NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Hospital Readmissions Among Nonvalvular Atrial Fibrillation Patients Treated with Oral Anticoagulants in the U.S.
Protocol number	B0661122
Version identifier of the final study report	1.0
Date	27-July-2020
EU Post Authorization Study (PAS) register number	EUPAS25230
Active substance	Apixaban
Medicinal product	Apixaban
Research question and objectives	The study addressed the following primary research question: What is the frequency of readmission for MB within 1 month after index hospitalization for NVAF patients treated with apixaban, warfarin, rivaroxaban, or dabigatran? • The primary objective of the study was to evaluate and compare 1-month MB-related readmission rates of hospitalized NVAF patients treated with warfarin, rivaroxaban, or dabigatran vs. apixaban. • The secondary objectives were: o To evaluate and compare 1-month all-cause readmission rates of hospitalized NVAF patients treated with warfarin, rivaroxaban, or dabigatran vs. apixaban o To determine average hospital length of stay (LOS) and costs associated

	with MB-related and all-cause readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF patients treated with warfarin, rivaroxaban, or dabigatran vs. apixaban • Exploratory objectives: o To describe 1-month stroke-related readmission rates of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban o To describe average hospital LOS and costs associated with stroke-related readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF of patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban
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Not applicable

Not applicable

Not applicable

Not applicable

Not applicable

Not applicable

1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: Hospital Readmissions Among Nonvalvular Atrial Fibrillation Patients Treated with Oral Anticoagulants in the U.S.

Date: 27-July-2020

Name and affiliation of the main author: Christine L. Baker, JD, MPH, Pfizer

Keywords: atrial fibrillation; oral anticoagulants; hospital readmissions; major bleeding

Research question and objectives: The study addressed the following primary research question: What is the frequency of readmission for MB within 1 month after index hospitalization for NVAF patients treated with apixaban, rivaroxaban, dabigatran, or warfarin?

- The primary objective of the study was to evaluate and compare 1-month MB-related readmission rates of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban.
- The secondary objectives were:
    - To evaluate and compare 1-month all-cause readmission rates of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban
    - To determine average hospital length of stay (LOS) and costs associated with MB-related and all-cause readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban
- The exploratory objectives were:
    - To describe 1-month stroke-related readmission rates of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban
    - To describe average hospital LOS and costs associated with stroke-related readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF of patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban

Study design: This study was a retrospective cohort analysis using the Premier Hospital database.

Setting and subjects: Adult patients (age ≥18 years) hospitalized for NVAF, based on a primary or secondary discharge diagnosis code indicating NVAF, were identified from the Premier Hospital database between January 1, 2013 and June 30, 2017. Patients who received apixaban, warfarin, rivaroxaban, or dabigatran during any time of the hospitalization (from admission to discharge) were identified and grouped into study cohorts based on the OAC initiated.

Data source: The Premier Hospital database (Premier, Inc, Charlotte, NC).

Variables: Demographic, patient clinical characteristics, and hospital characteristics were measured during the index hospitalization of NVAF patients. Other clinical characteristics (e.g., prior bleeding) of NVAF patients were measured during a 12-month baseline period. The proportions of patients treated with apixaban, warfarin, rivaroxaban, and dabigatran that have MB-related, all-cause, and stroke-related readmissions that occurred within 1 month of discharge of their initial hospitalization for NVAF were evaluated. Hospital LOS and associated costs of MB-related, all-cause, and stroke-related readmissions were determined and compared between each other OAC cohort and the apixaban cohort. Three-month readmission rates, associated LOS and costs of MB-related, all-cause, and stroke-related readmissions were also determined and compared between the other OAC cohorts and the apixaban cohort as a sensitivity analysis.

Results: NVAF patients treated with warfarin vs. apixaban had significantly greater risk of all-cause (odds ratio [OR]: 1.05; confidence interval [CI]: 1.02-1.08; p<0.001), MB-related (OR: 1.28; CI: 1.16-1.42; p<0.001), and stroke-related (OR: 1.33; CI: 1.11-1.58; p=0.002) readmissions; for all readmission categories, average LOS was significantly longer and costs significantly higher for warfarin treated patients. NVAF patients treated with rivaroxaban vs. apixaban had significantly greater risk of all-cause (OR: 1.06; CI: 1.02-1.09; p=0.001) and MB-related (OR: 1.62; CI: 1.44-1.83; p<0.001) readmissions, but not stroke-related readmission; for MB-related readmissions average LOS and costs were higher for rivaroxaban treated patients. Significant differences in risks of all-cause, MB-related, and stroke-related readmissions were not observed between the apixaban and dabigatran cohorts.

Discussion: According to this large-scale, retrospective, real-world, hospital analysis of NVAF patients, after controlling for differences in patient and hospital characteristics, apixaban treatment was associated with significantly lower all-cause, MB-related, and stroke-related hospital readmission risk than warfarin and significantly lower all-cause and MB-related hospital readmission risk, but not stroke-related readmission, than rivaroxaban. Significant differences in the risks of all-cause, MB-related, and stroke-related readmissions were not observed between the apixaban and dabigatran cohorts. Apixaban was also associated with significantly lower costs for all-cause readmission (vs. warfarin only), MB-related readmission (vs. warfarin and rivaroxaban), and stroke-related readmission (vs. warfarin only). The results of this study may be helpful to guide hospitals, payers, patients, and other stakeholders in determining the optimal oral anticoagulation therapy that provides the most benefit to NVAF patients, while reducing the hospital resource and economic burden.

Marketing Authorization Holder(s): Bristol Myers-Squibb

Names of principal investigators:

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial Fibrillation
AFL	Atrial Flutter
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DOAC	Direct Oral Anticoagulant
GLM	Generalized Linear Model
ICD-9 CM	International Classification of Diseases, 9th Revision
ICD-10 CM	International Classification of Diseases, 10th Revision
LOS	Length of Stay
MB	Major Bleeding
NVAF	Non Valvular Atrial Fibrillation
OAC	Oral Anticoagulant
OR	Odds Ratio
VTE	Venous Thromboembolism

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Cristine Baker	JD,MPH	Pfizer
Jay Lin	PhD, MBA	Novosys

Lead Country Investigator(s) of the Protocol

Not applicable

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	31 July 2018	31 July 2018	
End of data collection	07 Mar 2019	07 Mar 2019	
Registration in the EU PAS register	10 Aug 2018	10 Aug 2018	
Final report of study results	27 July 2020	27 July 2020	

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is a cardiac rhythm disorder that is predominately nonvalvular (NVAF). It becomes increasingly more prevalent as people age and is associated with up to a 5-fold higher stroke risk in the U.S.[1,2] Taking into consideration the growing elderly population in the U.S., the number of persons with NVAF is estimated to double or possibly triple by 2050.[1,2] Consequently, the economic burden of NVAF, largely related to hospitalizations, is also predicted to increase from an estimated $13.9 billion annually in 2010 to nearly $30 billion annually by 2050.[3]

Patients with NVAF have been reported to have high rates of hospital readmission.[4,5] A retrospective database analysis of 8,035 AF and AF flutter (AFL) patients between 2007 and 2008 reported that 38% of AF/AFL patients were readmitted to the hospital for all causes within 12 months after discharge, with the highest proportion occuring within the first 1 month after discharge.[4] This study also found that readmissions for AF and AFL had longer hospital stays and were more costly than the initial hospitalizations.[4] A second study of 6,439 NVAF patients reported an all-cause 1-month readmission rate of 18% and that predictors of readmission included longer initial hospital length of stay, higher Charlson Comorbidity Index score, and hospital admission via the emergency room.[5]

Hospital readmission rates are a critical concern in the U.S. and in October of 2012 the Hospital Readmissions Reduction Program was implemented by the Centers for Medicare and Medicaid Services (CMS) to reduce the frequency of readmission among Medicare patients.[6] This program involves assigning financial penalties to hospitals with readmission rates considered excessive.[6] In 2013, CMS reported that two-thirds of hospitals in the U.S. received penalties totaling ~$280 million and these penalties are expected to increase in the upcoming years.[6] It has therefore become increasingly important to examine hospital readmission rates and the factors associated with readmission. Although, readmission rates of NVAF patients have been studied to some extent in regard to all cause readmissions (most recent patient data from 2007 to 2008), little information exists in the published literature on bleeding-related readmissions. In the real-world setting bleeding is a significant burden healthwise and economic wise and represents a critical target for improving the quality of care of NVAF patients. In clinical trials NVAF patients treated with the different DOACs differed in bleeding rates and the DOACs with lower bleeding risk have potentially a greater likelihood of improving the anticoagulation management of NVAF patients in the real-world setting where bleeding rates are higher than observed in the clinical trial setting.[7-10] We previously conducted an early evaluation that investigated rates of all-cause and bleeding-related hospital readmissions among NVAF patients treated with dabigatran, rivaroxaban, and apixaban (January 1, 2012 through March 31, 2014).[11] In this early analysis of 74,730 patients identified from the Premier Hospital database, after controlling for differences in patient characteristics, compared with patients who received apixaban during their index hospitalizations, the odds of bleeding-related hospital readmissions were significantly greater by 1.4-fold ($p<0.01$) for patients who received rivaroxaban and 1.2-fold ($p=0.16$) numerically trending greater for patients who received dabigatran. This current analysis was a follow-up of our earlier assessment and includes in addition to NVAF patients treated with DOACs also

patients treated with warfarin. Patients hospitalized for NVAF and treated with OACs were identified from January 2013 through June 2017.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The study addressed the following primary research question: What is the frequency of readmission for MB within 1 month after index hospitalization for NVAF patients treated with apixaban, rivaroxaban, dabigatran, or warfarin?

