Predictors of Healthcare Costs After Initiating Dabigatran Versus Warfarin

Sabyasachi Ghosh, MS[1]; Jason P. Swindle, PhD, MPH[2]; John C. White, DPM, MS[2]; Stephen D. Sander, PharmD[1]; Cheng Wang, MD, PhD[1]

ABSTRACT

Objectives: To identify patient characteristics predictive of all-cause healthcare costs among individuals with newly diagnosed non-valvular atrial fibrillation (NVAF) who initiated oral anticoagulant therapy with dabigatran or warfarin.

Study Design: Retrospective analysis of administrative claims data of patients with newly diagnosed NVAF.

Methods: Dabigatran and warfarin cohorts were identified by first claim (index date) during 10/1/2010 to 11/30/2012. Episode-based costs (all-cause) were determined using Episode Treatment Group (ETG) methodology and computed as per-patient-per-month. Baseline predictors of cost included baseline characteristics and baseline Episode Risk Group (ERG) risk score, which was grouped into 6 categories. To assess cohort differences in subgroups of patients, predictor variables representing the interaction of treatment cohort with patient characteristics were of primary interest. Cost ratios were then computed for subgroups of patients with different characteristics.

Results: Cohorts included 4150 dabigatran- and 11,032 warfarin-treated patients. Compared with warfarin, dabigatran patients were younger (mean age: 67.3 vs. 72.5 years; P<0.001) and had lower mean ERG risk scores (4.1 vs. 5.6, P<0.001). Treatment cohort was not a statistically significant predictor of costs. Compared with warfarin, dabigatran was associated with higher cost at ERG risk scores of 2.1 to 4.0 and lower cost at scores of 6.1 to 8.0.

Conclusions: Adding to existing evidence that treatment with dabigatran (vs warfarin) for NVAF would not incur higher all-cause healthcare costs, this study found that differences in all-cause healthcare costs did not follow a trend across subgroups of patients with NVAF based on different ERG risk score categories, favoring either therapy.

Am J Pharm Benefits. 2018;10(1):22-30

Atrial fibrillation (AF) confers a 4- to 5-fold higher risk of stroke, resulting in great morbidity and substantial healthcare costs.[1-3] Oral anticoagulant (OAC) therapy is recommended to reduce risk of stroke among patients with AF at moderate-to-high risk of stroke.[4,5] Warfarin has historically been the mainstay of OAC therapy. However, since 2010, therapeutic options have expanded with the introduction of dabigatran[6] and other novel OACs indicated for nonvalvular AF (NVAF).[7] In the Randomized Evaluation of Long-Term Anticoagulant Therapy clinical trial, dabigatran was associated with lower rates of stroke and systemic embolism compared with dose-adjusted warfarin.[8]

Real-world economic comparisons of dabigatran and warfarin among patients with NVAF initiating OAC therapy have recently been conducted. These retrospective claims analyses of all-cause healthcare costs suggest that dabigatran is cost-neutral relative to warfarin.[9-12] In these studies, costs were reported for overall patient samples[13] and did not examine whether subgroups of patients with similar demographic/clinical profiles might incur different costs when initiated on dabigatran versus warfarin.

Clinical characteristics, including disease severity, have been studied widely as risk factors that, when adjusted for, enable more accurate assessment of healthcare costs. The importance of incorporating patient heterogeneity into economic evaluations is also recognized.[14] Patients with AF are a clinically heterogeneous population[5,13] and initiation on appropriate OAC therapy has the potential to improve clinical outcomes and reduce resource use and costs. The Affordable Care Act, which reimburses services based on clinical episodes, rather than on a fee-for-service basis,[15] has created opportunity to explore the episode-based approach for examining differences in costs among patients with different comorbidities undergoing treatment for their conditions. One such approach is Episode Treatment Group (ETG), a condition classification methodology that defines episodes of care for measurement of associated healthcare costs.[16] ETG methodology has been vetted in actuarial science[17-19] and in health economics and outcomes

research.[20] Episode Risk Group (ERG) is a medically meaningful metric to account for patient heterogeneity, which assesses risks of incurring costs according to comorbidities and medical complications.[16]

Given the gap in current literature regarding subgroups of real-world patients with NVAF who may incur different healthcare costs following initiation of dabigatran versus warfarin, we conducted exploratory modeling to assess whether ERG risk score and other patient characteristics were predictive of differential all-cause healthcare costs computed on an episode basis using ETG methodology among these 2 cohorts. We also examined traditional predictors of costs, namely patient demographics and Charlson Comorbidity Index (CCI) score, using a non–episode-based approach.

PRACTICAL IMPLICATIONS

- This study examined predictors of episode-based, all-cause healthcare costs of patients with NVAF who initiated therapy with dabigatran or warfarin, and found no difference in healthcare costs between the two treatment cohorts.
- Predictors included Episode Risk Group (ERG) score, a prospective measure of healthcare utilization based on Episode Treatment Group methodology across 6 risk score categories.
- Predictive analysis found that the dabigatran cohort was associated with higher costs for ERG risk scores of 2.1 to 4.0 (CR: 1.14) and lower costs for risk scores of 6.1 to 8.0, but no statistically significant differences between cohorts for the remaining ERG risk score categories indicating no definite direction favoring dabigatran or warfarin across ERG risk score categories.

METHODS

Study Design and Data Source

This was a retrospective cohort study of commercial and Medicare Advantage with Part D enrollees. The study utilized administrative claims data from a large national US health plan from April 1, 2009, through November 30, 2013 (*study period*). All data were accessed in accordance with the Health Insurance Portability and Accountability Act rules.

