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IMPACT OF OBESITY ON REAL-WORLD CLINICAL OUTCOMES IN PATIENTS WITH ATRIAL FIBRILLATION ON DIRECT ORAL ANTICOAGULANT THERAPY: A RETROSPECTIVE COHORT STUDY

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Impact of Obesity on Real-World Clinical Outcomes in Patients with Atrial Fibrillation on Direct Oral Anticoagulant Therapy: A Retrospective Cohort Study

by

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ABSTRACT

Impact of Obesity on Real-World Clinical Outcomes in Patients with Atrial Fibrillation on Direct Oral Anticoagulant Therapy: A Retrospective Cohort Study

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Objectives: To assess the impact of body mass index on real-world clinical outcomes in patients with atrial fibrillation taking direct oral anticoagulants (DOACs) within the Baylor Scott & White healthcare system.

Methods: This was a retrospective, observational cohort study of adult patients (≥18 years of age) with atrial fibrillation or atrial flutter with ≥1 pharmacy claim for a DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) between 2015 and 2017. Patients were stratified into cohorts based on body mass index: normal weight, overweight, obese class I, obese class II, obese class III. The primary effectiveness outcome was any stroke or systemic embolic event and the primary safety outcome was any major bleed event. Baseline characteristics across the cohorts were compared descriptively and using bivariate analyses. Unadjusted outcome event rates across the cohorts were compared descriptively.

Results: The primary analysis consisted of 1,035 patients (normal 245 (23.4%), overweight 352 (33.6%), obese class I 220 (21.0%), obese class II 132 (12.6%), and obese

class III 86 (8.2%)). Overweight and obese cohorts were younger and had a lower proportion of females, Medicare insurance, prior stroke/transient ischemic attack (TIA) and bleed history, higher proportions of hypertension and diabetes rates, and lower CHA_2DS_2-VASc and HAS-BLED scores than the normal weight cohort.. Eleven (1.1%) stroke or systemic embolic events were observed and similar rates were seen across the BMI cohorts (normal 3 (1.2%), overweight 3 (0.9%), obese class I 3 (1.4%), obese class II 1 (0.8%), obese class III 1 (1.2%)). About three percent (n= 29; 2.8%) of those studied had major bleed events and decreasing rates were seen with increasing BMI cohorts (normal 9 (3.7%), overweight 11 (3.1%), obese class I 5 (2.3%), obese class II 3 (2.3%), obese class III 1 (1.2%)).

Conclusion: A small percentage of stroke/systolic embolism and major bleed event rates were observed across all BMI groups, such that no statistical tests could be performed to compare the event rates among the BMI groups. DOAC-receiving atrial fibrillation patients who are overweight or obese may see similar, and potentially lower, rates of stroke and systemtic emoblism or major bleed events compared to normal weight patients.

TABLE OF CONTENTS

List of Tables

List of Figures

Chapter 1: Introduction

ATRIAL FIBRILLATION

Pathophysiology and Atrial Fibrillation Classifications

Atrial fibrillation, a type of supraventricular tachycardia, is the most common type of heart arrhythmia that is characterized by uncoordinated and ineffective atrial activation and contraction.[1,2] While its underlying mechanisms are multifactorial, atrial fibrillation primarily occurs from structural remodeling in the atria, resulting in electrophysiological abnormalities that promote and propagate abnormal impulse formation. After diagnosis with an electrocardiogram (ECG), atrial fibrillation can be distinguished from five, non-mutually exclusive classifications based on the duration and presentation of episodes (Table 1.1). These varying definitions of atrial fibrillation are clinically relevant in regards to therapy outcomes. It is not uncommon for atrial fibrillation to progress from paroxysmal to persistent and become resistant to therapy over time, indicative of its slow but progressive structural and electrical remodeling in the atria. This is consistent with evidence demonstrating that atrial fibrillation itself induces continual pathophysiological changes, such that "atrial fibrillation begets atrial fibrillation".[2,3]

In a 2019 focused update of the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guideline, the definition of valvular atrial fibrillation was modified to include only the presence of moderate-to-severe mitral stenosis or an artificial heart valve in light of clinical trial evidence. This notably excludes valvular heart disease. As such, nonvalvular atrial fibrillation is defined as the absence of moderate-to-severe mitral stenosis (that may require surgical intervention) or an artificial (mechanical) heart valve.[4]

Table 1.1. Classifications of Atrial Fibrillation per 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[2]

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 days of onset • Episodes may recur with variable frequency
Persistent AF	• Continuous AF that is sustained >7 days
Long-standing persistent AF	• Continuous AF >12 months 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 bioprospethic heart valve, or mitral valve repair.*

AF: atrial fibrillation
*Definition of nonvalvular AF has changed in the 2019 AHA/ACC/HRS guidelines to AF in the absence of moderate-to-severe mitral stenosis or a mechanical heart valve.

Epidemiology and Risk Factors

The prevalence of atrial fibrillation in the United States was estimated to be within a range of 2.7 to 6.1 million people in 2010, and this number is expected to increase to 12.1 million by 2030, partially attributable to an aging United States population.[4] Atrial fibrillation is found in a higher prevalence in elderly age; in 2010, 2% of the Medicare fee-for-service beneficiaries with atrial fibrillation were less than 65 years of age, whereas 9% were greater than 65 years of age.[2] Additionally, individuals of European ancestry have a significantly higher prevalence of atrial fibrillation than do African Americans, Asians, and Hispanics.[4] The age- and sex-standardized incidence rate in 2007 was reported to be 28.3 per 1,000 person-years in a Medicare sample, up from 27.3 per 1,000 person-years in 1993,

and of these individuals, a majority were female (55%) and white (91%). Previous lifetime risk estimates reported approximately 1 in 4 individuals at risk, but this estimate was recently modified to 1 in 3 among whites and 1 in 5 among blacks in the United States.[4]

In addition to increasing age and European ancestry, other commonly noted risk factors for incident atrial fibrillation reported across the literature include: smoking, body mass index and obesity, hypertension, diabetes mellitus, myocardial infarction, heart failure, coronary artery disease, valvular heart disease, obstructive sleep apnea, alcohol use, and hyperthyroidism.[2–4] One epidemiological study including 14,598 subjects found that 56% of the atrial fibrillation cases could be explained by having at least one common risk factor, which highlights the need to address risk factor modification to reduce the risk of incident atrial fibrillation.[5]

Morbidity, Mortality, and Healthcare Burden

Atrial fibrillation is associated with increased morbidity, such as an increased risk for systemic embolic events, stroke, heart failure, cognitive impairment, myocardial infarction, chronic kidney disease, and cardiovascular morbidity. Moreover, incidence rates of mortality, heart failure, myocardial infarction, stroke, and gastrointestinal bleeding after five years of diagnosis with atrial fibrillation were shown to be higher in older age groups vs. younger age groups.[3,4,6] Atrial fibrillation is associated with a two-fold and 1.5-fold higher risk of all-cause mortality in females and males, respectively.[6] In 2006, the age-adjusted mortality rate was 6.5 per 100,000 people.[4] The majority of deaths in patients with atrial fibrillation are from cardiovascular origins, such as heart failure. Mortality from strokes can be largely mitigated by anticoagulation.[3,4,6]

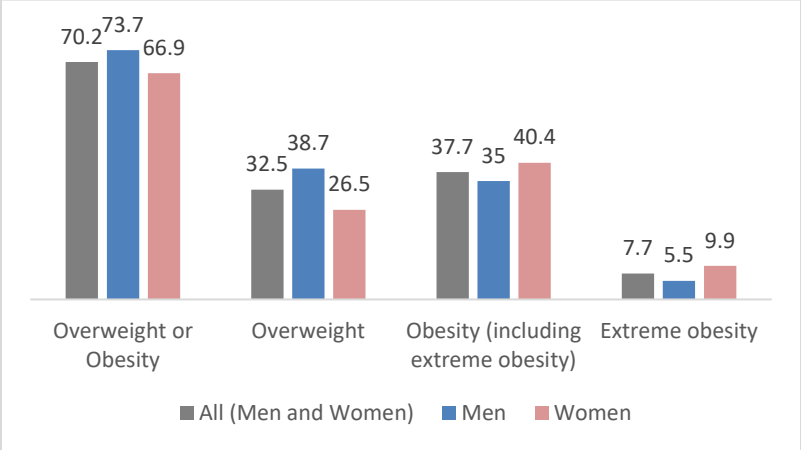
Atrial fibrillation is associated with high hospitalization rates, with an estimated 453,060 hospitalizations and 599,790 emergency department visits with atrial fibrillation listed as the primary diagnosis in 2014. Compared to age- and sex-matched cases, individuals with atrial fibrillation had approximately double the likelihood of being hospitalized on an annual basis compared to individuals without atrial fibrillation (37.5% and 17.5%, respectively).[4] This high healthcare burden correlates with its high economic burden to the United States. It was estimated that individuals aged 18 to 64 years with atrial fibrillation incurred higher average per capita medical spend compared to propensity-matched control subjects without atrial fibrillation ($38,861 vs. $28,506, respectively, in 2014 United States dollars). An older analysis that estimated costs in 2008 United States dollars found that the overall atrial fibrillation population costs an additional $26 billion to the United States healthcare system annually, of which $6 billion was attributed to atrial fibrillation, $9.9 billion to other cardiovascular-related expenses, and $10.1 billion to non-cardiovascular-related expenses.[2,4] Thus, atrial fibrillation – owing to its hemodynamic abnormalities, concomitant conditions and complications, frequent hospitalizations, and healthcare resource utilization – poses a substantial health and economic burden that requires continued efforts in population health improvement.

OBESITY

Parallel to the public health concern evidenced by atrial fibrillation, obesity is a large public health concern that has nearly tripled in global prevalence from 1975 to 2016.[7] According to 2013-2014 age-adjusted data from the National Health and Nutrition Examination Survey (NHANES), 70.2% of the United States population was overweight or obese and 37.7% was obese. While men account for a higher proportion of the

overweight population than women (38.7% men vs. 26.5% women), women comprise the majority in the obese population (35% men vs. 40.4% women) (Figure 1). Non-Hispanic blacks accounted for the highest percentage of the obese population (48.4%), followed by Hispanics (42.6%), non-Hispanic whites (36.4%), and non-Hispanic Asians (12.6%).[8] Texas has an estimated adult obesity rate of 34.8% in 2018, ranking it the 10th highest adult obesity rate in the nation. Texas showed similar trends to the NHANES national data in 2018 with respect to gender and racial differences in obesity rates. In 2018, slightly more women than men in Texas had obesity (36.2% vs. 33.5%, respectively). Additionally, Blacks had higher rates of obesity (40.0%), followed by Latinos (37.9%), and Whites (31.5%).[9]

Figure 1.1. Estimated (Age-Adjusted) Percentage of US Adults with Overweight and Obesity by Sex, 2013-2014 NHANES Data[8]



The economic burden of obesity is exorbitant, with an estimated $147 billion in annual medical expenditures in the United States, with each obese patient costing an

additional $1,429 in medical costs compared to normal weight patients, in 2008 United States dollars.[10]

Overweight and obesity are major risk factors for cardiovascular-related diseases, including stroke, atrial fibrillation, venous thromboembolism, and congestive heart failure.[1,4] A meta-analysis analyzing over 580,000 individuals, around 91,000 of whom were obese, demonstrated a higher risk of developing atrial fibrillation in obese individuals (risk ratio [RR] 1.51, 95% confidence interval [CI], 1.35-1.68). Nearly double the proportion of individuals with obesity compared to those without obesity developed atrial fibrillation (6.3% vs. 3.1%, respectively).[4] In a prospective study including subjects with incident atrial fibrillation, the composite endpoint of ischemic stroke, thromboembolism, or death was significantly higher for overweight (hazard ratio [HR] 1.31, 95% CI, 1.09-1.56) and obese patients (HR 1.55, 95% CI, 1.27-1.90) compared to normal weight patients.[11] Utilizing literature that demonstrated improvements in atrial fibrillation symptom burden and severity following weight loss management, the 2019 focused update of the ACC/AHA/HRS guidelines included a new recommendation for overweight and obese patients with atrial fibrillation. The update recommended clinicians to focus on patient weight loss in addition to risk factor modification.[4]

THROMBOEMBOLIC RISK AND DIRECT ORAL ANTICOAGULANTS

Stroke and thromboembolism prevention remains one of the top priority interventions in the management of atrial fibrillation. All types of atrial fibrillation – paroxysmal, persistent, or permanent – significantly increase the risk of thromboembolic ischemic stroke.[4] The formation and migration of atrial thrombi in patients with atrial fibrillation confers its high risk in developing stroke and/or peripheral thromboembolism.

