Real-World Health Care Costs Based on Medication Adherence and Risk of Stroke and Bleeding in Patients Treated with Novel Anticoagulant Therapy

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ABSTRACT

BACKGROUND: With the lack of real-world evidence, the challenge for drug reimbursement policy decision makers is to understand medication adherence behavior among users of novel oral anticoagulants (NOACs) and its effect on overall cost savings. No study has examined and quantified the burden of cost in high-risk patients taking NOAC therapy.

OBJECTIVE: To examine the association of cost with adherence, comorbidity, and risk of stroke and bleeding in patients taking NOACs (rivaroxaban and dabigatran).

METHODS: A retrospective cohort study used deidentified data from a commercial managed care database affiliated with Optum Clinformatics Data Mart (January 1, 2010–December 31, 2012). Patients aged 18 years and older with ≥ 1 diagnosis of atrial fibrillation/flutter, > 1 NOAC prescription, 6-month pre-index and 12-month post-index continuous enrollment, and CHA₂DS₂-VASc score ≥ 1 were included. Adherence was calculated using proportion of days covered (PDC $\geq 80\%$) over an assessment period of 3, 6, and 12 months and compared based on level of comorbidity, stroke, and bleeding risk. The adjusted annual health care costs per patient (drug, medical, and total) were calculated using multivariable gamma regression controlling for demographic and clinical characteristics and compared across groups based on adherence over 12 months, baseline level of comorbidity, and risk of stroke and bleeding.

RESULTS: Of 25,120 NOAC patients, 2,981 patients were included in the final cohort. Based on a PDC threshold of $\geq 80\%$, the adherence rate over 3, 6, and 12 months was 72%, 65%, and 54%, respectively. For all time periods, the level of adherence significantly increased ($P < 0.001$), with an increase in stroke risk (based on CHA₂DS₂-VASc scores of 1, 2–3, and 4+); comorbidity (Charlson Comorbidity Index scores of 0, 1–2, and 3+); and risk of bleeding (HAS-BLED scores of 0–1, 2, and 3+). Adjusted all-cause total cost calculated for a 12-month period was significantly lower (\$29,742 vs. \$33,609) among adherent versus nonadherent users. Drug cost was higher (\$5,595 vs. \$2,233) among adherent versus nonadherent patients but was offset by lower medical costs (\$23,544 vs. \$30,485) costs. The overall cost significantly increased for patients with a high risk of bleeding and a high level of comorbidity.

CONCLUSIONS: Adherence to NOAC therapy led to a reduction in overall health care cost, since higher drug costs were offset by lower medical (inpatient and outpatient) costs among adherent patients. Cost information based on adherence and risk of stroke and bleeding can help formulary decision makers to assess risk-benefit and help clinicians in developing interventions to reduce patient burden.

J Manag Care Spec Pharm. 2018;24(5):430–39

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What is already known about this subject

- Novel oral anticoagulants (NOACs) have shown better or similar efficacy in the reduction of stroke risk and noninferior risk of major bleeding versus warfarin in clinical trials.
- NOACs have a promising potential to improve medication adherence because of fewer dietary and drug-to-drug interactions, fixed dosage, and the need for minimal monitoring.

What this study adds

- This study provides new evidence based on real-world data that emphasizes the importance of considering overall cost and adherence information in conjunction with assessment of stroke and bleeding risk to inform the overall risk-benefit of NOAC therapy.
- Adherence to NOACs proportionally increased with a higher risk of stroke and bleeding and level of comorbidity.
- Study results showed that better adherence to NOACs leads to substantial overall cost savings (-\$3,867) over a follow-up period of 12 months, and the cost burden significantly increased with a higher risk of bleeding and a higher level of comorbidity.

Atrial fibrillation (AF) is a common condition that causes cardiac rhythm disturbance because of abnormal impulse formation, which can lead to numerous heart-related complications.¹ AF is one of the key risk factors for ischemic stroke, increasing the risk up to 5-fold.² In 2010, the prevalence of AF in the United States was 2.7 million and is expected to grow to 5.6 million by 2050.³ AF accounts for a substantial portion of the U.S. health care burden, with more than 467,000 hospitalizations annually and more than 99,000 deaths per year. AF is also responsible for adding \$26 billion to U.S. health care spending annually, which is mostly driven by inpatient and outpatient costs.¹ Adherence to anticoagulant therapy and accurate assessment of stroke and bleeding risk are vital for reducing the related health care burden and ensuring treatment success.

