At a Glance

Practical Implications p xxx
Author Information p xxx
Full text and PDF www.ajpb.com
Web exclusive eAppendix

Resource Use Among Nonvalvular Atrial Fibrillation Patients

Matthew Sussman, MA; Sameer Ghate, PhD; Samuel P. Sutherland, BS; Cheng Wang, MD, PhD; Stephen Sander, PharmD; and Robert I. Griffiths, ScD

ABSTRACT

Objective: To assess comparative resource use for patients given a new diagnosis of nonvalvular atrial fibrillation (NVAF) and newly treated with dabigatran or warfarin in a US real-world setting.

Study Design: A retrospective cohort analysis was conducted using de-identified electronic health record data from a large, nationwide database of integrated delivery networks (IDNs).

Methods: We identified newly diagnosed NVAF patients, newly treated with dabigatran or warfarin ≤90 days of diagnosis between October 1, 2010, and September 30, 2012. Patients had ≥1 year of data prior to initiating therapy (index date). Patients in the warfarin cohort were propensity score matched 1:1 to patients in the dabigatran cohort and were followed up to 1 year after index to assess all-cause, stroke-related, and bleed-related healthcare resource use.

Results: A total of 3890 patients (1945, dabigatran; 1945, warfarin) were included and balanced through the matching process. The probability of an all-cause hospitalization was significantly lower in the dabigatran cohort compared with the warfarin cohort (42.8% vs 47.5%; P = .007). The dabigatran cohort had significantly lower per-patient per-year (PPPY) hospital (1.07 vs 1.20), emergency department (ED) (0.36 vs 0.51), and physician office visits (10.64 vs 18.13), as well as mean length of hospital stay (4.0 vs 4.6 days), compared with the warfarin cohort (all P <.001). Total PPPY stroke-related hospitalizations and physician office visits, and total PPPY bleed-related ED visits, were also significantly lower for the dabigatran cohort compared with the warfarin cohort (all P <.05).

Conclusions: Newly diagnosed NVAF patients, newly treated with dabigatran and receiving care in US IDNs, experienced fewer all-cause healthcare resources than patients initiating warfarin.

Key Words: arrhythmia, anticoagulants, fibrillation, risk factors, stroke.

Am J Pharm Benefits. 2016;8(5):84-92

Nonvalvular atrial fibrillation (NVAF), which refers to atrial fibrillation (AF) without valvular disease, accounts for more than 95% of all cases of AF[1] in the United States. Clinical trial data have shown that oral anticoagulation therapy substantially reduces the risk of stroke in patients with AF.[2] Warfarin is the most prevalent anticoagulant prescribed in the United States today.[3,4] The drug has been shown to reduce the risk of stroke by about two-thirds compared with placebo.[5] However, warfarin is associated with a number of therapeutic challenges. For instance, warfarin requires frequent monitoring to maintain international normalized ratio (INR) within a narrow therapeutic range (2.0-3.0).[6-8] For INR values that fall outside of the optimal therapeutic range, the risk of hemorrhage increases with the level of INR,[9,10] with yearly rates of major bleeding ranging from 0.5% to 6.5% and fatal bleeding ranging from 0.1% to 1.0% among warfarin-treated patients.[11-16] Additional challenges of warfarin use include the ability of dietary vitamin K intake and concomitant medications to interact with warfarin, which may influence INR maintenance and the time spent within therapeutic range.[17]

Dabigatran, approved by the FDA in October 2010, is the first novel oral anticoagulant (NOAC) to become available for clinical use in more than 50 years.[18] It has been shown to be associated with significantly lower rates of stroke, systemic embolism, and intracranial hemorrhages compared with warfarin.[19] Due to the recent emergence of pharmaceutical alternatives to warfarin, payers in the United States have been faced with the option of placing NOACs on their formularies, thereby intensifying the need for evaluations of the overall economic impact—particularly healthcare resource utilization and direct medical costs—across treatment types.

Limited real-world data exist on healthcare utilization associated with NOAC therapies; as such, the primary objective of this analysis was to assess comparative resource use for patients receiving a new diagnosis of NVAF, and newly treated with dabigatran or warfarin, using de-identified electronic health record (EHR) data from integrated delivery networks (IDNs). With an emphasis on the continuum of healthcare

services, this unique data source provides additional insight on real-world estimates of resource utilization for this patient population.

PRACTICAL IMPLICATIONS

Patients with a newly nonvalvular atrial fibrillation (NVAF) diagnosis, newly treated with dabigatran and receiving care in US integrated delivery networks (IDNs), experienced fewer all-cause healthcare resources than patients initiating warfarin.

