Oral Anticoagulant Discontinuation in Patients With Nonvalvular Atrial Fibrillation

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ABSTRACT

Objectives: To identify factors associated with all-cause discontinuation (patient discontinued on their own or physician discontinuation) of oral anticoagulants (OACs) among nonvalvular atrial fibrillation (NVAF) patients.

Study Design: Retrospective cohort study.

Methods: We analyzed the MarketScan claims database from October 2009 to July 2012. Adult patients were eligible if they newly initiated an OAC in the study period, had an atrial fibrillation diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 427.31 or 472.32), and had at least 6 months of continuous enrollment after OAC initiation. Multivariable Cox proportional hazards regression was used to assess factors associated with discontinuation. Adjusted hazard ratios (HRs) and 95% CIs were reported.

Results: Among 12,129 eligible patients, 8143 (67.1%) initiated warfarin and 3986 (32.9%) initiated direct oral anticoagulants (DOACs). Overall, 47.3% of patients independently discontinued during follow-up (mean number of days of follow-up = 416.6 [SD ± 141.7]) with mean time to discontinuation of 120 days (SD ± 114.7). Patients significantly less likely to discontinue included those taking DOACs versus warfarin (HR, 0.91; 95% CI, 0.86-0.97), older patients (≥65 years vs 18 to 34 years) (HR, 0.32; 95% CI, 0.24-0.43), those with diabetes (HR, 0.84; 95% CI, 0.77-0.90), those with prior stroke/transient ischemic attack (HR, 0.65; 95% CI, 0.56-0.75), those with prior pulmonary embolism (HR, 0.71; 95% CI, 0.58-0.88), and those with congestive heart failure (HR, 0.80; 95% CI, 0.74-0.87). Patients with prior bleeding events were significantly more likely to independently discontinue (HR, 1.20; 95% CI, 1.08-1.34).

Conclusions: The risk of independent discontinuation of OAC treatment among NVAF patients was high. Patients on DOACs compared with warfarin and those with several comorbid conditions had significantly lower risk of discontinuation, while those with prior bleeding were more likely to discontinue.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice and is becoming a growing public health concern. Although the magnitude of future trends cannot be definitively predicted, current research indicates that the disease's incidence and prevalence will gradually increase. Go et al estimated in 2001 that approximately 2.3 million adults in the United States currently had AF, and projected an increase to more than 5.6 million by the year 2050 with more than 50% of affected individuals 80 years or older.[1] Colilla et al reported projections in 2013 that AF incidence will increase from 1.2 million in 2010 to 2.6 million in 2030, with the prevalence estimates increasing from 5.2 million in 2010 to 12.1 million in 2030.[2] In 2006, Miyaska et al reported the estimated prevalence to be more than 10 million by 2050.[3]

AF results in a 4- to 5-fold increase in the risk of stroke and thromboembolic events, accounting for approximately 15% of all strokes reported in the United States.[1,4,5] In addition, AF has been associated with increased risk of heart failure, cognitive dysfunction, left ventricular dysfunction, and death.[3,6] AF has enormous socioeconomic implications because, in addition to increasing medical costs and economic burden on the healthcare system, it can lead to a reduction in patients' quality of life (QOL) and functional status.[1,7-10] Coyne et al reported that the total annual medical costs for treatment of AF were approximately $6.65 billion in 2005 dollars.[11] Kim et al reported that the national incremental AF cost was between $6 and $26 billion in 2008 dollars.[12] The economic burden of stroke in the United States for 2008 was estimated at $65.5 billion, whereas the annual estimates for the 27 European Union countries and the United Kingdom were €27 billion and £8.9 billion, respectively, in 2008.[7,8] The QOL of patients with AF has been reported to be significantly poorer compared with the general population, as well as with patients with coronary heart disease.[9]

Historically, stroke-prevention guidelines for AF patients recommended aspirin or no therapy for those with an other-

Take-Away Points

As market experience with direct oral anticoagulant therapies (DOACs) grows, it is important to understand the real-world treatment patterns for stroke prevention in patients with atrial fibrillation (AF).