Novel oral anticoagulants (NOACs) are a new class of drugs that offer benefits such as quick time-to-peak effects, fewer drug-drug and dietary interactions, fixed dosing regimens, and minimal international normalized ratio (INR) monitoring. Overall, NOACs have shown better or similar efficacy in the reduction of stroke risk and noninferior risk of major

bleeding versus warfarin in the clinical trials. NOACs have also been prescribed for treatment of deep vein thrombosis and pulmonary embolism.^{4,5}

Adherence to long-term medication therapy is crucial for achieving efficacy and reducing cost and hospitalizations. Long-term treatment with NOACs is recommended for patients with AF for stroke prevention¹; however, adherence is suboptimal, with approximately half of patients being adherent to oral anticoagulation therapy.⁶⁻⁹

A study comparing the costs of rivaroxaban and warfarin using a Humana claims database reported that health care costs were comparable. The mean total costs for rivaroxaban was slightly lower compared with warfarin (\$17,590 vs. \$18,676), but higher pharmacy cost for rivaroxaban was offset by lower hospitalization cost.¹⁰ Similar cost comparison results were found between dabigatran and warfarin, using HealthCore data.¹¹ Overall, based on recently published literature, NOACs tend to demonstrate better or comparable economic outcomes than warfarin, but no data exist to highlight the effect of better adherence to NOACs on cost savings.

With inadequate real-world evidence, the challenge for drug reimbursement policy decision makers is to consider whether the high drug costs and copays for NOACs are offset by lower overall medical costs, better adherence, and quality of life. A comprehensive evaluation of overall cost and its components (drug and medical costs) in patients treated with NOACs across different levels of adherence, comorbidities, and stroke and bleeding risk is not yet available. Furthermore, the association of improved adherence NOACs and consequent cost savings has not yet been examined in real-world studies. This analysis addressed these gaps in the current literature.

Methods

Study Design and Cohort

A retrospective cohort study was conducted with deidentified medical and pharmacy claims data from January 1, 2010, to December 31, 2012, using a nationwide commercial U.S. managed care health plan affiliated with Optum Clinformatics Data Mart (Optum Insight, Eden Prairie, MN). Adult patients were included who were aged ≥ 18 years with at least 1 AF or atrial-flutter diagnosis claim identified using the medical file (inpatient or outpatient) with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code of 427.31/427.32 during the pre-index period. Patients with at least 2 pharmacy claims of dabigatran or rivaroxaban (NOACs) were identified based on National Drug Code numbers. Patients with at least 6 months of pre-index and 12 months of post-index continuous eligibility with a permissible gap of 45 days were included in the cohort. Patients with hyperthyroidism (ICD-9-CM code 242.9) were excluded from the cohort, since hyperthyroidism may be the probable cause

of AF. The CHA₂DS₂VASc score was used to quantify the stroke risk and was scored from 0-9 points based on risk factors for stroke that included congestive heart failure, hypertension, age 65-75 years, diabetes, peripheral vascular disease, female gender (constituting 1 point each), and previous occurrence of transient ischemic attack or stroke and age ≥ 75 years scored 2 points.¹²⁻¹⁴ Patients with CHA₂DS₂VASc scores ≥ 1 in the pre-index period were included in the cohort.^{13,14}

The index date was defined as the date of the first prescription fill of NOAC medication during the measurement period. Patients with concomitant use of warfarin and NOACs during the post-index period were excluded. To avoid exclusion of the few patients who used warfarin in the pre-index period before treatment with NOACs, NOAC users with pre-index warfarin use were included based on the definition of “warfarin-naïve” that was applied in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trials. Patients were considered to be warfarin-naïve if they had not used warfarin during the 2 months before initiation of a NOAC.¹⁵ Data from the RELY trials showed no heterogeneity between patients who had previous warfarin use and those with no previous warfarin therapy. We used this criterion to ensure that we captured all NOAC users and to avoid potential channeling bias regarding previous warfarin therapy for assessment of outcomes. Thus, the index date of warfarin-naïve users was based on the first prescription fill of NOACs. Patient outcomes were assessed over a post-index follow-up period of 12 months. The assessment period included index date to 3 months, 6 months, and 12 months.

Measurement of Medication Adherence

Proportion of days covered (PDC) was the preferred method to measure adherence, where the numerator was defined as number of days covered by NOAC drugs as a class (using first fill date and days of supply) and the denominator was the days between first fill and end of the study, disenrollment, or death, whichever occurred first. PDC also helped to adjust early refills.¹⁶ Overall adherence to NOAC use was calculated using PDC from the index date to the end of the assessment period (3, 6, and 12 months). Patients with a PDC $\geq 80\%$ were classified as adherent.^{6,17} Adherence was also calculated for an assessment period of 3, 6, and 12 months using the following 3 severity groups:

1. Stroke risk based on CHA₂DS₂VASc score. Risk was categorized as low risk (CHA₂DS₂VASc score of 1), moderate risk (CHA₂DS₂VASc score of 2-3), and high risk (CHA₂DS₂VASc score of 4+).
2. Bleeding risk based on HAS-BLED score calculated using hypertension, renal disease, liver disease, antiplatelet or nonsteroidal anti-inflammatory drug use, stroke history, previous bleeding, age ≥ 65 years, labile INR (therapeutic time in range $< 60\%$), and alcohol or drug use constituting

FIGURE 1 Cohort Selection Based on Inclusion and Exclusion Criteria

AF=atrial fibrillation; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; NOAC= novel oral anticoagulant.

