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ORIGINAL RESEARCH ARTICLE

Use of oral anticoagulants among individuals with cancer and atrial fibrillation in the United States, 2010–2016

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Abstract

Background: Anticoagulation among patients with cancer and atrial fibrillation is challenging due to elevated risk of bleeding and stroke. We characterized use of oral anticoagulants among patients with cancer and non-valvular atrial fibrillation (NVAF).

Methods: We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data and included patients with cancer aged ≥66 years with an incident diagnosis of NVAF from 2010 to 2016. We used a Cox proportional hazard model and multivariable logistic regression to identify factors associated with anticoagulant use versus no use and direct oral anticoagulants (DOACs) versus warfarin use, respectively.

Results: Of 27,702 patients with cancer and NVAF, 4469 (16.1%) used DOACs and 3577 (12.9%) used warfarin. Among 8046 anticoagulant users, DOACs use increased from 21.8% in 2011 to 76.2% in 2016, with a corresponding decline in warfarin use from 78.2% to 23.8%. Nearly 7 out of 10 patients with cancer and NVAF did not initiate anticoagulation in 2016. Anticoagulant use was more likely among those with higher CHA_2DS_2-VASc scores (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.27–1.90 for score ≥6 vs. 1) or with lower HAS-BLED scores (HR 1.96, 95% CI 1.67–2.30 for score 1 vs. ≥6). Among anticoagulant users, DOAC use was less likely than warfarin in those with higher CHA_2DS_2-VASc scores (odds ratio [OR] 0.53, 95% CI 0.33–0.84 for score ≥6 vs. 1).

Conclusions: Nearly 7 out of 10 patients with cancer and NVAF did not receive anticoagulation. Use of DOACs increased from 2010 to 2016, with a corresponding decline in warfarin use. DOACs are used less than warfarin among those at higher risk of stroke.

KEYWORDS
anticoagulation, atrial fibrillation, cancer, direct-acting oral anticoagulants

1 | INTRODUCTION

Patients with cancer are at increased risk of atrial fibrillation (AF). This is attributable to use of some chemotherapy agents, shared risk factors between cancer and AF (e.g., age and age-related comorbidities), pulmonary and pericardial cancer involvement, inflammation, and excessive oxidative stress.[1-4] Additionally, patients with cancer are at increased risk for both bleeding (as a result of cancer-related thrombocytopenia, disseminated intravascular coagulation, chemotherapy-related bone marrow suppression, tissue damage due to radiation, and surgery), and thrombosis events (due to increase in levels of procoagulants, inflammatory cytokines, cancer therapies, comorbidities, and patient-related factors such as age and extreme weight).[4] Major clinical trials have shown non-inferiority or superiority of direct oral anticoagulants (DOACs) over warfarin to reduce the risk of stroke or systemic embolism while having decreased risk of bleeding.[5,6] Despite this, randomized clinical trials of DOACs have included very few cancer patients and there is limited evidence regarding the safety and effectiveness of DOACs among cancer patients.[7-9] The current clinical guidelines recommend use of DOACs over warfarin in individuals with non-valvular atrial fibrillation (NVAF)[5]; however, there are no specific recommendations for patients with NVAF and cancer.

Anticoagulation among patients with cancer is challenging because of an increased risk of venous thromboembolism and bleeding, both due to cancer and its treatment.[4] Other factors such as drug–drug interactions, renal impairment, and thrombocytopenia may also complicate oral anticoagulant use in individuals with cancer.[4] A retrospective chart review of patients with cancer and AF from one large cancer center found that 44% of individuals who had elevated risk of stroke, but were not at high risk of bleeding, did not receive anticoagulation.[10] However, national patterns of oral anticoagulant use and factors associated with its use are lacking in patients with cancer and NVAF, and it is unclear how the introduction of DOACs has impacted overall anticoagulation rates and the use of warfarin. Identifying patient characteristics associated with oral anticoagulant use may help implement strategic plans to improve use of these medications among patients with cancer and NVAF.

We characterized use and patient characteristics associated with warfarin and DOACs among patients with cancer and incident NVAF. To do so, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data, a dataset containing detailed clinical information and medical and prescription claims for a large group of patients with cancer in the United States.

2 | METHODS

2.1 | Data source

We performed a retrospective cohort study using SEER linked to Medicare data from 2010 to 2016. The SEER-Medicare data reflect the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. SEER is a national cancer registry that collects patient demographic and cancer-related characteristics for approximately 35% of the U.S. population.[11] Medicare data include administrative claims of U.S. population predominantly aged greater than 65 years that provides information on beneficiaries' clinical diagnoses and treatments. More information about SEER-Medicare data and files can be found elsewhere.[11]

2.2 | Study population

We included patients who were diagnosed with the primary cancer (breast, bladder, colorectal, esophagus, lung, ovary, kidney, pancreas, prostate, stomach, and uterus) in SEER between 2010 and 2016, and newly diagnosed AF after cancer diagnosis. We identified AF using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) of 427.31[12] or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code of I48.0, I48.1x, I48.2x, or I48.91.[13] Individuals were included if they had one code for AF in an inpatient claim or at least 2 codes in outpatient or physician claims.[14] The date of NVAF diagnosis was considered the index date from which we measured time until oral anticoagulant use. Because DOACs are indicated for NVAF, we restricted the cohort to those with no diagnosis of mitral stenosis, heart valve surgery, or mitral/aortic valve surgery[5] within 12 months prior to AF diagnosis (Table S1). We included individuals in the cohort if they met the following criteria: (i) age over 66 years, (ii) continuous enrollment in fee-for-service Medicare plan with coverage for Medicare Parts A, B, and D in the 12 months prior to the index date, and (iii) no oral anticoagulant use in 1 year prior to the index date to capture new use of oral anticoagulants.

2.3 | Utilization measures

We assessed the following: (1) time to initiation of any oral anticoagulant, and (2) use of any DOACs or warfarin. Individuals were classified as oral anticoagulant users if they had at least one claim for warfarin or a DOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) after the index date. We also assessed first switching from warfarin to DOACs and switching from DOACs to warfarin.