Patient Identification and Study Cohorts

Patients with evidence of newly diagnosed NVAF initiating therapy with either dabigatran or warfarin were identified using enrollment data and medical and pharmacy claims from October 1, 2010, through November 30, 2012. Patients were selected for inclusion in a sequential manner:

1. Evidence of AF defined as at least 1 inpatient stay, 2 physician office visits, 2 emergency department (ED) visits, or a combination of office visit and ED visit on distinct service dates, with a diagnosis code for AF *(International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code 427.31, in any position) from October 1, 2010, through August 31, 2012 (*identification period*).[21] The *AF index date* was the date of the first qualifying claim with a diagnosis code for AF. Patients were aged ≥18 years as of AF index date, had 12 months continuous enrollment (no gaps >45 days) with medical and pharmacy benefits prior to AF index date, and had no medical claims with a diagnosis code for AF within 12 months prior to AF index date.
2. Excluded were patients with ≥1 medical claim with evidence of valvular heart disease or hyperthyroidism (reversible cause of AF[22]) prior to AF index date, and patients with evidence of transient AF within 3 months prior to AF index date.
3. Newly initiating OAC therapy with dabigatran or warfarin by meeting all of the following criteria: ≥1 pharmacy claim for warfarin or dabigatran on the AF index date or during the 3-month period following AF index date; the date of the first claim was defined as the OAC index date; continuous enrollment during the period of AF index date through OAC index date; and no pharmacy claims for any OAC for 12 months prior to OAC index date (*baseline period*).
4. Remaining patients were required to have ≥30 days follow-up after OAC index date. The follow-up period began on the OAC index date and ended at the earliest occurrence of the following: (a) end of study period; (b) death; (c) switch to another OAC without a claim for ischemic stroke and/or bleed; (d) discontinuation of index OAC with a gap >30 days from the run-out of the last fill without a claim for ischemic stroke and/or bleed; (e) end of continuous enrollment in health plan; or (f) greater than 364 days following OAC index date. Twelve months follow-up is similar to recent studies comparing resource utilization and costs between dabigatran and warfarin cohorts;[12,21] it also aligns with year budget allocation cycle by different payers and providers across the United States.

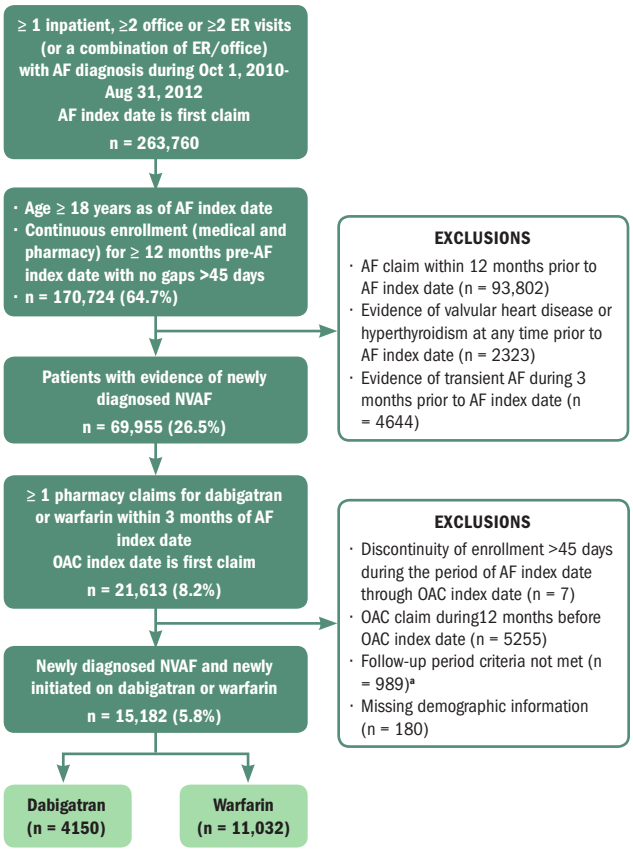
Patients were then assigned to 2 mutually exclusive study cohorts according to index OAC. Relevant codes for conditions used in patient selection are shown in **EAPPENDIX TABLE 1A** (eAppendices available at AJPB.com).

Model Variables

Follow-up Healthcare Costs

Two measures of all-cause healthcare costs (combined health plan and patient paid amounts) were computed during the variable length of follow-up period: (a) episode-based total

Figure 1. Sample Identification for Patients With Newly Diagnosed Nonvalvular Atrial Fibrillation Initiating Treatment with Dabigatran or Warfarin



aFollow-up criteria required patients have a minimum of 30 days follow-up. The follow-up period began on the OAC index date and ended at the earliest occurrence of the following: (1) end of study period (November 30, 2013); (2) death; (3) switch to an OAC other than the index OAC without a claim for ischemic stroke and/or bleed; (4) discontinuation of index OAC for more than a gap of 30 days from the run-out (days' supply) of the last fill without a claim for ischemic stroke and/or bleed; (5) end of continuous enrollment in the health plan (disenrollment); or (6) 364 days following OAC index date.
AF indicates atrial fibrillation; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant.
Source: Optum Research Database, April 1, 2009–November 30, 2013

costs (all-cause medical and pharmacy) were determined using ETG methodology[16] and included episode-based predictors of healthcare costs; (b) all-claims total costs (all-cause medical and pharmacy) were computed and only included non–episode-based predictors of healthcare costs. Both measures of costs were computed as per-patient per-month (PPPM) costs to adjust for variable length of follow-up. Costs were adjusted to 2013 US dollars using the annual medical care component of the Consumer Price Index to account for inflation between 2009 and 2013.[23]

