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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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