1 point each.¹⁴ Risk was categorized as low risk (HAS-BLED score of 0-1), moderate risk (HAS-BLED score of 2), and high risk (HAS-BLED score of 3+). Because data on labile INR values were unavailable, all patients were scored 0 in this category.

3. Comorbidity using Charlson Comorbidity Index (CCI) scores based on the adapted version by Deyo et al. (1992) for administrative claims data.^{14,18,19} CCI scores were subgrouped as CCI=0, CCI=1-2, and CCI=3+ comorbid disease conditions.¹⁸

Cost

The per-patient post-index cost for a follow-up of 12 months was calculated. The medical cost was defined as the total amount paid for inpatient and outpatient medical services plus inpatient and outpatient professional fees and copays. The total health care cost was the sum of all medical and drug costs using the amount paid by the patient through prescription fills (pharmacy claims and copays). The cost measures were expressed as average per-patient annual all-cause costs. The

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TABLE 1 Demographic Characteristics of Overall Sample and Cohorts Based on Adherence

Variable Description	Statistic Response Category	Total (N = 2,981)	Adherent ^a (n = 1,621)	Nonadherent (n = 1,360)	P Value (Chi-square test)
Age at index	Number	2,981	1,621	1,360	0.0009
	Mean (SD)	64.39 (10.72)	66.53 (10.05)	61.84 (10.95)	
	Median (IQR)	63 (58-72)	65 (60-74)	61 (55-68)	
	Range	26-86	34-86	26-86	
Gender, n (%)	Female	898 (30.13)	501 (30.91)	397 (29.19)	0.3039
	Male	2,082 (69.87)	1,119 (69.03)	963 (70.81)	
Insurance type, n (%)	EPO	349 (11.71)	172 (10.61)	177 (13.01)	<0.0001
	HMO	190 (6.37)	91 (5.61)	99 (7.28)	
	IND	452 (15.16)	313 (19.31)	139 (10.22)	
	POS	1,867 (62.63)	967 (59.65)	900 (66.18)	
	PPO	122 (4.09)	77 (4.75)	45 (3.31)	
Region, n (%)	Midwest	636 (21.34)	370 (22.83)	266 (19.56)	<0.0001
	Northeast	306 (10.27)	164 (10.12)	142 (10.44)	
	South	1,525 (51.17)	768 (47.38)	757 (55.66)	
	West	513 (17.21)	319 (19.68)	194 (14.26)	
Stroke risk (CHA ₂ DS ₂ VASc score) ^b n (%)	Low risk	575 (19.29)	237 (14.62)	338 (24.85)	<0.0001
	Moderate risk	1,336 (44.82)	692 (42.69)	644 (47.35)	
	High risk	1,070 (35.89)	692 (42.69)	378 (27.79)	
CCI category, n (%)	CCI score 0	602 (20.19)	284 (17.52)	318 (23.38)	0.0002
	CCI score 1-2	1,403 (47.06)	773 (47.69)	630 (46.32)	
	CCI score 3+	976 (32.74)	564 (34.79)	412 (30.29)	
Statin use, n (%)	No	1,512 (50.72)	735 (45.34)	777 (57.13)	<0.0001
	Yes	1,469 (49.28)	886 (54.66)	583 (42.87)	
ACE or ARB use, n (%)	No	1,551 (52.03)	785 (48.43)	766 (56.32)	<0.0001
	Yes	1,430 (47.97)	836 (51.57)	594 (43.68)	
Beta blocker use, n (%)	No	2,065 (69.27)	1,106 (68.23)	959 (70.51)	0.1780
	Yes	916 (30.73)	515 (31.77)	401 (29.49)	
Bleeding risk (HAS-BLED) ^c n (%)	Low risk	1,084 (36.36)	496 (30.60)	588 (43.24)	<0.0001
	Moderate risk	1,028 (34.49)	605 (37.32)	423 (31.10)	
	High risk	869 (29.15)	520 (32.08)	349 (25.66)	

^aAdherence was based on 12-month follow-up, and the adherence cohort was defined based on PDC ≥ 80%.

^bStroke risk was categorized as low risk (CHA₂DS₂VASc score of 1), moderate risk (CHA₂DS₂VASc score of 2-3), and high risk (CHA₂DS₂VASc score of 4+).

^cBleeding risk was classified as low risk (HAS-BLED score of 0-1), moderate risk (HAS-BLED score of 2), and high risk (HAS-BLED score of 3+).

ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCI = Charlson Comorbidity Index; EPO = exclusive provider organization; HMO = health maintenance organization; IND = indemnity insurance; IQR = interquartile range; POS = point of service; PPO = preferred provider organization; SD = standard deviation.

cost incurred for the years 2010-2012 was adjusted for inflation to 2016 U.S. dollars based on the Consumer Price Index.

Multivariate Analysis

A logistic regression model was used to examine the predictors of medication adherence based on PDC ≥ 80% over 12 months post-index (dependent variable, 1/0). Age, region, insurance plan type, gender at index date of NOAC use, pre-index CCI, stroke risk based on CHA₂DS₂VASc score, bleeding risk based on HAS-BLED score, and cardiac medication use that included statin use, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers (ACE-ARB) use, and beta blocker use were used as covariates and included in the full model.

Generalized linear models with gamma distribution and log link were also used to obtain and compare the adjusted annual costs between adherent and nonadherent patients, defined based on PDC ≥ 80%. The gamma distribution was preferred, since we expected a skewed distribution of the cost, and the gamma model is an acceptable approach to handle cost data.²⁰ Age, CCI scores, stroke risk based on CHA₂DS₂VASc scores, region, insurance type, gender, bleeding risk based on HAS-BLED scores, and cardiac medication use including statin, ACE-ARB, and beta blocker use were used as covariates. The total annual cost, along with its subcomponents (drug cost and medical cost) were also compared between the patients stratified based on CCI score and stroke and bleeding risk at

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TABLE 2 Adherence to NOAC Therapy over 12-Month Follow-up for Stroke and Bleeding Risk (N=2,981)

Outcome Cohort	Overall N	Patient Adherence PDC ≥80%		
		3-Month Follow-up n (%)	6-Month Follow-up n (%)	12-Month Follow-up n (%)
Overall adherence	2,981	2,144 (71.92)	1,935 (64.91)	1,621 (54.38)
Adherence by stroke risk ^a				
Low risk	575	344 (59.83)	300 (52.17)	237 (41.22)
Moderate risk	1,336	946 (70.81)	835 (62.50)	692 (51.80)
High risk	1,070	854 (79.81)	800 (74.77)	692 (64.67)
Overall P value		<0.0001	<0.0001	<0.0001
Adherence by bleeding risk ^b				
Low risk	1,084	711 (65.59)	623 (57.47)	496 (45.76)
Moderate risk	1,028	778 (75.68)	708 (68.87)	605 (58.85)
High-risk	869	655 (75.37)	604 (69.51)	520 (59.84)
Overall P value		<0.0001	<0.0001	<0.0001
Adherence by CCI ^c				
Low risk	602	408 (67.77)	355 (58.97)	284 (47.18)
Moderate risk	1,403	1,011 (72.06)	917 (65.36)	773 (55.10)
High risk	976	725 (74.28)	663 (67.93)	564 (57.79)
Overall P value		0.0199	0.0013	0.0002

^aStroke risk was categorized as low risk (CHA₂DS₂VASc score of 1), moderate risk (CHA₂DS₂VASc score of 2-3), and high risk (CHA₂DS₂VASc score of 4+).

^bBleeding risk was classified as low risk (HAS-BLED score of 0-1), moderate risk (HAS-BLED score of 2), and high risk (HAS-BLED score of 3+).

^cCCI scores were subgrouped as CCI=0, CCI=1-2, CCI=3+ comorbid conditions.

CCI=Charlson Comorbidity Index; NOAC= novel oral anticoagulant; PDC= proportion of days covered.

a significance level of $P \leq 0.05$. Data were analyzed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

Results

Cohort Selection

Of the 25,120 NOAC users identified during the study period, 14,618 had 2 or more prescription fills. Of these patients, 5,364 patients had used warfarin in the pre-index period, and, 3,726 patients who were not warfarin naive had been excluded, leaving 1,638 patients had been included as NOAC users because they fit the definition of warfarin naive. Because of concomitant use of warfarin and NOACs in the post-index period, 1,010 patients had also been excluded. Based on the other inclusion criteria (diagnosis of AF in the pre-index period, aged ≥ 18 years, continuous enrollment for 6-month pre-index and 12-month post-index, and a CHA₂DS₂VASc score ≥ 1), 2,891 NOAC patients formed the final cohort (Figure 1).

Overall Baseline Characteristics Across Cohorts

The mean age of the cohort was 64 years, with more men (70%) than women. Most of the patients were either from the South or the Midwest (68%). The proportion of patients with moderate and high risk of stroke was higher (high 36% vs. moderate 45% vs. low 19%) compared with low-risk patients. Based on CCI scores, most (80%) of the patients had at least 1 comorbid condition. Patients were well distributed across bleeding risk based

on the HAS-BLED scores. More than 45% of the cohort used statins and ACE-ARB class of cardiovascular drugs (Table 1).

