Higher Persistence in Newly Diagnosed Nonvalvular Atrial Fibrillation Patients Treated With Dabigatran Versus Warfarin

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Background—Oral anticoagulation therapy is the primary tool in reducing stroke risk in patients with nonvalvular atrial fibrillation but is underused. Patients nonpersistent with therapy contribute to this underuse. The objective of this study was to compare persistence rates in newly diagnosed nonvalvular atrial fibrillation patients treated with warfarin versus dabigatran as their oral anticoagulation.

Methods and Results—US Department of Defense administrative claims were used to identify patients receiving warfarin or dabigatran between October 28, 2010, and June 30, 2012. Patient records were examined for a minimum of 12 months before index date to restrict the analyses to those newly diagnosed with nonvalvular atrial fibrillation and naive-to-treatment, identifying 1775 on warfarin and 3370 on dabigatran. Propensity score matching was used to identify 1745 matched pairs. Persistence was defined as time on therapy to discontinuation. Kaplan–Meier curves were used to depict persistence over time. Cox proportional hazards model was used to determine the factors significantly associated with persistence. Using a 60-day permissible medication gap, the persistence rates were higher for dabigatran than for warfarin at both 6 months (72% versus 53%) and 1 year (63% versus 39%). Patients on dabigatran with a low-to-moderate risk of stroke ($CHADS_2$<2) or with a higher bleed risk ($HEMORR_2HAGES$>3) had a higher likelihood of nonpersistence (hazard ratios, 1.37; 95% confidence interval, 1.17–1.60; P<0.001; and hazard ratios, 1.24; 95% confidence interval, 1.04–1.47; P=0.016).

Conclusions—Patients who initiated dabigatran treatment were more persistent than patients who began warfarin treatment. Within each cohort, patients with lower stroke risk were more likely to discontinue therapy. (***Circ Cardiovasc Qual Outcomes*. 2013;6:567-574.**)

Key Words: anticoagulants ■ atrial fibrillation ■ dabigatran ■ persistence ■ warfarin

Atrial fibrillation (AF) is the most commonly sustained disorder of cardiac rhythm,[1] affecting >2.5 million adults in the United States.[2–6] AF is an important independent risk factor for stroke, accounting for 15% of all strokes and up to 36% of all strokes occurring in patients 80 to 89 years of age.[7] In patients >80 years of age, AF's prevalence rate is 9%, resulting in the high cost and morbidity associated with the condition.[2,8] Overall, AF confers a 4- to 5-fold increase in 2-year ischemic stroke risk,[2,4,9–11] with untreated patients facing a 4.5% annual risk of suffering stroke.[4]

Significant risk reduction can be accomplished with oral anticoagulation (OAC) therapy, traditionally demonstrated by the oral vitamin K antagonist, warfarin. Although warfarin can prevent 1 stroke for every 32 patients treated,[4,12–17] its use is associated with a risk of bleeding, regular blood monitoring (international normalized ratio [INR]), drug–drug and drug–food interactions, and often necessitates lifestyle change. These factors are linked to difficulty maintaining the optimal INR in some patients and result in both nonadherence and discontinuation of warfarin use.[1,2,4,18–24] Although the 2-year persistence on warfarin in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial was ≈83%,[4,25] real-world studies find 1-year persistence rates ranging from 65% to 74%.[1,4,18,20,21,23,24] Young age and lower stroke risk, as calculated using the $CHADS_2$ score, have been shown to be the primary factors significantly associated with warfarin discontinuation.[1,20] Discontinuation of therapy naturally leads to increased ischemic stroke risk and contributes to suboptimal outcomes of OAC treatment.[22,26]

Dabigatran, a direct thrombin inhibitor, was introduced in 2010 as an alternative to warfarin in treating patients with nonvalvular AF (NVAF). This oral anticoagulant demonstrated superiority compared with warfarin in terms of stroke reduction[27] without an increase in bleeding risk.[28] In addition, no INR monitoring is required.

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WHAT IS KNOWN

- Atrial fibrillation (AF) affects ≈2.5 million adults in the United States, most of whom have nonvalvular AF. The condition accounts for 15% of all strokes in the United States and confers a 5-fold increase in ischemic stroke risk.
- Warfarin is a common and effective oral anticoagulant used to prevent thromboembolic complications of AF. However, the dosing regimen can be complicated and requires regular international normalized ratio measurements. One-year discontinuation rates for patients beginning on warfarin are high (26% to 35%), placing patients at increased stroke risk.
- Dabigatran, a direct thrombin inhibitor introduced in 2010, is at least as safe and effective as warfarin in this context. It does not require international normalized ratio monitoring but must be taken twice daily. Persistence between these 2 therapies in the real world is not known.