As such, atrial fibrillation is correlated with a 4- to 5-fold increased risk of ischemic stroke, and the proportion of strokes attributed to atrial fibrillation increases substantially with age (1.5% in 50 to 59 years of age vs. 23.5% in 80 to 90 years of age individuals).[2,4] In addition, strokes occurring in patients with atrial fibrillation tend to be more severe and carry a greater risk of recurrence and mortality than patients without atrial fibrillation.[2]

Stroke and thromboembolic risk can be mitigated with the use of pharmacological therapy, specifically antithrombotics, which prevent stroke and systemic emboli in part by reducing the formation of thrombotic clots. The most widely used antithrombotic agents include oral anticoagulants (warfarin and direct oral anticoagulants) and oral antiplatelets (e.g. clopidogrel and aspirin).[2] Since guidelines have explicitly recommended against the use of antiplatelet therapy alone for stroke prevention in atrial fibrillation in light of clinical evidence, and because this study focuses solely on oral anticoagulants, the antiplatelet drugs will be not discussed further.[3,6] While oral anticoagulants have demonstrated efficacy in reducing stroke risk, they also carry a concomitant increased risk of bleeding, ranging from minor bleeds to fatal intracranial or extracranial hemorrhage.[4] Therefore, while the main benefit of anticoagulant agents is in reducing the risk of stroke and thromboembolism, they must be used with careful consideration to minimize their associated bleeding risks. Overall, appropriate use of anticoagulants and concurrent management of risk factors can substantially reduce stroke risk for atrial fibrillation patients.

Although warfarin, a vitamin K antagonist, has been in use since the 1950s as a mainstay anticoagulant treatment of stroke prevention in patients with atrial fibrillation, several limitations of its use have paved the way for newer anticoagulants to dominate the treatment landscape. Compared to warfarin, the direct oral anticoagulants (DOACs) have more predictable pharmacologic profiles, fewer drug-drug interactions, fewer monitoring requirements, limited dietary restrictions, and fixed dosing regimens.[2,12,13] In their pivotal

phase III trials, each of the DOACs demonstrated to be at least as effective and safe as warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation.[14–17] A meta-analyses on the DOAC trials reported superiority of DOACs over warfarin in preventing stroke or thromboembolism as well as reducing the risk of intracranial hemorrhage.[18] As such, DOACs are recommended as first-line treatments for eligible patients.[4]

Table 1.2. Direct Oral Anticoagulants

Generic Name	Dabigatran[19]	Rivaroxaban[20]	Apixaban[21]	Edoxaban[22]
Brand Name	Pradaxa®	Xarelto®	Eliquis®	Savaysa®
Company	Boehringer Ingelheim	Janssen	Bristol-Myers Squibb/Pfizer	Daiichi Sankyo
Approval Date	AF (10/2010) VTE (4/2014)	AF (11/2011) VTE (7/2011)	AF (12/2012) VTE (3/2014)	AF (1/2015) VTE (1/2015)
Class	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Pivotal Trial	RE-LY[14]	ROCKET-AF[15]	ARISTOTLE[16] AVERROES*[23]	ENGAGE-AF TIMI 48[17]

AF: atrial fibrillation; ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES: Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ENGAGE-AF TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48; VTE: venous thromboembolism; RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

*AVERROES is the only trial among the listed pivotal trials that uses aspirin as the comparator arm

Table 1.2 outlines key attributes of each of the DOACs. Dabigatran, the only direct thrombin inhibitor, was the first DOAC to be approved by the U.S. Food and Drug Administration (FDA) for atrial fibrillation, followed by rivaroxaban, apixaban, and edoxaban. The pivotal trials mentioned in Table 1.2 provided the necessary evidence of the

efficacy and safety of DOACs compared to warfarin (or, aspirin in the AVERROES trial) in nonvalvular atrial fibrillation patients for FDA approval. All of the DOACs have FDA-approved indications for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, as well as for the treatment and secondary prevention of venous thromboembolism (VTE).[19–22]

RISK STRATIFICATION TOOLS

Risk stratification tools have been developed to stratify patients into sequential levels of ischemic stroke risk. The $CHADS_2$ score (**C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus, **P**rior stroke or transient ischemic attack or thromboembolism) has a score range of 0 to 6 and has been validated in multiple nonvalvular atrial fibrillation patient populations. However, one of its main limitations is its inconsistent reliability and validity in properly determining stroke risk with scores of 2 or less.[4] In contrast, the CHA_2DS_2-VASc score (**C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus, **P**rior stroke or transient ischemic attack or thromboembolism, **V**ascular disease, **A**ge 65-74 years, **S**ex category) has a larger score range of 0 to 9, includes more conditions, and ultimately performed better than the $CHADS_2$ score at stratifying stroke risk. In addition, the CHA_2DS_2-VASc score automatically assigns a score of at least 1 for female patients (Table 1.3).[4] Due to its widespread use, the CHA_2DS_2-VASc score is recommended by many guidelines to estimate stroke risk in nonvalvular atrial fibrillation patients.[3,4,4,6]

Table 1.3. CHA_2DS_2-VASc Components and Scores

Component	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke / transient ischemic attack / thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 years	1
Sex category (i.e. female sex)	1
Maximum score	9

Risk stratification tools that stratify bleed risk among nonvalvular atrial fibrillation patients have also been developed. These include HAS-BLED (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR, **E**lderly, **D**rugs/alcohol concomitantly), HEMORR2HAGES (**H**epatic or renal disease, **E**thanol abuse, **M**alignancy, **O**lder age, **R**educed platelet count or function, **R**ebleeding, **H**ypertension, **A**nemia, **G**enetic factors, **E**xcessive fall risk, **S**troke), and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation). For the HAS-BLED score, scores of 3 or greater are considered high risk and warrant closer observation and management of any modifiable risk factors (Table 1.4). The HAS-BLED score performed better in stratifying bleed risk than the HEMORR2HAGES and ATRIA scores. While the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines deemed the bleed risk scores as insufficient in clinical utility, other, more recent guidelines recommend the use of HAS-BLED to address modifiable bleeding risk factors in atrial fibrillation patients.[2–4,6]

Table 1.4. HAS-BLED Components and Score

Component	Score
Hypertension	1
Abnormal renal function	1
Abnormal liver function	1
Stroke	1
Bleeding history or predisposition	1
Labile INR	1
Elderly	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

INR: international normalized ratio

CLINICAL GUIDELINES FOR MANAGEMENT OF THROMBOEMBOLIC RISK IN ATRIAL FIBRILLATION

Given the robust clinical evidence demonstrating substantial stroke risk reduction with oral anticoagulant therapy, published guidelines recommend thromboprophylaxis in atrial fibrillation patients at moderate to high risk of stroke. All of the following guidelines utilize the CHA_2DS_2-VASc score in their antithrombotic recommendations.

The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guideline for the Management of Patients with Atrial Fibrillation recommend oral anticoagulants (warfarin, dabigatran, rivaroxaban, or apixaban) in patients with nonvalvular atrial fibrillation with a CHA_2DS_2-VASc score of 2 or greater. For patients with a CHA_2DS_2-VASc score of 1, an oral anticoagulant or aspirin may be considered. For patients with a CHA_2DS_2-VASc score of 0, antithrombotic therapy is reasonable to omit.[4]

The 2016 European Society of Cardiology (ESC) Guidelines for the Management of Atrial Fibrillation recommends oral anticoagulants for male patients with a CHA_2DS_2-VASc score of 2 or greater and female patients with a CHA_2DS_2-VASc score of 3 or

greater. Oral anticoagulant therapy can be considered in male patients with a CHA_2DS_2-VASc score of 1 and female patients with a CHA_2DS_2-VASc score of 2. In addition, the 2016 ESC guidelines recommend DOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) over warfarin.[6]

The 2018 American College of Chest Physicians (CHEST) Guideline and Expert Panel Report on Antithrombotic Therapy for Atrial Fibrillation recommends antithrombotic therapy in atrial fibrillation patients at high risk of stroke (a CHA_2DS_2-VASc score of 2 or greater in males and 3 or greater in females). For patients with 1 non-sex CHA_2DS_2-VASc score, the guideline suggests antithrombotic therapy. Patients at low risk of stroke (a CHA_2DS_2-VASc score of 0 in males or 1 in females), the guideline suggests no antithrombotic therapy. Similar to the 2016 CHEST guidelines, the 2018 CHEST guidelines recommend DOACs over warfarin.[3]

The 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation updated its previous antithrombotic recommendations. For male patients with a CHA_2DS_2-VASc score of 2 or greater or female patients with a CHA_2DS_2-VASc score of 3 or greater, oral anticoagulants are recommended, which also newly includes edoxaban. DOACs are also recommended over warfarin. In male patients with a CHA_2DS_2-VASc score of 1 and female patients with a CHA_2DS_2-VASc score of 2, anticoagulant therapy may be considered. In male patients with a CHA_2DS_2-VASc score of 0 and female patients with a CHA_2DS_2-VASc score of 1, anticoagulant therapy is reasonable to omit. In addition, the new guidelines included recommendations for weight loss and risk factor modifications in patients who are overweight or obese with atrial fibrillation.[4]

CURRENT LITERATURE ON OBESITY IMPACT IN DIRECT ORAL ANTICOAGULANT THERAPY

While numerous publications assessing the efficacy, effectiveness, and safety of DOACs exist, limited data is available on how body weight influences the clinical outcomes of those DOAC-receiving patients with atrial fibrillation. None of the product labels for the approved DOACs include a dose adjustment recommendation for high body weight or body mass index (BMI).[19–22] While the package insert for apixaban includes language on weight, it is in reference to a low body weight (less than or equal to 60kg) as one of three criteria used to determine if a reduced dose is warranted.[21]

No known large randomized controlled trial evaluating the efficacy and safety of DOACs in obese atrial fibrillation patients has been conducted. In the five pivotal phase III randomized controlled trials of DOACs in nonvalvular atrial fibrillation patients, mean weights of 82kg and body mass index of 28 kg/m^2 were reported. Only two trials included subgroup analyses by weight: RE-LY for dabigatran and ROCKET-AF for rivaroxaban. Although ARISTOTLE, the pivotal trial for apixaban, did include a subgroup analysis by weight, the weight category was specific to underweight patients, using 60kg as the weight cut-off, and was therefore not included in this review.[16] Table 1.5 reports the weight categories delineated by both subgroup analyses, number of analyzed patients in the subgroups, and results for the efficacy outcome; Table 1.6 reports the same for the safety outcome.[14–17,23] The two subgroup analyses from the RE-LY and ROCKET-AF trials demonstrated that the DOACs were similar to warfarin in efficacy and safety in the highest weight categories, suggesting that DOACs are efficacious and safe in obese patients. Additionally, both subgroup anlyses demonstrated lower stroke and systemic embolic event and major bleed rates in higher weight categories compared to lower weight categories. As such, a consistent, albeit paradoxical, message is conveyed across the

studies: a higher body weight seems to be protective against stroke/systemic embolic and/or major bleed events.[14,15,26] However, the subgroup analyses offer challenges in interpretation for the following reasons: there is an inconsistency in the absolute weight cut-offs between the two analyses, the weight cutoffs do not follow the NIH weight classifications, RE-LY conducted the subgroup analyses only on efficacy and not safety outcomes, RE-LY provided only the total number of patients without a breakdown of the patient numbers by treatment group, and RE-LY reported results by an outcome rate per year. Additionally, the number and subgroup analyses results of patients with extreme obesity/class III (BMI >40 kg/m^2) were not reported in either analysis, demonstrating this population's relative underrepresentation in clinical trials. [14,15]

In addition to subgroup analyses, four post-hoc analyses of the pivotal phase III clinical trials have been identified.[24–27] The results of the post-hoc analyses are reported in Table 1.7 for efficacy and Table 1.8 for safety. All post-hoc analyses' efficacy results demonstrated lower stroke and systemic embolic events with increasing body weights, bolstering the paradoxical phenomenon seen in the subgroup analyses: a higher body weight is associated with a decreased risk of stroke. In regards to major bleeding events, results across the post-hoc analyses varied, where the highest weight categories conferred either higher or lower risks of major bleeding compared to the lowest weight categories. However, most of the comparisons were not statistically significant. Overall results of the post-hoc analyses demonstrated a favorable benefit-risk profile of higher weight patients versus normal weight patients with regards to prevention of stroke and systemic embolism and comparable rates of major bleeding events in atrial fibrillation.

