Research Article

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Journal of **Comparative Effectiveness Research**

Factors influencing dabigatran or warfarin medication persistence in patients with nonvalvular atrial fibrillation

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Factors influencing differences in persistence between dabigatran and warfarin in patients with nonvalvular atrial fibrillation (NVAF) remain unclear. **Aim:** Compare differences in persistence between new dabigatran and warfarin users in patients newly diagnosed with NVAF, adjusting for sociodemographics, clinical characteristics, patient out-of-pocket cost and other covariates. **Methods:** A retrospective matched-cohort study was conducted using a US claims database of Medicare and commercially insured patients with NVAF aged ≥18 years. Persistence and monthly out-of-pocket costs for dabigatran or warfarin were calculated and adjusted for covariates using Cox proportional hazard models. **Results & conclusion:** Unadjusted persistence was significantly lower among dabigatran users (n = 1025) compared with matched warfarin users (38 vs 46%). Adjusting for covariates rendered this difference insignificant (hazard ratio = 0.930).

First draft submitted: 04 October 2018; Accepted for publication: 11 April 2018; Published online: 29 May 2018

Keywords: dabigatran • nonvalvular atrial fibrillation • out of pocket cost • persistence • warfarin

Atrial fibrillation (AF) is the most common clinical arrhythmia, affecting approximately 2.3 million patients in the USA [1]. An estimated 15% of all strokes in the USA and up to 36% of all strokes for patients aged 80–89 years are attributable to the increased risk due to AF [2]. Nonvalvular atrial fibrillation (NVAF), AF in the absence of mitral valve disease, aortic valve disease or valvular prostheses, accounts for more than 95% of cases of AF in the USA [1,3].

Clinical trial data have shown that anticoagulation therapy substantially reduces the risk of stroke in patients with AF [4]. Based on results of the RE-LY randomized clinical trial, dabigatran (150 mg twice daily), an oral anticoagulant (OAC) was associated with significantly lower rates of stroke and systemic embolism, and intracranial hemorrhage, but increased risk of major gastrointestinal hemorrhage than those observed with adjusted-dose warfarin [5–7]. In a retrospective database study of Medicare patients, Graham *et al.* (2015) [8] found that patients treated with dabigatran had lower risk of ischemic stroke, intracranial bleeding and death compared with warfarin; however, demonstrated an increased risk of major gastrointestinal hemorrhage compared with warfarin. In addition, Seeger *et al.* (2015) [9] found a lower risk of stroke and major hemorrhage with dabigatran compared with warfarin.

Age and other sociodemographic factors have been reported to be associated with dabigatran and warfarin nonpersistence, as have thromboembolic event risk, major bleed/hemorrhage risk and complexity of comorbid conditions as measured by CHADS2, HEMORRHAGES2 and Charlson comorbidity index scores, respectively [10,11]. In addition, patients have expressed that higher out-of-pocket (OOP) costs are a major barrier to switch from warfarin to novel OAC therapies like dabigatran [12]. A study by Desai *et al.* (2014) observed fivefold higher average patient OOP spending for novel OACs compared with warfarin, in patients with NVAF from a commercial administrative claims database [13]. Previous real-world evidence studies among newly diagnosed NVAF patients and newly treated with dabigatran have shown improved medication persistence compared with those newly treated with warfarin, adjusting for covariates [10,14]; however, none have assessed differences in persistence using an administrative claims dataset specifically in a predominantly Medicare advantage population in the USA. In addition, none of the previous

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studies controlled for index medication OOP costs when assessing differences in persistence. The objective of this study was to compare differences in persistence between new users of dabigatran and warfarin in patients newly diagnosed with NVAF, adjusting for sociodemographic, clinical characteristics, index medication OOP cost and other covariates.

Methods

Study design & data source

A retrospective matched-cohort study was conducted using the Humana Inc. administrative claims database. This database contains integrated medical claims (inpatient stays, outpatient, office and emergency department [ED] visits), pharmacy claims and enrollment data, representing more than 12 million current and former Humana members enrolled in commercial, Medicare Advantage and prescription drug plans. The data have national coverage, with a high proportion of members from Texas, Florida and Ohio. For this study, Medicare Advantage and commercially insured populations were examined. The patient index date was defined as the date of initiation of dabigatran or warfarin during the patient identification period from January 2011 to December 2011. Data were extracted for each patient for the 12-month period before the index date to up to 12 months after the index date; therefore, the full study period was from January 2010 to December 2012. The protocol was approved by an independent institutional review board.