WHAT THE STUDY ADDS

- This study uses a large US administrative claims database to study the persistence rate in newly diagnosed propensity score–matched nonvalvular AF patients newly treated on dabigatran versus warfarin.
- Patients with nonvalvular AF beginning dabigatran therapy had significantly higher 1-year persistence rates than those who began warfarin therapy (63% versus 39%).

Dabigatran seems to have several benefits compared with warfarin, but whether that may also translate into increased adherence and persistence is unclear. In the RE-LY study, patients on dabigatran showed lower 2-year persistence on the drug compared with warfarin, although the difference was marginal (79% versus 83%, respectively).[25] The aim of this study was to compare real-world persistence rates of newly diagnosed NVAF patients who begin dabigatran or warfarin, and the factors associated with discontinuation of treatment.

Methods

Patient Cohort Assembly

This study used longitudinal electronic medical records and administrative claims from the US Department of Defense, which included inpatient, outpatient, and pharmacy data. Patients with AF were identified by searching for at least 1 inpatient claim or 2 outpatient claims within the same year, with a physician assigned International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) code for AF (427.31). Because a subclassification of NVAF was necessary and no specific ICD-9 code existed to differentiate NVAF from valvular fibrillation, patient claim history was required to identify NVAF patients. Patients with ≥1 claims in the 12 months before the patient's first AF claim with ICD-9 codes for valvular heart disease or replacement or hyperthyroidism (394.0, 242.x, procedure codes 35.20, 35.22, 35.24, 35.26, 35.28) were excluded from the NVAF cohort. To exclude transient or secondary NVAF, patients with ≥1 claims in the 3 months before the patient's first AF claim with ICD-9 codes for cardiac surgery (procedure codes 00.5x, 35.xx, 36.xx, 37.xx), pericarditis (391.x, 393, 420.x, 423.2, 0.36.41, 074.21, 093.81, 098.83), myocarditis (391.2, 422.xx, 074.23, 398.0, 429.0,032.82, 036.43, 093.82, 130.3), and pulmonary embolism (415.1x) were excluded from the NVAF cohort. Because a 12-month look-back period was required to identify NVAF patients, those not continuously enrolled in the US Department of Defense data for 12 months before the first AF claim were excluded from the analysis.

For the NVAF patient population, an index date was identified to create the dabigatran and warfarin patient cohorts. Dabigatran was launched into the market on October 28, 2010. Therefore, the index date was defined as the patient's first dabigatran or warfarin prescription on or after October 28, 2010. A diagram outlining patient identification is shown in Figure 1. Patients were sorted into treatment cohorts on the basis of their first prescription of either dabigatran or warfarin. Next, naive-to-treatment patients were identified as patients with no evidence of a dabigatran or warfarin prescription 12 months before the index date. Finally, patients were categorized by their duration of NVAF into prevalent versus newly diagnosed. To determine the cut-off, a sensitivity analysis was run to evaluate the duration between the date of the first AF claim and first prescription of dabigatran or warfarin. A drop-off was observed after 3 months, and therefore, this time period was used to define a newly diagnosed patient. Patients were categorized as newly diagnosed if the first NVAF claim occurred within 3 months before the index date. Those who were considered not new to treatment or newly diagnosed were excluded from analyses.

Definitions

Persistence is the duration of time from initiation to discontinuation of therapy.[29] A time-to-event approach was used to analyze patient persistence rates separately for each medication. Initiation of therapy was defined as the index date for the drug.[30] Several past studies examining warfarin persistence used time between consecutive fill dates and INR data to determine discontinuation.[1,18,20,21,23,24] Because of the fact that dabigatran does not require INR monitoring during therapy, only the time gap between consecutive medication fills could be used to determine discontinuation, which is defined as the time in between the last day covered by a previous prescription fill and the day of the subsequent prescription fill. Discontinuation was, therefore, determined by the time when patients failed to refill the prescription within the gap interval. The discontinuation date was then determined by the last day of therapy of each patient. Patients receiving dabigatran who subsequently switch to warfarin, and vice versa, were considered discontinued. For patients who switch, the last day of therapy would be defined as the start date of the drug/treatment switched onto.

