CLINICAL RESEARCH STUDY

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Patterns of Initiation of Oral Anticoagulants in Patients with Atrial Fibrillation—Quality and Cost Implications

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ABSTRACT

BACKGROUND: Dabigatran, rivaroxaban, and apixaban have been approved for use in patients with atrial fibrillation based upon randomized trials demonstrating their comparable or superior efficacy and safety relative to warfarin. Little is known about their adoption into clinical practice, whether utilization is consistent with the controlled trials on which their approval was based, and how their use has affected health spending for patients and insurers.

METHODS: We used medical and prescription claims data from a large insurer to identify patients with nonvalvular atrial fibrillation who were prescribed an oral anticoagulant in 2010-2013. We plotted trends in medication initiation over time, assessed corresponding insurer and patient out-of-pocket spending, and evaluated the cumulative number and cost of anticoagulants. We identified predictors of novel anticoagulant initiation using multivariable logistic models. Finally, we estimated the difference in total drug expenditures over 6 months for patients initiating warfarin versus a novel anticoagulant.

RESULTS: There were 6893 patients with atrial fibrillation that initiated an oral anticoagulant during the study period. By the end of the study period, novel anticoagulants accounted for 62% of new prescriptions and 98% of anticoagulant-related drug costs. Female sex, lower household income, and higher $CHADS_2$, CHA_2DS_2-VASC, and HAS-BLED scores were significantly associated with lower odds of receiving a novel anticoagulant ($P < .001$ for each). Average combined patient and insurer anticoagulant spending in the first 6 months after initiation was more than $900 greater for patients initiating a novel anticoagulant.

CONCLUSIONS: This study demonstrates rapid adoption of novel anticoagulants into clinical practice, particularly among patients with lower $CHADS_2$ and HAS-BLED scores, and high health care cost consequences. These findings provide important directions for future comparative and cost-effectiveness research.

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KEYWORDS: Factor Xa inhibitor; Novel anticoagulant; Patterns of use; Vitamin K antagonist; Warfarin

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Warfarin and other vitamin K antagonists significantly reduce the risk of stroke and death in patients with nonvalvular atrial fibrillation and have long been the cornerstone of therapy for this condition.[1] Although these drugs are inexpensive, they require monitoring, have a narrow therapeutic window, and patients frequently discontinue use.[2] Novel oral anticoagulants that require no monitoring have been approved for use based upon randomized trials

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demonstrating their comparable or superior efficacy and safety relative to warfarin.[3-5] Based on these studies, the US Food and Drug Administration (FDA) approved the direct thrombin inhibitor dabigatran in October 2010, followed by the Factor Xa inhibitors rivaroxaban and apixaban in November 2011 and December 2012, respectively.

A national audit of ambulatory practices evaluating trends in oral anticoagulant use from 2007 to 2011 found rapid adoption of dabigatran in clinical practice.[6] Similarly, a recent registry-based analysis of the use of dabigatran in patients with atrial fibrillation found significant uptake of dabigatran use in 2011.[7] However, little is known about how the availability of rivaroxaban and apixaban have affected utilization patterns, whether the adoption of the novel anticoagulants in typical practice is consistent with the controlled trials on which their approval was based, or how their use has affected spending for patients and insurers.

CLINICAL SIGNIFICANCE

- By mid-2013, novel anticoagulants accounted for 62% of new prescriptions and 98% of anticoagulant-related medication costs.
- Females, individuals in lower income areas, and those with higher $CHADS_2$ and HAS-BLED scores have significantly lower odds of novel anticoagulant initiation.
- Adoption patterns demonstrate divergence from the clinical trials on whose basis novel anticoagulants were approved; surveillance is needed to observe whether selection bias persists in patients initiating these medications.

METHODS

Study Population and Data Source

We used nationwide medical and prescription claims data from commercial patients covered by Aetna, a large health care benefits company, to create a cohort of patients with newly diagnosed nonvalvular atrial fibrillation who were prescribed an oral anticoagulant between October 1, 2010 and June 30, 2013.

