CLINICAL RESEARCH STUDY

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Bleeding Rates in Veterans Affairs Patients with Atrial Fibrillation Who Switch from Warfarin to Dabigatran

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ABSTRACT

OBJECTIVES: Clinical trial data suggest that dabigatran and warfarin have similar rates of major bleeding but higher rates of gastrointestinal bleeding. These findings have not been evaluated outside of a clinical trial. We evaluated the relative risks of any, gastrointestinal, intracranial, and other bleeding for Veterans Affairs patients who switched to dabigatran after at least 6 months on warfarin, compared with patients who continued on warfarin.

METHODS: We used national Veterans Affairs administrative encounter and pharmacy data from fiscal years 2010-2012 to identify 85,344 patients with atrial fibrillation who had been taking warfarin for at least 180 days before June 2011, of whom 1394 (1.7%) received dabigatran (150 mg) during the next 15 months. Dates of the first occurrence of each type of bleed and dates of death from June 2011 to September 2012 were determined. Baseline and time-dependent patient characteristics were identified, including comorbid conditions, stroke and bleeding risk scores, and time in therapeutic range for international normalized ratios. Marginal structural models were used to address selection bias in the longitudinal observational data. Weighted logistic regression models were fit using generalized estimating equations and reflected baseline and time-dependent covariates and weekly indicators of anticoagulant type (warfarin or dabigatran).

RESULTS: Compared with patients who never used dabigatran, patients who used dabigatran at least once were younger, were more likely to be white, had lower international normalized ratio time in therapeutic range on warfarin, had lower stroke risk scores, and had similar bleeding risk scores. Overall, 10,734 patients experienced bleeding events, including 131 events after dabigatran use. The risk-adjusted rate of any bleeding was higher with dabigatran compared with warfarin, which was largely driven by a 54% higher risk of gastrointestinal bleeding with dabigatran. Rates of intracranial, other bleeding, and death were similar for dabigatran and warfarin.

CONCLUSIONS: Dabigatran may increase the likelihood of gastrointestinal bleeds.

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KEYWORDS: Anticoagulation; Antithrombotic; Atrial fibrillation; Stroke

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Atrial fibrillation is the most common sustained arrhythmia affecting approximately 1% of the population and is associated with an increased risk of stroke.[1] Anticoagulation therapy is the cornerstone of stroke prophylaxis in atrial fibrillation. Until recently, warfarin has been the only available oral anticoagulant.[2] Warfarin is relatively inexpensive, and its use in preventing stroke is supported by more than 3 decades of research. However, a narrow pharmacokinetic profile and multiple food and drug interactions make anticoagulation by warfarin challenging. Patients taking warfarin must have their blood monitored regularly by the international normalized ratio (INR) to ensure therapeutic anticoagulation levels. INR values that are too high (>3) suggest excessive bleeding risk, whereas INR values that are too low (<2) suggest inadequate stroke prevention.

CLINICAL SIGNIFICANCE

- Clinical trial data showed that dabigatran has similar overall bleeding rates but higher gastrointestinal bleeding rates compared with warfarin. Little data are available outside clinical trials.
- By using a cohort of veterans with atrial fibrillation who switched to dabigatran after at least 6 months on warfarin, we determined that dabigatran increased the risk of gastrointestinal hemorrhage by 54% and was not associated with rates of other bleeding or death.

In October 2010, the US Food and Drug Administration (FDA) approved dabigatran (Pradaxa, Boehringer Ingelheim, Ingelheim, Germany), the first alternative to warfarin for stroke prevention in atrial fibrillation. Dabigatran has a more predictable anticoagulation response than warfarin and may be recommended for patients who are unable to maintain stable INR values on warfarin.[3] In addition, some patients may prefer dabigatran over warfarin to avoid diet restrictions and the inconvenience of frequent monitoring. Clinical trial data demonstrated similar rates of major bleeding for dabigatran and warfarin in patients with and without prior warfarin experience, but higher rates of gastrointestinal bleeding.[4-6] However, those data reflect experiences of carefully selected patients and may not reflect prescribing patterns in real-world clinical settings.