To determine the appropriate fill gap that could be applied consistently to both dabigatran patients and warfarin patients, sensitivity analyses were run to determine the proportion of medication gaps between consecutive fills falling below a certain number of days. The analysis showed that 95% and 89% of medication gaps between consecutive fills for patients prescribed dabigatran and warfarin, respectively, were <30 days. In addition, 98% and 94% of medication gaps between consecutive fills for patients prescribed dabigatran and warfarin, respectively, were <60 days. The distribution of medication gaps found in the sensitivity analysis are illustrated in Figure 2A and 2B. Given that the vast majority of gaps between medication refills

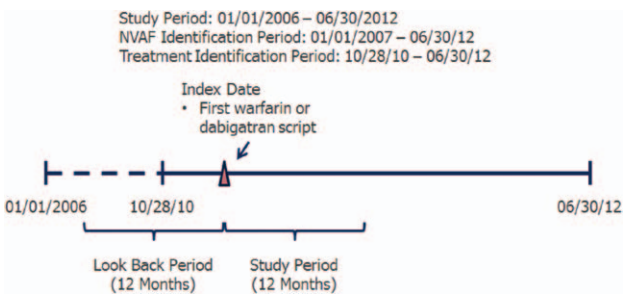

Figure 1. Patient cohort identification timeline. NVAF indicates nonvalvular atrial fibrillation.

were shorter than both 60 and 30 days, these 2 permissible gaps were used for persistence calculations.[31,32] Patients who did not discontinue treatment but died, disenrolled from the health plan, or continued therapy beyond the study period were considered censored within the discontinuation analysis.

Statistical Analysis

Because of potential imbalances in baseline covariates between patients prescribed dabigatran and patients prescribed warfarin, propensity score (PS) matching was used to minimize any differences. A multivariate logistic regression model to estimate PS was used for all patients. Variables used in the model, identified from data from the first inpatient, outpatient, or pharmacy claim before the index date and ICD-9 codes as defined in Table 1 in the online-only Data Supplement, included age at index date, gender, region of patient residence (Northeast, Midwest, South, West), history of intracerebral hemorrhage,[33] history of major bleeding,[33] history of congestive heart failure, history of diabetes mellitus, history of hypertension, history of stroke, $HEMORR_2HAGES$ score (a predictive score for bleeding incorporating history of bleed, hepatic or renal disease, alcohol abuse, malignancy, reduced platelet count, hypertension, anemia, excessive fall risk, neuropsychiatric disease, and previous stroke),[34] and the Charlson comorbidity index (CCI; a predictor of 10-year morbidity incorporating myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes mellitus, diabetes mellitus with chronic complications, hemiplegia or paraplegia, renal disease, malignancy, moderate-to-severe liver disease, metastatic solid tumor, and AIDS).[35] All measures of history and comorbidities used to calculate predictive scores, for $CHADS_2$ (a predictive score for stroke incorporating history of congestive heart failure, hypertension, diabetes mellitus, ischemic stroke or transient ischemic attack, and age ≥75),[36] $HEMORR_2HAGES$, and CCI, used a look-back period of 12 months before index date. Pairs of patients prescribed dabigatran and warfarin were matched one-to-one by PS using calipers of width 0.01 of the logit of the PS. χ^2 tests, and *t* tests were conducted to ensure that there were no significant differences in characteristics before the initiation of dabigatran or warfarin therapy. Kaplan–Meier estimates of survival (persistence curves) were used to assess time to discontinuation as well as persistence rate at the end of each time period.[37,38] Persistence rates were calculated at 6, 9, and 12 months for all patients and were compared using the log-rank test.

Multivariate Cox proportional hazard models were used to find the factors significantly associated with persistence. The possibility of nonproportional hazards was considered and testing was performed to assure covariates satisfied the requirement for proportionality. Covariates used in the multivariate model included age, gender, region (Northeast, Midwest, South, West), history of intracerebral hemorrhage, history of major bleeding, history of myocardial infarction, renal disease, $CHADS_2$ score, $HEMORR_2HAGES$, and CCI. First, univariate regressions were performed to assess the statistical significance of each potential factor and its association with the persistency outcome. Factors that were significant at an α=0.2 level were then fed into a stepwise multivariate regression model building procedure. The stepwise approach allowed factors to be entered into and removed from the model in such a way that each forward selection step could be followed by ≥1 backward elimination steps. The selection process terminated when all factors had been considered and all variables were significant at an $\alpha = 0.05$ level. Hazard ratios (HR), probability values, and confidence intervals (CI) were reported for all significant variables. All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). All *P* values and 95% CI reported are 2-sided.