Table 1.5. Subgroup Analyses for Efficacy Outcome by Weight in Two Pivotal Phase III Clinical Trials of DOACs in Patients with Atrial Fibrillation[†]

Drug, Trial	**Weight categories**	**Patients N (%)**	**Subgroup Analyses Results for Efficacy Outcome**
Dabigatran, RE-LY	<50kg	376/18,113 (2.1%)*	2.24% per year for dabigatran 150mg
	50-99kg	14,629/18,113 (80.8%)*	1.14% per year for dabigatran 150mg
	≥100kg	3,099/18,113 (17.1%)*	0.87% per year for dabigatran 150mg
	BMI <28 kg/m^2	9,131/18,113 (50.4%)*	1.17% per year for dabigatran 150mg
	BMI ≥28 kg/m^2	8,962/18,113 (49.5%)*	1.04% per year for dabigatran 150mg
Rivaroxaban, ROCKET-AF	≤70kg	2,013/7,081 (28.4%)**	4.62% (93/2,013) in rivaroxaban
	70-≤90kg	3,031/7,081 (42.8%)**	4.16% (126/3,031) in rivaroxaban
	>90kg	2,035/7,081 (28.7%)**	2.46% (50/2,035) in rivaroxaban
	BMI ≤25 kg/m^2	1,695/7,081 (23.9%)**	4.25% (72/1,695) in rivaroxaban
	BMI 25-≤35 kg/m^2	4,409/7,081 (62.3%)**	3.83% (169/4,409) in rivaroxaban
	BMI >35 kg/m^2	972/7,081 (13.7%)**	2.88% (28/972) in rivaroxaban

RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

[†]Only RE-LY and ROCKET-AF conducted subgroup analyses for efficacy outcome by weight

*The RE-LY trial only included numbers of total patients, not stratified by treatment group

**Specific to rivaroxaban treatment group only

Table 1.6. Subgroup Analyses for Safety Outcome by Weight in One Pivotal Phase III Clinical Trial of DOAC in Patients with Atrial Fibrillation[†]

Drug, Trial	**Weight categories**	**Patients N (%)**	**Subgroup Analyses Results for Safety Outcome**
Rivaroxaban, ROCKET-AF	≤70kg	2,004/7,061 (28.4%)*	3.14% (63/2,004) in rivaroxaban
	70-≤90kg	3,022/7,061 (42.8%)*	3.04% (93/3,022) in rivaroxaban
	>90kg	2,033/7,061 (28.8%)*	1.67% (34/2,033) in rivaroxaban
	BMI ≤25 kg/m^2	1,685/7,061 (23.9%)*	2.91% (49/1,685) in rivaroxaban
	BMI 25-≤35 kg/m^2	4,400/7,061 (62.3%)*	2.75% (121/4,400) in rivaroxaban
	BMI >35 kg/m^2	971/7,061 (13.8%)*	1.96% (19/971) in rivaroxaban

ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

[†]Only ROCKET-AF conducted subgroup analyses for safety outcome by weight

*Specific to rivaroxaban treatment group only

The findings from the subgroup and post-hoc analyses were consistent with the results of a recent meta-analysis conducted on 11 randomized controlled trials on DOACs in patients with atrial fibrillation and venous thromboembolism.[28] In this meta-analysis, a low body weight was associated with an increased risk of thromboembolism compared to patients in the non-low body weight group (relative risk [RR] 1.57, 95% CI 1.34-1.85). In an analysis of a subgroup of atrial fibrillation patients, higher body weights conferred a lower risk of thromboembolism compared to non-high body weight patients (RR 0.43, 95% CI 0.28-0.67). Major bleeding and clinically relevant non-major bleeding rates were comparable for all body weight comparisons. Given the results, the authors concluded that dose adjustments by weight for DOACs were not likely to improve efficacy or safety.

Table 1.7 Post-Hoc Analyses on Efficacy Outcomes of Pivotal Phase III Clinical Trials of DOACs in Patients with Atrial Fibrillation

	RE-LY post-hoc[a] One year stroke/SE rate (95% CI)	**ROCKET-AF post-hoc[b]** HR (95% CI)	**ARISTOTLE post-hoc[c]** HR (95% CI)	**ENGAGE-AF TIMI 48 post-hoc[d]** HR (95% CI)
Low Weight	2% (1.3-2.6)	Reference	Reference	Reference
Middle Weight	1.4% (1.2-1.6)	0.81 (0.66-0.99)	0.74 (0.65-0.84)	0.91 (0.78-1.07)
High Weight	1.1% (0.6-1.6)	0.69 (0.55-0.86)	0.68 (0.60-0.78)	0.82 (0.68-1.00)
High Weight II	N/A	N/A	N/A	0.68 (0.51-0.89)
High Weight III	N/A	N/A	N/A	0.54 (0.36-0.82)

ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BMI: body mass index; CI: confidence interval; ENGAGE-AF TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48; RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy; HR: hazard ratio; ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE: systemic embolism

[a]Low Weight defined as the bottom 10% of BMI (<22.5 kg/ m^2), Middle Weight defined as the middle 80% of BMI (22.5-36 kg/ m^2), and High Weight defined as upper 10% of BMI (>36 kg/m2); Results reported as one year stroke/systemic embolism rates for all treatment groups (dabigatran 110mg, dabigatran 150mg, and warfarin)

[b]Low Weight defined as BMI of 18.50-24.99 kg/ m^2, Middle Weight defined as BMI of 25.00-29.99 kg/ m^2), and High Weight defined as BMI of ≥30 kg/ m^2; Results reported as adjusted hazard ratios for both rivaroxaban and warfarin.

[c]Low Weight defined as BMI of 18.50-24.99 kg/ m^2), Middle Weight defined as BMI of 25.00-29.99 kg/ m^2), and High Weight defined as BMI of 30 kg/ m^2 or greater; Results reported as adjusted hazard ratios for both apixaban and warfarin.

[d]Low Weight defined as BMI of 18.50-24.99 kg/ m^2), Middle Weight defined as BMI of 25.00-29.99 kg/ m^2), High Weight defined as BMI of 30.00-34.99 kg/ m^2, High Weight II defined as BMI of 35.00-39.99 kg/ m^2, and High Weight III defined as BMI of >40 kg/ m^2; Results reported as adjusted hazard ratios for both edoxaban and warfarin.

Table 1.8 Post-Hoc Analyses on Safety Outcomes of Pivotal Phase III Clinical Trials of DOACs in Patients with Atrial Fibrillation

	RE-LY post-hoc[a] One year stroke/SE rate (95% CI)	**ROCKET-AF post-hoc[b]** HR (95% CI)	**ARISTOTLE post-hoc[c]** HR (95% CI)	**ENGAGE-AF TIMI 48 post-hoc[d]** HR (95% CI)
Low Weight	4.6% (3.6-5.6)	Reference	Reference	Reference
Middle Weight	3.6% (3.3-3.9)	1.09 (0.91-1.31)	0.82 (0.68-0.99)	1.03 (0.88-1.19)
High Weight	3.7% (2.8-4.6)	1.06 (0.87-1.29)	0.91 (0.74-1.10)	1.12 (0.94, 1.33)
High Weight II	N/A	N/A	N/A	1.18 (0.94, 1.47)
High Weight III	N/A	N/A	N/A	1.28 (0.97-1.70)

ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BMI: body mass index; CI: confidence interval; ENGAGE-AF TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48; RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy; HR: hazard ratio; ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE: systemic embolism

[a]Low Weight defined as the bottom 10% of BMI (<22.5 kg/ m^2), Middle Weight defined as the middle 80% of BMI (22.5-36 kg/ m^2), and High Weight defined as upper 10% of BMI (>36 kg/m2); Results reported as one year stroke/systemic embolism rates for all treatment groups (dabigatran 110mg, dabigatran 150mg, and warfarin)

[b]Low Weight defined as BMI of 18.50-24.99 kg/ m^2, Middle Weight defined as BMI of 25.00-29.99 kg/ m^2), and High Weight defined as BMI of ≥30 kg/ m^2; Results reported as adjusted hazard ratios for both rivaroxaban and warfarin.

[c]Low Weight defined as BMI of 18.50-24.99 kg/ m^2), Middle Weight defined as BMI of 25.00-29.99 kg/ m^2), and High Weight defined as BMI of 30 kg/ m^2 or greater; Results reported as adjusted hazard ratios for both apixaban and warfarin.

[d]Low Weight defined as BMI of 18.50-24.99 kg/ m^2), Middle Weight defined as BMI of 25.00-29.99 kg/ m^2), High Weight defined as BMI of 30.00-34.99 kg/ m^2, High Weight II defined as BMI of 35.00-39.99 kg/ m^2, and High Weight III defined as BMI of >40 kg/ m^2; Results reported as adjusted hazard ratios for both edoxaban and warfarin.

Pharmacokinetic/pharmacodynamic (PK/PD) studies of body weight groups in DOACs were conducted. An exposure-response analyses of dabigatran plasma concentrations in atrial fibrillation patients in the RE-LY clinical trial demonstrated that dabigatran trough levels were 21% lower for the high body weight group versus the reference body weight group, and a lower trough concentration was associated with a higher probability of ischemic stroke. However, weight was not a significant covariate in

the multivariate logistic regression.[29] A study on the effect of extreme body weight on the PK/PD of apixaban found a 31% lower peak plasma concentration and 23% lower drug exposure in the high body weight group compared to the reference body weight group.[30] In contrast to the results from the dabigatran and apixaban studies, a study on the effect of body weight on the PK/PD of rivaroxaban demonstrated similar peak plasma concentrations and drug exposures for high body weight groups and reference body weight groups. Thus, while obesity led to lower plasma concentrations for both dabigatran and rivaroxaban, it did not significantly affect the plasma concentration of rivaroxaban.[31] No known studies to date have analyzed the effects of body weight on the pharmacokinetics of edoxaban.