To date, warfarin remains the dominant anticoagulant for stroke prevention in the Veterans Affairs (VA) Health System. Nevertheless, many patients receiving warfarin may experience better outcomes with dabigatran, although the risks associated with dabigatran are relatively unknown. This study uses administrative encounter, pharmacy, and laboratory data from the VA to investigate the relative risk of any bleeding, gastrointestinal bleeding, intracranial bleeding, and death with dabigatran versus warfarin among patients who switched to dabigatran after at least 6 months of warfarin use. The study uses marginal structural logistic regression models, which address potential bias in time-to-event studies when a time-dependent covariate is a risk factor for the event and predicts subsequent exposure. For example, INR values for warfarin users may confound the relative likelihood of bleeding in patients who switch to dabigatran, because INR stability affects the likelihood that physicians recommend dabigatran and is also associated with bleeding. An important advantage of performing this research in the VA is the availability of INR values for patients receiving warfarin.

METHODS

Patients

Patients with atrial fibrillation who had been taking warfarin for at least 180 days before June 2011, with the most recent fill date within 90 days before June 2011, were identified in VA National Pharmacy Data. Patients without a diagnosis of atrial fibrillation (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 427.31) as identified on VA inpatient and outpatient encounter data during the 12 months before June 2011 were excluded, as were patients with a glomerular filtration rate <30 mL/min/1.73 m^2 during the prior 12 months (based on National Laboratory Extracts) or with a prosthetic heart valve (based on ICD-9-CM diagnosis and procedure codes from the prior 12 months) because dabigatran use is not appropriate for patients with severe renal disease or valvular atrial fibrillation. The final sample included 85,344 total patients, of whom 1394 (1.7%) switched from warfarin to dabigatran (150 mg) by September 30, 2012.

To estimate the marginal structural models, a separate record was created for each week that each patient was observed from June 1, 2011, until the outcome of interest occurred or the patient was censored. **Figure 1** provides a summary of each step in the dataset creation process. The final sample for analysis of any bleeding event included 46,786 weeks of dabigatran use and 5,214,364 weeks of warfarin use. Outcomes, censoring events, and patient characteristics are described in greater detail in the following section.

Measures

Outcomes. Dates of death were identified in VA enrollment files. Bleeding events, including gastrointestinal, intracranial, and other hemorrhage, were defined using ICD-9-CM codes validated previously[7] and used in previous studies of anticoagulation.[8-10] For each patient, the first occurrence of each type of bleeding event after June 1, 2011, was identified using the primary diagnoses on inpatient and outpatient VA encounter claims. Indicator variables for each type of bleed and each week were set to "1" in weeks with a given bleeding event and "0" otherwise. Patients who did not have a given bleeding event were censored on

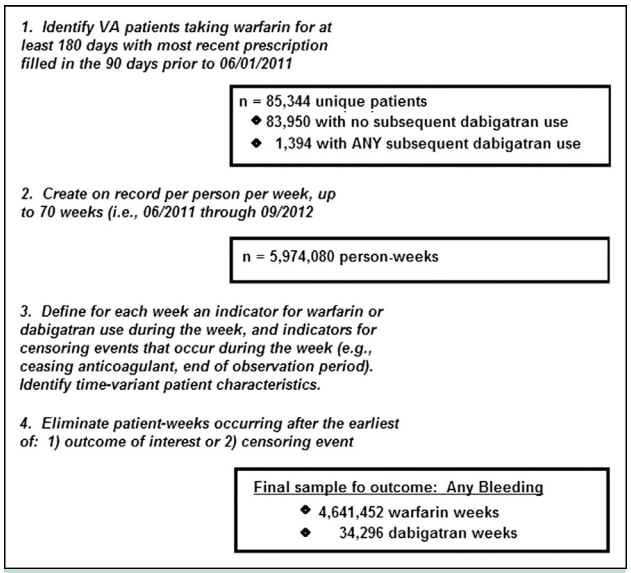

Figure 1 VA patient dataset creation for use in marginal structural models. VA = Veterans Affairs.

