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IMPACT OF CYP3A4/P-GP INTERACTING MEDICATIONS ON CLINICAL OUTCOMES IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS MANAGED ON RIVAROXABAN

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Impact of CYP3A4/P-gp interacting medications on clinical outcomes in nonvalvular atrial fibrillation patients managed on rivaroxaban

by

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Abstract

Impact of CYP3A4/P-gp interacting medications on clinical outcomes in nonvalvular atrial fibrillation patients managed on rivaroxaban

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Objectives: To analyze concurrent drug use and its association with outcomes in nonvalvular atrial fibrillation patients receiving rivaroxaban.

Methods: We included patients ≥ 18 years of age who had at least one prescription for rivaroxaban between January 1, 2012 and December 31, 2016 along with at least two diagnoses of atrial fibrillation during the pre-index period. Those on rivaroxaban with concurrent exposure to CYP3A4/P-gp interacting medications were placed in the concomitant interacting medication (CIM) user group, and those without exposure to CYP3A4/P-gp interacting medications were placed in the CIM non-user group. Patients were excluded if they did not have continuous enrollment in the 365 days before and after the first prescription of rivaroxaban during the study period (allowing for ≤ 90-day gaps in coverage). Baseline characteristics, comorbidities, medication use, and occurrence of adverse events between the two groups were compared using inferential statistics. Multivariate logistic regression models with modified Poisson distributions and Cox

proportional hazard models were used to address the hypotheses, assessing the effect of CIM on bleed and thromboembolism, adjusted for covariates.

Results: A total of 287 and 180 patients were included in the CIM users group and the CIM non-users group, respectively. At baseline, compared to CIM non-users, CIM users had a higher proportion of pre-index cardiovascular issues: myocardial infarction (12.2% versus 6.1%), heart failure (43.6% versus 29.4%), and coronary artery disease (42.9% versus 32.2%). The average pre-index $CHADS_2VASc$ (4.2) and Charlson Comorbidity Index scores (2.7) in both cohorts were similar. In unadjusted analyses, the CIM user cohort had similar rates of bleed (13.9% versus 16.7%) and lower rates of thromboembolism (13.2% versus 28.3%) compared to the CIM non-user group. When controlling for covariates, relative to CIM non-users, CIM users had a comparable risk of bleed (risk ratio [RR]: 0.73; $p = 0.14$) and a lower risk of thromboembolism (RR: 0.58; $p < 0.01$). When adjusted for covariates and assessing time to first event, the hazard of thromboembolism was about half for CIM users (hazard ratio [HR] = 0.58; 95% confidence interval [CI]: 0.39, 0.87; $p < 0.01$).

Conclusion: This study suggests that co-administered CYP3A4 and P-gp inhibitors reduce the risk of thromboembolism in patients prescribed rivaroxaban. While no alteration of bleeding risk was observed, this may be limited by event rates, sample size, and inability to assess risk at the individual drug level.

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CHAPTER 1: INTRODUCTION

Atrial Fibrillation

Atrial fibrillation, also referred to as AFib or AF, is the most common type of sustained cardiac arrhythmia. Atrial fibrillation is detected using an electrocardiogram (ECG) and can be characterized as a supraventricular tachyarrhythmia with uncoordinated atrial activation, resulting in ineffective atrial contraction.[1-4] Classification of atrial fibrillation is based on duration of episodes (Table 1) and is relevant to clinical decision making since outcomes of therapy vary based on type of atrial fibrillation.[1-4] Episodes of atrial fibrillation typically increase in frequency and duration over time.[4] Symptoms atrial fibrillation patients experience vary, ranging from no symptoms to fatigue, palpitations, dyspnea, hypotension, syncope, or heart failure.[5]

Table 1.1: Definitions of Atrial Fibrillation[4]

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Long-standing persistent AF	• Continuous AF >12 mo in duration.
Permanent AF	• The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF, atrial fibrillation.

Atrial fibrillation affects an estimated 2.7-6.1 million people in the United States and occurs more frequently in women, patients aged 65 years or older, and those of European descent.[4] Other important risk factors of atrial fibrillation include high blood pressure, obesity, diabetes, heart failure, ischemic heart disease, hyperthyroidism, chronic kidney disease, alcohol consumption, and electrocardiographic findings (left ventricle hypertrophy and left atrial enlargement).[6] With an aging US population, it is anticipated that the atrial fibrillation will double to more than 5.6 million by the year 2050, with more than 50% of affected individuals aged 80 years or older.[7,8]

Atrial fibrillation has a substantial health and economic burden in the United States. Patients with atrial fibrillation have a six-fold increased risk of stroke and a two-fold increased risk of mortality, which remains 1.5-fold after adjusting for comorbidities.[9,10] Stroke secondary to atrial fibrillation tends to be more severe than those resulting from other underlying causes.[6] More than 750,000 hospitalizations and 130,000 deaths each year can be attributed to atrial fibrillation, costing the US healthcare system $6 billion each year.[4,6,11,12] On average, medical costs for atrial fibrillation are $8,705 higher per year than individuals that do not have the disease.[4,6] This highlights a tremendous need for optimizing treatment of the atrial fibrillation population in the US.

Clinical Guidelines for the Management of Atrial Fibrillation

Atrial fibrillation patients require appropriate use of antithrombotic therapy as well as control of other risk factors, including hypertension and hypercholesterolemia, to effectively reduce the risk of thromboembolic stroke.[4,13-17] Antithrombotic agents routinely used for stroke prevention in atrial fibrillation include anticoagulant drugs (heparins, warfarin, direct thrombin inhibitors, and factor Xa inhibitors) and antiplatelet drugs (aspirin and clopidogrel). Use of anticoagulants has been shown to effectively reduce the risk of

ischemic stroke, however these medications carry an increased risk of bleeding, ranging from minor bleeding to fatal intracranial or extracranial hemorrhage. Platelet aggregation inhibitors are less effective than warfarin, are better tolerated by some patients, but also carry a risk of major bleeding.[18-22] Selection of antithrombotic therapy should be made with careful consideration of the risks of stroke and bleeding, in addition to patient preferences.[4]

Risk stratification tools have been developed to stratify ischemic stroke risk among nonvalvular atrial fibrillation patients (NVAF). The $CHADS_2$ score has been validated in multiple different cohorts since its development in 2001.[23,24] The acronym signifies the derivation of the score (**C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes, and prior **S**troke). Primary limitations of the $CHADS_2$ score is poor identification of risk for those with a score ≤ 1 and underestimation of risk in patients with a score of 2 due to prior stroke.[4] More recently, the CHA_2DS_2-VASc score has been validated in nonvalvular atrial fibrillation patients and has been shown to have better stroke risk prediction and clearer anticoagulation recommendations than the previous $CHADS_2$ score.[25,26] Compared to $CHADS_2$, the $CHADS_2$VASc score has a broader range of scores (0 to 9 versus 0 to 6, respectively) and includes additional risk factors (female sex, age 65 to 74, and vascular disease) (Table 2).[27-29] The CHA_2DS_2-VASc is now a standard rubric that physicians use to stratify patient risk of stroke.[4] The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society Guidelines for the Management of Patients with Atrial Fibrillation recommend omission of antithrombotic treatment for nonvalvular atrial fibrillation patients at low risk of stroke (CHA_2DS_2-VASc = 0).[4] In nonvalvular atrial fibrillation patients with a CHA_2DS_2-VASc of 1, treatment with either an oral anticoagulant or aspirin may be considered, or antithrombotic treatment can also be omitted. [4] Patients with a prior history of stroke, TIA, or CHA_2DS_2-VASc score ≥ 2 should be considered for oral anticoagulant therapy.[4]

Table 1.2: Definition and Scores for CHA_2DS_2-VASc[4]

Component	Score
Congestive HF	1
Hypertension	1
Age ≥ 75 years[a]	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65-74 years	1
Female	1

[a]If patient age is 75 years or older, two points would be included in the calculation; a total possible score on the CHA_2DS_2-VASc is 9 points. TIA = transient ischemic attack; TE = thromboembolism.

Oral Anticoagulants

Warfarin, a vitamin K antagonist, has been the standard of care for stroke prevention in atrial fibrillation patients for over 60 years. Despite strong evidence for the efficacy of warfarin in clinical trials, several limitations have led its underuse and subsequent development of other oral anticoagulants.[30-33] The narrow therapeutic range of warfarin efficacy and close monitoring requirements have hindered broad use. Additionally, several drug and food interactions make the dosing of warfarin very challenging for physicians and patients.

Direct oral anticoagulants (DOACs) represent a newer group of agents used for the prevention and treatment of several thromboembolic disorders. Dabigatran is direct

thrombin inhibitor and received FDA approval in 2010, representing the first DOAC marketed in the US. Direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) were approved thereafter. All DOACs have received an FDA-labeled indication for stroke and systemic embolism prevention in nonvalvular atrial fibrillation as well as for the treatment and secondary prevention of venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE). DOACs present a potential solution to overcome many shortcomings of warfarin, while ensuring at least equivalent , if not superior, efficacy and safety in nonvalvular atrial fibrillation patients.[34-37] DOACs have more predictable pharmacological profiles, fewer drug-drug interactions, no major dietary interactions, and less risk of intracranial bleeding.[4,38] With their more rapid onset and offset, bridging with parental anticoagulation for initiation or brief interruptions of therapy is not required.