Baseline Characteristics Among Adherent and Nonadherent NOAC Patients

Based on baseline characteristics, age, stroke risk, type of insurance, statin use, bleeding risk, CCI, and region were significantly ($P \leq 0.05$) different across the adherent and non-adherent patient groups. The mean age of patients classified as adherent was slightly higher (approximately 67 years [standard deviation (SD)=10]) compared with the nonadherent group (approximately 62 years [SD=11]). Gender and beta blocker use was consistent between the adherence-based cohorts. The proportion of patients with moderate to high risk of stroke (CHA₂DS₂VASc score ≥ 4) was substantially higher among adherent versus nonadherent patients (43% vs. 28%; Table 1).

Adherence Measured by PDC

Adherence was measured during follow-up periods of 3, 6, and 12 months. In the overall sample, the proportion of adherent patients (PDC $\geq 80\%$) declined during the period from 3, 6, and 12 months (72% for 3-month follow-up, 65% for 6-month follow-up, and 54% for 12-month follow-up). This trend was evident across all subgroups based on CCI, CHA₂DS₂VASc, and HAS-BLED scores (Table 2).

Adherence increased with a higher risk of stroke. Based on the 12-month follow-up, the proportion of patients adherent

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TABLE 3 Predictors of 12-Month Medication Adherence Using Logistic Regression Model (N=2,981)

Outcome	Reference	Effect	Odds Ratio	95% CI		P Value	Overall P Value
Age		—	1.035	1.024	1.046	<0.0001	<0.0001
Gender	Male	Female vs. male	0.907	0.762	1.079	0.2702	0.2702
Insurance type	HMO	EPO vs. HMO	1.240	0.860	1.789	0.9702	0.5744
		IND vs. HMO	1.395	0.952	2.045	0.9723	
		POS vs. HMO	1.235	0.906	1.684	0.9702	
		PPO vs. HMO	1.520	0.932	2.479	0.9738	
Region	Midwest	Northeast vs. Midwest	0.738	0.553	0.985	0.1088	0.0072
		South vs. Midwest	0.755	0.619	0.920	0.0301	
		West vs. Midwest	0.990	0.771	1.272	0.0891	
Stroke risk ^a	Low risk	High risk vs. low risk	1.556	1.144	2.117	0.0050	0.0173
		Moderate risk vs. low risk	1.209	0.967	1.512	0.7013	
CCI ^b	CCI=0	CCI score 1-2 vs. CCI score 0	1.249	1.011	1.542	0.0131	0.0453
		CCI score 3+ vs. CCI score 0	1.051	0.811	1.362	0.5536	
Statin use	No use	Yes vs. no use	1.305	1.114	1.530	0.0010	0.0010
ACE-ARB use	No use	Yes vs. no use	1.187	1.015	1.389	0.0320	0.0320
Beta blocker	No use	Yes vs. no use	1.032	0.874	1.218	0.7109	0.7109
Bleeding risk ^c	Low risk	High risk vs. low risk	0.760	0.584	0.990	0.0067	0.0100
		Moderate risk vs. low risk	1.069	0.877	1.303	0.0139	

^aStroke risk was categorized as low risk (CHA₂DS₂VASc score of 1), moderate risk (CHA₂DS₂VASc score of 2-3), and high risk (CHA₂DS₂VASc score of 4+).

^bCCI scores were subgrouped as CCI=0, CCI=1-2, CCI=3+ comorbid conditions.

^cBleeding risk was classified as low risk (HAS-BLED score of 0-1), moderate risk (HAS-BLED score of 2), and high risk (HAS-BLED score of 3+).

ACE=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CCI=Charlson Comorbidity Index; CI=confidence interval; EPO=exclusive provider organization; HMO=health maintenance organization; IND=indemnity insurance; IQR=interquartile range; POS=point of service; PPO=preferred provider organization; SD=standard deviation.

to NOACs in the low-risk and moderate-risk groups were 41% and 52%, respectively, and were significantly ($P<0.001$) lower compared with the proportion of adherent patients (65%) in the high-risk group. Similar results were observed during the follow-up periods of 3 and 6 months. Higher adherence among higher risk groups was evident in the subgroups based on bleeding risk and CCI scores over the 3 follow-up periods (3, 6, and 12 months; Table 2).

