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Original article

Healthcare utilization and costs associated with dabigatran compared to warfarin treatment in newly diagnosed patients with non-valvular atrial fibrillation

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Abstract

Purpose:
Real-world healthcare resource utilization and costs were compared among patients with non-valvular atrial fibrillation (NVAF) receiving either dabigatran or warfarin.

Methods:
A retrospective cohort study was conducted using administrative claims data from the United States Department of Defense (DOD) Military Health System. Patients with newly diagnosed AF initiated on dabigatran or warfarin were identified using ICD-9 diagnosis, procedure and drug codes. Patients were observed for 3 months prior to treatment initiation to ascertain a diagnosis of valvular heart disease and 12 months for exclusion of those with a history of anticoagulation therapy. Propensity score matching was used to balance baseline characteristics between the two treatment cohorts. Medical and pharmacy utilization and costs were compared between the dabigatran and warfarin treatment groups for 3 and 12 months following treatment initiation.

Results:
A total of 1102 patients with newly diagnosed NVAF initiated on dabigatran were matched with corresponding warfarin-treated patients. In the 12 months following initiation of anticoagulation, the mean medical costs for patients initiated on dabigatran were significantly lower than for patients initiated on warfarin (−$6299, $p<0.001$), largely due to fewer hospitalizations (−0.162, $p=0.009$). While pharmacy costs were higher ($4369, $p<0.001$) for dabigatran, overall healthcare costs were significantly lower compared with patients on warfarin (12 months: −$1940, $p<0.001$). Mean hospital length of stay between these two groups were similar (6.033 days for dabigatran vs 6.318 days for warfarin, $p=0.139$).

Conclusion:
Despite higher pharmacy costs for NVAF patients initiated on dabigatran vs warfarin, this was more than offset by lower utilization of medical care resources.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that affects more than 2.5 million adults in the US[1]. AF is a major risk factor for ischemic stroke, conferring a four- to five-fold increase in risk compared to adults without AF[1]. Overall, 15% of all strokes in the US each year are attributable to AF[2]. The incremental costs per year for AF patients in the US, relative to patients without

AF, was estimated to total a considerable $26.0 billion in 2008, with hospital costs accounting for 63% of these costs[3,4].

The annual incidence of ischemic stroke for patients with AF not treated with antithrombotic medication is 4.5%[1]. In clinical trials, dose adjusted warfarin was shown to reduce ischemic stroke risk by approximately 64%[5]. However, warfarin therapy requires long-term blood monitoring of the international normalized ratio (INR) and is associated with elevated risk of bleeding, drug–drug and drug–food interactions, and lifestyle changes[6]. Although the acquisition cost of warfarin is low, the associated monitoring and risk of complications place added clinical and economic burden on patients and the healthcare system[7]. Patients treated with warfarin that have poorly controlled INR values have higher rates of annual mortality and incidence of major bleeding[8]. Careful prothrombin testing improves INR control, but major bleeding events still occur in approximately 3% of AF patients on warfarin per year[9,10], causing excessive costs in managing the bleeding events[11].

Dabigatran, a direct thrombin inhibitor, was introduced in 2010 as an alternative to warfarin for reducing the risk of ischemic stroke in patients with non-valvular AF (NVAF). Clinical trials indicate that dabigatran is at least as effective as warfarin in ischemic stroke reduction[12]. Modeling based on clinical trial data suggests that dabigatran is a cost-effective alternative to warfarin[13–16]. However, there is limited real world longitudinal data on patients treated with different anticoagulants. The intent of this study was to compare the costs and resource utilization among patients with newly diagnosed NVAF beginning either dabigatran or warfarin treatment.