Evidence on the impact of obesity on real-world effectiveness of DOACs in atrial fibrillation is notably scarce. A retrospective, single-center study compared the efficacy and safety of DOACs (dabigatran, rivaroxaban, and apixaban) and warfarin in hospitalized atrial fibrillation patients who were morbidly obese (BMI >40 kg/m^2 or weight >120kg). With a primary efficacy outcome of ischemic stroke or transient ischemic attack, patients in the DOAC group had a lower primary outcome rate (1.75% per year) compared to patients in the warfarin group (2.07% per year) (rate ratio 0.84, 95% CI 0.23-3.14, P=0.80). With regards to the safety outcome, DOAC-receiving patients had lower rates of major bleeding (2.18% per year) versus warfarin-receiving patients (4.97% per year) (rate ratio 0.44, 95% CI 0.15-1.25, P=0.11). Neither of the results were statistically significant, which may be in part due to its low population count (N=64). Moreover, this study looked exclusively at morbidly obese patients and compared the DOAC vs. warfarin treatment group outcomes, and therefore cannot be used to assess the impact of body weight itself on the efficacy and safety of DOACs.[13] A second study aimed to evaluate the impact of body weight on DOACs in the treatment of atrial fibrillation and venous thromboembolism

based on a prospective registry in Dresden, Germany. While major bleeding events increased with increasing BMI, the composite rate of major thromboembolic events (stroke, transient ischemic attack, or systemic embolism) decreased with increasing BMI (for BMI 30-35 kg/m^2: 1.84 events per 100 patient-years, 95% CI 1.24-2.63; for BMI 35-40 kg/m^2: 1.56 events per 100 patient-years, 95% CI 0.71-2.96; for BMI >40 kg/m^2: 0.49 events per 100 patient-years, 95% CI 0.01-2.71). These findings are consistent with the paradoxical phenomenon of the protective effect of higher body weights on stroke risk seen in the subgroup and post-hoc analyses.[32]

STUDY RATIONALE

Atrial fibrillation confers a high risk of stroke and thromboembolism that can be avoided with appropriate anticoagulant treatment. DOACs are widely used in this setting and have demonstrated clinical benefit from its anticoagulant effects, although they should be used after careful consideration of the benefit-risk profile of each patient due to the risk of bleed. In the United States, the prevalence of atrial fibrillation is expected to increase, partly due to the aging population, and the prevalence of overweight and obese individuals has been on the rise in the past few decades. Moreover, literature points to obesity as a risk factor for cardiovascular-related diseases, including stroke, atrial fibrillation, venous thromboembolism, and congestive heart failure. This suggests that obesity and atrial fibrillation are interlinked epidemics, neither of which are expected to quell anytime soon. This highlights the need for further clinical evidence on the impact of body weight on clinical outcomes for individuals who are obese, have atrial fibrillation, and can benefit from DOAC therapy.

However, data on how obesity influences stroke and bleed risk in DOAC-receiving atrial fibrillation patients is very limited. Obese patients were not specifically sought after and analyzed by the DOAC pivotal randomized controlled trials, and subgroup and post-hoc analyses of the trials were either missing, inconsistent in weight classifications, and/or inconsistent in the reporting of their results. Pharmacokinetic and pharmacodynamic studies showed varying responses among the DOACs to increasing body weight in drug levels and exposures, which has unknown clinical implications. Real-world studies are scant, with one prospective registry study evaluating body weight impact in DOACs, which must be tempered with its limited generalizability to ex-Germany locations. Given the inadequacy of the available literature, two guidelines explicitly recommend against the use of DOACs in patients with extreme body weights (BMI >40 kg/m^2 or weight >120kg).[12,33]

The current available evidence also does not point to a clear direction on how body weight could influence DOAC efficacy and safety. The subgroup and post-hoc analyses suggested that DOACs are efficacious and safe in obese patients, although the results must be tempered by the limited available data for patients in the extremes of weight. In contrast, the PK/PD studies indicated for some DOACs that increasing body weights were associated with decreased drug peak concentrations, exposures, and shorter half-lives, which raises concerns about potential underdosing – and subsequent under-anticoagulation – of these fixed-dose regimen drugs in obese patients. Further evidence is needed to evaluate the clinical outcomes in this patient population.

As such, this real-world study aims to address this gap in evidence. The findings of this study will substantially contribute to the literature and can be used by healthcare professionals to provide evidence-based care for their overweight and obese individuals with atrial fibrillation who would benefit from DOAC therapy. While this analysis focuses on health plan patients primarily located in central Texas, an added goal of this study is to

provide a framework and an additional impetus for further analyses on larger, broader patient populations elsewhere.

Chapter 2: Methods

STUDY OBJECTIVES AND HYPOTHESES

The purpose of this study is to assess the impact of body weight on real-world clinical outcomes in patients with atrial fibrillation taking direct oral anticoagulants (DOACs). The clinical outcomes will be compared across five independent patient cohorts. The cohorts will be stratified by weight classifications by body mass index (BMI), as defined by the National Institutes of Health (NIH) (Table 2.1).[34]

Table 2.1. National Institutes of Health Weight Classifications by Body Mass Index[34]

Weight Classification	Body Mass Index (kg/m^2)
Underweight	<18.5
Normal	18.5-24.9
Overweight	25.0-29.9
Obesity, Class I	30.0-34.9
Obesity, Class II	35.0-39.9
Obesity, Class III/Extreme Obesity	≥40.0

The primary objective of this study is to evaluate the impact of body mass index on stroke or systemic embolism and major bleed events in patients with atrial fibrillation who are users of dabigatran, rivaroxaban, apixaban, or edoxaban. This study will address the following specific objectives and null hypotheses, with detailed case definitions of the corresponding variables listed in the sections "Baseline Characteristics" and "Outcome Measures" of Chapter 2:

1. To determine whether patient demographics (age, gender, race, ethnicity, primary insurance) differ among the patient cohorts stratified by NIH weight classifications.

$H_0$1.1: There is no statistically significant difference in patient age among the patient cohorts stratified by NIH weight classifications.

$H_0$1.2: There is no statistically significant difference in patient gender among the patient cohorts stratified by NIH weight classifications.

$H_0$1.3: There is no statistically significant difference in patient race among the patient cohorts stratified by NIH weight classifications.

$H_0$1.4: There is no statistically significant difference in patient ethnicity among the patient cohorts stratified by NIH weight classifications.

$H_0$1.5: There is no statistically significant difference in patient primary insurance among the patient cohorts stratified by NIH weight classifications.

2. To describe the clinical characteristics of weight and body mass index among the patient cohorts stratified by NIH weight classifications. No hypothesis testing is needed because no statistical tests are planned to be conducted.
3. To determine whether medication-related clinical characteristics (index DOAC medication, dose of index DOAC medication and prior warfarin use) differ among the patient cohorts stratified by NIH weight classifications.

    $H_0$3.1: There is no statistically significant difference in index DOAC medication among the patient cohorts stratified by NIH weight classifications.

    $H_0$3.2: There is no statistically significant difference in dose of index DOAC medication (Standard/Reduced) among the patient cohorts stratified by NIH weight classifications.

    $H_0$3.3: There is no statistically significant difference in previous anticoagulant treatment history with warfarin (Yes/No) during the baseline

period medication among the patient cohorts stratified by NIH weight classifications.

4. To determine whether the prevalence of comorbidities (congestive heart failure, hypertension, diabetes mellitus, history of stroke or transient ischemic attack, coronary artery disease, renal disease, liver disease, bleeding history or predisposition, myocardial infarction, venous thromboembolism, alcoholism) during the baseline period differs among the patient cohorts stratified by NIH weight classifications.

   $H_0$4.1: There is no statistically significant difference in the prevalence of congestive heart failure (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

   $H_0$4.2: There is no statistically significant difference in the prevalence of hypertension (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

   $H_0$4.3: There is no statistically significant difference in the prevalence of diabetes mellitus (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

   $H_0$4.4: There is no statistically significant difference in the prevalence of history of stroke or transient ischemic attack (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

   $H_0$4.5: There is no statistically significant difference in the prevalence of coronary artery disease (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

$H_0$4.6: There is no statistically significant difference in the prevalence of renal disease (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

$H_0$4.7: There is no statistically significant difference in the prevalence of liver disease (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

$H_0$4.8: There is no statistically significant difference in the prevalence of bleeding history or predisposition (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

$H_0$4.9: There is no statistically significant difference in the prevalence of myocardial infarction (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

$H_0$4.10: There is no statistically significant difference in the prevalence of venous thromboembolism (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

$H_0$4.11: There is no statistically significant difference in the prevalence of alcoholism (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.

5. To determine whether the calculated patient risk stratification indices (Charlson Comorbidity Index, CHA_2DS_2-VASc Score, HAS-BLED Score) differ among the patient cohorts stratified by NIH weight classifications.

   $H_0$5.1: There is no statistically significant difference in the calculated Charlson Comorbidity Indices among the patient cohorts stratified by NIH weight classifications.

$H_0$5.2: There is no statistically significant difference in the calculated CHA_2DS_2-VASc Scores among the patient cohorts stratified by NIH weight classifications.

$H_0$5.3: There is no statistically significant difference in the calculated HAS-BLED Scores among the patient cohorts stratified by NIH weight classifications.

6. To determine whether the unadjusted rate of stroke or systemic embolism differs among the patient cohorts stratified by NIH weight classifications.

   $H_0$6: There is no statistically significant difference in the proportion of patients experiencing a stroke or systemic embolic event among the patient cohorts stratified by NIH weight classifications.

7. To determine whether the unadjusted rate of major bleed differs among the patient cohorts stratified by NIH weight classifications.

   $H_0$7: There is no statistically significant difference in the proportion of patients experiencing a major bleed event among the patient cohorts stratified by NIH weight classifications.

8. To determine whether NIH weight classification by body mass index is associated with the hazard of stroke or systemic embolism.

   $H_0$8: Upon adjusting for covariates and assessing time to first event, there is no statistically significant association between underweight, overweight, obesity class I, obesity class II, and obesity class III weight cohorts with the normal weight cohort (reference cohort) and the hazard of stroke or systemic embolic event.

9. To determine whether NIH weight classification by body mass index is associated with the hazard of major bleed.

$H_0$9: Upon adjusting for covariates and assessing time to first event, there is no statistically significant association between underweight, overweight, obesity class I, obesity class II, and obesity class III weight cohorts with the normal weight cohort (reference cohort) and the hazard of major bleed.

STUDY SETTING AND DATA SOURCE

Baylor Scott & White Health (BSWH) is the largest, not-for-profit, integrated healthcare system in Texas that includes a network of 48 hospitals, over 600 clinics, over 7,800 active primary and specialty care physicians, and over 800 patient care sites.[35] Operating within the BSWH health system, Scott & White Health Plan (SWHP) is a local health plan that services 77 counties in the Central, East, North, and West Texas regions. SWHP provides health insurance to approximately 315,000 covered lives through various lines of business, including Commercial, Medicare, and Medicaid, with four types of plan products available: Preferred Provider Organizations (PPO), Point of Service (POS), Health Maintenance Organizations (HMO), and Exclusive Provider Organizations (EPO).[36] Rivaroxaban, apixaban, and dabigatran are preferred agents on the Texas Medicaid Preferred Drug List, and both rivaroxaban and apixaban are on Tier 2 on the SWHP Commercial plan formularies and Tier 3 on the SWHP Medicare plan formulary.[37,38]

This study analyzes pharmacy and medical claims data from the Virtual Data Warehouse (VDW). Pharmacy and medical claims data for SWHP members are housed under the VDW, a database that includes a variety of elements including enrollment, demographic characteristics, inpatient and outpatient utilization, diagnoses and procedures, and pharmacy dispensing. Pharmacy claims contain relevant information linked to

dispensed medications, including the drug name, drug dose, date filled, quantity supplied, days supplied, prescription instructions, and prescribing physician information. Medical claims contain relevant information on inpatient and outpatient services, including the encounter date, encounter type, place of service, procedure codes, provider seen at encounter, provider specialty, diagnosed medication, and up to 5 International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and Tenth Edition (ICD-10-CM) diagnosis codes per encounter. For the purposes of this study, the detailed information provided by medical and pharmacy claims of the beneficiaries in the VDW database will be retrieved to provide thorough patient-level information, including patient enrollment, encounters, diagnoses, medications, and clinical demographics and characteristics.