- Our study shows that the risk of discontinuation from any cause of OAC therapy among patients with nonvalvular AF was high.
- Newer medications—DOACs—may provide better patient outcomes; patients taking DOAC therapy were less likely to discontinue therapy.

wise low stroke risk, and an oral anticoagulant (OAC) for moderate- to high-risk patients.[4,13-15] With the recent adoption of the CHA_2DS_2-VASc score prediction rule, the number of patients recommended for OAC therapy has dramatically increased compared with those previously recommended under the $CHADS_2$ system. Many patients, especially women 75 years or older (now + 2 from + 1 in $CHADS_2$), have been reclassified as high- rather than low-risk, and OAC use has therefore significantly increased. It has increased even in those still classified as low risk.[16]

For several decades, warfarin has been the primary OAC used for stroke prevention in AF. While highly effective for preventing stroke in AF patients, its significant drawbacks include variable dose requirements and numerous dietary and medication interactions, as well as a commitment to lifelong, regular, frequent monitoring of the patient's international normalized ratio (INR) to ensure it is within the recommended range.[4,17-19] As a result, warfarin is associated with relatively frequent bleeding complications, resulting in a high proportion of patients discontinuing therapy (all-cause, initiated by either the patient or their doctor) or receiving suboptimal therapy in usual clinical practice.[4,17-21]

In recent years, 3 direct oral anticoagulants (DOACs)—dabigatran, rivaroxaban, and apixaban—have been approved in the United States for stroke prevention in nonvalvular AF (NVAF). In clinical trials, all 3 were shown to be safe and effective compared with warfarin.[22-24] These new agents have advantages over warfarin because their use doesn't require regular INR monitoring and they have fewer drug and food interactions. Recently published guidelines have also recommended the use of DOACs as alternatives to the conventional therapy (vitamin K antagonists or antiplatelet agents) in most NVAF patients requiring stroke prevention.[4]

Few studies have shown treatment discontinuation over time in the warfarin-treated patients.[20] However, it is absolutely essential to evaluate in detail the treatment patterns and the risk of discontinuation among NVAF patients in the real world, as well as to identify predictors of discontinuation. Although evidence exists for some rationales for discontinuation in warfarin-treated patients, such as bleeding complications,[4,17-20] little comparable information exists for DOAC-treated patients. Compared with warfarin, DOACs have a shorter half-life; therefore, if the drug is discontinued, noncompliance can result in the anticoagulation effect coming to a halt and thrombosis ensuing.[25-27] It is thus critical to understand real-world discontinuation patterns, including the reasons for discontinuation, for warfarin and DOACs.

Currently, however, little literature exists on recent real-world treatment patterns among AF patients on DOACs. A recent observational study in 70 patients starting on dabigatran (median treatment duration was 140.5 days) reported a discontinuation rate of 10%; 77% of these patients reported treatment satisfaction with dabigatran, although 79% of those previously treated with warfarin preferred dabigatran.[28] Another early real-world study on dabigatran adherence in 103 patients reported that only 12% had inadequate adherence. Rivaroxaban and apixaban were approved after dabigatran, and we identified no studies that reported real-world treatment patterns with these drugs.[29] As market experience with DOACs grows, it is important to understand the real-world treatment patterns for stroke prevention in patients with AF. The goals of this study were to assess the risk of discontinuation among AF patients on OACs (including DOACs) and to identify factors associated with such discontinuation.

METHODS

A retrospective cohort study was conducted using the Truven Health MarketScan Research Databases from October 2009 to July 2012. Patients were eligible if: they newly initiated an OAC (warfarin, dabigatran, or rivaroxaban) in the study period, were 18 years or older at the time of treatment initiation, had at least 1 diagnosis of AF in the 12 months prior to treatment initiation (identified by any medical claim associated with an *International Classification of Diseases, Ninth Revision, Clinical Modification* code of 427.31 [AF] or 427.32 [atrial flutter]), and had at least 6 months of continuous enrollment (ie, continuous health insurance coverage) after OAC initiation and continuous enrollment in the plan for 12 months prior to study entry. Patients were excluded if they had valvular heart disease, cardiac surgery during the 12-month pre-index period, or used any OAC treatment (warfarin or DOAC) in the 12 months prior to study entry. The index date was defined

as date of first OAC prescription after an AF diagnosis during the study eligibility period, and the baseline period was the 12 months prior to index date. The index prescription was defined as the first OAC prescribed in the study period (warfarin, dabigatran, rivaroxaban).

The DOACs included in this study were dabigatran and rivaroxaban, because apixaban was approved in December 2012, after the study's end date. Figures 1 and 2 show the study schematics and the flow chart for patient selection, respectively. Patients were followed until 1 of the following events, whichever earliest, occurred: an interruption in continuous enrollment, a switch or a discontinuation of index treatment, or the end of the study. Discontinuation was defined as having no claims for the index OAC prescription within 60 days of the final day's supply of the last filled prescription for the index OAC. Patients who received a prescription for an OAC other than the index OAC prescription during the follow-up period were considered switchers, and were thus excluded.