2.4 | Patient characteristics

We explored patient characteristics, identified during the 12-month period preceding the index date, as potentially predicting oral anticoagulant use.[15,16] We included sociodemographic characteristics including age, race/ethnicity (Non-Hispanic white, black, Hispanic, other), median household income (quartiles), Medicaid eligibility, and residential census region. Cancer-related characteristics included

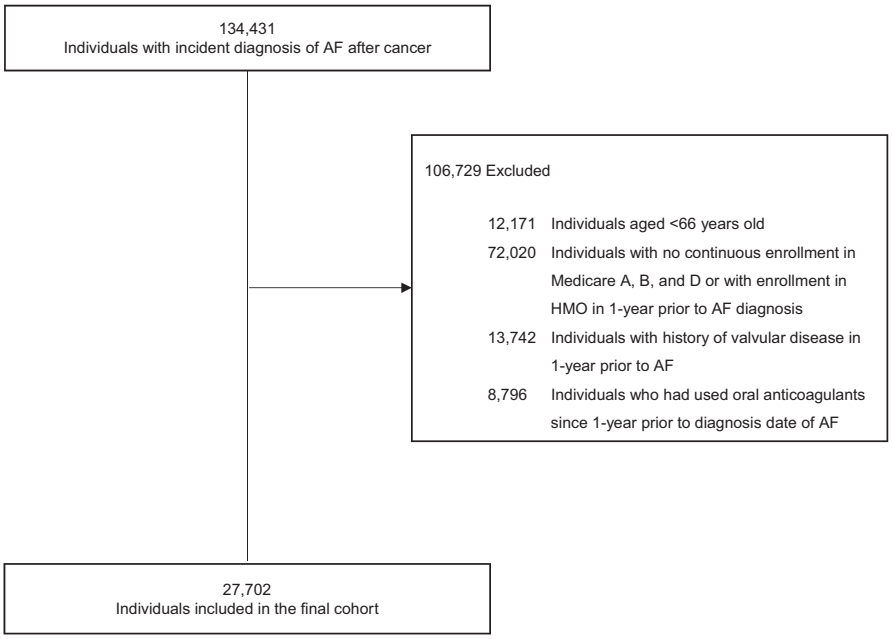


FIGURE 1 Cohort derivation. Abbreviations: AF, Atrial fibrillation; HMO, health maintenance organization

cancer site (breast, bladder, colorectal, esophagus, lung, ovary, kidney, pancreas, prostate, stomach, and uterus), cancer stage (stage 0 to IV as per American Joint Committee on Cancer classification system), cancer grade (grade I to IV), tumor size, and the receipt of chemotherapy. We defined active cancer if patients received radiotherapy or chemotherapy in 1 year prior to index date.

We also calculated the CHA_2DS_2-VASc and HAS-BLED scores for each individual. The CHA_2DS_2-VASc score, a point system indicating the risk of stroke, was calculated according to the following morbidities: congestive heart failure (1 point), hypertension (1 point), diabetes mellitus (1 point), prior stroke or transient ischemic attack or thromboembolism (2 points), vascular disease (1 point), age greater than 75 years (2 points), age 65–74 years (1 point), and sex category (female) (1 point).[17,18] The HAS-BLED score, for risk of bleeding, was calculated as follows: hypertension (1 point), renal disease (1 point), liver disease (1 point), stroke (1 point), bleeding history or predisposition (1 point), age >65 years (1 point), medications (antiplatelets and NSAIDs) and/or excessive alcohol intake (1 point), and labile international normalized ratio (INR) (1 point).[17,19] Since INR information is not included in claims data, we calculated the HAS-BLED score using all factors except labile INR, as has been done in previous studies.[16,20] Other clinical characteristics included the comorbidities of anemia, asthma, chronic obstructive lung disease (COPD), dementia, gout, hyperlipidemia, inflammatory arthritis, ischemic heart disease, cerebrovascular disease, and peptic ulcer disease.

We also explored whether use of other prescription medications was predictive of anticoagulant use: these included angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, antiangina vasodilators, antiarrhythmics, beta-blockers, calcium-channel blockers, diuretics, other antihypertensives, diabetes drugs, heparin and low-molecular-weight heparins, statins, non-statin lipid-lowering drugs, and proton-pump inhibitors.

2.5 | Statistical analysis

We used counts (proportions) and means (± standard deviation [SD]) to characterize baseline information on categorical and continuous variables, respectively. We compared characteristics of the oral anticoagulant users and non-users, and the DOACs users and warfarin users with Chi-square tests for categorical variables and *t*-tests for continuous variables. To assess the temporal changes in the use of oral anticoagulants, we described the annual proportion of patients with cancer and NVAF who received oral anticoagulants and tested the trend over time using the Cochrane–Armitage trend test. Among oral anticoagulant users, we calculated the proportions of warfarin and DOAC users by calendar year of medication initiation. We also described proportion of DOAC initiators who switched to warfarin and proportion of warfarin initiators who switched to DOAC.

We developed two regression models to determine the independent associations of patient characteristics with oral anticoagulant use. We assessed collinearity among all variables using variance inflation factor and there was no evidence of collinearity. First, we constructed a Cox proportional hazards regression model for time to initiation of oral anticoagulants, including all patient characteristics in the model. Individuals were censored at death, end of continuous enrollment in Medicare Part D, or end of study period, whichever occurred first. We reported adjusted hazard ratios (HR) and 95% confidence intervals (CI) from this model. Second, among individuals who received any oral anticoagulants, we constructed a multivariable logistic regression model for DOACs versus warfarin use that included all patient characteristics as covariates. We used indicator variable for missing values in all regression analyses. We reported adjusted odds ratios (OR) and 95% CI for each variable.

All analyses were performed using SAS version 9.4 (SAS Institute). The study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

3 | RESULTS

3.1 | Cohort characteristics

We identified 134,431 patients with a new diagnosis of AF after a cancer diagnosis from 2010–2016. After excluding individuals who did not meet inclusion criteria, the final cohort included 27,702 patients with a new diagnosis of NVAF (Figure 1). The mean age of patients in the cohort was 77.7 ± 7.6 years; 49.6% were female, and 84.4% were non-Hispanic white. Lung (27.0%), breast (16.3%), prostate (16.8%), and colorectal (15.0%) cancers accounted for three-fourth of the cohort. Of 27,702 individuals (median follow-up, 3.3 months; interquartile range, 16.0 months), 8046 (29.0%) initiated oral anticoagulants. Of whom, 4469 (55.5%) initiated DOACs and 3577 (44.5%) initiated warfarin. Among 8046 anticoagulant users, 71.4% initiated oral anticoagulation within 3 months, 7.0% within 4 to 6 months, 7.2% within 7–12 months, and 14.4% after more than 12 months after NVAF diagnosis.

Individuals who used oral anticoagulants differed significantly from non-users (Table 1). Oral anticoagulant users were younger and more commonly non-Hispanic white. Fewer oral anticoagulant users had active cancer compared to non-users. Also, fewer oral anticoagulant users had high HAS-BLED scores, anemia, or dementia ($p < 0.0001$ for all mentioned characteristics).

