Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban

Sally Tamayo, MD; W. Frank Peacock, MD; Manesh Patel, MD; Nicholas Sicignano, MPH; Kathleen P. Hopf, MPH; Larry E. Fields, MD, MBA; Troy Sarich, PhD; Shujian Wu, MD, PhD; Daniel Yannicelli, MD; Zhong Yuan, MD, PhD

Department of Cardiology (Tamayo), Naval Medical Center, Portsmouth, Virginia; Department of Emergency Medicine (Peacock), Baylor College of Medicine, Houston, Texas; Department of Cardiology (Patel), Duke University Health System and Duke Clinical Research Institute, Durham, North Carolina; Department of Clinical Epidemiology (Sicignano, Hopf), Health ResearchTx, Trevose, Pennsylvania; Department of US Medical Affairs (Fields, Yannicelli), Janssen Scientific Affairs, LLC, Raritan, New Jersey; Department of Real World Evidence (Sarich), Janssen Scientific Affairs, LLC, Titusville, New Jersey; Department of Global Medical Organization (Wu), Janssen Research and Development, LLC, Raritan, New Jersey; Department of Epidemiology (Yuan), Janssen Research and Development, LLC, Titusville, New Jersey

Background: In nonvalvular atrial fibrillation (NVAF), rivaroxaban is used to prevent stroke and systemic embolism.

Objective: To evaluate major bleeding (MB) in NVAF patients treated with rivaroxaban in a real-world clinical setting.

Methods: From January 1, 2013, to March 31, 2014, US Department of Defense electronic health care records were queried to describe MB rates and demographics. Major bleeding was identified using a validated algorithm.

Results: Of 27 467 patients receiving rivaroxaban, 496 MB events occurred in 478 patients, an incidence of 2.86 per 100 person-years (95% confidence interval: 2.61-3.13). The MB patients were older, mean (SD) age of 78.4 (7.7) vs 75.7 (9.7) years, compared with non-MB patients. Patients with MB had higher rates of hypertension (95.6% vs 75.8%), coronary artery disease (64.2% vs 36.7%), heart failure (48.5% vs 23.7%), and renal disease (38.7% vs 16.7%). Of MB patients, 63.2% were taking 20 mg, 32.2% 15 mg, and 4.6% 10 mg of rivaroxaban. Four percent of MB patients took warfarin within the prior 30 days. Major bleeding was most commonly gastrointestinal (88.5%) or intracranial (7.5%). Although 46.7% of MB patients received a transfusion, none had sufficient evidence of receiving any type of clotting factor. Fourteen died during their MB hospitalization, yielding a fatal bleeding incidence rate of 0.08 per 100 person-years (95% confidence interval: 0.05-0.14). Mean age at death was 82.4 years.

Conclusions: In this large observational study, the MB rate was generally consistent with the registration trial results, and fatal bleeds were rare.
**Introduction**

Atrial fibrillation (AF), the most common clinically significant cardiac arrhythmia, with an estimated lifetime risk of 22% to 26%, confers a 5-fold risk of stroke. Vitamin K antagonists (eg, warfarin) have been a standard prophylactic therapy in reducing the risk of stroke in patients with AF for several decades. Although warfarin is highly effective, there are a number of challenges associated with its use, including drug-drug interactions, drug-food interactions, and the requirement for frequent monitoring and dose titration to achieve and maintain an optimal therapeutic international normalized ratio of 2.0 to 3.0. Such challenges, coupled with the typically severe consequences of thrombotic events, have led to the research, discovery, and development of new oral anticoagulants for patients with AF and other thrombosis-related conditions.

Rivaroxaban (Xarelto) is a novel direct factor Xa inhibitor oral anticoagulant approved by the US Food and Drug Administration (FDA) in 2011 for prophylaxis of deep vein thrombosis following hip or knee replacement surgery, and to reduce the risk of stroke and systemic embolism in patients who have nonvalvular atrial fibrillation (NVAF). As with all anticoagulants, a frequently reported adverse event with rivaroxaban in the registration trial was bleeding. Though the majority of bleeding events might be considered minor from a clinical perspective (eg, dermal ecchymoses and superficial hematomas), severe bleeding events have been observed. The reported rates of rivaroxaban-associated major bleeding (MB) were 0.3% in patients with total hip replacement/total knee replacement (THR/TKR) procedures in the pooled Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) trials and 3.6 per 100 person-years in patients with NVAF in the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial. The question remains regarding the bleeding risk in rivaroxaban patients with THR/TKR and NVAF treated in real-world clinical settings.