Nonetheless, challenges exist with DOACs. Rapid onset and offset of pharmacologic effect highlights the importance of adherence to these medications. Even a single missed dose can result in a period of increased risk of stroke. This is a serious consideration since routine follow-up is not required and results in less opportunities for physicians or other members of the healthcare team to assess patient compliance. At this time, only one reversal agent exists for dabigatran. For other DOACs, emergent life-threatening major bleeding can only be managed by non-elective major surgery anticoagulation reversal strategies (i.e., fluids, oxygen, hemodynamic support, packed red blood cells, and platelets [when appropriate]).[39] While dose modifications exist for patients with chronic kidney disease (CKD), warfarin remains the anticoagulant of choice in severe or end-stage renal disease.[4]

Although less frequent, DOACs have important drug interactions to consider. All DOACs are substrates for the efflux transporter P-glycoprotein (P-gp). P-gp inhibitors such

as ketoconazole, verapamil, amiodarone, dronedarone, quinidine, and clarithromycin, may increase DOAC plasma concentrations. With except of dabigatran, DOACs have also been identified as a substrate of the Cytochrome P450 3A4 (CYP3A4) hepatic enzyme.[40-42] Agents with significant CYP3A4 inhibition activity include select cardiac medications (diltiazem, verapamil, dronedarone), azole antifungals (itraconazole, ketoconazole, posaconazole), antiretroviral protease inhibitors (ritonavir, indinavir, nelfinavir, saquinavir), macrolide antibiotics (clarithromycin, erythromycin) and nefazodone. Therefore, concomitant medications that affect the P-gp and CYP3A4 mechanisms of drug metabolism may have significant effects on concentrations in the body.[24,27,40-45] FDA labeling for rivaroxaban and apixaban recommend to avoid concomitant use with combined P-gp and strong CYP3A4 inhibitors due to increased DOAC exposure and a potential increased risk of bleeding.[46,47] Due to a lack of real world evidence on clinical outcomes, this drug interaction may be underappreciated by physicians.

Rivaroxaban Drug Interaction Studies

Previous studies have elucidated the significant increased risk of bleeding when antiplatelet therapy, or platelet aggregation inhibitors (PAIs) and Non-Steroidal Anti-inflammatory Drugs (NSAIDs) were given with rivaroxaban.[48-50] Kreutz et al analyzed data from the Phase IV XAMOS (Xarelto® in the prophylaxis of post-surgical venous thromboembolism after elective major orthopaedic surgery of hip or knee) study to determine the association of concurrent use of PAIs, NSAIDs, and CYP3A4/P-gp inhibiters and inducers with bleed and thromboembolic events in patients managed on rivaroxaban and standard of care (SOC). NSAID use was associated with higher risk of major bleed in both rivaroxaban and SOC groups, while PAIs showed no effect for major bleeds in either group.[48] CYP3A4/P-gp inhibitor and inducer use was too infrequent and

statistical analyses were not performed on these groups. A Denmark national registry study discerned that atrial fibrillation patients taking NSAIDs were at an increased risk of serious bleed regardless of oral anticoagulation therapy.[49]

Pharmacologic studies address the association of concomitant CYP3A4/P-gp inhibitor and inducer use with altered blood levels of rivaroxaban.[41,51] For example, early clinical testing has shown that single agents with CYP3A4 inhibitor activity, such as ketoconazole, can increase serum rivaroxaban levels by as much as 158%.[51] Some cardiac drugs (e.g., diltiazem and verapamil) affect both CYP3A4 and P-gp pathways. Case reports have identified spontaneous bleeding or thromboembolism in patients receiving rivaroxaban who are receiving drugs known to be metabolized through the CYP3A4 pathway.[52,53] In both instances, patients suffered adverse events secondary to a recent switch (i.e., within days or weeks) to or initiation of rivaroxaban therapy in the setting of concurrent use of medications that attenuate CYP3A4 metabolism. One patient was concurrently managed with rifampicin, a CYP3A4 inducer, resulting in a fatal pulmonary embolism with confirmed sub therapeutic rivaroxaban levels.[52] In the other scenario, a patient suffered hemopericardium with tamponade while managed on multiple CYP3A4 inhibitors (atorvastatin and dronedarone). These cases highlight the challenges of managing patients on DOAC therapy, especially in the setting of polypharmacy.

A recent analysis, by Chang et al., investigated the association between the DOAC use (dabigatran, rivaroxaban, and apixaban) with and without concurrent CYP3A4 and P-gp inhibitor use for risk of major bleeding in patients with nonvalvular atrial fibrillation.[54] Concurrent use of amiodarone, fluconazole, rifampin, and phenytoin was associated with an increased risk of major bleeding among DOAC users.[54] However, Chang and associates focused on quarterly incidence rates of medication exposure and bleeding events and did

not precisely measure the temporal relationship between DOAC initiation and the occurrence of bleeding events.

Study Rationale

Oral anticoagulants are the mainstay of antithrombotic therapy in patients with atrial fibrillation. For over 50 years, warfarin was the only oral anticoagulant available for clinical use in the US. Many limitations exist with warfarin, including challenges with inter-patient variability of dose response, several drug and food interactions, and a narrow therapeutic window that requires frequent monitoring of international normalized ratio (INR). DOACs present a potential solution to several of these shortcomings but are not absent of their own challenges. Particularly, DOAC drug interactions have serious implications and despite FDA labeling may be underappreciated in clinical practice. While data are available for multiple DOACs, this study will focus on rivaroxaban considering it was the first approved factor Xa inhibitor approved in the US and carries label recommendations against concomitant use among CYP3A4 and P-gp inhibitors. Uncertainty remains around thromboembolism and bleeding risk for specific DOAC use and concomitant interaction medications affecting metabolism via the CYP3A4 and P-gp systems. Moreover, understanding how this potential increased risk functions over time would help inform better medication management practices for patients on DOACs.

CHAPTER 2: METHODS

Study Objectives and Hypotheses

The aim of this present study is to analyze concomitant drug use and its association with bleed and thromboembolism outcomes in nonvalvular atrial fibrillation patients receiving rivaroxaban. Here we compare two mutually exclusive cohorts: 1) patients managed on rivaroxaban taking CIMs (CIM users) and 2) patients managed on rivaroxaban without exposure to CIMs (CIM non-users). Specific objectives and null hypotheses of this study include:

1. To determine whether the demographics differ between CIM users and CIM non-users.

   H_o1.1: The difference in age between CIM users and CIM non-users is not statistically significant.

   H_o1.2: The difference in gender between CIM users and CIM non-users is not statistically significant.

2. To determine whether the prevalence of comorbidities during the pre-index period differs between CIM users and CIM non-users.

   H_o2.1: The difference in prevalence of hypertension between CIM users and CIM non-users is not statistically significant.

   H_o2.2: The difference in prevalence of myocardial infarction between CIM users and CIM non-users is not statistically significant.

   H_o2.3: The difference in prevalence of dyslipidemia between CIM users and CIM non-users is not statistically significant.

   H_o2.4: The difference in prevalence of diabetes between CIM users and CIM non-users is not statistically significant.

H_o2.5: The difference in prevalence of heart failure between CIM users and CIM non-users is not statistically significant.

H_o2.6: The difference in prevalence of coronary artery disease between CIM users and CIM non-users is not statistically significant.

H_o2.7: The difference in prevalence of chronic kidney disease between CIM users and CIM non-users is not statistically significant.

H_o2.8: The difference in prevalence of cancer between CIM users and CIM non-users is not statistically significant.

H_o2.9: The difference in prevalence of history of stroke between CIM users and CIM non-users is not statistically significant.

H_o2.10: The difference in prevalence of history of bleed between CIM users and CIM non-users is not statistically significant.

H_o2.11: The difference in Charlson Comorbidity Index scores between CIM users and CIM non-users is not statistically significant.

H_o2.12: The difference in CHA_2DS_2-VASc scores between CIM users and CIM non-users is not statistically significant.

3. To determine whether pre-index anticoagulant treatment history differs between CIM users and CIM non-users.

   H_o3.1: The difference in pre-index warfarin use (yes/no) between CIM users and CIM non-users is not statistically significant.

4. To determine whether the rate of bleed differs between CIM users and CIM non-users.

   H_o4.1: The difference in the proportion of patients experiencing a bleed event between CIM users and CIM non-users is not statistically significant.

H_o4.2: The difference in the proportion of patients experiencing a major bleed event between CIM users and CIM non-users is not statistically significant.

5. To determine whether the rate of thromboembolism differs between CIM users and CIM non-users.

   H_o5.1: The difference in the proportion of patients experiencing a thromboembolic event between CIM users and CIM non-users is not statistically significant.

6. To determine whether any CIM use is associated with the risk of bleed.

   H_o6.1: When adjusted for covariates, the association between CIM use and the risk of bleed is not statistically significant.

7. To determine whether any CIM use is associated with the risk of thromboembolism.

   H_o7.1: When adjusted for covariates, the association between CIM use and the risk of thromboembolism is not statistically significant.

8. To determine whether CIM use is associated with the hazard of bleed.

   H_o8.1: When adjusted for covariates, and assessing time to first event, the association between CIM use and the hazard of bleed is not statistically significant.

9. To determine whether the CIM use is associated with the hazard of thromboembolism.

   H_o9.1: When adjusted for covariates, and assessing time to first event, the association between CIM use and the hazard of thromboembolism is not statistically significant.

Study Design and Data Source

This was a retrospective cohort study that will combine prescription and medical claims data from Baylor Scott & White Health (BSWH), Central region. BSWH is a non-profit, integrated health care system including a network of 48 acute care hospitals and more than 900 patient care sites with approximately 6,000 physicians and other healthcare providers. Pharmacy and medical claims were longitudinally linked to patient enrollment and medical care data containing demographic information. Pharmacy claims contain details from all dispensed prescriptions, including the drug name, date and quantity dispensed, days supplied, and prescriber information. Medical claims provide detailed information on inpatient and outpatient services, include date and place of service, payments, procedure codes, and up to 5 International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and Tenth Edition (ICD-10-CM) diagnosis codes per date of care.

The date of first prescription for rivaroxaban was referred to as the index date. A definition of at least two diagnoses of nonvalvular atrial fibrillation (ICD-9-CM: 427.31, ICD-10-CM: I48.0, I48.2, I48.91) was used to determine the patient cohort. Data were collected from one year prior to the index date through one year post-index including: healthcare resource utilization around outcomes of interest (i.e., bleeding and thromboembolism events). Collected variables are described in greater detail in the following sections. This study was approved by the University of Texas at Austin and the Baylor Scott & White Institutional review boards following expedited review.

Sample Selection

The sample will consist of patients aged 18 years or older initiating rivaroxaban therapy between January 1, 2012 and December 31, 2016. Atrial fibrillation was defined as requiring at least two occurrences where the diagnosis of atrial fibrillation was documented (ICD-9-CM: 427.31, ICD-10-CM: I48.0, I48.2, I48.91) from any setting (inpatient or outpatient) in the 12 months before the date when rivaroxaban was first dispensed (index date). We excluded patients with fewer than 365 days of continuous prescription and medical coverage immediately preceding and following the index date (with no more than a 90-day gap in coverage).