In comparison to individuals initiating warfarin, those who initiated DOACs were younger ($p = 0.0001$), more commonly non-Hispanic white ($p = 0.0013$), with a higher quartile of income per capita ($p < 0.0001$), and less commonly with a CHA_2DS_2-VASc score greater than 5 ($p < 0.0001$) (Table S2). In general, DOAC users had lower rates of comorbidities than warfarin users.

3.2 | Patterns of oral anticoagulant use

Overall, the use of oral anticoagulants ranged from 27.3% in 2010 to 26.0% in 2011, 27.2% in 2012, 28.1% in 2013, 31.1% in 2014, 29.5% in 2015, and 31.5% in 2016 ($p < 0.0001$ for trend). Similarly, among individuals who had CHA_2DS_2-VASc greater than 2, who made up the most of the NVAF study population ($N = 27,294$), the use of oral anticoagulants increased from 27.3% in 2010 to 31.5% in 2016 ($p < 0.0001$ for trend). Among individuals using oral anticoagulants, the use of DOACs increased from 21.8% in 2011 to 76.2% in 2016, with a corresponding decline in warfarin use from 78.2% in 2011 to 23.8% in 2016 (Figure 2). A greater proportion of individuals switched from warfarin to DOACs (243/3577, 6.8%) than switched from DOACs to warfarin (119/4469, 2.7%) at any time during the follow-up period. Among individuals who switched oral anticoagulants, 77.8% (189/243) switched from warfarin to DOAC and 82.4% (98/119) switched from DOAC to warfarin within the first 6 months after anticoagulation initiation.

3.3 | Characteristics independently associated with time to anticoagulant initiation

Oral anticoagulant initiation was less likely among older individuals (HR 0.92, 95% CI 0.91–0.94 for each 5-year increase), non-Hispanic black race (HR 0.81, 95% CI 0.73–0.89 compared to non-Hispanic White race), those who had higher cancer stage (e.g., cancer stage IV vs. stage 0, HR 0.68, 95% CI 0.60–76) or higher cancer grade (e.g., cancer grade IV vs. grade I, HR 0.83, 95% CI 0.73–0.95) as well as those who received chemotherapy (HR, 0.93, 95% CI 0.88–0.98) (Figure 3). Anticoagulant use was more likely among those with CHA_2DS_2-VASc score of 4 or more (e.g., HR 1.55, 95% CI 1.27–1.90 for CHA_2DS_2-VASc score ≥6 vs. 1) or those with lower HAS-BLED scores (e.g., HR 1.96, 95% CI 1.67–2.30 for score 1 vs. ≥6). Additionally, the presence of comorbidities, including anemia (HR 0.82, 95% CI 0.78–0.86), coronary revascularization (HR 0.53, 95% CI 0.44–0.64), or dementia (HR 0.54, 95% CI 0.48–0.61), reduced the likelihood of oral anticoagulant initiation. Individuals concurrently using antihypertensive medications, antiarrhythmics, statins, and heparin and low-molecular-weight heparin were more likely to use oral anticoagulants.

3.4 | Characteristics independently associated with direct-acting oral anticoagulant use

Figure 4 presents characteristics associated with DOAC use among oral anticoagulant users. Individuals with the highest income per capita (≥ $36,884) relative to the lowest income per capita (<$21,123) (OR 1.43, 95% CI 1.23–1.67), and those with AF diagnosis in the most recent calendar year (e.g., OR, 12.00, 95% CI, 9.11–15.79 for 2016 vs. 2010) were more likely to receive DOACs than warfarin. Compared to CHA_2DS_2-VASc score of 1, individuals with score of 5 (OR 0.63, 95% CI 0.40–0.99) or score of 6 or more (OR 0.53, 95% CI 0.33–0.84) had lower likelihood of using DOACs than warfarin.

4 | DISCUSSION

In this large study of patients with cancer and NVAF, oral anticoagulant use increased approximately 15%, from 27.3% to 31.5%, during the 7-year study period. Among oral anticoagulant users, DOACs use increased substantially from 21.8% in 2011 to 76.2% in 2016, with a corresponding reduction in warfarin use. Use of oral anticoagulants was greater among those with higher CHA_2DS_2-VASc scores or lower HAS-BLED scores. Among oral anticoagulant users, DOACs were used less than warfarin among those at higher risk of stroke.

Although use of anticoagulants increased from 2010 to 2016, our findings suggest potential underuse of oral anticoagulants, with nearly 7 out of 10 patients with cancer and NVAF not initiating anticoagulation in 2016. These findings persisted even after

TABLE 1 Individuals with non-valvular atrial fibrillation after a cancer diagnosis ($N = 27,702$)

Characteristics	Oral anticoagulant users, $N = 8046$	Oral anticoagulant non-users, $N = 19,656$	p-value
Sociodemographic characteristics			
Age, mean ± SD	76.5 ± 6.8	78.2 ± 7.8	<0.0001
Gender			
Male	4094 (50.9)	9879 (50.3)	0.35
Female	3952 (49.1)	9777 (49.7)	
Race/ethnicity			
Non-Hispanic White	7102 (88.3)	16,279 (82.8)	<0.0001
Black	475 (5.9)	1679 (8.5)	
Hispanic	108 (1.3)	332 (1.7)	
Other	361 (4.5)	1366 (7.0)	
Income			
Q1	1745 (21.7)	4994 (25.4)	<0.0001
Q2	1942 (24.1)	4780 (24.3)	
Q3	2009 (25.0)	4717 (24.0)	
Q4	2135 (26.5)	4601 (23.4)	
Not available	216 (2.7)	564 (2.9)	
Medicaid eligibility	1707 (21.2)	6123 (31.2)	<0.0001
Census region			
West	3472 (43.2)	8986 (45.7)	<0.0001
South	3290 (40.9)	7402 (37.7)	
Northeast	509 (6.3)	1243 (6.3)	
Midwest	703 (8.7)	1854 (9.4)	
Others	72 (0.9)	171 (0.9)	
Cancer characteristics			
Cancer site			
Bladder	681 (8.5)	1594 (8.1)	<0.0001
Breast	1673 (20.8)	2849 (14.5)	
Colorectal	1133 (14.1)	3020 (15.4)	
Esophagus	105 (1.3)	403 (2.1)	
Kidney	379 (4.7)	793 (4.0)	
Lung	1530 (19.0)	5951 (30.3)	
Ovary	121 (1.5)	360 (1.8)	
Pancreas	148 (1.8)	769 (3.9)	
Prostate	1847 (23.0)	2818 (14.3)	
Stomach	114 (1.4)	536 (2.7)	
Uterus	315 (3.9)	563 (2.9)	
Cancer stage			
Stage 0	737 (9.2)	1242 (6.3)	<0.0001
Stage I	2704 (33.6)	4803 (24.4)	
Stage II	2220 (27.6)	4291 (21.8)	
Stage III	1161 (14.4)	3103 (15.8)	
Stage IV	834 (10.4)	4615 (23.5)	
Not available	390 (4.9)	1602 (8.2)	