These data contained complete paid claims data for all procedures, physician encounters, hospitalizations, and filled prescriptions (including dose dispensed and amounts paid by the insurer and the patient). These data were linked to eligibility data that included patient age, sex, and zip code of residence. Aggregate data on socioeconomic status, race, and educational attainment were obtained by linking zip code of residence with data from the 2000 United States Census, which specified the median income as well as the distribution of race and educational achievement of the geographic population for each zip code. The Institutional Review Board of Brigham and Women's Hospital approved the study.

Study Cohort

Patients were included in the study if they filled a prescription for warfarin, dabigatran, rivaroxaban, or apixaban during the study period. All patients were required to have maintained continuous insurance eligibility for 6 months before their index date, during which time they must have had a diagnosis of atrial fibrillation (International Classification of Diseases, Ninth Revision [ICD-9]: 427.31) and no filled prescriptions for any anticoagulant agent (ie, they were new initiators). Patients with concomitant valvular heart disease (ICD-9: 394.x-397.x, 398.9, 42.4x, V42.2, V43.3, 35.1x, 35.2x) were excluded. Any subsequent re-initiation of therapy by a patient that met cohort entry criteria was excluded (ie, a patient could only appear in the cohort once). The date of the patient's first eligible prescription was defined as his or her index date.

We assessed differences in proportions and means with 95% confidence intervals for demographic, clinical, and health care utilization characteristics of initiators of warfarin, dabigatran, and rivaroxaban; apixaban was excluded from these statistical comparisons due to small sample size. Clinical and health care utilization characteristics were based on medical and pharmacy claims in the 6 months before initiation. The Congestive heart failure, Hypertension, Age $\geq$75 years, Diabetes mellitus, Stroke ($CHADS_2$) score,[8] the Congestive heart failure, Hypertension, Age $\geq$75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (CHA_2DS_2-VASc) score,[9] and the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (Age >65 years), Drugs/alcohol concomitantly (HAS-BLED) score[10] was calculated for each subject (note: one element of this score, labile international normalized ratio values, was not available in our claims dataset and therefore was not used in the HAS-BLED score calculation). Individuals of unknown sex were excluded.

Patterns and Predictors of Initiation

We categorized patients based on calendar month of their drug initiation and the oral anticoagulant they started, and plotted trends over time. We then assessed insurer drug spending (ie, plan-paid amount) and patient out-of-pocket drug spending (ie, copayments, coinsurance, deductible) based on the index prescription, and plotted the share of costs associated with each anticoagulant. Finally, we plotted the cumulative total monthly number of prescriptions of each anticoagulant after the index prescription, regardless of any switching that might have occurred, and computed the monthly costs associated with these prescriptions. Patients who lost eligibility were censored at loss of eligibility. We repeated our plots of trends in anticoagulant initiation stratified on $CHADS_2$ score,[8] a stroke prediction score.

We constructed 3 multivariable logistic models to identify predictors of initiation on a novel oral anticoagulant compared with warfarin. Potential predictors in all models included age, sex, race, income, geographic region, and calendar time. Comorbidity was adjusted for in several ways: 1) investigator-selected diagnoses; 2) $CHADS_2$ score; and 3) HAS-BLED score.

Economic Analysis

To evaluate patient and insurer costs associated with anticoagulant use over the 6-month period after treatment initiation, we restricted our cohort to those individuals with 180 days or more of continuous eligibility after their first prescription. For each patient, we calculated total patient out-of-pocket and insurer spending for all anticoagulant medication during the 180 days after treatment initiation, including anticoagulant medications the patients may have switched to during this period. We then subdivided these estimates into patient out-of-pocket and insurer spending for the index medication and for other anticoagulants. From this, we estimated the difference in total expenditures over 6 months for patients initiating warfarin compared with a novel anticoagulant.