Predictors of Healthcare Costs

Patient severity was captured using 2 measures: baseline CCI score for all-cause claims cost analysis and baseline ERG risk score for all-cause episode-based cost analysis. The CCI score[24-26] is a proxy for likelihood of mortality according to the burden of comorbidity; scores were grouped as 0, 1-2, 3-4, and ≥5. The ERG risk score assesses the prospective risk of healthcare utilization and costs according to comorbidities and medical complications. ERG risk scores were determined using ETG methodology, which defines episode of care for measurement of healthcare costs using diagnosis, procedure, and revenue codes; and National Drug Code numbers to formulate clinically homogeneous episodes of care (**EAPPENDIX FIGURE 1A**).[16] The ETG methodology allows for case-mix adjustment, clinical homogeneity, episode building, concurrent and recurrent episodes, and shifting episodes.[27] ETGs are then mapped to ERGs for each patient. Next, individual ERG risk scores are computed by summing weights assigned to each ERG and to the patient's demographic and healthcare resource utilization profile.[28] The ETG/ERG methodology is used by several health plans[29-35] and allows for customized categorization of ERG scores, but there is no guidance in current literature on grouping ERG risk score into specific categories. For this study, scores were grouped, *a priori,* into 6 categories: ≤2.0; 2.1 to 4.0; 4.1 to 6.0; 6.1 to 8.0; 8.1 to 10.0; and >10.0. A score of 1.0 indicates risk comparable with that of the overall population, while a score of 2.0 or greater indicates a 2-fold or greater risk of higher healthcare resource utilization and costs.

Additional variables considered for inclusion as predictors in multivariable modeling of follow-up costs were age, sex, geographic region, health plan type, baseline healthcare costs, and durations of treatment delay and follow-up for the all-claim cost analysis. For the episode-based cost analysis, all but age, gender, and baseline healthcare costs were included because ERG risk score accounts for these measures.

Statistical Analysis

Between-cohort comparisons of baseline characteristics, durations of follow-up and treatment delay, and follow-up unadjusted healthcare costs were examined with *t* tests (for continuous variables) and χ^2 tests (for categorical variables). Two predictive models of healthcare costs were developed: (1) the all-claims costs model, and (2) the episode-based costs model. To assess cohort differences in subgroups of patients, predictor variables representing interactions of cohort with patient characteristics were examined. Based on an *a priori* specified variables list, variables were entered using stepwise selection; *P* value thresholds of .15 and .20 were used for variable entry and exit into the model, respectively. There were 2 exceptions to the stepwise

selection of variables: (1) cohort indicator was forced into models, and (2) if an interaction term (with cohort) satisfied *P* value thresholds for selection, the corresponding main effect (ie, noninteraction term) was also forced into models. For the all-claims model, predictor variables subject to stepwise selection were as follows ("*" denotes interaction): age group, cohort*age group, baseline CCI score group, cohort*baseline CCI score group, gender, cohort*gender, geographic region, cohort*geographic region, health plan type, cohort*health plan type, baseline healthcare costs group, cohort*baseline healthcare costs group, duration of treatment delay, cohort*duration of treatment delay, duration of follow-up period, and cohort*duration of follow-up period. For the episode-based costs model, predictor variables subject to stepwise selection were baseline ERG risk score category, cohort*baseline ERG risk score category, geographic region, cohort*geographic region, health plan type, cohort*health plan type, duration of treatment delay, cohort*duration of treatment delay, duration of follow-up period, and cohort*duration of follow-up period.

Development and validation of predictive models utilized bootstrap methods. Using N of study sample, 100 bootstrapped samples (random samples with replacement) were used to run generalized linear models with gamma distribution and log-link function.[36,37] The concordance (c) index was computed to assess how well each model's predicted costs agreed with actual costs. A c-index of 0.50 indicates that model prediction is no better than chance; a value >0.50 indicates that the model has predictive value; and a value <0.50 indicates that the model's predictive value is worse than chance.

Statistically significant interactions with cohort ($P<.05$) were examined to determine patient characteristics predictive of differential costs between the 2 cohorts. Durations of treatment delay and follow-up (and their corresponding interactions with cohort) were entered into models using stepwise selection, though only for the purpose of model adjustment. Parameter estimates, 95% CIs, and *P* values were presented for predictors of each model. Estimated cost ratios (CRs) were derived from exponentiated parameter estimates. The Global Wald test was used to examine overall significance of polychotomous covariates and interaction terms. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc; Cary, North Carolina).

RESULTS

Patient Identification and Characteristics

A total of 15,182 patients with evidence of newly diagnosed NVAF who initiated OAC with dabigatran (n = 4150) or warfarin (n = 11,032) were included. Compared with the dabigatran cohort, the warfarin cohort was older (72.5 years vs 67.3 years), had higher mean CCI score (2.0 vs 1.4), and higher mean ERG risk score (5.6 vs 4.1) (all $P<.001$). Mean all-cause costs during baseline were also 59.1% higher ($26,240 vs $16,497; $P<.001$) among the warfarin cohort (**TABLE 1**).

Follow-Up All-Cause Episodes and Unadjusted Healthcare Costs

The total count of episodes was 31,906 in the dabigatran cohort and 100,502 in the warfarin cohort.

Unadjusted costs during follow-up did not differ between cohorts (**EAPPENDIX TABLE 1B**). Mean PPPM costs were $3003 for the dabigatran cohort and $3223 for the warfarin cohort ($P = .108$); mean episode-based PPPM costs were $2807 for the dabigatran cohort and $2905 for the warfarin cohort ($P = .412$).

Cost Predictors

Predictors retained in the all-claims model and their associated cost ratios are shown in **TABLE 2**. The main effect for cohort was not a statistically significant predictor of follow-up PPPM costs ($P = .635$). Further, no interaction terms between cohort and patient characteristics were statistically significant. Statistically significant main effect variables predictive of lower costs were female gender and groups aged 65 and older. The adjusted c-index for the model was 0.64.

The main effect for cohort was also not a statistically significant predictor of PPPM costs ($P = .208$) in the episode-based model (Table 2). However, 3 interaction terms were statistically significant, indicating that costs differed between treatment cohorts depending on the characteristics of patients: cohort*baseline ERG risk score category ($P = .017$), cohort*geographic region ($P = .047$), and cohort*health plan type ($P = .034$). The adjusted c-index for the model was 0.60.

