand Alone Prescription Drug Plans. Sixth, patients who had missing values for any covariate included in the study were excluded from the analysis. Finally, patients who took both warfarin and direct oral anticoagulants (DOACs) during the study period were excluded, since the potential overlapping days with supply of both medications could not have been controlled for. Finally, because some patients were diagnosed with AF for the first time when they had a stroke, we excluded patients who had a stroke or thromboembolic event within 30 days after AF diagnosis to reduce selection bias. The final study sample was followed for 12 months from date of AF diagnosis, until event of stroke or TE, or disenrollment from Stand Alone Prescription Drug Plans, or death, whichever happened first.

Exposure

Our exposure is trajectory of OAC use, defined as the proportion of days covered with OAC every 30-day interval after first AF diagnosis among patients who filled at least one OAC prescription in the first year after AF diagnosis. We extracted prescriptions for warfarin or DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban after AF diagnosis for each participant. Using the dates of fill and days of supply in each prescription, we calculated the proportion of days covered with OAC every 30 days during follow-up. To stabilize the variance of the measure, the proportion of days covered variable was transformed by taking the arcsine of the square root.(13)

The joint latent class mixed model was used for clustering participants with different patterns of OAC use and stroke or TE events into different groups. A total of 5 groups of OAC use patterns were identified. We treated the continuous users group as the reference group.

Outcome

Our outcome was the composite of stroke and TE during the 12 months after diagnosis of AF. Stroke was defined using the CMS CCW definition.(11) TE was defined as having an inpatient claim with ICD-9 of or ICD –10 code of TE after AF diagnosis (list of codes in Supplemental table S1).

Covariates

Demographics included age, gender, and race were obtained directly from the data source. Socioeconomic variables included eligibility for Medicaid coverage and low-income subsidy (measured at the patient level), as well as socioeconomic score (measured at the zip code level), and index of dissimilarity (measured at the Metropolitan Statistical Area level). The socioeconomic score and the index of dissimilarity were derived by linking the database with American Community Survey data obtained from the US Census Bureau using the zip code. Briefly, the socioeconomic score presents combined z scores of identified key census variables. The index of dissimilarity represents the fraction of blacks or whites who would have to move to a different neighborhood to achieve perfect integration. Methods used to calculate socioeconomic scores and index of dissimilarity have been previously described.(14–16) Clinical variables include CHAD₂S₂-VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) and HAS-BLED scores (hypertension, abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, elderly, concomitant drugs and/or alcohol excess), (17, 18) diagnoses of Alzheimer's disease or dementia, use of antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, or dipyridamole), and use of antiarrhythmic medications. Clinical characteristics were defined based on 12 months of claims data before AF diagnosis or CCW definitions. The algorithms and codes to define clinical variables are summarized in Supplemental table S1.

Statistical Analysis

We used the joint latent class mixed model to model simultaneously the clustering, the class-specific longitudinal pattern of OAC use, and time to stroke or TE. The joint latent class mixed model is composed of three sub models, including a multinomial logistic model for clustering, class-specific linear mixed models for the longitudinal “exposure” outcome (i.e. proportion of days covered with OAC in this case), and class-specific proportional hazard models for the time-to-event outcome (i.e. time to stroke or TE).(19) Maximum likelihood estimates of entire vector of parameters for the three sub models were obtained using an extended Marquardt algorithm from the Newton-Raphson family.(20) We included polynomial functions of time variable with up to fourth degree in the clustering and class-specific linear mixed models. The class-specific linear mixed models and the proportional hazard models include adjustment for age, race, CHAD₂S₂-VASc and HAS-BLED scores. Weibull function was used to describe the baseline hazards and baseline hazard in each latent group were set to be proportional. We evaluated the performance of models with 2–5 groups and selected the optimal number of groups based on goodness-of-fit, which was determined based on the Bayesian information criterion (BIC). Models with number of groups greater than 5 failed to converge, possibly because some of the groups were not distinguishable. We also evaluated the posterior class-membership probabilities for each model, which were computed using the Bayes theorem, given the longitudinal OAC use, the latent class information, and time-to stroke or TE of each participant obtained from the model.(19) The modeling process was conducted using the lcmm CRAN package in R software. Details of the package have been previously reported.(21)

Baseline characteristics stratified by OAC classes are summarized with number (%) for categorical variables and mean (standard deviation) for continuous variables. We reported the number of events by each class and also the rate of events per 100 person-years during the 12-month period following diagnosis for AF. Although the outcome of the joint latent class mixed model was the composite of stroke and TE, we also reported rates of death and bleeding events (definition in Supplemental table S1) to illustrate the incidence of other relevant events experienced by the sample.

The group-specific OAC use patterns were generated by plotting means of OAC coverage proportions every 30-day by groups. Kaplan-Meier curves were generated for each class. All the analyses were conducted in R software.

