Early Adoption of Dabigatran and Its Dosing in US Patients With Atrial Fibrillation: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation

ORIGINAL RESEARCH

Early Adoption of Dabigatran and Its Dosing in US Patients With Atrial Fibrillation: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation

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***Background*—**Dabigatran is a novel oral anticoagulant approved for thromboprophylaxis in atrial fibrillation. Adoption patterns of this new agent in community practice are unknown.

***Methods and Results*—**We studied patterns of dabigatran use among patients enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry between June 2010 and August 2011 and followed for 12 months. Among 9974 atrial fibrillation patients included, 1217 (12%) were treated with dabigatran during the study. Overall, patients receiving dabigatran were younger (median age 72 versus 75 years, $P<0.0001$), more likely to be white (92% versus 89%, $P=0.005$), more likely to have private insurance (33% versus 25%, $P<0.0001$), and less likely to have prior cardiovascular disease (4% versus 33%, $P<0.0001$). They had more new-onset atrial fibrillation (8.8% versus 4.1%, $P<0.0001$), lower $CHADS_2$ scores (estimated risk based on the presence of congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack; mean 2.0 versus 2.3, $P<0.0001$), and lower Anticoagulation and Risk Factors in Atrial Fibrillation scores (mean 2.4 versus 2.8, $P<0.0001$). More than half (n=14/25, 56%) of patients with severe kidney disease were not prescribed reduced dosing, whereas 10% (n=91/920) with preserved renal function received lower dosing. Among patients not on dabigatran at baseline, 8% had dabigatran initiated during follow-up. Patient education was significantly associated with switching from warfarin to dabigatran (adjusted odds ratio for postgraduate 1.73, $P=0.007$), whereas antiarrhythmic drug use significantly correlated with de novo adoption of dabigatran (adjusted odds ratio 2.4, $P<0.0001$).

***Conclusions*—**Patients receiving dabigatran were younger and at a lower risk of stroke and bleeding. Patients appeared to drive switching from warfarin, whereas clinical characteristics influenced de novo start of dabigatran. These data suggest cautious early uptake of dabigatran, and more careful attention to dosing adjustments is warranted.

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Key Words: anticoagulant • atrial fibrillation • dabigatran • dosing • pharmacoepidemiology

Atrial fibrillation (AF) increases the risk of stroke or systemic embolism in patients by up to 5-fold.[1] Traditional therapy with vitamin K antagonism (ie, warfarin) has reduced that risk to ≈1% annually, depending on the population treated.[2] However, warfarin has significant shortcomings, particularly its narrow therapeutic window, need for

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frequent monitoring, and numerous drug and food interactions. Alternatives to warfarin have been a long-sought goal in the clinical care of patients with AF. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial demonstrated that a novel direct thrombin inhibitor, dabigatran etexilate, could reduce risks of ischemic and overall strokes while having no higher risk of bleeding relative to warfarin.[3] Based on these data, dabigatran became the first alternative, novel oral anticoagulant (OAC) approved for thromboembolism prevention in nonvalvular AF.[3,4]

Many had predicted that the uptake of this alternative would be very rapid, given that it lacked many of warfarin's pitfalls. Patients no longer required routine monitoring, dietary intake did not alter anticoagulant effect, and dose adjustments were not required on a routine basis (eg, during temporary antibiotic therapy). However, there is limited knowledge regarding the uptake patterns of dabigatran for AF in contemporary US practice and available data are limited to physician surveys or administrative claims.[5,6] It is not clear what proportion of patients with AF in the United States is treated with dabigatran and what drives selection of such patients. Last, dosing of dabigatran presented a challenge for regulatory authorities,[4,7] and it is not clear how providers responded in routine practice, particularly for older patients and/or those with renal insufficiency. The objectives of the current analysis were to (1) describe early patterns of dabigatran use in community practice, (2) identify patient and/or provider factors associated with the use of dabigatran in patients with AF, and (3) describe dosing patterns of dabigatran.

Methods

The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a nationwide registry of outpatients with AF treated by primary care physicians, cardiologists, and/or electrophysiologists. Sites were invited to participate based on achieving a nationally representative sample, through an adaptive design geared toward heterogeneity of practice-type and geography. Site management and study coordination were performed by the Duke Clinical Research Institute. Each site enrolled consecutive patients, aged ≥18 years, with electrocardiographically documented AF that was not due to a reversible cause. They were expected to provide follow-up every 6 months for ≥2 years and could not be included if life expectancy was <6 months. A web-based case report form was used to gather data, primarily from the patient's medical record and treating physician. Data components included demographics, medical history, AF history (including symptoms), medical therapies, vital signs, laboratory and echocardiographic measures, and incident procedures and adverse events. Additional details of the ORBIT-AF design and rationale have been previously described.[8]

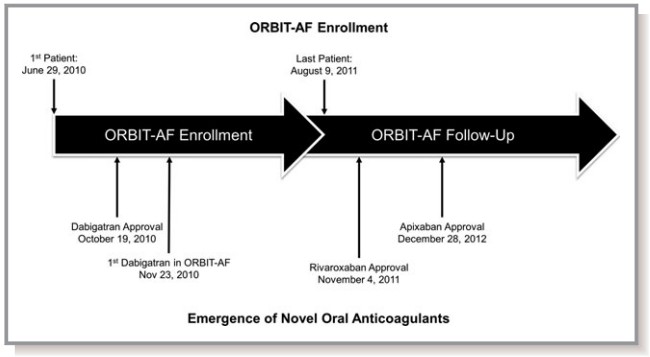

Figure 1. Timeline of ORBIT-AF enrollment vs emergence of novel oral anticoagulants in the US. ORBIT-AF indicates Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

The ORBIT-AF Registry began before the availability of any novel OACs (June 2010), however, dabigatran was approved shortly thereafter (October 2010).[9] The registry completed enrollment before approval of any other novel anticoagulants, and rivaroxaban and apixaban were subsequently approved during the follow-up phase (Figure 1).

