Comparison of the Incidence of Major Bleeding With Rivaroxaban Use Among Nonvalvular Atrial Fibrillation Patients With Versus Without Diabetes Mellitus

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Diabetes mellitus (DM) is a common co-morbidity in those with nonvalvular atrial fibrillation (NVAF). Most patients with DM and NVAF have a CHA_2DS_2-VASc score of ≥1 and should be considered for oral anticoagulation therapy for stroke prevention per treatment guidelines. The most important risk associated with anticoagulation is bleeding, which may be higher in those with NVAF plus DM. Our objective was to evaluate the incidence and characteristics of major bleeding (MB) in rivaroxaban users diagnosed with NVAF, further comparing those with DM versus those without DM, in a real-world clinical setting. Electronic medical records of >10 million patients from the Department of Defense Military Health System were queried to identify rivaroxaban users with NVAF over a 2.5-year period. Major bleeding–related hospitalization was identified by a validated case-finding algorithm. Patient characteristics, incidence and management of MB, and fatal outcomes were assessed by DM status. Of 44,793 rivaroxaban users with NVAF, 12,039 (26.9%) had DM, who were more likely men, younger, with more co-morbidity and higher CHA_2DS_2-VASc scores. Major bleeding incidence was higher among those with DM compared with those without, 3.68 (95% confidence interval [CI] 3.37 to 4.03) versus 2.51 (95% CI 2.34 to 2.69) per 100 person-years, and intracranial bleeding incidence was 0.19 (95% CI 0.13 to 0.28) versus 0.25 (95% CI 0.20 to 0.31) per 100 person-years. Fatal outcomes were rare for both cohorts, 0.09 per 100 person-years. In conclusion, in this post-marketing study of 44,793 rivaroxaban users with NVAF, patients with DM had more co-morbidities and higher incidence of MB compared with those without DM. © 2016 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). **(Am J Cardiol 2017;119:753–759)**

Rivaroxaban is a direct oral anticoagulant with a rapid onset of administration and has been Food and Drug Administration approved for multiple indications, including for reduction of risk of stroke and systemic embolism in patients with NVAF. The present study objective was to evaluate the incidence, management, and outcomes of major bleeding (MB) in patients with NVAF receiving rivaroxaban, comparing patients with versus without diabetes mellitus (DM).

Methods

This retrospective observational study used electronic medical records (EMRs) from the US Department of Defense (DoD) health care database. The DoD Military Health System (MHS) covers active and retired military service members and their families and is one of the largest electronic cradle-to-grave health care systems in the United States with nearly 10 million active beneficiaries.[1] The MHS contains longitudinal EMRs that are continually updated and comprised inhospital services, outpatient visits, and clinical/medical and pharmacy data. The MHS is not linked with data from the Veterans Affairs (VA). The MHS and the VA are separate entities and provide care through health care systems predominantly exclusive of one another; therefore, this study does not contain data from the VA patient population.

The patients in this study are insured through the MHS, although they are not required to use military medical facilities for care. Many patients use TRICARE, the insurance arm of the DoD, to obtain care in non-military

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See page 758 for disclosure information.

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(civilian) facilities. Regardless of whether care takes place in a military or civilian facility, all claims and related clinical information for each encounter are captured in the DoD MHS databases.[2]

The 2.5-year observational period for this study was January 1, 2013, to June 30, 2015, and the study population comprised patients with a diagnosis of NVAF who were taking rivaroxaban. Study subjects were identified using relevant *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis and procedure codes and Common Procedure Terminology/Healthcare Common Procedure Coding System procedure codes listed in any available procedure field within any medical encounter record. Eligible subjects were identified by searching care that was delivered in both military and civilian facilities, across all settings (inpatient, outpatient, emergency departments, etc.) within the MHS.

All patients meeting the definition for NVAF were included in the study, regardless of incident or prevalent rivaroxaban use, as long as the patient was identified as having NVAF before or concurrent with rivaroxaban use. Data were collected on NVAF rivaroxaban users with and without DM. The diagnosis of DM was defined as the presence of diagnosis code 250.xx within 6 months before the bleeding date for MB cases and end of study participation for patients without MB. Data regarding rivaroxaban exposure were also collected, including dose at time of bleeding and duration of rivaroxaban exposure. Medication data were collected using prescription dispensing information from the date of medication initiation. Rivaroxaban use was compared between patients with and without DM.