RESULTS

The study cohort consisted of 6893 patients with nonvalvular atrial fibrillation newly initiated on an oral anticoagulant between October 1, 2010 and June 30, 2013 (**Appendix**, available online). Patients had a mean age of 61.3 years, were predominantly male (72.8%), and had mean $CHADS_2$ and HAS-BLED scores of 1.7 and 2.0, respectively (**Table 1**). Approximately one third of patients had a history of coronary artery disease, and one quarter had diabetes. Heart failure, renal dysfunction, or history of stroke or transient ischemic attack was present in 17%, 12%, and 9% of patients, respectively, while 4% had a history of gastrointestinal bleeding. On average, patients had filled more than 8 medications in the 6 months before treatment initiation; 13% had received a nonsteroidal anti-inflammatory medication and 8% had received clopidogrel in the 6 months before initiation.

Patterns of Medication Initiation Over Time

Over the 36-month study period, there were a total of 45,472 prescriptions filled for anticoagulants, among which 26,253 (57.7%) were for warfarin, 14,922 (32.8%) for dabigatran, 4241 (9.3%) for rivaroxaban, and 56 (0.1%) for apixaban.

Dabigatran rapidly gained market share after entering the market in November 2010 (**Figure 1A**). By October 2011, patients were as likely to start on this drug as they were to initiate warfarin. After its introduction, rivaroxaban use increased rapidly, overtaking both warfarin and dabigatran in June 2013. Apixaban, FDA-approved as of December 2012, saw only modest uptake, accounting for only 2% of new anticoagulant prescriptions as of June 2013.

Predictors of Initiating Treatment with a Novel Oral Anticoagulant

As compared with patients initiating warfarin, those starting a novel oral anticoagulant had significantly fewer concomitant medications, office visits, hospital days, and hospitalizations within 30 days of initiation, but higher number of visits to a cardiologist ($P < .001$) (**Table 1**). Novel anticoagulant initiators tended to be younger and healthier, and with significantly lower $CHADS_2$, CHA_2DS_2-VASC, and HAS-BLED scores. As seen in **Figure 2**, 46% of patients with $CHADS_2$ scores of 0 or 1 initiated a novel anticoagulant, compared with just 39% and 26% for $CHADS_2$ scores of 2 and 3, respectively ($P < .0001$ for test of trend).

In multivariable models, increasing $CHADS_2$ and HAS-BLED scores were significantly associated with lower odds of novel anticoagulant initiation (**Table 2**). For every 1-point increase in $CHADS_2$, patients were 20% less likely to receive a novel anticoagulant (odds ratio [OR] 0.80; 95% confidence interval [CI], 0.76-0.84). Similarly, for every 1-point increase in HAS-BLED, patients were 18% less likely to receive a novel anticoagulant (OR 0.82; 95% CI, 0.78-0.87). In addition, women were 24% less likely to be initiated on a novel oral anticoagulant as compared with men (OR 0.76; 95% CI, 0.67-0.86). There was a significant, step-wise increase in the likelihood of receiving a novel agent with progressively increasing neighborhood household income, compared with median household income of $50,000 or less.

Economic Impact of Initial Medication Choice

Trends in monthly spending are shown in **Figure 1B**. Since the introduction of dabigatran in late 2010, novel anticoagulant spending has accounted for 98% of total spending. This corresponds to insurer spending of $5.82 million, of which warfarin accounted for $0.43 million (**Figure 3A**); and patient out-of-pocket spending of $1.3 million, of which warfarin accounted for $0.28 million (**Figure 3B**).

Considering only the first 6 months postinitiation, total out-of-pocket and insurer costs for patients initiating a novel anticoagulant were considerably higher than those for patients initiating warfarin (**Figure 4**). On average, patients initiating warfarin paid $54 for 6 months of medication, while those initiating dabigatran or rivaroxaban paid $205 and $221, respectively. Insurer spending for patients initiated on warfarin during this period was $68 for warfarin, compared with $852 and $865 for dabigatran and rivaroxaban, respectively. The average combined patient and insurer spending for anticoagulants over 6 months for patients initiating warfarin was $122, dabigatran $1053, and rivaroxaban $1084. This represents a difference over 6 months of more than $900 per patient.