Study population

The study population consisted of patients newly diagnosed with NVAF and newly treated with dabigatran or warfarin. Newly diagnosed was defined as the first AF diagnosis occurring within 3 months prior to index date and no other AF diagnosis in the >3 to 12 months before index date. Newly treated was defined as having no prescription fills for any OAC in the 12 months prior to index date. Patients were assigned to either the dabigatran or warfarin cohort based on the index OAC during the identification period. Patients were required to have ≥1 inpatient stay, ≥2 physician office visits, ≥2 ED visits or a combination of one physician office visit and ED visit with an ICD-9 code of 427.31 (AF) on distinct service dates during the 3-month pre-index period. Eligible patients were also required to have 12 months of continuous enrollment prior to the index date. Patients with a diagnosis of hyperthyroidism or valvular heart disease during the 12-month pre-index were excluded. Patients with a diagnosis of myocarditis, pericarditis or pulmonary embolism, or who had undergone cardiac surgery (see Supplementary Appendix A for codes) within 3 months prior to the first AF diagnosis were excluded.

Patient characteristics

Age, gender, race and geographic region, health plan type and income status were reported at the index date. The following variables were reported during the pre-index period: time from NVAF diagnosis to index date, month of index exposure, prescribing provider specialty, comorbidities (see codes in Supplementary Appendix A), use of other medications of interest (see Supplementary Appendix B for Generic Product Identifier codes), number of pharmacy claims for all unique medications (other than index medication) per patient and number of pharmacy claims for unique cardiovascular medications of interest (see Supplementary Appendix C for Generic Product Identifier codes). Clinical indexes to quantify thromboembolic event risk, major bleeds or hemorrhage risk, and clinical complexity of comorbidities, including $CHADS_2$, CHA_2DS_2VASc, $HEMORR_2HAGES$ and Deyo–Charlson comorbidity index score were calculated during the pre-index period (see codes in Supplementary Appendix A). Medical and pharmacy costs (total and OOP) in the pre-index period were determined. Monthly index medication OOP cost for each patient was the sum of all dabigatran (or warfarin) copayments and coinsurance payments made during the follow-up period divided by the total days supplied, and multiplied by 30 days. Deductibles were not included in this measure.

Propensity score matching

Propensity score matching (PSM) based on 1:1 nearest neighbor method with a caliper width of 0.2 standard deviations of the estimated logit was used to match patients in the dabigatran cohort to patients in the warfarin cohort [15]. Patients were matched using baseline demographic and clinical characteristics (except month of index exposure) as well as pre-index medical and pharmacy costs (total and OOP).

Outcomes

Patients were followed for up to 12 months post-index to evaluate impact of sociodemographic, clinical characteristics, index medication OOP cost and other covariates on persistence. The key study outcome was persistence, defined as a dichotomous measure of whether or not the patient exhibited an OAC fill/refill pattern in which there were no observed gaps greater than 30 days in the postindex period. If a patient had a gap greater than 30 days, discontinued their index OAC or switched to a different OAC, they were considered nonpersistent for their index medication. If a patient did not experience a discontinuation or switch before the end of continuous enrollment, end of study observation period (December 2012) or death; whichever occurs first, the patient was considered persistent and was censored at the end of the follow-up period. Duration of follow-up postindex was determined. For patients who had an oversupply of medications (refilled prescription before completing previously obtained medication), the extra medication was added to next month's supply.

Statistical analyses

Patient characteristics were compared among dabigatran and warfarin cohorts both pre- and post-PSM. χ^2 tests and t-tests or Wilcoxon rank-sum tests were conducted for categorical and continuous variables, respectively. Persistence until a 30-day gap was reported for each cohort. Mean (standard deviation) and median (interquartile) days on therapy before gap, discontinuation or switching, were also reported. Kaplan–Meier curves were used to depict probabilities of persistence using a 30-day gap among dabigatran and warfarin cohorts. Multivariable analysis using Cox regression model was conducted to determine significant predictors of persistence between dabigatran and warfarin treatment cohorts, after adjusting for demographic, clinical and index medication OOP costs. Pre-index medical and pharmacy cost (total and OOP) variables were not included in the model due to collinearity. Adjusted hazard ratios were reported with 95% confidence intervals. The *a priori* α-level for all inferential analyses was set at 0.05.