Study Variables

Outpatient pharmacy claims were used to characterize initiation and longitudinal exposure to rivaroxaban, and all possible doses and dosing regimens were allowed in the analysis for rivaroxaban. Baseline demographics and clinical characteristics were assessed using medical claims during the 12 months prior to the index date. Covariates included age, gender, and comorbidities. Comorbidities at baseline were identified using appropriate ICD-9-CM and ICD-10-CM codes from medical claims in the 1 year prior to index, as described in Appendix 2. Comorbidities of interest included dyslipidemia, history of MI, diabetes, heart failure, coronary artery disease, chronic kidney disease, cancer, history of stroke, and history of bleed, in addition to other conditions found in the Charlson Comorbidity Index. CHA_2DS_2-VASc scores were calculated across both cohorts to understand stroke risk. Prior use of warfarin was also collected. Oncology patients were included despite concerns for the possibility a of hypercoagulable state. The rationale for inclusion of this patient subset was that many oncology patients are commonly prescribed

the interacting medications of interest and may therefore be at a higher risk of adverse events.

Variables assessed during the 12 months following the index date were CIM use, and bleeding or thromboembolism. The primary independent measure was exposure (yes/no) to CIM including inhibitors of the CYP3A4 and/or P-gp systems, which was also derived from the outpatient pharmacy claims information. Selection of relevant agents in these respective groups were based on methods described in previous literature[48], which includes references from the Food and Drug Administration (FDA) guidance for drug interaction studies[55], the University of Indiana's Department of Clinical Pharmacology Flockhart Table™ of clinically relevant P450 drug interactions[56], and drugs identified in previous analyses and case reports.[49,51,52] Non-systemic formulations of CIM were excluded from the analysis since they are not anticipated to have an appreciable effect on blood concentrations of rivaroxaban. In this study, we characterized P-gp inhibitors and CYP3A4 inhibitors; however, for analyses, we will combine these groups into a single CIM variable to increase power. The use of PAIs in the 12 months following the index date was also examined to further elucidate their additive bleeding risk due to pharmacodynamic interactions with rivaroxaban demonstrated previously. Table 2.1 shows the medications of interest in this study.

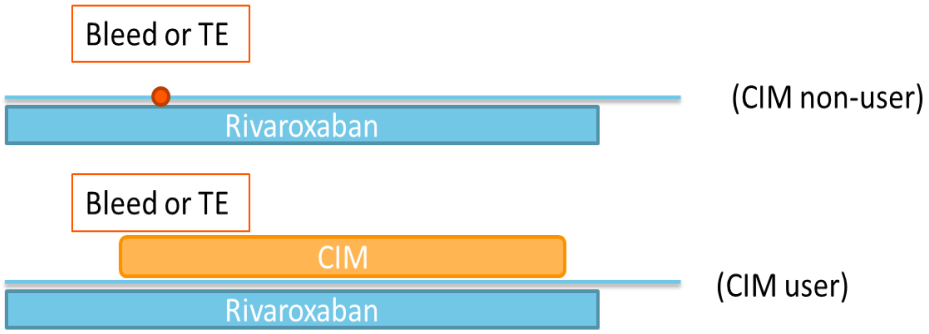
Table 2.1 Study Medications of Interest[a]

Oral Anticoagulants
Rivaroxaban, Warfarin
CYP3A4+P-gp ("Dual") Inhibitors
Clarithromycin, Diltiazem, Dronedarone, Erythromycin, Itraconazole, Ketoconazole, Ritonavir, Verapamil
CYP3A4 Inhibitors
Cobicistat, Indinavir, Nelfinavir, Nefazodone, Posaconazole, Saquinavir, Voriconazole
P-gp Inhibitors
Amiodarone, Azithromycin, Captopril, Carvedilol, Conivaptan, Cyclosporine, Felodipine, Quinidine, Ranolazine
Platelet Aggregation Inhibitors
Anagrelide, Aspirin, Cangrelor, Cilostazol, Clopidogrel, Defibrotide, Dipyridamole, Prasugrel, Ticagrelor, Ticlopidine, Vorapaxar, Abciximab, Eptifibatide, Tirofiban

Medication[a] use was identified in pharmacy claims using the National Drug Code (NDC). The NDC is a unique 10-digit, 3-segment number used as a universal product identifier for human drugs in the United States. A comprehensive list of NDC codes used for this analysis is attached in an ancillary Microsoft Excel file.

Bleeding and thromboembolism events were identified in the medical claims using ICD-9-CM and ICD-10-CM diagnosis codes (Appendix A). Major bleeds were defined as any bleeding event requiring inpatient hospitalization or an emergency department visit.[54] Bleeding and thromboembolism events were captured in the 12-month period following the index date and were analyzed separately. These events were attributed to rivaroxaban +/- CIM use when the date of bleed or thromboembolism overlapped with the dates of prescription fill coverage. CIM users were identified as patients that had overlapping use of CIM and rivaroxaban, and events must occur during this period to be considered an event in the CIM user cohort (Figure 2.1). Moreover, if a patient experienced a bleeding event while on rivaroxaban therapy alone and then initiated a CIM, this patient would be considered a non-CIM user (Figure 2.1). Separate analyses were conducted to assess bleed and thromboembolism rates across the two cohorts. Only the first event during the 1-year post-index period was counted towards the analysis. All patients were followed for up to one year following the index date.

Figure 2.1 Bleed and Thromboembolism Definition for CIM users and CIM non-users



TE = thromboembolism; CIM = concomitant interacting medication.

Statistical Analysis

Descriptive statistics (mean and standard deviation [SD], frequency and percentage) will characterize the covariates of interest in each group, (CIM users versus CIM non-users). Student t-test or nonparametric equivalent (Wilcoxon rank-sum) statistics were used for continuous measures and chi-square analysis for categorical measures to detect differences between groups. Chi-square tests were used to evaluate the difference in the proportion of patients with bleeding or thromboembolism among CIM users compared with CIM non-users.

Multivariate logistic regression using a modified Poisson distribution assessed the association of CIM for the outcomes of interest, adjusting for clinical and demographic covariates, reported as relative risks (RR) with their 95% confidence intervals (CIs). Poisson regression for our binary outcomes was selected due to the preference of reporting relative risk over odd ratios for rare events, understanding that odds ratios tend to overstate the estimation of treatment effects.[57,58] Time to bleed or thromboembolism from the index rivaroxaban prescription was described using a Cox proportional hazards model accounting for time-varying exposure to CIM and adjusting for differences among the treatment

cohorts was used to assess the risk of bleed or thromboembolism, reported as hazard ratios (HR) with their 95% CIs. Implementing a time-varying exposure model was essential in this analysis since some CIMs in the analysis may only be used for short durations of time (e.g., 7 to 14 day courses of antibiotics). In standard Cox models, the assumption that patients stay on treatment once started likely results in some misclassification of outcomes attributable to treatment and may result in biased treatment effect estimation.[59] Covariates in the adjusted analyses include age, gender, pre-index warfarin use (yes/no), bleed during the baseline period (yes/no), and CCI score. An $\alpha < 0.05$ was used as the criterion significance level. Statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

CHAPTER 3: RESULTS

Study Sample

During 2012 to 2016, a total of 1,836 patients with rivaroxaban were identified. Among them, 656 (35.7%) had two diagnoses for atrial fibrillation. Six hundred and twenty seven (95.6%) of the atrial fibrillation patients were adults. Of these, 467 (74.5%) met the continuous enrolment criteria to create our final study cohort. A total of 287 patients had CIM use, while 180 patients had no CIM use. Table 3.1 reports the study sample attrition.

Table 3.1: Sample selection

Selection Criteria	**N (%)**
Index prescription for rivaroxaban between January 1, 2012 and December 31, 2016	1,836 (100%)
At least two diagnoses of atrial fibrillation between January 1, 2011 and December 31, 2016	656 (35.7%)
≥ 18 years old	627 (95.6%)
≥365 days of continuous enrollment immediately preceding and following the index date (≤90-day gap in coverage)	**467 (74.5%)**
Prescription for at least one CYP3A4 or P-gp inhibitor between January 1, 2012 and December 31, 2016	287 (61.5%)

Baselines Demographics and Clinical Characteristics

Table 3.2 describes the baseline demographic and clinical characteristics for the 467 patients meeting the inclusion criteria. The mean age at index was 73.4 years (SD 9.9), and 55.9% of the studied population were men. The baseline average CHA_2DS_2-VASc was 4.2 (SD 1.9) and the Charlson Comorbidity Index scores were on average 2.7 (SD 2.4). More than 91% of the included patients were diagnosed with hypertension, and greater than 78% had a diagnosis of dyslipidemia. Other common comorbidities included diabetes (35.1%), heart failure (38.1%), and coronary artery disease (38.8%). Approximately one-fourth of patients had a history of stroke and nearly 23% had a history of bleed. One hundred and eleven (23.8%) patients had warfarin use prior to initiation of rivaroxaban.

Compared to CIM non-users, there were a significantly higher proportion of CIM users with prior myocardial infarction (n [%]: 35 [12.2] vs. 11 [6.1]; $p = 0.03$), heart failure (125 [43.6] vs. 53 [29.4]; $p < 0.01$), and coronary artery disease (123 [42.9] vs. 58 [32.2]; $p = 0.02$). A greater proportion of CIM non-users had cancer (29 [16.1] vs. 27 [9.4]; $p = 0.03$) and pre-index warfarin use (55 [30.6] vs. 56 [19.5]; $p < 0.01$) compared to CIM-users. Demographics and other clinical comorbidity variables were balanced across CIM users and CIM non-users.

