ABSTRACT

Objectives: Our primary objective was to determine the prevalence of novel anticoagulant use in patients with atrial fibrillation (AF) and venous thromboembolic disease (VTE) in a large multispecialty ambulatory practice.

Study Design: Retrospective cross-sectional study.

Methods: Our study included 5632 patients who had at least 1 outpatient provider visit and were actively being treated with an anticoagulant from April 2012 through March 2013. The primary outcome was the difference in proportion of patients receiving warfarin compared with a novel agent as of March 2013.

Results: Warfarin was an active medication for 83% of patients, while a novel agent was active for 17% of patients. Use of novel anticoagulants was higher among patients with AF compared with those with other indications for anticoagulation (24% of patients with AF were prescribed a novel, 3% of those with VTE, 5% with both conditions, 8% with other indications; P <.001). When adjusting for potential confounders, predictors of novel anticoagulant use among those with AF included younger age (odds ratio [OR]: 0.97 per 1-year increase in age; 95% CI, 0.96-0.97), higher risk of stroke (OR: 1.74; 95% CI, 1.27-2.37), and being seen in counties with lower poverty rates (OR: 0.94; 95% CI, 0.92-0.96).

Conclusions: Despite the availability of novel agents, warfarin remained the dominant anticoagulant prescribed for patients with AF and VTE in a large ambulatory practice. Further work is needed to examine the appropriateness of novel anticoagulant use and methods for optimizing the risks, benefits, and accessibility to therapy with regard to the prevention and treatment of thrombosis.


Prescribing Patterns of Novel Anticoagulants Within a Statewide Multispecialty Practice

Leigh E. Efird, PharmD, MPH; Jessica Chasler, PharmD; G. Caleb Alexander, MD, MS; and Maura McGuire, MD

or more than 50 years, warfarin was the sole oral anticoagulant in the United States. Although it is an effective agent for the prevention and treatment of thromboembolism, it interacts with many drugs and foods and requires close monitoring to prevent complications. Novel anticoagulants, including both direct thrombin inhibitors and Factor Xa inhibitors, entered the prescription drug market in 2010 as alternative agents to warfarin for the treatment and prevention of thrombosis in patients with nonvalvular atrial fibrillation (AF). These agents have a rapid onset of action, are prescribed in a fixed dosing regimen, do not require frequent monitoring, and have fewer drug-drug and drug-food interactions compared with warfarin. In clinical trials, they have equal or superior efficacy compared with warfarin while maintaining similar or lower rates of bleeding.

Despite these benefits, these agents are not without risks and come at a considerably greater drug acquisition cost. Their precise role in the pharmacotherapy of thromboembolism has yet to be well defined. Recently, several concerns about these agents have emerged, including warnings against use for patients with mechanical valves, and the potential utility of monitoring drug levels to improve the safety of these agents has been discussed.

While much is known about the benefits and risks of these novel anticoagulants, less information is available regarding how frequently these agents are prescribed in clinical practice. One investigation using IMS Health’s National Disease and Therapeutic Index data showed an increase in the use of dabigatran for AF from 4% to 17% from the last quarter of 2010 to the end of 2011 in the United States. Another study from a similar time period found that 12% of patients with AF were treated with dabigatran.

We sought to add to the literature by reporting on anticoagulant use for all indications in patients seen within a large ambulatory practice in Maryland. We hypothesized that warfarin would continue to be the most prevalent oral anticoagulant prescribed, as opposed to newer agents, for patients receiving care at this practice site. We performed specific
Patients who were prescribed novel agents for atrial fibrillation were more likely to be younger, to have higher stroke risk, and to be seen in counties with lower poverty rates.

In patients newly started on an anticoagulant, primary care provider prescribing of these newer agents appeared to be increasing.

In patients switching therapy from the previous year, patients with venous thromboembolism tended to be switched more commonly from warfarin to rivaroxaban.

analysis on a subset of patients with nonvalvular AF as a population with a consistent indication for novel agents over the study period.