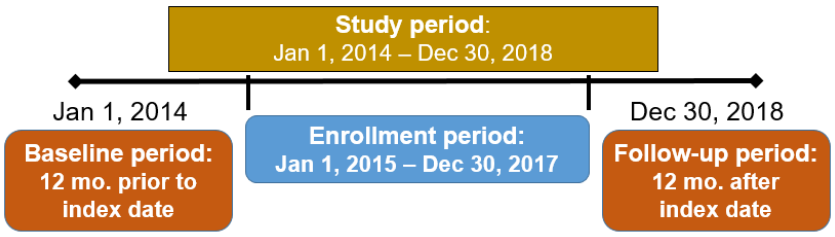
STUDY DESIGN

This is a retrospective, observational cohort study from the study period of January 1, 2014 to December 30, 2018, which includes the baseline period, enrollment period, and follow-up period (Figure 2.1). To be included in the study, patients are required to have at least one pharmacy claim for a direct oral anticoagulant (DOAC) during the enrollment period (January 1, 2015 to December 30, 2017). The index date is defined as the date of the first pharmacy claim of a DOAC, and this agent is defined as the index medication. During the 12 months prior to the index date (baseline period), all patients are required to have a diagnosis of atrial fibrillation or atrial flutter. In the follow-up period, patients are followed from the start of the index date until the earliest occurrence of either: (i) 12 months post-index date, (ii) occurrence of study outcome of interest, defined as a stroke or systemic embolic event and a major bleed event, or (iii) 30 days post-discontinuation date,

whichever occurs first. Discontinuation is defined as no evidence of DOAC filled for 30 days from the last days' supply of the last filled prescription date, unless the patient switches to another DOAC within this time period.

The Baylor Scott & White Health and the University of Texas at Austin Institutional Review Boards approved this study following expedited review.

Figure 2.1. Study Design



STUDY POPULATION

The study population consists of adult patients aged 18 years or older who are users of dabigatran, rivaroxaban, apixaban, or edoxaban with at least one atrial fibrillation or atrial flutter diagnosis on any diagnoses position from an inpatient, outpatient, or emergency department encounter during the baseline period (refer to Appendix I for included ICD-9/10 codes). In a systematic review, the ICD-9-CM diagnoses codes for atrial fibrillation or atrial flutter in any diagnoses position performed relatively well, with a positive predictive value (PPV) of 96% and a sensitivity of 99%.[39]

Patients with atrial flutter were included in the study due to the condition's similar stroke risk profile to atrial fibrillation and its high risk of developing atrial fibrillation; as

such, several guidelines recommend atrial flutter patients to be anticoagulated similarly to atrial fibrillation patients.[2,3,6] To consider a patient continuously on treatment with a DOAC therapy, fill dates and days supplied from pharmacy claims data were used, starting from the first fill date (index date) to 30 days following the date of which there are no residual days supply (discontinuation date). Because this study focuses on the impact of body weight on the DOAC class as a whole, switching was allowed, which is defined as a pharmacy fill of a DOAC agent different from the index medication within 30 days post-discontinuation date. Patients were excluded if their continuous enrollment in medical and pharmacy plans was fewer than 12 months prior to and after the index date, with an allowed gap of no more than 45 consecutive days.

For the comparative analyses, the study population was stratified into cohorts based on NIH weight classifications by body mass index (BMI): underweight (BMI <18.5 kg/m^2), normal (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obesity class I (BMI 30.0-34.9 kg/m^2), obesity class II (BMI 35.0-39.9 kg/m^2), obesity class III/extreme obesity (BMI ≥40.0 kg/m^2).

BASELINE CHARACTERISTICS

All baseline characteristics were collected during the baseline period. If multiple baseline measures existed within the baseline period, the measurement closest to the index date was used.

The following patient demographics were evaluated across each cohort: age at index date, gender (Male/Female), race (White, Black, Other), ethnicity (Hispanic, or Non-Hispanic), and primary insurance at index date (Commercial, Medicare, Medicaid, or Other).

Clinical and medication-related characteristics were also evaluated across each cohort and include: weight, BMI, index DOAC medication, dose of index DOAC medication (Standard/Reduced), and prior anticoagulant treatment with warfarin (Yes/No). The measurement of weight and BMI closest to the index date was collected and analyzed across the cohorts. The dose of a DOAC medication was considered to be Standard or Reduced given the doses supplied in Table 2.2, as extracted from each of the DOAC package inserts[19–22]. A patient was considered to have had prior warfarin treatment if at least one pharmacy claim for warfarin was filled in the baseline period prior to initiating a DOAC agent.

Table 2.2. Reduced or Standard Doses of DOAC Medications

	Standard Dose	Reduced Dose
Dabigatran	150mg twice daily	75mg twice daily
Rivaroxaban	20mg once daily	15mg once daily
Apixaban	5mg twice daily	2.5mg twice daily
Edoxaban	60mg once daily	30mg once daily

The prevalence of comorbidities (Yes/No) in the 12 months prior to the index date (baseline period) was collected and evaluated across each cohort. Comorbidities of interest included congestive heart failure, hypertension, diabetes mellitus, history of stroke or transient ischemic attack, coronary artery disease, renal disease, liver disease, bleeding history or predisposition, myocardial infarction, venous thromboembolism, and alcoholism. A patient was considered to have a comorbidity if there was evidence of at least one inpatient or outpatient medical claim with its corresponding ICD-9-CM or ICD-10-CM diagnoses code (Appendix II). The code lists were extracted from the Centers for Medicare and Medicaid (CMS) Chronic Conditions Data Warehouse (CCW) and similar,

previously published studies that evaluated the effectiveness of DOACs in real-world settings using administrative data.[40–46]

Baseline risk stratification indices – Charlson Comorbidity Index (CCI), CHA_2DS_2-VASc Score, and HAS-BLED Score – were calculated and assessed across the cohorts. The Quan variation of the CCI was used to assess comorbidity burden, which generates a single score per patient based on the sum of the weighted values of the following 17 conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy (including lymphoma and leukemia, except malignant neoplasm of the skin), moderate or severe liver disease, metastatic solid tumor, and AIDS/HIV. A higher CCI score indicates greater comorbidity burden.[47] The CHA_2DS_2-VASc Score (range 0 – 9), the components of which were previously mentioned in Chapter 1: Risk Stratification Tools (Table 1.3), measures stroke risk and is based on ICD-9-CM and ICD-10-CM codes on primary or secondary diagnoses positions on inpatient or outpatient claims (Appendix IV). The HAS-BLED Score (range 0 – 8), the components of which were previously mentioned in Chapter 1: Risk Stratification Tools (Table 1.4), measures bleed risk and is based on ICD-9-CM and ICD-10-CM codes on primary or secondary diagnoses positions on inpatient or outpatient claims (Appendix V). The component of labile international normalized ratio (INR) was not included in the HAS-BLED Score for this analysis due to DOAC medications, rather than warfarin, being the therapies of interest.

OUTCOME MEASURES

The primary effectiveness outcome was any stroke or systemic embolic (SE) event, which included ischemic stroke, hemorrhagic stroke, and systemic embolism. The primary safety outcome was any major bleed event, which included intracranial hemorrhage, gastrointestinal bleeding, or other major bleeding. These outcomes are consistent with the primary endpoints used in the pivotal trials of the DOAC medications.[14–17] All outcome measures were identified using appropriate ICD-9-CM and ICD-10-CM codes on primary or secondary positions of inpatient medical claims (Appendix VI). These codes and case definitions were based on previously published studies, with a positive predictive value (PPV) range from 85% to 95%, and validated administrative claims-based algorithms.[3,45,48–51]

Outcome measures that occurred on treatment are collected during the follow-up period, defined as the start of index date until the earliest occurrence of either: (i) 12 months post-index date, (ii) occurrence of study outcome of interest, or (iii) 30 days post-discontinuation date, whichever occurred first. Discontinuation was defined as no evidence of DOAC filled for 30 days from the last days' supply of the last filled prescription date, unless the patient switches to another DOAC within this time period.

The outcome measures were evaluated and compared among the patient cohorts stratified by NIH weight classifications by body mass index. To evaluate only the first event of stroke/SE and major bleed during the follow-up period, patients werecensored as of the first occurrence of each event. Stroke/SE and major bleed events were separately analyzed in order to individually evaluate effectiveness and safety outcomes across the cohorts.

STATISTICAL ANALYSES

The primary analysis involved evaluating mutually exclusive patient cohorts categorized by NIH weight classifications by BMI (Table 2.1). Baseline characteristics are presented using descriptive summary statistics (mean and standard deviation [SD] for continuous variables, frequency and percentage for categorical variables) for each patient cohort. Using the NIH weight categories as the dependent variable and baseline characteristics as the independent variables, the bivariate analyses listed in Table 2.3 were performed.

Table 2.3. Bivariate Analyses on Baseline Characteristics

Independent Variable	Statistical Test
Age	Spearman's Correlation
Gender	Wilcoxon Mann Whitney U
Race	Kruskal Wallis
Ethnicity	Kruskal Wallis
Primary insurance	Kruskal Wallis
Index DOAC medication	Kruskal Wallis
Dose of index DOAC medication	Wilcoxon Mann Whitney U
Prior warfarin use	Wilcoxon Mann Whitney U
All comorbidities*	Wilcoxon Mann Whitney U
Risk stratification indices**	Spearman's Correlation

CrCl: creatinine clearance, DOAC: direct oral anticoagulant, SCr: serum creatinine
*Congestive heart failure, hypertension, diabetes mellitus, history of stroke or transient ischemic attack, coronary artery disease, renal disease, liver disease, bleeding history or predisposition, myocardial infarction, venous thromboembolism, and alcoholism
**Charlson Comorbidity Index (CCI), CHA_2DS_2-VASc Score, and HAS-BLED Score

Unadjusted outcome event rates are descriptively reported for both stroke/systemic embolic events and major bleed events across all patient cohorts and graphically depicted in Kaplan-Meier cumulative incidence plots to characterize risk over time. Using the NIH weight categories as independent variables and the binary stroke/systemic embolism or major bleed outcome (Yes/No) as the dependent response variable, a logistic regressions were performed.

To estimate the differences in time to outcomes among the weight classification groups, cox proportional hazards regression was performed for each outcome measure across all patient cohorts. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for each outcome of interest. Covariates in the adjusted analyses included: age, gender, race, ethnicity, primary insurance, index DOAC medication, congestive heart failure, hypertension, diabetes mellitus, history of stroke or transient ischemic attack, coronary artery disease, renal disease, liver disease, bleeding history or predisposition, myocardial infarction, venous thromboembolism, and alcoholism.

Statistical significance was determined using an alpha level of 0.05 and two-sided tests. Statistical analyses are performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Chapter 3: Results

STUDY SAMPLE

Table 3.1 outlines the study sample attrition. There were 4,035 total patients identified with at least 1 pharmacy claim for a DOAC medication during the study enrollment period (January 1, 2015 to December 30, 2017). Nearly all patients (4,033) were 18 years of age or older. Of these adult patients receiving a DOAC, 2,337 (57.9%) had at least 12 months of continuous enrollment in medical and pharmacy plans prior to and after the index date, with an allowed gap of no more than 45 consecutive days. A majority of these patients (1,494; 63.9%) had a medical claim for atrial fibrillation or atrial flutter during the baseline period (12 months prior to the index date). A total of 1,049 (70.2%) patients had a recorded BMI value 12 months prior to or after the index date.

Table 3.1. Patient Attrition Table

Selection Criteria	N (%)
Patients with ≥1 pharmacy claim for a DOAC medication during the study enrollment period	4,035 (100%)
Adult patients (aged ≥18 years) on the index date	4,033 (100%)
12 month continuous enrollment criteria in medical and pharmacy plans prior to and after index date, with an allowed gap of no more than 45 consecutive days	2,337 (57.9%)
Patients with ≥1 inpatient or outpatient or emergency department medical claim for atrial fibrillation or atrial flutter, on any diagnoses position, during the baseline period	1,494 (63.9%)
Patients with at least one recorded BMI value 12 months pre- or post-index date	1,049 (70.2%)

Table 3.2 reports the distribution of patients across the weight categories. Due to the markedly small number of patients classified as underweight (14, 1.3%), this patient

cohort was excluded to provide more comparable cohorts for evaluation of outcome results. As such, the total population for the primary analysis of this study were 1,035 patients, consisting of only normal, overweight, obese class I, obese class II, and obese class III weight categories. The individual cohort with the largest proportion of patients was the overweight cohort (33.6%), and the collective obese categories (obesity classes I, II, and III) had a summed total of 438 (42.3%) patients.