Table 3.2: Baseline demographic and clinical comorbidity variables among nonvalvular atrial fibrillation patients on rivaroxaban

	Rivaroxaban users (n=467), N(%) or Mean (SD)	**CIM[a] users (n=287), N(%) or Mean (SD)**	**CIM non-users (n=180), N(%) or Mean (SD)**	***p*-value**
Demographics				
Age, years	73.4 (9.9)	73.0 (9.9)	74.1 (10.0)	0.30
Female	206 (44.1)	135 (47.0)	71 (39.4)	0.11
Comorbidities				
Hypertension	426 (91.2)	263 (91.6)	163 (90.6)	0.69
Dyslipidemia	366 (78.4)	228 (79.4)	138 (76.7)	0.48
Myocardial infarction	46 (9.9)	35 (12.2)	11 (6.1)	0.03
Diabetes	164 (35.1)	104 (36.2)	60 (33.3)	0.52
Heart failure	178 (38.1)	125 (43.6)	53 (29.4)	<0.01
Coronary artery disease	181 (38.8)	123 (42.9)	58 (32.2)	0.02
Chronic kidney disease	77 (16.5)	49 (17.1)	28 (15.6)	0.67
Cancer	56 (12.0)	27 (9.4)	29 (16.1)	0.03
History of stroke	128 (27.4)	74 (25.8)	54 (30.0)	0.32
History of bleed	106 (22.7)	70 (24.4)	36 (20.0)	0.27
Charlson Comorbidity Index	2.7 (2.4)	2.7 (2.4)	2.6 (2.5)	0.40
CHA_2DS_2-VASc	4.2 (1.9)	4.2 (2.0)	4.1 (1.9)	0.40
Medication				
Warfarin	111 (23.8)	56 (19.5)	55 (30.6)	<0.01

[a]CIM includes CYP3A4 and P-gp inhibitors. CIM, Concomitant interacting medication.

Medication Use

Table 3.3 shows the medication use during the 12 months following the index period. A total of 287 patients had CIM use, with 137 on CYP3A4 inhibitors, and 201 on P-gp inhibitors. Consequently, 27 patients had some combination of CYP3A4 and P-gp inhibitor use during the follow-up period. P-gp inhibitors were the most frequently used CIM (42.6%), primarily amiodarone (15.8%) and carvedilol (13.5%). All CYP3A4 inhibitors used during the study period were identified as dual inhibitory agents also affecting the P-gp system (29.3%). Utilization of these dual CYP3A4/P-gp inhibitors was highest for diltiazem (20.3%) followed by dronedarone (6.9%) and verapamil (2.1%).

PAI use was infrequent across the study cohort (13.1%), with 51 patients taking clopidogrel (10.9%) and eight patients taking aspirin (1.7%). Notably, use of prasugrel was absent from our cohort.

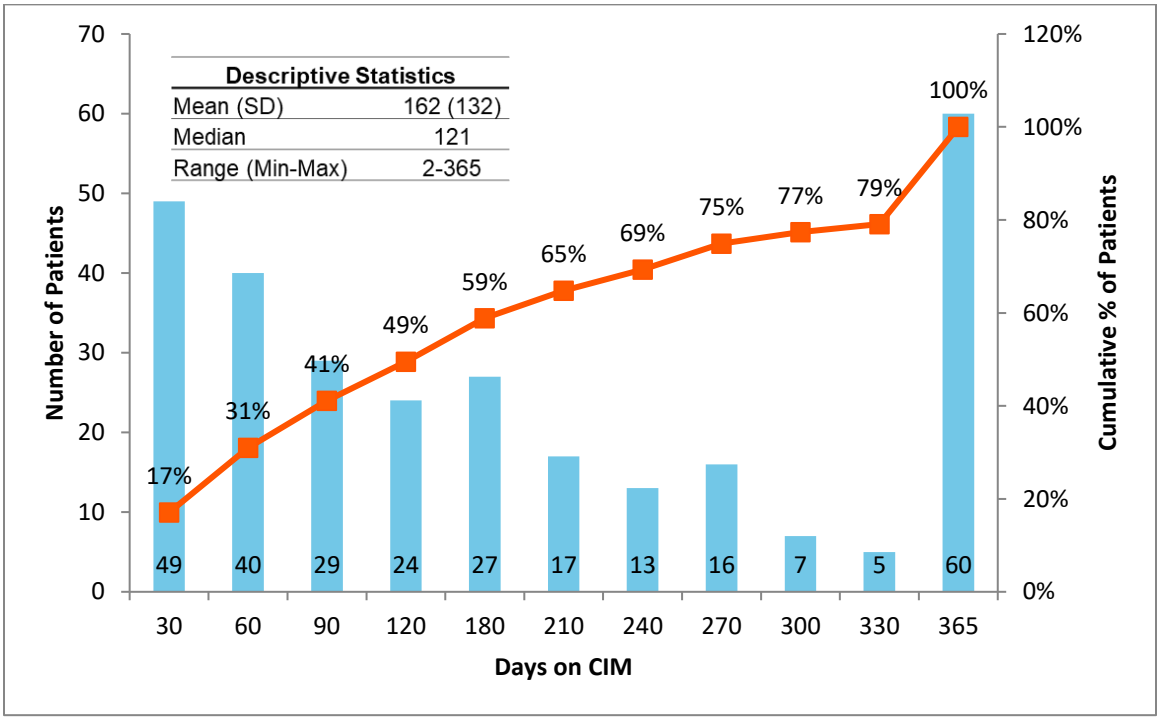
Table 3.3: Identified follow-up medication utilization

Drug Class	**Agents identified (# of patients on medication)**	**Utilization across cohort (n = 467), N(%)**
Any CIM[a]		287 (61.5%)
CYP3A4/P-gp inhibitor	Clarithromycin (3), diltiazem (95), dronedarone (32), verapamil (10)	140 (30.040300%)
P-gp inhibitor	Amiodarone (74), azithromycin (47), captopril (1), carvedilol (63), cyclosporine (1), felodipine (11), quinidine (1), ranolazine (3)	201 (43.020130%)
PAI	Anagrelide (1), aspirin (8), cilostazol (2), clopidogrel (51), ticagrelor (1)	633 (13.55%)

[a]CIM includes CYP3A4 and P-gp inhibitors. CIM, Concomitant interacting medication; PAI, platelet aggregation inhibitors.

On average, those patients prescribed concomitant interacting medications had 162 (SD 132) days of exposure during the 12 months following the index date (Figure 3.1). Of these, 49 (17%) patients had less than 30 days of exposure while 60 patients (21%) had exposure to a concomitant interacting medication during the entire follow-up period.

Figure 3.1 Distribution of CIM exposure in days (n = 287)



CIM, concomitant interacting medication. The horizontal axis represents the ordinal categories of CIM exposure days. The category label represents the upper limit of CIM exposure days (e.g. patients in category "30" had ≤30 days of CIM exposure during the follow-up period). The bars represent the number of patients in each category and the trend line represents cumulative percentage of patients with increasing CIM days.

Bleed and Thromboembolism

The incidence of bleed was assessed during the 12 months post-index (Table 3.4.). A bleed occurred in 90 (19.3%) patients across the cohort. Of these, 60 first bleed events occurred in those patients taking CIM; however, 20 events were removed from the analysis since the event occurred outside of CIM exposure. In unadjusted analyses, CIM users experienced similar bleeds compared to patients not taking CIM (n[%]: 40 [15.0] versus 30 [16.7]; p = 0.63). Major bleeds (defined as a primary diagnosis code for a hemorrhagic event requiring hospitalization or an emergency department visit) occurred less frequently, with 21 patients (4.5%) experiencing these events. Predicted cell sizes were too small to conduct inferential analyses on major bleeding events.

The incidence of thromboembolism was also assessed during the 12 months (Table 3.4). A thromboembolism occurred in 116 (24.8%) of patients across the cohort. Of these, 65 first thromboembolism events occurred in those patients taking CIM; however, 27 events were removed from the analysis since the event occurred outside of CIM exposure. In unadjusted analyses, CIM users experienced fewer thromboembolic events compared to patients not taking CIM (n[%]: 38 [14.6] versus 51 [28.3]; p < 0.001).

Table 3.4: Proportion of patients experiencing bleed and thromboembolism in the follow-up period

	Rivaroxaban users (n=467), N(%)	**CIM[a] users (n=287), N(%)**		**CIM non-users (n=180), N(%)**	***p*-value[b]**
		Synchronous to event	**Asynchronous to event**		
Bleed	90 (19.3)	40 (13.9)	20 (7.0)	30 (16.7)	0.63
Major Bleed	21 (4.5)	2 (0.7)	11 (3.8)	8 (4.4)	N/A
Thromboembolism	116 (24.8)	38 (13.2)	27 (9.4)	51 (28.3)	<0.001

[a]CIM includes CYP3A4 and P-gp inhibitors.
[b]Statistical analyses performed for CIM users synchronous event compared to CIM non-users.
CIM, Concomitant interacting medication.

When adjusted for baseline differences, there was no association between CIM exposure and risk of bleed (risk ratio [RR]: 0.73; 95% confidence interval [CI]: 0.47, 1.11; p = 0.14) (Table 3.5). Patients who used PAI during the follow-up period had 1.72 times the risk of bleed compared to those who did not (risk ratio [RR]: 1.72, 95% CI: 1.02, 2.91; p = 0.04). Patients with a prior bleed event that occurred before the index date had 2.17 times the risk of bleed compared to patients with no prior bleeding history (risk ratio [RR]: 2.17, 95% CI: 1.40, 3.38; p < 0.001).

Table 3.5: Multivariate logistic regression with modified Poisson distribution predicting bleed

Parameter	**RR**	**95% CI**	***p*-value**
CIM[a]	0.73	0.47-1.11	0.14
Age	1.12	0.90-1.40	0.32
Female	1.36	0.87-2.11	0.17
PAI	**1.72**	**1.02-2.91**	**0.04**
Pre-index warfarin	0.86	0.53-1.40	0.54
Pre-index bleed	**2.17**	**1.40-3.38**	**<0.001**
CCI	1.06	0.97-1.15	0.19

[a]CIM includes CYP3A4 and P-gp inhibitors. CCI, Charlson Comorbidity Index; CIM, concomitant interacting medication; PAI, platelet aggregation inhibitor.

When adjusted for baseline differences, patients with CIM exposure had lower risk of thromboembolism compared to those without CIM exposure (risk ratio [RR]: 0.58; 95% confidence interval [CI]: 0.39, 0.87; $p < 0.01$) (Table 3.6). Patients with a prior thromboembolism event that occurred before the index date had 4.56 times the risk of thromboembolism compared to those with no history of thromboembolism (risk ratio [RR]: 4.56, 95% CI: 2.82, 7.37; $p < 0.0001$).

