Treatment Patterns of Atrial Fibrillation (AF) Patients After Bleeding on Direct-Acting Oral Anticoagulants (DOACs)

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Abstract

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Background and Objective

Direct oral anticoagulants (DOACs) have vastly improved care for atrial fibrillation (AF) as well as prevention of strokes and heart attacks. Although clinical trials and observational studies have confirmed superior safety and reduced bleeding rates for DOACs compared to warfarin, the risk of bleeding though relatively small is not zero. Little is known about the drug-utilization patterns of patients after a major bleed on a DOAC. The aim of this study was to characterize the real-world treatment patterns and evaluate risk of change of treatment of AF patients after experiencing a major bleed on a DOAC.

Methods

This study was a retrospective cohort analysis conducted using the Marketscan Research Databases between October 1, 2015 and December 31, 2021. Patients were ≥ 18 years old and initiated a DOAC after AF diagnosis. Patients with a hospitalization for a major bleed were matched to patients that did not bleed through the follow-up period. Patients were followed until 12 months after index, 1st disenrollment, or 2nd hospitalization for a major bleed. Outcomes included discontinuation, treatment switching, dose change, and reinitiating the same DOAC after discontinuation. Time-to-event analyses were conducted using Cox proportional hazards regression to calculate risk of experiencing outcomes.

Results

The most common first outcome after a major bleed in the bleed group (n = 2,087) was discontinuation (54.8%) followed by no change in therapy (34.7%). Of patients who discontinued after a major bleed, 16.5% of patients reinitiated. The bleed group had a 3.84-fold increased risk (95% CI: 3.56 to 4.14, $p < 0.0001$) of change to treatment compared to the control group (n = 6,261). Among the bleed group, patients with prior warfarin use had a 2.93-fold increased risk (95% CI: 1.83 to 4.68, $p < 0.0001$) of switching and trended toward a decreased risk of discontinuation (HR: 0.87, 95% CI: 0.73 to 1.03, $p = 0.11$) compared to those without

prior warfarin use. Among the bleed group, those with high stroke risk had 29% reduced risk (95% CI: 0.55 to 0.92, p = 0.01) of discontinuation compared to those with low stroke risk.

Conclusions

Our study found AF patients to have significantly increased risk of DOAC discontinuation, switching, or dose changes after being hospitalized for a major bleed. Future studies focusing on DOACs may increase prescriber confidence in restarting anticoagulation after a major bleed.

Introduction

Direct oral anticoagulants (DOACs) have vastly improved care for conditions such as atrial fibrillation (AF) as well as prevention of strokes and heart attacks since FDA approval of the first DOAC, dabigatran, in 2010. AF affects up to 6.59 million individuals in the US and is expected to increase to 12.1 million by 2030[1,2].

DOACs were created not to improve upon the efficacy of warfarin for stroke prevention, but to decrease bleeding risk and increase convenience[3]. However, while clinical trials and observational studies have confirmed superior safety of DOACs compared to warfarin with a 21% reduced risk of bleeding compared to warfarin[4,5], the risk is not zero.

Clinical guidelines are unclear in terms of anticoagulation strategy after a bleed while patients are on DOACs. There are conflicting recommendations about if and when to restart anticoagulation in patients with bleeding, depending on factors such as thromboembolic risk, site of bleed, risk of rebleeding, and patient preference[6,7]. In addition, since DOACs have been shown to have superior safety profiles compared to warfarin in AF, patients who bleed on a DOAC may have limited alternative anticoagulant options to reduce bleeding risk[4,5].

Little is known about the drug-utilization patterns of patients after experiencing a major bleed on a DOAC. Vague clinical guidelines and a lack of effective alternative anticoagulation therapies warrant further investigation into the real-world drug-utilization pattens of AF patients after bleeding on a DOAC.

The aim of this study was to characterize the real-world treatment patterns and evaluate risk of change to treatment of AF patients after experiencing a major bleed on a DOAC. We hypothesized that those who bleed will have higher risk of changes to their treatment (discontinuation, switching, dose changes) than those who do not. In addition, we hypothesized that patients with exposure to warfarin before DOAC initiation will have a lower risk of switching and higher risk of discontinuation compared to those with no prior warfarin exposure. We also hypothesized that patients with high stroke risk would have lower risk of discontinuation than patients with high stroke risk.