Results

We identified 72,306 patients newly diagnosed with AF in 2014–2015. After the application of inclusion and exclusion criteria, the final study sample included 16,399 participants. (Supplemental Figure S1). About 1% of participants were lost to follow-up each month, and 11.8% of participants in our study were not followed up until 12 months (Supplemental Table S2).

The average age of participants was 76.4 (standard deviation=9). Out of the 16,399 participants, 6,970 (42%) were male, and 1,4545 (89%) were white. The average CHAD2S2-VASc score is 4.71 (standard deviation=1.7). The average HAS-BLED score is 2.93 (standard deviation=1.0). (Table 1)

3.1 Clustering

We selected the model with 5 groups as our final model, which has the lowest BIC among all the models fitted (Supplemental Table S3). More than 70% of individuals had posterior classification probabilities >70% for each group.

Five latent classes of participants were identified (Figure 1). The characteristics of these groups were summarized based on their longitudinal OAC use, including patients who initiated therapy at months 1–4 with optimal OAC use after month 4 (class 1, “late users”, n=2,926, 17.8%); patients who initiated therapy at months 4–10 (class 2, “late initiators”, n=2,053, 12.5%); patients who discontinued therapy at months 1–5 (class 3, “early discontinuers”, n=3,055, 18.6%); or at months 5–10 (class 4, “late discontinuers”, n=2,526, 15.4%); and continuous users (class 5, “users”, n=5,839, 35.6%).

3.2 Baseline Characteristics by Classes

The distribution of age was similar in the five OAC use groups with an average age close to 76 years (SD=9) in each group (Table 1). Overall, 43% of the participants were male, and 89% of them were white. The proportion of males was higher in the early discontinuers class. Late initiators and early discontinuers were more likely to be eligible for Medicaid coverage and low-income subsidy. Patients who were late users (class 1) and continuous users (class 5) had a lower prevalence of chronic conditions. CHAD2S2-VASc score was slightly higher in late initiators and late discontinuers classes. Proportions of participants

using antiplatelet were similar across groups. Proportions of antiarrhythmic medication use were slightly lower among late users (class 1) and late initiators (class 2).

3.3 Risk of outcomes by classes

The survival course after AF diagnosis is presented by class as Kaplan-Meier curves in Figure 2. The unadjusted rate of stroke or TE was higher in late initiators (rate=21.4 per 100 person-years) and late discontinuers (rate=14.8 per 100 person-years) than the other groups (Table 2). In addition, the incidence rate of bleeding was higher in late initiators (38.0 per 100 person-years), early discontinuers (40.3 per 100 person-years), and late discontinuers (41.6 per 100 person-years), than the other two groups (Supplemental Table S5). Similarly, the highest rate of mortality was observed among late initiators (14.1 per 100 person-years), followed by early discontinuers (12.7 per 100 person-years), late discontinuers (12.6 per 100 person-years), late users (7.8 per 100 person-years), and continuous users (6.1 per 100 person-years). Continuous users had the lowest unadjusted rate of stroke or TE, bleeding, and death outcomes. (Table 2, supplemental table S5)

Results of the proportional hazard models adjusted for age, race, CHAD2S2-VASc score and HAS-BLED score are presented in Figure 3. Compared to continuous users, risk of stroke or TE was higher for participants in late initiators (HR=1.73, 95%CI: 1.49, 2.01) and late discontinuers (HR=1.23, 95%CI: 1.04, 1.45) classes. The hazards of stroke or TE did not differ between continuous users and late users (HR=1.05, 95%CI: 0.88, 1.25) and early discontinuers (HR=1.07, 95%CI: 0.92, 1.25). In addition, black race (HR=1.41, 95%CI: 1.21, 1.63), higher CHAD2S2-VASc score (HR per unit increase=1.28, 95%CI: 1.23, 1.32), and higher HAS-BLED score (HR per unit increase=1.23, 95%CI: 1.17, 1.29) were associated with higher hazards of stroke or TE.

Discussion

To our knowledge, our study is the first to leverage novel joint latent class mixed models to simultaneously identify trajectories of medication use and test their association with clinical outcomes. We identified five latent classes of trajectories of OAC use that are associated with risk of stroke or TE among Medicare beneficiaries newly diagnosed with AF who initiated treatment with OAC. These included patients who were continuous users after month 4, late initiators, early discontinuers, late discontinuers, and continuous users. Risk of stroke or TE was higher among late initiators and late discontinuers compared to continuous users.