DISCUSSION

This study of a contemporary cohort of patients with atrial fibrillation starting oral anticoagulant therapy demonstrates

Table 1 Baseline Demographic Characteristics, Clinical Characteristics, and Health Care Utilization of the Study Cohort

	All	Warfarin	Dabigatran	Rivaroxaban	Apixaban	*P*-Value*
Demographics						
Members	6893	4070	1982	821	20	
Sex (female)	27.2%	30.0%	23.0%	23.5%	5.0%	<.0001
Age, years						
Average age	61.3	61.8	60.7	60.5	58.4	<.0001
Age 18-54	22.3%	21.5%	23.6%	23.4%	20.0%	
Age 55-64	44.8%	44.1%	44.4%	48.4%	60.0%	
Age 65-74	23.1%	22.8%	24.8%	20.6%	15.0%	
Age 75+	9.8%	11.6%	7.2%	7.7%	5.0%	
Region						
Northeast	32.7%	33.8%	31.9%	29.4%	40.0%	.04
South	38.2%	36.0%	41.0%	42.1%	35.0%	<.0001
Midwest	8.3%	8.2%	9.1%	7.2%	10.0%	.24
West	19.9%	21.2%	17.4%	20.1%	10.0%	.002
Comorbidity: Mean (SD)						
$CHADS_2$ score	1.67 (1.10)	1.79 (1.18)	1.50 (0.94)	1.53 (0.97)	1.40 (0.68)	<.0001
CHA_2DS_2-VASC score	2.57 (1.62)	2.83 (1.71)	2.19 (1.37)	2.23 (1.43)	2.05 (0.94)	<.0001
HAS-BLED	1.96 (1.16)	2.08 (1.22)	1.77 (1.01)	1.81 (1.08)	1.60 (0.82)	<.0001
%						
Coronary artery disease	31%	33%	28%	30%	30%	<.0001
Congestive heart failure	17%	20%	12%	12%	5%	<.0001
Hypertension	91%	91%	91%	92%	95%	.68
Diabetes mellitus	24%	26%	21%	20%	25%	<.0001
Deep vein thrombosis or pulmonary embolism	10%	15%	2%	3%	5%	<.0001
Liver disease	5%	6%	4%	3%	5%	.001
Renal dysfunction	12%	16%	7%	8%	5%	<.0001
Previous ischemic stroke or transient ischemic attack	9%	10%	6%	8%	5%	<.0001
Hemorrhagic stroke	1%	1%	0%	0.1%	0%	.003
Gastrointestinal bleeding	4%	4%	3%	3%	0%	.001
Urogenital bleeding	12%	15%	6%	9%	10%	<.0001
Other major bleeding	4%	5%	2%	2%	0%	<.0001
Bleeding history or predisposition	18%	22%	12%	14%	10%	<.0001
Healthcare utilization: Mean (SD)						
Number of medications	8.25 (4.92)	8.63 (5.15)	7.56 (4.48)	8.05 (4.61)	7.15 (3.60)	<.0001
Hospitalizations	0.51 (0.72)	0.59 (0.80)	0.40 (0.58)	0.40 (0.57)	0.20 (0.41)	<.0001
Hospital days	4.52 (13.64)	6.28 (16.86)	2.07 (6.36)	1.82 (4.18)	0.65 (1.42)	<.0001
Office visits	9.59 (9.99)	10.25 (11.18)	8.71 (7.81)	8.45 (8.04)	8.75 (8.75)	<.0001
Cardiologist visits	2.07 (2.65)	1.92 (2.77)	2.35 (2.54)	2.14 (2.21)	2.40 (2.72)	<.0001
Neurologist visits	0.11 (0.53)	0.12 (0.57)	0.08 (0.46)	0.11 (0.53)	0.00 (0.00)	.08
%						
Hospitalization in 30 days before treatment initiation	30%	34%	26%	25%	15%	<.0001

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke; CHA_2DS_2-VASC = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, sex category; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age >65 years), drugs/alcohol concomitantly.

**P*-value for warfarin versus dabigatran or rivaroxaban.

rapid adoption of novel anticoagulants into clinical practice, utilization associated with lower $CHADS_2$ and HAS-BLED scores, and significant health care cost implications. This study is the first, to our knowledge, to evaluate real-world use of all novel anticoagulants currently on the market.[6]

We observed a significant decline in the proportion of patients with atrial fibrillation starting warfarin concurrent with the availability of novel anticoagulants beginning in October 2010. By June 2013, more than 60% of patients newly initiating an oral anticoagulant were being prescribed dabigatran, rivaroxaban, or apixaban. Before the introduction of rivaroxaban in November 2011, dabigatran accounted for 44% of anticoagulant initiation, but this dropped to approximately 15% of starts in the subsequent 12 months, a reversal that may have been related to reports beginning in late 2011 of increased risk of myocardial infarction and

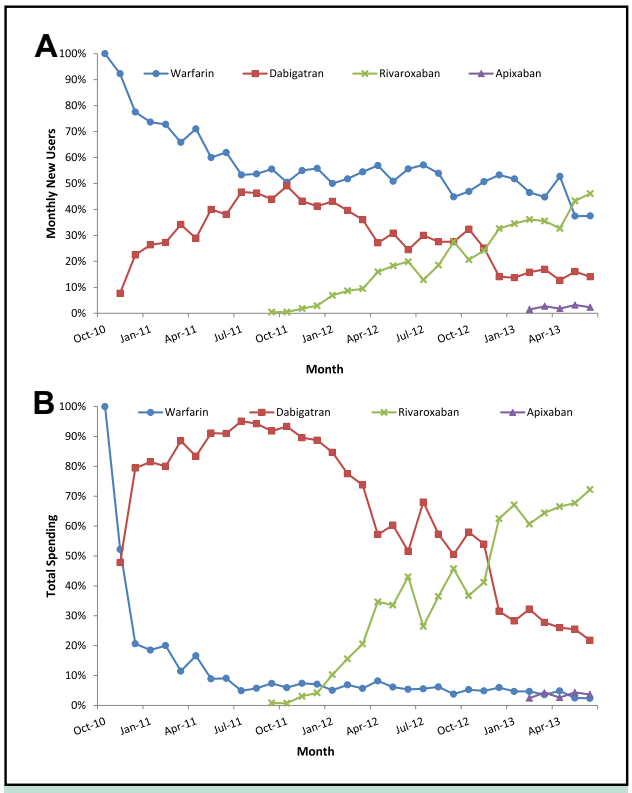

Figure 1 Monthly trends in oral anticoagulant initiation (panel **A**) and total spending (panel **B**).

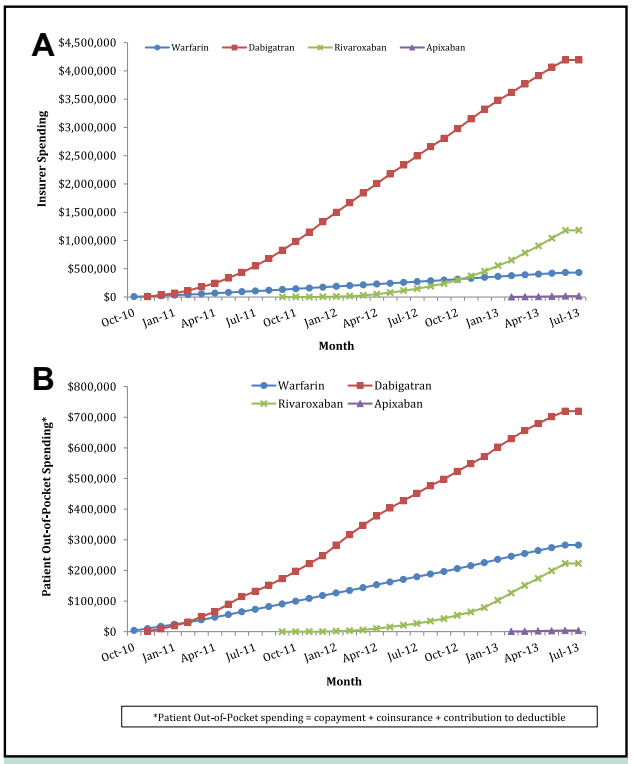

Figure 3 Accumulated insurer amount (panel **A**) and patient out-of-pocket amount (panel **B**) by anticoagulant.

serious and fatal bleeding events in dabigatran users.[11-13] The once-daily dosing of rivaroxaban as compared with twice daily for dabigatran may also be a factor in the substitution away from dabigatran.

With only 2% of market share 6 months after approval, it remains to be seen whether the adoption of apixaban will follow the same trajectory as dabigatran and rivaroxaban.

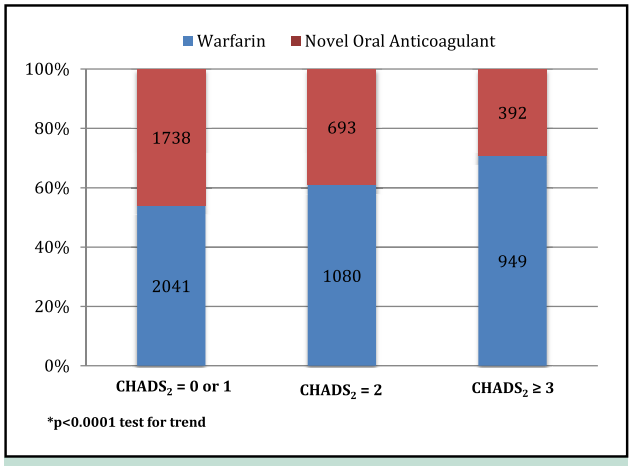

Figure 2 Number of warfarin and novel anticoagulant initiators by $CHADS_2$ score during study period. $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke.

The impending FDA approval of new factor Xa inhibitors such as edoxaban[14,15] and betrixaban[16] may also influence an increasingly crowded market for therapeutic alternatives to warfarin. It remains unclear whether the market for novel anticoagulants has been fully saturated and whether uptake of one drug will generally occur at the expense of other novel agents, or whether aggressive promotion of this class will result in an overall increase in the use of anticoagulants in patients with atrial fibrillation and market expansion for all therapies.

We found similar use of warfarin and novel anticoagulants among patients with $CHADS_2$ score of 0 or 1, with progressively higher use of warfarin among patients with $CHADS_2$ of 2 and then predominant use of warfarin among patients with $CHADS_2$ of 3 or greater. In a multivariate model, higher $CHADS_2$ and HAS-BLED scores were associated with a significantly lower odds of initiating therapy with a novel agent, results corroborated by a recent registry-based analysis of the adoption of dabigatran.[7] These patterns of adoption demonstrate some divergence from the clinical trials on whose basis the novel anticoagulants were approved. Notably, the mean $CHADS_2$ scores for the Randomized Evaluation of Long-Term Anticoagulation therapy[3] (RE-LY), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF),[4] and Apixaban for Reduction in Stroke

Table 2 Multivariable Analysis Predicting Initiation with a Novel Anticoagulant versus Warfarin Among Patients with Atrial Fibrillation

	Odds Ratio (95% CI) of Initiating Therapy With a Novel Anticoagulant vs Warfarin		
Predictor	Model 1*	Model 2†	Model 3‡
Age, years (vs under 50)			
50-65	0.98 (0.82-1.16)	—	—
65+	0.92 (0.76-1.12)	—	—
Calendar month from October 2010	1.06 (1.05-1.06)	1.06 (1.05-1.06)	1.06 (1.05-1.06)
Sex (female)	0.76 (0.67-0.86)	0.76 (0.67-0.86)	0.76 (0.67-0.86)
Region (vs Northeast)			
Midwest	1.18 (0.96-1.44)	1.17 (0.95-1.43)	1.15 (0.94-1.41)
South	1.36 (1.20-1.55)	1.37 (1.21-1.56)	1.37 (1.21-1.56)
West	0.87 (0.74-1.01)	0.85 (0.73-0.99)	0.86 (0.74-1.00)
Median household income in zip code (vs <$50,000)			
$50,000-$99,999	1.20 (1.05-1.38)	1.21 (1.06-1.38)	1.21 (1.06-1.38)
$100,000-$149,999	1.69 (1.21-2.36)	1.69 (1.22-2.35)	1.74 (1.25-2.43)
$150,000-$200,000	1.90 (0.62-5.79)	1.98 (0.65-6.07)	2.03 (0.66-6.23)
Percent black in zip code	1.06 (0.75-1.50)	0.98 (0.70-1.38)	0.98 (0.70-1.37)
Percent graduated college or high school in zip code	1.01 (1.01-1.02)	1.01 (1.01-1.02)	1.02 (1.01-1.02)
Comorbidity			
Coronary artery disease	1.00 (0.88-1.14)	0.92 (0.81-1.04)	0.92 (0.81-1.04)
Deep vein thrombosis or pulmonary embolism	0.17 (0.13-0.23)	0.15 (0.11-0.19)	0.16 (0.12-0.20)
Congestive heart failure	0.72 (0.61-0.84)	—	—
Previous myocardial infarction	0.82 (0.60-1.11)	—	—
Diabetes mellitus	0.86 (0.75-0.98)	—	—
Alcohol use	1.12 (0.80-1.57)	—	—
NSAID, aspirin, clopidogrel, prasugrel, or ticagrelor use	1.00 (0.88-1.15)	—	—
Stroke	0.71 (0.60-0.84)	—	—
Bleeding history or predisposition	0.64 (0.55-0.75)	—	—
Abnormal liver function	0.92 (0.70-1.20)	—	—
Hypertension	1.20 (0.99-1.45)	—	—
Renal dysfunction	0.64 (0.52-0.77)	—	—
$CHADS_2$ score (per 1-point increase)	—	0.80 (0.76-0.84)	—
HAS-BLED score (per 1-point increase)	—	—	0.82 (0.78-0.87)

CHADS = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke; CI = confidence interval; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age >65 years), drugs/alcohol concomitantly; NSAID = nonsteroidal anti-inflammatory drug.

*Model 1 includes age, sex, race, income, geographic region, calendar time, and investigator-selected clinical diagnoses.

†Model 2 includes age, sex, race, income, geographic region, calendar time, and $CHADS_2$ score.

‡Model 3 includes age, sex, race, income, geographic region, calendar time and HAS-BLED score.

and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[5] trials were 2.1, 3.5, and 2.1, respectively, and eligibility criteria for the ROCKET-AF trial was based on a $CHADS_2$ score of at least 2 (in fact, enrollment for patients with $CHADS_2$ of 2 was limited to 10%).[4] The greatest absolute benefit from novel anticoagulants has been shown to be among patients at highest baseline risk for stroke or systemic embolization, which is at odds with our observation of selection of seemingly lower-risk patients for these drugs. Such a finding may reflect provider conservatism for new drug adoption, particularly given longitudinal experience with warfarin. Nonetheless, given this finding as well as the potential disparities in the use of novel anticoagulants based on geography, sex, and income, it will be important to conduct ongoing surveillance of the penetration of novel anticoagulants and whether this initial phase with dominant use among lower-risk patients is followed by use in more high-risk patients or whether a significant selection bias persists in the patients for whom they are prescribed.

Our observation that users of the newer anticoagulants were generally healthier and had a lower stroke risk than warfarin users has important implications for surveillance data concerning their propensity to cause bleeding, as well as likely future observational comparative effectiveness studies. An early population-based assessment performed by the FDA documented substantially lower rates of intracerebral and gastrointestinal hemorrhage in atrial fibrillation patients taking dabigatran versus warfarin,[17] but did not adjust for any differences in risk among the 2 patient groups, nor for age or sex.[18] The differences we have documented in the levels of comorbidity among users of these agents will