Predictors of Medication Adherence

Based on the logistic regression model, age, region, CCI scores, stroke risk, statin and ACE-ARB use, and bleeding risk were significant predictors of medication adherence to NOACs. Adherence rate was higher with increasing age (odds ratio [OR]=1.04, 95% confidence interval [CI]=1.02-1.05), and patients in the Midwest had higher adherence compared with the other regions. Patients with higher stroke risk were 1.56 times (95% CI=1.14-2.12) more likely to be adherent compared with low-risk patients. Similarly, patients with CCI scores of 1-2 had higher odds (OR=1.25, 95% CI=1.01-1.54) of being adherent than those with CCI scores of 0. Patients using statins and ACE-ARBs tended to be more adherent (OR for statins=1.31, 95% CI=1.11-1.53 and OR for ACE-ARBs=1.19, 95% CI=1.02-1.39) to NOAC therapy compared with patients who were not taking these cardiovascular medications. Finally,

patients with a moderate risk of bleeding were 1.07 times (95% CI=0.88-1.30) more likely to be adherent compared with low-risk patients (Table 3).

Comparison of Annual All-Cause Health Care Costs

As expected, the annual adjusted per-patient drug cost for adherent users was significantly higher compared with non-adherent users (\$5,595 vs. \$2,233; $P\leq 0.001$). However, the annual adjusted per-patient medical cost that included all inpatient and outpatient costs was significantly lower for adherent users compared with nonadherent users (\$23,544 vs. \$30,485; $P\leq 0.001$). The total annual adjusted per-patient cost for adherent users was also significantly lower than nonadherent users (\$29,742 vs. \$33,609; $P=0.005$). Overall, the high drug cost among adherent users was offset by lower inpatient and outpatient costs (medical costs) compared with nonadherent users (Table 4).

Comparison of Adjusted Costs by Stroke Risk

Most of the patients had moderate to high risk of stroke based on the CHA₂DS₂VASc score (low risk 19.29%, moderate risk 44.82%, and high risk 35.89%). The annual per-patient drug cost was slightly lower in patients with low risk of stroke compared with patients with moderate and high risk (low risk \$3,347 vs. moderate risk \$3,664 vs. high risk \$3,602). The

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TABLE 4 Adjusted Annual All-Cause Per-Patient Cost by Adherence, Stroke Risk, Bleeding Risk, and Comorbidity Level (N=2,981)

Outcome Cohort	Overall N	Average Adjusted Annual Pharmacy Cost, \$ (95% CI) ^a	Average Adjusted Annual Medical Cost, \$ (95% CI) ^a	Average Adjusted Annual Total Cost, \$ (95% CI) ^a
Adherence				
Nonadherent	1,360	2,233 (1,898-2,628)	30,485 (21,348-43,535)	33,609 (24,938-45,297)
Adherent	1,621	5,595 (4,758-6,750)	23,544 (16,506-33,583)	29,742 (22,091-40,043)
Overall P value		<0.0001	<0.0001	0.0005
Stroke risk (CHA₂DS₂VASc)^b				
Low risk	575	3,347 (2,830-3,958)	33,007 (22,849-47,681)	37,972 (27,906-51,668)
Moderate risk	1,336	3,664 (3,113-4,312)	27,271 (19,081-38,976)	32,036 (23,756-43,201)
High risk	1,070	3,602 (3,055-4,247)	21,362 (14,901-36,626)	25,981 (19,214-35,242)
Overall P value		0.0049	<0.0001	<0.0001
Bleeding risk (HAS-BLED)^c				
Low risk	1,084	3,596 (3,053-4,236)	22,516 (15,744-32,201)	27,189 (20,149-36,689)
Moderate risk	1,028	3,508 (2,978-4,132)	24,916 (17,411-35,656)	29,641 (21,956-40,018)
High risk	869	3,501 (2,966-4,132)	34,276 (23,823-49,315)	39,216 (28,919-53,179)
Overall P value		0.5752	<0.0001	<0.0001
CCI^d				
Low risk	602	3,437 (2,911-4,059)	18,482 (12,828-26,609)	22,912 (16,886-31,089)
Moderate risk	1,403	3,575 (3,037-4,207)	25,149 (17,603-35,929)	29,719 (22,043-40,066)
High risk	976	3,595 (3,052-4,234)	41,369 (28,910-59,199)	46,416 (34,384-62,657)
Overall P value		0.2893	<0.0001	<0.0001

^aCost estimates were calculated based on gamma models controlling for age, gender, insurance, region, stroke risk, bleeding risk, CCI, and cardiovascular drug use.

^bStroke risk was categorized as low risk (CHA₂DS₂VASc score of 1), moderate risk (CHA₂DS₂VASc score of 2-3), and high risk (CHA₂DS₂VASc score of 4+).

^cBleeding risk was classified as low risk (HAS-BLED score of 0-1), moderate risk (HAS-BLED score of 2), and high risk (HAS-BLED score of 3+).

^dCCI scores were subgrouped as CCI=0, CCI=1-2, CCI=3+ comorbid conditions.

CCI=Charlson Comorbidity Index; CI=confidence interval.

annual per-patient medical cost for NOAC users with high risk of stroke was lower than the cost of patients with low risk of stroke. A similar trend was evident for the total cost in which the cost incurred by high-risk patients was lower than the cost incurred by low-risk patients (Table 4).