Methods

Study sample

This study utilized the US Department of Defense (DoD) Military Health System administrative claims data, which included hospital, outpatient, and pharmacy data for over 10 million active service and retired military personnel and family members. Patients were identified using an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) code for AF (427.31) in any diagnostic position in at least one hospital claim or two outpatient claims between January 2008 and May 2012[11]. Study subjects were required to have 12 months of continuous data prior to their first AF claim. Patients with claims indicating valvular heart disease in the 12 months prior to their first AF claim were excluded. Supplementary Online Appendix A contains the ICD-9 codes used to identify AF patients and to exclude AF patients with valvular heart disease. Patients were excluded if they had one or more claims for cardiac surgery, pericarditis, myocarditis or pulmonary embolism in the 3 months prior to or hyperthyroidism in the 12 months prior to their first AF claim to ensure that the study sample did not include patients at risk of having transient AF.

Patients with at least one pharmacy claim for dabigatran or warfarin following the first AF claim were assigned to the respective treatment cohort. Supplementary Online Appendix B is a list of drugs with corresponding codes used for identification of dabigatran or warfarin use. Each patient was assigned an index date based on when dabigatran or warfarin was first filled, after 28 October 2010, the approval date for dabigatran (Figure 1)[17]. Patients who had a dabigatran or a warfarin prescription during the 12 months prior to the index date were excluded from the analysis. To include only newly diagnosed patients, only those with the first AF claim that occurred within the 3 months prior to the index date were included. Patient demographics consisting of age, gender, and region (Northeast, Midwest, South, West) were identified from the closest claim prior to the index date. In addition, history of major bleeding, months since AF diagnosis, $CHADS_2$ score (used to estimate stroke risk)[18], $HEMORR_2HAGES$ score (used to estimate bleeding risk)[19], and Charlson Comorbidity Index (CCI)[20] were assessed for each patient based on the data from

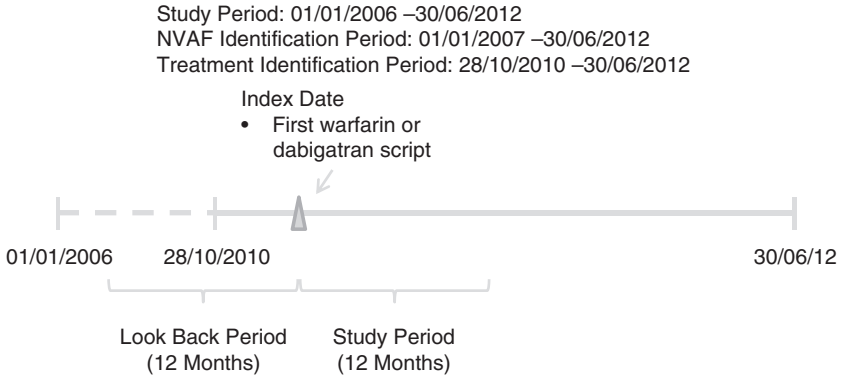

Figure 1. Schematic representation of study design.

12 month period prior to the index date. The patient selection steps are depicted in Figure 2.

Outcomes

Outcomes of interest were medical and pharmacy utilization and associated costs. Medical costs were computed from claims for all hospital, outpatient, and emergency visits and for any cause. Total pharmacy costs for each treatment cohort were based on all-cause outpatient, retail, and mail order claims. Costs specifically for dabigatran and warfarin (dabigatran- and warfarin-related pharmacy costs) were broken out separately. Medical and total pharmacy costs were combined to calculate mean total healthcare costs. All costs were amounts paid by the DoD. Time periods analyzed were 0 to 3 months for patients with at least 3 months of continuous data and 0 to 12 months for patients with at least 12 months of continuous data following the index date for each patient.

Within the outpatient data, the number of visits was identified by the number of distinct days that a patient had an outpatient claim. This methodology was used to address cases where patients received multiple claims on a single day for different services. Primary care visits were identified based on the provider specialty on the claim. Emergency room (ER) related metrics, except ER visits that resulted in hospitalizations, were broken out from the outpatient data where the place of service was identified as the ER. Number of ER visits that resulted in hospitalizations was identified through hospital claims where the source of admission was the ER. Although this study was not designed to detect differences in clinical outcomes, resource use such as costs and number of hospitalizations related to ischemic stroke and bleeding were calculated to provide insight into drivers of utilization[21]. Supplementary Online Appendices C and D contains the ICD-9 codes for identification of ischemic stroke and bleeding events among patients with newly diagnosed NVAF in each treatment cohort.