Methods

Data Source

This study was a retrospective cohort analysis conducted using the Merative Marketscan Research Databases between October 1, 2015 and December 31, 2021. Marketscan is a proprietary database, maintained by Merative, containing healthcare claims data from employer-sponsored health insurance and Medicare supplemental insurance plans in the United States. The database includes medical and prescription drug claims, enrollment, and demographic data.

Study Population

Inclusion Criteria

To be included in this analysis, patients had to have at least one inpatient or two outpatient diagnoses of AF at least two days apart be newly initiated on a DOAC (apixaban, rivaroxaban, or dabigatran) after AF diagnosis. Patients had to be ≥ 18 years old as of their DOAC initiation date. Patients' index date could only be between October 1, 2016, and December 31, 2020. Patients had to have continuous medical and pharmacy enrollment for at least 12 months before their index date and 6 months before their DOAC initiation date. To ensure that patients were DOAC-naive before their initiation date, they could not have any claims for a DOAC within 6 months prior to initiation date.

Exclusion Criteria

Patients were excluded from the study if they had claims for any of the following during the baseline period: transient AF, cardiac surgery, hip or knee replacement, deep vein thrombosis (DVT), or pulmonary embolism (PE).

Potential controls were excluded if they did not have at least two claims in a row for the same DOAC in order to control for any patients who may have immediately discontinued treatment due to side effects, adverse reactions, or insurance coverage issues.

Bleed group patients were excluded if they switched agents between their DOAC initiation and first major bleed in order to ensure the bleed occurred while on their initial DOAC.

Study Design

Eligible patients were placed into a bleed or control cohort and matched based on a propensity score calculated from demographic and clinical characteristics of interest. Patients in the bleed group had claims for a hospitalization due to a major bleed as their primary diagnosis while controls had no claims for hospitalizations due to a major bleed throughout the whole study period.

The *index date* for patients in the bleed group was the first date of admission to a hospital for a major bleed after DOAC initiation. For controls, *index date* was the date of their 2nd claim for the same DOAC after DOAC initiation. The *baseline period* in this study was the 12-month period before DOAC initiation in which demographic and clinical characteristics were collected in order to conduct propensity score matching and patients were confirmed to be DOAC-naive. The *follow-up period* in this study was earliest date between: 12 months from the index date, date of 2nd hospitalization for a major bleed for those in the bleed group, or disenrollment from the Marketscan database (Figure 1).

Outcomes (Treatment Patterns)

We observed four different outcomes during the follow-up period: complete discontinuation, temporary discontinuation with re-initiation, switching, and dose change. Complete discontinuation was defined as a patient having no claim for an anticoagulant for at least 1.25x the day supply after their expected fill date. Temporary discontinuation with re-initiation was defined as a patient's next claim for an anticoagulant after discontinuation being the same agent and daily dose that as they had previously discontinued. Discontinuation encompassed both complete and temporary discontinuations. Switching was defined as a patient's next anticoagulant claim being for a different anticoagulant than their prior claim. Dose change was defined as a patient's next anticoagulant claim being for the same anticoagulant as their prior claim but with a different daily dose.

Subgroups

Two subgroups were chosen to separately explore the effect of (a) prior warfarin use and (b) stroke risk on treatment patterns.

For the first subgroup analysis, we compared bleed patients that had been exposed to warfarin in the 6 months prior to DOAC initiation versus bleed patients without prior warfarin use. We hypothesized that the group with prior warfarin use may have fewer alternative treatment options after bleeding on a DOAC if the reason for their switch to DOACs was a bleeding event, and would be less likely to switch and more likely to discontinue treatment, either completely or temporarily.