- The primary objective of the study was to evaluate and compare 1-month MB-related readmission rates of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban.
- The secondary objectives were:
    - To evaluate and compare 1-month all-cause readmission rates of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban
    - To determine average hospital length of stay (LOS) and costs associated with MB-related and all-cause readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban

<u>Exploratory objectives</u>:

- To describe 1-month stroke-related readmission rates of hospitalized NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban
- To describe average hospital LOS and costs associated with stroke-related readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF of patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	3/1/2019	Administrative	7,8.10	Changed 3-month follow-up analysis from exploratory to sensitivity analysis to evaluate the robustness of findings with respect to changes in the follow-up time.	Sensitivity analysis more accurately reflects study teams' intent of the analysis

9. RESEARCH METHODS

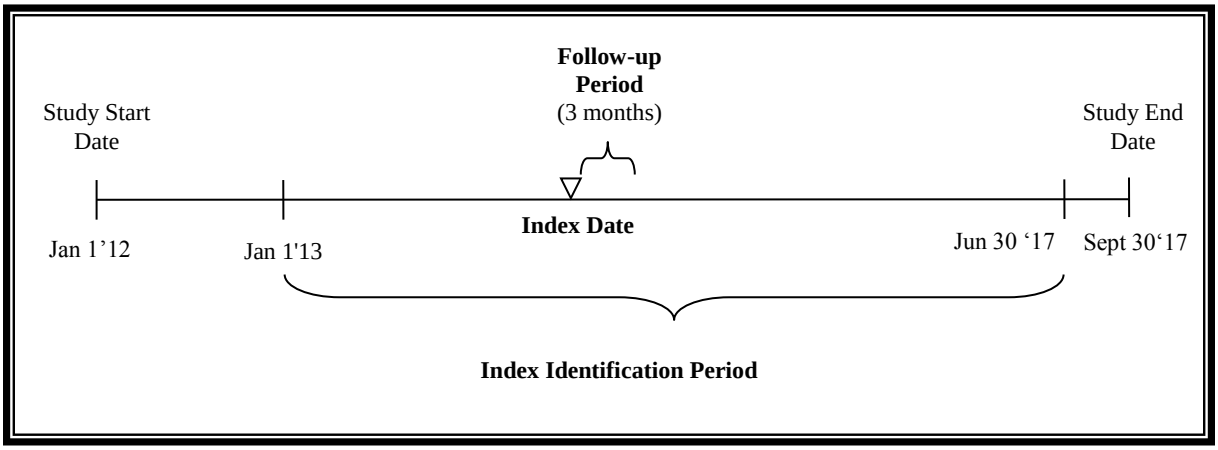
9.1. Study design

This study was a retrospective cohort analysis using the Premier Hospital database. The data source used was the Premier Hospital database, which provides hospital billing information on a patient's hospital stay as well as information on ICD-9 and ICD-10 codes and current procedural terminology codes. Specifically, the database contains a date-stamped log of all billed items, including medications, laboratory, diagnostic, and therapeutic services, and primary and secondary diagnoses for each patient's hospitalization. Identifier-linked files provide demographic and payer information. Detailed service-level information for each hospital day is recorded and this includes details on medication received. Billed items are standardized by the database vendor after the hospital both reviews and consents to the items. The Premier Hospital database is the largest inpatient drug utilization database in the US and contains complete billing and coding history for more than 45 million hospital inpatient discharges across the US.

9.2. Setting

The overall study period was from January 1, 2012 through September 30, 2017, to allow for a 3-month follow-up period for observation of readmissions and a 1-year baseline observation period. Adult patients (age ≥18 years) hospitalized for NVAF, based on a primary or secondary discharge diagnosis code indicating NVAF, were identified from the Premier Hospital database between January 1, 2013 and June 30, 2017. Patients who received apixaban, rivaroxaban, dabigatran, or warfarin during any time of the hospitalization (from admission to discharge) were identified and grouped into study cohorts based on the OAC initiated. The first of such NVAF hospitalizations was defined as the index hospitalization. Patients with more than one type of OAC drug usage during the index hospitalizations were excluded so that patients could be exclusively assigned into each OAC patient cohorts. Demographic, patient clinical characteristics, and hospital characteristics were measured during the index hospitalization of NVAF patients. Other clinical characteristics (e.g., prior bleeding) of NVAF patients were measured during a 12-month baseline period. The proportions of patients treated with apixaban, rivaroxaban, dabigatran, and warfarin that have MB-related, all-cause, and stroke-related readmissions that occurred within 1 month of discharge of their initial hospitalization for NVAF were evaluated. Hospital LOS and associated costs of MB-related, all-cause, and stroke-related readmissions were determined and compared between each other OAC cohort and the apixaban cohort. Three-month readmission rates, associated LOS and costs of MB-related, all-cause, and stroke-related readmissions were also determined and compared between the other OAC cohorts and the apixaban cohort, as an exploratory analysis.

Figure 1. Study Time Periods (for illustration purposes, not proportional)



9.3. Subjects

9.3.1. Inclusion criteria

Patients needed to have met the following inclusion criteria to be eligible for inclusion in the study:

- Have a hospital discharge ICD-9-CM code of 427.31 or 427.32 (and corresponding ICD-10 codes) indicating a primary or secondary diagnosis of AF identified from the Premier Hospital database between January 1, 2013 and September 30, 2017.
- Received any of the OACs, apixaban, rivaroxaban, dabigatran, or warfarin during any time of the hospitalization from admission to discharge
- Have an age ≥18 years as of the initial hospitalization with an AF diagnosis

9.3.2. Exclusion criteria

Patients meeting any of the following criteria based on records during index hospitalizations were not included in the study:

- Had medical claims indicating one of the following conditions or procedures during the index hospitalizations or within 12 months prior to the index date:
    1. Rheumatic mitral valvular heart disease or mitral valve stenosis:
        - ICD-9 diagnosis codes 394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.8, 396.9, 424.0
        - ICD-10 diagnosis codes I05.x, I08.0, I08.8, I08.9, and I34.x
    2. Heart valve replacement/transplant:
        - ICD-9 diagnosis codes V422 and V433
        - ICD-10 diagnosis codes Z95.2, Z95.3, Z95.4
        - ICD-9 procedure codes 35.05-35.09, 35.20-35.28, and 35.97

- ICD-10 procedure codes 02RFx-02RJ0KZ, 02RJ4x, 02UG3JZ, and X2RFx

3. Dialysis, kidney transplant, or end-stage chronic kidney disease:
   - ICD-9 diagnosis codes 585.6, 996.73, V45.1x, and V56.x
   - ICD-10 diagnosis codes N18.6, T82.8x8A, Z49.x, Z91.15, Z99.2
   - ICD-9 procedure codes 55.6x.
   - ICD-10 procedure codes 0TS00ZZ, 0TS10ZZ, and 0TYx.
   - Current Procedural Terminology (CPT) codes 90935, 90937, 90945, 90947, 90967 00868, 50300, 50320, 50323, 50325, 50327, 50328, 50329, 50340, 50360, 50365, and 50380
4. Venous thromboembolism (VTE):
   - Deep vein thrombosis (DVT):
     - ICD-9 diagnosis codes 451-453, 671.3, 671.4, and 671.9
     - ICD-10 diagnosis codes I80.00-I82.91, O22.3x, O22.9x, O87.1, and O87.9
   - Pulmonary embolism (PE):
     - ICD-9 diagnosis codes 415.1, 673.2, and 673.8
     - ICD-10 diagnosis codes I26.x, O88.2x, O88.8x, T80.0XXA, T81.718A, T81.72XA, T82.817A, and T82.818A
5. Reversible AF:
   - Pericarditis:
     - ICD-9 diagnosis codes 006.8, 017.9, 036.41, 074.21, 093.81, 098.83, 115.93, 390, 391, 392.0, 393, 411.0, 420.90, 420.91, 420.99, 423.0, 423.1, 423.2, 423.8, and 423.9
     - ICD-10 diagnosis codes A06.3, A06.8x, A17.83, A17.9, A18.82, A18.84, A18.89, A39.53, A52.06, A54.83, B33.23, B39.9, I00-I02.0, I09.2, I24.1, I30.x, I31.0, I31.1, I31.2, I31.3, I31.8, I31.9, I32
   - Hyperthyroidism or thyrotoxicity:
     - ICD-9 diagnosis codes 242.0, 242.1, 242.2, 242.3, 242.4, 242.8, and 242.9
     - ICD-10 diagnosis codes E05.x
   - Acute myocardial infarction:
     - ICD-9 diagnosis codes 410.x
     - ICD-10 diagnosis codes I21.01-I21.4, and I22.x
   - Acute myocarditis:
     - ICD-9 diagnosis codes 422.x
     - ICD-10 diagnosis codes A18.84, I40.x, and I41