- The introduction of novel oral anticoagulants (NOACs) in recent years, including dabigatran, has provided clinicians with alternative options for stroke risk reduction.
- Despite the recent introduction of NOACs, limited real-world data exist on healthcare utilization associated with these therapies.
- Our findings indicate that patients given a new diagnosis of NVAF, who were receiving care in US IDNs and newly treated with dabigatran, experienced fewer all-cause annual medical services. These findings may assist clinicians when determining options for oral anticoagulation among treatment-naïve patients with NVAF.

METHODS

Study Design and Data Source

A retrospective cohort analysis was conducted using de-identified EHR data from October 1, 2010, through September 30, 2013. During the study period, the Humedica EHR database contained de-identified data on more than 30 million individuals across 38 states. Humedica integrates claims, prescription, and practice management data by partnering with medical groups, IDNs, and hospital chains to directly obtain data from EHRs in real time. Approximately 40% of patients in the Humedica database have linked inpatient and outpatient records, allowing for a complete analysis of a patient's full experience in the IDN system. This subset of patients in the EHR who are from an IDN setting formed the basis for the patient population in this study.

Primary Patient Selection

The population of interest for this analysis included adult patients ≥18 years, newly diagnosed with NVAF and newly treated with an oral anticoagulant (OAC), either dabigatran or warfarin. The date of the first OAC prescription was defined as the index date, which must have occurred between October 1, 2010, and September 30, 2012, to allow for 1-year baseline and follow-up periods. To ensure cohorts of newly treated patients, patients were only included if they had no prescriptions for any OAC during the 12-month pre-index period. Additionally, to ensure cohorts of newly diagnosed NVAF patients, the first observed NVAF diagnosis (identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* code 427.31 in any position) during the 12-month pre-index period was required to appear on the index date or within 3 months prior to the index date. Patients were required to have ≥1 EHR encounter in the 12 months prior to the index date (defined as the baseline period) and ≥1 EHR encounter following the index date (defined as the follow-up period). Furthermore, patients must have had integrated inpatient and outpatient data, which allow for a complete picture of resource utilization in the IDN setting. Patients in the warfarin cohort were propensity score matched 1:1 to patients in the dabigatran cohort, and only matched pairs were included in the final data set.

Additional Inclusion/Exclusion Criteria

Patients were required to have ≥2 prescriptions of the index OAC (including the prescription on the index date) for study inclusion. Additionally, on the index date or within 3 months prior to the index date, patients were required to have ≥1 inpatient, ≥2 physician office visits, ≥2 emergency department (ED) visits, or ≥1 physician office visit and ≥1 ED visit on distinct service dates with an NVAF diagnosis.

Patients with the following were excluded from the study sample: diagnosis of hyperthyroidism (potentially reversible underlying cause of AF) or valvular heart disease during the 12 months pre-index or an indication of cardiac surgery or diagnosis of pericarditis, myocarditis, or pulmonary embolism within 3 months prior to the first NVAF diagnosis.

Patients were followed for a maximum of 12 months. The follow-up period commenced on the index date and ended on the earlier of the following: (a) last EHR encounter date in the observed data or (b) the last day of the 12-month postindex period.

Additional Details on the Matching Process

Patients in the warfarin cohort were matched 1:1 to patients in the dabigatran cohort using the propensity score matching (PSM) method. The propensity score was defined as the probability of being treated with dabigatran (dependent variable) based on a set of baseline characteristics, including sex, age, geographic region, month of index date, Deyo-Charlson comorbidity index, $CHADS_2$ stroke risk score, $HEMORR_2HAGES$ bleeding risk score, and selected comorbidities (ie, acute myocardial infarction, cardiomyopathy, congestive heart failure, chronic obstructive pulmonary disease/emphysema, diabetes, hyperlipidemia, hypertension, peptic ulcer/gastroesophageal reflux disease, ischemic stroke/transient ischemic attack, venous thromboembolism). PSM by logistic regression, with the Nearest Neighbor method within a caliper of

0.20 of the standard deviation of the estimated logit, was used to match dabigatran and warfarin cohorts.

Study Outcomes

Comparative healthcare resource utilization during the follow-up period was the primary outcome of interest for this analysis. Incidence rates for the first healthcare resource use were reported by type of service (ie, hospitalization, ED visit, physician office visit) for all-cause, stroke-related, and bleed-related events. The total number of all-cause, stroke-related, and bleed-related resource utilization events were assessed and reported by type of service (ie, hospitalization, ED visit, physician office visit). Among patients with at least 1 hospitalization, the average length of stay per all-cause hospitalization was estimated.