Statistical analysis

Patients with at least 3 months of data after the index date were matched using propensity scores based on a 1:1 greedy matching algorithm with a caliper width of 0.1. Propensity scores (PS) were computed using logistic regression based on age, gender, region, history of ICH, history of major bleeding, months since AF diagnosis, $CHADS_2$ score, $HEMORR_2HAGES$ score, and CCI. Chi-square tests and *t*-tests were conducted for categorical and continuous variables respectively, to test for significant differences in baseline characteristics before and after matching.

Costs and resource utilization were estimated at both 3 and 12 months after index date. Patients who disenrolled or died between 3 and 12 months after the index date were included in the 3 month cohort, but excluded from the

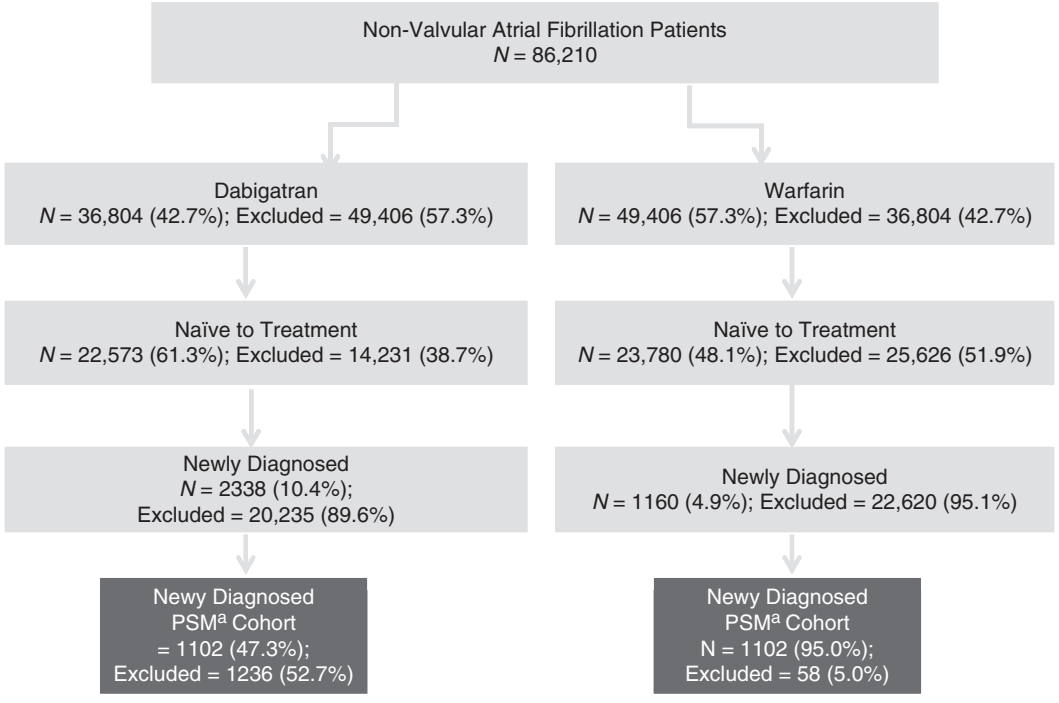

Figure 2. Flowchart describing the process of sample selection (inclusion/exclusion).

12 month cohort. The Wilcoxon signed-rank test was used to test for significant differences in resource utilization and costs between patients receiving dabigatran and warfarin.

All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA). All p values reported are two sided and significant at the $\alpha = 0.05$ level.

Results

Within the DoD data, 86,210 patients with NVAF were identified, of which 2338 and 1160 were newly diagnosed and naïve to dabigatran and warfarin treatment respectively (Figure 2). The propensity score matching resulted in 1102 of patients in each treatment group for analysis. Baseline characteristics before and after the PS match are shown in Table 1. The chi-square test indicated that baseline characteristics between the two treatment groups were comparable except there was a significant difference in regional makeup of the cohorts after matching.