(Continues)

TABLE 1 (Continued)

Characteristics	Oral anticoagulant users, *N* = 8046	Oral anticoagulant non-users, *N* = 19,656	*p*-value
Cancer grade			
Grade I	926 (11.5)	1583 (8.1)	<0.0001
Grade II	2968 (36.9)	5752 (29.3)	
Grade III	2289 (28.5)	5228 (26.6)	
Grade IV	370 (4.6)	1063 (5.4)	
Cell type not determined	1493 (18.6)	6030 (30.7)	
Tumor size (cm)			
0–1	719 (8.9)	1211 (6.2)	<0.0001
1.1–2	1231 (15.3)	2140 (10.9)	
2.1–3	948 (11.8)	2376 (12.1)	
3.1–4	750 (9.3)	2045 (10.4)	
4.1–5	554 (6.9)	1663 (8.5)	
>5	1170 (14.5)	3756 (19.1)	
Not available	2674 (33.2)	6465 (32.9)	
Use of chemotherapy	1892 (23.5)	5467 (27.8)	<0.0001
Receipt of radiation	1072 (13.3)	2960 (15.1)	0.0008
Time from cancer diagnosis to AF diagnosis (years)			
<2	2406 (29.9)	4361 (22.2)	<0.0001
2–5	5205 (64.7)	14,503 (73.8)	
≥5	435 (5.4)	792 (4.0)	
Active cancer			
Yes	2350 (29.2)	6547 (33.3)	
No	5696 (70.8)	13,109 (66.7)	<0.0001
Clinical characteristics			
CHA_2DS_2-VASc score			
1	130 (1.6)	278 (1.4)	<0.0001
2	707 (8.8)	1407 (7.2)	
3	1415 (17.6)	2972 (15.1)	
4	1820 (22.6)	4271 (21.7)	
5	1582 (19.7)	4130 (21.0)	
≥6	2392 (29.7)	6598 (33.6)	
HAS-Bled score			
1	315 (3.9)	566 (2.9)	<0.0001
2	1767 (22.0)	3039 (15.5)	
3	2591 (32.2)	5808 (30.0)	
4	1741 (21.6)	5132 (26.1)	
5	991 (12.3)	2758 (14.0)	
≥6	641 (8.0)	2353 (12.0)	
Anemia	3135 (39.0)	10,122 (51.5)	<0.0001
Asthma	942 (11.7)	2416 (12.3)	0.18
COPD	2621 (33.8)	8262 (42.0)	<0.0001
Coronary revascularization	121 (1.5)	410 (2.1)	0.002
Dementia	282 (3.5)	1873 (9.5)	<0.0001
Gout	661 (8.2)	1300 (6.6)	<0.0001
Hyperlipidemia	5953 (74.0)	13,365 (68.0)	<0.0001

TABLE 1 (Continued)

Characteristics	Oral anticoagulant users, *N* = 8046	Oral anticoagulant non-users, *N* = 19,656	*p*-value
Inflammatory arthritis	267 (3.3)	736 (3.7)	0.08
Other Ischemic heart disease	3161 (39.3)	8288 (42.2)	<0.0001
Other cerebrovascular disease	272 (3.4)	843 (4.3)	0.0005
Peptic ulcer disease	224 (2.8)	927 (4.7)	<0.0001
Co-medication use			
ACE inhibitors or ARB	5952 (74.0)	12,842 (65.3)	<0.0001
Antiangina vasodilators	1832 (22.8)	4182 (21.3)	0.006
Antiarrhythmics	3782 (47.0)	6554 (33.3)	<0.0001
Beta-Blockers	6833 (84.9)	13,627 (69.3)	<0.0001
Calcium-channel blockers	3534 (43.9)	7802 (39.7)	<0.0001
Diuretics	5988 (74.4)	12,655 (64.4)	<0.0001
Other antihypertensives	1388 (17.3)	3044 (15.5)	0.0003
Diabetes drugs	2564 (31.9)	5762 (29.3)	<0.0001
Heparin and low-molecular-weight heparins	1335 (16.6)	1304 (6.6)	<0.0001
Statins	5801 (72.1)	12,331 (62.7)	<0.0001
Non-statin lipid-lowering drugs	1254 (15.6)	2547 (13.0)	<0.0001
Proton-pump inhibitors	4812 (59.8)	11,384 (57.9)	0.004

Abbreviations: ACE, angiotensin-converting enzyme; AF, Atrial fibrillation; ARB, angiotensin-receptor blockers; cm, centimeter; COPD, chronic obstructive pulmonary disease; *N*, number; Q, quartile; SD, standard deviation.