Data Analysis

Kaplan-Meier survival analyses were conducted to assess the time to first all-cause hospitalization, time to first stroke-related hospitalization, and time to first bleed-related hospitalization following index for each cohort. A log-rank sum test was used to test the significant differences between survival curves. In addition to using a PSM method for identifying matched patients, a sensitivity analysis was conducted using a doubly robust approach in the form of a multivariate Cox proportional hazards model; this was to assess the association between OAC treatment and risk of first all-cause hospitalization, first all-cause ED visit, and first all-cause physician office visit. The primary covariate used in the model included the presence of dabigatran as the index therapy. Incidence rates were presented as a rate per 100 patient-years to allow for variable follow-up. Incidence rates were calculated using the number of patients identified in each cohort having an event during the follow-up period as the numerator. The denominator consisted of all patients with NVAF in the cohort (the denominator was censored based on the date of first all-cause or disease-specific event, last EHR encounter date in the observed data, or the last day of the 12-month postindex period). For each incidence rate, a 95% confidence interval was derived assuming a binomial distribution.

Outcomes tested for statistical significance (defined as $P < .05$) between the dabigatran and warfarin cohorts, including baseline demographic and clinical characteristics and number of healthcare resource utilization events. Chi-squared contingency tests were used for comparison of proportions, while nonparametric Wilcoxon rank sum tests were used to evaluate the statistical significance of differences in continuous variables.

RESULTS

Baseline Demographic and Clinical Characteristics

Prior to matching, 1945 patients with NVAF who met the inclusion criteria initiated treatment on dabigatran, while 11,473 initiated treatment on warfarin. The matched analysis included 1945 patients in the dabigatran and warfarin cohorts, nearly 58% of them male and with a mean age of approximately 70 years (**Table 1**).

Following the PSM process, mean $CHADS_2$ and CHA_2DS_2-VASc scores were approximately 1.3 and 2.5, indicating moderate to high stroke risk, respectively.[20] Additionally, the $HEMORR_2HAGES$ score was approximately 1.50, indicating low to moderate bleeding risk.[21] Coronary artery disease, diabetes, hyperlipidemia, and hypertension were the most common comorbid conditions identified among the matched study population. Dabigatran and warfarin patients were well matched on demographic and clinical characteristics, with no significant differences observed in age, sex, region, selected comorbidities, Deyo-Charlson comorbidity index, Elixhauser comorbidity index, stroke risk ($CHADS_2$), and bleeding risk ($HEMORR_2HAGES$). The average duration of follow-up was 342 days (±64) for the dabigatran index cohort and 332 days (±79) for the warfarin cohort ($P < .001$).

Resource Utilization

Results from the Kaplan-Meier analyses demonstrated the time to first all-cause hospitalization to be significantly ($P = .007$) longer for the dabigatran cohort compared with the warfarin cohort (**Figure 1**). In fact, only 42.8% of the dabigatran cohort had an all-cause hospitalization at the end of 1 year compared with 47.5% of the warfarin cohort. Similarly, the time to first stroke-related hospitalization was significantly ($P = .024$) longer for the dabigatran cohort (**Figure 2**). Moreover, just 3.5% of the dabigatran cohort had a stroke-related hospitalization at the end of 1 year compared with 4.9% of the warfarin cohort. Results from the analysis of time to first bleed-related hospitalization were not significant.

First all-cause hospitalization and ED visits per 100 patient-years were considerably lower in the dabigatran cohort compared with the warfarin cohort (**Table 2**). Incidence rates for first stroke-related and bleed-related events (hospitalizations, ED visits, physician office visits) were also lower in the dabigatran cohort.

The per-patient per-year (PPPY) total number of all-cause hospitalizations, ED visits, and physician office visits were all significantly ($P < .001$) lower for the dabigatran cohort compared with the warfarin cohort (mean all-cause PPPY hospitalizations, 1.07 vs 1.20; mean all-cause PPPY ED visits, 0.36 vs 0.51; mean all-cause PPPY physician office visits, 10.64 vs 18.13) (Table 2). Additionally, the

Table 1. Baseline Demographic and Clinical Characteristics in Newly Diagnosed NVAF Patients Newly Treated With Dabigatran or Warfarin, Among Pre-Matched and Postmatched Cohorts