Results

Sample characteristics

A total of 1123 patients newly diagnosed with NVAF and newly initiated on dabigatran, and 2729 patients newly diagnosed with NVAF and newly initiated on warfarin were identified (Supplementary Appendix D). Post-PSM, 1025 patients were retained in each cohort. A summary of standardized differences for baseline patient characteristics pre- and post-PSM between the two cohorts are presented in Table 1. All assessed demographic and clinical characteristics are presented in Supplementary Appendices E & F. Among all matched patients across the two treatment cohorts, the mean age was 74 years (Table 1). Males comprised 54% of the dabigatran cohort and 55% of the warfarin cohort. Demographic characteristics were similar between the two cohorts (Table 1, Supplementary Appendix E). Fewer patients in the dabigatran cohort compared with warfarin cohort had venous thromboembolism (<10 vs 37, respectively) and coagulopathies (<10 vs 16, respectively, Supplementary Appendix F); all other clinical characteristics were similar between the two cohorts. Mean unadjusted monthly index medication OOP costs were significantly higher in the dabigatran cohort compared with the warfarin cohort (US$63 vs US$4 for dabigatran and warfarin cohorts, respectively; $p < 0.0001$). Distributions of monthly OOP costs for dabigatran and warfarin are presented in Supplementary Appendix G.

Persistence

Persistence rate at 1 year was significantly lower in the dabigatran cohort compared with the warfarin cohort (38 vs 46%; $p = 0.0001$; Table 2). Both cohorts had a median follow-up period of 365 days although median number of days on therapy was significantly lower in the dabigatran cohort compared with the warfarin cohort (182 vs 240; $p < 0.0001$). After adjusting for demographic and clinical covariates, and index medication OOP cost, there was no significant difference in persistence among dabigatran users compared with warfarin users (hazard ratio = 0.930 [0.766–1.123]) (Table 3). Parameters from the regression analysis are presented in Supplementary Appendix H. Kaplan–Meier curves depicting persistence, adjusted for covariates, in dabigatran and warfarin cohorts, are presented in Figure 1.

Discussion

Mean monthly index medication OOP costs were significantly higher in the dabigatran cohort compared with the warfarin cohort (US$63 vs US$4; $p < 0.0001$). Not surprisingly, due to higher acquisition cost, the OOP

Table 1. Standardized differences for patient characteristics between dabigatran and warfarin cohorts.

Measure	Dabigatran cohort	Warfarin cohort	Standardized differences	
n	1025	1025	Before PSM	After PSM
Demographic characteristics				
Age, mean (SD)	73.91 (±8.07)	74.04 (±8.23)	0.238	0.016
Gender = female (vs male), n (%)	474 (46.2%)	456 (44.5%)	0.077	0.035
Race/ethnicity[†], n (%):				
– White	881 (92.6%)	865 (91.1%)	0.152	0.044
– Black	43 (4.5%)	57 (6.0%)	0.092	0.063
– Hispanic	<10	15 (1.6%)	0.057	0.054
– Other	16 (1.7%)	10 (1.1%)	0.033	0.052
– Unknown	<10	<10	0.292	0.007
Geographic region, n (%):				
– Northeast	25 (2.4%)	28 (2.7%)	0.010	0.018
– Midwest	250 (24.4%)	252 (24.6%)	0.144	0.005
– South	660 (64.4%)	651 (63.5%)	0.182	0.018
– West	90 (8.8%)	94 (9.2%)	0.078	0.014
Line of business = Medicare (vs commercial), n (%)	951 (92.8%)	950 (92.7%)	–	–
Clinical characteristics				
Deyo–Charlson comorbidity index, mean (SD)	2.12 (±2.07)	2.22 (±2.27)	0.355	0.043
Deyo–Charlson comorbidity index, median [IQR]	2.00 [2.00]	2.00 [2.00]		
Baseline stroke risk:				
– $CHADS_2$stroke risk score, mean (SD)	2.20 (±1.25)	2.26 (±1.26)	0.320	0.047
– $CHADS_2$stroke risk score, median [IQR]	2.00 [2.00]	2.00 [2.00]		
– CHA_2DS_2-VASc stroke risk score, mean (SD)	3.75 (±1.52)	3.80 (±1.56)	0.340	0.029
– CHA_2DS_2-VASc stroke risk score, median [IQR]	4.00 [2.00]	4.00 [2.00]		
Baseline bleeding risk: $HEMORR_2HAGES$ score, mean (SD)	2.37 (±1.47)	2.43 (±1.51)	0.355	0.039
Baseline bleeding risk: $HEMORR_2HAGES$ score, median [IQR]	2.00 [2.00]	2.00 [2.00]		

[†]Default race for Medicare members only.
IQR: Interquartile range; PSM: Propensity score matching; SD: Standard deviation.