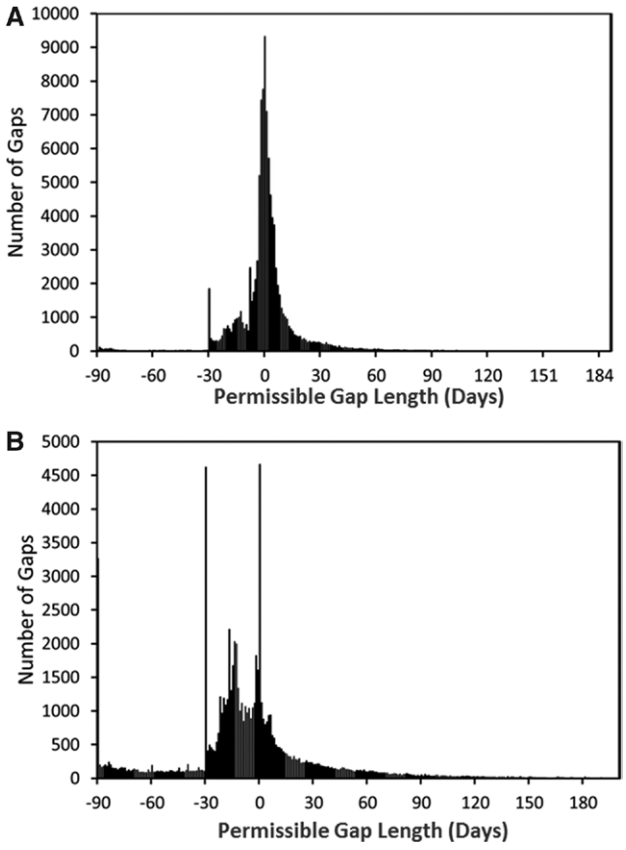

Figure 2. A, Sensitivity analysis for permissible gap of dabigatran, 95% of all gaps are <30 days. **B**, Sensitivity analysis for permissible gap of warfarin, 89% of all gaps are <30 days; 95% of all gaps are <60 days.

Results

Patient Identification and Characteristics

Overall, we identified 86 210 NVAF patients prescribed either dabigatran or warfarin, of which 55 948 (64.9%) patients were identified as naive-to-treatment, split between 26 139 (46.7%) patients prescribed dabigatran and 29 809 (53.3%) patients prescribed warfarin. Totally, 5145 (5.97%) patients were identified as newly diagnosed. Of these newly diagnosed naive-to-treatment patients, 3370 (65.5%) patients began treatment with dabigatran, whereas 1775 (34.5%) patients began treatment with warfarin.

Table 1 shows the discontinuation and switch rates for all patients before matching using both a 30-day and a 60-day medication gap. Patients prescribed warfarin were more likely to discontinue treatment during the study period than patients prescribed dabigatran when analyzed with both a 30-day (55.6% versus 35.6%) and 60-day (44.3% versus

Table 1. Patient Switch and Discontinuation Counts Before Matching

	30-Day Medication Gap		60-Day Medication Gap	
	Dabigatran	Warfarin	Dabigatran	Warfarin
n	3370	1775	3370	1775
Discontinued, n (%)	1199 (35.6)	987 (55.6)	874 (25.9)	787 (44.3)
Switched, n (%)	71 (2.1)	92 (5.2)	72 (2.1)	93 (5.2)
Switched/discontinued, %	5.9	9.4	8.2	11.8
Censored, n (%)	2171 (64.4)	788 (44.4)	2496 (74.1)	988 (55.7)

Table 2. Baseline Patient Characteristics Before and After PS Matching

	Before PS Matched			After PS Matched		
Baseline Characteristics	Dabigatran	Warfarin	*P* Value*	Dabigatran	Warfarin	*P* Value*
n	3370	1775		1745	1745	
Age, mean (SD)	73.0 (9.7)	72.8 (10.8)	0.436	73.2 (9.7)	72.8 (10.8)	0.290
Women, n (%)	1325 (39.2)	697 (39.3)	0.972	700 (40.1)	690 (39.5)	0.730
Region			<0.001			0.804
Midwest, n (%)	267 (7.9)	112 (6.3)		125 (7.2)	111 (6.3)	
Northeast, n (%)	445 (13.2)	274 (15.4)		263 (15.1)	262 (15.0)	
South, n (%)	1302 (38.6)	600 (33.8)		613 (35.1)	598 (34.3)	
West, n (%)	906 (26.9)	485 (27.3)		462 (26.5)	478 (27.4)	
History of ICH, n (%)	10 (0.3)	8 (0.5)	0.374	8 (0.5)	8 (0.5)	1.000
History of major bleeding, n (%)	1312 (38.9)	787 (44.3)	<0.001	717 (41.1)	764 (43.8)	0.108
History of CHF, n (%)	929 (27.6)	622 (35.0)	<0.001	592 (33.9)	595 (34.1)	0.915
History of diabetes mellitus, n (%)	1035 (30.7)	642 (36.2)	<0.001	607 (34.8)	621 (35.6)	0.62
History of hypertension, n (%)	2842 (84.3)	1530 (86.2)	0.075	1512 (86.7)	1502 (86.1)	0.622
History of stroke, n (%)	380 (11.3)	240 (13.5)	0.019	214 (12.3)	237 (13.6)	0.246
$CHADS_2$, mean (SD)†	2.1 (1.2)	2.3 (1.3)	<0.001	2.3 (1.2)	2.3 (1.3)	0.326
$HEMORR_2HAGES$, mean (SD)	2.4 (1.5)	2.7 (1.6)	<0.001	2.6 (1.6)	2.6 (1.6)	0.781
CCI, mean (SD)	2.2 (2.3)	2.7 (2.5)	<0.001	2.5 (2.4)	2.6 (2.4)	0.101