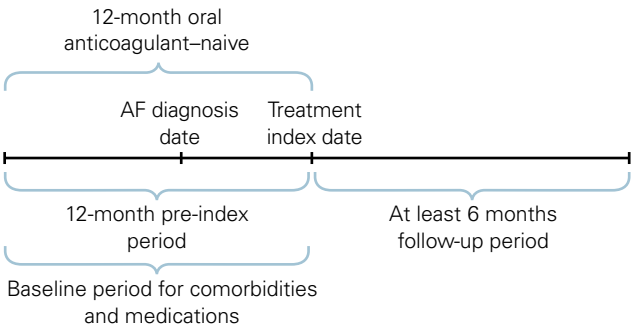
Statistical Analysis

The absolute rate of discontinuation of OAC therapy was determined; additionally, time to discontinuation (in days) and the length of follow-up (in days) were calculated. Patients were censored on the date of discontinuation, end of study period, or interruption in continuous enrollment—whichever occurred earliest. Multivariable Cox proportional hazards regression analysis was conducted to assess the clinical and demographic factors associated with discontinuation in warfarin initiators and DOAC initiators. Hazard ratios (HRs) and the corresponding 95% CIs were calculated. Demographic factors such as insurance type and geographic region, as well as clinical characteristics from the 12-month baseline period—such as bleeds, stroke, deep vein thrombosis, pulmonary embolism (PE), diabetes, hypertension, myocardial infarction, dyspepsia, renal disease, and congestive heart failure (CHF)—were included. All analyses were done using SAS version 9.3 (SAS Institute, Cary, North Carolina) and STATA version 13 (STATACorp, College Station, Texas).

RESULTS

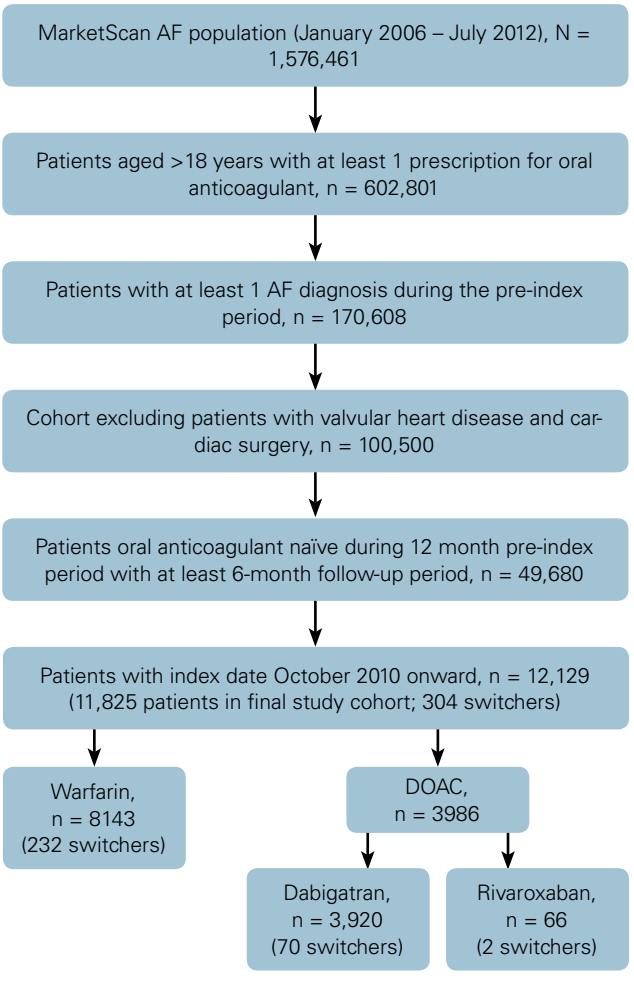
A total of 11,825 patients with diagnosis from October 2009 to July 2012 were available for the analyses. Table 1 presents the baseline demographics and baseline comorbidities. A total of 5598 (47.34%) NVAF patients discontinued treatment with OACs. The majority of the total population of patients was 65 years or older (55.07%) and male (59.5%). The most common comorbidities were hy-

Figure 1. Schematic Representation of Overall Study Design



AF indicates atrial fibrillation.
The lowest quintile represents the 20% of HRRs with the lowest per capita spending in the baseline (no policy intervention). The highest quintile represents the 20% of HRRs with the highest per capita spending in the baseline (no policy intervention).