- Had medical claims indicating a hip or knee replacement surgery during the index hospitalizations or within a 6-week period prior to the index date
    1. ICD-9 diagnosis codes V43.64 and V43.65
    2. ICD-10 diagnosis codes Z96.64x and Z96.65x
    3. ICD-9 procedure codes 81.40, 81.51, 81.52, 81.53, 81.54, and 81.55
    4. ICD-10 procedure codes 0SQ9x, 0SQBx, 0SR9019-0SR904Z, 0SR907Z, 0SR90Jz, 0SR90KZ, 0SRAx, 0SRB019-0SRB04Z, 0SRB07Z, 0SRB0Jx, 0SRB0KZ, 0SRC07Z, 0SRC0Jx, 0SRC0KZ, 0SRC0Lx, 0SRD07Z, 0SRD0Jx, 0SRD0KZ, 0SRD0Lx, 0SREx, 0SRRx-0SRWx, 0SW90JZ, 0SW93JZ, 0SW94JZ, 0SWA0JZ, 0SWA3JZ, 0SWA4JZ, 0SWB0JZ, 0SWB3JZ, 0SWB4JZ, 0SWC0JC, 0SWC0JZ, 0SWC3JC, 0SWC3JZ, 0SWC4JC, 0SWC4JZ, 0SWD0JC, 0SWD0JZ, 0SWD3JC, 0SWD3JZ, 0SWD4JC, 0SWD4JZ, 0SWE0JZ, 0SWE3JZ, 0SWE4JZ, 0SWR0JZ, 0SWR3JZ, 0SWR4JZ, 0SWS0JZ, 0SWS3JZ, 0SWS4JZ, 0SWT0JZ, 0SWT3JZ, 0SWT4JZ, 0SWU0JZ, 0SWU3JZ, 0SWU4JZ, 0SWV0JZ, 0SWV3JZ, 0SWV4JZ, 0SWW0JZ, 0SWW3JZ, and 0SWW4JZ.
- Had medical claims indicating pregnancy at any time during the study period
    1. ICD-9 diagnosis codes 630-679, V22, V23, V24, V27, V28, V61.6, V61.7, 792.3, and 796.5
    2. ICD-10 diagnosis codes A34, O00.00-O9A.53, Z33.1-Z37.9, Z39.x, and Z64.0
    3. ICD-9 procedure codes 72-75.9
    4. ICD-10 procedure codes 0DQPx-0DQQ8ZZ, 0DQRx, 0JCBx, 0Q82x, 0Q83x, 0TQBx, 0TQDx, 0U7C7ZZ, 0UCG0ZZ, 0UCG3ZZ, 0UCG4ZZ, 0UCM0ZZ, 0UJD7ZZ, 0UQ9x, 0UQCx, 0UQGx, 0UQMx, 0US90ZZ, 0US94ZZ, 0US9XZZ, 0W3Rx, 0W8NXZZ, 0WQNXZZ, 109x, 10A00ZZ, 10A03ZZ, 10A04ZZ, 10A07Z6, 10A07ZX, 10A07ZZ, 10A08ZZ, 10D0x, 10D1xZZ, 10Ex-10S0x, 10T20ZZ-10T24ZZ, 10Yx, 2Y44X5Z, 3027x, 3E030VJ, 3E033VJ, 3E040VJ, 3E043VJ, 3E050VJ, 3E053VJ, 3E060VJ, 3E063VJ, 3E0DXGC, 3E0E305-3E0E3TZ, 3E0E705, 3E0E729-3E0E7TZ, 3E0E805, 3E0E829-3E0E8TZ, 3E0P7GC, 4A0Hx, 4A0Jx, 4A1Hx, and 4A1Jx
- Received edoxaban during the index hospitalization or within 12 months prior to the index date
- Received multiple types of OACs during the index hospitalization
- Patients who died during the index hospitalizations

All the ICD-10 codes corresponding to the ICD-9 codes listed above were also used to identify the conditions and procedures in the inclusion and exclusion criteria.

These inclusion and exclusion criteria are aligned with the Eliquis Harmonized Retrospective Study Protocol and are consistent with other previous apixaban retrospective database studies of patients with NVAF.

After applying the inclusion and exclusion criteria, eligible patients will be assigned to the following cohorts based on the OAC treatment received during index hospitalizations.

1. **Apixaban Cohort:** NVAF patients who initiated apixaban during hospitalization.
2. **Dabigatran Cohort:** NVAF patients who initiated dabigatran during hospitalization.
3. **Rivaroxaban Cohort:** NVAF patients who initiated rivaroxaban during hospitalization.
4. **Warfarin Cohort:** NVAF patients who initiated warfarin during hospitalization

9.4. Variables

Table 1. Demographic and Patient Clinical Characteristic Variables and Hospital Characteristic Variables

Variable	Role	Operational definition
Age	Patient characteristic and potential confounder	Age was defined as of the index date. Mean, standard deviation (SD), and median are reported.
Gender	Patient characteristic and potential confounder	Distribution of female and male patients and reported as count and percentage.
Race	Patient characteristic and potential confounder	Patients with White, Black, and other/unknown race and reported as counts and percentages.
Payer Type	Patient characteristic and potential confounder	Patients with Medicare, Medicaid, commercial, and other/unknown insurance coverage and reported as counts and percentages.
Index Hospitalization Deyo-Charlson Comorbidity Index	Patient characteristic and potential confounder	The Deyo-Charlson Comorbidity Index was calculated for the index hospitalization. Mean, SD, and median are reported.
APR-DRG Severity	Patient characteristic and potential confounder	The APR-DRG severity level (1-minor, 2-moderate, 3-major, 4-extreme) was determined for the index hospitalization and reported as counts and percentages.
Baseline $CHADS_2$	Patient characteristic and potential confounder	The $CHADS_2$ score evaluated from the available records of the index hospitalization and baseline period was used to estimate stroke risk. Mean, SD, and median are reported.
Baseline $CHADS_2$-VASc Score	Patient characteristic and potential confounder	The $CHADS_2VASc$ score evaluated from the available records of the index hospitalization and baseline period was used to estimate stroke risk. Mean, SD, and median are reported.

Variable	Role	Operational definition
Baseline HAS-BLED Score	Patient characteristic and potential confounder	HAS-BLED score evaluated from the available records of the index hospitalization and baseline period was used to estimate the risk of MB for patients. Mean, SD, and median are reported.
Index Bleed	Patient characteristic and potential confounder	Patients with a bleed diagnosis on hospital records during their index hospitalization and reported as count and percentage.
Baseline Prior Bleed	Patient characteristic and potential confounder	Patients with a bleeding diagnosis on hospital records during the baseline period and reported as count and percentage.
Index Stroke	Patient characteristic and potential confounder	Patients with a stroke diagnosis on hospital records during their index hospitalization and reported as count and percentage.
Baseline Prior Stroke	Patient characteristic and potential confounder	Patients with a stroke diagnosis on hospital records during the baseline period and reported as count and percentage.
Index Hospital Admission Source	Patient characteristic and potential confounder	Physician referral/home, transfer, other/unknown- reported as count and percentage
Index Hospital LOS	Patient characteristic and potential confounder	The number of days from admission to discharge for index hospitalizations were determined for each patient. Mean, SD, and median are reported.
Index Hospital Urban/Rural Status	Patient characteristic and potential confounder	Rural, urban- reported as count and percentage
Index Hospital Teaching Status	Patient characteristic and potential confounder	Yes/No- reported as count and percentage
Index Hospital Bed Size	Patient characteristic and potential confounder	0-99, 100-199, 200-200, 300-399, 400-499, ≥500- reported as count and percentage
Index Hospitalization Cost	Patient characteristic and potential confounder	The total costs of index hospitalizations were determined for each patient. Mean, SD, and median are reported.

Table 2. Outcome Measurements: Readmissions, Associated LOS and Cost

Variable	Role	Operational definition
MB-related Readmission	Outcome	Defined as readmissions with a bleeding diagnosis at the first position of the hospital discharge diagnosis codes (Appendix). Number of patients with MB-related readmissions within 1 or 3 months of initial NVAF hospitalization in study cohorts. Mean, SD, and median were reported. Associated LOS and cost for MB-related readmissions were determined. Mean, SD, and median were reported. Likelihood of first MB-related readmission was assessed for each OAC cohort vs. the apixaban cohort. LOS and hospital cost per patient for cohorts were estimated and compared by multivariable regression analysis. Measurements for 3-month readmissions were evaluated using descriptive statistics as an exploratory analysis.
All-cause Readmission	Outcome	Number of patients with all-cause readmissions within 1 or 3 months of initial NVAF hospitalization in study cohorts. Mean, SD, and median were reported. Associated LOS and cost for all-cause readmissions were determined. Mean, SD, and median were reported. Likelihood of first all-cause readmission was assessed for each OAC cohort vs. the apixaban cohort. LOS and hospital cost per patient for cohorts were estimated and compared by multivariable regression analysis. Measurements for 3-month readmissions were evaluated using descriptive statistics as an exploratory analysis.
Stroke-related Readmission	Outcome	Defined as readmissions with a stroke diagnosis at the first position of the hospital discharge diagnosis codes (Appendix). Cases were excluded if traumatic brain injury (ICD-9: 800-804, 850-854) was present during hospitalization. Number of patients with stroke-related readmissions within 1 or 3 months of initial NVAF hospitalization in study cohorts. Mean, SD, and median were reported. Associated LOS and cost for stroke-related readmissions were determined. Mean, SD, and median were reported. Likelihood of first stroke-related readmission was assessed for each OAC cohort vs. the apixaban cohort. LOS and hospital cost per patient for cohorts were estimated and compared by multivariable regression analysis. Measurements for 3-month readmissions were evaluated using descriptive statistics as an exploratory analysis.

Variable	Role	Operational definition
MB- or Stroke-related Readmission	Outcome	Number of patients with MB- or stroke-related readmissions within 1 or 3 months of initial NVAF hospitalization in study cohorts. Mean, SD, and median were reported. Associated LOS and cost were determined. Mean, SD, and median were reported. Likelihood of first MB- or stroke-related readmission was assessed for each OAC cohort vs. the apixaban cohort. LOS and hospital cost per patient for cohorts were estimated and compared by multivariable regression analysis. Measurements for 3-month readmissions were evaluated using descriptive statistics as an exploratory analysis.

9.5. Data sources and measurement

The study will be conducted using the Premier Hospital database which is a nationally representative inpatient hospitalization records database that captures more than 45 million hospital discharges from greater than 600 acute care hospitals, representing approximately 20% of all hospital admissions in the U.S.