To gain further knowledge and insight regarding MB with rivaroxaban in the postapproval setting in the United States, a 5-year observational, post-marketing safety surveillance study was initiated, using fully integrated electronic medical records (EMRs). The study protocol, including the ascertainment method of MB events, was reviewed and approved by the FDA prior to its finalization. The objective of this ongoing observational study is to provide longitudinal safety data by actively obtaining information associated with MB among rivaroxaban users with NVAF or undergoing THR and/or TKR procedures in the postapproval setting, complementary to the clinical-trial data and that being collected by the spontaneous adverse event reporting process. This current report describes patients with NVAF who received rivaroxaban therapy; the results for the hip/knee replacement surgery (orthopedic) cohort will be reported separately.

**Methods**

**Patient Population and Data Source**

This analysis used US Department of Defense (DoD) EMRs, which served as the sole data source for this study. The observational period for this report was January 1, 2013, to March 31, 2014, and only patients with confirmed NVAF were included. The DoD Military Health System (MHS) exclusively covers military service members and their families and has one of the largest health systems in the United States, with nearly 10 million patients (51% males and 49% females). The MHS is not linked with the data streams from Veterans Affairs (VA); this study population does not contain data from the VA patient population.

The MHS population has relatively high representation from the elderly population. Patients age ≥65 years make up 21% of the MHS population, as compared with 13% of the total US population. The MHS databases consist of longitudinal EMRs that are continually updated and contain administrative, pharmacy, laboratory, and clinical data. Inpatient and outpatient data are integrated, which ensures robust capture of MB events along with associated pharmacy data. Because the DoD health care system is paperless, all patient-level medical information and clinical data are kept in one electronic format. Incoming records are checked against a set of minimum standards for quality to ensure the integrity of the data. Incoming records are verified to be constructed in a standardized format respective to the data source, and all data elements are inspected for acceptable formats and to be void of improbable values. Duplicate records are identified in the background processing of each dataset, and any secondary record deemed an exact duplicate is removed.

The patients in this study were insured through the MHS; however, they are not required to use military medical facilities. Many patients use their MHS coverage to obtain care in civilian facilities. If a rivaroxaban user experienced a MB and was hospitalized anywhere, the claim and related clinical information were routed back to the DoD MHS databases and therefore were captured in this study.

Patients with NVAF were identified via relevant International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes and Common Procedure Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) procedure codes that were listed in any available procedure field within any medical encounter record. This encompassed all MHS inpatient and outpatient care delivered within a military or civilian facility. All patients meeting the definition for NVAF were included in the study, regardless of incident or prevalent rivaroxaban usage, as long as the patient was identified as having NVAF prior to or concurrent with rivaroxaban usage. The NVAF definition was based on ≥1 medical encounters with an AF diagnosis plus the absence of valvular exclusion criteria.

**Rivaroxaban Exposure and Bleed Event Identification**

Adherence and potential gaps in therapy were assessed by compiling all consecutive dispensings of rivaroxaban into a single timeline of exposure. Because subsequent refills...
are often dispensed to the patient early, the timeline was extended by the respective number of days to account for this phenomenon.

The drug-exposure period for patients was captured from the date of rivaroxaban therapy initiation until its discontinuation. Discontinuation was defined as meeting either of 2 criteria: a therapeutic switch identified via a subsequent dispensing of an alternative oral anticoagulant or a gap of ≥30 days from the end of a rivaroxaban dispensing period without a subsequent refill. The distinction between temporary and permanent discontinuation cannot be made using this database; therefore, subsequent resumption of rivaroxaban was allowed. Major bleeding events were included in this analysis if they occurred anytime during rivaroxaban exposure +7 days post-discontinuation.