September 30, 2012, or on the date of death if before September 30, 2012.

Anticoagulant Use. For each week, a single variable indicated whether the patient was using dabigatran as of the start of the week (ie, indicator variable set to "1") or remained on warfarin (indicator variable set to "0"). The use of dabigatran or warfarin was identified for each week using the fill dates and days of medication supplied from the VA National Pharmacy Data. When new dabigatran prescriptions were identified, we assumed that the patient ceased warfarin and started dabigatran on the date of the first dabigatran fill. Patients who switched from warfarin to dabigatran were censored on the day their dabigatran supply ran out if there was a gap in dabigatran that was more than twice the number of days of medication supplied, whether or not they subsequently returned to warfarin use. Likewise, patients who stopped taking warfarin without initiating dabigatran were censored when their warfarin supply ran out.

Patient Characteristics. Patient characteristics at baseline were derived from VA inpatient and outpatient encounter data during the 12 months before June 2011. Characteristics included history of VA service use (eg, cardiology visits, primary care visits, inpatient admissions), comorbid conditions as defined by Quan et al,[11] and additional conditions relevant to atrial fibrillation, including bleeding history,[9] prior stroke,[12] cardiomyopathy, and the presence of a prior implantable cardiac device. Laboratory INR values during the 6 months before June 2011 were identified in VA National Laboratory Data, and time in the therapeutic range was calculated using the method of Rosendaal et al.[13] Other laboratory values included a measure of renal function (defined as the mean creatinine glomerular filtration rate) and liver function (defined as mean alanine transaminase) during the 6 months before June 2011. (For multivariable models, laboratory values were categorized and included a category representing patients missing values for a given measure.) A stroke risk score was calculated on the basis of the presence of Congestive heart failure, Hypertension, Age>75, Diabetes, and Stroke ($CHADS^2$).[12] The $CHADS^2$ score ranges from 0 to 6, with higher scores indicating greater risk of stroke. A bleeding risk score was calculated on the basis of the presence of Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio, Elderly age [>65 years], and Drug/alcohol concomitant use (HAS-BLED), with higher scores indicating a higher risk of a bleeding event.[14] Finally, baseline warfarin adherence was calculated as the proportion of days covered during the 180 days before June 2011.[15]

Time-varying covariates represented patients' comorbid conditions and laboratory values during the 90 days before the start of each week. Time-varying covariates were determined using definitions similar to baseline covariates but were calculated using VA encounter data during the 90 days before the start of each follow-up week.

Analysis

We used marginal structural models to determine the odds of any bleeding, gastrointestinal hemorrhage, intracranial hemorrhage, other hemorrhage, or death for patients taking dabigatran relative to warfarin. Marginal structural models reduce bias by weighting the contribution of each patient during a given week by "stabilized" weights, where stabilized weights reflect both baseline and time-varying patient covariates. By using the approach of Hernan et al,[16] 2 sets of weights were calculated for each patient-week: one reflecting patient covariates that affect anticoagulant selection and the other reflecting characteristics that affect censoring events. Weighting observations effectively creates, for each week, a pseudo-population in whom patient covariates are no longer related to dabigatran use or censoring. With the use of the weights, the relationship between dabigatran use and each outcome was determined using separate weighted pooled logistic regression models for each outcome. Models were estimated using generalized estimating equations and robust standard errors.

Three sets of sensitivity analyses were generated for each outcome. First, because bleeding events that are recorded on outpatient visits may be relatively minor, we also defined bleeding episodes using inpatient claims only (as a proxy for severe bleeds). Second, rather than censoring patients who died in analysis of bleeding events, we defined a composite outcome as bleeding or death. Finally, in contrast to our primary analysis in which patients were censored on the day their medication supply ran out, we used an "intent-to-treat" approach. That is, we assumed that patients continued dabigatran (if they switched to dabigatran) or warfarin (if they did not switch) even when the days of medication

supplied was insufficient for 100% medication compliance. For each sensitivity analysis, stabilized weights were recalculated and weighted pooled logistic regression models were generated. SAS version 9.3 (SAS Institute Inc, Cary, NC) was used for all analyses. This study was approved by the institutional review board of the Iowa City VA Medical Center.