Further analysis of the association between cohort and all-cause costs within each ERG category (**TABLE 3**) revealed that compared with warfarin, the dabigatran cohort was associated with higher costs for ERG risk scores of 2.1 to 4.0 (CR, 1.14) and lower costs for risk scores of 6.1 to 8.0 (CR, 0.78). There were no statistically significant differences among cohorts for remaining ERG risk score categories.

DISCUSSION

Previous studies demonstrated that patients with newly diagnosed NVAF have similar average healthcare costs following initiation on dabigatran versus warfarin,[9-12] wherein higher average medical resource utilization by patients on

Table 1. Baseline Patient Characteristics and Duration of Follow-Up of Patients With Newly Diagnosed Nonvalvular Atrial Fibrillation Initiating Treatment With Dabigatran or Warfarin.

Characteristic	All Patients (N = 15,182)	Dabigatran (n = 4150)	Warfarin (n = 11,032)	*P* value[a]
Age, years, mean (SD)[b]	71.0 (11.5)	67.3 (11.9)	72.5 (11.1)	<.001
Age group, years, n (%)[b]				
18-44	304 (2.0)	130 (3.1)	174 (91.6)	<.001
45-54	1041 (6.7)	455 (11.0)	586 (5.3)	<.001
55-64	2887 (19.0)	1154 (27.8)	1733 (15.7)	<.001
65-74	4363 (28.7)	1188 (28.6)	3175 (28.8)	.852
75-84	4718 (31.1)	907 (21.9)	3811 (34.5)	<.001
≥85	1869 (12.3)	316 (7.6)	1553 (14.1)	<.001
Female, n (%)	6420 (42.3)	1492 (36.0)	4928 (44.7)	<.001
Geographic region, n (%)				
Northeast	1708 (11.3)	504 (12.1)	1204 (10.9)	.032
Midwest	5311 (35.0)	1111 (26.8)	4200 (38.1)	<.001
South	6363 (41.9)	2060 (49.6)	4303 (39.0)	<.001
West	1800 (11.9)	475 (11.5)	1325 (12.0)	.337
Health plan type, n (%)				
Commercial	6565 (43.2)	2584 (62.3)	3981 (36.1)	<.001
MAPD	8617 (56.8)	1566 (37.7)	7015 (63.9)	<.001
CCI score, mean (SD)	1.9 (1.93)	1.4 (1.7)	2.0 (2.0)	<.001
CCI score group, n (%)				
0	5271 (34.7)	1833 (44.2)	3438 (31.2)	<.001
1-2	5020 (33.1)	1412 (34.0)	3608 (32.7)	.124
3-4	3492 (23.0)	711 (17.1)	2781 (25.2)	<.001
≥5	1399 (9.2)	194 (4.7)	1205 (10.9)	<.001
ERG risk score, mean (SD)	5.2 (4.0)	4.1 (3.0)	5.6 (4.2)	<.001
ERG risk score categories, n (%)				
≤2.0	2254 (14.9)	904 (21.8)	1350 (12.2)	<.001
2.1-4.0	5156 (34.0)	1704 (41.1)	3452 (31.3)	<.001
4.1-6.0	3443 (22.7)	831 (20.0)	2612 (23.7)	<.001
6.1-8.0	1826 (12.0)	355 (8.6)	1471 (13.3)	<.001
8.1-10.0	1046 (6.9)	173 (4.2)	873 (7.9)	<.001
>10.0	1457 (9.6)	183 (4.4)	1274 (11.5)	<.001
12-month healthcare costs, US$, mean (SD)	23,577 (37,925)	16,497 (26,711)	26,240 (41,051)	<.001
Duration of treatment delay,[c] days, mean (SD)	14.7 (20.0)	16.6 (20.9)	13.9 (19.6)	<.001
Duration of follow-up period, days, mean (SD)	190.4 (133.7)	187.8 (137.5)	191.4 (132.3)	.147

[a]By *t* test for means and by χ^2 test for proportions.
[b]Age as of OAC index date; OAC index date: the date of the earliest pharmacy claim for dabigatran or warfarin.
[c]Days from AF index date to OAC index date. AF index date: the date of the earliest medical claim with diagnosis code for AF (patients excluded with baseline evidence of valvular heart disease or hyperthyroidism).
AF indicates atrial fibrillation; CCI, Charlson Comorbidity Index; ERG, Episode Risk Group; MAPD, Medicare Advantage with Part D prescription drug coverage; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant.
Source: Optum Research Database, April 1, 2009–November 30, 2013

warfarin may offset their lower average pharmacy cost.[38] However, current literature lacks guidance on identifying subgroups of patients with NVAF who may incur lower costs when initiated on these medications. This retrospective analysis explored the role of patient characteristics as predictors of differential healthcare costs in patients with NVAF who initiated therapy with dabigatran versus warfarin. Specifically, we explored subgroups of patients based on ERG risk scores or CCI scores that may influence all-cause costs for patients initiated on dabigatran versus warfarin. Compared with dabigatran patients, those initiated on warfarin were older, had greater risk of mortality (per CCI score), and higher baseline prospective risk of healthcare utilization (per ERG risk score). This finding suggests that, in a US managed care population, warfarin is more likely to be prescribed to older patients and to patients at higher risk for needing healthcare services and who, therefore, incur higher health-related costs. With the lower cost of warfarin, it is possible that older patients with Medicare coverage, taking several medications for multiple comorbidities, intend to minimize risk of entering a prescription drug plan coverage gap by managing pharmacy expenses. In addition, incentives provided by drug companies that often bring patients' monthly drug cost to a minimum is only available for patients with commercial insurance, not those with Medicare and may, therefore, favor the use of drugs with lower costs among Medicare patients. However, this interpretation cannot be validated with the study because the claims database used does not capture relevant information.

