Adherence to Direct Oral Anticoagulants and Incidence of Stroke/Acute Coronary Syndrome/Systemic Embolism among Patients with Atrial Fibrillation Using a Marginal Structural Model

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Mohan A[1], Chen H[1], Wanat M[1], Deshmukh A[2], Essien EJ[1], Paranjpe R[1], Majd Z[1], Abughosh SM[1]

[1]College of Pharmacy, University of Houston, Houston, TX, USA ; [2]Medical University of South Carolina, Charleston, SC, USA

Contact Information:
Zahra Majd
University of Houston
Email:
zmajd@central.uh.edu

BACKGROUND

- Atrial Fibrillation (AF) is a common supraventricular cardiac arrhythmia that predominantly affects older patients with chronic illness and increases the risk of cardioembolic stroke.
- Direct oral anticoagulants (DOACs) are the standard of care for preventing stroke and systemic thromboembolism among AF patients.
- Adherence to DOACs is lower in real-life settings than in clinical trials, with studies reporting adherence rates ranging from 40.1% to 72.8%.
- Given the short half-life of DOACs, poor adherence to these medications is associated with an increased risk of adverse events such as stroke and all-cause mortality.

OBJECTIVE

- To investigate the association between adherence to DOACs and the risk of stroke, systemic embolism, and acute coronary syndrome using a marginal structural model.

METHODS

- **Study Design:** Retrospective cohort
- **Data Source:** Claims data from a Texas Medicare Advantage Plan
- **Study Period:** January 2016-December 2020
- **Inclusion Criteria:**
  - Non-valvular AF
  - A refill for any of the DOACs during July 2016 to December 2017
  - Continuously enrolled during the entire study period
- **Exclusion Criteria:**
  - Concomitantly using warfarin
  - Valvular heart disease, prosthetic valve replacements, systemic embolism from January 2016-December 2017
  - Disenrolled from the plan
- **DOAC Adherence Measurement**
  - Proportion of days covered (PDC): ≥ 0.80 considered adherent
  - Measured at different time intervals (Δ1-Δ3)
  - Time-varying exposure in the MSM model

METHODS

- **Outcome Measurement**
  - ✓Composite efficacy events including stroke, systemic embolism, and acute coronary syndrome, identified by ICD-10 codes
  - ✓Measured separately for different time periods (T1-T4)
- **Covariate Measurement**
  - ✓Time-dependent covariate: stroke risk scores measured using CHA2DS2VASC
  - ✓Time-dependent confounder: cumulative prior composite events affected by prior exposure (adherence during the previous time period) was measured during each of the time periods
- **Marginal Structural Model (MSM)**
  - ✓MSM accounts for time-varying confounders affected by prior exposure
  - ✓This study used MSM to evaluate the association between time-dependent exposure (adherence to DOACs) on the outcome of composite efficacy, adjusting for time-dependent covariates and time-dependent confounders for each time period

Figure 1. Study design

C_0: Time fixed covariates (baseline characteristics)
Δ0 – Δ3 : Time varying covariates : adherence, composite events, stroke risk scores

Table 1. Assessment of Stroke Risk using CHA2DS2-VASc in Atrial Fibrillation

CHA_2DS_2-VASc score	Score
Heart failure	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65 to 74 y	1
Sex category (ie, female sex)	1
Maximum score	**9**

TIA ,transient ischemic attack; TE, thromboembolic; MI, myocardial infarction; and PAD, peripheral artery disease.
CHA2DS2-VASc score of 0: recommend no antithrombotic therapy

RESULTS

Table 2. Baseline characteristics of the study population

Variables	Total Patients (N=1969)
Age	
<75 years	799 (40.58)
≥75 years	1170 (59.42)
Gender	
Female	1075 (54.60)
Male	894 (45.40)
Health plan	
No subsidy	1245 (63.23)
Low-income subsidy	724 (36.77)
Prevalent users	
No	933 (47.38)
Yes	1036 (52.62)
CHA2DS2-VASc score	
Score < 3	899 (45.66)
Score ≥3	1070 (54.34)
HAS-BLED score	
Score < 2	1247 (63.33)
Score ≥2	722 (36.67)
PCP visits	
No	1501 (76.23)
Yes	468 (23.77)
Comorbidities	
Diabetes Mellitus	
No	1749 (88.83)
Yes	220 (11.17)
Hypertension	
No	1587 (80.60)
Yes	382 (19.40)
Coronary Artery Disease	
No	1731 (87.91)
Yes	238 (12.09)
Renal disease	
No	1845 (93.70)
Yes	124 (6.30)
Anemia	
No	1828 (92.84)
Yes	44 (9.13)
Comedications	
Antiplatelet agents	
No	1798 (91.32)
Yes	171 (8.68)
Antiarrhythmic agents	
No	1491 (75.72)
Yes	478 (24.28)
NSAID	
No	1817 (92.28)
Yes	152 (7.72)
CMS Risk score	2.05 (1.20)

CHA2DS2-VASc score: a validated stroke risk measure in patients with atrial fibrillation
CMS: Centers for Medicare & Medicaid Services
HAS-BLED score: a scoring system to estimate bleeding risk in patient with atrial fibrillation
NSAID: Non-Steroidal Anti-Inflammatory Drugs
PCP: primary care provider

Table 3. MSM to evaluate the association between adherence and composite efficacy events

Variables	Adjusted OR (95% CI)	P value
Adherent vs. Not Adherent (PDC)	1.17 (0.86-1.58)	0.30
Age		
≥75 years vs <75 years	1.14 (0.61-2.11)	0.66
Gender		
Male vs. Female	1.07 (0.59-1.91)	0.81
Health plan		
No subsidy vs. Low-income subsidy	1.05 (0.61-1.79)	0.84
Prevalent users		
Yes vs. No	1.50 (0.88-2.55)	0.12
CHA2DS2-VASc score		
Score ≥ 3 vs. Score < 3	0.99 (0.48-2.03)	0.99
HAS-BLED score		
Score ≥ 2 vs. Score < 2	0.38 (0.14-0.98)	0.045
PCP visits		
Yes vs. No	0.66 (0.38-1.15)	0.14
Comorbidities		
Diabetes Mellitus		
Yes vs. No	0.89 (0.36-2.19)	0.80
Hypertension		
Yes vs. No	2.54 (0.96-6.73)	0.05
Coronary Artery Disease		
Yes vs. No	1.30 (0.61-2.76)	0.48
Renal disease		
Yes vs. No	1.04 (0.31-3.51)	0.94
Anemia		
Yes vs. No	1.69 (0.59-4.84)	0.32
Antiplatelet agents		
Yes vs. No	1.06 (0.39-2.83)	0.92
Antiarrhythmic agents		
Yes vs. No	0.81 (0.45-1.47)	0.50
Antihyperlipidemic agents		
Yes vs. No	1.31 (0.73-2.33)	0.36
NSAID use		
Yes vs. No	1.94 (0.40-9.42)	0.40
CMS Risk Score	0.94 (0.75-1.16)	0.58
Time period		
2 vs 1	0.34 (0.14-0.84)	0.01
3 vs 1	0.76 (0.36-1.63)	0.49
4 vs 1	1.38 (1.10-3.09)	0.0001

CONCLUSION

- Adherence to DOACs decreased over time. During the 6-monthly time intervals (T0-T4), the adherence rates were 53.12%, 44.74%, 43.12%, 40.33%, and 39.82%.
- After adjusting for time-varying exposure and confounding factors, our findings indicate no significant association between adherence to DOACs and composite events.
- Longer follow-up period and larger samples may be needed to evaluate the impact of adherence on composite events.

References

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