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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%, \(P<0.001\)), 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 \(\geq 75\) 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, \(P<0.001\)).

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.

Clinical Trial Registration—URL: Clinicaltrials.gov. Unique identifier: NCT01165710. (J Am Heart Assoc. 2013;2:e000535 doi: 10.1161/JAHA.113.000535)

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 \(\approx 1\)% annually, depending on the population treated.\(^2\) However, warfarin has significant shortcomings, particularly its narrow therapeutic window, need for

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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

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-
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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 \( \chi^2 \) 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 \( \geq 1 \) follow-up visit but not necessarily full follow-up.

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-site 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 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 \( \geq 60 \) days before baseline, with \( \geq 2 \) INR values measured before baseline. Overall, 5315 patients (89% of those on warfarin at baseline for \( \geq 60 \) days) had \( \geq 2 \) 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
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 9,974 patients from 176 sites. Of these, 1,217 (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/m²             | 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 m² | 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.
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 \(\geq 75\) 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, 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%
received 150 mg twice daily). Of patients aged ≥80 years with CrCl >30 mL/min per 1.73 m² (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

| 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* |
| CHADS₂ score, mean (SD)                                | 2.3 (1.3) | 2.0 (1.2) | 2.3 (1.3) | <0.0001* |
| CHADS₂ 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* |
| Flecaïnide                                             | 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; CHADS₂, 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.
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risk (n\textsuperscript{adhere to and/or monitor warfarin (n\textsuperscript{}}

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75). Addition of TTR at baseline contributed minimally to the

38 to 73) versus 60% among patients not switched (IQR 42 to

In patients receiving warfarin at baseline, median TTR at

Sensitivity Analyses

In patients receiving warfarin at baseline, median TTR at

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 cardiovas-
cular disease. A significant proportion (56%) of patients with
severe kidney disease did not receive adjusted-dose dabiga-
tran, 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,\textsuperscript{5} patients treated
with dabigatran in our study were at lower risk of stroke,
according to CHADS\textsubscript{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, transition-
ing 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 nonintra-
cranial bleeding among individuals aged \(\geq 75\) years, compared
with warfarin. As more methodologically rigorous data have

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\textsuperscript{2}. CrCl indicates creatinine clearance calculated by the
Cockcroft-Gault formula.\textsuperscript{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 hospital-
ization 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 discrimi-
native 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 dabiga-
tran 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.
emerged, 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. 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 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/m² | 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 m² | 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.
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/
Our data demonstrate that for 14% of patients aged \( \geq 80 \) 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

| 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 | |
| \(\geq 2\) | 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 | 0.22 | 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 | 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 \( \geq 75 \) years, diabetes mellitus, and prior stroke or transient ischemic attack; OAC, oral anticoagulation.

*Provider specialty is not mutually exclusive; each patient may have \( \geq 1 \) specialists involved in the care of AF patients.
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. 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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