This exploratory study adds to the body of literature examining characteristics of newly diagnosed patients with NVAF in clinical practice. First, both cost models found that main treatment effect for cohort was not statistically significant in predicting difference in total all-cause healthcare costs. Second, neither model found any trend in differences in all-cause costs across CCI score groups or ERG risk score categories favoring

Table 2. Generalized Linear Models of Follow-Up PPPM Healthcare Costs for Patients With Newly Diagnosed Nonvalvular Atrial Fibrillation Initiating Treatment With Dabigatran or Warfarin

	All-Claims Model[b] Dependent Variable: Follow-Up PPPM Healthcare Costs			Episode-Based Model[c] Dependent Variable: Follow-Up PPPM Episode-Based Healthcare Costs		
Independent Variables[a]	**Estimate**	**95% CI**	***P* value**	**Estimate**	**95% CI**	***P* value**
Dabigatran cohort (ref: warfarin)	0.05	–0.16, 0.26	.635	0.14	–0.08, 0.35	.208
Baseline CCI score (ref: 0)			<.001[d]			
1-2	0.08	0.00, 0.16	.053			
3-4	0.25	0.16, 0.34	<.001			
≥5	0.48	0.35, 0.60	<.001			
Interaction: cohort x baseline CCI score (ref: dabigatran cohort and comorbidity score 0)			.162[d]			
Dabigatran cohort and comorbidity score 1-2	0.12	–0.02, 0.26	.104			
Dabigatran cohort and comorbidity score 3-4	–0.06	–0.23, 0.11	.474			
Dabigatran cohort and comorbidity score ≥5	0.11	–0.16, 0.39	.417			
Baseline ERG risk score (ref: ≤2.0)						<.001[d]
2.1-4.0				0.13	0.03, 0.22	.009
4.1-6.0				0.22	0.11, 0.32	<.001
6.1-8.0				0.43	0.31. 0.54	<.001
8.1-10.0				0.61	0.48, 0.74	<.001
>10.0				1.02	0.92, 1.13	<.001
Interaction: cohort x baseline ERG risk score (ref: dabigatran cohort and ERG risk score ≤2.0)						.017[d]
Dabigatran cohort and ERG risk score 2.1-4.0				0.17	0.01, 0.33	.040
Dabigatran cohort and ERG risk score 4.1-6.0				0.11	–0.08, 0.31	.254
Dabigatran cohort and ERG risk score 6.1-8.0				–0.20	–0.43, 0.03	.087
Dabigatran cohort and ERG risk score 8.1-10.0				–0.08	–0.36, 0.20	.575
Dabigatran cohort and ERG risk score >10.0				–0.04	–0.28, 0.20	.739
Age group (ref: 18-44 years)			<.001[d]			
45-54	–0.13	–0.34, 0.09	.247			
55-64	–0.17	–0.37, 0.03	.102			
65-74	–0.59	–0.79, –0.39	<.001			
75-84	–0.79	–1.00, –0.58	<.001			
≥85	–0.76	–0.98, –0.54	<.001			
Female gender (ref: male)	–0.08	–0.14, –0.02	.007			
Geographic region (ref: West)			.062[d]			.016[d]
Northeast	0.13	0.00, 0.26	.049	0.17	0.04, 0.31	.011
Midwest	–0.02	–0.12, 0.09	.769	0.00	–0.10, 0.11	.970
South	0.02	–0.09, 0.12	.760	0.05	–0.06, 0.16	.360
Interaction: cohort x geographic region (ref: dabigatran cohort and West region)			.058[d]			.047[d]
Dabigatran cohort and Northeast region	–0.33	–0.58, –0.09	.008	–0.31	–0.56, –0.05	.017
Dabigatran cohort and Midwest region	–0.11	–0.32, 0.01	.305	–0.03	–0.24, 0.19	.817
Dabigatran cohort and South region	–0.13	–0.32, 0.07	.214	–0.09	–0.29, 0.11	.378
MAPD health plan (ref: commercial)	0.16	0.08, 0.24	<.001	–0.30	–0.37, –0.24	<.001
Interaction: cohort x health plan type (ref: dabigatran cohort and commercial plan)						
Dabigatran cohort and MAPD plan				–0.14	–0.27, –0.01	.034

(continued)

Table 2. (Continued) Generalized Linear Models of Follow-Up PPPM Healthcare Costs for Patients With Newly Diagnosed Nonvalvular Atrial Fibrillation Initiating Treatment With Dabigatran or Warfarin

	All-Claims Model[b] Dependent Variable: Follow-Up PPPM Healthcare Costs			Episode-Based Model[c] Dependent Variable: Follow-Up PPPM Episode-Based Healthcare Costs		
Independent Variables[a]	Estimate	95% CI	*P* value	Estimate	95% CI	*P* value
Baseline healthcare costs, US$ (ref: 0.00-9999.99)			<.001[d]			
10,000.00-19,999.99	0.34	0.27, 0.41	<.001			
20,000.00-29,999.99	0.57	0.47, 0.67	<.001			
30,000.00-39,999.99	0.68	0.56, 0.80	<.001			
40,000.00-49,999.99	0.72	0.58, 0.86	<.001			
≥50,000.00	1.05	0.94, 1.15	<.001			