9.6. Bias

A propensity score matching (PSM) 1:1 technique was used to control for confounders when comparing each of the OAC cohorts vs. the apixaban cohort. The matching covariates included age, gender, race, payer type, index hospitalization Deyo-Charlson Comorbidity Index, baseline $CHADS_2$, baseline CHA_2DS_2-VASc score, baseline HAS-BLED score, index bleed, baseline prior bleed, index stroke, baseline prior stroke, index hospital LOS, index hospital urban/rural status, index hospital teaching status, index hospital bed size, and index hospitalization cost. Each of the other OAC cohorts were matched to the apixaban cohort (reference) separately. Thus, there were the following PSM matched pairs: rivaroxaban vs. apixaban, dabigatran vs. apixaban, and warfarin vs. apixaban. More specifically, in such PSM processes, each subject in the apixaban cohort (reference cohort) was matched to a subject in one of the other OAC cohorts with the closest propensity score. The matched two subjects were also required to have their propensity scores to be within 0.001 of each other (matching caliper). Thus, as in a true randomized controlled trial, the 'control treatment subject' (a subject in the apixaban cohort) functioned as the control group for the other OAC subject.

9.7. Study Size

The preliminary data evaluation of the Premier database indicated that there are at least 30,000 patients for each of OAC cohort during the study period described for this study. With a two-sided test, an alpha-level of 0.05, and a 1:1 ratio of the comparison cohorts, and the assumed one-month MB-related readmission rate of 1.4%, and the assumed MB-related readmission rate difference of 0.5% between cohorts treated with other OACs vs. apixaban, we have estimated the following power calculation:

Power Calculation		
Nominal Power	**Actual Power**	**N Total-One Arm**
0.7	0.7	11,226
0.75	0.75	12,622
0.8	0.8	14,274
0.85	0.85	16,328
0.9	0.9	19,108
0.95	0.95	23,630

Thus, the study is expected to have sufficient sample sizes for the study measurements.

9.8. Data transformation

This study used secondary data collected in the Premier Database, which is de-identified and HIPAA compliant.

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the statistical analysis plan, which is dated, filed, and maintained by the sponsor.

9.9. Statistical methods

9.9.1. Main summary measures

Means, SDs, and medians were provided for continuous variables. Numbers and percentages were provided for categorical variables. Bivariate comparisons of baseline patient and hospital characteristics and readmission measurements were provided, with appropriate tests (e.g., ANOVA test, chi-square test) used based on the distribution of the measure.

9.9.2. Main statistical methods

A propensity score matching (PSM) 1:1 technique was used to control for confounders when comparing each of the OAC cohorts vs. the apixaban cohort. The matching covariates included age, gender, race, payer type, index hospitalization Deyo-Charlson Comorbidity Index, baseline $CHADS_2$, baseline CHA_2DS_2-VASc score, baseline HAS-BLED score, index bleed, baseline prior bleed, index stroke, baseline prior stroke, index hospital LOS, index hospital urban/rural status, index hospital teaching status, index hospital bed size, and index hospitalization cost. Each of the other OAC cohorts were matched to the apixaban cohort (reference) separately. Thus, there were the following PSM matched pairs: rivaroxaban vs. apixaban, dabigatran vs. apixaban, and warfarin vs. apixaban. More specifically, in such PSM processes, each subject in the apixaban cohort (reference cohort) was matched to a subject in one of the other OAC cohorts with the closest propensity score. The matched two subjects were also required to have their propensity scores to be within 0.001 of each other (matching caliper). Thus, as in a true randomized controlled trial, the ‘control treatment

subject' (a subject in the apixaban cohort) functioned as the control group for the other OAC subject.

After PSM, no statistically significant differences were observed among all pre-index measures between the patient cohorts. After the PSM process the potential impact of treatment with the different OACs compared vs. treatment with apixaban on 1-month MB-related, all-cause, and stroke-related readmissions was evaluated.

Logistic regression analyses were carried out on the matched patient cohorts to further evaluate the potential impact of treatment with each of the different OACs vs. treatment with apixaban on the risk for 1-month MB-related, all-cause, and stroke-related readmissions. Only the index drug was used as a covariate, since other patient characteristics were similar after PSM.

Generalized linear model regression analyses were carried out on the matched patient cohorts to further evaluate the potential impact of treatment with each of the different OACs vs. treatment with apixaban on the average readmission LOS per patient related to 1-month MB-related, all-cause, and stroke-related readmissions. Only the index drug was used as a covariate, since other patient characteristics were similar after PSM.

Two-part regression analyses were conducted to examine the differences in MB-related, all-cause, and stroke-related readmission costs between the 3 different OAC cohorts and the apixaban cohort, separately. In the two-part model, the first part was multivariable logistic regression, which was used to evaluate the impact of OAC treatment on the risk of MB-related, all-cause, and stroke-related readmissions. The second part was a generalized linear model GLM with log transformation and gamma distribution applied to the corresponding cost data. Thus, for example for the MB-related cost evaluation, this evaluated the incremental MB-related cost among patients with MB readmissions. Then the odd ratio estimated from the first part was combined with the incremental MB-related costs estimated from the second part to estimate the incremental MB-related cost among all patients. Such two-part calculations were carried out in 1,000 cycles of random bootstrapping resampling to generate 1,000 such estimates. The univariate statistics of the 1,000 incremental MB-related costs among all patients were used to evaluate the MB-related cost distribution. The 2.5-percentile and 97.5-percentile of the incremental MB-related costs estimated from the 1,000 cycles of bootstrapping were used to represent the lower and upper level of 95% confidence interval.

These regression analysis approaches are consistent with the methods approved for previous Eliquis alliance retrospective database analyses.

All data analyses were executed using statistical software SAS version 9.4.

9.9.3. Missing values

None

9.9.4. Sensitivity analyses

A sensitivity analysis was performed to describe readmission rates, hospital LOS and costs associated with all-cause, MB-related, and stroke-related readmissions occurring within 3 months of initial hospitalizations of NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban

9.9.5. Amendments to the statistical analysis plan

Not applicable

9.10. Quality control

Data in Premier database are collected periodically in an electronic format. Premier database employs a number of subsequent quality assurance procedures and undertakes routine audits to ensure the quality of information. The data analysis follows our good data analysis practices which have been demonstrated in many past research studies and publications. The analysis is also inspected with at least two independent researchers to for quality control purpose.

9.11. Protection of human subjects

Subject information and consent

Not applicable

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

IRB/IEC review is not required.

Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).

10. RESULTS

10.1. Participants

Patient Flow

Patients	Count
Number of patients hospitalized with AF between 1/2013 and 6/2017	1,980,450
Number of patients ≥18 years of age	1,979,762
Number of patients treated with warfarin or a DOAC in hospitals	922,071
Number of patients without other exclusion criteria	**529,984**

10.2. Descriptive data

Table W1. Demographics and Clinical Characteristics of Matched Apixaban and Warfarin Study Cohorts

	Apixaban		Warfarin		
Characteristic	**N**	**%**	**N**	**%**	**p-value**
Age (years)					
N	69,765		69,765		
Mean	76.01		76.04		0.6397
SD	9.83		9.80		
Median	77		77		
Gender					0.4157
Female	35,239	50.51%	35,391	50.73%	
Male	34,526	49.49%	34,374	49.27%	
Race					0.3561
White	58,851	84.36%	59,045	84.63%	
Black	4,647	6.66%	4,570	6.55%	
Other/missing	6,267	8.98%	6,150	8.82%	
Health Plan Type					0.1855
Commerical	7,034	10.08%	7,074	10.14%	
Medicare	58,467	83.81%	58,582	83.97%	
Medicaid	2,090	3.00%	2,073	2.97%	
Other health plan	2,174	3.12%	2,036	2.92%	
APR-DRG Severity					0.2398
1-Minor	7,036	10.09%	6,882	9.86%	
2-Moderate	30,662	43.95%	30,670	43.96%	
3-Major	28,257	40.50%	28,506	40.86%	
4-Extreme	3,810	5.46%	3,707	5.31%	
CCI Score					
N	69,765		69,765		
Mean	2.28		2.27		0.4470
SD	1.72		1.68		
Median	2		2		
Total Patient Count	69,765		69,765		

APR-DRG: All Patient Refined Diagnosis Related Groups
CCI: Charlson Comorbidity Index
SD: Standard Deviation

Table W2. Index Hospitalization Characteristics of Matched Apixaban and Warfarin Study Cohorts

Characteristic	Apixaban		Warfarin		p-value
	N	%	N	%	
Hospital Admission Source					0.3601
Physician referral/home	55,952	80.20%	55,841	80.04%	
Transfer	6,722	9.64%	6,878	9.86%	
Other/unknown	7,091	10.16%	7,046	10.10%	
Length of Stay (LOS)					
N	69,765		69,765		
Mean	4.39		4.40		0.3395
SD	3.36		3.28		
Median	3		4		
Urban/Rural Status					0.3081
Rural	9,862	14.14%	9,995	14.33%	
Urban	59,903	85.86%	59,770	85.67%	
Teaching Status					0.0886
Yes	26,778	38.38%	26,469	37.94%	
No	42,987	61.62%	43,296	62.06%	
Hospital Bed Size					0.0974
0 - 99 beds	4,408	6.32%	4,524	6.48%	
100 - 199 beds	11,308	16.21%	11,194	16.05%	
200 - 299 beds	13,202	18.92%	13,468	19.30%	
300 - 399 beds	12,544	17.98%	12,630	18.10%	
400 - 499 beds	9,354	13.41%	9,396	13.47%	
≥ 500 beds	18,949	27.16%	18,553	26.59%	
Index Hospitalization Cost					
N	69,765		69,765		
Mean	$9,219.55		$9,176.99		0.2810
SD	$7,398.05		$7,350.35		
Median	$7,031.72		$6,918.42		
Total Patient Count	69,765		69,765		