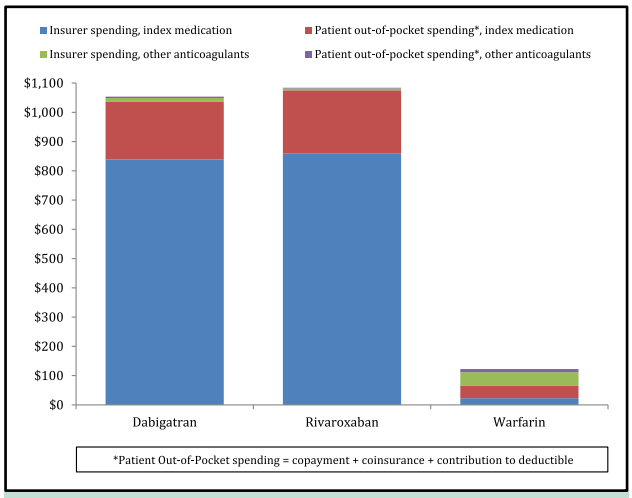

Figure 4 Total patient and insurer spending during 6 months after initiation stratified by anticoagulant on which patients were started.

need to be taken into account in any future observational studies of the drugs' outcomes.

The observed patterns of anticoagulant initiation among patients with atrial fibrillation additionally have important economic implications for patients, payers, and the health care system. Average patient out-of-pocket and insurance spending was more than 5-fold and 15-fold higher, respectively, for novel anticoagulants as compared with warfarin. Novel anticoagulants have only recently attained >50% of market share, yet have accounted for more than 90% of insurer spending on anticoagulants since the introduction of dabigatran in 2010. A 6-month difference in total costs of $900 in our cohort translates into billions of dollars at a national level.

Whereas registration trials for these agents have demonstrated clinical superiority and at least equal safety to warfarin,[3-5] the cost effectiveness of these drugs in routine care has not been evaluated conclusively. Early analyses were limited by uncertainty or error concerning the pricing of both warfarin and its newer competitors.[19] Canestaro et al[20] found that apixaban appears to be cost-effective at a willingness-to-pay threshold of $100,000, but noted substantial uncertainty in this estimate in probabilistic sensitivity analyses. Limone et al's[21] meta-analysis of cost-effectiveness models for novel anticoagulants showed high model heterogeneity, including incremental cost-effectiveness ratios for dabigatran as compared with warfarin ranging from $3547 to $86,000. An analysis based on the RE-LY clinical trial concluded that, contrary to the patterns of anticoagulant use we observed, warfarin is the optimal strategy among patients with lower $CHADS_2$ scores.[22]

There are several limitations to our analysis. First, our study relied on administrative claims data for study inclusion as well as clinical characteristics. Although misclassification of patients with nonvalvular atrial fibrillation could have occurred, we used well-standardized methods and approaches.[23,24] While we lacked detailed clinical information, we did integrate medical claims data with prescription claims data to more fully examine patterns of novel anticoagulant utilization. Second, several demographic factors, including race, income level, and educational attainment were derived from census data, assessed at the zip-code level. Third, our analysis of anticoagulant use among privately insured patients might not be representative of treatment patterns among patients with Medicare, Medicaid, or uninsured patients. However, to the extent that claims data reflect the full spectrum of patient exposure and outcomes, we believe our results are generalizable to the US insured population. Finally, our economic analysis did not include international normalized ratio testing for patients taking warfarin. Eliminating the need for these tests would reduce the relative expenditure for the novel anticoagulants compared with warfarin, but only modestly.

Current European Society of Cardiology and Canadian Cardiovascular Society guidelines[19] recommend use of one of the 3 novel agents over warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation. In contrast, the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines offer no such preference.[25] Our results demonstrate rapid adoption of novel anticoagulants, particularly among lower-risk patients with atrial fibrillation, and correspondingly high health care cost burden. These findings point to the need to conduct ongoing surveillance of the adoption of new agents into clinical practice, as well as the need for robust, real-world comparative-effectiveness analyses of these medications, to enable patients and providers to make informed decisions about their relative benefit, safety, and cost-effectiveness.

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Appendix A: Study Cohort Construction