RESULTS

Characteristics of patients who did and did not switch from warfarin to dabigatran at any time over the observation period are shown in Table 1. Patients who initiated dabigatran use were more likely to be aged less than 75 years, to be white, and to live farther from the nearest VA medical center. They had slightly lower $CHADS^2$ stroke risk scores but slightly higher HAS-BLED bleeding risk scores. They also had lower time in INR therapeutic range and slightly lower warfarin adherence at baseline. Patients initiating dabigatran had more cardiac disease at baseline, including higher proportions with cardiomyopathy, heart failure, prior myocardial infarction, prior cardiac device, other dysrhythmia, and previous inpatient admissions for atrial fibrillation.

Overall, 10,734 patients experienced any bleeding event, including 131 that occurred during weeks of dabigatran use (Table 2). Gastrointestinal hemorrhage comprised the majority of bleeding events, with 5890 gastrointestinal bleeds, including 88 during weeks of dabigatran use. In addition, 6941 patients died during the observation period, including 49 who died during weeks of dabigatran use. When bleeding events were defined using inpatient episodes only, we identified 4971 bleeding events, of which 54 occurred during dabigatran use. The majority (80%) of inpatient bleeding episodes were gastrointestinal hemorrhages.

In unadjusted analyses, the odds of any bleeding event were 36% higher ($P < .001$) with dabigatran use and the odds of gastrointestinal hemorrhage were 71% higher ($P < .001$). In weighted logistic regression models, the relative odds were 1.27 ($P < .001$) and 1.54 ($P < .001$) for any bleeding and gastrointestinal hemorrhage, respectively. Dabigatran use was not significantly associated with intracranial bleeding or other hemorrhage. Dabigatran use was associated with a significantly lower odds of death in unadjusted analysis, but this difference was eliminated after controlling for patient characteristics (Table 3).

In sensitivity analysis using an intent-to-treat approach, gastrointestinal hemorrhage was still significantly more likely during weeks of dabigatran use compared with warfarin use (odds ratio [OR], 1.57; $P < .001$). When outcomes were defined as a composite representing bleeding or death, the odds of gastrointestinal hemorrhage or death for dabigatran relative to warfarin were 1.29 (1.04-1.61; $P = .021$). Finally, there were no significant differences in bleeding rates using inpatient claims only (Table 4).

DISCUSSION

With the use of national data from the VA health system, this study investigated bleeding rates in patients with atrial fibrillation who switched from warfarin to dabigatran. Not surprisingly, patients who switched to dabigatran were more likely to have a history of labile INR while taking warfarin. They were also somewhat younger but appeared to have more advanced heart disease. We found that the use of dabigatran increases the risk of hemorrhage among patients with atrial fibrillation, with this increase largely attributed to an increase in the likelihood of gastrointestinal hemorrhage. This finding persisted in several sensitivity analyses, although it was not found for the most severe bleeds that require inpatient admission. Dabigatran initiation was not associated with rates of intracranial or other bleeding, although the number of these events was small. There was also no association between death and dabigatran after controlling for differences in the characteristics of patients who did and did not switch to dabigatran.

To our knowledge, this is the first study to investigate bleeding rates in real-world settings for patients who switch from warfarin to dabigatran. The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) clinical trial, which was the basis for FDA approval, found higher rates of gastrointestinal hemorrhage for patients taking dabigatran (150 mg) compared with warfarin, with a relative risk of 1.56 for anticoagulant-naïve patients and 1.42 for patients with prior warfarin experience.[4,6] Likewise, a subsequent meta-analysis[17] found a 52% higher risk of gastrointestinal hemorrhage for patients taking dabigatran for atrial fibrillation. However, a postmarketing analysis of data from the FDA's Mini-Sentinel program found a lower risk of gastrointestinal hemorrhage in patients taking dabigatran.[18] As in our study, that analysis relied on observational data, although it did not address possible confounding.