Table W3. Bleeding Risk Scores for Matched Apixaban and Warfarin Study Cohorts*

Risk Score	Apixaban	Warfarin	p-value
$CHADS_2$ Score			
N	69,765	69,765	
Mean	2.64	2.64	0.3088
SD	1.24	1.24	
Median	3	3	
$CHADS_2$-VASc Score			
N	69,765	69,765	
Mean	4.23	4.23	0.8434
SD	1.57	1.57	
Median	4	4	
HAS-BLED Score			
N	69,765	69,765	
Mean	3.15	3.15	1.0000
SD	1.07	1.07	
Median	3	3	

*Baseline period and index hospitalization

Table W4. Bleed and Stroke Events Among Matched Apixaban and Warfarin Study Cohorts

Event	Apixaban		Warfarin		p-value
	N	%	N	%	
Prior Bleed Event	1,206	1.73%	1,270	1.82%	0.1944
Index Hospitalization Bleed Event	5,201	7.46%	5,187	7.43%	0.8865
Prior Stroke	1,444	2.07%	1,369	1.96%	0.1531
Index Hospitalization Stroke	4,845	6.94%	4,855	6.96%	0.9162

Table R1. Demographics and Clinical Characteristics of Matched Apixaban and Rivaroxaban Study Cohorts

Characteristic	Apixaban		Rivaroxaban		p-value
	N	%	N	%	
Age (years)					
N	59,747		59,747		
Mean	72.84		72.73		0.0865
SD	11.48		11.2		
Median	74		74		
Gender					0.8124
Female	28,750	48.12%	28,709	48.05%	
Male	30,997	51.88%	31,038	51.95%	
Race					0.1241
White	50,625	84.73%	50,383	84.33%	
Black	4,117	6.89%	4,271	7.15%	
Other/missing	5,005	8.38%	5,093	8.52%	
Health Plan Type					0.9464
Commerical	10,107	16.92%	10,178	17.04%	
Medicare	45,167	75.60%	45,080	75.45%	
Medicaid	2,372	3.97%	2,385	3.99%	
Other health plan	2,101	3.52%	2,104	3.52%	
APR-DRG Severity					0.9804
1-Minor	8,499	14.22%	8,505	14.24%	
2-Moderate	27,042	45.26%	26,975	45.15%	
3-Major	21,478	35.95%	21,542	36.06%	
4-Extreme	2,728	4.57%	2,725	4.56%	
CCI Score					
N	59,747		59,747		
Mean	2.12		2.12		0.6185

SD	1.89	1.92	
Median	2	2	
Total Patient Count	59,747	59,747	

APR-DRG: All Patient Refined Diagnosis Related Groups
CCI: Charlson Comorbidity Index
SD: Standard Deviation

Table R2. Index Hospitalization Characteristics of Matched Apixaban and Rivaroxaban Study Cohorts

	Apixaban		Rivaroxaban		
Characteristic	**N**	**%**	**N**	**%**	**p-value**
Hospital Admission Source					0.0750
Physician referral/home	48,250	80.76%	48,304	80.85%	
Transfer	5,328	8.92%	5,472	9.16%	
Other/unknown	6,169	10.33%	5,971	9.99%	
Length of Stay (LOS)					
N	59,747		59,747		
Mean	4.0		4.0		0.5608
SD	3.0		3.0		
Median	3		3		
Urban/Rural Status					0.3626
Rural	7,916	13.25%	8,023	13.43%	
Urban	51,831	86.75%	51,724	86.57%	
Teaching Status					0.2328
Yes	22,476	37.62%	22,676	37.95%	
No	37,271	62.38%	37,071	62.05%	
Hospital Bed Size					0.4365
0 – 99 beds	3,648	6.11%	3,670	6.14%	
100 – 199 beds	9,414	15.76%	9,372	15.69%	
200 - 299 beds	11,618	19.45%	11,611	19.43%	
300 - 399 beds	10,984	18.38%	10,810	18.09%	
400 - 499 beds	7,286	12.19%	7,506	12.56%	
≥ 500 beds	16,797	28.11%	16,778	28.08%	
Index Hospitalization Cost					
N	59,747		59,747		
Mean	$8,580.14		$8,569.23		0.7786
SD	$6,714.33		$6,703.71		
Median	$6,591.34		$6,557.62		

Total Patient Count	59,747	59,747

Table R3. Bleeding Risk Scores of Matched Apixaban and Rivaroxaban Study Cohorts*

Risk Score	Apixaban	Rivaroxaban	p-value
$CHADS_2$ Score			
N	59,747	59,747	
Mean	2.34	2.4	0.1187
SD	1.21	1.21	
Median	2	2	
$CHADS_2$-VASc Score			
N	59,747	59,747	
Mean	3.80	3.81	0.4191
SD	1.60	1.61	
Median	4	4	
HAS-BLED Score			
N	59,747	59,747	
Mean	2.90	2.90	1.0000
SD	1.06	1.06	
Median	3	3	

*Baseline period and index hospitalization

Table R4. Bleed and Stroke Events of Matched Apixaban and Rivaroxaban Study Cohorts

	Apixaban		Rivaroxaban		
Event	**N**	**%**	**N**	**%**	**p-value**
Prior Bleed Event	766	1.28%	755	1.26%	0.7765
Index Hospitalization Bleed Event	3,666	6.14%	3,762	6.30%	0.2501
Prior Stroke	208	0.35%	208	0.35%	1.0000
Index Hospitalization Stroke	3,300	5.52%	3,401	5.69%	0.2041

10.3. Outcome data

Table W5. Hospital Readmissions w/in 1 Month of Index Hospitalization for Matched Apixaban and Warfarin Study Cohorts

Readmission Type Characteristic	Apixaban N	Apixaban %	Warfarin N	Warfarin %	p-value
All-cause Readmission	9,844	14.11%	10,280	14.74%	0.0009
# of All-cause Readmissions					
N	69,765		69,765		
Mean	0.164		0.174		0.0001
SD	0.437		0.454		
Median	0		0		
All-cause Readmission LOS					
N	69,765		69,765		
Mean	1.020		1.132		<0.0001
SD	3.623		3.935		
Median	0		0		
All-cause Readmission Cost					
N	69,765		69,765		
Mean	$2,250.86		$2,378.33		0.0175
SD	$9,864.58		$10,179.59		
Median	$0.00		$0.00		
Major Bleed-related Readmission	651	0.93%	834	1.20%	<0.0001
# of Major Bleed-related Readmissions					
N	69,765		69,765		
Mean	0.010		0.012		<0.0001
SD	0.102		0.115		
Median	0		0		
Major Bleed-related Readmission LOS					
N	69,765		69,765		
Mean	0.056		0.073		0.0001
SD	0.787		0.864		
Median	0		0		
Major Bleed-related Readmission Cost					
N	69,765		69,765		
Mean	$132.50		$156.92		0.0424
SD	$2,511.08		$1,947.95		
Median	$0.00		$0.00		

Stroke-related Readmission	222	0.32%	294	0.42%	0.0015
# of Stroke-related Readmissions					
N	69,765		69,765		
Mean	0.003		0.004		0.0005
SD	0.058		0.070		
Median	0		0		
Stroke-related Readmission LOS					
N	69,765		69,765		
Mean	0.019		0.027		0.0028
SD	0.425		0.562		
Median	0		0		
Stroke-related Readmission Cost					
N	69,765		69,765		
Mean	$44.83		$63.28		0.0313
SD	$1,303.76		$1,850.78		
Median	$0.00		$0.00		

LOS: Length of Stay
SD: Standard Deviation
Note: Some patients may have both major bleed and/or stroke events (not mutually exclusive).

Table W6. Hospital Readmissions w/in 3 Months of Index Hospitalization for Matched Apixaban and Warfarin Study Cohorts

	Apixaban		Warfarin		
Readmission Type Characteristic	**N**	**%**	**N**	**%**	**p-value**
All-cause Readmission	13,890	19.91%	14,991	21.49%	<0.0001
# of All-cause Readmissions					
N	69,765		69,765		
Mean	0.259		0.284		<0.0001
SD	0.590		0.624		
Median	0		0		
All-cause Readmission LOS					
N	69,765		69,765		
Mean	1.505		1.714		<0.0001
SD	4.488		4.907		
Median	0		0		
All-cause Readmission Cost					
N	69,765		69,765		
Mean	$3,395.04		$3,746.21		<0.0001

SD	$11,872.46	$12,916.49	
Median	$0.00	$0.00	
Major Bleed-related Readmission	1,000 1.43%	1,296 1.86%	<0.0001
# of Major Bleed-related Readmissions			
N	69,765	69,765	
Mean	0.015	0.020	<0.0001
SD	0.133	0.146	
Median	0	0	
Major Bleed-related Readmission LOS			
N	69,765	69,765	
Mean	0.086	0.109	<0.0001
SD	0.970	1.041	
Median	0	0	
Major Bleed-related Readmission Cost			
N	69,765	69,765	
Mean	$205.65	$241.41	0.0132
SD	$2,909.28	$2,463.31	
Median	$0.00	$0.00	
Stroke-related Readmission	345 0.49%	452 0.65%	0.0001
# of Stroke-related Readmissions			
N	69,765	69,765	
Mean	0.005	0.007	<0.0001
SD	0.073	0.086	
Median	0	0	
Stroke-related Readmission LOS			
N	69,765	69,765	
Mean	0.028	0.039	0.0006
SD	0.509	0.666	
Median	0	0	
Stroke-related Readmission Cost			
N	69,765	69,765	
Mean	$66.83	$93.18	0.0060
SD	$1,466.30	$2,063.99	
Median	$0.00	$0.00	

LOS: Length of Stay
SD: Standard Deviation
Note: Some patients may have both major bleed and/or stroke events (not mutually exclusive).