Table 3.2 Distribution of Patients by Weight Classifications by Body Mass Index

Weight Classification (BMI [kg/m^2])	**N of 1,035 (%)**
Underweight (<18.5)	14 (1.3%)
Normal (18.5-24.9)	245 (23.4%)
Overweight (25.0-29.9)	352 (33.6%)
Obesity, Class I (30.0-34.9)	220 (21.0%)
Obesity, Class II (35.0-39.9)	132 (12.6%)
Obesity, Class III (≥40.0)	86 (8.2%)

BASELINE CHARACTERISTICS

Table 3.3 reports the baseline characteristics of the 1,035 patients who met the inclusion and exclusion criteria. The mean age at index date was 75.9 years (standard deviation [SD] 10.2 years). A Spearman's Correlation test showed a significant difference in mean age across the BMI cohorts (P<0.0001). The total population consisted of an even number of male (50.9%) and female (49.1%) patients. A Wilcoxon Mann Whitney U test showed a significant difference in gender across the BMI cohorts (P=0.0005). A majority of the population was of White race (96.2%) and non-Hispanic ethnicity (97.7%). In addition, a majority of the patients had Medicare as their primary insurance (70.6%),

followed by Commercially insured patients (24.4%). No patients had Medicaid insurance. A Kruskal Wallis test found no significant difference in race and ethnicity (P=0.0987 and P=0.2073, respectively) and a significant difference in primary insurance (P<0.0001) across BMI cohorts.

As expected, the mean weight and BMI increased as BMI cohorts increased from normal to obese class III (141.9lb and 22.6 kg/m^2 vs. 303.1lb and 45.8 kg/m^2, respectively). Most patients had an index medication of either apixaban (57.4%) or rivaroxaban (37.4%), followed by dabigatran (5.1%). Only 1 patient received edoxaban. A Kruskal Wallis test showed no significant difference in index DOAC medication across the BMI cohorts (P=0.1185). A majority of the patients received a standard dose of a DOAC (72.3%) and did not receive prior warfarin therapy (84.9%). A Wilcoxon Mann Whitney U showed a significant difference in dose of index DOAC medication (P<0.0001) and no significant difference in prior warfarin use (P=0.1430) across BMI cohorts.

A majority of the total population had hypertension in the baseline period (90.0%), followed by CAD (44.0%), CHF (35.1%), bleed history (32.2%), and diabetes (27.4%). A Wilcoxon Mann Whitney U test showed significant differences in hypertension (P=0.0027), diabetes (P<0.0001), prior stroke/TIA (P<0.0001), and bleed history (P=0.0349) and no significant differences in other comorbidities across the BMI cohorts.

The baseline means of the risk stratification indices in the total study population were as follows: 2.5 (SD 2.3) for CCI score, 4.3 (SD 1.7) for CHA_2DS_2-VASc score, and 2.4 (SD 1.0) for HAS-BLED score. A Spearman's Correlation test showed significant differences in CHA_2DS_2-VASc score (P<0.0001) and HAS-BLED score (P<0.0001) but no significant difference in CCI score (P=0.1535) across the BMI cohorts.

Table 3.3. Baseline Characteristics

	Total study population (N=1,035), N (%) or mean (SD)	Normal (N=245), N (%) or mean (SD)	Overweight (N=352), N (%) or mean (SD)	Obese I (N=220), N (%) or mean (SD)	Obese II (N=132), N (%) or mean (SD)	Obese III (N=86), N (%) or mean (SD)	P-value*
Demographics							
Age (years)	75.9 (10.2)	81.5 (7.9)	77.0 (9.7)	74.7 (9.2)	71.2 (10.0)	66.0 (9.8)	***<.0001***
Gender							
Male	527 (50.9%)	87 (35.5%)	200 (56.8%)	131 (59.5%)	62 (47.0%)	47 (54.7%)	
Female	508 (49.1%)	158 (64.5%)	152 (43.2%)	89 (40.5%)	70 (53.0%)	39 (45.3%)	***0.0005***
Race							
White	996 (96.2%)	240 (98.0%)	336 (95.5%)	209 (95.0%)	128 (97.0%)	83 (96.5%)	
Black	17 (1.6%)	1 (0.4%)	5 (1.4%)	6 (2.7%)	2 (1.5%)	3 (3.5%)	
Other	22 (2.1%)	4 (1.6%)	11 (3.1%)	5 (2.3%)	2 (1.5%)	0 (0.0%)	0.0987
Ethnicity							
Hispanic	24 (2.3%)	4 (1.6%)	9 (2.6%)	2 (0.9%)	4 (3.0%)	5 (5.8%)	
Non-Hispanic	1011 (97.7%)	241 (98.4%)	343 (97.4%)	218 (99.1%)	128 (97.0%)	81 (94.2%)	0.2073
Insurance							
Commercial	252 (24.3%)	23 (9.4%)	77 (21.9%)	60 (27.3%)	50 (37.9%)	42 (48.8%)	
Medicare	731 (70.6%)	219 (89.4%)	261 (74.1%)	145 (65.9%)	72 (54.5%)	34 (39.5%)	
Medicaid	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	52 (5.0%)	3 (1.2%)	14 (4.09%)	15 (6.8%)	10 (7.6%)	10 (11.6%)	***<.0001***
Clinical and Medication-Related Characteristics							
Weight (lb)	197.0 (53.9)	141.9 (22.5)	180.4 (24.6)	217.2 (26.9)	241.0 (33.1)	303.1 (49.9)	N/A
BMI (kg/m^2)	30.1 (6.9)	22.6 (1.7)	27.4 (1.4)	32.3 (1.5)	37.3 (1.6)	45.8 (5.8)	N/A
Index DOAC							
Apixaban	594 (57.4%)	153 (62.4%)	204 (58.0%)	124 (56.4%)	72 (54.5%)	41 (47.7%)	
Rivaroxaban	387 (37.4%)	79 (32.2%)	134 (38.1%)	82 (37.3%)	56 (42.4%)	36 (41.9%)	
Dabigatran	53 (5.1%)	13 (5.3%)	13 (3.7%)	14 (6.4%)	4 (3.0%)	9 (10.5%)	
Edoxaban	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.1185

Table 3.3 continued

Dose of DOAC							
Standard	748 (72.3%)	133 (54.3%)	254 (72.2%)	181 (82.3%)	104 (78.8%)	76 (88.4%)	
Reduced	287 (27.7%)	112 (45.7%)	98 (27.8%)	39 (17.7%)	28 (21.2%)	10 (11.6%)	***<.0001***
Prior warfarin	156 (15.1%)	42 (17.1%)	53 (15.1%)	36 (16.4%)	17 (12.9%)	8 (9.3%)	0.1430
Comorbidities							
CHF	363 (35.1%)	87 (35.5%)	118 (33.5%)	74 (33.6%)	46 (34.8%)	38 (44.2)	0.4827
HTN	931 (90.0%)	214 (87.3%)	308 (87.5%)	204 (92.7%)	122 (92.4%)	83 (96.5%)	***0.0027***
DM	284 (27.4%)	35 (14.3%)	76 (21.6%)	75 (34.1%)	47 (35.6%)	51 (59.3%)	***<.0001***
Stroke/TIA	150 (14.5%)	52 (21.2%)	59 (16.8%)	21 (9.5%)	11 (8.3%)	7 (8.1%)	***<.0001***
CAD	455 (44.0%)	100 (40.8%)	159 (45.2%)	99 (45.0%)	63 (47.7%)	34 (39.5%)	0.5051
Renal disease	200 (19.3%)	46 (18.8%)	66 (18.8%)	45 (20.5%)	23 (17.4%)	20 (23.3%)	0.6077
Liver disease	44 (4.3%)	6 (2.4%)	17 (4.8%)	7 (3.2%)	9 (6.8%)	5 (5.8%)	0.1125
Bleed hx	333 (33.2%)	91 (37.1%)	115 (32.7%)	64 (29.1%)	38 (28.8%)	25 (29.1%)	***0.0349***
MI	69 (6.7%)	12 (4.9%)	30 (8.5%)	13 (5.9%)	10 (7.6%)	4 (4.7%)	0.8694
VTE	62 (6.0%)	17 (6.9%)	23 (6.5%)	13 (5.9%)	5 (3.8%)	4 (4.7%)	0.2135
Alcoholism	18 (1.7%)	2 (0.8%)	9 (2.6%)	4 (1.8%)	2 (1.5%)	1 (1.2%)	0.8019
Risk Stratification Indices							
CCI	2.5 (2.3)	2.5 (2.3)	2.5 (2.5)	2.6 (2.4)	2.5 (2.1)	3.0 (2.3)	0.1535
CHA_2DS_2-VASc	4.3 (1.7)	4.8 (1.6)	4.2 (1.8)	4.1 (1.6)	4.0 (1.7)	3.8 (1.4)	***<.0001***
HAS-BLED	2.4 (1.0)	2.6 (1.0)	2.5 (1.0)	2.4 (1.0)	2.3 (1.0)	2.1 (0.9)	***<.0001***

Bleed hx: bleeding history or predisposition; BMI: body mass index; CAD: coronary artery disease; CCI: Charlson Comorbidity Index; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; CHF: congestive heart failure; CrCl: creatinine clearance; DM: diabetes mellitus; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; HTN: hypertension; MI: myocardial infarction; SCr: serum creatinine; SD: standard deviation; TIA: transient ischemic attack; VTE: venous thromboembolism

*Refer to Table 2.3 for the corresponding bivariate analyses performed. P-values are bolded and italicized when statistically significant.

THROMBOEMBOLISM AND BLEED

The incidence of a stroke/SE event and major bleed event were assessed during the follow-up period. A total of 11 (1.1%) stroke or systemic embolic events and 29 (2.8%) major bleed events occurred during the follow up period (Table 3.4). Stroke/SE event rates were comparable across the cohorts: normal 3 (1.2%), overweight 3 (0.9%), and the collective obese cohorts 5 (1.1%). Major bleed event rates saw a decreasing trend with higher BMI cohorts, and the obese class III cohort had the smallest numerical event rate (1.2%) whereas the normal weight cohort saw the highest (3.7%).

Table 3.4. Unadjusted Proportion of Patients Experiencing a Stroke/Systemic Embolic Event or Major Bleed in the Follow-Up Period

	Total (N=1,035), N (%)	Normal (N=245), N (%)	Overweight (N=352), N (%)	Obese I (N=220), N (%)	Obese II (N=132), N (%)	Obese III (N=86), N (%)
Stroke/SE	11 (1.1%)	3 (1.2%)	3 (0.9%)	3 (1.4%)	1 (0.8%)	1 (1.2%)
Major Bleed	29 (2.8%)	9 (3.7%)	11 (3.1%)	5 (2.3%)	3 (2.3%)	1 (1.2%)

Due to the significantly low number of event rates for both the effectiveness and safety outcomes, further analyses could not be conducted. As such, time to event analyses using cox proportional hazards regression were not performed.

SUMMARY OF RESULTS

Table 3.5 lists the summary of the study results for each hypothesis. Patient demographics (Objective 1) across the cohorts were generally balanced for race and ethnicity, whereas significant differences in age, gender, and primary insurance were seen. Clinical characteristics (Objective 2) demonstrated increasing weight and BMI with higher BMI cohorts, as expected. Medication-related characteristics (Objective 3) were balanced across cohorts, except for dose of index DOAC medication. Comorbidities (Objective 4) that were significantly different across the cohorts were hypertension, diabetes, prior stroke/TIA, and bleed history. Risk stratification indices (Objective 5) were similar across cohorts for the CCI score (except numerically in the obese claass III cohort), but significantly different for the CHA_2DS_2-VASc and HAS-BLED scores. The rates of stroke or systemic embolism (Objective 6) and major bleed (Objective 7) were too small to compare across the groups. As such, the hazard rate of stroke or systemic embolism and major bleed could not be computed (Objectives 8 and 9).