Different trajectory patterns of OAC use were identified among suboptimal users, including late initiation and discontinuation. Initiation on months 4–10 after diagnosis was associated with a 73% elevated risk of stroke or TE compared to continuous users after adjusting for age, race, CHAD2S2-VASc score and HAS-BLED score. However, the risk of stroke or TE among those who initiated therapy at months 1–4 was similar to continuous users. This might indicate that patients used samples in the first months after diagnosis, which would not be captured in claims data. Discontinuation at months 5–10 after diagnosis was associated with a 23% higher risk of stroke or TE than continuous users. However, we observed similar risk among participants who discontinued therapy at months 1–5 and

continuous users. This may be due to competing risks of other adverse events, suggested by higher rates of bleeding and death among this group than continuous users (Supplemental table S5).

Reasons for suboptimal use of OAC among patients diagnosed with AF could be limitations related to warfarin therapy, including requirement of intense monitoring and difficulty in management, or costs of DOACs.(22) Consistent with the literature, factors associated with suboptimal OAC use included female sex, black race, eligibility for Medicaid and income subsidy, not residing in the Northeast, lower CHA2DS2-VASc score, and higher HAS-BLED score.(5, 22)

Our results are consistent with previous studies evaluating patterns of OAC use and the association between OAC use and risk of stroke or TE.(4) Prior studies evaluating OAC use found that around 40%–50% of OAC initiation had 80% days covered by OAC in the first year after AF diagnosis.(23) In our study, a slightly lower percentage (35.6%) of participants who initiated OAC were categorized as continuous users. The difference in estimates could be due to the use of a stricter definition of continuous users, since this trajectory had on average 88% of days covered with OAC throughout follow-up (Supplemental table S4).

Prior studies testing the association between OAC use and outcomes treated OAC use as a time-dependent variable or as proportion of days covered during follow-up.(4, 23, 24) However, these approaches do not account for the underlying patterns of OAC use. By assuming heterogeneity of both OAC use trajectory patterns and time to stroke or TE, we are able to identify latent classes of participants with distinct patterns and compare survival outcomes of stroke or TE across classes, while keep the interpretation relatively easy. Our model produced a good fit to the data for trajectory of OAC use and time to stroke or TE. Models with variant number of latent classes were conducted. The BIC criterion indicates that the model with 5 classes had the best goodness-of-fit among all models fitted with 2–5 classes. This suggests that there is heterogeneity in OAC use and risk of stroke or TE among participants. Most of the participants had posterior classification probability greater than 70%, which is considered as a good discrimination between latent classes.(25)

By jointly modeling the longitudinal use of OAC among initiators and survival of stroke or TE, we were able to compare the risk of stroke or TE across classes of different longitudinal patterns of OAC use. Joint latent class mixed model assumes heterogeneity of the study sample and assigns participants into latent classes, allowing for pattern-wise analyses based on the OAC use and risk of stroke or TE. As an extension of the mixed model, the joint latent class mixed model also allows for drop-out during follow-up and incomplete data of participants, so that selection bias due to missing data is minimized.

4.1 Limitations

Our study is subject to several limitations. First, our dataset only includes records for filling of prescriptions, so we were unable to tell whether participants actually took the medications as prescribed. In addition, prescriptions paid with cash were not captured. The evaluations of the exposure could be an underestimate of the actual prescription of OAC. Second, there could be selection bias if those who drop out from the study during follow-up were different

from those remain in the study until 12 months. However, the bias is likely to be limited as only a small proportion of participants (11.8%) in our study were not followed up for 12 months, and mixed models can handle data missing at random. Third, the interpretation of our results may be limited by competing risks of other outcomes, particularly, death. Fourth, because of the computational burden, limited number of covariates were included in our model, and thus, the results could still be subject to confounding due to unobserved effects. However, the bias due to confounding issue is likely to be limited because of relatively balanced profile across latent classes in terms of the characteristics measured at baseline, and adjustment for the major risk factors for thromboembolic events. Fifth, we did not assess the use of warfarin and DOACs on risk of stroke and TE separately, even though the risk of stroke or TE associated with patterns of warfarin or DOAC use could be different. Finally, our results need to be interpreted with caution as analyses are data driven without further verification, and thus findings could be affected by artifacts.⁽²⁵⁾ Instead of evaluating the effect of OAC use on stroke or TE outcome under hypothesis test setting, we modeled them simultaneously for clustering and described the results after. Future studies based on hypothesis test setting are needed to confirm our results on stroke and TE prevention among AF patients with longitudinal OAC treatment patterns. Our results only apply to patients of AF who have initiated OAC and have greater risks of stroke or TE. Effect of dementia and other cognitive diseases on trajectory of OAC use and its association with risk of stroke or TE was not evaluated in this study, and should be assessed in future research.