Figure 2. Patient Selection Flowchart



AF indicates atrial fibrillation; DOAC, direct oral anticoagulant.

Table 1. Patient Demographics and Baseline Comorbidities

	N = 11,825	N (%)
Patients who discontinued OAC	5598	47.34
Age, years: mean (SD)	68.2 (13.05)	
18-34	90	0.76
35-44	331	2.80
45-54	1270	10.74
55-64	3622	30.63
≥65	6512	55.07
Gender		
Female	4789	40.50
Male	7036	59.50
Insurance		
Commercial	5530	46.77
Medicare	6295	53.23
Baseline comorbidities		
Prior gastrointestinal bleeding	241	2.04
Prior intracerebral bleeding	37	0.31
Other bleeding	516	4.36
Prior bleeds (GI + IC + other)	794	6.71
Prior stroke / TIA	554	4.68
Prior deep vein thrombosis	321	2.71
Prior pulmonary embolism	245	2.07
Diabetes	1808	15.29
Hypertension	5040	42.62
Coronary artery disease	1735	14.67
Prior myocardial infarction	283	2.39
Dyspepsia	667	5.64
Renal disease	828	7.00
Congestive heart failure	1754	14.83

GI indicates gastrointestinal; IC, intracerebral; OAC, oral anticoagulant; TIA, transient ischemic attack.

pertension (42.62%), diabetes (15.29%), CHF (14.83%), and coronary artery disease (14.67%).

Table 2 presents the overall discontinuation rate and the days to discontinuation for both warfarin users and DOAC users. Figure 3 depicts the Kaplan-Meier (K-M) curves that show risk of discontinuation for warfarin and DOAC therapy with time, and Table 3 shows the factors associated with the risk of discontinuation. Patients taking DOAC therapy were significantly less likely to discontinue compared with patients taking warfarin (reference = warfarin) (HR, 0.91; 95% CI, 0.86-0.97; P = .002). As age increased (reference group = aged 18-34 years), the magnitude of risk of discontinuation decreased, with significant results for patients in the age groups 45 to 54 years (HR, 0.56; 95% CI, 0.44-0.71; P = .000), 55 to 64 years (HR, 0.42; 95% CI, 0.33-0.53; P = .000), and 65 years or older (HR, 0.32; 95% CI, 0.24-0.43; P = .000). The patients from the western region of the United States were significantly more likely to discontinue (reference = northeast region) (HR, 1.14; 95% CI, 1.04-1.24; P = .003). Patients with prior bleeding events were also more likely to discontinue (HR, 1.20; 95% CI, 1.08-1.34; P = .001). The baseline comorbidities that significantly decreased the risk of discontinuation include prior stroke/transient ischemic attack (TIA) (HR, 0.65; 95% CI, 0.56-0.75; P = .000), prior PE (HR, 0.71; 95% CI, 0.58-0.88; P = .001), a diagnosis of diabetes (HR, 0.84; 95% CI, 0.77-0.90; P = .000), and a diagnosis of CHF (HR, 0.80; 95% CI, 0.74-0.87; P = .000).

DISCUSSION

This study highlights the high frequency of all-cause discontinuation of OAC therapy among NVAF patients. Close to half (47%) discontinued during follow-up with a mean time to discontinuation of 120 days. This is consistent with the current literature. Patel et al reported that about 37% of warfarin initiators had discontinued warfarin within 90 days after the initiation of therapy, with 65% discontinuing warfarin therapy within 1 year.[30] Deitelzweig et al reported that 51.4% of warfarin initiators with NVAF discontinued warfarin therapy at least once during follow-up.[31] Several other studies suggest that approximately 25% of patients on warfarin discontinue therapy within the first year of use.[32-37] Casciano et al have also reported that the underutilization of warfarin is prevalent in NVAF patients and, in addition, nonadherence to warfarin therapy presents additional economic burden on the healthcare system.[38] Adherence to therapy is absolutely essential for NVAF patients, as stroke risk is significantly higher during the warfarin discontinuation periods in comparison with periods when the patients are on therapy.[31] Ewen et al have also reported that patients who experience 2 or more interruptions in warfarin use have more than twice the risk for stroke (mean follow-up period = 3.4 years) compared with patients with no interruptions.[39]