[a]Stepwise selection (inclusion and exclusion of variables in both models selected at levels of probability *P* = .15 and *P* = .20, respectively); cohort forced into both models; variables excluded from models: cohort*age group (all-claims model only), cohort*gender (all-claims model only), cohort*health plan type (all-claims model only), cohort*baseline healthcare costs (all-claims model only), cohort*duration of treatment delay, cohort*duration of follow-up period (episode-based model only); variables retained in models only for adjustment: duration of treatment delay (all-claims model: estimate, 0.00; *P* <.001; episode-based model: estimate, 0.00; *P* = .008), duration of follow-up period (all-claims model: estimate, 0.00; *P* <.001; episode-based model: estimate, 0.00; *P* <.001), cohort*duration of follow-up period (all-claims model only: estimate, 0.00; *P* = .018).
[b]Generalized linear models with a gamma distribution and log-link function; observations read = 15,182, observations used = 15,182; adjusted c-index = 0.64.
[c]Generalized linear models with a gamma distribution and log-link function; observations read = 15,182, observations used = 15,182; adjusted c-index = 0.60.
[d]Global Wald test.
CCI indicates Charlson Comorbidity Index; MAPD, Medicare Advantage with Part D prescription drug coverage; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; PPPM, per-patient per-month; ref, reference.
Source: Optum Research Database, April 1, 2009–November 30, 2013

either cohort. While there were no statistically significant interactions among cohort and variables of interest in the all-claims model, in the episode-based model, dabigatran was associated with higher costs among patients with ERG risk score 2.1 to 4.0 and with lower costs with ERG risk score 6.1 to 8.0, compared with warfarin, indicating no linear trend in cost differences among cohorts across all 6 ERG risk score categories. As such, the possibility remains that newly diagnosed patients with NVAF, regardless of their CCI score or the ERG risk score subgroups to which they belong, may not incur different costs if treated with dabigatran versus warfarin. Interactions between treatment cohort and geographic region and, separately, health plan type, were also significant in the episode-based model. These interactions lend support to the possibility of differential cost profiles for dabigatran versus warfarin among subsets of patients.

Patient characteristics predictive of costs in cardiovascular disease have been well studied,[39,40,41] and our study contributes to this body of research by examining the utility of ERG and CCI scores in predicting all-cause costs among newly diagnosed patients with NVAF who are initiated on dabigatran or warfarin. As a meaningful risk measure for incurring costs, ERG risk score may be a useful tool for identifying patients who could benefit from more aggressive disease and/or medical therapy management.[35] However, application to specific diseases/therapies is a unique perspective in this study, and it has not been validated. Separately, the mix of medical comorbidities present in the dabigatran cohort versus the warfarin cohort may differ even when the ERG risk score categorization is the same. The authors recommend that the results of this study be emphasized as hypothesis-generating, and this application must be further validated with other OAC treatments (ie, rivaroxaban, apixaban), other retrospective populations, and prospective populations with randomization.

Limitations

The results of this study should be considered in the context of several limitations. ERG risk scores were grouped into 6 distinct categories; however, this categorization scheme is not an established methodology. ETG/ERG methodology relies on the accuracy and completeness of claims submitted for reimbursement. Missing or incorrect codes for important comorbidities would underestimate ERG risk score. The same would apply to diseases that were not coded but are included in CCI score (eg, liver disease, chronic pulmonary disease). Claims data lack certain clinical assessments that also may be important risk factors for healthcare utilization. For example, an important measure in determining congestive heart failure risk is left ventricular ejection fraction, which is not captured in claims data. Lab-based parameters such as time within therapeutic range, which measures the patient's level of anticoagulation, can be calculated based on merging laboratory results data with administrative claims; however, missing data is frequently an issue. This lab-based measure is currently used to monitor and manage the risk of stroke and/or bleed with different therapeutic options in long-term care of patients with NVAF. However, the study intended to provide different perspectives in managing these patients with consideration of a prospective risk of healthcare costs that is

easier to track and measure consistently across large patient populations by payers, integrated delivery networks, and accountable care organizations. It is likely that increasing ERG risk score would serve as a proxy marker for increased difficulty with warfarin management. As comorbidity burden increases, the capacity to maintain international normalized ratio (INR) within a therapeutic range decreases. Different clinical practice methods—lab practice in particular—may be applied to improve the safety and efficacy of warfarin therapy (ie, use of home monitoring devices for INR, use of dedicated anticoagulation management clinicians). These practices may have an underlying role among the subgroups as specified for ERG risk score categorization. The authors of the ROCKET AF study[42] (a randomized trial of rivaroxaban versus warfarin that was designed to demonstrate noninferiority of rivaroxaban) conducted a post hoc analysis of their data to account for the variation in warfarin dosing that might have resulted from using home monitoring devices for INR by group of patients; the device was systematically undermeasuring INR and thus potentially introducing bias into the rates of bleeding complications in the warfarin group. Similar factors may have been at play that were missed in the current analysis; this is an inherent limitation of claims-based retrospective cohort study design.

The creation of predictors that were derived from a patient's medical history relied on 1 year of baseline data only; conditions occurring outside baseline were not included in ERG risk score or CCI score. The *a priori* grouping of ERG risk scores into 6 categories might have limited the model in identifying the linear relationship in difference of costs across ERG risk categories.

There may have also been other, unmeasured factors (eg, patient behavioral/ socioeconomic characteristics, clinical practice) that may have influenced costs. Claims data do not indicate whether the patient took medications as prescribed. Although follow-up ended if there were gaps in index OAC supply for more than 30 days, measures of medication possession ratio during follow-up were not evaluated. Despite these limitations, the findings provide insight about ERG risk and CCI categories in predicting all-cause healthcare costs and establish the basis for future research in identifying newly diagnosed patients with NVAF who would incur differential all-cause healthcare costs following initiation of dabigatran versus warfarin.