Demographic and baseline characteristic data were collected on all participants. Baseline characteristics included age, gender, DM status, and co-morbid conditions of interest, including cardiovascular conditions and history of bleeding. All co-morbid conditions were collected by querying the EMRs for the relevant diagnosis codes. CHA_2SD_2-VASc and modified HAS-BLED (no INR values included) scores were calculated for each patient. Patient characteristics were compared between those with and without DM.

The primary outcome of interest was MB, as defined by the Cunningham algorithm,[3] a validated method that uses administrative data for identification of MB events that result in a hospitalization. The algorithm identifies MB events from a primary discharge diagnosis using *ICD-9-CM* diagnosis and *ICD-9-CM*/Common Procedure Terminology procedure codes. Identification of MB events was differentiated by bleeding site: gastrointestinal bleeding, intracranial bleeds, and bleeding at other sites. The use of bleeding diagnoses showed a positive predictive value of 89% to 99% in Cunningham's validation study, and this algorithm has been used in other clinical studies to identify serious bleeding events.[4–9]

Major bleeding events were included in our analyses if they occurred during rivaroxaban exposure plus 7 days post-discontinuation. Patients were evaluated for MB throughout the study period until censored at the earliest occurrence of any of the following events: an MB event, death, loss of MHS eligibility, or end of study. Fatal outcomes, defined as deaths occurring during MB-related hospitalizations, were also evaluated. For patients who experienced an MB event, additional data points were collected on inpatient MB management.

Baseline patient characteristics were evaluated between patients whom developed an MB versus who did not and further stratified by DM status. Means and SD were reported for continuous variables, whereas frequencies were reported for categorical variables. Differences in categorical variables were tested with the chi-square tests, and differences in continuous variables were tested with *t* tests, although no a priori hypothesis testing was planned. Given the large sample size of the study, any differences observed based on statistical testing should be interpreted within the proper context (e.g., clinical importance).

Major bleeding incidences, patient characteristics, medication use, MB management, and patient outcomes were evaluated by DM status. The incidences for MB and fatal outcomes were calculated using a person-time approach: the number of patients with a first episode of MB divided by the rivaroxaban exposure time at risk, presented per 100 person-years. Incidences are reported with 95% confidence intervals (CIs). All analyses were performed using SAS, v9.4 (SAS Institute Inc., Cary, North Carolina).

This Post-marketing Safety Surveillance study was funded by Janssen Scientific Affairs, LLC, and Bayer HealthCare. Health ResearchTx conducted the analyses. The research data were derived from an approved Naval Medical Center, Portsmouth, VA IRB protocol, and the research was conducted in compliance with federal and state laws, including the Health Insurance Portability and Accountability Act of 1996.

Results

We identified 44,793 rivaroxaban users with NVAF, of which 12,039 (26.9%) had DM.

Regardless of bleeding status, those with DM were more likely men, younger, and had more co-morbidities and higher CHA_2DS_2-VASc scores (Table 1). Patients with DM appeared to have more co-morbid conditions and more frequent use of baseline medications compared with those without DM (Table 1). Across the overall NVAF cohort, the most common co-morbidities were hypertension, coronary heart disease, and heart failure. Those with DM who experienced MB had the highest prevalence of these conditions, 94.5%, 59.5%, and 46.8%, respectively (Table 2). In fact, patients who experienced MB tended to have more co-morbidities regardless of DM status (Table 2).

In the DM group that experienced MB, a higher proportion of subjects (35.8%) were prescribed the 15-mg dose compared with the dosing distribution in the other groups. The approved labeling for rivaroxaban recommends a dose of 15 mg daily for patients with CrCl 15 to 50 ml/min, suggesting that these subjects may have had some degree of renal impairment.

Major bleeding incidence was higher among those with DM compared with those without DM, 3.68 (95% CI 3.37 to 4.03) versus 2.51 per 100 person-years (95% CI 2.34 to 2.69), respectively. With regard to bleeding site, rates were highest for bleeding of gastrointestinal origin regardless of DM