Table W7. Predictors of All-Cause Hospital Readmissions within 1 Month of Index

		95% Confidence Limits		
	Odds Ratio	**Lower**	**Upper**	**p-value***
Index Drug				
Warfarin vs. Apixaban	1.052	1.021	1.084	0.0009

*p-value determined by analysis of Maximum Likelihood Estimates

Table W8. Predictors of Major Bleed-related Hospital Readmissions within 1 Month of Index

		95% Confidence Limits		
	Odds Ratio	**Lower**	**Upper**	**p-value***
Index Drug				
Warfarin vs. Apixaban	1.284	1.159	1.424	<0.0001

*p-value determined by analysis of Maximum Likelihood Estimates

Table W9. Predictors of Stroke-related Hospital Readmissions within 1 Month of Index

		95% Confidence Limits		
	Odds Ratio	**Lower**	**Upper**	**p-value***
Index Drug				
Warfarin vs. Apixaban	1.326	1.113	1.579	0.0016

*p-value determined by analysis of Maximum Likelihood Estimates

Table W10. Impact of Index OAC on LOS for All-Cause Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Warfarin vs. Apixaban	0.113	0.020	0.073	0.152	<0.0001

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Warfarin	1.132	0.014	1.104	1.161
Apixaban	1.020	0.014	0.992	1.048

Table W11. Impact of Index OAC on LOS for Major Bleed-related Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Warfarin vs. Apixaban	0.017	0.004	0.008	0.026	0.0001

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Warfarin	0.073	0.003	0.067	0.079
Apixaban	0.056	0.003	0.050	0.062

Table W12. Impact of Index OAC on LOS for Stroke-related Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Warfarin vs. Apixaban	0.008	0.003	0.003	0.013	0.0028

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Warfarin	0.027	0.002	0.023	0.030
Apixaban	0.019	0.002	0.015	0.022

Table W13a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for All-Cause Readmissions within 1-Month of Index

				Confidence Interval		
Comparison	N	Mean	Median	Lower	Upper	p-value
Warfarin vs. Apixaban	1,000	$134.17	$132.04	$31.94	$243.37	0.0100

Table W13b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

				Confidence Interval	
Index Drug	N	Mean	Median	Lower	Upper
Warfarin	1,000	$2,386.97	$2,386.30	$2,301.56	$2,478.64
Apixaban	1,000	$2,252.80	$2,252.37	$2,193.53	$2,316.26

Table W14a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for Major Bleed-related Readmissions within 1-Month of Index

Comparison	N	Mean	Median	Confidence Interval		p-value
				Lower	Upper	
Warfarin vs. Apixaban	1,000	$25.44	$25.22	$2.08	$50.32	0.0360

Table W14b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

Index Drug	N	Mean	Median	Confidence Interval	
				Lower	Upper
Warfarin	1,000	$157.80	$157.36	$138.94	$179.66
Apixaban	1,000	$132.37	$131.88	$119.01	$150.36

Table W15a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for Stroke-related Readmissions within 1-Month of Index

Comparison	N	Mean	Median	Confidence Interval		p-value
				Lower	Upper	
Warfarin vs. Apixaban	1,000	$19.14	$18.68	$2.96	$38.34	0.0180

Table W15b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

Index Drug	N	Mean	Median	Confidence Interval	
				Lower	Upper
Warfarin	1,000	$64.09	$63.57	$49.83	$81.00
Apixaban	1,000	$44.95	$44.66	$38.12	$53.70

Table R5. Hospital Readmissions w/in 1 Month of Index Hospitalization for Matched Apixaban and Rivaroxaban Study Cohorts

Readmission Type Characteristic	Apixaban		Rivaroxaban		p-value
	N	%	N	%	
All-cause Readmission	7,778	13.02%	8,155	13.65%	0.0013
# of All-cause Readmissions					
N	59,747		59,747		0.0005

Mean	0.151	0.159	
SD	0.419	0.434	
Median	0	0	
All-cause Readmission LOS			
N	59,747	59,747	
Mean	0.896	0.954	0.0036
SD	3.376	3.498	
Median	0	0	
All-cause Readmission Cost			
N	59,747	59,747	
Mean	$2,003.47	$2,052.84	0.3223
SD	$8,943.04	$8,287.06	
Median	$0.00	$0.00	
Major Bleed-related Readmission	452 0.76%	730 1.22%	<0.0001
# of Major Bleed-related Readmissions			
N	59,747	59,747	
Mean	0.008	0.013	<0.0001
SD	0.093	0.117	
Median	0	0	
Major Bleed-related Readmission LOS			
N	59,747	59,747	
Mean	0.044	0.065	<0.0001
SD	0.700	0.745	
Median	0	0	
Major Bleed-related Readmission Cost			
N	59,747	59,747	
Mean	$104.90	$147.24	0.0004
SD	$2,311.19	$1,816.34	
Median	$0.00	$0.00	
Stroke-related Readmission	153 0.26%	158 0.26%	0.7765
# of Stroke-related Readmissions			
N	59,747	59,747	
Mean	0.003	0.003	0.6658
SD	0.052	0.055	
Median	0	0	
Stroke-related Readmission LOS			
N	59,747	59,747	0.4661

Mean	0.014	0.016	
SD	0.380	0.421	
Median	0	0	
Stroke-related Readmission Cost			
N	59,747	59,747	
Mean	$37.68	$37.00	0.9248
SD	$1,284.64	$1,212.79	
Median	$0.00	$0.00	

LOS: Length of Stay
SD: Standard Deviation
NOTE: Some patients may have both major bleed and/or stroke events (not mutually exclusive).

Table R6. Hospital Readmissions w/in 3 Months of Index Hospitalization for Matched Apixaban and Rivaroxaban Study Cohorts

Readmission Type Characteristic	Apixaban		Rivaroxaban		p-value
	N	%	N	%	
All-cause Readmission	11,033	18.47%	11,833	19.81%	<0.0001
# of All-cause Readmissions					
N	59,747		59,747		
Mean	0.238		0.259		<0.0001
SD	0.568		0.598		
Median	0		0		
All-cause Readmission LOS					
N	59,747		59,747		
Mean	1.331		1.454		<0.0001
SD	4.179		4.403		
Median	0		0		
All-cause Readmission Cost					
N	59,747		59,747		
Mean	$3,046.27		$3,262.71		0.0007
SD	$10,876.03		$11,176.00		
Median	$0.00		$0.00		
Major Bleed-related Readmission	716	1.20%	1,115	1.87%	<0.0001
# of Major Bleed-related Readmissions					
N	59,747		59,747		
Mean	0.013		0.020		<0.0001
SD	0.122		0.152		

Median	0	0	
Major Bleed-related Readmission LOS			
N	59,747	59,747	
Mean	0.071	0.105	<0.0001
SD	0.869	1.016	
Median	0	0	
Major Bleed-related Readmission Cost			
N	59,747	59,747	
Mean	$169.28	$242.66	<0.0001
SD	$2,696.16	$2,780.47	
Median	$0.00	$0.00	
Stroke-related Readmission	248 0.42%	265 0.44%	0.4519
# of Stroke-related Readmissions			
N	59,747	59,747	
Mean	0.004	0.005	0.3987
SD	0.067	0.070	
Median	0	0	
Stroke-related Readmission LOS			
N	59,747	59,747	
Mean	0.023	0.025	0.4202
SD	0.455	0.505	
Median	0	0	
Stroke-related Readmission Cost			
N	59,747	59,747	
Mean	$56.69	$56.37	0.9680
SD	$1,421.18	$1,385.89	
Median	$0.00	$0.00	

LOS: Length of Stay
SD: Standard Deviation
NOTE: Some patients may have both major bleed and/or stroke events (not mutually exclusive).

Table R7. Predictors of All-Cause Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits		p-value*
		Lower	Upper	
Index Drug				
Rivaroxaban vs. Apixaban	1.056	1.021	1.092	0.0013

*p-value determined by analysis of Maximum Likelihood Estimates

Table R8. Predictors of Major Bleed-related Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits		p-value*
		Lower	Upper	
Index Drug				
Rivaroxaban vs. Apixaban	1.623	1.442	1.826	<0.0001

*p-value determined by analysis of Maximum Likelihood Estimates

Table R9. Predictors of Stroke-related Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits		p-value*
		Lower	Upper	
Index Drug				
Rivaroxaban vs. Apixaban	1.033	0.827	1.290	0.7765

*p-value determined by analysis of Maximum Likelihood Estimates

Table R10. Impact of Index OAC on LOS for All-Cause Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Rivaroxaban vs. Apixaban	0.06	0.020	0.02	0.10	0.0036

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Rivaroxaban	0.95	0.014	0.926	0.981
Apixaban	0.90	0.014	0.868	0.923

Table R11. Impact of Index OAC on LOS for Major Bleed-related Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Rivaroxaban vs. Apixaban	0.021	0.004	0.013	0.029	<0.0001

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Rivaroxaban	0.065	0.003	0.060	0.071
Apixaban	0.044	0.003	0.039	0.050

Table R12. Impact of Index OAC on LOS for Stroke-related Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Rivaroxaban vs. Apixaban	0.002	0.002	-0.003	0.006	0.4661

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Rivaroxaban	0.016	0.002	0.013	0.019
Apixaban	0.014	0.002	0.011	0.018

Table R13a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for All-Cause Readmissions within 1-Month of Index

				Confidence Interval		
Comparison	N	Mean	Median	Lower	Upper	p-value
Rivaroxaban vs. Apixaban	1,000	$54.67	$51.99	-$43.98	$156.28	0.2800

Table R13b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

				Confidence Interval	
Index Drug	N	Mean	Median	Lower	Upper
Rivaroxaban	1,000	$2,058.07	$2,056.48	$1,984.81	$2,137.49
Apixaban	1,000	$2,003.39	$2,003.61	$1,944.02	$2,060.72

Table R14a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for Major Bleed-related Readmissions within 1-Month of Index

Comparison	N	Mean	Median	Confidence Interval		p-value
				Lower	Upper	
Rivaroxaban vs. Apixaban	1,000	$43.04	$42.61	$16.22	$68.51	<0.0001