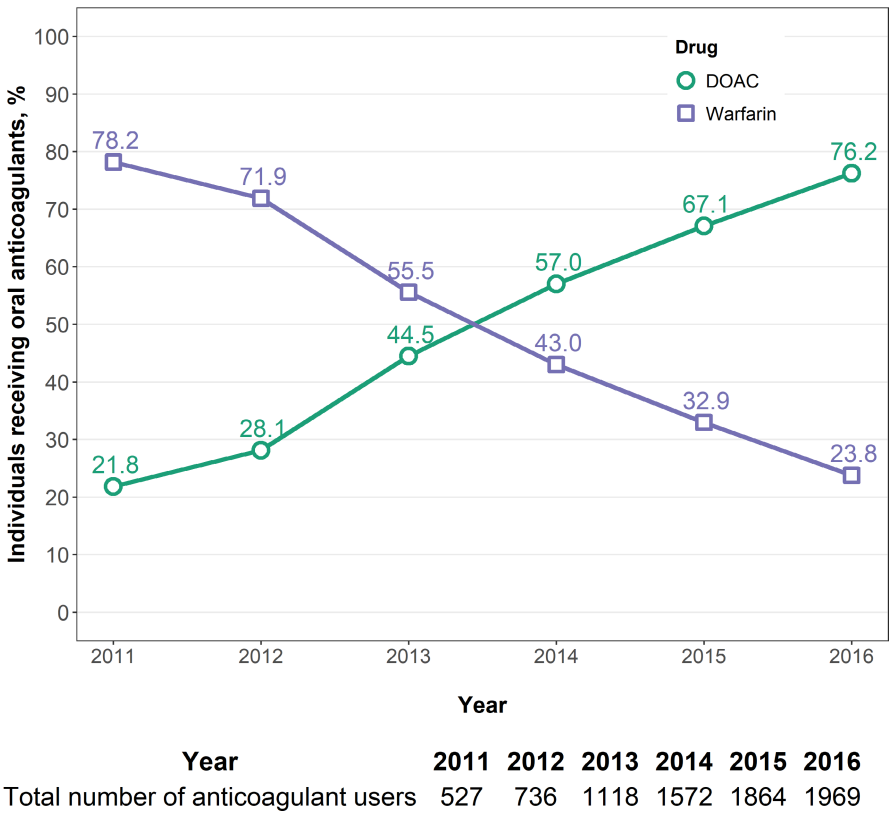
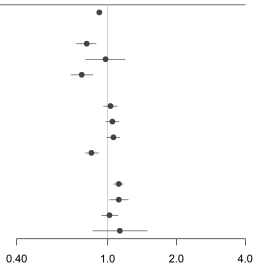


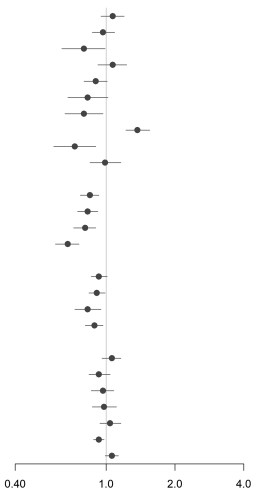
FIGURE 2 Trends in direct-acting oral anticoagulant and warfarin use among individuals with cancer and non-valvular atrial fibrillation who received at least one oral anticoagulants, *N* = 8046. *Note*: We did not report data for 2010 because the SEER policy requires cells with 11 or fewer individuals to be suppressed. Abbreviations: DOAC, direct-acting oral anticoagulants

limiting our cohort to those with CHA_2DS_2-VASc greater than 2. This extends the results of a single-center study in 2016 of patients with cancer and AF, which found that nearly half of the eligible patients did not receive oral anticoagulants.[10] Our results are consistent with prior findings of underuse of anticoagulants in a general population, with only 50% to 60% of patients with AF who are

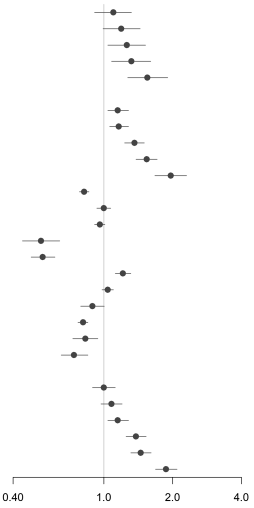
Sociodemographic characteristics	All patients N=27,702	Oral anticoagulants rate, %	Hazard ratio (95% CI)
Age (5 years)			0.92 (0.91, 0.94)
Race/ethnicity (ref: Non-Hispanic White)	23,381 (84.4)	30.4	
Black	2,154 (7.8)	22.1	0.81 (0.73, 0.89)
Hispanic	440 (1.6)	24.6	0.98 (0.80, 1.19)
Other	1,727 (6.2)	20.9	0.77 (0.69, 0.86)
Income (ref: Q1)	6,739 (24.3)	25.9	
Q2	6,722 (24.3)	28.9	1.03 (0.96, 1.10)
Q3	6,725 (24.3)	29.9	1.05 (0.98, 1.12)
Q4	6,736 (24.3)	31.7	1.06 (0.99, 1.13)
Medicaid eligibility	7,830 (28.3)	21.8	0.85 (0.80, 0.91)
Census region (ref: West)	12,458 (45.0)	27.9	
South	10,692 (38.6)	30.8	1.12 (1.06, 1.17)
Northeast	1,752 (6.3)	29.1	1.12 (1.02, 1.23)
Midwest	2,557 (9.2)	27.5	1.02 (0.94, 1.11)
Others	243 (0.9)	29.6	1.13 (0.86, 1.49)



Cancer characteristics	All patients N=27,702	Oral anticoagulants rate, %	Hazard ratio (95% CI)
Cancer site (ref: Bladder)	2,275 (8.2)	29.9	
Breast	4,522 (16.3)	37.0	1.07 (0.95, 1.20)
Colorectal	4,153 (15.0)	27.3	0.97 (0.87, 1.09)
Esophagus	508 (1.8)	20.7	0.80 (0.64, 0.99)
Kidney	1,172 (4.2)	32.3	1.07 (0.92, 1.23)
Lung	7,481 (27.0)	20.5	0.90 (0.80, 1.01)
Ovary	481 (1.7)	25.2	0.83 (0.68, 1.02)
Pancreas	917 (3.3)	16.1	0.80 (0.66, 0.97)
Prostate	4,665 (16.8)	39.6	1.37 (1.22, 1.55)
Stomach	650 (2.4)	17.5	0.73 (0.59, 0.90)
Uterus	878 (3.2)	35.9	0.99 (0.85, 1.16)
Cancer stage (ref: Stage 0)	1,979 (7.1)	37.2	
Stage I	7,507 (27.1)	36.0	0.85 (0.77, 0.93)
Stage II	6,511 (23.5)	34.1	0.83 (0.75, 0.92)
Stage III	4,264 (15.4)	27.2	0.81 (0.72, 0.90)
Stage IV	5,449 (19.7)	15.3	0.68 (0.60, 0.76)
Cancer grade (ref: Grade I)	2,509 (9.1)	36.9	
Grade II	8,720 (31.5)	34.0	0.93 (0.86, 1.01)
Grade III	7,517 (27.1)	30.5	0.91 (0.84, 0.99)
Grade IV	1,433 (5.2)	25.8	0.83 (0.73, 0.95)
Cell type not determined	7,523 (27.2)	19.9	0.89 (0.81, 0.97)
Tumor size (cm) (ref: 0-1)	1,930 (7.0)	37.3	
1.1 - 2	3,371 (12.2)	36.5	1.06 (0.96, 1.16)
2.1 - 3	3,324 (12.0)	28.5	0.93 (0.84, 1.04)
3.1 - 4	2,795 (10.1)	26.8	0.97 (0.86, 1.08)
4.1 - 5	2,217 (8.0)	25.0	0.98 (0.87, 1.11)
>5	4,926 (17.8)	23.8	1.04 (0.94, 1.16)
Use of chemotherapy	7,359 (26.6)	25.7	0.93 (0.88, 0.98)
Use of radiation	4,032 (14.6)	26.6	1.06 (0.99, 1.13)