	Pre-Match			Postmatch†		
Characteristic	**Dabigatran**	**Warfarin**	***P***	**Dabigatran**	**Warfarin**	***P***
N	1945	11,473		1945	1945	
Male, %	58.2%	53.3%	<.001	58.2%	57.4%	.65
Age (years)						
Mean (±SD)	69.6 (10.5)	72.8 (10.1)	<.001	69.6 (10.5)	69.9 (11.4)	.07
Region, %			<.001			.77
Northeast	4.5%	6.5%		4.5%	5.1%	
Midwest	53.0%	35.1%		53.0%	53.6%	
South	39.6%	54.3%		39.6%	38.1%	
West	1.2%	2.6%		1.2%	1.1%	
Other/Unknown	1.7%	1.5%		1.7%	2.0%	
Deyo-Charlson Comorbidity Index						
Mean (±SD)	0.97 (1.53)	1.32 (1.83)	<.001	0.97 (1.53)	1.00 (1.43)	.24
0, %	54.1%	46.4%		54.1%	53.0%	
1, %	22.2%	20.5%		22.2%	20.8%	
≥2, %	23.7%	33.0%		23.7%	26.3%	
Stroke Risk ($CHADS_2$)						
Mean (±SD)	1.34 (1.11)	1.58 (1.21)	<.001	1.34 (1.11)	1.37 (1.13)	.44
0 or 1, %	61.3%	52.6%		61.3%	52.6%	
2, %	24.4%	26.6%		24.5%	32.5%	
3-6, %	14.2%	20.9%		14.2%	14.9%	
Stroke Risk (CHA_2DS_2-VASc)						
Mean (±SD)	2.52 (1.59)	2.96 (1.60)	<.001	2.52 (1.59)	2.59 (1.55)	0.10
0, %	11.0%	5.8%		11.0%	9.4%	
1, %	17.3%	12.8%		17.0%	16.5%	
≥2, %	71.7%	81.3%		72.0%	74.1%	
Bleeding Risk ($HEMORR_2HAGES$)						
Mean (±SD)	1.50 (1.42)	1.81 (1.64)	<.001	1.49 (1.42)	1.52 (1.46)	.48
0 or 1, %	61.6%	52.3%		61.6%	58.7%	
2 or 3, %	29.4%	34.0%		29.5%	32.5%	
≥4, %	8.9%	13.6%		9.0%	8.8%	
Comorbidities, %						
Acute myocardial infarction	0.5%	1.2%	.01	0.5%	0.6%	.66
Ischemic stroke/TIA	2.6%	2.3%	.55	3.2%	2.3%	.07
Congestive heart failure	5.1%	8.9%	<.001	5.1%	5.3%	.83
Diabetes	16.1%	16.4%	.78	16.1%	15.8%	.83
Hypertension	44.2%	41.4%	0.03	44.2%	45.4%	.44
Pre-index medication use, %						
Low molecular weight heparin	6.8%	7.2%	.50	6.8%	6.6%	.85
Unfractionated heparin	5.9%	8.2%	<.001	5.9%	6.6%	.35
Antiarrhythmics	4.2%	2.6%	<.001	4.2%	2.8%	.02
Antihyperlipidemics	38.4%	32.3%	<.001	38.4%	31.3%	<.001
Antiplatelets	18.3%	15.8%	.007	18.3%	15.8%	.04
Beta-blockers	39.3%	36.3%	.013	39.3%	35.2%	.01
Calcium channel blockers	25.0%	22.1%	.005	25.0%	20.6%	<.001
Other antihypertensives*	45.6%	39.6%	<.001	45.6%	40.0%	<.001

NVAF indicates nonvalvular atrial fibrillation; TIA, transient ischemic attack.

*Includes angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers, and diuretics.

†Patients were matched based on: sex, age, geographic region, month of index date, selected comorbidities (ie, acute myocardial infarction, cardiomyopathy, congestive heart failure, chronic obstructive pulmonary disease/emphysema, diabetes, hyperlipidemia, hypertension, peptic ulcer/gastroesophageal reflux disease, transient ischemic attack, venous thromboembolism), Deyo-Charlson comorbidity index, $CHADS_2$ stroke risk score, and $HEMORR_2HAGES$ bleeding risk score.