Table R14b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

Index Drug	N	Mean	Median	Confidence Interval	
				Lower	Upper
Rivaroxaban	1,000	$148.24	$147.74	$128.34	$170.93
Apixaban	1,000	$105.20	$104.39	$91.05	$123.53

Table R15a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for Stroke-related Readmissions within 1-Month of Index

Comparison	N	Mean	Median	Confidence Interval		p-value
				Lower	Upper	
Rivaroxaban vs. Apixaban	1,000	-$0.12	-$0.43	-$13.69	$14.99	0.96

Table R15b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

Index Drug	N	Mean	Median	Confidence Interval	
				Lower	Upper
Rivaroxaban	1,000	$37.77	$37.14	$27.21	$51.10
Apixaban	1,000	$37.89	$37.68	$30.30	$47.27

Table D5. Hospital Readmissions w/in 1 Month of Index Hospitalization for Matched Apixaban and Dabigatran Study Cohorts

Readmission Type Characteristic	Apixaban		Dabigatran		p-value
	N	%	N	%	
All-cause Readmission	5,353	13.52%	5,196	13.12%	0.1006
# of All-cause Readmissions					0.3477

N	39,604	39,604	
Mean	0.158	0.155	
SD	0.431	0.432	
Median	0	0	
All-cause Readmission LOS			
N	39,604	39,604	
Mean	0.976	0.978	0.9367
SD	3.604	3.641	
Median	0	0	
All-cause Readmission Cost			
N	39,604	39,604	
Mean	$2,267.56	$2,178.15	0.1939
SD	$10,347.49	$8,971.86	
Median	$0.00	$0.00	
Major Bleed-related Readmission	348 0.88%	392 0.99%	0.1041
# of Major Bleed-related Readmissions			
N	39,604	39,604	
Mean	0.009	0.010	0.2254
SD	0.102	0.103	
Median	0	0	
Major Bleed-related Readmission LOS			
N	39,604	39,604	
Mean	0.055	0.064	0.1105
SD	0.803	0.840	
Median	0	0	
Major Bleed-related Readmission Cost			
N	39,604	39,604	
Mean	$134.81	$159.64	0.2350
SD	$2,820.39	$3,059.91	
Median	$0.00	$0.00	
Stroke-related Readmission	103 0.26%	116 0.29%	0.3790
# of Stroke-related Readmissions			
N	39,604	39,604	
Mean	0.003	0.003	0.4627
SD	0.052	0.054	
Median	0	0	
Stroke-related Readmission LOS			
N	39,604	39,604	
Mean	0.016	0.022	0.1584
SD	0.431	0.767	

Median	0	0	
Stroke-related Readmission Cost			
N	39,604	39,604	
Mean	$39.82	$50.80	0.3010
SD	$1,383.15	$1,597.95	
Median	$0.00	$0.00	

LOS: Length of Stay
SD: Standard Deviation
NOTE: Some patients may have both major bleed and/or stroke events (not mutually exclusive).

Table D6. Hospital Readmissions w/in 3 Months of Index Hospitalization for Matched Apixaban and Dabigatran Study Cohorts

	Apixaban		Dabigatran		
Readmission Type Characteristic	**N**	**%**	**N**	**%**	**p-value**
All-cause Readmission	7,439	18.78%	7,640	19.29%	0.0689
# of All-cause Readmissions					
N	39,604		39,604		
Mean	0.244		0.254		0.0104
SD	0.575		0.595		
Median	0		0		
All-cause Readmission LOS					
N	39,604		39,604		
Mean	1.405		1.476		0.0242
SD	4.392		4.525		
Median	0		0		
All-cause Readmission Cost					
N	39,604		39,604		
Mean	$3,372.17		$3,399.75		0.7461
SD	$12,439.26		$11,519.56		
Median	$0.00		$0.00		
Major Bleed-related Readmission	521	1.32%	592	1.49%	0.0321
# of Major Bleed-related Readmissions					
N	39,604		39,604		
Mean	0.014		0.016		0.1346
SD	0.130		0.132		
Median	0		0		

Major Bleed-related Readmission LOS			
N	39,604	39,604	
Mean	0.082	0.092	0.1669
SD	0.970	0.989	
Median	0	0	
Major Bleed-related Readmission Cost			
N	39,604	39,604	
Mean	$204.47	$226.92	0.3397
SD	$3,235.96	$3,380.30	
Median	$0.00	$0.00	
Stroke-related Readmission	163 0.41%	184 0.46%	0.2586
# of Stroke-related Readmissions			
N	39,604	39,604	
Mean	0.004	0.005	0.2759
SD	0.067	0.070	
Median	0	0	
Stroke-related Readmission LOS			
N	39,604	39,604	
Mean	0.024	0.032	0.0954
SD	0.503	0.822	
Median	0	0	
Stroke-related Readmission Cost			
N	39,604	39,604	
Mean	$58.39	$74.84	0.1667
SD	$1,507.29	$1,825.41	
Median	$0.00	$0.00	

LOS: Length of Stay
SD: Standard Deviation
NOTE: Some patients may have both major bleed and/or stroke events (not mutually exclusive).

Table D7. Predictors of All-Cause Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits		p-value*
		Lower	Upper	
Index Drug				
Dabigatran vs. Apixaban	0.966	0.927	1.007	0.1006

*p-value determined by analysis of Maximum Likelihood Estimates

Table D8. Predictors of Major Bleed-related Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits		p-value*
		Lower	Upper	
Index Drug				
Dabigatran vs. Apixaban	1.128	0.975	1.304	0.1043

*p-value determined by analysis of Maximum Likelihood Estimates

Table D9. Predictors of Stroke-related Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits		p-value*
		Lower	Upper	
Index Drug				
Dabigatran vs. Apixaban	1.127	0.864	1.469	0.3793

*p-value determined by analysis of Maximum Likelihood Estimates

Table D10. Impact of Index OAC on LOS for All-Cause Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Dabigatran vs. Apixaban	0.002	0.026	-0.048	0.053	0.9367

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Dabigatran	0.978	0.018	0.942	1.014
Apixaban	0.976	0.018	0.940	1.012

Table D11. Impact of Index OAC on LOS for Major Bleed-related Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Dabigatran vs. Apixaban	0.009	0.006	-0.002	0.021	0.1105

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Dabigatran	0.064	0.004	0.056	0.072
Apixaban	0.055	0.004	0.047	0.063

Table D12. Impact of Index OAC on LOS for Stroke-related Hospital Readmissions within 1 Month of Index

Analysis of Maximum Likelihood Estimates					
			95% Confidence Limits		
Parameter	Estimate (day)	Standard Error	Lower	Upper	p-value
Dabigatran vs. Apixaban	0.006	0.004	-0.002	0.015	0.1584

Least Square Means				
			Confidence Interval	
Index OAC	Mean (day)	Standard Error	Lower	Upper
Dabigatran	0.022	0.003	0.016	0.028
Apixaban	0.016	0.003	0.010	0.022

Table D13a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for All-Cause Readmissions within 1-Month of Index

				Confidence Interval		
Comparison	N	Mean	Median	Lower	Upper	p-value
Dabigatran vs. Apixaban	1,000	-$75.48	-$71.57	-$210.69	$52.40	0.2460

Table D13b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

				Confidence Interval	
Index Drug	N	Mean	Median	Lower	Upper
Dabigatran	1,000	$2,194.12	$2,192.68	$2,087.65	$2,298.21
Apixaban	1,000	$2,269.60	$2,269.69	$2,187.38	$2,355.79

Table D14a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for Major Bleed-related Readmissions within 1-Month of Index

Comparison	N	Mean	Median	Confidence Interval		p-value
				Lower	Upper	
Dabigatran vs. Apixaban	1,000	$26.65	$25.42	-$15.00	$71.49	0.2140

Table D14b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

Index Drug	N	Mean	Median	Confidence Interval	
				Lower	Upper
Dabigatran	1,000	$161.74	$160.41	$130.28	$199.25
Apixaban	1,000	$135.09	$134.12	$113.25	$162.36

Table D15a. Two-Part Regression Analysis: Estimated Readmission Cost Difference per Patient for Stroke-related Readmissions within 1-Month of Index

Comparison	N	Mean	Median	Confidence Interval		p-value
				Lower	Upper	
Dabigatran vs. Apixaban	1,000	$11.26	$10.83	-$9.48	$35.33	0.2940

Table D15b. Two-Part Regression Analysis: Readmission Cost for Each Cohort (1000 cycles of bootstrapping with 2-part regression)

Index Drug	N	Mean	Median	Confidence Interval	
				Lower	Upper
Dabigatran	1,000	$51.25	$50.42	$35.23	$71.22
Apixaban	1,000	$39.99	$39.49	$30.15	$53.89

10.4. Main results

10.4.1. Primary Objective

To evaluate and compare 1-month MB-related readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban.