Clinical characteristics	All patients N=27,702	Oral anticoagulants rate, %	Hazard ratio (95% CI)
CHA2DS2-VASc Score (ref: 1)	408 (1.5)	31.9	
2	2,114 (7.6)	33.4	1.10 (0.91, 1.32)
3	4,387 (15.8)	32.3	1.19 (0.99, 1.44)
4	6,091 (22.0)	29.9	1.26 (1.04, 1.52)
5	5,712 (20.6)	27.7	1.32 (1.08, 1.60)
>=6	8,990 (32.5)	26.6	1.55 (1.27, 1.90)
HAS-Bled score (ref: >= 6)	2,994 (10.8)	21.4	
5	3,749 (13.5)	26.4	1.15 (1.04, 1.28)
4	6,873 (24.8)	25.3	1.16 (1.06, 1.28)
3	8,399 (30.3)	30.9	1.36 (1.23, 1.50)
2	4,806 (17.4)	36.8	1.54 (1.38, 1.71)
1	881 (3.2)	35.8	1.96 (1.67, 2.30)
Anemia	13,257 (47.9)	23.7	0.82 (0.78, 0.86)
Asthma	3,358 (12.1)	28.1	1.000 (0.93, 1.07)
COPD	10,983 (39.7)	24.8	0.96 (0.91, 1.01)
Coronary revascularization	531 (1.9)	22.8	0.53 (0.44, 0.64)
Dementia	2,155 (7.8)	13.1	0.54 (0.48, 0.61)
Gout	1,961 (7.1)	33.7	1.21 (1.12, 1.31)
Hyperlipidemia	19,318 (69.7)	30.8	1.04 (0.98, 1.10)
Inflammatory arthritis	1,003 (3.6)	26.6	0.89 (0.79, 1.003)
Other Ischemic heart disease	11,449 (41.3)	27.6	0.81 (0.77, 0.85)
Other cerebrovascular disease	1,115 (4.0)	24.4	0.83 (0.73, 0.94)
Peptic ulcer disease	1,151 (4.2)	19.5	0.74 (0.65, 0.85)
Year of atrial fibrillation diagnosis (ref: 2010)	1,800 (6.5)	27.3	
2011	2,875 (10.4)	26.0	0.998 (0.89, 1.12)
2012	3,580 (12.9)	27.2	1.08 (0.97, 1.20)
2013	4,371 (15.8)	28.1	1.15 (1.04, 1.28)
2014	5,165 (18.6)	31.1	1.38 (1.25, 1.53)
2015	5,772 (20.8)	29.5	1.45 (1.31, 1.61)
2016	4,139 (14.9)	31.5	1.87 (1.68, 2.09)



Co-medication use	All patients N=27,702	Oral anticoagulants rate, %	Hazard ratio (95% CI)
ACE inhibitors or ARBs	18,794 (67.8)	31.7	1.14 (1.07, 1.20)
Antiangina vasodilators	6,014 (21.7)	30.5	0.95 (0.90, 1.01)
Antiarrhythmics	10,336 (37.3)	36.6	1.34 (1.28, 1.40)
Beta-Blockers	20,460 (73.9)	33.4	1.67 (1.56, 1.78)
Calcium-channel blockers	11,336 (40.9)	31.2	1.03 (0.98, 1.08)
Diuretics	18,643 (67.3)	32.1	1.29 (1.22, 1.36)
Other antihypertensives	4,432 (16.0)	31.3	0.98 (0.92, 1.04)
Diabetes drugs	8,326 (30.1)	30.8	0.97 (0.92, 1.03)
Heparin and low-molecular-weight heparins	2,639 (9.5)	50.6	1.96 (1.85, 2.08)
Statins	18,132 (65.5)	32.0	1.15 (1.08, 1.22)
Non-statin lipid-lowering drugs	3,801 (13.7)	33.0	1.03 (0.97, 1.10)
Proton-pump inhibitors	16,196 (58.5)	29.7	0.98 (0.93, 1.02)

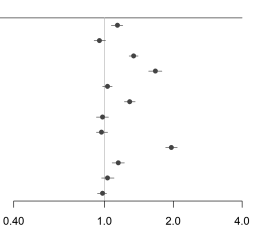


FIGURE 3 Patient characteristics associated with initiation of oral anticoagulants among patients with non-valvular atrial fibrillation after cancer diagnosis. *Note*: Hazard ratios are from multivariable models including all variables displayed in the forest plot. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; COPD, chronic obstructive pulmonary disease; Q, quartile; ref, reference

Sociodemographic characteristics	All patients N=8,046	DOAC rate,%	Odds ratio (95% CI)
Age (5 years)			0.96 (0.92, 0.999)
Race/ethnicity (ref: Non-Hispanic White)	7,102 (88.3)	56.0	
Black	475 (5.9)	48.6	0.80 (0.64, 0.998)
Hispanic	108 (1.3)	45.4	0.98 (0.63, 1.52)
Other	361 (4.5)	58.7	1.10 (0.86, 1.40)
Income (ref: Q1)	1,745 (21.7)	52.3	
Q2	1,942 (24.1)	49.6	0.79 (0.69, 0.92)
Q3	2,009 (25.0)	55.5	1.02 (0.88, 1.19)
Q4	2,135 (26.5)	63.1	1.43 (1.23, 1.67)
Medicaid eligibility	1,707 (21.2)	50.0	0.98 (0.86, 1.12)
Census region (ref: West)	3,472 (43.2)	56.5	
South	3,290 (40.9)	53.2	0.86 (0.77, 0.96)
Northeast	509 (6.3)	65.0	1.74 (1.39, 2.16)
Midwest	703 (8.7)	54.3	0.94 (0.78, 1.13)
Others	72 (0.9)	61.1	0.71 (0.38, 1.30)