CCI indicates Charlson comorbidity index; CHF, congestive heart failure; ICH, intracerebral hemorrhage; and PS, propensity scores.

*Two-tailed *t* test and χ^2 test were used to compare continuous and categorical variables, respectively.

†All components of $CHADS_2$ score were used in PS model, but overall $CHADS_2$ score was not used as a matching variable.

25.9%) medication gap. Of these patients who discontinued their index treatment, a higher portion of patients prescribed warfarin switched therapies (9.4% versus 5.9% using a 30-day gap and 11.8% versus 8.2% using a 60-day gap). Switch rates increased when analyzed with a 60-day gap because of fewer discontinuing patients as opposed to more patients switching because of a prolonged permissible gap. Mean follow-up time was 292 days for dabigatran and 314 days for warfarin. Mean prescription size was 46.7 days for dabigatran and 52.0 days for warfarin.

Median Persistence and Persistence Rate in PS-Matched Patients

The 2 cohorts were PS-matched to produce 1745 matched pairs of patients prescribed dabigatran and warfarin. Totally, 1645 dabigatran and 30 warfarin patients were not matched. Baseline characteristics for each of the covariates before and after the PS-matching exercise are shown in Table 2. Within these PS-matched cohorts, there were no significant statistical differences in patient characteristics.

The persistence rates of patients prescribed dabigatran were higher than that of patients prescribed warfarin at all time periods, 6, 9, and 12 months, respectively, analyzed with both a 30-day (63.9% versus 41.3%; 56.3% versus 30.7%; 50.3% versus 24.1%) and 60-day (71.8% versus 53.3%; 66.9% versus 44.0%; 63.3% versus 38.8%) medication gap (Table 3). Patients prescribed dabigatran had significantly longer median persistence than patients prescribed warfarin (389 versus 135 days; $P<0.001$ using a 30-day gap and >400 versus 222 days; $P<0.001$ using a 60-day gap). The drop-off of patients illustrated by the Kaplan–Meier survival curves are shown in Figure 3A and 3B.

Factors Significantly Associated With Nonpersistence for Newly Diagnosed Newly Treated Patients

When analyzed by stroke risk ($CHADS_2$ score), patients with a low-to-moderate risk of stroke ($CHADS_2$ <2) were less persistent than patients with greater stroke risk for both treatment cohorts. The drop-off of patients illustrated by the Kaplan–Meier survival curves for this analysis are shown in Figure 4A and 4B. Patients prescribed dabigatran with a $CHADS_2$ score <2 had lower 6-month and 12-month persistence, respectively, than patients with a $CHADS_2$ score 2+ analyzed with both a 30-day (62.1% versus 65.9%; 47.3% versus 52.0%) and 60-day (69.4% versus 74.0%; 60.1% versus 65.1%) medication gap. The same trend was observed for patients prescribed warfarin analyzed with both a 30-day (36.9% versus 43.0%; 20.2% versus 25.3%) and 60-day (33.8% versus 40.3%) medication gap.

Factors significantly associated with nonpersistence from the multivariate Cox model are identified in Table 4. With the

Table 3. Persistence of Propensity Score–Matched Patients

	30-Day Medication Gap		60-Day Medication Gap	
Time Period	Dabigatran	Warfarin	Dabigatran	Warfarin
n	1745	1745	1745	1745
6-mo persistence rate, %	63.9	41.3	71.8	53.3
9-mo persistence rate, %	56.3	30.7	66.9	44.0
1-y persistence rate, %	50.3	24.1	63.3	38.8
P value*	<0.001		<0.001	

*The persistence rates were compared using a log-rank test.