Major bleeding events among rivaroxaban users were identified within the cohorts via prespecified periodic querying of the EMR data. A previously validated computer database definition developed by Cunningham et al, for identification of MB events that result in a hospitalization, was used for this study.10 This algorithm employed a systematic approach to identify MB events using ICD-9-CM diagnosis and ICD-9-CM/CPT procedure codes. Per the algorithm, bleeding events determined to be trauma-related were excluded. Major bleeding within this analysis was defined by the Cunningham algorithm, which identifies bleeding-related hospitalizations from a primary discharge diagnosis. The use of bleeding diagnoses has shown a positive predictive value of 89% to 99% in Cunningham’s validation study.10 and this method has been used in other clinical studies to identify serious bleeding events.11 The types of serious bleeding events considered included gastrointestinal (GI) bleeding, hemorrhagic strokes and other intracranial bleeds, genitourinary bleeding, and bleeding at other sites.10 Additional data were collected on fatal outcomes, surgical interventions, and transfusions. Although the Cunningham algorithm is comprehensive and well-designed, the definition for MB is not an exact match with the clinical trial (ROCKET-AP), because the algorithm is applied retrospectively and relies on the information available in the EMRs. As a comparison, the clinical-trial definition of MB was defined as clinically overt bleeding associated with a fall in hemoglobin of ≥2 g/dL, or a transfusion of ≥2 units of packed red blood cells or whole blood, or MB in a critical site, or a fatal outcome.

Statistical Analysis
Descriptive statistics have been produced using SAS version 9.2 (SAS Institute, Inc., Cary, NC) to quantify characteristics of the study cohort including data on demographics and other patient characteristics, comorbid conditions, concomitant medications, rivaroxaban usage, hospitalization and treatment data, bleed characteristics, and outcomes. Both CHADS212 (congestive heart failure; hypertension; age ≥75 years; diabetes mellitus; and prior stroke, transient ischemic attack, or thromboembolism) and CHA2DS2-VASc13 (CHADS2 + vascular disease, age 65–74 years, and sex category) scores were calculated to further characterize the study population. No a priori hypothesis testing was planned or performed.

Because the cohort denominator was also available, event rates with 95% confidence intervals (CIs) are reported. The incidence rate of MB was calculated using a person-time approach: the number of patients with a first episode of MB divided by the 100 person-years exposure time at risk. Secondary MB events in patients experiencing multiple bleeds were not included in the incidence-rate calculation.

This post-marketing safety surveillance study is funded by Janssen Scientific Affairs, LLC and Bayer HealthCare. Health ResearchTx conducted the study analyses. The research data are derived from an approved Naval Medical Center, Portsmouth, VA, institutional review board protocol and the research was conducted in compliance with federal and state laws, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Results
Major Bleeding Incidence
Overall, 27 467 rivaroxaban users with NVAF were identified during the period of January 1, 2013, to March 31, 2014. Four hundred ninety-six MB events among 478 patients were identified, representing an incidence rate of 2.86 per 100 person-years (95% CI: 2.61-3.13) within the 15-month time period, based on a patient’s first MB event. The incidence rate was 2.68 (95% CI: 2.37-3.04) and 2.99 (95% CI: 2.63-3.41) for males and females, respectively.

Patient Characteristics
Patients with MB were older, with a mean (SD) age of 78.4 (7.7) vs 75.7 (9.7) years, for those without MB (Table 1). Because the database contained limited data on smoking, alcohol, race, and body mass index, these variables are not presented.

There was a general pattern that comorbidities were more prevalent in the MB cohort as compared with the non-MB group. The most commonly observed comorbidities included hypertension (95.6% vs 75.8%), coronary heart disease (64.2% vs 36.7%), heart failure (48.5% vs 23.7%), and renal disease (38.7% vs 16.7%) in those with MB vs no MB, respectively.

The CHADS2 and CHA2DS2-VASc scores were calculated to assess stroke risk among the study cohort patients. The mean (SD) CHADS2 score among the MB patients was 3.0 (1.2), compared with 2.2 (1.3) in the non-MB cohort, whereas the mean (SD) CHA2DS2-VASc score among the MB patients was 4.8 (1.5), compared with 3.7 (1.7) in the non-MB cohort.

Overall, 29.1% (139 of 478) of MB patients and 36.6% (987 of 26 989) of non-MB patients had a prescription for a concomitant medication of interest. Statins, proton pump inhibitors, and amiodarone were the most frequent concomitant medications within the MB group.