Cancer characteristics	All patients N=8,046	DOAC rate, %	Odds ratio (95% CI)
Cancer site (ref: Bladder)	681 (8.5)	57.6	
Breast	1,673 (20.8)	59.7	1.01 (0.78, 1.31)
Colorectal	1,133 (14.1)	46.6	0.79 (0.60, 1.03)
Esophagus	105 (1.3)	49.5	0.94 (0.58, 1.54)
Kidney	379 (4.7)	50.4	0.71 (0.51, 0.98)
Lung	1,530 (19.0)	48.6	0.83 (0.64, 1.09)
Ovary	121 (1.5)	43.0	0.95 (0.60, 1.52)
Pancreas	148 (1.8)	35.8	0.65 (0.42, 1.02)
Prostate	1,847 (23.0)	65.6	1.09 (0.82, 1.43)
Stomach	114 (1.4)	50.0	1.04 (0.65, 1.67)
Uterus	315 (3.9)	60.0	1.15 (0.82, 1.62)
Cancer stage (ref: Stage 0)	737 (9.2)	59.4	
Stage I	2,704 (33.6)	60.0	1.10 (0.88, 1.37)
Stage II	2,220 (27.6)	57.7	0.96 (0.75, 1.21)
Stage III	1,161 (14.4)	48.7	0.86 (0.66, 1.11)
Stage IV	834 (10.4)	43.1	0.74 (0.57, 0.98)
Cancer grade (ref: Grade I)	926 (11.5)	58.2	
Grade II	2,968 (36.9)	57.6	1.21 (1.02, 1.44)
Grade III	2,289 (28.5)	55.5	1.13 (0.94, 1.37)
Grade IV	370 (4.6)	50.3	0.99 (0.74, 1.33)
Cell type not determined	1,493 (18.6)	51.2	1.25 (1.02, 1.53)
Tumor size (cm) (ref: 0-1)	719 (8.9)	60.9	
1.1 - 2	1,231 (15.3)	57.8	1.01 (0.82, 1.25)
2.1 - 3	948 (11.8)	52.9	1.001 (0.79, 1.27)
3.1 - 4	750 (9.3)	50.5	0.98 (0.76, 1.26)
4.1 - 5	554 (6.9)	48.7	0.96 (0.73, 1.26)
>5	1,170 (14.5)	47.7	0.97 (0.76, 1.24)
Use of chemotherapy	1,892 (23.5)	55.6	1.05 (0.92, 1.19)
Use of radiation	1,072 (13.3)	46.5	0.99 (0.85, 1.16)

Clinical characteristics	All patients N=8,046	DOAC rate, %	Odds ratio (95% CI)
CHA2DS2-VASc Score (ref: 1)	130 (1.6)	63.9	
2	707 (8.8)	63.5	0.81 (0.52, 1.26)
3	1,415 (17.6)	62.1	0.77 (0.50, 1.19)
4	1,820 (22.6)	58.2	0.69 (0.44, 1.07)
5	1,582 (19.7)	54.7	0.63 (0.40, 0.99)
>=6	2,392 (29.7)	47.3	0.53 (0.33, 0.84)
HAS-Bled score (ref: >= 6)	641 (8.0)	48.4	
5	991 (12.3)	52.0	1.11 (0.89, 1.39)
4	1,741 (21.6)	51.5	0.95 (0.76, 1.17)
3	2,591 (32.2)	56.4	1.07 (0.86, 1.32)
2	1,767 (22.0)	62.9	1.20 (0.94,1.53)
1	315 (3.9)	55.6	0.83 (0.58, 1.19)
Anemia	3,135 (39.0)	52.4	0.99 (0.89, 1.11)
Asthma	942 (11.7)	54.5	1.01 (0.86, 1.19)
COPD	2,621 (33.8)	52.1	0.94 (0.84, 1.05)
Coronary revascularization	121 (1.5)	53.7	0.54 (0.36, 0.80)
Dementia	282 (3.5)	51.4	0.91 (0.69, 1.20)
Gout	661 (8.2)	53.1	0.84 (0.70, 1.002)
Hyperlipidemia	5,953 (74.0)	56.1	1.08 (0.95, 1.23)
Inflammatory arthritis	267 (3.3)	50.9	0.95 (0.72, 1.24)
Other Ischemic heart disease	3,161 (39.3)	53.1	1.01 (0.90, 1.13)
Other cerebrovascular disease	272 (3.4)	72.4	1.17 (0.86, 1.60)
Peptic ulcer disease	224 (2.8)	45.5	0.88 (0.65, 1.19)
Year of atrial fibrillation diagnosis (ref: 2010)	491 (6.1)	20.2	
2011	746 (9.3)	30.2	1.64 (1.24, 2.18)
2012	974 (12.1)	39.0	2.39 (1.83, 3.12)
2013	1,227 (15.3)	49.9	3.80 (2.94, 4.93)
2014	1,604 (19.9)	61.0	6.09 (4.72, 7.86)
2015	1,704 (21.1)	68.0	8.02 (6.21, 10.36)
2016	1,303 (16.2)	78.1	12.00 (9.11, 15.79)

Co-medication use	All patients N=8,046	DOAC rate, %	Odds ratio (95% CI)
ACE inhibitors or ARBs	5,952 (74.0)	56.1	1.23 (1.08, 1.39)
Antiangina vasodilators	1,832 (22.8)	51.2	0.90 (0.79, 1.02)
Antiarrhythmics	3,782 (47.0)	55.4	1.15 (1.04, 1.27)
Beta-Blockers	6,833 (84.9)	55.6	1.002 (0.87, 1.16)
Calcium-channel blockers	3,534 (43.9)	54.6	0.95 (0.86, 1.06)
Diuretics	5,988 (74.4)	54.0	0.93 (0.83, 1.06)
Other antihypertensives	1,388 (17.3)	51.3	0.93 (0.81, 1.06)
Diabetes drugs	2,564 (31.9)	51.3	0.85 (0.76, 0.96)
Heparin and low-molecular-weight heparins	1,335 (16.6)	30.3	0.32 (0.28, 0.37)
Statins	5,801 (72.1)	56.1	1.11 (0.98, 1.26)
Non-statin lipid-lowering drugs	1,254 (15.6)	58.0	1.24 (1.08, 1.43)
Proton-pump inhibitors	4,812 (59.8)	53.7	1.07 (0.96, 1.19)