For the second subgroup analysis, we compared bleed patients with low stroke risk vs. bleed patients with high stroke risk. Stroke risk was defined according to whether the patient was indicated for an oral anticoagulant based on their CHA_2DS_2-VASc score according to clinical guidelines by the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS)[8]. A CHA_2DS_2-VASc score of >= 2 for men and >= 3 for women was considered as high stroke risk. We hypothesized that prescribers would evaluate a patient's need for thromboembolic prevention after a major bleed and discontinue treatment for those with low stroke risk more often than for those with high stroke risk.

Statistical Analysis

Matching

To account for potential confounding, patients with a bleed on a DOAC were matched to patients without a bleed in a 1:3 ratio using propensity scores based on age (continuous, years) , sex (binary), Quan-Charlson comorbidity index (QCI)[9,10] category, region, insurance type, modified HAS-BLED2 score[11], CHA_2DS_2-VASc Score[11], prior warfarin use, and initial DOAC agent. We matched with a caliper of 0.1. Modified HAS-BLED2 score did not include "labile INR" category because of a lack of ability to observe INR in Marketscan.

Baseline Variable Definitions

Age was defined as a continuous variable in years at index date. Sex was a binary variable taken from claims data at index date. Region was a categorical variable defined by regions of US specified in Marketscan data (northeast, north central, south, west, unknown). Insurance type was a binary indicator of either Medicare supplemental or commercial insurance at index date. QCI, HAS-BLED2, and CHA_2DS_2-VASc scores were calculated using inpatient and outpatient claims within 12 months before index date. HAS-BLED2 and CHA_2DS_2-VASc scores were treated as continuous variables. QCI scores were split into categories 0, 1, 2 or >=3 and treated as an ordinal variable. Prior warfarin use was a binary indicator of whether or not a patient had used warfarin within 6 months before their DOAC initiation date. Initial DOAC agent was a categorical variable with levels: apixaban, rivaroxaban, and dabigatran based on which agent the patient was first initiated on.

Baseline Characteristics

Baseline characteristics were analyzed descriptively. Means and standard deviations were calculated for continuous variables. Categorical variables were summarized as counts and proportions. All variables were compared between cohorts by calculating the standardized mean differences.

Primary Analysis

Treatment patterns in the bleed group were characterized by recording every event of interest that occurred from index to end of follow-up. Patients were categorized by their initial DOAC medication and a Sankey diagram was created to display all treatment pathways[12].

In order to assess the risk of changes to treatment in the bleed group, we used a Cox proportional hazards regression to conduct a time-to-first-event (discontinuation, switching, dose change)

analysis of bleed group vs controls group[13]. This regression was adjusted for all covariates included in matching. In addition to our time-to-event analysis, we also calculated the three most common agents that patients switched to for each initial DOAC. Discontinuation included those who discontinued completely as well as those who experienced a temporary discontinuation with re-initiation.

Subgroup Analyses

Subgroup analyses were conducted only in the bleed group. For our prior warfarin use analysis, we conducted two time-to-first-event analyses using Cox proportional hazards regression with switching and discontinuation as the outcomes. Switches could be to warfarin, DOACs other than the patient's initial DOAC, or other anticoagulants. Patients with prior warfarin use were compared to those without prior warfarin use.

For our stroke risk analysis, we conducted a time-to-first-event analysis using a Cox proportional hazards regression with discontinuation as the outcome. Patients with high stroke risk were compared to those with low stroke risk.

Discontinuation in both subgroup analyses included those who discontinued completely as well as those who experienced a temporary discontinuation with re-initiation.

Data Retrieval and Hypothesis Testing

Data was be retrieved and formatted using SAS (version 9.4), with analysis performed with RStudio (version 2022.12.0+353). A two-sided alpha-level of 0.05 was chosen a priori, with p-values ≤0.05 considered statistically significant.

Results

Study Population

We identified 652,201 patients with AF between October 1, 2015 and December 31, 2020. Of patients with AF, 105,644 met the inclusion criteria for the study, of whom 28,314 were excluded according to our exclusion criteria. There were 2,087 eligible patients for the bleed group and 68,183 eligible patients for the control group. After matching, there were 2,087 patients in the bleed group and 6,261 patients in the control group (Figure 2). Baseline characteristics are reported in Table 1.