Major Bleed Characteristics
As shown in Table 2, the most common bleeding site among those in the MB cohort was GI (88.5% [423 of 478]), followed by intracranial (7.5% [36 of 478]). Fourteen patients each experienced 2 MBs and 2 patients each experienced 3 MBs during the study period.
## Baseline Characteristics of Rivaroxaban Users Within the NVAF Cohort, by MB Status

| Characteristic                  | MB, n = 478 | No MB, n = 26,989 |
|--------------------------------|-------------|-------------------|
| **Age, y, mean (SD)**           | 78.4 (7.7)  | 75.7 (9.7)       |
| **Sex, %**                      |             |                   |
| Male                            | 52.0        | 55.5              |
| Female                          | 48.0        | 44.5              |
| **Comorbid condition, %**       |             |                   |
| Hemophilia                      | 0.4         | 0.0               |
| Ulcer                           | 8.2         | 0.8               |
| History of seizures             | 3.6         | 1.7               |
| Diagnosed dementia              | 13.0        | 6.7               |
| Hepatic disease                 | 11.7        | 5.8               |
| Renal disease                   | 38.7        | 16.7              |
| Prior ischemic stroke           | 9.0         | 4.8               |
| HF                              | 48.5        | 23.7              |
| Previous cerebrovascular event  | 34.5        | 16.4              |
| Hypertension                    | 95.6        | 75.8              |
| DM                              | 35.4        | 29.1              |
| CHD                             | 64.2        | 36.7              |
| VTE                             | 9.2         | 5.8               |
| Malignancy                      | 19.0        | 18.3              |
| CHADS₂ score, mean (SD)         | 3.0 (1.2)   | 2.2 (1.3)         |
| CHA₂DS₂-VASc score, mean (SD)   | 4.8 (1.5)   | 3.7 (1.7)         |
| **Had prescription for concomitant medication, %** | 29.1 | 36.6 |

### Hospitalization Data

Among the 464 MB patient hospitalizations that did not include a fatal outcome, the average (SD) length of stay was 3.8 (3.0) days. Almost half of the MB patients, 46.7% (223 of 478), received a blood transfusion; however, data were not available for the number of units transfused, and none of the MB events had explicit evidence of administration of receiving any type of blood clotting factor. A transfer to the intensive care unit was observed for 43.3% (207 of 478) of MB patients, and 25.1% (120 of 478) had a surgical intervention during their MB hospitalization. Among the MB patients, 74.9% (358 of 478) were discharged, 15.3% (73 of 478) were transferred to another facility, 5.6% (27 of 478) were transferred to a skilled nursing facility, 2.9% (14 of 478) died, 0.8% (4 of 478) went to a hospice, and 0.4% (2 of 478) left against medical advice (Table 2).

### Fatal Outcomes

As shown in Table 3, 14 of the 478 patients experienced a fatal outcome during their MB hospitalization (a case fatality rate of 2.9%), reflecting a fatal bleeding rate of 0.08 per 100 person-years (95% CI: 0.05-0.14)]. None of the fatal cases

---

### Table 1. Continued

| Characteristic                  | MB, n = 478 | No MB, n = 26,989 |
|--------------------------------|-------------|-------------------|
| Fluconazole                     | –           | 0.8               |
| Gemfibrozil                     | 0.4         | 0.3               |
| Carbamazepine                   | –           | 0.1               |
| Phenytoin                       | –           | 0.1               |
| Phenobarbitone                  | –           | 0.0               |
| Rifampicin                      | –           | 0.0               |

Rivaroxaban prescribed daily dose, mg, %

| Dose | MB | No MB |
|------|----|-------|
| 10   | 4.6| 5.9   |
| 15   | 32.2| 23.4 |
| 20   | 63.2| 70.7 |

Abbreviations: CHADS₂, congestive heart failure, hypertension, age ≥75 years, DM, prior stroke, TIA or non–central nervous system thromboembolism (doubled); CHA₂DS₂-VASc, congestive heart failure, hypertension, age >75 years, DM, prior stroke or TIA or systemic embolism, vascular disease, age 65–75 years, sex F; CHD, coronary heart disease; DM, diabetes mellitus; HF, heart failure; MB, major bleeding; NSAID, nonsteroidal anti-inflammatory drug; NVAF, nonvalvular atrial fibrillation; PPI, proton pump inhibitor; SD, standard deviation; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack; VT, venous thromboembolism.

A dash (—) represents that there were no patients taking the relevant medication in this category.