Comparison of Adjusted Costs by Bleeding Risk

Patients were well distributed by bleeding risk based on the HAS-BLED score (low risk 36.36%, moderate risk 34.49%, and high risk 29.15%). The annual adjusted per-patient drug cost did not significantly differ across groups based on the risk of bleeding (low risk \$3,596 vs. moderate risk \$3,508 vs. high risk \$3,501). However, the annual adjusted per-patient medical cost increased significantly with an increased bleeding risk (low risk \$22,516 vs. moderate risk \$24,916 vs. high risk \$34,276; $P \leq 0.001$). High medical cost was the driver for the total annual cost, in which the same trend of higher total cost with increased risk of bleeding was consistent (Table 4).

Comparison of Adjusted Costs by CCI

Most of the patients had at least 1 comorbidity (79.8%) based on CCI scores. There were 32.74% of patients with 3 or more comorbid conditions. Similar to the subgroups based on bleeding risk, the annual adjusted per-patient drug cost did not

significantly differ across groups based on CCI scores. However, the total adjusted per-patient cost increased significantly with increase in CCI scores (low risk \$27,189 vs. moderate risk \$29,641 vs. high risk \$39,216; $P \leq 0.001$), which was mostly driven by the high medical costs across highly comorbid patients (Table 4).

Discussion

This study found that the economic burden of NOAC users based on total annual health care cost was substantial (>\$30,000). However, better long-term adherence to NOACs directly translated in overall cost savings. The medical (inpatient and outpatient) costs for adherent users were significantly lower (-\$6,941) than nonadherent patients, which offset the higher drug cost (+\$3,362) among adherent users. The drug cost was comparable between groups categorized based on stroke risk, bleeding risk, and CCI scores. However, total cost was driven mostly by medical cost, which increased proportionally with a higher risk of bleeding and comorbidity. A similar trend was not observed for cost by stroke risk.

We also found that adherence to NOACs in our sample was suboptimal (<60% with PDC $\geq$ 80%) and was better among patients with higher comorbidity and a higher risk of stroke and bleeding. The high-risk population benefited from

frequent physician visits, focused interventions, aggressive efforts by physicians for improving care and adherence to treatment guidelines, better awareness among severe patients, and motivation to feel better, which can potentially lead to better patient-provider interaction and improvement in overall adherence among these patients.

Based on a large database study by Yao et al. (2016), adherence to NOACs at the end of follow-up at 1.1 years was low (47.5%), which is similar to our estimate of adherence (54%) at 12 months.⁶ Based on another study using commercial insured patients taking NOACs, the proportion of patients with PDC $\geq$ 80% at 9 months was suboptimal, with 55.0% for rivaroxaban, 56.8% for apixaban, and 46.7% for dabigatran users.²¹ It is noteworthy that advantages of NOAC over warfarin are promising and that NOAC therapy has a potential to improve overall medication adherence, which is evident from recently published studies.²²⁻²⁴

In our sample, it was clearly observed that adherence to NOACs was driven by baseline risk of stroke and bleeding and CCI scores. A study by Brown et al. (2016) reported an increase in adherence to NOAC medication from 58% in patients with CHA₂DS₂VASc scores of 2-3 and 62% in patients with a higher risk of stroke (CHA₂DS₂VASc score of 4+) based on the 9-month follow-up.²¹ Another study based on insurance claims data concluded that patients with a higher risk of stroke were more adherent to NOAC medication than patients at lower risk (CHA₂DS₂VASc score 0 or 1, 30.5%; CHA₂DS₂VASc score 2 or 3, 43.4%; and CHA₂DS₂VASc score $\geq$ 4, 45.3%).⁶ Our study differs from these studies because it presents new evidence in the form of better adherence from groups based on a risk of bleeding and comorbidity, which are integral to the selection of optimal anticoagulation treatment.

Our results also highlighted stroke and bleeding risk as a major predictor of medication adherence. Other predictors such as age, region, CCI score, and statin and ACE-ARB use were consistent with the previous studies.^{9,25-27} In addition, younger age, male gender, low stroke risk, poverty, higher education, and poor cognitive function have been associated with lower adherence.²⁸ A recent study based on the Danish National Patient Registry reported an overall 1-year PDC equal to 83.9% and found that females (OR = 1.06), patients using cardiovascular drugs, and a CHA₂DS₂VASc score of $\geq$ 2 (OR = 1.12) were major predictors of adherence among dabigatran users.²²

Our study is the first to compare the real-world cost between adherent and nonadherent NOAC patients. We found a positive association of adherence with cost saving (-\$3,867) over a 12-month period that can be attributed to lower health care utilization (e.g., fewer hospital visits and shorter hospital stays).