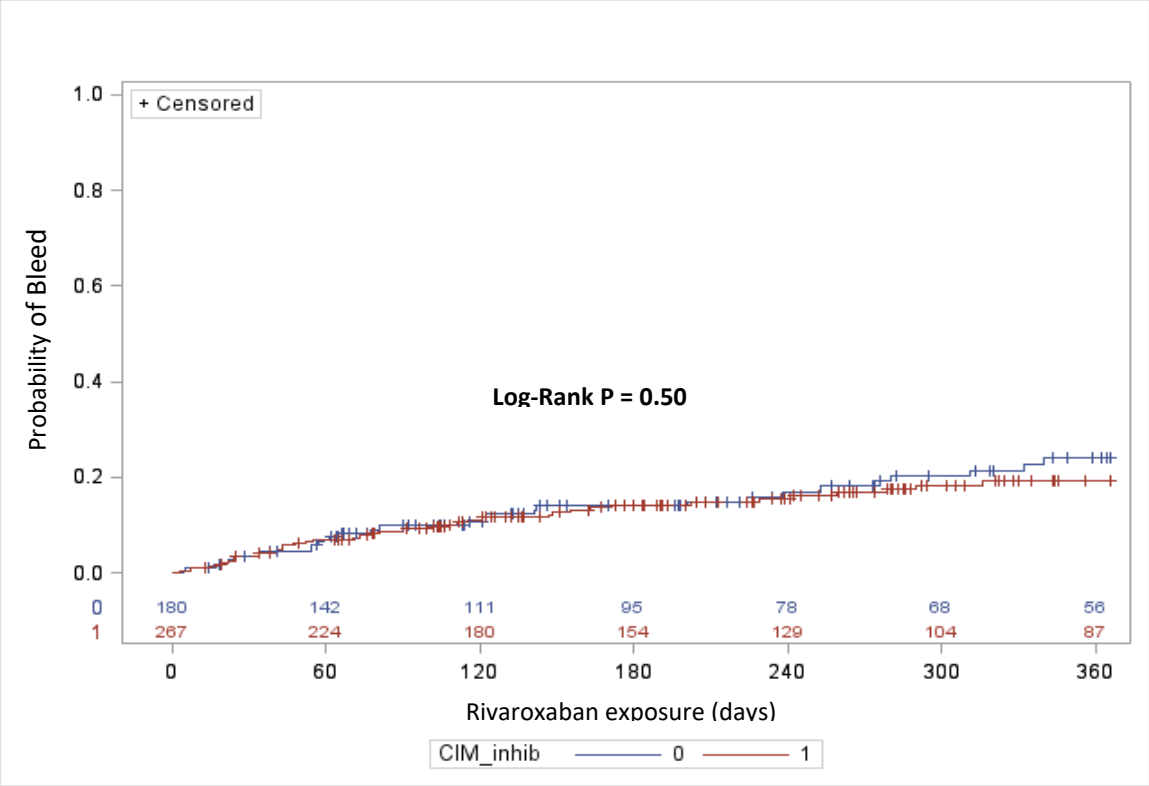
Table 3.6: Multivariate logistic regression with modified Poisson distribution predicting thromboembolism

Parameter	**RR**	**95% CI**	***p*-value**
CIM[a]	**0.58**	**0.39-0.87**	**<0.01**
Age	0.91	0.75-1.10	0.32
Female	1.05	0.71-1.55	0.81
PAI	1.51	0.89-2.57	0.13
Pre-index warfarin	1.22	0.81-1.84	0.34
Pre-index thromboembolism	**4.56**	**2.82-7.37**	**<0.0001**
CCI	1.00	0.92-1.09	0.97

[a]CIM includes CYP3A4 and P-gp inhibitors. CCI, Charlson Comorbidity Index; CIM, concomitant interacting medication; PAI, platelet aggregation inhibitor.

The mean time to bleed from rivaroxaban initiation for CIM users and CIM non-users was 234 and 206 days, respectively (log-rank test p = 0.50). The greatest proportion patients with events in CIM users or CIM non-users occurred in the first 120 days (10.1% and 9.4%, respectively) (Table 3.7). The unadjusted time to bleed for the rivaroxaban cohort using Kaplan Meier analysis is shown in Figure 3.2.

Figure 3.2 Kaplan Meier analysis of time to bleed



CIM, concomitant interacting medication. CIM users whose events were asynchronous to CIM exposure were removed from the analysis.

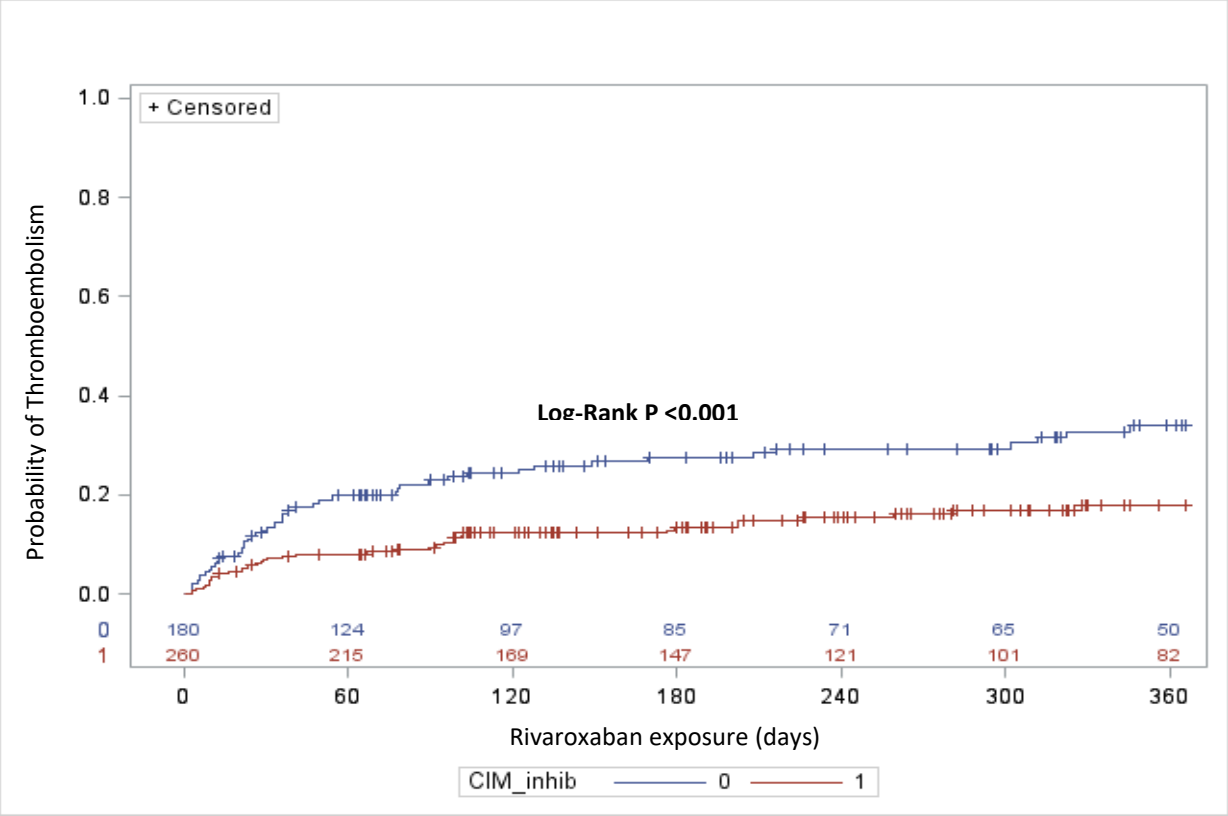
Table 3.7 Kaplan Meier analysis of time to bleed

	Mean (days)	IQR (days)	Proportion of patients with event (%)		
			120 days	240 days	360 days
CIM non-user (n = 180)	206.0	(66.5, 365.0)	9.4%	13.3%	16.7%
CIM user (n = 267)	234.0	(102.0, 365.0)	10.1%	13.1%	15.0%

CIM, concomitant interacting medication; IQR, interquartile range.

The mean time to thromboembolism from rivaroxaban initiation for CIM users and CIM non-users was 199 and 186 days, respectively (log-rank test p = 0.14). The greatest proportion patients with events in CIM users or CIM non-users occurred in the first 120 days (11.5% and 22.7%, respectively) (Table 3.8). The unadjusted time to thromboembolism for the rivaroxaban cohort using Kaplan Meier analysis is shown in Figure 3.3.

Figure 3.3 Kaplan Meier analysis of time to thromboembolism



CIM, concomitant interacting medication. CIM users whose events were asynchronous to CIM exposure were removed from the analysis.

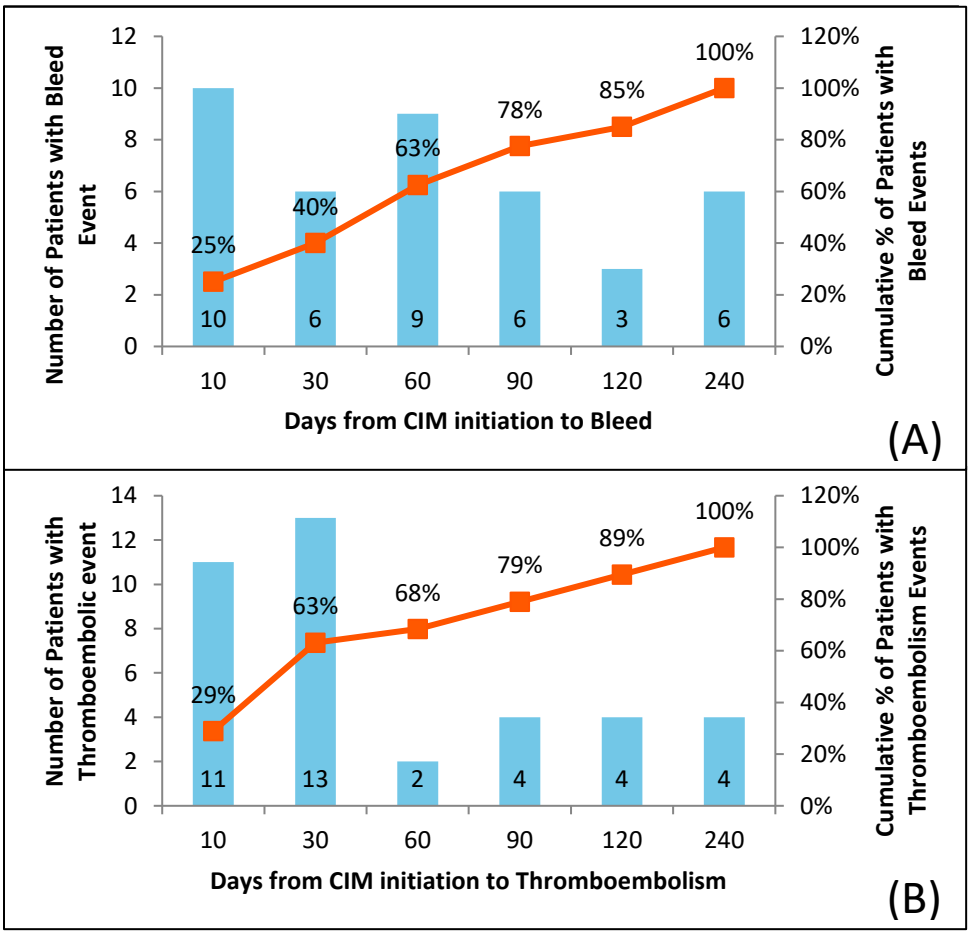
Table 3.8 Kaplan Meier analysis of time to thromboembolism