Healthcare costs and utilization results are summarized in Table 2 and Table 3, respectively. Patients on dabigatran treatment accrued significantly lower total mean healthcare costs relative to warfarin both at 3 months ($8682 vs $ 6261, $p<0.001$) and at 12 months ($19,557 vs $17,617, $p<0.001$). While the pharmacy costs accrued by dabigatran cohort was significantly greater ($1693 vs $3002, $p<0.001$), total medical costs for dabigatran patients were significantly lower than warfarin at 3 months ($6989 vs $3259, $p=0.002$) and at 12 months ($13,909 vs $7610, $p<0.001$). The hospitalization costs were significantly lower in the dabigatran group at 3 months. During this period while the mean numbers of hospitalizations were similar between the two treatment groups (0.471 vs 0.420, $p=0.172$), the mean hospital length of stay for dabigatran treated patients was significantly shorter compared to patients on warfarin (6.814 vs 5.271 days, $p<0.001$). At 12 months, significant lower hospitalization costs were observed in the dabigatran group, but unlike the 3 month results, significantly lower mean numbers of hospitalizations in dabigatran-treated patients were observed compared to patients on warfarin (0.871 vs 0.709, $p=0.009$) with a similar mean hospital length of stay between these two groups (6.033 vs 6.318 days, $p=0.139$). Outpatient costs were consistently greater for the warfarin group over both 3 and 12 months. The two groups incurred similar ER costs over the shorter and longer periods. Hospital utilization and costs related to bleeding and ischemic stroke observed were similar between the two treatment groups.

Discussion

The study results based on DoD healthcare claims data indicated that, while pharmacy costs were higher among patients with NVAF treated with dabigatran relative to warfarin over the course of 3 months and 12 months, mean healthcare costs were significantly lower. These results can be explained by the significantly lower medical costs in the dabigatran group that offset the higher pharmacy costs over warfarin. The drivers of medical cost difference were length of stay and physician visits at 3 months and number of hospitalizations and physician visits at 12 months. The consistently larger number of physician visits observed in the warfarin group is likely due to the requirement of INR monitoring and dose adjustments, a key attribute difference.

The mean medical costs of $13,909 for newly diagnosed patients on warfarin over 12 months in our analysis is lower

Table 1. Baseline patient characteristics before and after propensity score matching (PSM).

Baseline Characteristics	Before PSM			After PSM		
	Dabigatran	Warfarin	p-value[a]	Dabigatran	Warfarin	p-value[a]
$N=$	2338	1160	—	1102	1102	—
Age, mean (SD[b])	73.3 (9.3)	72.3 (11.1)	0.006	72.3 (10.0)	72.4 (11.0)	0.732
Gender (female), count (%)	928 (39.7)	445 (38.4)	0.448	418 (37.9)	428 (38.8)	0.661
Region	—	—	<0.001	—	—	0.043
Midwest, count (%)	176 (7.5)	68 (5.9)	—	70 (6.4)	68 (6.2)	—
Northeast, count (%)	312 (13.3)	182 (15.7)	—	210 (19.1)	181 (16.4)	—
South, count (%)	937 (40.1)	409 (35.3)	—	374 (33.9)	409 (37.1)	—
West, count (%)	623 (26.6)	313 (27.0)	—	255 (23.1)	274 (24.9)	—
History of ICH, count (%)	5 (0.2)	8 (0.7)	0.030	5 (0.5)	6 (0.5)	0.762
History of major bleeding, count (%)	916 (39.2)	506 (43.6)	0.012	491 (44.6)	475 (43.1)	0.492
Time since AF diagnosis (months), mean (SD[b])	1.5 (1.1)	1.3 (1.1)	0.001	1.3 (1.1)	1.4 (1.1)	0.133
$CHADS_2$, mean (SD[b])	2.1 (1.2)	2.3 (1.3)	<0.001	2.4 (1.3)	2.3 (1.3)	0.106
$HEMORR_2HAGES$, mean (SD[b])	2.4 (1.5)	2.6 (1.6)	0.010	2.6 (1.6)	2.5 (1.6)	0.538
CCI, mean (SD[b])	2.2 (2.2)	2.5 (2.4)	<0.001	2.5 (2.3)	2.5 (2.4)	0.681

ICH, intracranial hemorrhage; AF, atrial fibrillation; CCI, Charlson Comorbidity Index.
[a]All p-values calculated using chi-square and t-test for categorical and continuous variables respectively.
[b]SD indicates standard deviation.

Table 2. Healthcare costs in patients with newly diagnosed NVAF.

	3 months			12 months		
	Dabigatran	Warfarin	*p*-value[a]	Dabigatran	Warfarin	*p*-value[a]
N =	1102	1102	—	591	673	—
Total Healthcare Costs, Costs Per Patient						
Mean	$6261	$8682	<0.001	$17,617	$19,557	<0.001
SD[b]	$9215	$20,564	—	$19,067	$35,054	—
Total Medical Costs, Costs Per Patient						
Mean	$3259	$6989	0.002	$7610	$13,909	<0.001
SD[b]	$8804	$20,087	—	$16,263	$33,175	—
Hospital Costs						
Total All-Cause Hospital Costs, Costs Per Patient						
Mean	$1766	$4928	0.011	$3463	$7994	<0.001
SD[b]	$7351	$17,593	—	$12,992	$26,787	—
Bleeding Related Hospital Costs, Costs Per Patient						
Mean	$148	$84	0.845	$293	$203	0.711
SD[b]	$3853	$2010	—	$5311	$2844	—
Ischemic Stroke Related Hospital Costs, Costs Per Patient						
Mean	$144	$77	0.596	$285	$168	0.184
SD[b]	$2730	$1265	—	$4817	$1901	—
Outpatient Costs						
Total Outpatient Costs Per Patient						
Mean	$1493	$2061	0.004	$4147	$5916	<0.001
SD[b]	$2821	$4584	—	$5836	$9549	—
ER Costs Per Patient						
Mean	$95	$125	0.204	$255	$381	0.006
SD[b]	$326	$394	—	$753	$1447	—
Total Pharmacy Costs (Outpatient, Retail, and Mail Order) Per Patient						
Mean	$3002	$1693	<0.001	$10,007	$5647	<0.001
SD[b]	$2637	$2571	—	$9003	$8157	—
Dabigatran/Warfarin Related Pharmacy Costs Per Patient						
Mean	$632	$30	<0.001	$1715	$72	<0.001
SD[b]	$302	$32	—	$943	$83	—

NVAF, non-valvular atrial fibrillation.
[a]All *p*-values calculated with the Wilcoxon signed-rank test.
[b]SD indicates standard deviation.

than two similar studies: $18,621 in Mercaldi *et al.*[11], and $24,129 in Ghate *et al.*[22]. The latter is notable as patients with bleeding were excluded. Two factors may potentially account for the lower costs in the current analysis compared to previous studies. First, the cost variables in the dataset were limited to the total DoD paid amount, which may be lower than other health systems. Second, the patients in our study differ from those in past studies. Compared to the population from Mercaldi *et al.*[11], the PS-matched population in this study was on average younger and had lower $CHADS_2$ and $HEMORR_2HAGES$ scores. While patients in the current study are somewhat older on average than those in the study by Ghate *et al.*[22], patients in our study had less comorbidity, reflected in lower CCI scores.

No significant differences in hospital costs and resource utilization attributable to bleeding or to ischemic stroke were detected at any time point. While, ischemic stroke- and bleeding-related resource utilization and costs were captured to determine the extent to which these events drive any observed differences in medical costs, this study was not powered to detect a difference in clinical outcomes.

The DoD data is subject to limitations common to other administrative healthcare claims datasets. Incomplete claims or missing claims may result in under-reporting of healthcare costs and resource utilization. As such, inconsistencies in the coding systems for procedures and treatment may be present.

Limitations also exist in calculating unique visit days from the outpatient data. Multiple claims for any given unique visit may exist in the data due to the number of procedures or providers encountered by a patient during the visit. In our analysis, we defined a unique visit as distinct number of days where a patient has an encounter with any provider. This attempts to limit instances where multiple procedures or visits to multiple providers can inflate the overall number of visits per patient. However, any errors or delays in the billing date would result in an inflated number of unique outpatient visit days.

This study has several notable strengths. Unlike previous studies on this topic, DoD data provided an opportunity to capture the entire spectrum of healthcare resources that were necessary for care of NVAF patients, because of limited restriction on medical and pharmacy benefits. DoD data is geographically diverse with 14% of the beneficiaries

Table 3. Healthcare resource utilization in patients with newly diagnosed NVAF.

	3 months			12 months		
	Dabigatran	Warfarin	*p*-value[a]	Dabigatran	Warfarin	*p*-value[a]
N =	1102	1102	—	591	673	—
Hospital Related Healthcare Resource Utilization						
Number of Hospitalizations Per Patient						
Mean	0.420	0.471	0.172	0.709	0.871	0.009
SD[b]	0.658	0.712	—	1.061	1.262	—
Length of Stay Per Hospitalization						
N =	462	519	—	419	586	—
Mean	5.271	6.814	<0.001	6.318	6.033	0.139
SD[b]	7.546	8.085	—	8.439	7.329	—
Number of Bleeding Related Hospitalizations Per Patient						
Mean	0.014	0.012	0.845	0.030	0.033	0.850
SD[b]	0.144	0.108	—	0.199	0.223	—
Number of Ischemic Stroke Related Hospitalizations Per Patient						
Mean	0.018	0.015	0.396	0.024	0.025	0.393
SD[b]	0.134	0.127	—	0.239	0.166	—
Outpatient Related Healthcare Resource Utilization						
Number of Outpatient Visits Per Patient						
Mean	15.971	17.907	0.001	54.528	55.441	0.459
SD[b]	8.887	11.433	—	28.944	35.405	—
Number of Outpatient Visits to the PCP Per Patient						
Mean	2.975	4.103	<0.001	8.371	10.834	<0.001
SD[b]	3.839	5.440	—	9.298	10.817	—
Number of ER Visits Per Patient						
Mean	0.390	0.456	0.265	1.073	1.227	0.059
SD[b]	0.818	0.926	—	1.895	2.576	—
Number of ER Visits That Resulted in Hospitalizations Per Patient						
Mean	0.060	0.132	<0.001	0.076	0.211	<0.001
SD[b]	0.276	0.425	—	0.343	0.722	—

NVAF, non-valvular atrial fibrillation; PCP, primary care physician; ER, emergency room.
[a]All *p*-values calculated with the Wilcoxon signed-rank test.
[b]SD indicates standard deviation.

in active duty. The rest of the population consists of dependents or retirees. Moreover 78% of the DoD population is 18 years and older compared to 75% of the US population. Lastly, the size of the population allowed PS matching of treatment groups, which substantially reduces imbalances of observed covariates.

Conclusion

The study findings showed that among newly diagnosed patients with NVAF the initiation of warfarin relative to dabigatran was associated with significantly greater medical costs, driven by increased healthcare utilization likely for anticoagulation management and dose adjustment. Despite the pharmacy cost differential of dabigatran relative to warfarin, in newly diagnosed patients with NVAF, costs savings may be obtained with use of dabigatran over warfarin.

Transparency

Declaration of funding
This study was funded by Boehringer Ingelheim Pharmaceuticals Inc.

Author contributions: All authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE), were fully responsible for all content and editorial decisions, and were involved at all stages of manuscript development.

Declaration of financial/other relationships
K.F., Y.R., and H.S. have disclosed that they are employees of Trinity Partners, a company that received funding from Boehringer Ingelheim to help conduct this study. C.Y. and H.A. have disclosed that they were employees at Trinity Partners during the conduct of the study. S.S. and S.G. have disclosed that they are employees of Boehringer Ingelheim Pharmaceuticals Inc. D.M. has disclosed that he is a paid consultant to Boehringer Ingelheim.

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