Treatment Patterns after a Major Bleed

In the bleed group, the most common first outcome after a major bleed was discontinuation (54.8%), followed by no change in treatment (34.7%), switch (5.7%), and dose change (4.8%) as shown in Figure 3. Patients included in the "no outcome" group either had no outcome over a

full 365 days of follow-up or were censored due to disenrollment or a 2nd hospitalization for a major bleed. Out of all bleed patients, 9.0% temporarily discontinued and re-initiated their initial DOAC. Forty (1.9%) patients experienced >4 outcomes of interest over their follow-up period.

In the bleed group, the three most common anticoagulants that patients switched to from apixaban (n = 53) were warfarin (67.9%), enoxaparin (18.9%), and rivaroxaban (13.2%). The three most common anticoagulants that patients switched to from rivaroxaban (n = 88) were apixaban (73.9%), warfarin (18.2%), and enoxaparin (8.0%). The three most common anticoagulants that patients switched to from dabigatran (n = 25) were apixaban (72.0%), rivaroxaban (24.0%), and warfarin (4.0%) (Table 2).

Primary Time-to-event analysis

After adjusting for all covariates, the hazard ratio (HR) for treatment changes (discontinuation, switch, or dose change) between patients in the bleed group and control group was 3.84 (95% CI: 3.56 to 4.14, $p < 0.0001$). This indicates a significantly elevated risk of treatment changes in the bleed group compared to the control group (Table 3).

Prior Warfarin Use

These analyses comparing discontinuation and switching between those with and without warfarin exposure prior to DOAC initiation were conducted only within the bleed group. After adjusting for all covariates, except warfarin exposure, the hazard ratio for switching treatments between those with prior warfarin exposure and those without prior warfarin exposure was 2.93 (95% CI: 1.83 to 4.68, $p < 0.0001$). This indicates a significantly elevated risk of switching treatments after a major bleed in patients with prior warfarin use compared to those without prior warfarin use (Table 4).

After adjusting for all covariates, except warfarin exposure, the hazard ratio for discontinuation between those with prior warfarin exposure and those without prior warfarin exposure was 0.87 (95% CI: 0.73 to 1.03, $p = 0.11$). This indicates an insignificant trend toward a decreased risk of discontinuation after a major bleed in patients with prior warfarin use compared to those without prior warfarin use (Table 5).

Stroke Risk

This analysis comparing discontinuation between those with high and low stroke risk according to clinical guidelines were conducted only within the bleed group.

After adjusting for all covariates included in matching except warfarin exposure, the hazard ratio for discontinuation between those with high and low stroke risk was 0.71 (95% CI: 0.55 to 0.92 to $p = 0.01$). This indicates a significantly decreased risk of discontinuation after a major bleed in patients with high stroke risk compared to those with low stroke risk (Table 6).

Discussion

This retrospective cohort analysis of real-world medication use data aimed to characterize the treatment patterns of AF patients on a DOAC after a major bleed and evaluate their risk of changes to treatment. In our study, we found that discontinuation was the most common outcome after a major bleed (54.8%) followed by no change in treatment (34.7%). Less than 10% of patients experienced either switching or a dose change as their first outcome after a major bleed. These outcomes are consistent with conflicting recommendations in the literature about the best course of anticoagulation management after a major bleed. A small percentage (1.9%) of patients experienced more than 4 outcomes over their follow-up period. Out of those who discontinued after a major bleed, 16.5% of patients reinitiated on the same agent and dose within 25% of their last claim's day supply from their next expected fill date. It should be noted that those with no change in treatment could have been censored at any time after their bleed, so there is uncertainty in the interpretability of this result.

Our primary time-to-first-event analysis showed that after a major bleed, AF patients on a DOAC are at a significantly elevated risk of changes to treatment compared to those who do not bleed on a DOAC. These findings suggest that clinicians believe that a major bleed warrants a change to anticoagulation strategy.