Figure 1. Time to first all-cause hospitalization in newly diagnosed NVAF patients newly treated with dabigatran or warfarin, following propensity score matching

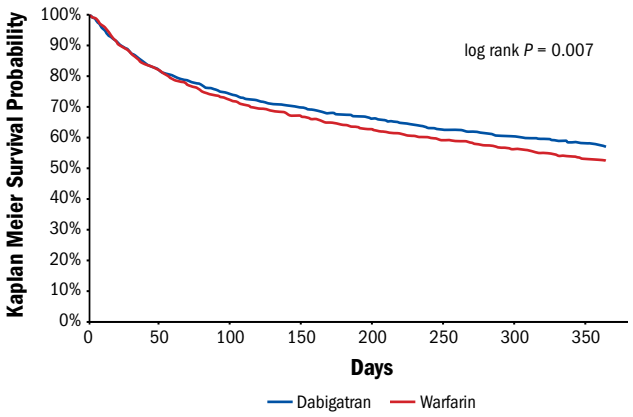
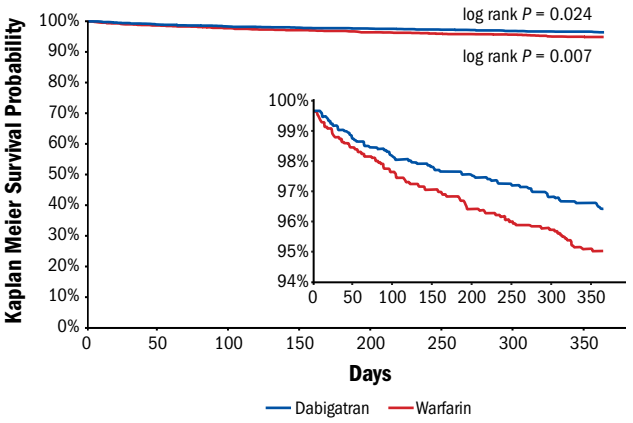


Figure 2. Time to first stroke-related hospitalization in newly diagnosed NVAF patients newly treated with dabigatran or warfarin, following propensity score matching



*Note: the inset provides a blown-up version of the survival analysis, provided on a more defined scale

dabigatran cohort had a significantly lower mean length of stay for all-cause inpatient admissions (4.0 vs 4.6 days; P <.001) compared with the warfarin cohort. Moreover, the PPPY total of stroke-related hospitalizations and physician office visits was significantly lower for the dabigatran cohort compared with the warfarin cohort (mean stroke-related PPPY hospitalizations, 0.06 vs 0.10, P = .03; mean stroke-related PPPY ED visits, 0.00 vs 0.01, P = .65; mean stroke-related PPPY physician office visits, 0.16 vs 0.29, P = .02) (Table 2). The PPPY total number of bleed-related ED visits were significantly (P = .02) lower for the dabigatran cohort, while the bleed-related hospitalizations and physician office visits were not statistically significantly different between cohorts (mean bleed-related PPPY hospitalizations, 0.05 vs 0.03, P = .49; mean bleed-related PPPY ED visits, 0.01 vs 0.03, P = .02; mean bleed-related PPPY physician office visits, 0.05 vs 0.15, P = .57) (Table 3).

Results of the sensitivity analysis using adjusted Cox regression models to predict risk of first all-cause hospitalization, ED visit, or physician office visit were consistent with the unadjusted matched results. In particular, treatment with dabigatran was associated with a significantly (P <.01) lower likelihood of a first all-cause event.

DISCUSSION

Summary

A total of 1945 matched patients, newly diagnosed with NVAF and newly treated with dabigatran or warfarin, were

Table 2. All-cause and Disease-specific Incidence Rates of Healthcare Resource Utilization in Newly Diagnosed NVAF Patients Newly Treated With Dabigatran or Warfarin, Following Propensity Score Matching

Measure	Dabigatran	Warfarin	Relative Rates
N	1945	1945	
All-cause resource use, per 100 patient-years (95% CI)			
First all-cause hospitalization	62.29 (58.16-66.72)	72.19 (67.62-77.06)	0.86 (0.71-1.05)
First all-cause ED visit	24.57 (22.26-27.12)	30.34 (27.71-33.23)	0.81 (0.51-1.28)
First all-cause physician office visit	685.81 (655.29-717.78)	672.94 (642.52-704.83)	1.02 (0.97-1.04)
Stroke-related resource use, per 100 patient-years (95% CI)			
First stroke-related hospitalization	3.56 (2.79-4.54)	5.17 (4.21-6.36)	0.69 (0.18-2.58)
First stroke-related ED visit	0.49 (0.26-0.93)	0.62 (0.35-1.11)	0.79 (0.02-33.15)
First stroke-related physician office visit	6.27 (5.20-7.55)	8.66 (7.36-10.18)	0.72 (0.27-1.95)
Bleed-related resource use, per 100 patient-years (95% CI)			
First bleed-related hospitalization	2.03 (1.48-2.80)	2.44 (1.81-3.28)	0.83 (0.13-5.24)
First bleed-related ED visit	0.82 (0.50-1.35)	1.69 (1.19-2.42)	0.49 (0.04-6.69)
First bleed-related physician office visit	3.27 (2.54-4.21)	3.70 (2.91-4.72)	0.88 (0.20-3.81)

ED indicates emergency department; NVAF, nonvalvular atrial fibrillation.