Table 2. Persistence until a 30-day gap: dabigatran as compared with warfarin cohort.

Measurement (unadjusted)	Dabigatran cohort (n = 1025)	Warfarin cohort (n = 1025)	p-value
Persistence rate at 1 year (%), [95% CI][†]	38% [35, 41%]	46% [43, 49%]	0.0001
Days on therapy, median [95% CI][‡]	182 [162, 203]	240 [210, 285]	<0.0001

[†]Based on cumulative incidence estimates; p-value from Gray's test.
[‡]Based on KM estimates; p-value from log-rank test.
KM: Kaplan–Meier.

Table 3. Association of nonpersistence with treatment cohort (dabigatran vs warfarin), adjusting for covariates.

Parameter	Estimate	Standard error	χ^2	p-value	Hazard ratio	Lower 95% CI	Upper 95% CI
Cohort (dabigatran vs warfarin, 1 = dabigatran)	-0.073	0.098	0.559	0.455	0.930	0.766	1.123

cost for dabigatran is significantly higher than warfarin [16]. Unadjusted medication persistence measured using a 30-day permissible gap was significantly lower in the dabigatran cohort compared with the warfarin cohort (38.0 vs 45.9%; p = 0.0003). Persistence on OAC treatment is important in achieving optimal anticoagulation in AF patients. Previous studies have examined the relationship between sociodemographic and clinical variables and their impact on medication persistence [10,11]. However, this is the first study to test the influence of index medication OOP costs, in addition to sociodemographic, clinical and other covariates, on differences in persistence between dabigatran and warfarin. Goldman *et al.* (2004) [17] suggest that an increase in OOP costs is associated with a reduction in drug utilization, and price sensitivity to different drugs varies by their therapeutic class. Demand

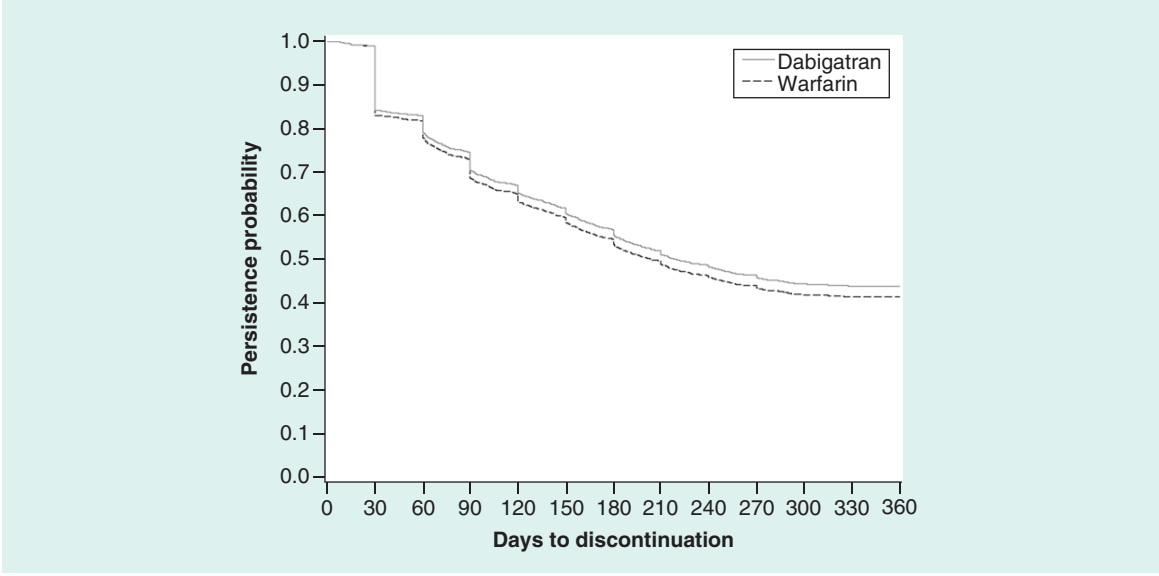

Figure 1. Kaplan–Meier plots for persistence, adjusted for baseline covariates and out-of-pocket costs, dabigatran and warfarin cohorts.

for costlier drugs and drugs that have lower-cost substitutes tends to be more elastic [17]. In this study, we found that after controlling for covariates including OOP costs, persistence between dabigatran and warfarin treatment cohorts was no longer significantly different.

We found that unadjusted persistence in dabigatran cohort was significantly lower than in warfarin cohort (38.0 vs 45.9%). In contrast, separate studies by Zalesak *et al.* [10] and Bancroft *et al.* [14] found significantly higher persistence in the dabigatran cohort compared with warfarin cohort (50.3 vs 24.1%, Zalesak *et al.*; 48.1 vs 38.4%, Bancroft *et al.*) using a 30-day permissible gap. In addition, patients prescribed dabigatran were observed to have significantly higher median persistence than patients prescribed warfarin (389 vs 135 days, Zalesak *et al.*; 204 vs 161 days, Bancroft *et al.*). Median number of days on therapy in our study was significantly lower in the dabigatran cohort compared with the warfarin cohort (182 vs 240; $p < 0.0001$). Several plausible reasons explain these discrepant findings. The studies differ in patient demographic and clinical characteristics, and plan type. For instance, Bancroft *et al.* and Zalesak *et al.* were based on younger populations (mean ages of 73.0 and 67.8 years, respectively) than the present study (mean age: 74 years). Bancroft and colleagues utilized data from a large US commercial managed care organization consisting of 65% commercially insured patients; whereas, the US Department of Defense administrative claims database data utilized by Zalesak *et al.* consists of active and retired military personnel and their families. In contrast, the present study was based on a predominantly Medicare sample (93%) from the Humana claims database. After adjusting for covariates including patient demographic and clinical characteristics, and index medication OOP costs, we found no significant difference in nonpersistence between the two treatment cohorts.

Limitations

Limitations associated with this study should be considered when interpreting the study findings. The results of this study were based on administrative claims data from a large national health plan (Humana) in the US and may not be generalizable to populations other than the Humana population. The majority of patients in the study population were enrolled in Medicare Advantage plans. These patients are older and have different plan benefits compared with those enrolled in commercial plans. Database studies using administrative claims are prone to coding errors of omission and commission and incomplete claims information which may lead to misclassification of exposure or the outcome. Patients with need for short term OAC, such as those with deep vein thrombosis or joint replacement surgery were not excluded. OOP costs were estimated using claims data and may not reflect final cost to patient after application of secondary insurance or patients assistance programs. Using the entire follow-up period to calculate index medication OOP cost used as a variable predicting persistence may bias the analysis. PSM

was conducted to balance the two treatment cohorts on known baseline characteristics; however, it does not account for unobserved characteristics which may result in residual confounding. For instance, it is important to assess drug-related adverse events and its influence on persistence. PSM also leads to attrition in sample size; however, the proportion of excluded patients varies between dabigatran and warfarin cohorts and may limit generalizability. In addition, physician's prescribing patterns, patient preferences and patient-provider communication can influence the choice of OAC treatment and may have influenced persistence observed in this study [18]. Therefore, it is likely for residual confounding to exist within the matched cohorts.

Conclusion

Unadjusted medication persistence was significantly lower in the dabigatran cohort compared with the warfarin cohort. However, after adjusting for sociodemographic, clinical characteristics and index medication OOP costs, no significant differences in persistence were observed between dabigatran and warfarin users.

Summary points

- This study compares differences in persistence between new dabigatran and warfarin users in patients newly diagnosed with nonvalvular atrial fibrillation after adjusting for sociodemographics, clinical characteristics, patient out-of-pocket cost and other covariates.
- Unadjusted medication persistence was significantly lower in the dabigatran cohort compared with the warfarin cohort. However, after adjusting for covariates, no significant differences in persistence were observed between dabigatran and warfarin users.

Financial & competing interests disclosure

This study was funded by Boehringer Ingelheim Pharmaceuticals, Inc. and Humana Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No funded writing assistance was utilized in the production of this manuscript. Copy editing was provided by M Costantino (Comprehensive Health Insights).

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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