In addition, a key highlight of the present study is that patients taking DOAC therapy were less likely than patients taking warfarin to discontinue. This result, however, needs to be interpreted with caution. Although the overall risk of discontinuation via the Cox Hazard Model demonstrates the lower risk for DOAC patients compared with warfarin patients (Table 3), it is unclear whether this translates into a meaningful clinical benefit. The K-M curves for discontinuation (Figure 3) show little difference

Table 2. Discontinuation Rate and Time to Discontinuation

	Warfarin (N = 7911)	DOAC (N = 3914)
Length of follow-up, days: mean (SD)	272 (199)	247 (177)
Discontinuation (%)		
≤180 days	36.68	38.71
180-365 days	12.42	9.75
>365 days	5.86	1.93
Overall discontinuation rate	47.79	46.42
Time to discontinuation, days: mean (SD)	127 (121)	105 (99)

DOAC indicates direct oral anticoagulant.

for those patients continuing OAC therapy between the warfarin and DOAC cohorts. Further, the mean time to discontinuation (Table 2) indicates that among patients who discontinue, warfarin patients remain on therapy slightly longer than DOAC patients.

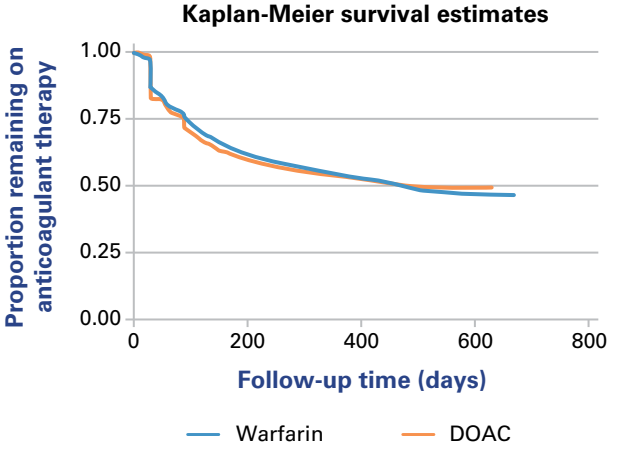
The existing literature has well documented the challenges that plague warfarin therapy, including variable dose requirements and numerous dietary and medication interactions, as well as a lifelong, regular, frequent monitoring of INR to ensure it is within the recommended range.[4,17-19,40,41] On the other hand, DOACs offer patients flexibility, with the absence of required frequent anticoagulation monitoring. Further, DOACs have a more favorable dietary and medication interaction profile compared with warfarin.[42-44]

A major reason for discontinuing warfarin therapy is its associated bleeding complications and the resulting costs. In their study assessing warfarin-associated bleeding in AF patients, Ghate et al reported the mean adjusted all-cause annual costs as $42,574, $36,571, $22,824, and $22,507 for subjects with intracranial hemorrhage, major gastrointestinal (GI) bleeding, minor GI bleeding, and no bleeding, respectively.[45] Kim et al reported a mean cost of $10,819 (SD = $11,536) for hospitalizations due to warfarin-associated bleeding.[46] On the other hand, clinical trials and published meta-analyses of the DOACs have shown lower bleeding rates compared with warfarin.[22-24,47,48]

The findings of this study suggest that certain clinical, demographic, and/or healthcare-related characteristics were significantly associated with discontinuation of OACs. We observed that patients with prior bleeding events were more likely to discontinue. Suh et al reported that patients with recent bleeding were more likely to discontinue warfarin compared with patients without recent bleeding (relative risk, 1.35; 95% CI, 1.16-1.58).[49] The baseline comorbidities that significantly decreased the risk of discontinuation included increasing age, prior stroke/TIA, prior PE, a diagnosis of diabetes, and a diagnosis of CHF. Fang et al reported that the risk of discontinuation was higher in patients 65 years or older compared with patients 85 years or older (HR, 1.33; 95% CI, 1.03-1.72).[33] On the contrary, Suh et al reported older age as a risk factor for discontinuation.[49] It would be difficult to draw definitive conclusions on the impact of clinical, demographic, and/or healthcare-related characteristics on the discontinuation of OACs. Additional research is needed to build a more detailed understanding, as well as to conduct a comprehensive evaluation on treatment patterns with DOACs using real-world data.