Table 3. Unadjusted PPPY Healthcare Resource Utilization in Newly Diagnosed NVAF Patients Newly Treated With Dabigatran or Warfarin, Following Propensity Score Matching

Measure	Dabigatran	Warfarin	*P*
N	1945	1945	
All-cause resource use			
Hospitalizations			
Mean (±SD)	1.07 (5.41)	1.20 (2.70)	<.001
P25	0	0	
Median	0	0	
P75	1.01	1.14	
ED visits			
Mean (±SD)	0.36 (1.11)	0.51 (1.51)	<.001
P25	0	0	
Median	0	0	
P75	0	0	
Physician office visits			
Mean (±SD)	10.64 (10.26)	18.13 (18.41)	<.001
P25	3.99	4.99	
Median	7.98	14.19	
P75	13.96	27.00	
Stroke-related resource use			
Hospitalizations			
Mean (±SD)	0.06 (0.59)	0.10 (1.44)	.03
P25	0	0	
Median	0	0	
P75	0	0	
ED visits			
Mean (±SD)	0 (0.07)	0.01 (0.08)	.65
P25	0	0	
Median	0	0	
P75	0	0	
Physician office visits			
Mean (±SD)	0.16 (0.94)	0.29 (1.54)	.02
P25	0	0	
Median	0	0	
P75	0	0	
Bleed-related resource use			
Hospitalizations			
Mean (±SD)	0.05 (0.88)	0.03 (0.31)	.49
P25	0	0	
Median	0	0	
P75	0	0	
ED visits			
Mean (±SD)	0.01 (0.09)	0.03 (0.39)	.02
P25	0	0	
Median	0	0	
P75	0	0	
Physician office visits			
Mean (±SD)	0.05 (0.43)	0.15 (2.96)	.57
P25	0	0	
Median	0	0	
P75	0	0	

ED indicates emergency department; NVAF, nonvalvular atrial fibrillation; PPPY, per-patient per-year.

analyzed from the de-identified EHR IDN dataset. The time to first all-cause hospitalization and time to first stroke-related hospitalization were significantly longer for the dabigatran cohort. Moreover, total PPPY all-cause resource use (hospitalizations, ED visits, and physician office visits), total PPPY stroke-related hospitalizations and physician office visits, and total PPPY bleed-related ED visits were significantly lower for the dabigatran cohort compared with the warfarin cohort during the 1-year follow-up period.

Comparison to Other Literature

To the best of our knowledge, no other published articles of retrospective database design have compared resource utilization using IDN data in this population of newly diagnosed NVAF patients who have been newly treated with dabigatran or warfarin. Other recently published retrospective database studies of dabigatran users have focused on characteristics affecting OAC treatment selection among patients with NVAF,[22] treatment patterns,[23-26] and clinical outcomes,[27,28] thus demonstrating an important need to measure economic outcomes in this population.

Using prospectively collected data from the RE-LY (Randomized Evaluation of Long-term anticoagulant therapY: dabigatran vs. warfarin) clinical trial, Connolly et al estimated the risk of stroke or systemic embolism among patients with AF randomized to 1 of 2 fixed dose arms of dabigatran (110 or 150 mg twice daily) or adjusted-dose warfarin.[19] Compared with the warfarin arm, the authors found a statistically significant reduction in the primary outcome measure associated with the 150-mg dose of dabigatran. Despite differences in sample selection criteria between the RE-LY trial and our EHR-based study, we, too, found a statistically significant reduction in stroke events (ie, stroke-related hospitalizations) among patients newly treated with dabigatran.

Limitations

Our study is subject to certain limitations that are inherent in EHR data in general, primarily the lack of continuous eligibility/enrollment data, which potentially underestimates the level of observed utilization events. As a proxy for ensuring continuous eligibility, patients were required to have at least 1 medical encounter in the baseline period and at least 1 follow-up encounter, which assumes continuous enrollment in the health plan before and after index. Additionally, National Drug Code (NDC) information was not reliably provided by data sources contributing to the EHR database, making it difficult to identify prescriptions. To avoid misclassifying prescriptions, this study used the drug name field, rather than the NDC field, for dabigatran or warfarin identification.