Collection of data on medical therapies included historical anticoagulation use, current anticoagulants, dosing, monitoring of international normalized ratios (INRs, where appropriate), and reasons for any discontinuations or contraindications. Warfarin monitoring (INR) was reported throughout follow-up and was requested at baseline (but subject to availability at enrollment). Dosing for dabigatran is recorded as total daily dosing, and sites are prompted to confirm each entry of anticoagulant dosing to ensure appropriate dose reporting. Individual twice-daily dosing levels were calculated from the total daily dose. Sites were instructed to record the present medical therapy, as well as the reasons for any discontinuations in therapies, every 6 months. The present analysis includes patient follow-up to 1 year.

Study Population

The overall study population included all patients in the registry who had ≥1 visit (baseline or follow-up) on or after the first reported use of dabigatran in the registry and thus were eligible for treatment with dabigatran. First, we assessed temporal uptake of dabigatran chronologically. Next, patients who were treated with dabigatran during the study period were compared with patients who did not receive dabigatran. Additionally, we described dabigatran dosing patterns overall and by age and renal function.

Patients Adopting Dabigatran During Follow-up

To identify specific factors associated with the initiation of dabigatran, the population of dabigatran users was subse-

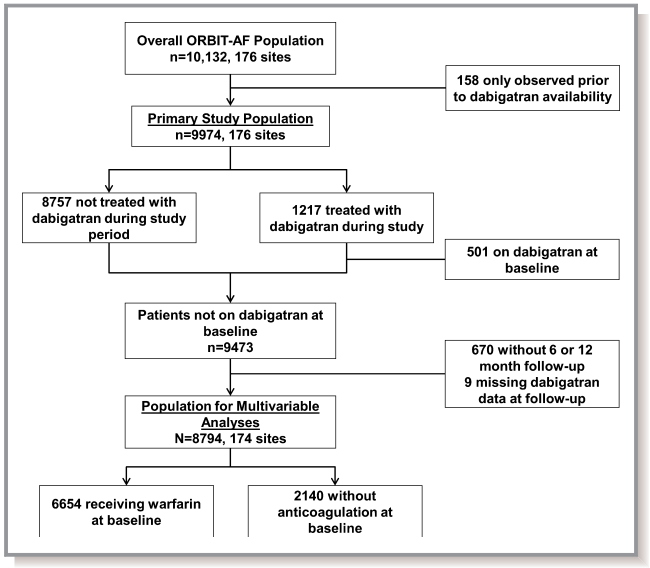

Figure 2. Patient inclusion and exclusion in the current analysis. ORBIT-AF indicates Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

quently limited to 2 populations: (1) patients receiving warfarin at baseline and (2) patients without OAC at baseline (antiplatelet agents may have been used). To assess baseline and follow-up characteristics that may have influenced dabigatran adoption, we purposefully did not include patients already taking dabigatran at baseline (n=501; no other OACs were used at baseline). Patients without follow-up visits at 6 or 12 months (n=670) and those missing data on dabigatran at follow-up (n=9) were also excluded (Figure 2). Each of these groups was queried for rates of dabigatran use at subsequent follow-up (6 or 12 months), and comparison was made between patients who did not adopt dabigatran and those who did. Multivariable models were used to identify factors associated with dabigatran adoption at follow-up.

Statistical Methods

All baseline characteristics and univariate data are presented as frequencies and percentages for categorical variables and medians (IQR) or means (SD) for continuous variables. The baseline characteristics were compared using the χ^2 for categorical variables and the Wilcoxon rank sum test for continuous variables.

We identified factors associated with initiating dabigatran in 2 distinct populations: (1) those taking warfarin at baseline (switched to dabigatran versus those not) and (2) those without OACs at baseline (started dabigatran versus those not). Dabigatran use was captured in discrete time intervals at 6 and 12 months, rather than specific dates. We therefore used a proportional odds model for discrete time to identify factors related to starting dabigatran at either time interval. This method essentially fit a logistic regression model for the binary occurrence of event, at each discrete time point, and combined the results to provide a single odds ratio (OR) for the effect of covariates. The method can also be viewed as a discrete time Cox model for time-to-starting dabigatran. As with time-to-event analyses, individuals contributed all available follow-up information and were censored (removed from the risk set) when the patient was lost to follow-up. Thus, these models included patients with ≥1 follow-up visit but not necessarily full follow-up.[10,11]

Candidate variables included demographics, medical history, vital signs, laboratory data, AF status, pharmacotherapy, contraindication to OAC, functional status, and provider specialty. All continuous variables were evaluated for nonlinearity with the outcome, and nonlinear relationships were addressed using linear splines.