Table 3.5. Summary of Results by Objective and Hypothesis Testing

Objective and Null Hypotheses (H_0)	**Result**
Objective 1: To determine whether patient demographics differ among the patient cohorts stratified by NIH weight classifications	
$H_0$1.1: There is no statistically significant difference in patient age among the patient cohorts stratified by NIH weight classifications.	Reject
$H_0$1.2: There is no statistically significant difference in patient gender among the patient cohorts stratified by NIH weight classifications.	Reject
$H_0$1.3: There is no statistically significant difference in patient race among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$1.4: There is no statistically significant difference in patient ethnicity among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$1.5: There is no statistically significant difference in patient primary insurance among the patient cohorts stratified by NIH weight classifications.	Reject

Table 3.5 continued

Objective 2: To describe the clinical characteristics of weight and body mass index among the patient cohorts stratified by NIH weight classifications.	
No hypothesis testing is needed because no statistical tests are planned to be conducted	N/A
Objective 3: To determine whether medication-related clinical characteristics (index DOAC medication, dose of index DOAC medication and prior warfarin use) differ among the patient cohorts stratified by NIH weight classifications.	
$H_0$3.1: There is no statistically significant difference in index DOAC medication among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$3.2: There is no statistically significant difference in dose of index DOAC medication among the patient cohorts stratified by NIH weight classifications.	Reject
$H_0$3.3: There is no statistically significant difference in previous anticoagulant treatment history with warfarin (Yes/No) during the baseline period medication among the patient cohorts stratified by NIH weight classifications.	Fail to reject
Objective 4: To determine whether the prevalence of comorbidities during the baseline period differs among the patient cohorts stratified by NIH weight classifications.	
$H_0$4.1: There is no statistically significant difference in the prevalence of congestive heart failure (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$4.2: There is no statistically significant difference in the prevalence of hypertension (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications	Reject
$H_0$4.3: There is no statistically significant difference in the prevalence of diabetes mellitus (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Reject
$H_0$4.4: There is no statistically significant difference in the prevalence of history of stroke or transient ischemic attack (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Reject
$H_0$4.5: There is no statistically significant difference in the prevalence of coronary artery disease (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$4.6: There is no statistically significant difference in the prevalence of renal disease (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$4.7: There is no statistically significant difference in the prevalence of liver disease (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$4.8: There is no statistically significant difference in the prevalence of bleeding history or predisposition (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Reject

Table 3.5 continued

$H_0$4.9: There is no statistically significant difference in the prevalence of myocardial infarction (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$4.10: There is no statistically significant difference in the prevalence of venous thromboembolism (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$4.11: There is no statistically significant difference in the prevalence of alcoholism (Yes/No) during the baseline period among the patient cohorts stratified by NIH weight classifications.	Fail to reject
Objective 5: To determine whether the calculated patient risk stratification indices differ among the patient cohorts stratified by NIH weight classifications.	
$H_0$5.1: There is no statistically significant difference in the calculated Charlson Comorbidity Indices among the patient cohorts stratified by NIH weight classifications.	Fail to reject
$H_0$5.2: There is no statistically significant difference in the calculated CHA_2DS_2-VASc Scores among the patient cohorts stratified by NIH weight classifications.	Reject
$H_0$5.3: There is no statistically significant difference in the calculated HAS-BLED Scores among the patient cohorts stratified by NIH weight classifications.	Reject
Objective 6: To determine whether the unadjusted rate of stroke or systemic embolism differs among the patient cohorts stratified by NIH weight classifications	
$H_0$6: There is no statistically significant difference in the proportion of patients experiencing a stroke or systemic embolic event among the patient cohorts stratified by NIH weight classifications.	Not calculable
Objective 7: To determine whether the unadjusted rate of major bleed differs among the patient cohorts stratified by NIH weight classifications.	
$H_0$7: There is no statistically significant difference in the proportion of patients experiencing a major bleed event among the patient cohorts stratified by NIH weight classifications.	Not calculable
Objective 8: To determine whether NIH weight classification by body mass index is associated with the hazard of stroke or systemic embolism.	
$H_0$8: Upon adjusting for covariates and assessing time to first event, there is no statistically significant association between underweight, overweight, obesity class I, obesity class II, and obesity class III weight cohorts with the normal weight cohort (reference cohort) and the hazard of stroke or systemic embolic event.	Not calculable
Objective 9: To determine whether NIH weight classification by body mass index is associated with the hazard of major bleed.	
$H_0$9: Upon adjusting for covariates and assessing time to first event, there is no statistically significant association between underweight, overweight, obesity class I, obesity class II, and obesity class III weight	Not calculable

Table 3.5 continued

cohorts with the normal weight cohort (reference cohort) and the hazard of major bleed	

Chapter 4: Discussion and Conclusion

DISCUSSION

Baseline Demographics and Clinical Characteristics

The results of this study found that there are some notable differences in baseline characteristics across the BMI cohorts. Of the patient demographics, race and ethnicity were balanced across the cohorts, with non-Hispanic Whites comprising a majority of the population. The mean age of 75.9 years (SD 10.2 years) reported in the total study population is slightly higher than, but comparable to, the mean and median ages reported in the pivotal phase III trials of the DOACs (70-73 years).[14-16,23] As expected, Medicare was the primary insurance for a majority of the patients. Of note, similar decreasing trends were seen in mean age and the proportion of Medicare insurance with higher BMI cohorts; overweight and obese individuals had lower mean ages and lower proportion of Medicare insured compared to normal weight individuals. While the total population had an even proportion of male and female patients, lower proportions of female patients were seen in overweight and obese cohorts vs. the normal weight cohort.

Of the clinical medication-related characteristics, index DOAC medication and prior warfarin use were balanced across the BMI cohorts. The majority of the total population using apixaban or rivaroxaban in this study was as expected given both of these DOACs are placed in lower tiers compared to dabigatran and edoxaban on the SWHP formularies. While most patients did not receive prior warfarin therapy, the overweight and obese cohorts showed a smaller proportion of patients with prior warfarin therapy than normal weight cohorts, which may reflect clinicians' preferences between anticoagulants when initiating treatment for higher weight patients. This may be, in part, due to the advantages of DOACs over warfarin as listed previously, but goes contrary to the dearth

of evidence of DOAC use in higher weight populations. Reduced doses of DOACs are available options for patients with impaired renal functions. Lower proportions of patients in the overweight and obese cohorts were taking reduced doses of their DOACs vs. the normal weight cohort, although inferences cannot be made about clinician dosage considerations in high body weights without further information on the creatinine clearance of the cohorts.

Baseline comorbidities were varied across the BMI cohorts, and significant differences were seen for hypertension, diabetes, prior stroke/TIA, and bleed history. A higher proportion of patients had diabetes and hypertension in the overweight and obese cohorts compared to the normal weight cohort. Inversely, a lower proportion of patients had a prior stroke/TIA event and prior bleed history in the overweight and obese cohorts compared to the normal weight cohort. This may be reflective of the paradoxical phenomenon – the protective effect of higher body weights in stroke and bleed risk – as seen in the pivotal trials' subgroup and post-hoc analyses and the real-world analysis in Dresden, Germany.[14,15,24-27,32]

Of the risk stratification indices, only the CCI score remained relatively stable with increasing BMI cohorts, but jumped to a mean of 3.0 (SD 2.3) in the obese class III cohort (vs. 2.5 (SD 2.3) in the normal weight cohort). The mean CHA_2DS_2-VASc score (4.3 (SD 1.7)) of the total study population is an expected stroke-risk profile of an atrial fibrillation patient population receiving DOACs. The mean HAS-BLED score of 2.4 (SD 1.0) for this study population implies they may not be at high risk for bleeds, per previously mentioned guideline that defines high bleed risk a threshold score of 3 or higher. Interestingly, we see observations reflective of the paradoxical phenomenon in the baseline cohort again, where patients in increasingly higher BMI cohorts have incrementally lower mean CHA_2DS_2-VASc and HAS-BLED score, implying lower stroke and bleed risks, respectively.

Thromboembolism and Major Bleed

This study found that there was a very small stroke/SE and major bleed event rate in patients with atrial fibrillation taking oral DOACs. While stroke/SE event rates were comparable across the BMI cohorts, a smaller proportion of patients experiencing a major bleed event rate was observed in overweight and obese cohorts versus normal weight cohorts. Also, a decreasing trend was noted: incrementally lower proportions of major bleed events were observed with each increasing BMI cohort. While speculations can be drawn about the potential paradoxical phenomenon or the need to adjust for HAS-BLED score given its similarly decreasing baseline mean values with each increasing BMI cohort, no inferences or conclusions can be drawn due to the small event rates.

Our total stroke/SE event rate of 1.1% is comparable to those reported in the literature. In the RE-LY dabigatran pivotal trial, stroke or systemic embolism occurred 1.11% per year in patients receiving dabigatran 150mg.[14] In the ROCKET-AF rivaroxaban pivotal trial, stroke or systemic embolism occurred 1.7% per year in rivaroaxaban-receiving patients.[15] The ARISTOTLE trial and AVERROES trials saw stroke of systemic embolism rates of 1.27% per year and 1.6% per year in apixaban-receiving patients, respectively.[16,23] In the real-world registry study in Germany, rate for stroke, TIA, and systemic embolism in atrial fibrillation patients were 1.6/100 patient-years (95% CI 1.3-2.0).[32] A potential reason for a lower stroke/SE rate seen in our study compared to the literature could be the difference in stroke definitions: in addition to hemorrhagic and ischemic stroke, the ARISTOTLE apixaban trial also allowed strokes of uncertain type, and the Germany registry study defined its primary effectiveness outcome as a composite of stroke, TIA, and systemic embolism.

Our total major bleed event rate of 2.8% is also comparable to those reported in the literature. In the RE-LY dabigatran trial, major bleeding occurred 3.11% per year in patients receiving dabigatran 150mg.[14] In the ROCKET-AF rivaroxaban trial, major bleeding occurred in 3.6% of the rivaroxaban-receiving patients.[15] The ARISTOTLE and AVERROES trials saw major bleeding rates of 2.13% per year and 1.4% per year in the apixaban-receiving patients, respectively.[16,23] In the real-world registry study in Germany, major bleeding events were 2.7/100 patient-years (95% CI 2.2-3.1) in atrial fibrillation patients.[32]

LIMITATIONS

The primary limitation of this study is its small population size available for the primary analysis, which conferred an absolute number of event rates too low for statistical comparison. This is in part due to a second limitation of the study – the study population included only Baylor Scott & White healthcare system patients who were also enrolled members in the Scott & White Health Plan in Texas – which reduces the generalizability of the results to populations in other geographical locations. As is the nature of all observational studies, a third limitation is its reliance on administrative claims and EMR documentation. Claims and EMR data have the potential for inaccurate coding or incomplete coding, e.g. patients who receive DOACs with copay coupons or out of pocket are not captured in this analysis. However, the aim of the study was to compare relative rates across the BMI cohorts, and miscoding or use of DOACs outside of claims data is not expected to differ across the BMI groups. Additionally, given the less conservative diagnoses code requirements for inclusion in the study, patients captured in this study

population may not truly have clinical atrial fibrillation or atrial flutter. However, this study required patients to be continuously on treatment with DOACs which are only FDA-indicated for atrial fibrillation or venous thromboembolism, and it is reasonable to not exclude venous thromboembolism patients since we can expect similar benefit-risk profiles of the DOACs in both patient populations.

While the limitations warrant caution when interpreting the results, this study is the first known study aimed to assess the association of increasing BMI on outcomes in Baylor Scott & White Health patients with atrial fibrillation who are users of DOACs. Understanding this association is paramount to optimizing population health given three primary reasons: the prevalence of obesity and atrial fibrillation continue to remain high and ever-increasing, obesity is a risk factor for atrial fibrillation, and DOAC medications are becoming increasingly ubiquitous, first-line therapies in stroke prevention for atrial fibrillation. This study has highlighted the need for future, larger-scale studies on this topic.

CONCLUSION

In this retrospective observational cohort analysis using a single health plan's claims database, low stroke/SE and major bleed event rates were observed across all BMI groups. Given the low sample size and event rates conferring reduced statistical power, no statistical tests could be performed to compare the event rates among the BMI groups. Consequently, inferences cannot be made on the association of elevated BMI on outcomes. However, comparable outcome rates were seen across all BMI cohorts, suggesting that DOAC-receiving atrial fibrillation patients who are overweight or obese may see similar, and potentially lower, rates of stroke and systemtic emoblism or major bleed events

compared to normal weight patients. Future research with larger population sizes is warranted to assess the impact of body weight on the safety and effectiveness of DOACs.

Appendices

APPENDIX I. ATRIAL FIBRILLATION AND ATRIAL FLUTTER DIAGNOSES CODES

Code Type	Code	Code Description
ICD-9	427.31	Atrial fibrillation
ICD-10	I48.0	Paroxysmal atrial fibrillation
ICD-10	I48.1	Persistent atrial fibrillation
ICD-10	I48.2	Chronic atrial fibrillation
ICD-10	I48.91	Unspecified atrial fibrillation
ICD-9	427.32	Atrial flutter
ICD-10	I48.3	Typical atrial flutter
ICD-10	I48.4	Atypical atrial flutter
ICD-10	I48.92	Unspecified atrial flutter

ICD-9: International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10: International Classification of Diseases, 10th Revision, Clinical Modification

APPENDIX II. COMORBIDITIES DIAGNOSES CODES

Comorbidity	ICD-9-CM or ICD-10-CM Diagnoses Codes
Congestive heart failure[40–44]	428.xx, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 398.91, I50.xx, I11.0, I13.0, I13.2, I09.81
Hypertension[40–44]	401.x, 402.x, 403.x, 404.x, 405.x, I10, I11.x, I12.x, I13.x, I15.x
Diabetes mellitus[40–44]	250.xx, 357.2, 362.0x, 366.41, E08.xx, E09.xx, E10.xx, E11.xx, E13.xx
Previous stroke or transient ischemic attack[40,41]	430.x, 431.x, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.x, 436, I60.xx, I61.xx, I63.xxx, I67.84x, I67.89, I97.81x, I97.82x, G45.0, G45.1, G45.2, G45.8, G45.9, G46.x, G97.3x,
Coronary artery disease[40–42,45]	410.x, 411.x, 412.x, 413.x, 414.x, I20.xx, I21.xx, I22.xx, I23.xx, I24.xx, I25.xx, I73.8
Renal disease[40–44]	403.01, 403.11, 403.91, 404.xx, 581.x, 582.x, 583.x, 584.x, 585.x, 586, 588.x, V42.0, V45.1, V56.x, I12.x, I13.x, N01.x, N03.x, N04.x, N05.x, N08, N18.x, N19.x, N25.x, Z94.0, Z99.2, Z49.x
Liver disease[40,41,43,44,46]	070.x, 570, 571.x, 572.x, 573.x, V42.7, B15.x, B16.x, B17.x, B18.x, B19.x, K70.x, K71.x, K72.x, K73.x, K74.x, K75.x, K76.x, K77.x, Z48.23, Z94.4
Bleeding history or predisposition[41]	280.x, 281.x, 282.x, 283.x, 284.x, 285.x, 286.x, 287.x, 430.x, 431.x, 432.x, 852.x, 853.x, 456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x,

	532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x, 423.0, 459.0, 596.7, 599.71, 719.1x, 782.7, 784.7, 784.8, 786.3, 360.43, 362.81, 362.43, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 602.1, 958.2, D50.x, D51.x, D52.x, D53.x, D55.x, D56.x, D57.x, D58.x, D59.x, D60.x, D61.x, D62.x, D63.x, D64.x, D65.x, D66.x, D67.x, D68.x, D69.x, I60.xx, I61.xx, I62.xx, S06.34xx, S06.35xx, S06.36xx, S06.37xx, S06.4xxx, S06.5xxx, S06.6xxx, I85.01, I85.11, K22.11, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K55.21, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K62.5, K66.1, K92.0, K92.1, K92.2, I31.2, R58, R31.0, R31.9, M25.0xx, R23.3, R04.xx, H44.81x, H35.6x, H35.73x, H31.30x, H31.31x, H31.41x, H21.0x, H11.3x, H05.2x, H47.02x, H43.1x, N42.1, T79.2xxx
Myocardial infarction[40–45]	410.x, 412.x, I21.xx, I22.xx
Venous Thromboembolism (including deep vein thrombosis and pulmonary embolism)[52]	415.1x, 451.1x, 451.2, 451.81, 451.83, 451.89, 451.9, 453.1, 453.2, 453.4x, 453.5x, 453.7x, 453.8x, 453.9, I26.9x, T80.0xxx, T82.81xx, I80.1x, I80.2x, I80.3, I80.8, I80.9, I82.1, I82.2xx, I82.4xx, I82.5xx, I82.60x, I82.62x, I82.70x, I82.72x, I82.89x, I82.9x
Alcoholism[40]	291.x, 303.x, 305.0x, 357.5, 425.5, 535.3x, 571.0, 571.1, 571.2, 571.3, 980.0, V11.3, V65.42, E860.0, F10.xxx, G62.1, I42.6, K29.2x, K70.x, T51.0xxx, Q86.0, Z71.41

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APPENDIX III. CHARLSON COMORBIDITY INDEX

APPENDIX IV. CHA_2DS_2-VASC SCORE DIAGNOSIS CODES

CHA_2DS_2-VASc	Score	ICD-9-CM or ICD-10-CM Diagnoses Codes

Congestive heart failure	1	428.xx, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 398.91, I50.xx, I11.0, I13.0, I13.2, I09.81
Hypertension	1	401.x, 402.x, 403.x, 404.x, 405.x, I10, I11.x, I12.x, I13.x, I15.x
Age ≥75 years	2	
Diabetes mellitus	1	250.xx, 357.2, 362.0x, 366.41, E08.xx, E09.xx, E10.xx, E11.xx, E13.xx
Stroke/TIA/TE	2	430.x, 431.x, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.x, 436, 444.x, 445.x, I74.xx, I75.xx, I60.xx, I61.xx, I63.xxx, I67.84x, I67.89, I97.81x, I97.82x, G45.0, G45.1, G45.2, G45.8, G45.9, G46.x, G97.3x
Vascular disease (prior MI, PAD, or aortic plaque)	1	410.x, 411.x, 412.x, 413.x, 414.x, 443.8x. 443.9, 440.x, I20.xx, I21.xx, I22.xx, I23.xx, I24.xx, I25.xx, I73.8, I73.9, I70.xx
Age 65-74 years	1	
Female sex	1	
Maximum score	9	

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ICD-10: International Classification of Diseases, 10th Revision, Clinical Modification
TIA: transient ischemic attack
TE: thromboembolism

APPENDIX V. HAS-BLED SCORE DIAGNOSIS CODES

HAS-BLED*	Score	ICD-9-CM or ICD-10-CM Diagnoses Codes
Hypertension	1	401.x, 402.x, 403.x, 404.x, 405.x, I10, I11.x, I12.x, I13.x, I15.x
Abnormal renal function	1	403.01, 403.11, 403.91, 404.xx, 581.x, 582.x, 583.x, 584.x, 585.x, 586, 588.x, V42.0, V45.1, V56.x, I12.x, I13.x, N01.x, N03.x, N04.x, N05.x, N08, N18.x, N19.x, N25.x, Z94.0, Z99.2, Z49.x
Abnormal liver function	1	070.x, 570, 571.x, 572.x, 573.x, V42.7, B15.x, B16.x, B17.x, B18.x, B19.x, K70.x, K71.x, K72.x, K73.x, K74.x, K75.x, K76.x, K77.x, Z48.23, Z94.4
Stroke	1	430.x, 431.x, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, I60.xx, I61.xx, I63.xxx, I67.89
Bleeding history or predisposition	1	280.x, 281.x, 282.x, 283.x, 284.x, 285.x, 286.x, 287.x, 430.x, 431.x, 432.x, 852.x, 853.x, 456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x,

		533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x, 423.0, 459.0, 596.7, 599.71, 719.1x, 782.7, 784.7, 784.8, 786.3, 360.43, 362.81, 362.43, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 602.1, 958.2, D50.x, D51.x, D52.x, D53.x, D55.x, D56.x, D57.x, D58.x, D59.x, D60.x, D61.x, D62.x, D63.x, D64.x, D65.x, D66.x, D67.x, D68.x, D69.x, I60.xx, I61.xx, I62.xx, S06.34xx, S06.35xx, S06.36xx, S06.37xx, S06.4xxx, S06.5xxx, S06.6xxx, I85.01, I85.11, K22.11, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K55.21, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K62.5, K66.1, K92.0, K92.1, K92.2, I31.2, R58, R31.0, R31.9, M25.0xx, R23.3, R04.xx, H44.81x, H35.6x, H35.73x, H31.30x, H31.31x, H31.41x, H21.0x, H11.3x, H05.2x, H47.02x, H43.1x, N42.1, T79.2xxx
Elderly (>65 years)	1	
Antiplatelet or NSAID use**	1	Z79.02, Z79.1
Alcoholism	1	291.x, 303.x, 305.0x, 357.5, 425.5, 535.3x, 571.0, 571.1, 571.2, 571.3, 980.0, V11.3, V65.42, E860.0, F10.xxx, G62.1, I42.6, K29.2x, K70.x, T51.0xxx, Q86.0, Z71.41
Maximum score	8	

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*Labile INR not included because patients are not on warfarin
**At least one pharmacy claim for any of the following medications: dipyridamole, ticagrelor, prasugrel, clopidogrel, cilostazol, ticlopidine, aspirin, cangrelor, abciximab, tirofiban, eptifibatide, celecoxib, diclofenac, ibuprofen, indomethacin, meloxicam, naproxen

APPENDIX VI. OUTCOME MEASURES DIAGNOSIS CODES

Outcome	ICD-9-CM or ICD-10-CM Diagnoses Codes
Stroke/Systemic Embolism	
Ischemic Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, I63.xxx, I67.89

Hemorrhagic Stroke	430.x, 431.x, 432.x, I60.xx, I61.xx, I62.xx,
Systemic Embolism	444.x, 445.x, I74.xx, I75.xx
Major Bleed	
Intracranial Hemorrhage	430.x, 431.x, 432.x, 852.x, 853.x, I60.xx, I61.xx, I62.xx, S06.34xx, S06.35xx, S06.36xx, S06.37xx, S06.4xxx, S06.5xxx, S06.6xxx
Major Gastrointestinal Bleed	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x, I85.01, I85.11, K22.11, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K55.21, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K62.5, K66.1, K92.0, K92.1, K92.2
Major Other Hemorrhage	423.0, 459.0, 596.7, 599.71, 719.1x, 782.7, 784.7, 784.8, 786.3, 360.43, 362.81, 362.43, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 602.1, 958.2, I31.2, R58, R31.0, R31.9, M25.0xx, R23.3, R04.xx, H44.81x, H35.6x, H35.73x, H31.30x, H31.31x, H31.41x, H21.0x, H11.3x, H05.2x, H47.02x, H43.1x, N42.1, T79.2xxx

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Glossary

Baseline period: 12-month time period prior to index date

Discontinuation date: No evidence (no pharmacy claims) or the index DOAC medication filled for 30 days from the last day of the supply of the last prescription date, unless the patient has switched to another DOAC ("switching")

Follow-up period: Time period from which patient is followed for study analysis, starting from the index date until the earliest occurrence of: (i) 12 months post-index date, (ii) occurrence of study outcome of interest, (iii) 30 days post-discontinuation date unless switching has occurred, or (iv) end of study period, whichever occurs first.

Index date: Date of first pharmacy fill of a direct oral anticoagulant

Index medication: The direct oral anticoagulant filled on the index date

Switching: When a pharmacy claim is filled for a different DOAC medication than the index medication, or immediately preceding DOAC medication, within 30 days of the discontinuation date.

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