Table 3. PPPM Episode-Based Healthcare Costs for Patients With Newly Diagnosed Nonvalvular Atrial Fibrillation Initiating Treatment With Dabigatran or Warfarin: Comparisons by Cohort Within Baseline Episode Risk Group (ERG) Risk Score Category

Cohort Comparison (ref: warfarin) Within Baseline ERG Risk Score Category	Dependent Variable: Follow-Up PPPM Episode-Based Healthcare Costs[a]		
	Estimate	95% CI	*P* value
Dabigatran vs warfarin, within baseline ERG risk score ≤2.0	–0.04	–0.17, 0.09	.528
Dabigatran vs warfarin, within baseline ERG risk score 2.1-4.0	0.13	0.01, 0.25	.033
Dabigatran vs warfarin, within baseline ERG risk score 4.1-6.0	0.07	–0.09, 0.23	.379
Dabigatran vs warfarin, within baseline ERG risk score 6.1-8.0	–0.24	–0.44, –0.04	.017
Dabigatran vs warfarin, within baseline ERG risk score 8.1-10.0	–0.12	–0.38, 0.14	.352
Dabigatran vs warfarin, within baseline ERG risk score >10.0	–0.08	–0.29, 0.13	.442

[a]Generalized linear models with a gamma distribution and log-link function.
PPPM indicates per-patient per-month; ref, reference.
Source: Optum Research Database, April 1, 2009–November 30, 2013

CONCLUSIONS

This retrospective cohort study, based on a real-world sample of US patients with newly diagnosed NVAF, offers evidence for comparing dabigatran versus warfarin for different subgroups of ERG risk score. Adding to existing literature on this topic, the findings indicated that there was no definitive evidence of a trend in difference of total all-cause costs favoring dabigatran or warfarin across 6 ERG risk score categories employed in this study. ajpb

[1]Health Economics & Outcomes Research, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; [2]Health Economics and Outcomes Research, Optum, Inc, Eden Prairie, MN

Corresponding author: Sabyasachi Ghosh, MS Health Economics & Outcomes Research, Manager Boehringer Ingelheim Pharmaceuticals, Inc 900 Ridgebury Road, Ridgefield, CT 06877 Tel: (800) 243-0127 Fax: (203) 791-6234 E-mail: tito.ghosh@boehringer-ingelheim.com

Disclosure: Support for this work was provided by Boehringer Ingelheim Pharmaceuticals, Inc (BIPI). Drs Swindle and White were employees of Optum, Inc, which was contracted by BIPI to perform the study; employment was not contingent on this funding. Mr Ghosh, Dr Sander, and Dr Wang were employees of BIPI at the time of this study.

REFERENCES

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98(10):946-952.
2. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes.* 2011;4(3):313-320. doi: 10.1161/CIRCOUTCOMES.110.958165.
3. Miller PS, Andersson FL, Kalra L. Are cost benefits of anticoagulation for stroke prevention in atrial fibrillation underestimated? *Stroke.* 2005;36(2):360-366.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64(21):e1-e76.
5. Agewall S, Camm J. New ESC/EACTS Guidelines for the management of atrial fibrilation. *Eur Heart Cardiovasc Pharmacother.* [Published online Dec 25, 2016]. pii: pvw038. doi: 10.1093/ehjcvp/pvw038. [Epub ahead of print]. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28025214
6. PRADAXA [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2014. http://bidocs.boehringer-ingelheim.com/BIWebAccess/

ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. Accessed February 8, 2017.
7. Granger CB, Armaganijan LV. Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism. *Circulation.* 2012;125(1):159-164; discussion 164. doi: 10.1161/CIRCULATIONAHA.111.031146.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151. doi: 10.1056/NEJMoa0905561.
9. Francis K, Yu C, Alvrtsyan H, et al. Healthcare utilization and costs associated with dabigatran compared to warfarin treatment in newly diagnosed patients with non-valvular atrial fibrillation. *Curr Med Res Opin.* 2015:1-7. doi: 10.1185/03007995.2015.1092124.
10. Fu A, Jain R, Sander S, et al. Healthcare resource utilization and costs among patients with nonvalvular atrial fibrillation using dabigatran or warfarin for stroke prevention. Poster presented at: Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke (QCOR); June 2-4, 2014; Baltimore, MD.
11. Michels SL, Sheer R, Ghate R, et al. Healthcare costs among newly diagnosed nonvalvular atrial fibrillation patients newly initiating treatment with dabigatran or warfarin. Poster presented at: American Society of Health-System Pharmacists Annual Meeting; June 1-4, 2014; Las Vegas, NV.
12. Sussman M, Sutherland S, Ghate SR, Wang C, Sander S, Griffiths R. All-cause healthcare resource utilization and associated medical costs among newly diagnosed nonvalvular atrial fibrillation patients newly treated with dabigatran or warfarin within integrated healthcare delivery networks. Presented at the Academy of Managed Care Pharmacy 2014 Nexus Meeting; October 7-10, 2014; Boston, MA.
13. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation.* 2012;126(7):860-865. doi: 10.1161/CIRCULATIONAHA.111.060061.
14. Ramaekers BL, Joore MA, Grutters JP. How should we deal with patient heterogeneity in economic evaluation: a systematic review of national pharmacoeconomic guidelines. *Value Health.* 2013;16(5):855-862. doi: 10.1016/j.jval.2013.02.013.
15. Mechanic RE. Opportunities and challenges for episode-based payment. *N Engl J Med.* 2011;365(9):777-779. doi: 10.1056/NEJMp1105963.
16. OptumInsight. Symmetry Episode Treatment Groups. Measuring health care with meaningful episodes of care. https://www.optum.com/content/dam/optum/resources/whitePapers/symmetry_episode_treatment_groups_wp_06_2012.pdf. Published 2012. Accessed February 8, 2017.
17. Thomas JW, Grazier KL, Ward K. Comparing accuracy of risk-adjustment methodologies used in economic profiling of physicians. *Inquiry.* 2004;41(2):218-231.
18. Thomas JW, Grazier KL, Ward K. Economic profiling of primary care physicians: consistency among risk-adjusted measures. *Health Serv Res.* 2004;39(4 Pt 1):985-1003.
19. Thomas JW. Should episode-based economic profiles be risk adjusted to account for differences in patients' health risks? *Health Serv Res.* 2006;41(2):581-598.
20. Halpern R, Kothari S, Fuldeore M, et al. GERD-related health care utilization, therapy, and reasons for transfer of GERD patients between primary care providers and gastroenterologists in a US managed care setting. *Dig Dis Sci.* 2010;55(2):328-337. doi: 10.1007/s10620-009-0927-9.
21. Bancroft T, Lim J, Wang C, Sander SD, Swindle JP. Health care resource utilization, costs, and persistence in patients newly diagnosed as having nonvalvular atrial fibrillation and newly treated with dabigatran versus warfarin in the United States. *Clin Ther.* 2016;38(3):545-556,e546. doi: 10.1016/j.clinthera.2016.01.008.
22. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J.* 2009;157(5):805-810,810,e801-e802. doi: 10.1016/j.ahj.2009.02.005.
23. US Department of Labor, Bureau of Labor Statistics. Consumer Price Index. Chained Consumer Price Index for all urban consumers (C-CPI-U) 1999-2013, Medical Care. Series ID: SUUR0000SAM. Washington, DC: U.S. Dept. of Labor, Bureau of Labor Statistics, 2014. http://data.bls.gov/cgi-bin/surveymost?su. Accessed February 8, 2017.
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
25. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol.* 2011;173(6):676-682. doi: 10.1093/aje/kwq433.
26. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in *ICD-9-CM* and *ICD-10* administrative data. *Med Care.* 2005;43(11):1130-1139.
27. UnitedHealth Premium Physician Designation Program. Detailed methodology. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Unitedhealth%20Premium/Detailed_Methodology_2013-2014.pdf. Accessed February 8, 2017.
28. Optum. HealthNumerics-RISC Predictive Models. A successful approach to risk stratification. http://www.optum.com/content/dam/optum/resources/whitePapers/Optum_HNRISC_White%20Paper.pdf. Accessed February 8, 2017.
29. Episode Risk Groups approaches 30 million covered Lives; leading heatlhcare organizations adopt new risk assessment rechnology [press release]. Phoenix, AZ: Symmetry Health Data Systems, Inc.; December 17, 2001. http://www.prnewswire.com/news-releases/episode-risk-groupstm-approaches-30-million-covered-lives-leading-healthcare-organizations-adopt-new-risk-assessment-technology-74623737.html. Accessed March 2, 2017.
30 Blue Cross Blue Shield chooses Symmetry; insurer to use Arizona firm's ETG and ERG health care software products [press release]. Phoenix, AZ: Symmetry Health Data Systems, Inc.; March 4,2002. http://www.prnewswire.com/news-releases/blue-cross-blue-shield-of-arizona-chooses-symmetry-insurer-to-use-arizona-firms-etg-and-erg-health-care-software-products-76264307.html. Accessed: February 28, 2017.
31. CIGNA Care Designation and Physician Quality and Cost-Efficiency Display 2011/2012 Methodologies. https://www.cigna.com/pdf/CCD_WhitePaper.pdf. Accessed March 2, 2017.
32. Aetna. A physician's guide to Aextel. http://www.aetna.com/healthcare-professionals/assets/documents/aexcel-physician-guide.pdf. Published 2013. Accessed March 3, 2017.
33. Episode treatment groups identified as 'industry leading methodology' by Blue Shield Association [press release]. Phoenix, AZ: Symmetry Health Data Systems, Inc.; April 15,1999. http://www.prnewswire.com/news-releases/episode-treatment-groups-identified-as-the-industry-leading-methodology-by-blue-cross-blue-shield-association-74037487.html. Accessed March 3, 2017.
34. Aexcel Specialist Designation in Aetna Performance Network Methodology Guide. 2010. http://www.aetna.com/plansandproducts/health/medical/Aexcel_Methodology_v3_2010.pdf. Published June 12, 2009. Accessed March 3, 2017.
35. UnitedHealth Premium Physician Designation Program Detailed Methodology. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Unitedhealth%20Premium/Detailed_Methodology_2013-2014.pdf. Published 2014. Accessed March 3, 2017.
36. Miao Y, Cenzer IS, Kirby KA, Boscardin WJ. Estimating Harrell's optimism on predictive indices using bootstrap samples. Presented at: SAS Global Forum 2013 - Statistics and Data Analysis. 2013; Paper 504-2013. http://support.sas.com/resources/papers/proceedings13/504-2013.pdf. Accessed February 8, 2017.
37. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol.* 2001;54(8):774-781.
38. Iorga SR, T B, Lim J, Wang C, Sander SD, P. SJ. Comparing medication persistence and healthcare resource utilization among newly diagnosed, newly treated patients using dabigatran vs warfarin. Poster presented at: American College of Clinical Pharmacy (ACCP) Virtual Poster Symposium; May 20-21, 2014. https://www.accp.com/docs/meetings/abstracts/2014_virtual.pdf.
39. Bennell MC, Qiu F, Micieli A, et al. Identifying predictors of cumulative healthcare costs in incident atrial fibrillation: a population-based study. *J Am Heart Assoc.* 2015;4(4). doi:
40. Greiner MA, Hammill BG, Fonarow GC, et al. Predicting costs among medicare beneficiaries with heart failure. *Am J Cardiol.* 2012;109(5):705-711. doi: 10.1161/JAHA.114.001684.
41. Smith DH, Johnson ES, Blough DK, et al. Predicting costs of care in heart failure patients. *BMC Health Serv Res.* 2012;12:434. doi: Z 10.1186/1472-6963-12-434.
42. Patel MR, Hellkamp AS, Fox K. Point-of-care Warfarin monitoring in the ROCKET AF trial. *N Engl J Med*. 2016;374(8):785-787. doi: 10.1056/NEJMc1604020.