Missing data were multiply imputed, and final estimates and standard errors reflect the combined analysis over 5 imputed datasets (missingness was <5% for all the candidate variables except serum creatinine [7%], hematocrit [11%], and left ventricular ejection fraction [11%]). Model selection using backward selection with a stay criterion of 0.05 using the first imputed dataset was used to obtain a model in which each factor was independently associated with switching to dabigatran within 1 year. The model was fit using logistic generalized estimating equations with exchangeable working correlation matrix to account for within-site clustering because patients at the same site are more likely to have similar responses relative to patients at other sites (ie, within-center correlation for responses). We used empirical standard errors, robust to mis-specification of the correlation structure. Backward selection with an inclusion criterion of 0.05 was used to build the models. Adjusted associations for outcomes were displayed as ORs with 95% CIs.

Two separate sensitivity analyses were performed. In the first, the time-in-therapeutic range (TTR) of baseline INR data was calculated using a modification of the Rosendaal method[12] and was included as a predictor in the multivariable model for switching to dabigatran (among patients receiving warfarin at baseline). We imputed daily INR values between the first and last measured INR among INR values obtained before baseline. This analysis was performed only for patients receiving warfarin for ≥60 days before baseline, with ≥2 INR values measured before baseline. Overall, 5315 patients (89% of those on warfarin at baseline for ≥60 days) had ≥2 INR values available at baseline and TTR was calculated using these values. For the remaining 11%, TTR was imputed using multiple imputation for the sensitivity analysis. The second sensitivity analysis was performed to evaluate the contribution of post baseline events into the models for switching. In both patient populations (warfarin and no OAC at baseline), separate, time-dependent covariates for cause-specific

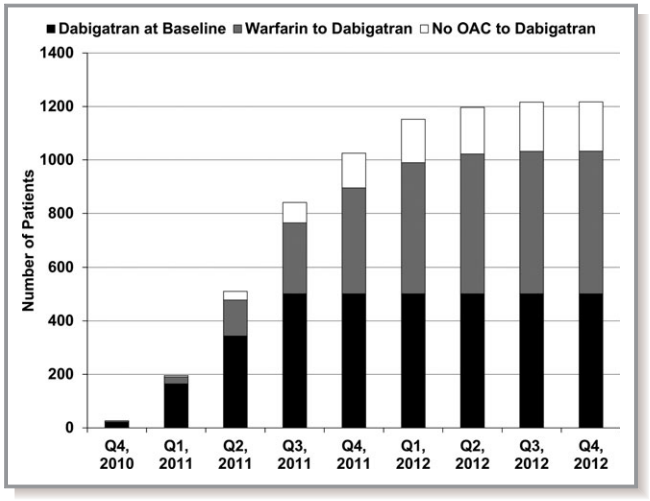

Figure 3. Temporal adoption of dabigatran in ORBIT-AF. OAC indicates oral anticoagulation; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

hospitalizations were added to the baseline models for switching to dabigatran. Cause-specific events were classified by the investigator and included cardiovascular, bleeding, or noncardiovascular, nonbleeding and hospitalization. If a cardiovascular event occurred before 6 months, the time-dependent covariate would take a value of 1 at both the 6-month and 12-month intervals. To the extent that events preceded switching, these associations are predictive. It is also possible that switching preceded events but was not measured until a later interval.

All analyses of the aggregate, deidentified data were performed at the Duke Clinical Research Institute using SAS software (version 9.3, SAS Institute).

Results

The overall ORBIT-AF population included 10 132 patients from 176 sites from June 29, 2010, through August 9, 2011 (Figure 2). Dabigatran use was first reported in the registry on November 23, 2010. After excluding 158 patients who were not observed after that date, there was a study population of 9974 patients from 176 sites. Of these, 1217 (12%) were treated with dabigatran during the study period. Temporal use of dabigatran is shown in Figure 3.

Table 1. Demographics, Past Medical History, and Laboratory Studies of Study Population

	Total (N=9974)	Dabigatran Treatment (n=1217)	No Dabigatran Treatment (n=8757)	*P* Value
Age, y	75 (67 to 82)	72 (64 to 80)	75 (67 to 82)	<0.0001*
Female sex	42	41	43	0.3
Race				
White	89	92	89	0.005
Black or African American	4.9	3.5	5.1	
Hispanic	4.3	2.9	4.4	
Other	1.4	1.6	1.4	
Health insurance status				
Medicare or Medicaid	70	63	71	<0.0001*
Private	26	33	25	
Other	4.9	4.7	4.9	
Hypertension	83	82	83	0.6
Hyperlipidemia	72	70	72	0.1
Diabetes	29	26	30	0.004*
COPD	16	13	17	0.002*
Osteoporosis	13	12	13	0.1
Prior gastrointestinal bleeding	9.0	7.2	9.3	0.02*
Cognitive impairment or dementia	3.1	3.1	3.1	0.9
Frailty	5.7	3.5	6.0	0.0005*
BMI, kg/m^2	29 (25 to 34)	30 (26 to 35)	29 (25 to 34)	<0.0001*
Hemoglobin, g/dL	13.5 (12.3 to 14.6)	13.7 (12.6 to 14.9)	13.5 (12.2 to 14.6)	<0.0001*
Calculated creatinine clearance*, mL/min per 1.73 m^2	70 (50 to 97)	78 (57 to 105)	69 (49 to 95)	<0.0001*

Values are presented as % or median (interquartile range), unless noted otherwise. BMI indicates body mass index; COPD, chronic obstructive pulmonary disease.
*As calculated by the Cockcroft-Gault formula.

Table 2. Cardiovascular History

	Total (N=9974)	Dabigatran Treatment (n=1217)	No Dabigatran Treatment (n=8757)	*P* Value
Peripheral vascular disease	13	11	14	0.002
Coronary artery disease	32	24	33	<0.0001
Prior MI	16	10	17	<0.0001
Prior CABG	15	10	15	<0.0001
Prior PCI	17	13	18	<0.0001
Heart failure	32	25	33	<0.0001
Implanted cardiac device	27	20	28	<0.0001
Significant valve disease	25	18	26	<0.0001
Moderate/severe mitral stenosis	1.4	0.6	1.5	0.009
Prior valve replacement	8.1	3.2	8.8	<0.0001
Mechanical valve	3.1	0.5	3.5	<0.0001
Prior cerebrovascular events	16	13	16	0.001
Stroke (all-cause)	8.8	6.7	9.1	0.005
Stroke—nonhemorrhagic	7.9	6.0	8.2	0.009
Stroke—hemorrhagic	0.8	0.6	0.8	0.4
Other intracranial bleeding	0.9	1.0	0.9	0.8
TIA	8.1	6.9	8.2	0.1
Cardiac medications				
β-Blocker	64	62	64	0.10
Nondihydropyridine calcium channel blocker	17	18	16	0.3
ACEI or ARB	51	52	51	0.6
Statin	55	54	55	0.4
LVEF, %	55 (50 to 61)	58 (52 to 65)	55 (50 to 60)	<0.0001
LA diameter, cm	4.4 (3.9 to 5.0)	4.4 (3.9 to 4.9)	4.4 (3.9 to 5.0)	0.0498

Values are presented as % or median (IQR). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft surgery; LA, left atrium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Patients treated with dabigatran were younger (median age 72 versus 75 years, $P<0.0001$), more likely to be white (92% versus 89%, $P=0.005$), more likely to have private insurance (33% versus 25%, $P<0.0001$), and had higher calculated creatinine clearance (CrCl, median 78 versus 69 mL/min per 1.73 m^2, $P<0.0001$) compared with patients who did not receive dabigatran (Table 1).

Those receiving dabigatran were less likely to have any form of cardiovascular disease (Table 2), including peripheral vascular disease (11% versus 14%, $P=0.002$), coronary artery disease (24% versus 33%, $P<0.0001$), and cerebrovascular disease (13% versus 16%, $P=0.001$). Left ventricular ejection fraction was higher in patients treated with dabigatran (median 58% versus 55, $P<0.0001$).

Historical AF data and anticoagulation history are presented in Table 3. Compared with patients not treated with dabigatran, those receiving dabigatran were more likely to have new-onset AF at baseline (8.8% versus 4.1%) and had lower $CHADS_2$ scores (estimated risk based on the presence of congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack; mean 2.0 versus 2.3, $P<0.0001$) and Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) scores (mean 2.4 versus 2.8, $P<0.0001$). They were more likely to be managed with a rhythm control strategy (38% versus 31%, $P<0.0001$), including prior cardioversion (35% versus 29%, $P<0.0001$), prior antiarrhythmic therapy (50% versus 45%, $P=0.0001$), and prior catheter ablation for AF (8.7% versus 5.1%, $P<0.0001$). Management by an electrophysiology provider was slightly more common in patients receiving dabigatran (19% versus 17%, $P=0.03$).

Dabigatran Dosing

Dosing strategies of dabigatran, stratified by age and CrCl,[13] are shown in Figure 4. The use of 150 mg twice daily was the prevailing dosing strategy, across subgroups, except in patients with CrCl 15 to 30 mL/min per 1.73 m^2 (56%

Table 3. Atrial Fibrillation and Anticoagulation History

	Total (N=9974)	Dabigatran Treatment (n=1217)	No Dabigatran Treatment (n=8757)	*P* Value
AF type at baseline				
New onset	4.7	8.8	4.1	<0.0001*
Paroxysmal	51	49	51	
Persistent	17	18	17	
Longstanding persistent	28	23	29	
Time from AF diagnosis >12 mo	81	70	83	<0.0001*
Rhythm control treatment strategy reported	32	38	31	<0.0001*
$CHADS_2$ score, mean (SD)	2.3 (1.3)	2.0 (1.2)	2.3 (1.3)	<0.0001*
$CHADS_2$ score groups				
0	6.6	7.6	6.4	<0.0001*
1	22	30	21	
≥2	71	62	72	
ATRIA score, mean (SD)	2.8 (2.0)	2.4 (1.8)	2.8 (2.0)	<0.0001*
Prior cardioversion	30	35	29	<0.0001*
Prior catheter ablation for AF	5.5	8.7	5.1	<0.0001*
Prior antiarrhythmic therapy	45	50	45	0.0001*
Current antiarrhythmic therapy	29	36	28	<0.0001*
Amiodarone	10.0	9.5	10.0	0.5
Sotalol	6.1	8.1	5.9	0.002*
Dronedarone	4.6	7.6	4.2	<0.0001*
Flecainide	2.9	4.0	2.8	0.02*
Propafenone	2.4	2.7	2.3	0.4
Dofetilide	1.9	2.6	1.8	0.08
Baseline antiplatelet therapy				
Aspirin	44	39	45	0.0002*
Clopidogrel	7.0	4.2	7.4	<0.0001*
Anticoagulation clinic management at baseline	43	36	44	0.0003*
Relative or absolute contraindication to anticoagulation	13	11	13	0.049*
Treating provider specialty*				
Primary care provider	67	65	68	0.06
Cardiologist	80	81	80	0.4
Electrophysiologist	17	19	17	0.03*
Neurologist	2.1	1.5	2.2	0.1