Moreover, due to the lack of detailed prescription data, discontinuation of the index therapy (ie, dabigatran, warfarin) was not assessed in the postindex period; as a result, study outcomes were assessed among an intent-to-treat population only (ie, regardless of whether patients discontinued therapy in the postindex period). Furthermore, the EHR database, with data sourced from different EHRs, contains prescriptions ordered but not prescriptions filled, which may have overestimated the use of selected medications. Finally, as is the case with most EHR data sources, cost data were not available in this data set, thereby limiting an assessment of direct medical costs associated with observed resource utilization.

CONCLUSIONS

The introduction of NOACs, such as dabigatran, in recent years has provided clinicians with alternative options for effective stroke risk reduction.[19] Although the current literature provides insight into the cost-effectiveness of dabigatran versus warfarin, by way of economic modeling,[29-37] limited published estimates of resource use among patients with NVAF treated with dabigatran or warfarin exist using real-world data. Our analysis fills this data gap by providing estimates, from EHR data from US IDNs, which expand upon the cost-effectiveness results and clinical findings observed in large-scale randomized trials.

Patients with newly diagnosed NVAF receiving care in US IDNs, newly treated with dabigatran, experienced fewer all-cause annual hospitalizations, ED visits, and physician office visits than patients newly treated with warfarin. These findings should be of use to clinicians when determining options for oral anticoagulation among patients who are treatment-naïve.

Acknowledgments

For his contribution to manuscript development, the authors would like to acknowledge Michael Munsell, BA, an employee of Boston Health Economics, Inc.

Author Affiliations: Boston Health Economics, Inc (MS, SPS, RIG), Waltham, MA; Boehringer Ingelheim Pharmaceuticals, Inc (SG, CW, SS), Ridgefield, CT.

Source of Funding: This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc (BIPI). All authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, were fully responsible for all content and editorial decisions, and were involved at all stages of manuscript development.

Author Disclosures: MS, SPS, and RIG are employees of Boston Health Economics, Inc, and were funded by BIPI for this study. SG, CW, and SS are employees of the sponsor, BIPI. The authors report no other relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (MS, SG, CW, RIG); acquisition of data (MS, SPS); analysis and interpretation of data (MS, SG, SPS, CW, RIG); drafting of the manuscript (MS, RIG); critical revision of the manuscript for important intellectual content (MS, SG, SPS, CW, SS, RIG); statistical analysis (MS, SPS, RIG); obtaining funding (MS); administrative, technical, or logistic support (MS); supervision (MS, SG, RIG).

Address correspondence to: Joseph Menzin, PhD, Boston Health Economics, Inc, 20 Fox Rd, Waltham, MA 02451.

E-mail: jmenzin@bhei.com.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA.* 2001;285(18):2370-2375.

2. Albers GW, Sherman DG, Gress DR, Paulseth JE, Petersen P. Stroke prevention in nonvalvular atrial fibrillation: a review of prospective randomized trials. *Ann Neurol.* 1991;30(4):511-518.

3. Johnson JA. Warfarin pharmacogenetics: a rising tide for its clinical value. *Circulation.* 2012;125(16):1964-1966. doi: 10.1161/CIRCULATIONAHA.112.100628.

4. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. *Circ Cardiovasc Qual Outcomes.* 2012;5(5):615-621.

5. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999;131(7):492-501.

6. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med.* 1996;335(8):540-546.

7. Singer DE, Albers GW, Dalen JE, et al; American College of Chest Physicians. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(suppl 6):546S-592S. doi: 10.1378/chest.08-0678.

8. Camm AJ, Kirchhof P, Lip GY, et al; European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery; ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace.* 2010;12(10):1360-1420. doi: 10.1093/europace/euq350.

9. Perret-Guillaume C, Wahl DG. Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose--a meta-analysis. *Thromb Haemost.* 2004;91(2):394-402.

10. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest.* 2001;119(suppl 1):108S-121S.

11. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. analysis of pooled data from five randomized controlled trials [published correction appears in *Arch Intern Med.* 1994;154(19):2254]. Arch Intern Med. 1994;154(13):1449-1457.

12. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105(2):91-99.

13. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. the National Consortium of Anticoagulation Clinics. *Ann Intern Med.* 1996;124(11):970-979.

14. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ.* 2013;185(2):E121-E127. doi: 10.1503/cmaj.121218.

15. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. *Am J Med.* 1993;95(3):315-328.

16. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet.* 1996;348(9025):423-428.

17. Keeling D, Baglin T, Tait C, et al; British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol.* 2011;154(3):311-324. doi: 10.1111/j.1365-2141.2011.08753.x.

18. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran). a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Heart Rhythm.* 2011;8(3):e1-e8. doi: 10.1016/j.hrthm.2011.01.032.

19. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151. doi: 10.1056/NEJMoa0905561.

20. You JJ, Singer DE, Howard PA, et al; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e531S-e575S. doi: 10.1378/chest.11-2304.

21. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J.* 2006;151(3):713-719.

22. AbuDagga A, Stephenson JJ, Fu AC, Kwong WJ, Tan H, Weintraub WS. Characteristics affecting oral anticoagulant therapy choice among patients with non-valvular atrial fibrillation: a retrospective claims analysis. *BMC Health Serv Res.* 2014;14:310. doi: 10.1186/1472-6963-14-310.

23. Zalesak M, Siu K, Francis K, et al. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. *Circ Cardiovasc Qual Outcomes.* 2013;6(5):567-574. doi: 10.1161/CIRCOUTCOMES.113.000192.

24. Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the Veterans Health Administration. *Am Heart J.* 2014;167(6):810-817. doi: 10.1016/j.ahj.2014.03.023.

25. Cutler TW, Chuang A, Huynh TD, et al. A retrospective descriptive analysis of patient adherence to dabigatran at a large academic medical center. *J Manag Care Spec Pharm.* 2014;20(10):1028-1034.

26. Carley B, Griesbach S, Larson T, Krueger K. Assessment of dabigatran utilization and prescribing patterns for atrial fibrillation in a physician group practice setting. *Am J Cardiol.* 2014;113(4):650-654. doi: 10.1016/j.amjcard.2013.11.008.

27. Hernandez I, Baik SH, Piñera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med.* 2015;175(1):18-24. doi: 10.1001/jamainternmed.2014.5398.

28. Alonso A, Bengtson LG, MacLehose RF, Lutsey PL, Chen LY, Lakshminarayan K. Intracranial hemorrhage mortality in atrial fibrillation patients treated with dabigatran or warfarin. *Stroke.* 2014;45(8):2286-2291. doi: 10.1161/STROKEAHA.114.006016.

29. Zheng Y, Sorensen SV, Gonschior AK, et al. Comparison of the cost-effectiveness of new oral anticoagulants for the prevention of stroke and systemic embolism in atrial fibrillation in a UK setting. *Clin Ther.* 2014;36(12):2015-2028.e2. doi: 10.1016/j.clinthera.2014.09.015.

30. Chevalier J, Delaitre O, Hammès F, de Pouvourville G. Cost-effectiveness of dabigatran versus vitamin K antagonists for the prevention of stroke in patients with atrial fibrillation: a French payer perspective. *Arch Cardiovasc Dis.* 2014;107(6-7):381-390. doi: 10.1016/j.acvd.2014.04.009.

31. Hesselbjerg LJ, Pedersen HS, Asmussen MB, Petersen KD. Is dabigatran considered a cost-effective alternative to warfarin treatment: a review of current economic evaluations worldwide. *J Med Econ.* 2013;16(7):845-858. doi: 10.3111/13696998.2013.800523.

32. Harrington AR, Armstrong EP, Nolan PE Jr, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke.* 2013;44(6):1676-1681. doi: 10.1161/STROKEAHA.111.000402.

33. González-Juanatey JR, Álvarez-Sabin J, Lobos JM, et al. Cost-effectiveness of dabigatran for stroke prevention in non-valvular atrial fibrillation in Spain. *Rev Esp Cardiol (Engl Ed).* 2012;65(10):901-910. doi: 10.1016/j.recesp.2012.06.006

34. Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-valvular atrial fibrillation. applying RE-LY to clinical practice in Denmark. *J Med Econ.* 2012;15(4):695-703. doi: 10.3111/13696998.2012.673525.

35. Kamel H, Johnston SC, Easton JD, Kim AS. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke.* 2012;43(3):881-883. doi: 10.1161/STROKEAHA.111.641027.

36. Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost.* 2011;105(5):908-919. doi: 10.1160/TH11-02-0089.

37. Clemens A, Peng S, Brand S, et al. Efficacy and cost-effectiveness of dabigatran etexilate versus warfarin in atrial fibrillation in different age subgroups. *Am J Cardiol.* 2014;114(6):849-855. doi: 10.1016/j.amjcard.2014.06.015. ajpb