	Mean (days)	IQR (days)	Proportion of patients with event (%)		
			120 days	240 days	360 days
CIM non-user (n=180)	185.9	(38.0, 365.0)	22.7%	26.1%	28.3%
CIM user (n=260)	213.2	(91.5, 365.0)	11.5%	13.5%	14.6%

CIM, concomitant interacting medication; IQR, interquartile range.

For those CIM users who experienced a bleed or thromboembolism, all events were experienced within 240 days of initiation of the interacting medication (Figure 3.4). The mean time to bleed and thromboembolism from CIM initiation was 106 and 70 days, respectively. For CIM non-users who experienced an event, time from rivaroxaban initiation to bleed and thromboembolism were similar (126 and 70 days, respectively).

Figure 3.4 Time from CIM initiation to bleed (A) or thromboembolism (B)



CIM, concomitant interacting medication. The horizontal axis represents the ordinal categories of CIM exposure days from initiation to bleed (A) or thromboembolism (B). The category label represents the upper limit of the days from CIM initiation to event (e.g. patients in category "30" had >10-30 days of CIM exposure prior to event). The bars represent the number of patients in each category and the trend line represents cumulative percentage of patients with increasing days from CIM initiation to event.

Table 3.9 shows the results of the Cox proportional hazards model predicting time to bleed. When adjusted for baseline differences, the hazard of bleed was similar for CIM users compared to non-users (hazard ratio [HR]: 0.73; 95% CI: 0.45-1.18; p = 0.20). A prior history of bleed was the only predictor indicative of a higher hazard of bleed (HR: 2.50; 95% CI: 1.52-4.10; p<0.001).

Table 3.9: Cox proportional hazard regression model predicting bleed

Parameter	**HR**	**95% CI**	***p*-value**
CIM[a]	0.73	0.45-1.18	0.20
Age	1.10	0.83-1.44	0.42
Female	1.45	0.88-2.38	0.15
PAI	1.73	0.96-3.10	0.07
Pre-index warfarin	0.93	0.54-1.62	0.80
Pre-index bleed	**2.50**	**1.52-4.10**	**<0.001**
CCI	1.08	0.99-1.18	0.08

[a]CIM includes CYP3A4 and P-gp inhibitors. CCI, Charlson Comorbidity Index; CIM, concomitant interacting medication; PAI, platelet aggregation inhibitor.

Table 3.10 shows the results of the Cox proportional hazards model predicting time to thromboembolism. When adjusted for baseline differences, the hazard of thromboembolism was lower for CIM users compared to non-users (HR: 0.54; 95% CI: 0.35-0.83; p < 0.01). A prior history of thromboembolism was the only predictor indicative of a higher hazard of thromboembolism (HR: 4.88; 95% CI: 3.03-7.85; p<0.0001).

Table 3.10: Cox proportional hazard regression model predicting thromboembolism

Parameter	**HR**	**95% CI**	***p*-value**
CIM[a]	**0.54**	**0.35-0.83**	**<0.01**
Age	0.94	0.75-1.18	0.59
Female	1.14	0.74-1.75	0.55
PAI	1.32	0.74-2.35	0.35
Pre-index warfarin	1.17	0.74-1.87	0.50
Pre-index thromboembolism	**4.88**	**3.03-7.85**	**<0.0001**
CCI	1.01	0.93-1.11	0.78

[a]CIM includes CYP3A4 and P-gp inhibitors. CCI, Charlson Comorbidity Index; CIM, concomitant interacting medication; PAI, platelet aggregation inhibitor.

Summary of Results

A summary of results for each hypothesis is provided in Table 3.11. Demographics (Objective 1) were generally balanced between the two groups. CIM users had higher prevalence of prior myocardial infarction, heart failure, and coronary artery disease (Objective 2) while CIM non-users had higher baseline rates of cancer and prior warfarin use (Objective 3). The proportion of patients experiencing a bleed (Objective 4) between the two groups were similar. Major bleeds were too rare to compare across the two groups. CIM users had a lower proportion of patients experiencing thromboembolism (Objective 5). There was no association of CIM use with risk (Objective 6) or hazard (Objective 7) of bleed. CIM use was associated with a lower risk (Objective 8) and hazard (Objective 9) of thromboembolism.

Table 3.11 Summary of Results by Objectives and Hypothesis Testing

Objectives and Alternative Hypotheses (H_a)	**Result**
Objective 1: To determine whether the demographics differ between CIM users and CIM non-users.	
H_a1.1: The difference in age between CIM users and CIM non-users is statistically significant.	Rejected
H_a1.2: The difference in gender between CIM users and CIM non-users is statistically significant.	Rejected
Objective 2: To determine whether the prevalence of comorbidities during the pre-index period differs between CIM users and CIM non-users.	
H_a2.1: The difference in prevalence of hypertension between CIM users and CIM non-users is statistically significant.	Rejected
H_a2.2: The difference in prevalence of myocardial infarction between CIM users and CIM non-users is statistically significant.	Failed to reject
H_a2.3: The difference in prevalence of dyslipidemia between CIM users and CIM non-users is statistically significant.	Rejected
H_a2.4: The difference in prevalence of diabetes between CIM users and CIM non-users is statistically significant.	Rejected

Table 3.11, cont.

H_a2.5: The difference in prevalence of heart failure between CIM users and CIM non-users is statistically significant.	Failed to reject
H_a2.6: The difference in prevalence of coronary artery disease between CIM users and CIM non-users is statistically significant.	Failed to reject
H_a2.7: The difference in prevalence of chronic kidney disease between CIM users and CIM non-users is statistically significant.	Rejected
H_a2.8: The difference in prevalence of cancer between CIM users and CIM non-users is statistically significant.	Failed to reject
H_a2.9: The difference in prevalence of history of stroke between CIM users and CIM non-users is statistically significant.	Rejected
H_a2.10: The difference in prevalence of history of bleed between CIM users and CIM non-users is statistically significant.	Rejected
H_a2.11: The difference in Charlson Comorbidity Index scores between CIM users and CIM non-users is statistically significant.	Rejected
H_a2.12: The difference in CHA_2DS_2-VASc scores between CIM users and CIM non-users is statistically significant.	Rejected
Objective 3: To determine whether pre-index anticoagulant treatment history differs between CIM users and CIM non-users.	
H_a3.1: The difference in pre-index warfarin use (yes/no) between CIM users and CIM non-users is not statistically significant.	Failed to reject
Objective 4: To determine whether the rate of bleed differs between CIM users and CIM non-users.	
H_a 4.1: The difference in the proportion of patients experiencing a bleed event between CIM users and CIM non-users is statistically significant.	Rejected
H_a 4.2: The difference in the proportion of patients experiencing a major bleed event between CIM users and CIM non-users is statistically significant.	Not calculable
Objective 5: To determine whether the rate of thromboembolism differs between CIM users and CIM non-users.	
H_a5.1: The difference in the proportion of patients experiencing a thromboembolic event between CIM users and CIM non-users is statistically significant.	Failed to reject
Objective 6: To determine whether any CIM use is associated with the risk of bleed.	
H_a6.1: When adjusted for covariates, the association between CIM use and the risk of bleed is not statistically significant.	Rejected
Objective 7: To determine whether any CIM use is associated with the risk of thromboembolism.	
H_a7.1: When adjusted for covariates, the association between CIM use and the risk of thromboembolism is statistically significant.	Failed to reject

Table 3.11, cont.

Objective 8: To determine whether CIM use is associated with the hazard of bleed.	
H_a8.1: When adjusted for covariates, and assessing time to first event, the association between CIM use and the hazard of bleed is statistically significant.	Rejected
Objective 9: To determine whether the CIM use is associated with the hazard of bleed.	
H_a9.1: When adjusted for covariates, and assessing time to first event, the association between CIM use and the hazard of thromboembolism is statistically significant.	Failed to reject

CHAPTER 4: DISCUSSION AND CONCLUSION

Discussion

Baseline Demographics and Clinical Characteristics

The results of the study sample table showed that of the patients prescribed rivaroxaban within our institution, only about one-third (35.7%) have diagnoses for nonvalvular atrial fibrillation. The average age of these patients was 73.4 years, which is consistent with other studied atrial fibrillation populations in the real world setting.[54,60] Males represented the majority of the cohort, which is inconsistent with the notion that atrial fibrillation has higher prevalence in women.[4] Although, more recent studies have identified cumulative incidence of atrial fibrillation increases markedly after the age of 50 years in men and after 60 years in women.[61] The mean baseline CHA_2DS_2-VASc score across the cohort was 4.2 (SD 1.9), representing an adjusted annual stroke risk between 4.0-6.7%.[26,28,29] The prescribing of rivaroxaban is consistent with clinical recommendations from the 2014 ACC/AHA Guidelines that suggest prescribing oral anticoagulation in patients with CHA_2DS_2-VASc scores $\geq$ 2. Further, this finding compliments a recent Canadian population-based study that identified an increase in the proportion of person-years on DOACs over time, particularly in nonvalvular atrial fibrillation patients with moderate to severe stroke risk.[62]

Cardiovascular comorbidities were highly prevalent within our population, with hypertension (91.2%), dyslipidemia (78.4%), coronary artery disease (38.8%) and heart failure (38.1%) as the most commonly identified diagnoses. Notably, history of myocardial infarction and stroke were identified in 9.9% and 27.4%, respectively. Combined clopidogrel and aspirin use accounted for only 12.6% of the cohort; however, this should be interpreted with caution since aspirin is commonly prescribed without a prescription and would be inherently underrepresented in any claims study.