This study also demonstrates the use of marginal structural models as an emerging statistical technique for comparative effectiveness research using observational data. An important drawback to conducting comparative effectiveness research with observational data is the potential for confounding due to nonrandom assignment of treatment. In the current study, patients may switch to dabigatran for a variety of clinical reasons or patient preferences, thereby introducing potential for confounding if treatment assignment is related to outcomes. The use of marginal structural models attempts to create a "pseudo-population" in whom patients who receive dabigatran or warfarin have similar observed patient characteristics, thereby mimicking randomization. This approach is effective at addressing confounding to the extent that unobserved patient characteristics are also similar in the pseudo-population.

Study Limitations

First, the study has low power because of the relatively few patients who switched to dabigatran during our

Table 1 Baseline Characteristics of Patients Who Did and Did Not Initiate Dabigatran Use During Observation Period (June 1, 2011)

	Patients Who Never Initiated Dabigatran Use	Patients Initiating Dabigatran Use	*P* Value
No. of New AF Episodes	N = 83,950	1394 (1.7%)	
Patient Age			
<55 y	2044 (2.5%)	53 (3.8%)	<.001
55-<65 y	13,004 (15.8%)	366 (26.3%)	
65-<75 y	24,398 (30.0%)	547 (39.2%)	
75-<85 y	27,519 (33.3%)	338 (24.2%)	
≥85 y	15,591 (18.9%)	90 (6.5%)	
Mean age in years (SD)	74.4 (10.1)	69.7 (9.0)	<.001
Female, No. (%)	1158 (1.4%)	20 (1.4%)	.92
Race			
White, No. (%)	64,790 (78.5%)	1142 (81.9%)	.002
Black,No. (%)	6059 (7.3%)	78 (5.6%)	
Other nonwhite, No. (%)	3833 (4.6%)	54 (3.9%)	
Missing race	7874 (9.5%)	120 (8.6%)	
Distance to Nearest VA Medical Center			
<10 miles	18,884 (22.9%)	298 (21.4%)	<.001
10-<30 miles	23,380 (28.3%)	373 (26.8%)	
30-<60 miles	20,819 (25.2%)	320 (23.0%)	
60-<120 miles	16,156 (20.0%)	379 (27.2%)	
≥120 miles	3257 (3.9%)	84 (6.0%)	
$CHADS^2$ Score			
0	4038 (4.9%)	91 (6.5%)	<.001
1	17,487 (21.2%)	331 (23.8%)	
2	31,031 (37.6%)	516 (37.0%)	
3	20,766 (25.2%)	337 (24.2%)	
4	6863 (8.3%)	81 (5.8%)	
5-6	2471 (3.0%)	38 (2.7%)	
Mean (SD)	2.21 (1.12)	2.08 (1.12)	<.001
HAS-BLED			
0-1	12,766 (15.5%)	110 (7.9%)	.04
2	30,168 (36.6%)	477 (34.2%)	
3	24,110 (29.2%)	370 (26.5%)	
4 +	15,629 (18.9%)	317 (22.7%)	
Mean (SD)	2.63 (1.18)	2.67 (1.23)	.14
INR Time in Therapeutic Range			
0%-30%	6348 (7.7%)	189 (13.6%)	<.001
<30%-50%	15,028 (18.2%)	330 (23.7%)	
>50%-80%	37,660 (45.6%)	589 (42.2%)	
>80%	17,440 (21.1%)	190 (13.6%)	
No INR recorded	6080 (7.4%)	96 (6.9%)	
Mean (SD) INR	0.57 (0.27)	0.51 (0.26)	<.001
Warfarin Proportion Days Covered Prior 6 Mo			
<0.30	5137 (6.2%)	139 (10.0%)	<.001
0.30-<0.60	11,170 (13.5%)	164 (11.8%)	
0.60-<0.90	18,370 (22.3%)	284 (20.4%)	
≥0.90	47,879 (58.0%)	807 (57.9%)	
Heart Disease in Prior 12 Mo			
Cardiomyopathy	8471 (10.3%)	193 (13.9%)	<.001
Other dysrhythmia	12,663 (15.3%)	285 (20.5%)	<.001
Heart failure	2458 (29.8%)	475 (34.1%)	<.001
Rheumatic/ other valve disorder	7225 (8.8%)	102 (7.3%)	.03
Prior MI	3663 (4.4%)	81 (5.8%)	.014
Prior cardiac device	12,097 (14.7%)	231 (16.6%)	.045
Any prior inpatient admission for AF	4390 (5.3%)	160 (11.5%)	<.001
Key Laboratory Values (Based on Mean Value in Prior 12 Mo)			
Kidney function (GFR mL/min/ 1.73 m^2)			
Normal GFR or mild disease (GFR ≥60)	43,083 (52.2%)	904 (64.9%)	<.001
Moderate (GFR 30-59)	25,726 (31.2%)	326 (23.4%)	
Missing	13,747 (16.7%)	164 (11.8%)	
Liver function (ALT)			
Normal (10-40 U/L)	69,346 (84.0%)	994 (71.3%)	<.001
Abnormal (<10 or >40 U/L)	11,916 (14.4%)	275 (19.7%)	
Missing	10,300 (12.5%)	125 (9.0%)	