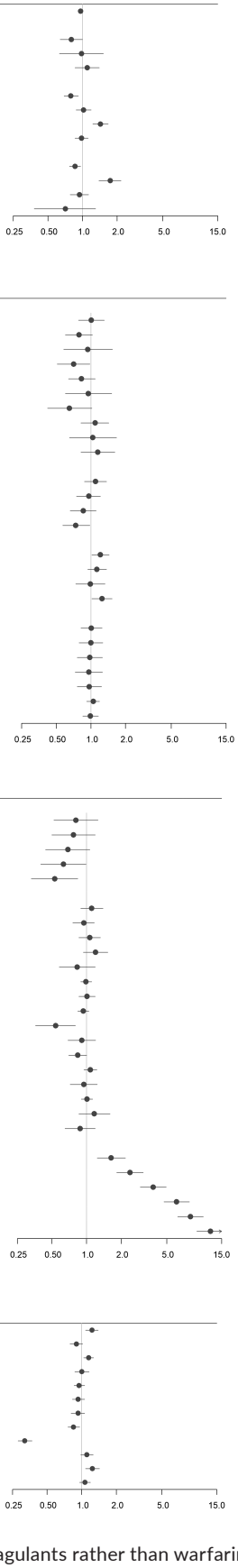


FIGURE 4 Patient characteristics associated with initiation of direct-acting oral anticoagulants rather than warfarin among patients with non-valvular atrial fibrillation after cancer diagnosis. *Note*: Odds ratios are from multivariable models including all variables displayed in the forest plot. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; COPD, chronic obstructive pulmonary disease; Q, quartile; ref, reference

eligible for anticoagulants actually receiving these medications.[21] Concerns about increased risk of bleeding due to cancer-related thrombocytopenia, which is common among patients with cancer, or chemotherapy-related bone marrow suppression may have contributed to limited use of oral anticoagulants among patients with cancer and NVAF.[22] Patients with AF and cancer are also less likely to see cardiologists compared to those without cancer, which may also contribute to suboptimal anticoagulation.[23]

We also found that 21.6% of the study population started anticoagulants beyond 6 months after NVAF diagnosis. Although we did not evaluate factors associated with delayed initiation of anticoagulants, another study[21] found that Medicaid eligibility and region of residence were associated with higher odds of late initiation of DOACs (6 to 11 months after AF diagnosis); while higher HAS-BLED score was associated with higher odds of late initiation of warfarin.

Our findings showed widespread substitution of DOACs for warfarin among patients with cancer and NVAF, a pattern that has also been observed among individuals with NVAF without cancer.[24,25] In 2016, among those receiving oral anticoagulants, three-fourths of individuals received DOACs. DOACs might be more preferred over warfarin in patients with cancer as they do not require frequent INR monitoring, and have less drug-food and drug–drug interactions.[26,27] In the absence of specific guideline recommendations for patients with cancer and NVAF, clinical guidelines directed at the general population and favorable safety and effectiveness profile of DOACs, may have driven their increased use.[5,17,28]

CHA_2DS_2-VASc score is recommended by guidelines and commonly used to assess stroke risk in general population with AF,[5] but its predictive value to assess stroke risk among patients with cancer and AF is limited.[29-31] Although anticoagulants are recommended for individuals with NVAF having CHA_2DS_2-VASc scores greater than 2,[5] we found higher use of oral anticoagulants among individuals with CHA_2DS_2-VASc score of greater than 4 indicating that clinicians are reserving anticoagulants for individuals at even higher risk of stroke, which might reflect concerns about higher risk of bleeding in individuals with cancer.[32] Consistent with prior study, we found lower likelihood of use of DOACs relative to warfarin in those having a high risk of stroke (CHA_2DS_2-VASc score greater than 5).[25,31] Limited evidence on the safety and effectiveness of DOACs among individuals with cancer and NVAF, and the lack of reversal agents at the time studied here, may explain lower use of DOACs compared to warfarin.

The appropriate use of anticoagulation is balance between stroke prevention and bleeding risk over time. We found several clinical factors that may increase the risk of bleeding that were associated with less oral anticoagulant use. For example, higher cancer stage and higher grade reduced the likelihood of oral anticoagulant use. This is not surprising as individuals with advanced cancer have higher risks of bleeding due to tumor invasion,[33] thrombocytopenia, and need for invasive procedures.[32] We also found higher HAS-BLED scores were associated with reduced likelihood of oral anticoagulant use, a finding reflecting clinical guidelines governing the risk/benefit balance of these products in the general poulation.[5,17] Our findings mirror the results of a single-center study that found that a higher CHA_2DS_2-VASc score was associated with a greater likelihood of anticoagulant use; while a higher HAS-BLED score or receipt of chemotherapy was associated with a lower likelihood of use of these medications.[10]

Our findings are consistent with previous studies indicating that not only clinical factors but also sociodemographic characteristics, such as age and race, are associated with initiation of oral anticoagulants.[34,35] Association of higher income with greater likelihood of DOACs versus warfarin use may be due to better ability to cover higher out-of-pocket costs associated with the DOACs.[36-38]

Our study had limitations. First, the generalizability of our findings is limited to older individuals with cancer with fee-for-service Medicare coverage. In addition, SEER registry database is not completely generalizable to U.S. cancer population.[39] Second, administrative claims data cannot capture clinical details used to make individual care decisions, such as low platelet counts leading to no initiation of anticoagulants in some patients. Therefore, we cannot determine underuse of oral anticoagulants with certainty. To define NVAF, we used a comprehensive set of ICD and procedural codes to exclude patients who may have had AF associated with valvular disease. This may have excluded a small set of patients with valve surgeries who would be appropriately treated with DOACs according to guidelines. However, the ICD or procedural codes used to define NVAF were commonly used by previous studies using claims and registry data to define patients with non-valvular atrial firillation.[36,40-42] Third, we did not evaluate oral anticoagulant use among individuals who are actively receiving cancer treatment. Fourth, we characterized oral anticoagulant and DOAC use only until 2016 and noted potential underuse of oral anticoagulants. Further work is warranted to ascertain how potential underuse of oral anticoagulants in patients with cancer and NVAF may affect cardiovascular morbidity and mortality in this population. Importantly, effective and safe anticoagulation strategies should be studied in the cancer population since these patients have higher life expectancy as the result of targeted-therapies and thus, are at higher risk of cardiovascular diseases such as NVAF.[4]

5 | CONCLUSION

This national study of patients with cancer and NVAF showed that nearly 7 out of 10 patients with cancer and NVAF did not receive oral anticoagulation during 2010 to 2016, which may represent potential underuse of oral anticoagulants in this vulnerable population. Increasing DOAC use from 2010 to 2016 was offset by decreasing warfarin use. DOACs are used less than warfarin among those at higher risk of stroke.

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Services, Inc.; and the Surveillance, Epidemiology, and End Results (SEER) program tumor registries for their work in creating the SEER database.

CONFLICT OF INTEREST

Dr. Alexander is past Chair and current member of FDA's Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and has served as a member of OptumRx's National P&T Committee. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. All other authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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