Conclusion

Joint latent class mixed models identified 5 latent classes of trajectories of OAC use that are associated with time to stroke or TE among patients newly diagnosed with AF who filled at least one OAC prescription in the first year after diagnosis. Late initiators and late discontinuers had higher risk of stroke or TE than continuous users. Our study suggests the importance of early initiation and continuation of OAC therapy in preventing stroke and TE among patients with atrial fibrillation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Observed Oral Anticoagulant (OAC) Use Over Follow-up by Classes Identified from Joint Latent Class Mixed Model.

The model identified 5 classes: 1) Patients who initiated therapy at 1–4 with optimal OAC use after month 4 (“late users”, n=2,926, 17.8%); 2) patients who therapy at 4–10 with suboptimal OAC use through follow-up (“late initiators”, n=2,053, 12.5%); 3) patients who discontinued therapy at months 1–5 (“early discontinuers”, n=3,055, 18.6%); 4) patients who discontinued therapy at months 5–10 (“late discontinuers”, n=2,526, 15.4%); 5) patients who continuously used therapy (“continuous users”, n=5,839, 35.6%).

Figure 2.

Kaplan-Meier Curves of Observed Class-Specific Survival Probabilities for the Composite of Stroke and Thromboembolism (TE).

The unadjusted survival probability from stroke or TE was lower in late initiators (class 2) and late discontinuers (class 4) than the other groups.

Figure 3.

Hazard Ratio of Stroke or Thromboembolism for Classes of Oral Anticoagulation Use and Risk Factors.

Hazard ratios and 95% confidence intervals for classes and defined risk factors were estimated from multivariable adjusted class-specific proportional hazard models inherent in the joint latent class mixed model.

Table 1.

Baseline Characteristics, By Class

	Class 1, Late Users (n=2,926)	Class 2, Late Initiators (n=2,053)	Class 3, Early Discontinuers (n=3,055)	Class 4, Late Discontinuers (n=2,526)	Class 5, Continuous Users (n=5,839)
Age, mean (SD)	76.82 (8.83)	76.41 (9.46)	76.06 (9.56)	76.42 (8.94)	76.43 (8.92)
Male, n (%)	1,144 (39)	817 (40)	1,389 (45)	1,106 (44)	2,511 (43)
Race					
White	2,661 (91)	1,808 (88)	2,625 (86)	2,227 (88)	5,224 (89)
Black	150 (5)	149 (7)	269 (9)	187 (7)	336 (6)
Other	115 (4)	96 (5)	161 (5)	112 (4)	279 (5)
Eligibility for Medicaid	638 (22)	539 (26)	782 (26)	575 (23)	1,329 (23)
Eligibility for Low-income Subsidy	897 (31)	765 (37)	1,130 (37)	852 (34)	1,737 (30)
SES	0.211 (1.04)	0.147 (1.05)	0.141 (1.04)	0.179 (1.06)	0.264 (1.04)
Dissimilarity	0.490 (0.17)	0.487 (0.17)	0.486 (0.17)	0.490 (0.18)	0.492 (0.17)
Rural	699 (24)	498 (24)	740 (24)	642 (25)	1,403 (24)
Region					
Midwest	806 (28)	496 (24)	773 (25)	711 (28)	1,662 (28)
Northeast	688 (24)	458 (22)	671 (22)	549 (22)	1,510 (26)
Southeast	828 (28)	653 (32)	873 (29)	716 (28)	1,503 (26)
Southwest	256 (9)	195 (9)	300 (10)	216 (9)	414 (7)
West	348 (12)	250 (12)	438 (14)	334 (13)	750 (13)
CHA2DS2-VASc, mean (SD)	4.69 (1.65)	4.83 (1.67)	4.70 (1.68)	4.81 (1.66)	4.64 (1.63)
HAS-BLED, mean (SD)	2.89 (1.05)	3.02 (1.07)	3.00 (1.04)	2.97 (1.05)	2.87 (1.01)
AD or dementia	412 (14)	320 (16)	471 (15)	354 (14)	762 (13)
Antiplatelet use	349 (12)	280 (14)	434 (14)	343 (14)	730 (13)
Antiarrhythmic medication use	182 (6)	128 (6)	326 (10)	224 (9)	450 (8)

Abbreviations: SES, social economic score; AD, Alzheimer's disease

Table 2.
Rate of Stroke or Thromboembolism, by Class within 12 months of AF diagnosis

	Class 1, Late Users (n=2,926)	Class 2, Late Initiators (n=2,053)	Class 3, Early Discontinuers (n=3,055)	Class 4, late Discontinuers (n=2,526)	Class 5, Continuous Users (n=5,839)	Total (N=16,399)
N of stroke or TE	295	361	337	322	581	1,896
Mean follow up (number of 30 day intervals)	10.73	10.02	10.65	10.48	10.91	10.65
Rate of stroke or TE per 100 person-years	11.4	21.4	12.6	14.8	11.1	13.2

Abbreviations: TE, thromboembolism