Values are presented as% or median (IQR), unless noted otherwise. AF indicates atrial fibrillation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; $CHADS_2$, estimated risk based on the presence of congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack.
*Provider specialty is not mutually exclusive; each patient may have ≥1 specialists involved in the care of AF patients.

received 150 mg twice daily). Of patients aged ≥80 years with CrCl >30 mL/min per 1.73 m^2 (n=256), 14% were prescribed 75 mg twice daily. Ten percent of patients under the age of 80, with preserved renal function, were prescribed 75 mg twice daily. P-glycoprotein inhibitors were used in a minority of these patients with preserved renal function receiving the lower dabigatran dose (10.8% received dronedarone, 17% received nondihydropyridine calcium channel blockers, 6.7% received amiodarone, and 0.8% received quinidine).

Adoption of Dabigatran During Follow-up

Among 6654 patients receiving warfarin at baseline, 532 (8.0%) were switched to dabigatran at 6- or 12-month follow-up. As described by the site investigator, major reasons for

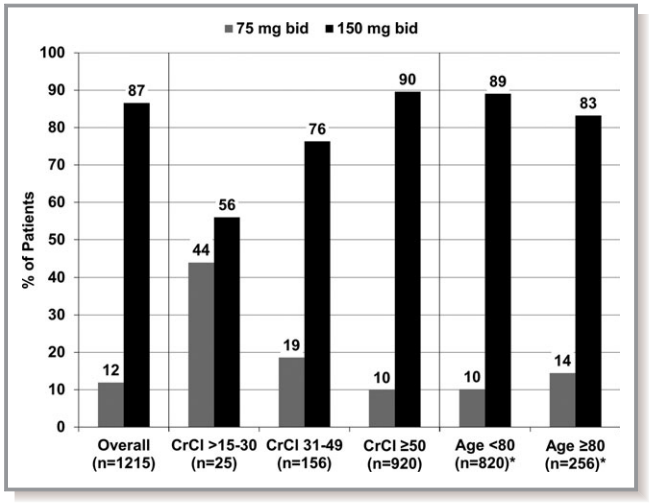

Figure 4. Distribution of dabigatran dosing overall and in high-risk subgroups. Numbers may not sum to 100% due to reporting of other dosing regimens. *Excludes patients with CrCl <30 mL/min per 1.73 m^2. CrCl indicates creatinine clearance calculated by the Cockcroft-Gault formula.[13]

the discontinuation of warfarin in these patients included (reasons are not mutually exclusive) physician preference (n=213, 40%), patient preference (n=171, 32%), inability to adhere to and/or monitor warfarin (n=32, 6.0%), high bleeding risk (n=10, 1.9%), incident bleeding event (n=4, 0.8%), and "other" (n=96, 18%). Warfarin discontinuation reason was not available for 182 (34%) of patients. Of 2140 patients not receiving OAC at baseline, 184 (8.6%) adopted dabigatran at follow-up. Demographics (Table 4), cardiovascular history (Table 5), and AF history (Table 6) are shown for patients who did and those who did not adopt dabigatran during follow-up.

Multivariable models of factors associated with adoption of dabigatran during follow-up are shown in Figure 5. They differed for patients receiving warfarin at baseline versus those receiving no OAC at baseline. In patients receiving warfarin, advanced education (adjusted OR for postgraduate 1.73, 95% CI 1.16 to 2.57, P=0.007) and cognitive impairment (adjusted OR 1.92, 95% CI 1.20 to 3.07, P=0.007) were associated with adoption of dabigatran. Among patients not receiving OAC at baseline, current antiarrhythmic use (adjusted OR 2.37, 95% CI 1.69 to 3.33, P<0.0001) was significantly associated with dabigatran initiation.

Sensitivity Analyses

In patients receiving warfarin at baseline, median TTR at baseline among patients switched to dabigatran was 55% (IQR 38 to 73) versus 60% among patients not switched (IQR 42 to 75). Addition of TTR at baseline contributed minimally to the overall model (c-index from 0.65 to 0.66, adjusted OR for dabigatran adoption per 5% increase in TTR=0.99, 95% CI 0.97 to 1.01, P=0.2). Addition of interim cause-specific hospitalization during follow-up (as defined by the site investigator) to patients receiving warfarin at baseline model also contributed minimally to model discrimination (c-index from 0.65 to 0.66). Interim cardiovascular hospitalization (adjusted OR 1.32, 95% CI 1.04 to 1.68, P=0.02) and noncardiovascular, nonbleeding hospitalization (adjusted OR 1.42, 95% CI 1.09 to 1.85, P=0.01) were both significantly associated with dabigatran adoption, whereas bleeding hospitalization did not have a significant association (adjusted OR 0.84, 95% CI 0.41 to 1.73, P=0.6).

In patients not receiving OAC at baseline, addition of interim hospitalization data modestly improved the discriminatory power of the model (c-index from 0.71 to 0.73). Cardiovascular hospitalization (adjusted OR 2.72, 95% CI 1.89 to 3.93, P<0.0001) was significantly associated with dabigatran adoption, but bleeding (adjusted OR 1.09, 95% CI 0.3 to 5.65, P=0.9) or noncardiovascular, nonbleeding (adjusted OR 1.31, 95% CI 0.78 to 2.2, P=0.3) hospitalizations were not.

Discussion

The development of dabigatran heralded a new era in the use of OACs, and this analysis is among the first to provide the details of its uptake in the clinical care of US patients with AF. Use of dabigatran was modest in this population (12% overall) and appeared to plateau in late 2012. Patients receiving dabigatran were generally younger, more likely to have private health insurance, and less likely to have comorbid cardiovascular disease. A significant proportion (56%) of patients with severe kidney disease did not receive adjusted-dose dabigatran, whereas 10% of patients with normal renal function received reduced dosing.

An alternative to warfarin has been a long-sought goal and highly anticipated therapeutic option. yet a minority of patients in clinical practice received dabigatran during the study period. Furthermore, despite robust data demonstrating lower rates of stroke in patients receiving dabigatran compared with those receiving warfarin,[3] patients treated with dabigatran in our study were at lower risk of stroke, according to $CHADS_2$ scores. They were also at lower risk of bleeding, as represented by prior gastrointestinal bleeding rates and ATRIA bleeding score. These data suggest a conservative adoption strategy by many providers, transitioning patients to dabigatran who are least likely to experience an adverse event. It is possible that physicians were influenced by early case reports of fatal bleeding, coupled with the caveat in the package insert of increased nonintracranial bleeding among individuals aged ≥75 years, compared with warfarin. As more methodologically rigorous data have

Table 4. Demographics, Past Medical History, and Laboratory Studies

	Use of Warfarin at Baseline			No OAC at Baseline		
	Not Switched to Dabigatran (n=6122)	Switched to Dabigatran (n=532)	*P* Value	Not Switched to Dabigatran (n=1956)	Switched to Dabigatran (n=184)	*P* Value
Age, y	76 (68 to 82)	73 (64 to 80)	<0.0001	74 (64 to 82)	68 (62 to 80)	0.005
Female	43	41	0.4	43	41	0.5
Race						
White	89	94	0.002	89	90	0.9
Black or African American	4.7	2.8		5.1	4.4	
Hispanic	4.5	1.7		3.6	3.8	
Other	1.3	1.9		1.7	1.1	
Health insurance status						
Medicare or Medicaid	73	66	0.001	65	55	0.01
Private	22	29		30	40	
Other	4.5	5.1		5.3	4.9	
Hypertension	85	84	0.4	78	79	0.7
Hyperlipidemia	74	72	0.3	69	65	0.3
Diabetes	31	24	0.002	26	25	0.8
COPD	17	14	0.1	17	13	0.2
Osteoporosis	14	13	0.5	14	10	0.2
Prior gastrointestinal bleeding	8.2	7.3	0.5	13	7.1	0.01
Cognitive impairment or dementia	2.5	3.8	0.09	3.7	1.7	0.1
Frailty	5.2	4.1	0.3	8.2	2.7	0.007
BMI, kg/m^2	29 (26 to 34)	29 (26 to 35)	0.3	28 (25 to 33)	30 (26 to 36)	0.0002
Hemoglobin, g/dL	13.5 (12.3 to 14.6)	13.7 (12.6 to 14.8)	0.004	13.4 (12.1 to 14.5)	13.7 (12.5 to 14.9)	0.03
Calculated creatinine clearance*, mL/min per 1.73 m^2	69 (50 to 94)	77 (55 to 101)	<0.0001	69 (48 to 99)	77 (59 to 107)	0.003

Values are presented as % or median (IQR). BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; OAC, oral anticoagulant.
*As calculated by the Cockcroft-Gault formula.

emerged,[14] the rates of dabigatran use may increase. It is noteworthy that patient preference triggered the switch from warfarin for one-third of the patients, reinforcing the importance of patient engagement in treatment decisions. This is also evidenced in the multivariable analysis, demonstrating patient-related characteristics, such as education level and age, closely related to the switch from warfarin to dabigatran. In contrast, characteristics of AF disease (eg, AF persistence, antiarrhythmic use) more closely correlated with de novo initiation of dabigatran.

Our data might seem to contrast those from Kirley et al, who used broad US administrative claims data to show a significant increase in use of dabigatran, for both AF and other indications.[6] They demonstrated an overall increase in dabigatran treatment from 3% to 19% of anticoagulation visits, but they also noted that in the last period of follow-up (late 2011), only 63% of these dabigatran prescriptions were for AF. Furthermore, it is not clear what proportion of those patients had new or recent diagnoses of AF (a minority of our cohort). Our cohort more specifically addresses the question of implementing dabigatran in a population of AF patients with a previously established care plan for the prevention of thromboembolism. While some providers advocate uniformly transitioning patients from warfarin to new anticoagulants, others are more hesitant and the prevailing strategy had been unclear. These results from ORBIT-AF demonstrate that most providers and patients have not been aggressive about adopting this new therapy but seem to reserve it for specific situations.

The appropriate level of penetrance for dabigatran use in AF patients is not clear. The early selection of lower-risk younger patients for this breakthrough therapy may reflect physician reaction to isolated case reports of serious hemorrhage and concerns regarding prescription of the

Table 5. Cardiovascular History

	Use of Warfarin at Baseline			No OAC at Baseline		
	Not Switched to Dabigatran (n=6122)	Switched to Dabigatran (n=532)	*P* Value	Not Switched to Dabigatran (n=1956)	Switched to Dabigatran (n=184)	*P* Value
Peripheral vascular disease	14	10.0	0.01	13	14	0.6
Coronary artery disease	34	22	<0.0001	33	26	0.03
Prior MI	17	8.5	<0.0001	18	13	0.08
Prior CABG	16	9.6	0.0001	15	10	0.1
Prior PCI	18	12	0.001	18	16	0.4
Heart Failure	35	26	<0.0001	27	18	0.01
Implanted cardiac device	30	22	0.0002	25	17	0.02
Significant valve disease	29	19	<0.0001	20	16	0.2
Moderate/severe mitral stenosis	1.9	0.6	0.03	0.7	0.5	0.8
Prior valve replacement	10.3	4.1	<0.0001	5.0	1.1	0.02
Mechanical Valve	4.4	0.6	<0.0001	1.0	0	0.2
Prior cerebrovascular events	17	14	0.06	13	9.2	0.1
Stroke (all cause)	9.7	7.9	0.2	7.0	4.9	0.3
Stroke—nonhemorrhagic	9.0	7.3	0.2	5.6	3.8	0.3
Stroke—hemorrhagic	0.6	0.6	0.98	1.3	1.1	0.8
Other intracranial bleeding	0.6	0.9	0.4	1.8	1.6	0.8
TIA	9.2	7.9	0.3	5.7	3.3	0.2
Cardiac medications						
β-Blocker	67	61	0.006	58	62	0.2
Nondihydropyridine calcium channel blocker	17	21	0.053	14	16	0.5
ACEI or ARB	54	56	0.2	45	41	0.3
Statin	57	55	0.3	51	52	0.8
LVEF, %	55 (50 to 60)	57 (50 to 64)	0.003	60 (53 to 64)	59 (53 to 65)	0.7
LA diameter, cm	4.5 (4.0 to 5.1)	4.5 (3.9 to 5.0)	0.09	4.2 (3.7 to 4.7)	4.3 (3.9 to 4.9)	0.09

Values are presented as % or median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft surgery; LA, left atrium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

higher dose for older patients. It may also reflect overall conservatism in new drug adoption respectful of the years of experience with warfarin and the significant toxicity that emerged in postmarketing surveillance with the previous generation of oral, direct-thrombin inhibitors.[15,16]

Initial descriptions of dabigatran uptake from administrative data in Denmark are consistent with ours. Sorensen et al demonstrated modest early use of dabigatran in patients with AF (5%), as well as significant deviations from recommended dosing practices.[17] Furthermore, they demonstrated the preferred use of dabigatran in younger patients, with less comorbidity. The risk-treatment paradox observed in our study and the Danish population highlights the reticence of providers to expose patients to the potential risk of a new anticoagulant, despite proved safety and efficacy. Of note, outcomes in Danish patients receiving dabigatran compared favorably with those of matched controls receiving warfarin.[18]

Older patients with AF represent a significant challenge in the management of stroke prevention, as the risks of both ischemic stroke and major hemorrhage (including intracranial hemorrhage) are increased.[19–22] One strategy proposed to mitigate this risk treatment paradox is the use of modified dosing of novel anticoagulants in older patients. Guidelines in both Canada and Europe suggest the use of the 110-mg dose of dabigatran for older individuals (≥80 years), even in the absence of renal dysfunction. In the United States, the Food and Drug Administration did not approve this dose, as it found no patient subgroup in which the benefit outweighed the risk.[4,7] However, a 75-mg twice-daily dose was approved for individuals with severe renal impairment (CrCl 15 to 30 mL/

Table 6. Atrial Fibrillation and Anticoagulation History

	Use of Warfarin at Baseline			No OAC at Baseline		
	Not Switched to Dabigatran (n=6122)	Switched to Dabigatran (n=532)	*P* Value	Not Switched to Dabigatran (n=1956)	Switched to Dabigatran (n=184)	*P* Value
AF type at baseline						
New onset	3.0	5.1	0.04	6.1	10	0.003
Paroxysmal	46	48		66	53	
Persistent	18	17		13	16	
Longstanding persistent	33	30		14	20	
Time from AF diagnosis >12 mo	85	78	<0.0001	78	76	0.5
Rhythm control treatment strategy reported	28	32	0.04	41	46	0.2
$CHADS_2$ score, mean (SD)	2.4 (1.3)	2.1 (1.2)	<0.0001	2.0 (1.4)	1.8 (1.1)	0.02
$CHADS_2$ score groups						
0	4.3	5.6	<0.0001	13	11	0.2
1	19	29		26	34	
≥2	77	65		61	54	
ATRIA Score, mean (SD)	2.8 (1.9)	2.5 (1.8)	0.0001	2.8 (2.1)	2.5 (1.9)	0.3
Prior cardioversion	32	35	0.2	22	30	0.02
Prior catheter ablation for AF	5.0	7.7	0.006	5.7	7.6	0.3
Prior antiarrhythmic therapy	44	51	0.004	48	54	0.1
Current antiarrhythmic therapy	26	31	0.01	35	43	0.03
Amiodarone	10.0	8.1	0.2	11	6.5	0.08
Dronedarone	3.8	7.0	0.0004	5.8	8.7	0.1
Sotalol	5.3	7.5	0.03	7.4	9.2	0.4
Flecainide	2.1	2.4	0.6	5.0	5.4	0.8
Propafenone	1.9	2.1	0.7	3.8	7.1	0.03
Dofetilide	1.9	3.0	0.08	1.8	1.6	0.8
Baseline antiplatelet therapy						
Aspirin	36	37	0.6	74	67	0.046
Clopidogrel	4.8	3.6	0.2	16	10	0.04
Anticoagulation clinic management at baseline	45	36	<0.0001	—	—	—
Relative or absolute contraindication to anticoagulation	4.7	3.4	0.2	40	26	0.0001
Treating provider specialty*						
Primary care provider	69	66	0.1	65	71	0.1
Cardiologist	81	82	0.6	77	82	0.1
Electrophysiologist	17	19	0.3	16	16	0.9
Neurologist	2.5	1.7	0.2	1.2	0	0.1