At baseline, the comorbidities of nonvalvular atrial fibrillation patients taking rivaroxaban with concurrent interacting medication use were generally comparable to those patients not taking concurrent interacting medications. However, there was a significant difference in the prevalence of certain comorbidities between the two groups. CIM users had a higher prevalence of prior myocardial infarction, heart failure, and coronary artery disease compared to CIM non-users. Each of these comorbidities have a considerable influence on stroke risk and are represented in the CHA_2DS_2-VASc score. On the other hand, CIM non-users had higher rates of cancer. Deep vein thrombosis (a sub-component of the thromboembolism endpoint in this study) is widely recognized in clinical practice as a complication of cancer due to genetic changes and treatment with chemotherapy.[63-65] Nonetheless, CHA_2DS_2-VASc and Charlson Comorbidity Index scores were balanced between the two groups, indicating the risk of stroke and multimorbidity (respectively) were alike.

Medication Use

Nearly two-thirds (62%) of the nonvalvular atrial fibrillation patients were identified to have some exposure to a concomitant interacting medication while managed on rivaroxaban. Despite warnings in product information, agents such as diltiazem, amiodarone, and carvedilol are routinely prescribed in patients taking rivaroxaban; reflecting a general under appreciation or disregard for the underlying potential of increased hemorrhagic risk. Clinical studies with rivaroxaban do not report concomitant use of these agents. Concurrent amiodarone was reported in 11% of patients in the RCTs of other DOACs.[34,36] However, these reported rates reflect the treatment status of patients at baseline in a clinical trial and do not reflect the dynamic prescribing patterns seen in real-world settings. Concurrent use of verapamil, cyclosporine and captopril was rare.

On average, those patients prescribed concomitant interacting medications had 138 (SD 224) days of exposure during the 12 months following the index date, with the majority of patients (51%) having at least 120 days of exposure. This finding is consistent with CIM prescribing patterns, since the majority of prescribed CIMs were cardiovascular medications including diltiazem (n=94), amiodarone (n=74), carvedilol (n=63) and dronedarone (n=32) indicated for chronic use. Only 17% of CIM users had CIM exposure that was less than 30 days. This may be reflective of either short duration use of CIMs (e.g. azithromycin) or discontinuation of the CIM following an event. The latter precludes testing for any association of days of CIM exposure with risk of events. Overall, the majority of patients had exposure to an interacting medication for at least 120 days during the follow-up period.

Major Bleed and Overall Bleed

The rate of overall bleed and major bleeds seen in this study was 19.3% and 4.5%, respectively. This finding is approximately equivalent or slightly higher than in clinical trials and other observational studies using rivaroxaban.[35,66] The higher rate of major bleeds identified in this study compared to the ROCKET-AF trial (3.4%) is reflective of the difference in endpoint definition. ROCKET-AF identified major bleeds through clinical observation rather than administrative claims data. However, the authors of this study note that the sample size was underpowered to detect a difference in major bleeds between groups, therefore inferential statistics cannot be relied upon to draw meaningful conclusions regarding the incidence of major bleeds in this study.

The incidence of overall bleed was used to conduct inferential analyses on the impact of concomitant interacting medication exposure on bleed outcomes. Compared to non-users, those taking CYP3A4 and P-gp inhibitors had similar rates of bleed (n[%]: 30

[16.7] versus 40 [15.0]; p = 0.63). When controlling for other covariates, CYP3A4 and P-gp inhibitor users had a similar risk (RR: 0.73; 95% CI: 0.47, 1.11; p = 0.14) and hazard (HR: 0.73; 95% CI: 0.45-1.18; p = 0.20) of bleed. This suggests that regardless of time considerations, concomitant interacting medications were not associated with bleeding outcomes. Interestingly, this directly conflicts with pharmacokinetic studies that have demonstrated increased rivaroxaban levels when combined with some of these agents.[41,51] Moreover, many of these studies are typically conducted in healthy subjects and do not reflect our older, more comorbid study population–whose blood levels of rivaroxaban would be expected to be even higher. Our results have some consistency with a recent analysis conducted in Taiwanese national claims database, that evaluated major bleeding outcomes among patients with NVAF who were DOAC users taking concomitant interacting medication. Chang et al. determined that among rivaroxaban users, certain concomitant interacting medications increased major bleeding risk, including amiodarone (Adjusted Incidence Rate Ratio [IRR]: 1.38; 95% CI: 1.21-1.58), fluconazole (Adjusted IRR: 2.25; 95% CI: 1.54-3.30) and phenytoin (Adjusted IRR: 1.85; 95% CI: 1.36-2.51). Meanwhile agents that did not increase risk included digoxin (Adjusted IRR: 0.96; 95% CI: 0.83-1.11), verapamil (Adjusted IRR: 1.17; 95% CI: 0.90-1.52), diltiazem (Adjusted IRR: 1.03; 95% CI: 0.89-1.19), cyclosporine (Adjusted IRR: 0.58; 95% CI: 2.40), clarithromycin (Adjusted IRR: 0.79; 95% CI: 0.58-1.06), and dronedarone (Adjusted IRR: 0.92; 95% CI: 0.68-1.24).[54] While Chang et al. powered their analysis to detect per drug risk, our study grouped CYP3A4 and P-gp inhibitors into a single dependent variable–giving rise to the opportunity of differential risk effects to nullify each other. An analysis that detects per drug risk accounting for time-varying exposure to CYP3A4 and P-gp inhibitors would be an advancement on the existing literature.

For those concomitant interacting medication users who experienced a bleed (n=40), the mean days from agent initiation to event was 59 (SD 56) days. The majority of these patients (78%) had a bleed within 90 days from CIM initiation; the remaining nine patients had events beyond 90 days, with some experiencing bleeds as long as 240 days after CIM initiation. This suggests a potential delayed effect from the alteration of rivaroxaban levels to the occurrence of the untoward effect (i.e. bleed outcomes). While it is well documented that concomitant use of amiodarone and warfarin can result in supratherapeutic INR levels, it is instructive to note that many patients do not suffer a bleed when experiencing this excessive level of anticoagulation.[67] An actual hemorrhagic event is both related to level of anticoagulation as well as a given patient's underlying predisposition to bleeding or thromboembolism (e.g., underlying gastric ulcer disease, exposed diverticuli, intracranial aneurism predisposition). Furthermore, time in therapeutic range as measured by periodic measurement of INR has been identified as a reliable predictor for major bleeds for patients managed on warfarin.[68] This underscores the risk involved with DOACs and concomitant CYP3A4 and P-gp use, as there is no blood test for routine monitoring as therein the case of warfarin.

Thromboembolism

The rate of thromboembolism seen in this study was 22.1%, accounting for rates of stroke, systemic embolism as well as pulmonary embolism and deep vein thrombosis. Compared to non-users, those taking CYP3A4 and P-gp inhibitors had lower rates of thromboembolism (n[%]: 38 [14.6] versus 51 [28.3]; $p < 0.001$). Adjusted analyses showed that relative to non-users, CYP3A4 and P-gp inhibitor users had a lower risk (RR: 0.58; 95% CI: 0.39, 0.87; $p < 0.01$) and hazard (HR: 0.54; 95% CI: 0.35-0.83; $p < 0.01$) of

thromboembolism. This indicates that CYP3A4 and P-gp inhibitor users were at a lower risk of thromboembolic events, irrespective of the timing of their exposure.

For those concomitant interacting medication users who experienced a thromboembolism (n=38), the mean days from agent initiation to event was 47 (SD 53) days. Similar to those with bleeds, the majority of CIM-users who experienced a thromboembolism (79%) had an event within 90 days of CIM initiation. Those with events beyond >90 days (21%) had events as long as 240 days after CIM initiation. This study looked at event rates during a one-year follow-up period, mirroring DOAC pivotal trials that typically include at least one year of follow-up for assessment of bleed and thromboembolic events.[34-36] In other observational studies employing time to event analyses to assess the impact of concurrent medication use, trends of 90-day thromboembolism rates are a primary exposure window of interest.[69] Consequently, events occurring >90 days after CIM initiation may not be of particular interest for clinical decision-making, and are most likely not associated with the concomitant use of an interacting medication due to other confounding factors that may arise during longer follow-up.

Overall, these results suggest that when prescribed CYP3A4 and P-gp inhibitors concomitantly with rivaroxaban, nonvalvular atrial fibrillation patients have fewer thromboembolic events while maintaining similar levels of bleed events. Although some agents may be driving these associations, it is not possible to make individual recommendations for use. Due to limitations in our classification of exposure status, patients with CYP3A4 or P-gp inhibitor use during follow-up whose events occurred prior to exposure were removed from the analysis. Consequently, incidence rates of bleed and

thromboembolism are underreported in non-users. This suggests that CYP3A4 and P-gp inhibitor use would be associated with even fewer bleeds and thromboembolic events. The outcomes of interest (bleed, major bleed, and thromboembolism) were relatively rare among our study sample. Therefore, future studies powered to detect significant differences in these endpoints are needed to further elucidate the effect of CYP3A4 and P-gp inhibitors on risk of bleed and thromboembolism.

Limitations

This study has several limitations. First, our cohort was developed based on pharmacy and medical claims information, which may include missing or incorrect data. There is also a risk that data were incomplete, as this information only accounts for healthcare services received and billed to the regional healthcare payer. To account for this, patients without continuous enrollment during the study period were excluded from the analysis. As with all retrospective claims analyses, true medication adherence behaviors cannot be ascertained and are limited to the rate at which the medication is filled. Dosages of rivaroxaban may have changed over the course of the study period, which in turn could influence bleeding risk. Despite this fact, we did not adjust for dosages as to not overcomplicate the models. Differences in baseline demographic and clinical covariates may influence the risk of bleeding and thromboembolism. This is a common limitation found in retrospective observational studies, and therefore unadjusted comparisons of the primary outcomes rates should be interpreted with caution. Multivariate logistic regression and Cox proportional hazard models are common methodologies to analyze the potential association of a primary independent factor (in our case CIM exposure) while controlling for differences across study cohorts that could otherwise present confounding results.