We also conducted subgroup analyses in the bleeding group to explore the impact of prior warfarin use and stroke risk on treatment patterns after a major bleed. The rationale behind comparing patients with prior warfarin use to those without any prior warfarin use was that patients with prior warfarin use may have been switched to DOACs due to a prior bleeding event, leaving them with fewer alternative anticoagulant options. We hypothesized that patients with prior warfarin use would be less likely to switch and more likely to discontinue treatment than those without prior warfarin use. Our results, however, did not support this hypothesis and showed that patients with prior warfarin use were at significantly higher risk of switching and trended slightly toward lower risk of discontinuation. One possible explanation for the higher risk of switching in the prior warfarin use group are that providers may have been hesitant to keep patients on the same DOAC if they had already bled previously on warfarin. Another possible explanation is that these patients switched to a DOAC from warfarin for convenience instead of safety reasons, and the provider may have decided it was safer to switch them back to warfarin if they had no major adverse events while taking warfarin.

We decided to compare discontinuation rates in bleed patients with low stroke risk to patients with high stroke risk according to their CHA2DS2-VASc score in order to evaluate how closely providers were following recommendations from the ACC, AHA, and HRS for management of bleeding in patients on oral anticoagulants[6]. These guidelines recommend discontinuation of anticoagulation after a major bleeding event in women with a CHA2DS2-VASc score <3, and <2

in men[6]. Our results showed a significantly decreased risk of discontinuation after a major bleed in patients with low stroke risk. This suggests that these recommendations from the ACC, AHA, and HRS may have a meaningful influence on clinical practice.

Most recommendations about anticoagulation management after a major bleed are extrapolated from studies about warfarin, with very few studies focused on DOACs[7]. This is due to the long history of use of warfarin as the primary agent for anticoagulation.

To the best of our knowledge, this is the first study examining treatment patterns of AF patients taking DOACs after a major bleed. Our study provides insight into the anticoagulation strategies prescribers are using in the real-world after a major bleed.

Most evidence available for anticoagulation after a major bleed is focused on GI bleeding, as it is the most common site of bleeding for AF patients. Evidence for intracranial hemorrhage (ICH) is less clear with recommendations ranging from restarting anticoagulation at 72 hours after ICH to between 10 and 30 weeks after presentation[14].

A systematic review of 5 retrospective cohort studies conducted by researchers at the State University of New York (SUNY) Upstate Medical University indicated that resuming anticoagulation between 2 to 6 weeks after discharge from a GI bleeding event was optimal to balance thromboembolic and bleeding risk[7]. According to a 2016 systematic review of 4 observational studies, the optimal timing to resume anticoagulation after GI bleeding was approximately 14 days, with increased risk of recurrent GI bleed with re-initiation within 7 days[14]. However, guidelines from the British Society of Gastroenterology and the European Society of Gastrointestinal Endoscopy recommend restarting anticoagulation within 3 days after discharge for patients at high thrombotic risk and as soon as possible after 7 days after discharge for those at low thrombotic risk[7].

Overall, the majority of evidence, although mainly focused on GI bleeding and warfarin, indicates that resumption of anticoagulation after a major bleed is recommended in most cases. The results of our study, however, indicate that almost 40% of patients did not resume any sort of anticoagulation after a major bleed. This may indicate that prescribers are uncomfortable with the risks of recurrent bleeding and may require more robust evidence or safer anticoagulant options.

Limitations

This study was subject to limitations inherent to any administrative claims database such as data entry errors. This analysis was limited to individuals with commercial or private Medicare supplemental coverage. As a result, the results may not be generalizable to the full Medicare population.

Since we did not match patients on index date, it is possible that changes in access to care during the height of the Covid-19 pandemic could have possibly affected how often patients were seen by their physicians, and subsequently their treatment patterns. This is unlikely to have affected results for the bleed group, as hospitalization for a bleed is a severe event for which care would not have been majorly interrupted during the pandemic. However, as the control group did not necessarily have any severe healthcare event during the follow-up period, the Covid-19 pandemic may have had differential effects on frequency of physician visits in the bleed and control group. In addition, discontinuation is not defined consistently in other treatment pattern studies, so results regarding discontinuation rates may not be comparable across similar studies.