AF = atrial fibrillation; ALT = alanine transaminase; $CHADS^2$ = Congestive heart failure, Hypertension, Age>75, Diabetes, and Stroke; GFR = glomerular filtration rate; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio, Elderly age [>65 years], and Drug/alcohol concomitant use; INR = international normalized ratio; MI = myocardial infarction; SD = standard deviation; VA = Veterans Affairs.

observation period. Thus, our ability to detect significant differences for rare outcomes, such as intracranial bleeding or bleeds requiring inpatient admission, was limited. Second, our assessment of bleeding history and outcomes depends on the accuracy of the ICD-9-CM diagnosis codes. However, the algorithm we used to define bleeding events has been validated. We were not able to assess the severity of bleeding events, and some events recorded in outpatient clinic visits may be of minor clinical relevance. Third, findings based on the VA patient population may not generalize to the entire country. The majority of VA patients are men, and VA patients typically have more chronic conditions compared with other

Table 2 Any Bleeding, Gastrointestinal Hemorrhage, Intracranial Hemorrhage, or Death per 52 Person-Weeks

	Inpatient or Outpatient Events	
	Dabigatran	Warfarin
Any Bleeding		
No. of person-wk before any first hemorrhage or censoring	46,786	5,214,364
No. of patients with any bleeding event	131	10,603
No. patients with any bleeding event per 52 person-wk	0.146	0.106
Gastrointestinal Hemorrhage		
No. of person-wk before first GI hemorrhage or censoring	49,470	5,391,105
No. of patients with GI hemorrhage	88	5802
No. of patients with GI hemorrhage per 52 person-wk	0.093	0.056
Intracranial Hemorrhage		
No. of person-wk before first cranial hemorrhage or censoring	52,804	5,585,317
No. of patients with intracranial hemorrhage	4	349
No. of patients with intracranial hemorrhage per 52 person-wk	0.004	0.003
Hemorrhage—Other Site		
No. of person-wk before first other hemorrhage or censoring	50,148	5,415,530
No. of patients with hemorrhage—other site	46	5085
No. of patients with hemorrhage (other site) per 52 person-wk	0.048	0.049
Death		
No. of person-wk before death or censoring	53,010	5,597,015
No. of patients who died	49	6892
No. of patient deaths per 52 person-wk	0.048	0.064

GI = gastrointestinal.