*Age is at time of MB. †Individual variables of interest identified within the 6-month period prior to MB for cases and within the 6-month period prior to the end of each study quarter for non-MB patients. ‡The time period queried for concomitant medications of interest (within MB cases) was 14 days prior to MB hospitalization. For non-MB patients, if taken within 14 days prior to the study period through the end of the recent quarter.
Table 2. MB Event Rates, Bleed Locations, and Hospitalization Data

| MB Cases (N = 478) | |
|--------------------|---|
| MB cases with fatal outcome | 14 |
| Patients with multiple MB events | 16 |
| MB incidence rate per 100 person-years (95% CI) | 2.86 (2.61-3.13) |
| Bleeding cases with fatal outcome (95% CI) | 0.08 (0.05-0.14) |
| MB location, n | |
| GI hemorrhage | 423 |
| Esophageal | 4 |
| Gastroduodenal | 87 |
| Lower GI | 125 |
| Unspecified GI | 207 |
| ICH | 36 |
| Genitourinary hemorrhage | 2 |
| Other | 12 |
| Unspecified | 5 |
| Length of hospitalization, d, mean (SD) | 3.8 (3.0) |
| Blood transfusion received, % | 46.7 |
| Transferred to ICU, % | 43.3 |
| Surgical intervention needed, % | 25.1 |
| Hospitalization outcome, % | |
| Discharged | 74.9 |
| Transferred to other facility | 15.3 |
| Transferred to SNF | 5.6 |
| Died | 2.9 |
| Hospice | 0.8 |
| Left AMA | 0.4 |

Abbreviations: AMA, against medical advice; CI, confidence interval; GI, gastrointestinal; ICH, intracranial hemorrhage; ICU, intensive care unit; MB, major bleeding; SD, standard deviation; SNF, skilled nursing facility.

a All MB cases were hospitalized due to the requirement within the algorithm used for the study.

b The MB incidence rate was calculated using person-time for the denominator value (exposure time at risk) for all first MBs within the period under study.

c Patients with MB who experienced fatal outcomes (n=14) were excluded from length-of-stay analyses.

Table 3. Fatal Outcomes Among MB Patients

| MB Cases, N = 478 | |
|-------------------|---|
| Fatal outcomes in rivaroxaban users who experienced a MB event, n | 14 |
| No. of days between hospitalization for MB event and death | |
| Mean | 3.9 |
| SD | 6.3 |
| Median | 1.5 |
| Min | 0 |
| Max | 22 |
| Age at time of death for those who experienced a MB event, y | |
| Mean | 82.4 |
| SD | 5.4 |
| Median | 82 |
| Min | 74 |
| Max | 92 |
| Primary hospital admission diagnosis of those who experienced a fatal outcome, % | |
| Intracerebral hemorrhage | 50.0 |
| GI hemorrhage NOS | 21.4 |
| Blood in the stool | 14.3 |
| Subdural hemorrhage | 7.1 |
| ICH NOS | 7.1 |

Abbreviations: GI, gastrointestinal; ICH, intracranial hemorrhage; MB, major bleeding; Max, maximum; Min, minimum; NOS, not otherwise specified; SD, standard deviation.

a Fatal outcome that occurred during patient’s hospitalization for the MB event.

Discussion

We report that in this observational post-marketing study of 27,467 rivaroxaban users with NVAF who were followed for 455 days in this real-world clinical setting, the rate of MB was 2.86 per 100 person-years (95% CI: 2.61-3.13). Further, and not unexpectedly, patients who experienced MB were older and more likely to have comorbidity at baseline. The most common bleeding site was GI (88.5%, n=423), followed by intracranial (7.5%, n=36). Of the 478 patients who suffered a MB, 14 died, yielding a fatal bleeding rate of 0.08 per 100 person-years (95% CI: 0.05-0.14). Seven of the patients who died had suffered an intracerebral hemorrhage. These outcomes are similar to those reported in the registration trial (eg, ROCKET-AF), and add valuable complementary safety data associated with rivaroxaban use in the post-marketing place. Our results are not intended for any direct comparison with clinical trials of rivaroxaban for a number of reasons that include differences in design, patient population, inclusion and exclusion criteria, data collection, and exposure and safety outcomes ascertainment. However,
the data from clinical trials might be generally informative to put the results of the current report into proper context. For example, the reported rates of MB (per 100 person-years) were 3.6 for rivaroxaban and 3.5 for warfarin in patients with NVAF in the ROCKET-AF trial. In addition, the majority of MB in the ROCKET study was classified in the categories of hemoglobin/hematocrit drop or transfusion, which is consistent with the observation of bleeding in the GI system reported in the current study. Ad hoc analysis was performed on the original ROCKET-AF trial data to investigate the pattern of MB by age group presented in this report. In the ROCKET-AF trial, the MB incidence rates were 2.47, 3.03, 4.66, and 7.65 per 100 person-years for the age groups of 55 to 64, 65 to 74, 75 to 84, and 85 years in the rivaroxaban group, respectively, compared with 1.61, 2.00, 3.38, and 3.46 in this report.