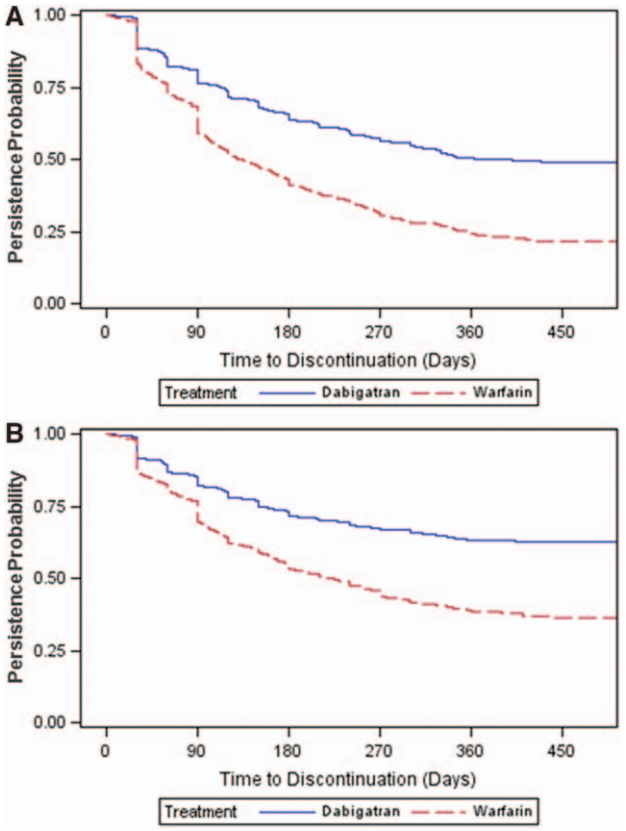

Figure 3. Kaplan–Meier survival curves for propensity scores matched patients by treatment group analyzed with a 30-day medication gap (**A**) and a 60-day medication gap (**B**).

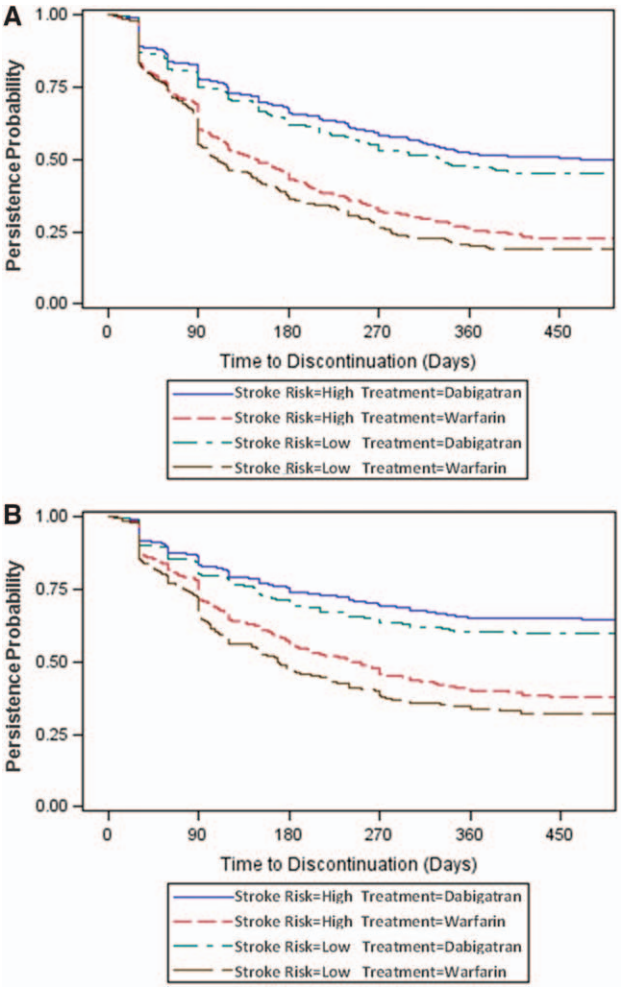

Figure 4. Kaplan–Meier survival curves for patients by treatment group and risk of stroke analyzed with a 30-day gap (**A**) and a 60-day gap (**B**).