Our estimates of health care costs (drug, medical, and total) were consistent with the existing literature. Based on data from the U.S. Department of Defense Military Health System, drug costs were higher (\$4,369, $P < 0.001$) for dabigatran compared with warfarin, which is similar to our estimated drug costs.²⁹ Also, Bancroft et al. (2016) studied dabigatran costs using a managed care data (2009-2012) and reported annual drug costs as \$6,122, medical costs as \$19,195, and total costs as \$25,370.³⁰ According to another database study by Fonseca et al. (2015), the total cost for patients taking dabigatran and warfarin after propensity score matching was \$14,794 vs. \$16,826.³¹

Drug cost was similar across subgroups based on CCI scores and stroke and bleeding risks. Medical and total costs were higher for patients with higher comorbidities and increased risk of bleeding. Conversely, we found that medical and total costs were higher for patients with a low risk of stroke compared with high-risk patients. Better adherence in the high-risk group might lead to lower incidence of stroke and its related lower cost burden. In addition, complications related to low-risk patients might be aggressively treated, leading to higher medical (inpatient and outpatient) costs. Cost and adherence information by stroke and bleeding risks and CCI scores can serve as crucial parameters informing the risk-benefit of treatment.

One of the strengths of this study was the use of a nationwide database with a large sample size. In addition, HAS-BLED was preferred because of its widespread use and better discrimination and prediction of bleeding risk compared with HEMORR₂HAGES and ATRIA.^{32,33} An inclusion criteria of at least 2 prescription refills ensured the exclusion of possible intermittent users (i.e., multiple periods of use but none exceeding 3 months) or patients who might use NOACs as concomitant therapy or for other indications. Furthermore, 2 prescription refills enabled calculation of adherence using PDC.

Limitations

A few limitations need to be considered when interpreting our results. Although PDC has been widely used and accepted, it is an indirect method of assessing adherence because it is based on insurance claims (prescription fills). It should also be acknowledged that Optum Clinformatics Data Mart is a nationwide database, but the majority of the study patients were from the southern and midwestern regions. This database also underrepresents the older Medicare population.

As with all studies using claims databases, our data lacked information on race and ethnicity, long-term disease history, reasons for therapy discontinuation, and clinical variables such as INR values and body mass index. However, clinical

markers of severity, such as CHA₂DS₂VASc, HAS-BLED, and CCI, reflected risk due to hypertension, previous cardiovascular disease, diabetes, and other comorbidities. Aspirin use was not comprehensively captured in the claims database because of its availability as an over-the-counter drug; however, since all patients were prescribed NOACs, the differential use of aspirin might be unlikely among patients with a CHA₂DS₂VASc score > 1, who are recommended anticoagulant therapy based on guidelines from the American College of Cardiology and the American Heart Association.

It is also important to acknowledge the differences in mechanism of action and costs between dabigatran and rivaroxaban. A higher proportion of our sample was prescribed dabigatran, since it was approved earlier. The newer drugs apixaban and edoxaban, which came into the market after 2012, were not included in our analysis. Since the measurement of PDC and cost was in the same period, inferences suggest a cross-sectional association instead of a sequential (longitudinal) causal relationship. This is a question that can be explored in future studies.

Despite these limitations, this study provides new evidence that emphasizes the importance of considering overall cost and adherence information in conjunction with the assessment of stroke and bleeding risk to inform the optimal choice of anticoagulant therapy and ascertain the overall risk-benefit of NOAC therapy.

Conclusions

Adherence to NOAC therapy over a follow-up period of 12 months was suboptimal (54%) and increased with a higher level of comorbidities and risk of stroke and bleeding. The health care cost burden on AF patients using NOACs was substantial. Adherence to NOAC therapy was associated with a reduction in overall health care costs, since higher drug costs were offset by lower medical costs among adherent patients.

Our results provide valuable evidence regarding adherence and its related effect on total health care costs, which adds to our understanding of the risk-benefits of NOAC therapy and provides evidence for better decision-making processes by health care providers and managed care organizations. These findings underscore the need for encouraging and supporting patient adherence with NOAC therapy. Furthermore, the real-world estimates for drug and medical costs can be applied to future economic models, meta-analyses, indirect comparisons, and cost-effectiveness analyses. More studies that provide event-specific estimates (related to stroke, bleeding, deep vein thrombosis, and pulmonary embolism) of cost and adherence for newer NOAC drugs are warranted.

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DISCLOSURES

Funding to acquire the data source was provided by the University of Rhode Island College of Pharmacy, Kingston, to support PhD dissertation work. Deshpande is currently an employee of Pharmerit International.

ACKNOWLEDGMENTS

Data from the Optum Clinformatics Data Mart were accessed through the data server at the University of Rhode Island. The authors thank the data manager and the University of Rhode Island College of Pharmacy for their assistance.

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