For this study, we combined CYP3A4 inhibitors and P-gp inhibitors into a single primary independent variable. Therefore, any associations explored in this analysis were limited to the pharmacodynamic drug class level, as opposed to individual drug risk. This study considers the primary dependent variables of interest, bleed and thromboembolism, as dichotomous rather than count variables. This was done to focus on the first relevant event experienced by the patient and to avoid counting patients twice in the analysis for different outcomes. Nonetheless, our analysis methodology was based on a clear temporal relationship between medication use and events attributable to rivaroxaban drug-drug interactions. Specifically, our criteria included defining bleed and thromboembolism outcomes that overlapped with the dates of prescription fill coverage. Stroke and major bleed are relatively rare events. Therefore, the thromboembolism endpoint included a composite of all potential clotting complications (pulmonary embolism, deep venous thrombosis, stroke, and systemic embolism) relevant to anticoagulation therapy in the studied population. The definition of bleed included all bleeding events requiring medical care. Lastly, our cohort is derived from a highly comorbid nonvalvular atrial fibrillation patient cohort managed by a healthcare system in central Texas and may not be generalizable to other populations.

Conclusion

This retrospective claims database study is the first to explore the association of CYP3A4 and P-gp inhibitor use with the time to bleed among patients with atrial fibrillation managed on rivaroxaban over 1 year in a real-world setting. This study suggests that co-administered CYP3A4 and P-gp inhibitors modify the occurrence of thromboembolism in patients prescribed rivaroxaban. While no alteration of bleeding risk was observed, this may be limited by event rates, sample size, and inability to assess risk at the individual drug level.

We believe this is the first observational study to investigate the hazard of bleed and thromboembolism over time for patients concurrently managed on rivaroxaban and CYP3A4 and P-gp inhibitors. As rivaroxaban and other DOACs become mainstay therapies in cardiology practice, developing a comprehensive appraisal of their risks and benefits is paramount for optimizing patient outcomes. There is increasing opportunity for electronic health records systems to alert prescribing physicians of potential interaction and to perhaps recommend substitutions. Such a system might reduce adverse drug events and thereby improve patient safety.

APPENDICES

Appendix A: Diagnosis Codes for Thromboembolism & Bleed[54,70,71]

Thromboembolism	**ICD-9-CM Codes**	**ICD-10-CM Codes**
Pulmonary embolism	415.0, 415.1x	I26.09, I26.90, I26.92, I26.99, T80.0XXA, T81.718A, T81.72XA, T82.817A, T82.818A
Deep venous thromboembolism	451.1x, 451.2x, 453.xx	I80.10, I80.209, I80.3, I82.0, I82.1, I82.220, I82.221, I82.3, I82.409, I82.419, I82.429, I82.439, I82.4Y9, I82.449, I82.4Z9, I82.509, I82.599, I82.519, I82.529, I82.539, I82.5Y9, I82.549, I82.5Z9, I82.819, I82.719, I82.729, I82.709, I82.A29, I82.B29, I82.C29, I82.291, I82.891, I82.619, I82.629, I82.609, I82.A19, I82.B19, I82.C19, I82.290, I82.890, I82.91
Stroke	362.34, 430.x-438.x	G45.x, G46.x, H34.0, I60.x-I69.x
Systemic embolism	444.x, 445.x	I74.x, I75.x
Bleed	**ICD-9-CM Codes**	**ICD-10-CM Codes**
Hemorrhage and infarction of thyroid	246.3	E07.89
Acute posthemorrhagic anemia	285.1	D62
Hemorrhagic disorder due to circulating anticoagulants	286.5	D68.318
Communicating hydrocephalus	331.3	G91.0
Retinal hemorrhage	362.81	H35.60
Choroidal hemorrhage	363.61, 363.62	H31.309, H31.319
Conjunctival hemorrhage	372.72	H11.33
Orbital hemorrhage	376.32	H05.239
Vitreous hemorrhage	379.23	H43.13

Hematoma of auricle or pinna	380.31	H61.129
Hemopericardium	423	I31.2
Intracranial	430, 431, 432.xx, 852.0x, 853.0x	I60, I60.9, I61.9, I62.00, I62.1, I62.9, S06.6X0A, S06.6X1A, S06.6X2A, S06.6X4A S06.6X5A, S06.6X6A, S06.6X7A, S06.6X8A, S06.6X9A, S06.360A, S06.361A, S06.362A, S06.363A, S06.364A, S06.365A, S06.366A, S06.367A, S06.368A, S06.369A
Gastroesophageal laceration-hemorrhage syndrome	530.7	K22.6
Esophageal varices with bleeding	456.0, 456.20	I85.01, I85.11
Hemorrhage, unspecified	459	R58
Esophageal hemorrhage	530.82	K22.8
Acute gastric ulcer with hemorrhage	531.0x, 531.2x	K25.0, K25.2
Chronic or unspecified gastric ulcer with hemorrhage	531.4x, 531.6x	K25.4, K25.6
Acute duodenal ulcer with hemorrhage	532.0x, 532.2x	K26.0, K26.2
Chronic or unspecified duodenal ulcer with hemorrhage	532.4x, 532.6x	K26.4, K26.6
Acute peptic ulcer with hemorrhage	533.0x, 533.2x	K27.0, K27.2
Chronic or unspecified peptic ulcer with hemorrhage	533.4x, 533.6x	K27.4, K27.6
Acute gastrojejunal ulcer with hemorrhage	534.0x, 534.2x	K28.0, K28.2
Chronic or unspecified gastrojejunal ulcer with hemorrhage	534.4x, 534.6x	K28.4, K28.6

Gastritis and duodenitis with hemorrhage	535.x1	K29.01, K29.41, K29.51, K29.61, K29.21, K29.71, K29.91, K29.81, K52.81
Angiodysplasia of stomach and duodenum with hemorrhage	537.83	K31.811
Dieulafoy lesion (Hemorrhagic) of stomach and duodenum	537.84	K31.82
Diverticulosis and diverticulitis of small intestine with hemorrhage	562.02, 562.03	K57.11, K57.13
Diverticulosis and diverticulitis of colon with hemorrhage	562.12, 562.13	K57.31, K57.33
Hemoperitoneum	568.81	K66.1
Hemorrhage of rectum and anus	569.3	K62.5
Angiodysplasia of intestine with hemorrhage	569.85	K55.21
Gastrointestinal hemorrhage	578.x	K92.0, K92.1, K92.2
Vascular myelopathies	336.1	G95.19
Hemorrhage in optic nerve sheaths	377.42	H47.029
Vascular disorders of kidney	593.81	N28.0
Hematoma of kidney	866.01, 866.11	S31.001A, S37.019A, S37.029A
Laceration of kidney	866.02, 866.12	S31.001A, S37.039A, S37.049A, S37.059A
Hemorrhage into bladder wall	596.7	N32.89
Hemorrhage of prostate	602.1	N42.1
Hematometra	621.4	N85.7
Vaginal hematoma	623.6	N89.8
Metorrhageia	626.6	N92.1
Hemarthrosis	719.1x	M25.00, M25.019, M25.029, M25.039, M25.049, M25.059, M25.069, M25.073, M25.076, M25.08

Hematoma of soft tissue	729.92	M79.81
Spontaneous ecchymoses	782.7	R23.3
Epistaxis	784.7	R04.0
Hemorrhage from throat	784.8	R04.1
Hemoptysis	786.3	R04.2, R04.9
Iatrogenic cerebrovascular infarction or hemorrhage	997.02	I97.811, I97.821
Adverse effects related to therapeutic use of anticoagulants	E934.2	None

Appendix B: Diagnosis Codes for Comorbidities[54]

Comorbidity	ICD-9-CM Codes	ICD-10-CM Codes
Atrial fibrillation	427.31	I48.0, I48.2, I48.91
Hypertension	401.x, 402.xx	I10, I11.0, I11.9
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2
Dyslipidemia	272.0, 272.1, 272.2, 272.4	E78.0, E78.1, E78.2, E78.4-E78.5
Diabetes mellitus	250	E10.0, E10.1, E10.9, E11.0,E11.1,E11.9
Diabetes mellitus with complications	250.4-250.7	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Congestive heart failure	398.91, 402.01, 402.11, 402.91,404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.xx	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Coronary artery disease	414.0-414.9	I25.10, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, I25.3, I25.82, I25.83, I25.84, I25.5, I25.89, I25.9
Chronic kidney disease	585	N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9
Chronic pulmonary disease	416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Cancer	140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Cerebrovascular disease	362.34, 430.x–438.x G45.x, G46.x, H34.0, I60.x–I69.x	362.34, 430.x–438.x G45.x, G46.x, H34.0, I60.x–I69.x,
Ischemic stroke	433-434, 436, 852, 853	I67.89, I63-I64, G45.8-45.9, S01.90XA, S06.4X0A-S06.4X9A,

		S06.5X0A-S06.5X9A, S06.6X0A- S06.6X9A, S06.340A-S06.349A, S06.350A-S06.359A, S06.360A-S06.369A
Transient ischemic attack	435	G45
Paraplegia and Hemiplegia	334.1, 342.x, 343.x, 344.0– 344.6,	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Dementia	290.x, 294.1, 331.2	F00.x–F03.x, F05.1, G30.x, G31.1
Renal disease	580, 581, 582, 583, 584, 585, 586, 587, 588, 589	I12, I13, N00-N05, N07, N11, N14, N17, N18, N19, Q61
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Connective tissue disease-rheumatic disease	446.5, 710.0–710.4, 714.0– 714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x– M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	531.x–534.x	K25.x-K28.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Metastatic solid tumor	196.x-199.x	C77.x-C80.x
Moderate or severe liver disease	456.0–456.2, 572.2–572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
HIV/AIDs	042.x-044.x	B20.x-B22.x, B24.x
Previous Bleed	(See ICD-9-CM & ICD-10-CM codes from Appendix A)	

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