METHODS
Setting
We included patients from a large, academically affiliated multispecialty ambulatory practice (MAP) in the study. At the time of this study, the MAP cared for 250,000 patients in 35 primary care practices (staffed by approximately 180 primary care providers) and 2 cardiology practices (staffed by 12 cardiologists). We were able to extract data from 24 primary care and both cardiology sites. These sites served diverse patient populations including residents of inner cities, rural counties, and the affluent suburbs of Washington, DC; they are located across the District of Columbia and 13 Maryland counties. Twelve of the primary care practices and both cardiology practices had established anticoagulation clinics, and all practices used the same algorithms and integrated electronic medical record (EMR)."11

Patients
We included patients who had at least 1 office visit, either a provider visit or a provider support visit (ie, nurse-managed anticoagulation clinic visit), to practice sites within the MAP between April 1, 2012, and April 3, 2013, and had warfarin, dabigatran, or rivaroxaban on their active drug list during the study period. EMR. We excluded patients seen at specialty sites for obstetrics and gynecology and for surgical care, because it is unlikely that these providers were managing patients’ anticoagulation therapy. Data abstracted from the EMR included the last active oral anticoagulant on the medication list during the study period; date of birth; sex; practice site; and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

ICD-9-CM codes were grouped into categories to identify major indications (AF, thromboembolic disease, antiphospholipid syndrome, or a valvular heart condition) as well as medical conditions used for the calculation of the risk-scale score known as CHADS2 (an acronym for Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke). 12

From the EMR, we extracted the total numbers of office visits, provider support visits, and whole-blood and point-of-care international normalized ratio (INR) values by the patient during the study time frame, and if the patient was also taking aspirin. In order to better characterize changes in anticoagulant prescribing over time, we created a comparison group by collecting similar information from the year prior to our study period, including the last active anticoagulant agent on the medication list during that year. A patient was considered to have switched anticoagulant therapy if the active drug from the previous year differed from the active drug during the study period. We grouped practice sites by their county of location, and assigned poverty rates based on US Census Bureau data for Maryland’s counties from 2009-2011.13 We also classified counties as urban or rural based on US Census Bureau data. The study was approved by the Johns Hopkins Institutional Review Board.

Statistical Analysis
We used descriptive statistics to determine baseline patient characteristics and proportions throughout the analysis. We first used $\chi^2$ tests and Wilcoxon rank sum tests to examine the bivariate association among patient (age, sex, CHADS2 score, heart failure, hypertension, diabetes, stroke history, aspirin use, number of INR values), provider (number of provider office visits), and practice (urban vs rural setting, poverty rate in the county, cardiology vs general medicine site) characteristics, and our outcome of interest. Next, we performed bivariate and multivariate analyses to examine predictors of novel oral anticoagulant use, focusing solely on individuals with AF only, given that this represented 61% of all study subjects and that all of the agents examined were FDA approved for this indication during the study period. Model fit was determined by stepwise model selection. The 2-sided a priori level of significance was 0.05 for all analyses. Analyses were conducted using STATA 13 (StataCorp LP, College Station, TX).

RESULTS
Participants
A total of 5632 patients were included in the study. The mean age of eligible patients was 70 years (SD 15),
56% were male, 61% had AF only, 16% had venous thromboembolic disease (VTE) only, 4% had both AF and VTE, and 19% had other indications for anticoagulation (Table 1). Warfarin was an active medication for 4675 (83%) patients, while a novel agent was active for 957 (17%) patients. Of the 3424 patients with only AF, 76% were prescribed warfarin, compared with 24% prescribed a novel anticoagulant. In 881 patients with only VTE, 3% were treated with novel anticoagulants, while 12 (1%) patients with both AF and VTE were treated with these newer agents.

**Table 1. Baseline Demographics**

| Characteristic       | Overall  (n = 5632) | Warfarin (n = 4675) | Novel anticoagulant (n = 957) | P value*
|----------------------|---------------------|---------------------|-----------------------------|-----
| Age, years: mean (SD)| 69.7 (14.7)         | 69.2 (15.2)         | 71.9 (11.2)                 | .001
| Female sex: n (%)    | 2496 (44.3)         | 2121 (45.4)         | 375 (39.2)                  | <.001
| Indication: n (%)    |                     |                     |                             |     
| Atrial fibrillation (AF) | 3424 (60.8)         | 2597 (55.6)         | 827 (86.4)                  |     
| Venous thromboembolic disease (VTE) | 881 (15.6)         | 885 (18.3)         | 26 (2.7)                    |     
| Both AF and VTE      | 238 (4.2)           | 226 (4.8)           | 12 (1.3)                    |     
| Other                | 1089 (19.3)         | 997 (21.3)          | 92 (9.6)                    |     
| Aspirin use: n (%)   | 794 (14.1)          | 636 (13.6)          | 158 (16.5)                  | .02  

*P value indicates statistical difference in the characteristic between the warfarin and novel anticoagulant groups.

**Bivariate Predictors of Novel Oral Anticoagulant Use in Patients with Only Atrial Fibrillation**

For those with AF, there were statistically significant differences in all baseline characteristics except for sex, history of stroke, and aspirin use between those receiving warfarin and those receiving novel agents (Table 2). The majority of patients had a CHADS2 score of 2 or 3 (63% for warfarin and 61% for novels). Those with the lowest stroke risk (CHADS2 score of 0 or 1) were more likely to receive a novel agent (22% for novels compared with 18% for warfarin), while those at highest risk (CHADS2 of 4-6) were more likely to receive warfarin (20% for warfarin vs 17% for novels; overall P value .02). The 2 cardiology practices accounted for 45% of patients on a novel anticoagulant, while the other patients on novel agents were distributed across the 24 general medicine practices. Those receiving a novel agent tended to reside in a county with a lower poverty rate (mean rate 8.2%; SD 3.9), compared with those receiving warfarin (mean rate 9.8%; SD 6.0).

**Multivariate Predictors of Novel Oral Anticoagulant Use in Patients with Atrial Fibrillation**

Based on the multivariate model (Table 3), the odds of being prescribed a novel oral anticoagulant decreased by 3% for each additional year in age (odds ratio [OR]: 0.97; 95% CI, 0.96-0.97) when controlling for confounders. Those carrying a diagnosis of heart failure had 46% lower odds of being prescribed a novel agent (OR: 0.54; 95% CI, 0.45-0.64). The odds of being prescribed a novel anticoagulant increased 44% (OR: 1.44; 95% CI, 1.14-1.82) for those with a moderate-risk CHADS2 score compared with a low-risk score, while those with a high-risk score had 74% higher odds (OR: 1.74; 95% CI, 1.27-2.37) of receiving a novel agent. The odds for novel agent use decreased by 6% (OR: 0.94; 95% CI, 0.92-0.96) for every 1% increase in the poverty rate by county of practice site.

**Switching Among Novel Oral Anticoagulants and Warfarin in the Overall Population**

There were 3906 patients within the ambulatory practice actively receiving an anticoagulant during the April 2012-to-March 2013 time frame who had also received an anticoagulant in the previous year. In this subset of patients, there was no significant change in the overall numbers being treated with warfarin versus a novel anticoagulant, with therapeutic changes occurring in relatively few patients. Between study periods, 11 (0.3%) patients were switched from warfarin to dabigatran, 17 (0.4%) from warfarin to rivaroxaban, 23 (0.6%) from dabigatran to warfarin, and 16 (0.4%) from dabigatran to rivaroxaban. More than 90% of patients who switched from warfarin to dabigatran, dabigatran to warfarin, or dabigatran to rivaroxaban only had AF as an indication for anticoagulation, whereas patients switching from warfarin to rivaroxaban had a higher incidence of VTE (29%). In those with AF who did not switch therapy, 82% were prescribed warfarin while 18% were prescribed a novel anticoagulant.

**All Patients Initiating Anticoagulation Therapy in 2013**

There were 1726 patients in the overall study population who did not have an anticoagulant on their medication list in the previous year and appeared to be newly started on anticoagulation. Of these patients, 1284 (74%) were prescribed warfarin, 240 (14%) dabigatran, and 202 (12%) rivaroxaban. Compared with the overall study population, novel anticoagulant use increased by 9% in 2013, leading to a reduction in warfarin prescribing (P <.001). Among these patients newly started on novel agents, 44% were managed by cardiologists and 56% by primary care providers (P <.05).
When comparing across indications for all new starts, 80% of novel prescribing was for patients with only AF, 4% for patients with VTE, 1% for patients with both conditions, and 15% for patients with indications other than AF or VTE ($P < .001$). Dabigatran was initiated more frequently than rivaroxaban in those with only AF (22% vs 16%, respectively) while rivaroxaban was more commonly initiated compared with dabigatran in those with a VTE indication (5% vs 1%, respectively). Warfarin continued to be initiated in 85% of patients with indications for anticoagulation other than AF and VTE; 8% of these patients were prescribed rivaroxaban, while 7% were prescribed dabigatran. Primary care providers initiated novel anticoagulants for 36% of their new patients with only AF, while cardiologists initiated these agents in 41% of similar new patients ($P = .09$).