Values are presented as %, unless noted otherwise. AF indicates atrial fibrillation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; $CHADS_2$, estimated risk based on the presence of congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack; OAC, oral anticoagulation.
*Provider specialty is not mutually exclusive; each patient may have ≥1 specialists involved in the care of AF patients.

min per 1.73 m^2). Our data demonstrate that for 14% of patients aged ≥80 years (with preserved renal function), physicians are opting for the 75-mg twice-daily dose, possibly to offset bleeding risk. However, the sequelae of this dosing strategy are unknown. Notably, the prescribing information for the newest anticoagulant, apixaban, provides alternative

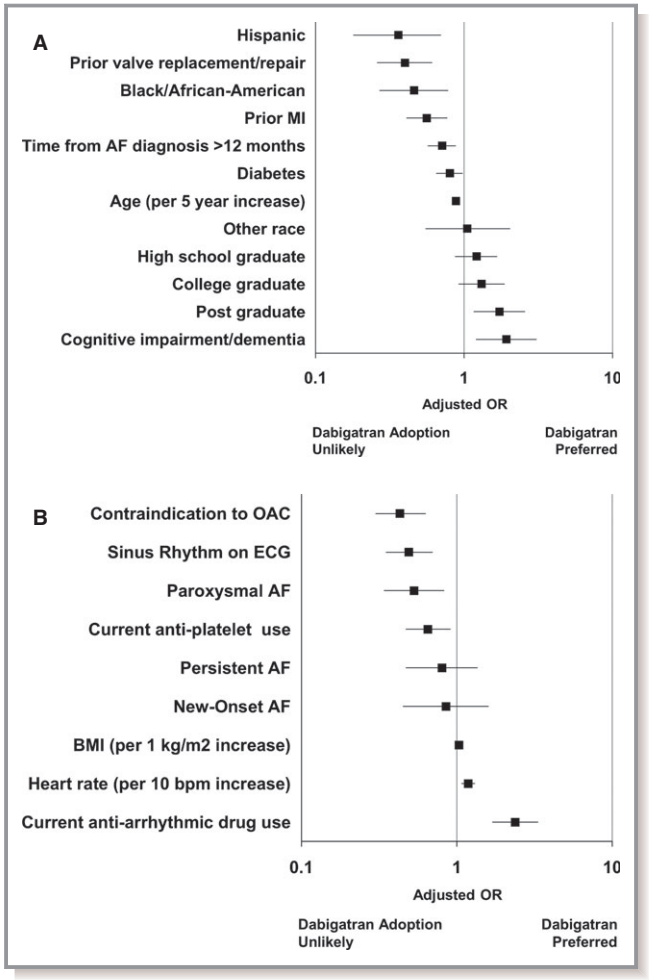

Figure 5. Factors significantly associated with adoption of dabigatran at follow-up in patients receiving warfarin at baseline (A, c-index=0.65) and in patients not using anticoagulation at baseline (B, c-index=0.71). Reference groups: Race (vs white), AF type (vs long-standing persistent), Education level (vs some school). AF indicates atrial fibrillation; BMI, body mass index; ECG, electrocardiogram; MI, myocardial infarction; OAC, oral anticoagulation.

dosing for elderly patients of low weight (with or without renal function impairment), based on the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[23,24] While preliminary data on dabigatran have failed to show a significant increased risk of bleeding with the US dosing regimen,[14] more detailed correlations among dose, age, and outcomes are needed to guide management.

Limitations

These data are derived from an observational cohort of patients in clinical practice participating in a voluntary registry and thus subject to the limitations inherent of such methods. Specifically, sampling and/or reporting bias may influence the results of dabigatran uptake. Data were acquired via chart review, and their accuracy is therefore dependent on completeness of initial documentation and thoroughness of subsequent abstraction. Additionally, factors associated with adoption of dabigatran cannot be interpreted as causal relationships for switching therapies, and residual measured and unmeasured confounding may account for some or all of these findings. Similarly, precise timing of dabigatran initiation, relative to interim events such as hospitalization, cannot be precisely ascertained; this also limits any causal inferences that can be made from these data. Last, the collection period of the registry overlapped with the approval of dabigatran in October 2010, thus capturing an early phase of adoption following approval. This could have a significant impact on the rate of uptake observed in our study.

Conclusions

A modest number of US patients with AF have adopted the use of dabigatran. A significant proportion of these transitions appear to be driven by the patients. Patients receiving dabigatran were younger, had less comorbidity, and were at lower risk of stroke and bleeding compared with those not treated with dabigatran. They are often prescribed doses of dabigatran that are not consistent with their renal function. These findings of modest update of dabigatran coupled with selection of lower-risk AF patients suggest that there has been an initially conservative approach to the use of this new therapy in clinical practice.

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