Understanding the real-world usage of warfarin and DOACs is needed to improve existing treatment algorithms. The consequences of discontinuation are immense, often leading to negative health outcomes and increased healthcare costs.[38,45,46] Given that existing research indicates that the bleeding complications associated with warfarin are a major reason for the drug's discontinuation,[20,49] it is necessary to thoroughly evaluate how DOACs—which reduce bleeding and/or have a comparatively better bleeding profile[50,51]—may encourage improved compliance and thereby provide continuous, uninterrupted stroke protection.

Figure 3. Kaplan-Meier Curves for Discontinuation of Anticoagulant Therapy



DOAC indicates direct oral anticoagulant.

Table 3. Risk of Discontinuation (Cox Hazard Model)

	Hazard Ratio (95% CI)	*P*
Type of OAC		
Warfarin	Ref	
DOAC	**0.91 (0.86-0.97)**	**.002**
Age, years		
18-34	Ref	
35-44	0.79 (0.61-1.03)	.078
45-54	**0.56 (0.44-0.71)**	**.000**
55-64	**0.42 (0.33-0.53)**	**.000**
≥65	**0.32 (0.24-0.43)**	**.000**
Gender		
Female	Ref	
Male	0.98 (0.92-1.03)	.410
Insurance		
Commercial	Ref	
Medicare	0.94 (0.79-1.11)	.467
Region		
Northeast	Ref	
North central	0.96 (0.89-1.04)	.346
South	0.96 (0.89-1.04)	.349
West	**1.14 (1.04-1.24)**	**.003**
Unknown	1.06 (0.86-1.28)	0.617
Baseline comorbidities		
Prior bleeds	**1.20 (1.08-1.34)**	**.001**
Prior stroke / TIA	**0.65 (0.56-0.75)**	**.000**
Prior DVT	0.86 (0.72-1.02)	.088
Prior PE	**0.71 (0.58-0.88)**	**.001**
Diabetes	**0.84 (0.77-0.90)**	**.000**
Hypertension	1.00 (0.95-1.06)	.862
Prior MI	1.01 (0.85-1.20)	.911
Dyspepsia	1.05 (0.94-1.18)	.380
Renal disease	1.10 (0.99-1.22)	.090
CHF	**0.80 (0.74-0.87)**	**.000**

CHF indicates congestive heart failure; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; OAC, oral anticoagulant; MI, myocardial infarction; PE, pulmonary embolism; Ref, reference; TIA, transient ischemic attack.
Bold font indicates statistically significant result, $P < .05$.

Strengths and Limitations

One key strength of our study is its analysis of real-world data on DOACs. The MarketScan claims database, which provides data on patients across the United States, incorporates all medical and pharmacy claims of patients and allows for longitudinal analysis. However, our analysis also has several limitations. The database does not uniformly capture the use of over-the-counter medications, such as aspirin, which are used to help prevent stroke in AF patients and could have an impact on the treatment patterns of the anticoagulants being studied. Also, while the discontinuation of therapy was based on a 60-day gap in pharmacy claims, a lack of INR monitoring means we can't assess whether the gap was clinically meaningful. In this study, too, we haven't separately accounted for AF patients who are on short courses of anticoagulation for specific reasons (ie, scheduled for imminent cardioversion or AF ablation procedures). Also, we were not able to identify patients with AF postoperatively, who may have had a short course of anticoagulation therapy. In addition, our analysis was based on early utilization of DOAC, which may change over time. Also, generalizability may be limited because the portion of the study population insured by Medicare only includes that subset of Medicare recipients who are Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. This patient population may not be representative of all AF patients 65 years or older. In addition, the data do not include uninsured patients.

CONCLUSIONS

This study highlights the high risk of discontinuation of OAC therapy among NVAF patients. Despite the Cox Hazard Model indicating a statistically significant reduction in risk of discontinuation for DOAC versus warfarin, the K-M curves are very similar and it is unlikely the small difference seen in discontinuation is clinically relevant. More research utilizing real-world data needs to be conducted to foster detailed understanding of DOAC treatment patterns.

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Authorship Information: Concept and design (JB, DB, XL, MH, XP); acquisition of data (JB); analysis and interpretation of data (JB, DB, SK, XL, MH, XP, NM); drafting of the manuscript (JB, SK, XL, MH, XP, NM); critical revision of the manuscript for important intellectual content (JB, SK, XL, MH, XP, NM); statistical analysis (JB, SK, DB); obtaining funding (JB, DB); administrative, technical, or logistic support (JB); and supervision (JB).

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