Clinical data for a number of baseline variables were presented to describe patient characteristics. However, a priori statistical testing was neither planned nor performed in this report. A nested case–control study was planned (and the development is ongoing) in the original study protocol to further evaluate those issues using an incidence density sampling method to control for exposure time. The main purpose of the proposed analyses for this future study is to examine whether the risk of MB during anticoagulation therapy is related to patient characteristics other than the indication for use of anticoagulation.

Study Limitations
This current study has limitations. This is a retrospective study, using data points that were originally collected for EMR and accounting/claims purposes, rather than research. Additionally, pharmacy records capture the drug-dispensing information rather than the actual administration of the drug, and connecting the use of rivaroxaban to a bleeding event only establishes temporal association rather than a causal relationship. Whereas MB might be underreported due to limitations of the databases, there is also the possibility of capturing false positives (eg, minor or clinically relevant bleeds that required medical attention). The major bleed transfusion rate of 46.7% was similar to the clinical-trial data.14

A patient suffering from sudden death due to intracerebral hemorrhage at home, with no subsequent autopsy, might not be correctly classified. Because immediately fatal intracerebral hemorrhage is not common, we do not believe this would substantially impact our findings.14

The results regarding concomitant medications need to be interpreted with caution, since the index windows for the medications are different. Major bleeding in this study is not an exact match with clinical trials, because the algorithm was applied retrospectively and relied on information available in the database. Additionally, MB in this study did not go through an adjudication process.

Conclusions
Data from a large US DoD EMR-based cohort of 27,467 NVAF patients, treated with rivaroxaban and followed for 15 months, show that the MB rate was 2.86 per 100 person-years; when MB occurred, it was usually GI in origin (88.5%), and fatal intracranial hemorrhages were rare (n = 9). Though the results are not intended for any direct comparison, these findings are generally consistent with those reported in the previous large randomized FDA registration trial of rivaroxaban.

Acknowledgments
The authors acknowledge and thank Dr. Roger Mills for his expertise and writing assistance.

References
1. Andrade J, Khairy P, Dobrev D, et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res. 2014;114:1453–1468.
2. Mant J, Edwards D. Stroke prevention in atrial fibrillation: putting the guidelines into practice. Drugs Aging. 2010;27:859–870.
3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014;130:2107–2140.
4. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–992.
5. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears in N Engl J Med. 2010;363:1877]. N Engl J Med. 2009;361:1139–1151.
6. Patel MR, Mahafey KW, Garg J, et al; ROCKET-AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:893–891.
7. Turpie AG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty: pooled analysis of four studies. Thromb Haemost. 2011;105:444–453.
8. Goodman SG, Woidyla DM, Piccini JP, et al; ROCKET-AF Investigators. Factors associated with major bleeding events: insights from the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF). J Am Coll Cardiol. 2014;63:891–900.
9. US Census Bureau. Age and sex composition in the United States: 2011. http://www.census.gov/population/age/data/2011 comp.html. Updated November 28, 2012. Accessed May 19, 2014.
10. Cunningham A, Stein CM, Chung CP, et al. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20:560–566.
11. Lamberts M, Giššon GH, Lil’ GY, et al. Antiplaet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. Circulation. 2014;129:1577–1585.
12. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–2870.
13. Lip GYH, Nieuwlaat R, Francis R, Lane DA, Crijns HJGM. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach: The Euro Heart Survey on Atrial Fibrillation. Chest. 2010;137:263–272.
14. Piccini JP, Garg J, Patel MR, et al; ROCKETF-AF Investigators. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKETF-AF trial. Eur Heart J. 2014;35:1873–1880.