MB-related Hospital Readmissions w/in 1 Month of Index Hospitalization for Matched Apixaban and Warfarin Study Cohorts

Readmission Type Characteristic	Apixaban N	Apixaban %	Warfarin N	Warfarin %	p-value
Major Bleed-related Readmission	651	0.93%	834	1.20%	<0.0001
# of Major Bleed-related Readmissions					
N	69,765		69,765		
Mean	0.010		0.012		<0.0001
SD	0.102		0.115		
Median	0		0		
	Apixaban		**Rivaroxaban**		
Major Bleed-related Readmission	452	0.76%	730	1.22%	<0.0001
N	59,747		59,747		
Mean	0.008		0.013		<0.0001
SD	0.093		0.117		
Median	0		0		
	Apixaban		**Dabigatran**		
Major Bleed-related Readmission	348	0.88%	392	0.99%	0.1041
N	39,604		39,604		
Mean	0.244		0.254		0.2254
SD	0.575		0.595		
Median	0		0		

Predictors of Major Bleed-related Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits Lower	95% Confidence Limits Upper	p-value*
Index Drug				
Warfarin vs. Apixaban	1.284	1.159	1.424	<0.0001
Rivaroxaban vs. Apixaban	1.623	1.442	1.826	<0.0001
Dabigatran vs. Apixaban	1.128	0.975	1.304	0.1043

10.4.2. Secondary Objectives

1. To evaluate and compare 1-month all-cause readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban:

All-Cause Hospital Readmissions w/in 1 Month of Index Hospitalization for Matched Apixaban and Warfarin Study Cohorts

Readmission Type Characteristic	Apixaban N	Apixaban %	Warfarin N	Warfarin %	p-value
All-cause Readmission	9,844	14.11%	10,280	14.74%	0.0009
N	69,765		69,765		0.0001
Mean	0.164		0.174		
SD	0.437		0.454		
Median	0		0		
	Apixaban		**Rivaroxaban**		
All-cause Readmission	11,033	18.47%	11,833	19.81%	<0.0001
N	59,747		59,747		
Mean	0.238		0.259		<0.0001
SD	0.568		0.598		
Median	0		0		
	Apixaban		**Dabigatran**		
All-cause Readmission	5,353	13.52%	5,196	13.12%	0.1006
N	39,604		39,604		
Mean	0.158		0.155		0.3477
SD	0.431		0.432		
Median	0		0		

Predictors of All-Cause Hospital Readmissions within 1 Month of Index

	Odds Ratio	95% Confidence Limits Lower	95% Confidence Limits Upper	p-value*
Index Drug				
Warfarin vs. Apixaban	1.052	1.021	1.084	0.0009
Rivaroxaban vs. Apixaban	1.056	1.021	1.092	0.0013
Dabigatran vs. Apixaban	0.966	0.927	1.007	0.1006

2. To determine average hospital length of stay (LOS) and costs associated with MB-related and all-cause readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban:

Readmission Type Characteristic	Apixaban N	Apixaban %	Warfarin N	Warfarin %	p-value
Major Bleed-related Readmission LOS					
N	69,765		69,765		
Mean	0.056		0.073		0.0001
SD	0.787		0.864		
Median	0		0		
Major Bleed-related Readmission Cost					
N	69,765		69,765		
Mean	$132.50		$156.92		0.0424
SD	$2,511.08		$1,947.95		
Median	$0.00		$0.00		
All-cause Readmission LOS					
N	69,765		69,765		
Mean	1.020		1.132		<0.001
SD	3.623		3.935		
Median	0		0		
All-cause Readmission Cost					
N	69,765		69,765		
Mean	$2,250.86		$2,378.33		0.0175
SD	$9,864.58		$10,179.59		
Median	$0.00		$0.00		
	Apixaban		**Rivaroxaban**		**p-value**
Major Bleed-related Readmission LOS					
N	59,747		59,747		
Mean	0.044		0.065		<0.0001
SD	0.700		0.745		
Median	0		0		
Major Bleed-related Readmission Cost					
N	59,747		59,747		
Mean	$104.90		$147.24		<0.0001
SD	$2,311.19		$1,816.34		
Median	$0.00		$0.00		
All-cause Readmission LOS					
N	59,747		59,747		
Mean	0.896		0.954		0.0036
SD	3.376		3.498		
Median	0		0		
All-cause Readmission Cost					
N	59,747		59,747		

Mean	$2,003.47	$2,052.84	0.3223
SD	$8,943.04	$8,287.06	
Median	$0.00	$0.00	
	Apixaban	**Dabigatran**	**p-value**
Major Bleed-related Readmission LOS			
N	39,604	39,604	
Mean	0.055	0.064	0.1105
SD	0.803	0.840	
Median	0	0	
Major Bleed-related Readmission Cost			
N	39,604	39,604	
Mean	$134.81	$159.64	0.2350
SD	$2,820.39	$3,059.91	
Median	$0.00	$0.00	
All-cause Readmission LOS			
N	39,604	39,604	
Mean	0.976	0.978	0.9367
SD	3.604	3.641	
Median	0	0	
All-cause Readmission Cost			
N	39,604	39,604	
Mean	$2,267.56	$2,178.15	0.1939
SD	$10,347.49	$8,971.86	
Median	$0.00	$0.00	

10.5. Other analyses

Sensitivity analysis: To describe readmission rates, hospital LOS and costs associated with all-cause, MB-related, and stroke-related readmissions occurring within 3 months of initial hospitalizations of NVAF patients treated with rivaroxaban, dabigatran, or warfarin vs. apixaban. See Tables W6, R6 and D6 for results.

10.6. Adverse events / adverse reactions

This study includes unstructured data (e.g., narrative fields in the database) that were converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for

reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

11. DISCUSSION

11.1. Key results

Among matched cohorts treated with warfarin vs. apixaban:

- After PSM, patient and hospital characteristics were similar (statistically not significant).
- After PSM, the findings of the regression analyses were that for patients treated with warfarin vs. apixaban:
    - Treatment with warfarin was associated with significantly greater risks for 1-month MB-related, all-cause, and stroke-related readmissions and significantly higher costs for all readmission categories.

Among matched cohorts treated with rivaroxaban vs. apixaban:

- After PSM, the findings of the regression analyses were that for patients treated with rivaroxaban vs. apixaban:
    - Treatment with rivaroxaban was associated with a greater risk for 1-month MB-related readmission and higher MB-related readmission cost.
    - Treatment with rivaroxaban was associated with a greater risk for 1-month all-cause readmission and trending higher all-cause readmission cost.
    - Treatment with rivaroxaban was associated with a similar risk for 1-month stroke-related readmission and stroke-related readmission cost.

Among matched cohorts treated with dabigatran vs. apixaban:

- After PSM, patient and hospital characteristics were similar (statistically not significant).
- After PSM, the findings of the regression analyses were that for patients treated with dabigatran vs. apixaban:
    - Treatment with dabigatran was associated with similar risks for 1-month MB-related, all-cause, and stroke-related readmissions.
    - Costs for all readmission categories were not statistically significantly different between study cohorts.

11.2. Limitations

This study was a retrospective observational study that used a nationally representative hospital database, and some limitations require consideration when interpreting the results. The information reported in the deidentified patient records of the Premier Hospital database pertain mostly to only hospitals and thus outpatient healthcare utilization and costs could not

be evaluated in this study. In the case of patients treated with warfarin in which usage of an injectable anticoagulant was required for study inclusion, the purpose and durations of such injectable anticoagulant usage was not recorded in the database or assessed in the study. Furthermore, utilization of outpatient routine monitoring and associated costs were not evaluated in this study among the warfarin treated patients. Thus, follow-up studies using other data sources are warranted. Additionally, only readmissions to the same hospital or hospital system within the Premier network are captured in the database, which may have led to an underestimation of actual readmission rates. However, such an underestimation of readmission rates likely applies to both cohorts of apixaban and warfarin treated patients in the study. Although the Premier Hospital database is national in scope, the database populations may not be representative of localized geographic regions or the entire US population of VTE patients. This was an observational study, and patients were not randomized. Thus, despite statistical adjustments, unobserved confounders may still potentially exist for which the analysis did not control. Lastly, as this was a retrospective observational study, no causal relationship between the OAC treatments and outcomes can be concluded.

Strengths	**Limitations**
• This was a real-world data analysis comparing readmissions and the associated hospitalization utilization and cost of NVAF patients treated with OACs. • The Premier database is a hospital dataset that captures hospital utilization and costs. • Costs in Premier database reflect costs to hospitals. • Findings were obtained from the largest hospital database in the US.	• The data on patient records in the Premier hospital database are the costs to hospitals only, therefore outpatient healthcare utilization and costs not received in a hospital are excluded. Thus, in the case of warfarin the outpatient routine monitoring care and associated costs were excluded from our analysis. • While the Premier Hospital database contains information from a substantial number of hospitals across the US, the database populations may not be representative of the entire US population of NVAF patients. • Also, only readmissions to the same hospital or hospital system within the Premier network could be identified in the database, which may have led to an underestimate of actual readmission rates. • MB-related and stroke/SE-related readmissions were evaluated by the primary hospital discharge diagnoses for the readmissions, which may or may not fully capture the entire cause of readmissions. • As with all studies relying on administrative billing information, there may have been inaccuracies from hospital, billing and coding errors, as well as missing data.

	• Although PSM was used to control for multiple confounders, there is potential for residual bias in this study. For instance, the PSM did not take into account other confounding factors that were not included in the covariate list of the PSM process. • No causal relationship between OAC treatment and outcomes can be concluded based on this retrospective observational analysis. • This was not a cost-effectiveness evaluation based on a head-to-head, comparative, randomized clinical trial with efficacy or safety data - There are no head-to-head clinical trials comparing the efficacy and safety of any of the DOACs for reducing the risk of stroke or systemic embolism in patients with NVAF. This cost calculation does not imply comparable efficacy, safety, or product interchangeability - The follow-up period for patients was not uniform or consistent with those in the clinical trials • Unobserved confounders, such as over-the-counter medications (eg, aspirin), exist. The analysis did not control for them • No adjustments were made for multiple testing

11.3. Interpretation

See Key results (11.1) and Conclusions (13) sections

11.4. Generalizability

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

According to this large-scale, retrospective, real-world, hospital analysis of NVAF patients, after controlling for differences in patient and hospital characteristics, apixaban treatment was associated with better hospital readmission outcomes and lower hospital resource burden and costs for readmissions than warfarin and rivaroxaban. The results of this study may be helpful to guide hospitals, payers, patients, and other stakeholders in deciding on the optimal oral anticoagulation therapy that provides the most benefit to NVAF patients, while reducing the hospital resource and economic burden.

14. REFERENCES

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable