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Research paper

Delayed treatment initiation of oral anticoagulants among Medicare patients with atrial fibrillation

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ABSTRACT

Study objective: This study aimed to identify factors associated with delayed oral anticoagulant (OAC) treatment initiation among atrial fibrillation (AF) patients in United States (US) clinical practice.
Participants: Medicare beneficiaries newly diagnosed with AF without moderate-to-severe mitral stenosis or a mechanical heart valve, were aged ≥65 years and prescribed OAC on or after 10/1/2015 through 2019 were included. Delayed and early OAC initiation were defined as >3 months and 0–3 months initiation from first AF diagnosis, respectively.
Main outcome measures: Association between delayed OAC initiation and patient demographics, clinical and index OAC coverage and formulary characteristics was examined using multivariable logistic regression.
Results: A total of 446,441 patients met the inclusion criteria; 30.0 % ($N = 131,969$) were identified as delayed and 70.0 % ($N = 314,472$) as early OAC initiation. Median age for both cohorts was 78 years. In the early and delayed OAC cohorts, 47.1 % and 47.6 % were male and 88.8 % and 86.6 %, were White, respectively. Factors associated with delayed OAC initiation (odds ratio; 95 % confidence interval) included Black race (1.29; 1.25 to 1.33), west region (1.29; 1.26 to 1.32), comorbidities such as dementia (1.27; 1.23 to 1.30), recent bleeding hospitalization (1.22; 1.18 to 1.27), prior authorization (1.69; 1.66 to 1.71), tier 4 formulary for index OAC at AF diagnosis (1.26; 1.22 to 1.30).
Conclusion: Our study revealed that nearly one-third of Medicare patients with AF experienced delayed OAC initiation. Key patient characteristics found to be associated with delayed OAC initiation included race and ethnicity, comorbidities, and formulary restrictions.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States (US) [1], affecting 4 million people in 2019 [2] and up to 12 million by 2030 [2,3]. AF is associated with increased risk of stroke [4,5], contributing to approximately 15 % of strokes and over 150,000 deaths each year in the US [1].

Oral anticoagulants (OACs), including vitamin K antagonists and direct OACs, are the primary treatment to reduce the risk of stroke in patients with AF [6–8]. However, despite guidelines recommending treatment with OACs in AF patients [6,9], recent evidence suggests that many patients with AF may fail to receive timely treatment [10–15]. A 2020 US commercial claims analysis reported underuse of OACs in patients with AF despite no clear contraindications — 36 % of eligible AF patients receiving early education intervention on the use of OACs had no evidence of OAC use in the prior 12 months [16]. An analysis using the Centers for Medicare & Medicaid Services (CMS) fee-for-service Medicare dataset (100 %) from 2012 to 2017 found that 51.3 % of patients with AF did not receive any OAC during a 6-month follow-up period after their first AF diagnosis [17]. Moreover, government and

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commercial payers have increasingly implemented more stringent formulary restrictions to contain costs, introducing additional hurdles to patient access to treatment. While these formulary restrictions are intended to manage payer costs, these initiatives can risk delaying or even preventing treatment and may impact patient health [18,19].

Using data from patients with traditional Medicare coverage from 1 October 2014 to 31 December 2019, this study aimed to examine factors associated with delayed vs early OAC initiation after diagnosis of AF without moderate-to-severe mitral stenosis or a mechanical heart valve (hereafter referred to as AF) in US clinical practice.

2. Materials and methods

This retrospective cohort study was conducted using administrative claims data from the Medicare Research Identifiable File (RIF) from 1 October 2014 to 31 December 2019. Medicare patients with a diagnosis for AF (International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM): I48.0, I48.1x, I48.2x, I48.91) in any setting and first observed AF diagnosis on or after October 1st, 2015 were identified. The date of a patient's first observed AF diagnosis on or after October 1st, 2015 was defined as index date and the 12 months prior to the index date was defined as baseline period. Eligible patients were required to have continuous enrollment in Medicare Parts A, B, and D for ≥12 months prior to and after the index date (or until death date if death <12 months after the index date), be ≥65 years of age at the index date, and had CHA_2DS_2-VASc score ≥ 2 for male patients or CHA_2DS_2-VASc score ≥ 3 for female patients [9]. Patients were excluded if they had hip or knee replacement surgery during the 6 weeks prior to the index date, VTE diagnosis during baseline or anytime post the index date, any of the following during baseline period: claim indicating transient AF, valvular heart disease or mechanical valve replacement, pregnancy at any time, and an OAC claim anytime prior to the index date. Patients were also required to be prescribed an OAC treatment after index date (i.e., patients with no OAC claim after the index date were excluded). Patient's first observed OAC (dabigatran, rivaroxaban, apixaban, edoxaban, or warfarin) after the index date was defined as the index OAC.

Baseline demographic and clinical characteristics included: age, sex, race, geographic region, types of Medicare coverage, type of AF, Charlson Comorbidity Index (CCI) score and its individual components [20], other AF-related comorbidities and procedures, CHA_2DS_2-VASc score [21], HAS-BLED score [22], clinical events related to stroke/systemic embolism or bleeding, and selected classes of medications. Drug access coverage characteristics for the index OAC at the time of the index date included: formulary tier, utilization management restrictions (prior authorizations, step therapy requirement, and quantity limit imposed), and patient cost-sharing for a 30-day supply.

Time from AF diagnosis (i.e., index date) to first OAC claim was summarized and plotted using cumulative incidence functions. Early OAC initiation was defined as having a first OAC claim within the 3 months from the index date and delayed OAC initiation was defined as having a first OAC claim >3 months after the index date. Patient and index OAC characteristics were described for the delayed and early OAC initiation cohorts. Factors, such as baseline demographic and clinical characteristics and index drug access coverage characteristics with potential clinical and policy relevance and importance were assessed for their associations with delayed (vs. early) OAC initiation from AF diagnosis using univariable logistic regression. Selected factors were included in the multivariable logistic regression based on clinical input, strength of association from the univariable regression (for indicators of patient's comorbidity), and considerations to prevent multicollinearity. Odds ratios, confidence intervals, and *p*-values were reported. A two-sided $p < 0.05$ was considered statistically significant.

Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996; therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4) (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#46.101).

3. Results

There were 446,441 patients meeting eligibility criteria (Fig. 1). Time from first AF diagnosis to OAC initiation was <1 month for 52.4 % of patients, 1–≤3 months for 18.1 %, >3–≤6 months for 7.1 %, >6–≤12 months for 6.8 %, and >12 months for 15.7 % (Fig. 2). Accordingly, 70.0 % of patients ($N = 314,472$) were identified as early OAC initiation while 30.0 % ($N = 131,969$) as delayed OAC initiation (referred to as early OAC cohort and delayed OAC cohort thereafter, respectively). Time from AF diagnosis to OAC initiation was of a mean (SD) of 0.6 months (0.7) in the early OAC cohort and 15.7 months (11.0) in the delayed OAC cohort. Among patients with an OAC claim, apixaban is the most common (56.6 %) first treatment observed after AF diagnosis, followed by rivaroxaban (23.0 %), warfarin (17.5 %), dabigatran (2.8 %), and edoxaban (0.1 %).

Baseline demographic, clinical, and index drug access coverage characteristics for the early and delayed OAC cohorts are provided in Table 1. Across cohorts, median age was 78 years, and a little more than half of the patients were female. White patients comprised 88.8 % and 86.6 %, and Black patients 4.0 % and 5.7 %, in the early and delayed OAC cohorts, respectively. All US regions were represented, with the highest representation from the South, with 36.7 % and 39.5 % of patients in the early and delayed OAC cohorts, respectively. The early OAC cohort patients were less likely to be covered by the Medicare low-income subsidy (17.7 % vs. 21.6 %), or have dual eligibility with Medicaid (14.9 % vs. 18.5 %).

Paroxysmal AF was the most common type of AF in both cohorts, 37.5 % and 41.5 % in early and delayed OAC cohorts, respectively. Mean comorbidity burden score (CCI, mean [SD]: 2.4 [2.2] vs. 2.8 [2.4]), CHA_2DS_2-VASc (mean [SD]: 4.0 [1.4] vs. 4.2 [1.4]), and HAS-BLED scores (mean [SD]: 2.9 [1.1] vs. 3.1 [1.2]) were lower in the early vs. delayed cohorts. Hospitalization within three months of the index AF due to stroke or systemic embolism occurred in 2.4 % and 3.0 %, and bleeding in 2.9 % and 4.5 %, of early and delayed OAC cohorts, respectively.

At the time of index date, a majority of patients had their index OAC covered through formulary tier 3, 67.9 % and 66.3 % in the early and delayed cohorts, respectively, followed by tier 1 with 16.8 % and 13.4 %, respectively. The early OAC cohort was less likely to have prior authorizations (16.3 % vs. 24.7 %) or quantity limits (46.4 % vs. 49.3 %) than the delayed cohort. Results from univariate logistic regression analysis on comparison of baseline patient characteristics between the early and delayed OAC cohorts are reported in Supplemental Material Table S1.

Fig. 3 shows factors associated with delayed OAC initiation based on multivariable logistic regression model. Main factors associated with increased odds of delayed (> 3 months) OAC initiation included Black race (OR: 1.29 [95 % CI: 1.25 to 1.33]) and Native American (OR: 1.14 [1.02 to 1.29]) relative to White race (Fig. 3). Patients from the South (OR: 1.22 [1.19 to 1.24]) and the West (OR: 1.29 [1.26 to 1.32]) had increased odds of delayed OAC initiation relative to the Northeast region. Patients enrolled in the Medicare Part D low-income subsidy program were also more likely (OR: 1.06 [1.02 to 1.10]) to experience delayed OAC initiation, so were those with dual eligibility with Medicaid (OR: 1.09 [1.05 to 1.14]). Comorbidities associated with higher odds of delayed OAC initiation included dementia (OR: 1.27 [1.23 to 1.30]), congestive heart failure (OR: 1.20 [1.18 to 1.22]), coronary artery disease (OR: 1.19 [1.17 to 1.21]), and dyspepsia or stomach discomfort (OR: 1.14 [1.12 to 1.16]). Patients hospitalized for bleeding within the three months before their index date also had increased odds of delayed OAC initiation (OR: 1.22 [1.18 to 1.27]). A patient's index OAC listed in formulary tier 4 was (OR: 1.26 [1.22 to 1.30]) relative to index OAC listed in formulary tier 1 and a requirement for prior authorization (OR: 1.69 [1.66 to 1.71]) also increased odds of

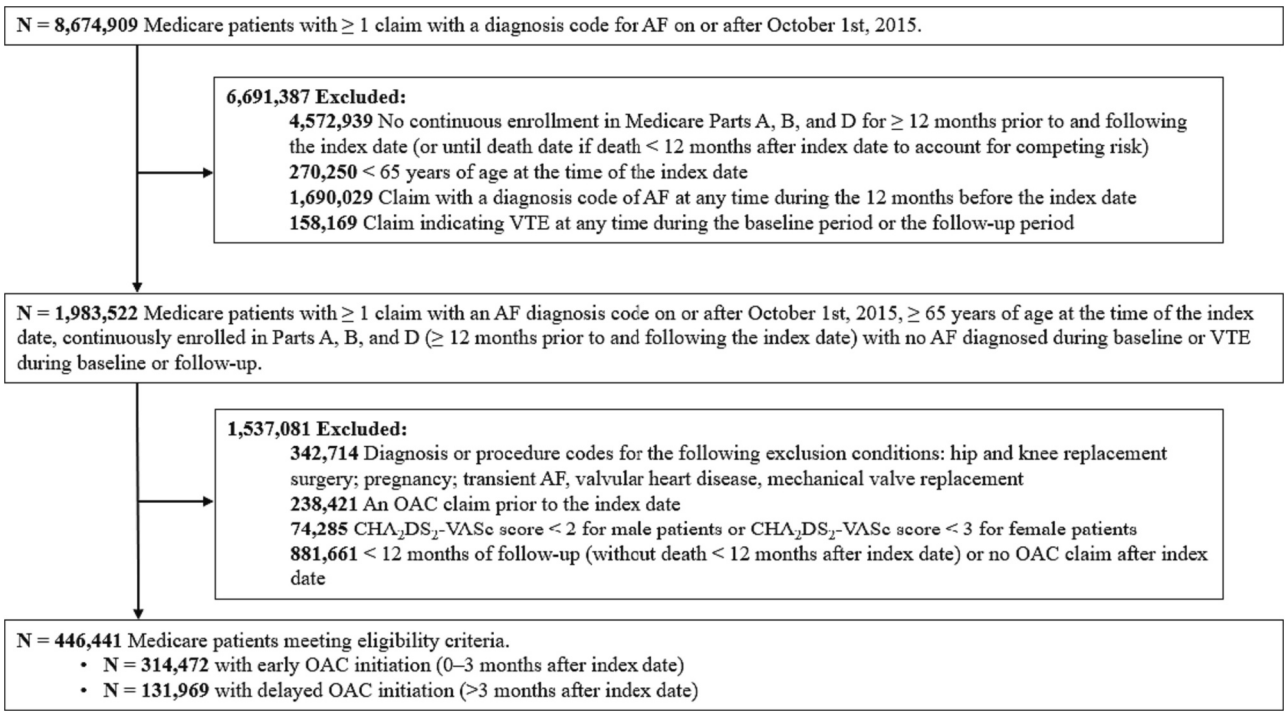

Fig. 1. Identification of the study sample.
Abbreviations: AF = atrial fibrillation; CHA_2DS_2-VASc = congestive heart failure; hypertension; age ≥ 75 years; diabetes mellitus; prior stroke, transient ischemic attack or thromboembolism; vascular disease; age 65–74 years; and sex category (female); OAC = oral anticoagulant; VTE = venous thromboembolism.

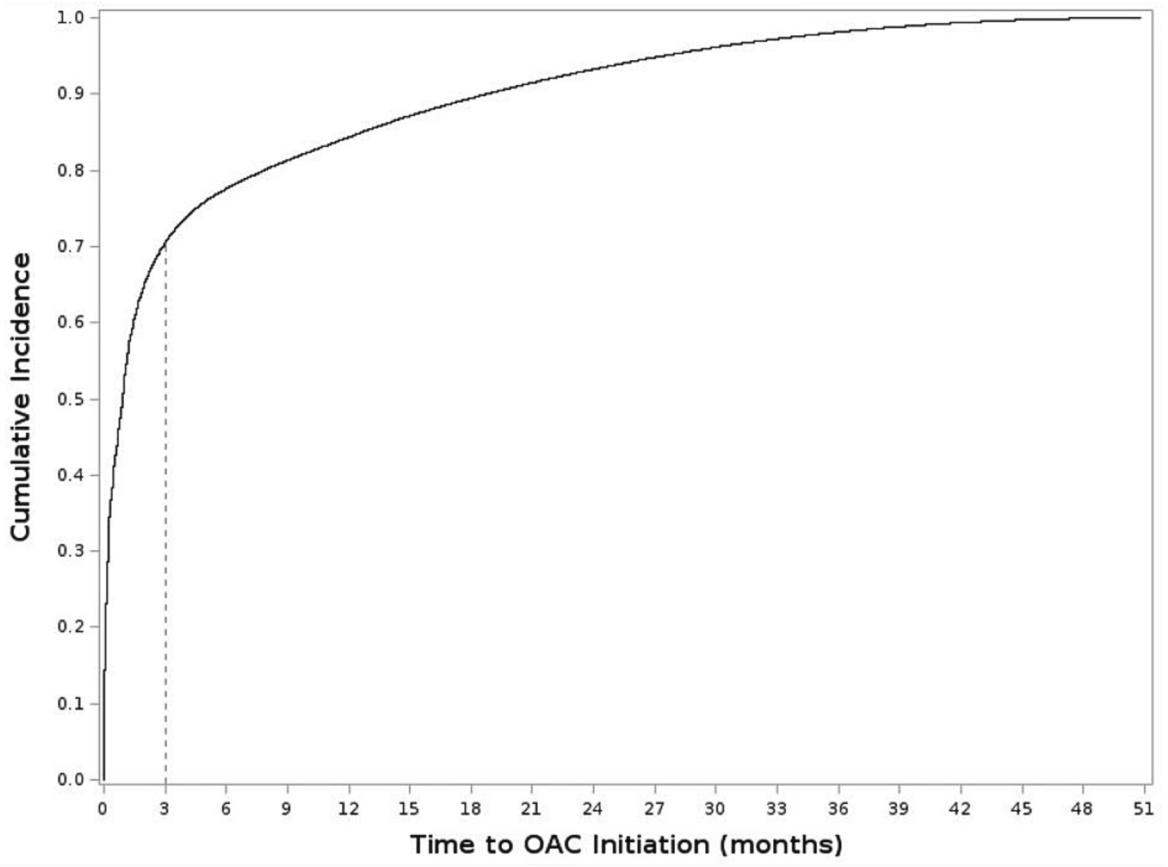

Fig. 2. Incidence of OAC initiation.
Abbreviation: OAC = oral anticoagulant.

Table 1
Patient baseline period characteristics for patients newly diagnosed with atrial fibrillation.

	Early OAC initiation (0–3 months after index date)	Delayed OAC initiation (>3 months after index date)
	(N = 314,472)	(N = 131,969)
Demographics at index date (i.e., start of outcome observation period)[a]		
Age (years)		
Mean ± SD (median)	78.1 ± 7.2 (78.0)	78.2 ± 7.4 (78.0)
Categories, N (%)		
65–74 years	106,927 (34.0 %)	45,463 (34.4 %)
75–84 years	142,965 (45.5 %)	57,536 (43.6 %)
≥85 years	64,580 (20.5 %)	28,970 (22.0 %)
Sex, N (%)		
Female	166,399 (52.9 %)	69,109 (52.4 %)
Male	148,073 (47.1 %)	62,860 (47.6 %)
Race/ethnicity,[b] N (%)		
White	279,178 (88.8 %)	114,241 (86.6 %)
Black	12,458 (4.0 %)	7520 (5.7 %)
Asian	5930 (1.9 %)	2499 (1.9 %)
Hispanic	11,067 (3.5 %)	5439 (4.1 %)
North American Native	884 (0.3 %)	492 (0.4 %)
Other/Unknown	4955 (1.6 %)	1778 (1.3 %)
Geographic region, N (%)		
Northeast	66,133 (21.0 %)	24,660 (18.7 %)
Midwest	80,845 (25.7 %)	31,274 (23.7 %)
South	115,387 (36.7 %)	52,130 (39.5 %)
West	51,599 (16.4 %)	23,671 (17.9 %)
Other/Unknown[c]	508 (0.2 %)	234 (0.2 %)
Special types of Medicare coverage at index date, N (%)		
Low-income subsidy	55,536 (17.7 %)	28,464 (21.6 %)
Dual eligibility[d]	46,806 (14.9 %)	24,455 (18.5 %)
Time from AF diagnosis to OAC initiation (in months), mean (SD)	0.6 ± 0.7 (0.3)	15.7 ± 11.0 (12.9)
Type of AF at the index date[f]		
Paroxysmal AF	122,156 (38.8 %)	48,103 (36.5 %)
Persistent AF	20,842 (6.6 %)	3967 (3.0 %)
Chronic AF	13,835 (4.4 %)	7908 (6.0 %)
Unspecified AF	157,639 (50.1 %)	71,991 (54.6 %)
Type of AF at time of OAC initiation[e,f]		
Paroxysmal AF	117,839 (37.5 %)	54,739 (41.5 %)
Persistent AF	23,843 (7.6 %)	7396 (5.6 %)
Chronic AF	17,474 (5.6 %)	11,957 (9.1 %)
Unspecified AF	155,316 (49.4 %)	57,877 (43.9 %)
Comorbidity profile in the baseline period		
Charlson Comorbidity Index (CCI) using Quan 2005, mean ± SD (median)[g]	2.4 ± 2.2 (2.0)	2.8 ± 2.4 (2.0)
CCI of 0	69,858 (22.2 %)	24,239 (18.4 %)
Individual comorbidities within CCI, N (%)		
AIDS/HIV	328 (0.1 %)	197 (0.1 %)
Any malignancy[h]	44,476 (14.1 %)	19,799 (15.0 %)
Cerebrovascular disease	56,583 (18.0 %)	27,595 (20.9 %)
Chronic pulmonary disease	82,488 (26.2 %)	39,275 (29.8 %)
Congestive heart failure	48,353 (15.4 %)	27,327 (20.7 %)
Dementia	15,647 (5.0 %)	9481 (7.2 %)
Diabetes with chronic complication	52,571 (16.7 %)	25,091 (19.0 %)
Diabetes without chronic complication	61,922 (19.7 %)	26,896 (20.4 %)
Hemiplegia or paraplegia	4560 (1.5 %)	2692 (2.0 %)
Metastatic solid tumor	4875 (1.6 %)	2525 (1.9 %)
Mild liver disease	14,287 (4.5 %)	6983 (5.3 %)
Moderate or severe liver disease	755 (0.2 %)	530 (0.4 %)
Myocardial infarction	22,410 (7.1 %)	11,777 (8.9 %)
Peptic ulcer disease	4620 (1.5 %)	2757 (2.1 %)
Peripheral vascular disease	71,565 (22.8 %)	36,249 (27.5 %)
Renal disease	57,766 (18.4 %)	28,465 (21.6 %)
Rheumatic disease	15,196 (4.8 %)	7431 (5.6 %)
Other AF-related comorbidities and procedures, N (%)		
Alcoholism	3789 (1.2 %)	2152 (1.6 %)
Anemia and coagulation defects	99,886 (31.8 %)	49,175 (37.3 %)
Cardioversion	741 (0.2 %)	163 (0.1 %)
Catheter ablation	192 (0.1 %)	79 (0.1 %)
Coronary artery disease	103,865 (33.0 %)	52,271 (39.6 %)
Dyspepsia or stomach discomfort	54,887 (17.5 %)	27,813 (21.1 %)
Hypertension	276,372 (87.9 %)	116,547 (88.3 %)
Transient ischemic attack	24,277 (7.7 %)	11,743 (8.9 %)
Stroke and bleeding risk scores in the baseline period		
CHA_2DS_2-VASc score, mean ± SD (median)	4.0 ± 1.4 (4.0)	4.2 ± 1.4 (4.0)
Categories, N (%)		
2 (high risk)	33,983 (10.8 %)	13,384 (10.1 %)
3–4 (high risk)	180,054 (57.3 %)	69,648 (52.8 %)
5–6 (high risk)	83,787 (26.6 %)	39,202 (29.7 %)
≥7 (high risk)	16,648 (5.3 %)	9735 (7.4 %)
HAS-BLED score, mean ± SD (median)	2.9 ± 1.1 (3.0)	3.1 ± 1.2 (3.0)
Categories, N (%)		
0 (low risk)	0 (0.0 %)	0 (0.0 %)
1–2 (moderate risk)	124,616 (39.6 %)	45,535 (34.5 %)
≥3 (high risk)	189,856 (60.4 %)	86,434 (65.5 %)
Clinical event in the baseline period (all settings and diagnoses), N (%)		
Any occurrence of the following events	59,334 (18.9 %)	30,389 (23.0 %)
Stroke/systemic embolism	20,880 (6.6 %)	10,887 (8.2 %)
Hemorrhagic stroke	976 (0.3 %)	754 (0.6 %)
Ischemic stroke	18,872 (6.0 %)	9661 (7.3 %)
Systemic embolism	1884 (0.6 %)	1060 (0.8 %)
Bleeding	43,386 (13.8 %)	22,543 (17.1 %)
Gastrointestinal bleeding	13,361 (4.2 %)	7733 (5.9 %)
Intracranial hemorrhage	2117 (0.7 %)	1618 (1.2 %)
Other major bleeding	33,171 (10.5 %)	16,764 (12.7 %)
Clinical event within three months before the index date (hospitalization), N (%)		
Any occurrence of the following events	15,253 (4.9 %)	9007 (6.8 %)
Stroke/systemic embolism	7518 (2.4 %)	3996 (3.0 %)
Hemorrhagic stroke	498 (0.2 %)	380 (0.3 %)
Ischemic stroke	6964 (2.2 %)	3614 (2.7 %)
Systemic embolism	465 (0.1 %)	250 (0.2 %)
Bleeding	9011 (2.9 %)	5895 (4.5 %)
Gastrointestinal bleeding	2825 (0.9 %)	2266 (1.7 %)
Intracranial hemorrhage	853 (0.3 %)	734 (0.6 %)
Other major bleeding	6963 (2.2 %)	4339 (3.3 %)
Use of selected classes of medications in the baseline period, N (%)		
Angiotensin converting enzyme inhibitor	110,305 (35.1 %)	44,743 (33.9 %)
Amiodarone	1614 (0.5 %)	2527 (1.9 %)
Angiotensin receptor blocker	89,452 (28.4 %)	35,127 (26.6 %)
Beta blockers	156,905 (49.9 %)	71,151 (53.9 %)
H2-receptor antagonist	20,486 (6.5 %)	9694 (7.3 %)
Proton pump inhibitor	87,873 (27.9 %)	40,951 (31.0 %)
Anti-platelets	40,555 (12.9 %)	21,515 (16.3 %)
Statins	186,114 (59.2 %)	76,486 (58.0 %)
Coverage of the index OAC[i], N (%)	312,247 (99.3 %)	130,840 (99.1 %)
Formulary tier for the index OAC, N (%)		
1	52,689 (16.8 %)	17,656 (13.4 %)
2	17,949 (5.7 %)	7771 (5.9 %)
3	213,619 (67.9 %)	87,453 (66.3 %)
4	22,195 (7.1 %)	12,065 (9.1 %)
Prior authorizations needed	51,111 (16.3 %)	32,630 (24.7 %)
Quantity limit imposed	146,065 (46.4 %)	65,119 (49.3 %)
Step therapy requirement needed	123 (0.0 %)	24 (0.0 %)
Missing formulary information[j]	8020 (2.6 %)	7024 (5.3 %)

Abbreviations: AIDS = acquired immune deficiency syndrome; AF = atrial fibrillation; CCI = Charlson Comorbidity Index; CHA_2DS_2-VASc = congestive heart failure, hypertension, Age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack or thromboembolism (prior), vascular disease, Age 65–74 years, sex category; HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage; HIV = human immunodeficiency virus; NVAF = non-valvular atrial fibrillation; OAC = oral anticoagulant; SD = standard deviation.

[a] The baseline period is defined as the 12 months prior to index date.

[b] Race/ethnicity are presented as mutually exclusive categories, as coded in the data.

[c] Other includes U.S. territories such as Puerto Rico and Virgin Islands.

[d] This category includes patients enrolled in Medicare and getting full Medicaid benefits (i.e., enrolled in Medicaid) and/or assistance with Medicare premiums or cost sharing through the Medicare Savings Program.

[e] AF subtype at time of OAC initiation considers the claims before and closest to time of OAC initiation (including the date of OAC initiation).

[f] Patients with claims for more than one AF subtype were reclassified to prioritize, in order, chronic AF, persistent AF, paroxysmal AF, and unspecified AF.

[g] The Charlson Comorbidity Index was defined based on criteria by Charlson (1987), adapted by Deyo (1992), and updated by Quan (2005). Citation: Quan, H. et al., 2005. Coding algorithms and for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical Care, 43(11), pp.1130–1139.

[h] Including lymphoma and leukemia, except malignant neoplasm of skin.

[i] Patients who were on multiple formularies during the year of their index date were not considered to have index OAC coverage at index date, as the formulary they would have been on at index date could not be identified with certainty.

[j] Patients with no formulary characteristics information on the pharmacy claim for their index OAC fill, with no formulary characteristics information for their index OAC on the formulary they were on during the year of their index date, or with multiple formularies during the year of their index date were considered to have missing formulary information for the index OAC characteristics at index date.

delayed OAC initiation. Similar results were observed in a sensitivity analysis that included the CHA_2DS_2-VASc and the HAS-BLED scores but not the individual comorbidity components included in the scores in a multivariable regression model (Supplemental Material Table S2).

4. Discussion

In this study consisting of 446,441 Medicare patients diagnosed with AF, who were at high risk of stroke and were prescribed OACs in the period from October 2014 through 2019, nearly one-third of patients delayed OAC initiation after AF diagnosis. An analysis of demographic, clinical, and drug access coverage factors revealed that specific patient characteristics including race, region, comorbidities, and formulary restrictions were associated with delayed OAC initiation.

We found that Black and Native American patients had significantly increased odds of delayed OAC initiation vs. White patients. Our observations from a large dataset extend previously published results showing racial/ethnicity disparities in OAC utilization following AF diagnosis which persist in more recent years. For example, two studies using older CMS Medicare data (2012–2017 and 2014–2015) found that compared with White race, Black race was associated with lower utilization of OACs within 6 months after patient's first AF diagnosis [17] or was associated with not being prescribed OACs, delayed initiation, and early discontinuation [23], respectively. A longitudinal study of patients newly diagnosed with AF in 2011–2017 from the Northwestern Medicine Enterprise Data Warehouse reported significantly lower odds of receiving any OAC within 1 year of AF diagnosis in Black and Asian patients compared with White patients [15]. Studies based on a more homogeneous retired or current military patient population reported similar findings regarding racial/ethnic disparities: significantly lower odds of initiating OACs was observed for Black and Asian AF patients in the Veterans Health Administration in 2014–2018 [10]; Black patients

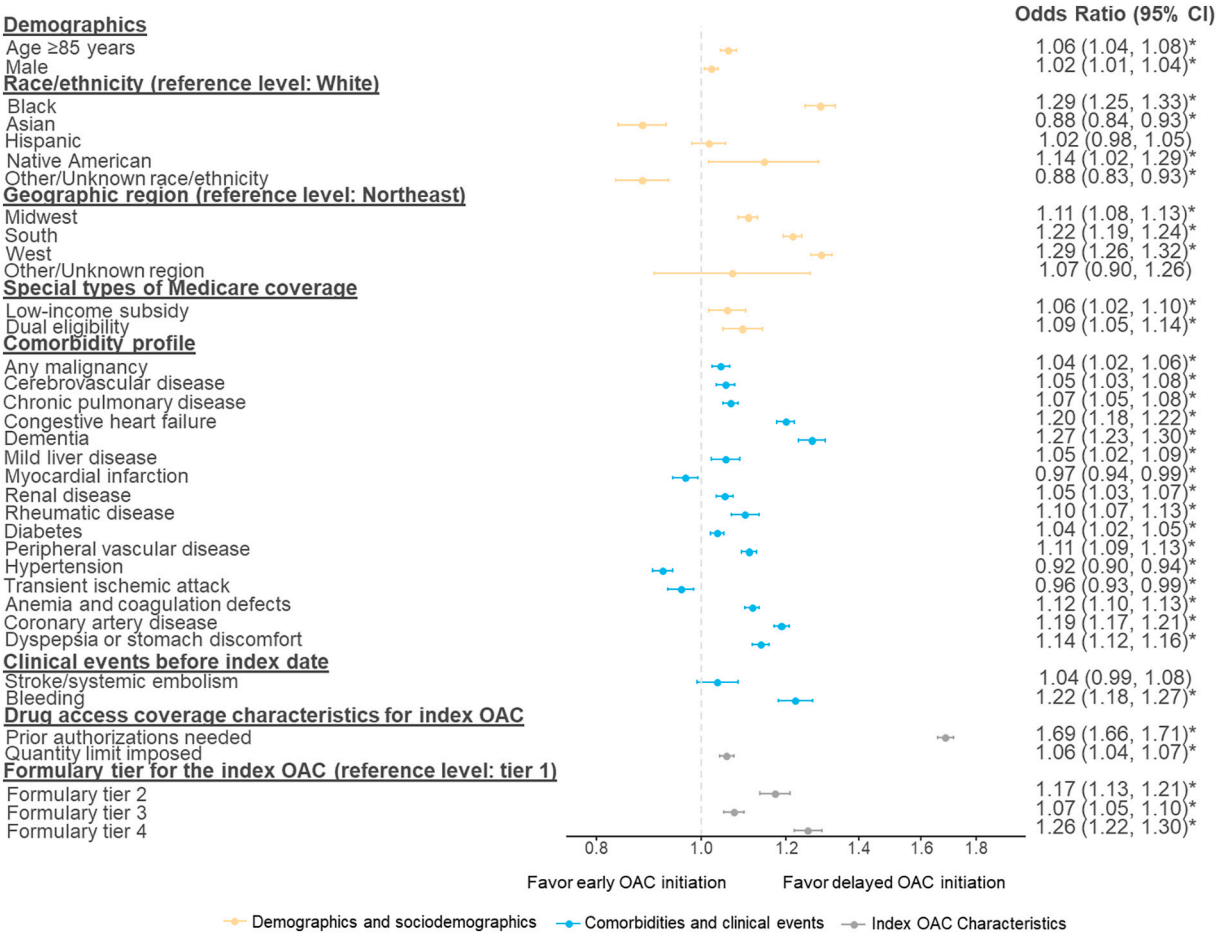

Fig. 3. Factors associated with delayed OAC initiation in patients newly diagnosed with atrial fibrillation.
*P value <0.05
Abbreviations: OAC = oral anticoagulant; CI = confidence interval.

with AF diagnosis in 2018–2019 within the US Military Health System, compared with White counterparts, had significantly reduced odds of being prescribed a newer generation direct OAC [24]. These studies complemented by the current study indicate that AF patients from racial/ethnic minorities particularly for Blacks were less likely to access timely OAC treatment.

In addition to the Black and Native American race, our study also found that having a Medicare Part D low-income subsidy or having dual eligibility for Medicare and Medicaid were associated with increased odds of delayed OAC initiation. Disparities in timely OAC initiation related to race/ethnicity may also be related to the influence of OAC coverage. Some patients faced with formulary restrictions may prefer to switch plans or pay extra out-of-pocket to bypass a non-medical switch and retain access to a treatment they are comfortable with, but these options may not be available to many in minority groups, who may forego medications to prioritize rent or food as a trade-off [25]. At the patient level, other possible reasons for racial/ethnic disparities in OAC initiation may include reluctance to accept novel treatments/technologies or to engage with healthcare practitioners based on historic distrust [26,27], or simply reduced access to specialty cardiologists [28]. Our findings indicate potential health care disparities in initiating timely OAC treatment. Future studies are warranted to understand how to reduce the health disparities in access to timely OAC treatment.

Results from this study indicate that formulary restrictions such as formulary tier 4 (highest tier), and prior authorization for the index OAC were associated with delayed OAC initiation, with the latter being the strongest predictor among all factors considered in this study. Formulary tier 4 has the highest out-of-pocket cost for patients. The higher drug costs may force patients to make difficult choice between daily essentials and lifesaving drugs [29,30], and may ultimately delay treatment initiation. The prior authorization process includes multiple steps such as application, review, approval, or re-application if rejected [18]. Each step may take time and may delay OAC initiation. Alternative approaches to manage payer costs may need to be explored to avoid the delay in OAC treatment.

This study also examined regional differences in OAC initiation following a diagnosis of AF. Patients from the South and West were found to have higher odds of delayed OAC initiation compared to patients from the Northeast. A previous study based on Medicare Part D beneficiaries also found that patients with newly diagnosed AF from the Southeast or Southwest were more likely to delay OAC initiation and discontinue early [23].

Additional factors that increased odds of delayed OAC initiation included comorbidities of congestive heart failure, dementia, coronary artery disease, and bleeding hospitalization within three months before the index date. Congestive heart failure can increase the risk and complicate the management of AF [31], potentially delaying OAC initiation. Coronary artery disease is known to be a common comorbidity in patients with AF, estimated to occur in 25 % – 35 % of AF patients [32–34]. In this population, combination with OAC and antiplatelet therapy is generally indicated, which is considered to be challenging, given the more complex balancing between risks of thromboembolic events and bleeding compare with OAC therapy alone [35]. Delayed OAC initiation in these patients may therefore be due to a more cautious approach based on risk-benefit assessment. The same may be said of patients who have been hospitalized for a bleeding event, given the risk of bleeding with OAC treatment [6]. Indeed, the higher rate of hospitalizations for bleeding in the 3 months preceding the index date in the delayed OAC cohort compared with the early OAC cohort suggests that OAC initiation may have been delayed for patients in whom bleeding risk was a concern. In patients with AF with comorbid dementia, the risk of thrombolysis-related intracerebral hemorrhage may limit the use of thrombolytic agents and anticoagulants [36]; although the delayed OAC cohort had higher rates of intracranial hemorrhage in the baseline period than the early OAC cohort, the association between intracerebral hemorrhage and OAC initiation was not evaluated in the multivariable regression analysis due to low prevalence of intracerebral hemorrhage events in the study sample (0.7 % and 1.2 % in the early OAC cohort and delayed OAC cohort, respectively).

This study included more recent data from a nationally representative sample of Medicare beneficiaries over a period when all four FDA-approved direct OACs were available. Medicare patients are a highly relevant population for atrial fibrillation; moreover, the data for this study included claims for the entire universe of traditional Medicare (Parts A and B) patients in the US with Medicare Part D coverage. In addition to demographic, socioeconomic and clinical characteristics, the Medicare data also include information on drug plan formularies (e.g., formulary coverage of drugs, tier placement), patient cost-sharing and utilization management restrictions. The comprehensive list of patient characteristics allows us to have a better understanding about factors associated with delayed OAC initiation.

The present study has some limitations. Diagnosis and procedure codes recorded in claims are used for administrative purposes and may be subject to inaccuracies or omissions (e.g., undercoding). Type of AF (e.g., paroxysmal vs. persistent) was not included in the multivariable regression models due to a large number of patients with unspecified type of AF which may cause misclassification on the type of AF. Some clinically relevant data such as lab measurements and factors related to physician prescribing behaviors or patient preference were not available in claims data and were not considered in the model. Payer approval of drug claims does not guarantee that the dispensed drug was consumed by the patient. Because of the high collinearity between drug access coverage characteristics and treatment agent, treatment agent was not included in the multivariable regression model. The multivariable analysis assessed the association between patient factors and delayed OAC initiation, but did not establish causality and may also be subject to uncontrolled confounding. Lastly, the generalizability of the findings may be limited by the underrepresentation of non-White patients, patients <65 years of age, and other patients with AF in the US who did not meet the inclusion criteria.

5. Conclusions

In this study of Medicare patients diagnosed with AF and prescribed OACs, nearly one-third of patients delayed OAC initiation. Specific patient characteristics such as black race, formulary restriction and some comorbidities were found to be associated with delayed OAC. Future studies are needed to better understand how to address barriers to timely OAC access for patients diagnosed with AF.

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Ethics statement

Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996; therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4) (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#46.101).

Previous presentations

Part of the results from the current study has been included in a poster presentation at the European Society of Cardiology Congress 2023.

CRediT authorship contribution statement

Xuemei Luo: Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Jose Chaves:** Writing – review & editing, Methodology. **Amol D. Dhamane:** Writing – review & editing, Methodology, Conceptualization. **Feng Dai:** Writing – review & editing, Methodology, Conceptualization. **Dominick Latremouille-Viau:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Aolin Wang:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

Dominick Latremouille-Viau and Aolin Wang are employees of Analysis Group who were paid consultants to Pfizer and Bristol Myers Squibb in connection with the development of this manuscript. Amol D. Dhamane is an employee and shareholder of Bristol Myers Squibb, one of the study sponsors. Xuemei Luo, Jose Chaves, and Feng Dai are employees and shareholders of Pfizer, one of the study sponsors.

Data availability

This study used the Medicare RIF data (DUA# RSCH-2021-56783). Data are stored at Center for Medicare and Medicaid Services (CMS) and accessed via an online portal, the Virtual Research Data Center (VRDC), managed by CMS. Data are not publicly accessible.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100369.

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