**DISCUSSION**

This retrospective cross-sectional study reviewed oral anticoagulant use among 5647 patients who were seen at a large multispecialty practice in Maryland from April 2012 through March 2013, and it helps to shed light on the uptake of these agents in primary and specialty care settings.

We found that for patients with AF, 23% were treated with novel anticoagulants, compared with 6% for patients with indications other than AF. These rates may be a result of the timing of use approval for these medications in comparison with our study period. Dabigatran was approved for use in nonvalvular AF in 2010 and in VTE in 2014, while rivaroxaban was approved for use in nonvalvular AF in 2011 and in VTE in 2012. While lower rates of use in VTE are therefore not surprising, limited data exist on the prevalence of novel anticoagulant use for this indication in the ambulatory setting.

After adjustment for potentially confounding covariates, novel anticoagulant use for AF was greater among younger individuals and those seen in counties with lower poverty rates, while lower prescribing of novel agents was seen in patients with heart failure and diabetes. Comparable results were reported by Desai and colleagues in a commercial population, which showed that patients prescribed novel agents tended to be male and younger, to have fewer comorbidities, and to live in areas with higher incomes.$^{14}$ Unlike the Desai study, our report is based on a more diverse population, as our statewide cohort included the uninsured as well as patients with Medicare, Medicaid, and commercial insurance. The Desai study reported an increase in initiation of novels over time in patients with AF. While it was difficult for us to assess trends in use of these agents over time due to the cross-sectional nature of our study, we did see significantly more patients with new anticoagulation initiated on novel agents if they had AF, versus other indications, in 2013.$^{14}$

By utilizing data from the year prior to our study period, we were able to capture limited information on patients who switched therapy. The majority of switching between warfarin and dabigatran, or dabigatran and rivaroxaban, occurred in patients with AF, while we observed more patients with VTE switching from warfarin to rivaroxaban. Overall, few patients switched therapy from one year to the next. This is not necessarily unexpected; studies have shown a mitigated reduction in stroke risk, as well as negligible cost-benefit ratio, when patients with a stable INR are compared with patients treated with dabigatran.$^{15}$ Additionally,

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### Table 2. Bivariate Predictors of Anticoagulant Treatment for Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Warfarin (n = 2597)</th>
<th>Novel Anticoagulant (n = 827)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (SD)</td>
<td>74.6 (11.0)</td>
<td>71.7 (10.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1080 (41.6)</td>
<td>320 (38.7)</td>
<td>.14</td>
</tr>
<tr>
<td>CHADS2 score for patients with AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (0-1)</td>
<td>458 (17.6)</td>
<td>180 (21.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Moderate risk (2-3)</td>
<td>1632 (62.8)</td>
<td>504 (60.9)</td>
<td></td>
</tr>
<tr>
<td>High risk (4-6)</td>
<td>507 (19.5)</td>
<td>143 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1172 (45.1)</td>
<td>258 (31.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1862 (71.7)</td>
<td>617 (74.6)</td>
<td>.10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>654 (25.2)</td>
<td>165 (20.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>431 (16.6)</td>
<td>146 (17.7)</td>
<td>.48</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>424 (16.3)</td>
<td>134 (16.2)</td>
<td>.93</td>
</tr>
<tr>
<td>Total number of INR values collected: mean (SD)</td>
<td>2.5 (5.5)</td>
<td>0 (0.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of provider visits: mean (SD)</td>
<td>4.1 (3.1)</td>
<td>3.8 (2.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Urban practice site location</td>
<td>2186 (84.2)</td>
<td>656 (79.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Poverty rate in county of practice site: mean (SD)</td>
<td>9.8 (6.0)</td>
<td>8.2 (3.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Practice site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>1043 (40.2)</td>
<td>369 (44.6)</td>
<td>.02</td>
</tr>
<tr>
<td>General medicine</td>
<td>1554 (59.8)</td>
<td>458 (55.4)</td>
<td></td>
</tr>
</tbody>
</table>

CHADS2 indicates risk scale for Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke; INR, international normalized ratio.

*Except where otherwise specified.
patients on warfarin in our study popula-
tion are generally followed in clinics
staffed by nurses, who are unable to
prescribe medications and therefore un-
able to independently initiate a switch
in therapy. Of those patients who did
switch therapy, we did not observe a
consistent trend toward use of novel
agents. Changes in therapy from dabi-
gatran may reflect changing indications
during this time, as well as availability
of newer agents with daily, rather than
twice daily, dosing, which facilitates ad-
herence to therapy.6,8

We noted a trend toward increasing
use of novel agents in a subset of
1726 patients who had anticoagulants
newly added to their medication lists
during the study period. In this subset
of patients, warfarin remained the most
commonly prescribed anticoagulant agent; however, in
those patients with AF, novel anticoagulant use was signifi-
cantly higher compared with those with other indications
for anticoagulant therapy. There was a near doubling of
the use of novel agents in newly initiated patients with AF,
compared with those patients who continued therapy from
the previous year. This trend indicates an uptake in pre-
scribing of these agents for newly diagnosed AF patients
and a continued use of warfarin in those patients who have
been on therapy over time, which may be expected. With
2 newly FDA-approved novel agents on the market since
our study period, we would expect this trend to continue
to increase over time for patients with both AF and VTE,
as each of these agents offers recommendations for use in
special populations.

**Limitations**

Our study has several limitations. First, many baseline
characteristics were statistically different between patients
on novel anticoagulants versus those on warfarin, and this
may reflect a selection bias in our study population. We
were limited in the information we were able to abstract
from the EMR, and we lacked the cross-section of pharma-
cy claims available in other studies that used administra-
tive data; however, the EMR also presented an advantage
in that clinician-verified data were used in the analysis.
Characteristics that were not measured in our study popu-
lation that may have also influenced choice of therapy
include a history of falls, history of major bleeding, renal
or hepatic dysfunction, patient preference, or provider
comfort with prescribing these different anticoagulant
agents. We also were not able to collect prescription in-
urance information: Higher medication copays, lack of
insurance, or a requirement for prior authorization may
have deterred the use of newer agents for some patients,
which was not assessed in our study population. Finally,
the number of available agents and indications changed
during the study period, making the analysis of clinically
appropriate therapies more complex. Rivaroxaban gained
approval for VTE during our study time period while the
other novel agents have been approved for this indica-
tion since conclusion of our study. Therefore, use of these
agents for VTE was not expected to be high and our data
for this indication should be viewed as limited.

**CONCLUSIONS**

A significant proportion of patients seen at a large am-
bulatory practice in Maryland and the District of Columbia
were prescribed warfarin rather than a novel anticoagulant
for the prevention and treatment of several thromboem-
bolic conditions. Novel anticoagulants were used more
commonly in patients with atrial fibrillation compared with
those with other indications for anticoagulation, although
less than a quarter of patients in the overall study popula-
tion with AF received novel therapies. Our study provides
further insight into how these agents have been adopted
into practice; further studies should be performed to assess
the appropriateness of anticoagulant choice, especially in
female, urban, and poor populations in light of available
data related to the efficacy and safety of newer agents.

**Table 3. Multivariate Analysis of Patient Factors Predicting Use of Novel Agents Compared with Warfarin for Patients with Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Multivariate Logistic Regression</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.97 (0.96-0.97)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male compared with female</td>
<td>1.0 (0.85-1.19)</td>
<td>.97</td>
</tr>
<tr>
<td>CHADS2 score, scale 0-6*</td>
<td>1.44 (1.14-1.82)</td>
<td>.002</td>
</tr>
<tr>
<td>Moderate compared with low risk</td>
<td>1.74 (1.27-2.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart failure diagnosis compared with no heart failure diagnosis</td>
<td>0.54 (0.45-0.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes diagnosis compared with no diabetes diagnosis</td>
<td>0.69 (0.56-0.86)</td>
<td>.001</td>
</tr>
<tr>
<td>County of practice site</td>
<td>1.09 (1.05-1.12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rural compared with urban practice site</td>
<td>0.98 (0.76-1.26)</td>
<td>.86</td>
</tr>
<tr>
<td>Poverty rate in county of practice site</td>
<td>0.94 (0.92-0.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiology compared with general medicine practice site</td>
<td>0.87 (0.69-1.10)</td>
<td>.25</td>
</tr>
<tr>
<td>Total provider office visits</td>
<td>0.99 (0.96-1.02)</td>
<td>.50</td>
</tr>
</tbody>
</table>

*Outcome of interest: prescribing of a novel anticoagulant versus warfarin.
*CHADS2 score categories: low risk score 0-1, moderate risk score 2-3, high risk score 4-6.
CHADS2 indicates risk scale for Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke; INR, international normalized ratio; OR, odds ratio.
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REFERENCES
7. Cohen D. Dabigatran: how the drug company withheld important analyses. BMJ. 2014;349:g4670. doi: 10.1136/bmj.g4670.