populations,[19] including conditions that are associated with poor time in therapeutic INR range.[20] Moreover, the availability of dabigatran within individual VA facilities may be subject to restrictions. Nevertheless, a key advantage of conducting this research in the VA is the availability of INR laboratory values for veterans who receive warfarin through VA pharmacies. Finally, some VA patients also may receive health services, including pharmaceuticals, in the private sector. Therefore, it is possible that some patients who were treated as censored in our study because of medication termination actually started receiving anticoagulants outside the VA. It is also possible that bleeding episodes may have occurred outside the VA. This might be particularly true for serious bleeding events that required treatment at the nearest facility, which is often not a VA facility. However, this would affect our conclusions only if bleeding episodes associated with dabigatran were more (or less) likely to be seen outside the VA compared with episodes associated with warfarin. We conducted additional analysis in which patients were stratified by the distance to the nearest VA medical center (as a proxy for likelihood of using a VA facility) and found similar results. For example, the relative likelihood of gastrointestinal hemorrhage was consistently higher among patients living 60 miles or more from a VA medical center (OR, 1.70; $P = .01$) versus less than 60 miles from a VA medical center (OR, 1.52; $P < .01$).

CONCLUSIONS

As of 2010, it was estimated that approximately 2.7 million individuals in the United States have atrial fibrillation, and just more than half of those receive warfarin therapy.[21] The introduction of new anticoagulants in recent years provides alternatives to warfarin for the first time in decades for individuals with nonvalvular atrial fibrillation. Because of the low cost and the paucity of information about novel oral anticoagulants outside of clinical trials, physicians are likely to continue recommending warfarin as a first-line oral anticoagulation. Nevertheless, many patients may experience better quality of life with dabigatran, and physicians must weigh the

Table 3 Risk-Adjusted Relative Odds of Any Bleeding Event, Gastrointestinal Hemorrhage, Intracranial Hemorrhage, or Other Hemorrhage During Weeks of Dabigatran Use Relative to Weeks of Warfarin Use

	Odds Ratio (95% CI; *P* Value)	
	Unadjusted	Adjusted for Baseline and Time-Varying Patient Characteristics
Outpatient or Inpatient Bleeding Episodes		
Any bleeding	1.36 (1.12-1.65; $P = .002$)	1.27 (1.03-1.56; $P = .02$)
GI hemorrhage	1.71 (1.36-2.16; $P < .001$)	1.54 (1.20-1.97; $P < .001$)
Intracranial hemorrhage	0.91 (0.23-3.63; $P = .90$)	0.86 (0.21-3.53; $P = .84$)
Other site hemorrhage	0.95 (0.68-1.31; $P = .73$)	0.97 (0.68-1.39; $P = .88$)
Death	0.75 (0.56-0.99; $P = .04$)	0.76 (0.49-1.17; $P = .20$)

CI = confidence interval; GI = gastrointestinal.

Table 4 Risk-Adjusted Results in Sensitivity Analysis Using an Intent-to-Treat Approach, Including Death in Composite Outcome or Inpatient Bleeding Episodes Only

	Intent-to-Treat Analysis	Composite Outcome Includes Death	Inpatient Bleeding Episodes Only
Any hemorrhage	1.40 (1.15-1.70; $P < .001$)	1.19 (0.98-1.43; $P = .07$)	1.17 (0.87-1.58; $P = .30$)
GI hemorrhage	1.57 (1.25-1.98; $P < .001$)	1.29 (1.04-1.61; $P = .022$)	1.28 (0.93-1.75; $P = .13$)
Intracranial	1.18 (0.41-3.42; $P = .76$)	0.86 (0.58-1.30; $P = .48$)	*
Other	1.01 (0.73-1.40; $P = .93$)	0.94 (0.72-1.24; $P = .67$)	0.99 (0.49-2.00; $P = .95$)

GI = gastrointestinal.
*There were no inpatient intracranial bleeding events associated with dabigatran in VA hospitals and 167 events associated with warfarin.

relative risks of bleeding, stroke, and other outcomes in light of the patient's clinical conditions and preferences. Our results suggest that the decision to recommend dabigatran requires careful evaluation of patient characteristics that may increase the likelihood of gastrointestinal bleeding. Adverse events may be reduced by educating patients about the effects and half-life of dabigatran, the importance of adhering to the dosing regimen, and the early signs of potential hemorrhage.

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