multivariate model using a 30-day medication gap analyzing patients prescribed dabigatran, younger patients (HR, 0.99; CI, 0.98–1.00; *P*=0.001) with a lower risk of stroke (HR, 1.17; 95% CI, 1.01–1.36; *P*=0.032), a greater risk of bleeding (HR, 1.25; 95% CI, 1.08–1.46; *P*=0.003), and a higher CCI (HR, 1.04; 95% CI, 1.01–1.07; *P*=0.019) were significantly more likely to be nonpersistent. For patients prescribed warfarin using the 30-day medication gap, younger patients (HR, 0.99; 95% CI, 0.98–0.99; *P*<0.001) with a history of intracerebral bleeding (HR, 3.61; 95% CI, 1.80–7.25; *P*<0.001) were significantly more likely to be nonpersistent. With the multivariate model using a 60-day medication gap analyzing patients prescribed dabigatran, patients with a lower risk of stroke (HR, 1.37; 95% CI, 1.17–1.60; *P*<0.001), higher risk of bleeding (HR, 1.24; 95% CI, 1.04–1.47; *P*=0.016), and higher CCI (HR, 1.05; 95% CI, 1.01–1.08; *P*=0.007) were significantly more likely to be nonpersistent. For patients prescribed warfarin using a 60-day medication gap, younger (HR, 0.98; 95% CI, 0.98–0.99; *P*<0.001) patients with a history of intracerebral bleeding (HR, 3.41; 95% CI, 1.62–7.19; *P*=0.001) were significantly more likely to be nonpersistent, whereas patients residing in the Midwest (HR, 0.56; 95% CI, 0.40–0.79; *P*=0.001) and the South (HR, 0.81; 95% CI, 0.68–0.96; *P*=0.001) were significantly less likely to be nonpersistent. Although the HR for age is very close to 1, this is over a change in 1 year. For patients multiple years apart, the HR would move away from 1. For example, if we compare 2 patients with 10 years of age difference, then the HR of nonpersistence would be 0.99^10.

Discussion

When treatment guidelines are followed, OAC with warfarin has been demonstrated to be effective for preventing ischemic stroke in patients with AF.[18] However, largely because of the complex dosing regimen requiring frequent INR monitoring, treatment with warfarin has been associated with both adherence and persistence issues,[1,2,4,18–24] potentially resulting in suboptimal outcomes.

Since 2010, the oral direct thrombin inhibitor dabigatran has been available for patients with NVAF. This OAC has been demonstrated to be superior to warfarin, reducing stroke risk 35% compared with warfarin,[27] without an increase in bleeding risk.[28] In addition, no INR monitoring is required.

Dabigatran, therefore, seems to present several benefits compared with warfarin, but whether these characteristics may also translate into increased adherence and persistence was unclear. In the RE-LY study, patients on dabigatran showed slightly lower 2-year persistence on the drug compared with warfarin, although the difference was marginal (79% versus 83%, respectively).[25] In this study, we sought to compare real-world persistence on the 2 OAC therapies using Department of Defense claims data and to determine factors significantly

Table 4. Factors Significantly Associated With Nonpersistence

	Dabigatran/Warfarin		
	HR	95% CI	*P* Value
30-day medication gap			
Dabigatran patients (n=3370)			
Age, y	0.99	0.98–1.00	0.001
$CHADS_2$ <2	1.17	1.01–1.36	0.032
$HEMORR_2HAGES$ >3	1.25	1.08–1.46	0.003
CCI	1.04	1.01–1.07	0.019
Warfarin patients (n=1775)			
Age, y	0.99	0.98–0.99	<0.001
History of ICH bleeding	3.61	1.80–7.25	<0.001
60-day medication gap			
Dabigatran patients (n=3370)			
$CHADS_2$ <2	1.37	1.17–1.60	<0.001
$HEMORR_2HAGES$ >3	1.24	1.04–1.47	0.016
CCI	1.05	1.01–1.08	0.007
Warfarin patients (n=1775)			
Age, y	0.98	0.98–0.99	<0.001
Region (reference level: West)			
Midwest	0.56	0.40–0.79	0.001
South	0.81	0.68–0.96	0.018
History of ICH bleeding	3.41	1.62–7.19	0.001

CI indicates confidence interval; CCI, Charlson comorbidity score; and HR, hazard ratio.

associated with persistence on therapy. Our analysis shows that 6-, 9-, and 12-month persistence on dabigatran significantly exceeds that of warfarin in patients newly diagnosed with NVAF. Using exploratory retrospective analysis with persistence defined as a function of the gaps between medication refills,[30,32] the 1-year persistence on dabigatran was 63% compared with 39% on warfarin when a 60-day permissible medication gap was used.

This difference in persistence cannot be explained by differences in patient characteristics because the persistence rate was determined using a PS-matched cohort that included 1745 matched pairs on the 2 different treatments. This PS matching included measures previously identified as potential factors significantly associated with persistence on warfarin, including age, $CHADS_2$, $HEMORR_2HAGES$, and the CCI scores.[20,21,23]

In previous studies, warfarin persistence was somewhat higher than reported here, ranging from 65% to 74% at 1 year,[1,4,20,21,23,24] although some of these studies were not restricted to newly diagnosed patients.[4,20,21] These studies also permitted longer medication gaps (ie, 90[1,20,24] to 120[21] to 180[23] days) and were of older patients on average.[23] In our study, permissible gaps of 30 and 60 days were used to account for the standard monthly prescription of dabigatran and then applied to both therapies consistently. Previous studies typically allowed longer medication gaps for warfarin to accommodate for potential dose adjustments and reinitiation of medication in case a short discontinuation occurred. In this sense, our analysis dictated by the prescribing protocol for dabigatran was stricter. Because of the concern that this stricter medication gap period used could result in potentially losing some warfarin patients who may be prolonging their time between refills because of dose adjustments, we ran a sensitivity analysis examining the number of medication gaps falling into the 30- and 60-day periods. This sensitivity analysis showed that 89% and 95% of medication gaps for patients on warfarin were <30 and 60 days, respectively, providing us with additional confidence that patients identified as discontinued in this study presented true discontinuations.

Most of the factors significantly associated with nonpersistence with dabigatran identified in this study were analogous to the ones previously found to be predictive of nonpersistence with warfarin, namely, age, $CHADS_2$, $HEMORR_2HAGES$, and CCI scores.[20,21,23] Persistence increased with increasing age and higher stroke risk (as measured by $CHADS_2$) and decreased with higher bleed risk (as measured by $HEMORR_2HAGES$) and the number of comorbidities (as measured by the CCI). As in previous studies, the dependence on $CHADS_2$ and $HEMORR_2HAGES$ may reflect a rational assessment of the risk/benefit ratio by prescribing physicians and their patients.[20] Lower persistence in patients with higher CCI scores may reflect the lesser suitability of dabigatran in patients with complicating factors, such as renal or hepatic disease.

In comparison, persistence with warfarin in this study was associated with age, history of intracranial hemorrhage, and region of patient residence, whereas $CHADS_2$ and CCI were not found to be associated with persistence. These findings confirm previously reported lower persistence with warfarin in younger patients[20,21,23] and indicate physicians' propensity for rapid discontinuation of warfarin in patients with a history of intracranial bleeds. Regional differences in persistence rates for patients on warfarin exist, namely, lower persistence rates are found in the West compared with the Midwest and the South, which is of unclear significance, although it may be reflective of different ethnic structures of the different regions. Differences in persistence on warfarin depending on ethnicity have been previously reported.[24]

Limitations

Although analysis of claims data provides a good indication of real-world persistence of OAC therapy as compared with more controlled environments, such as clinical trials, it also carries significant limitations. The most important limitation is the inability to determine discontinuation of treatment was patient- versus physician-initiated. This limitation, however, applies to both OAC therapies examined in this study equally. It is plausible that for some younger patients with moderate-to-lower stroke risk as indicated by $CHADS_2$ <2, the physician or patient may determine that the risk of bleeding may outweigh the benefit of the therapy. Furthermore, OAC may be discontinued for a wide variety of interventions that may not have been fully captured and examined in our data, such as surgeries and procedures.[26]

Fluctuations in INR values may result in warfarin dose adjustments, potentially leading to longer medication gaps. Previous studies accounted for this possibility by using

permissible medication gaps of up to 120 to 180 days. In our study, the choice of shorter medication gaps of 30 and 60 days was dictated by consistency with standard dabigatran prescribing. However, the fact that 89% and 95% of medication gaps for patients on warfarin were <30 and 60 days, respectively, confirmed that lower persistence rate on warfarin was not because of this choice of shorter medication gaps.

Although there are a large number of variables used to estimate the PS, 1 variable not accounted for was prescription date. This variable was not included because of the short time period (<2 years) for which data were available. Therefore, the effects of the introduction of rivaroxaban toward the end of the study period were not analyzed. In future studies with longer timeframes of data, prescription date should be a factor to analyze changes in patient persistence over different time points.

Conclusion

In this retrospective study of newly diagnosed NVAF patients initiating treatment with dabigatran versus warfarin using a large claims database, we found consistently higher persistence with therapy in those treated with dabigatran at 6, 9, and 12 months. To our knowledge, this is the first study comparing persistence of dabigatran and warfarin in NVAF patients. Persistence was defined in terms of a permissible medication gap and was higher for dabigatran using both a 30- and a 60-day permissible gap. In addition to offering superior stroke risk reduction with no increase in concomitant bleed risk, dabigatran may, therefore, also contribute to improved outcomes through increasing patients' persistence with therapy. As in previous studies of persistence with OAC therapy, we found persistence to increase with increasing patient's age and stroke risk and persistence to decrease with increasing risk of hemorrhage.

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Disclosures

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