The ICD coding algorithms used to find AF patients and patients with a major bleed may not have accurately identified all eligible patients in the Marketscan database or may have unintentionally included patients that were not actually eligible due to data entry errors and imperfect algorithms. Results regarding pharmacologic treatments were based on the assumption that filled prescriptions were taken by the patient. However, it cannot be confirmed that treatments were taken as prescribed.

Finally, since we did not explicitly evaluate the time to event for each separate outcome in our primary analysis, we do not know if results were driven by any one specific outcome out of: discontinuation, switching, or dose change. This study may have also been subject to misclassification bias in regards to discontinuation because we were unable to capture if a patient was discontinued for a short time after their bleed and reinitiated before their next expected fill date due to the nature of claims data.

Conclusions

Our study indicated that AF patients on DOAC's have a significantly increased risk of discontinuation, switching, or dose changes after being hospitalized for a major bleed. The most common outcome was discontinuation, which is contrary to the bulk of recommendations from literature. Future studies focusing on treatment with DOACs may increase prescriber confidence in restarting anticoagulation after a major bleed. In addition, a consensus statement from multiple major cardiology societies could help reduce confusion about optimal anticoagulation management strategies after a major bleed.

TABLES AND FIGURES

Figure 1: Study Timeline

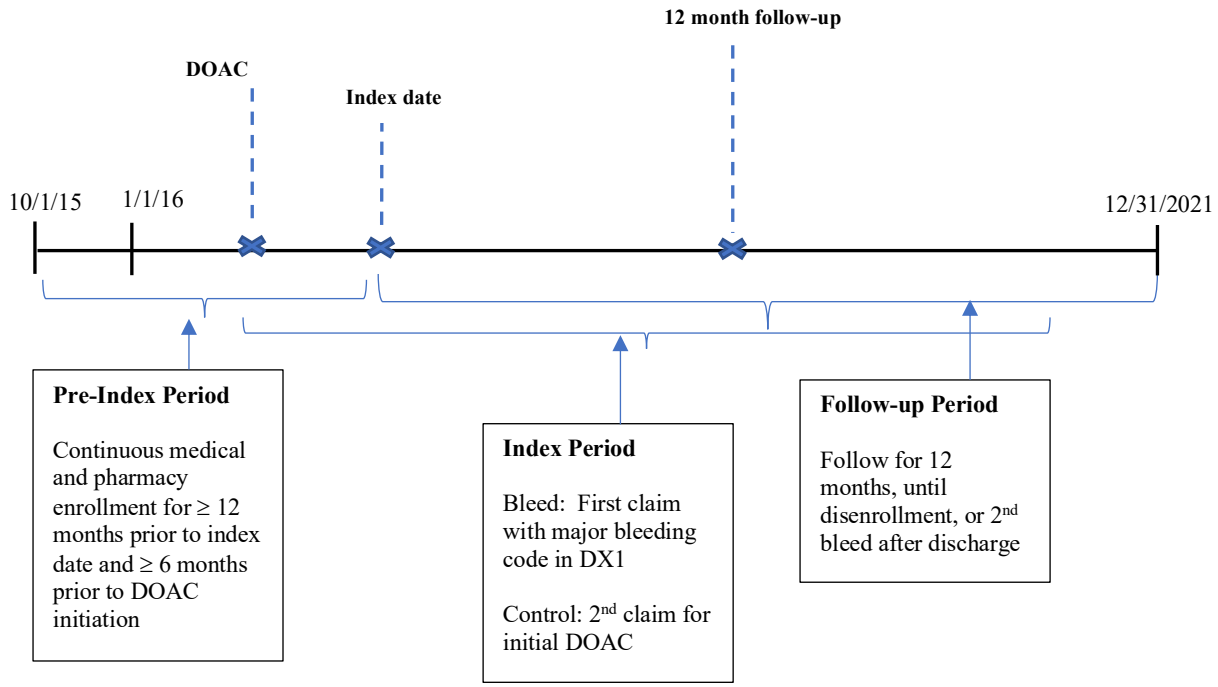


Figure 2: Patient Selection Flowchart

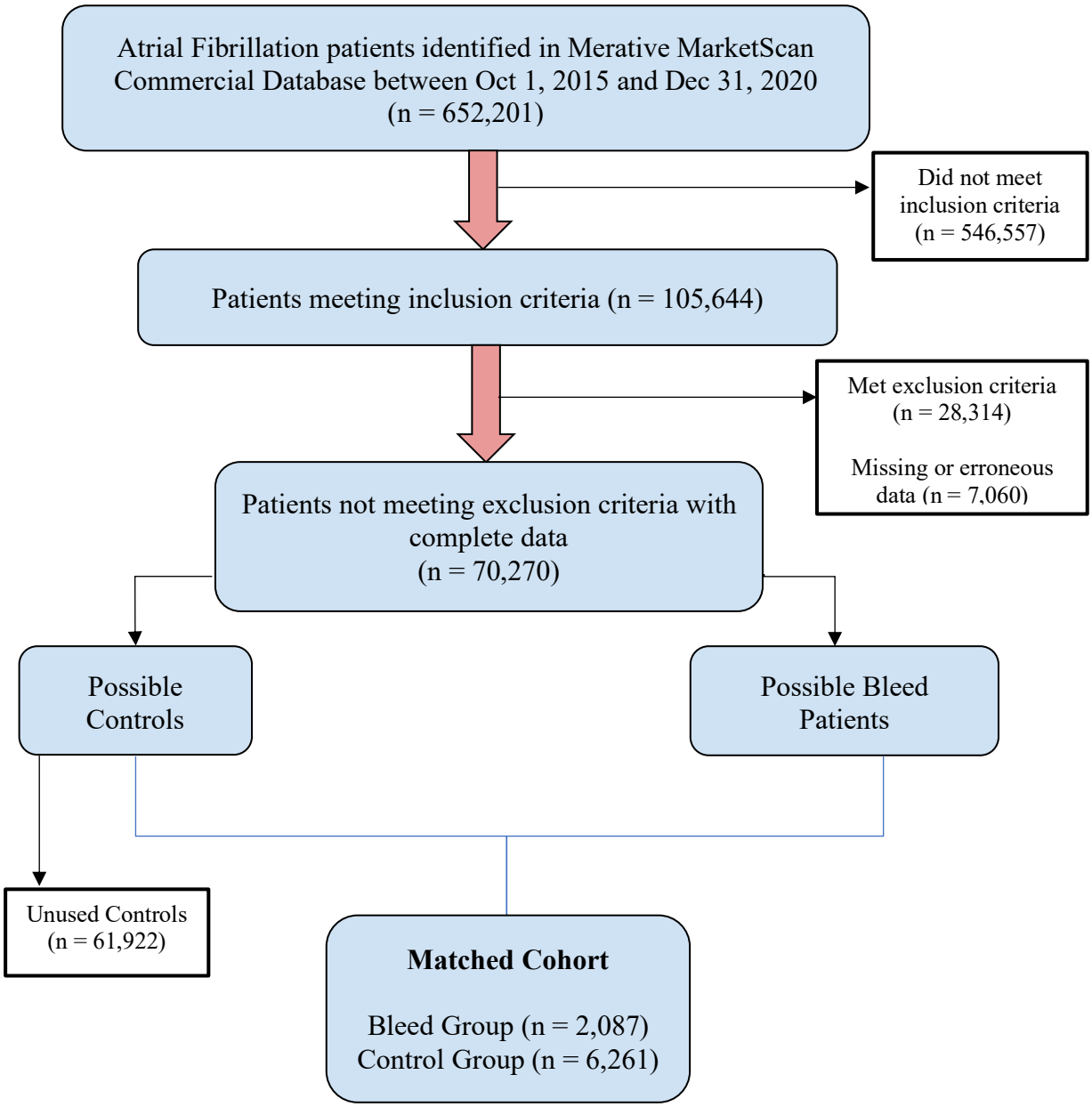
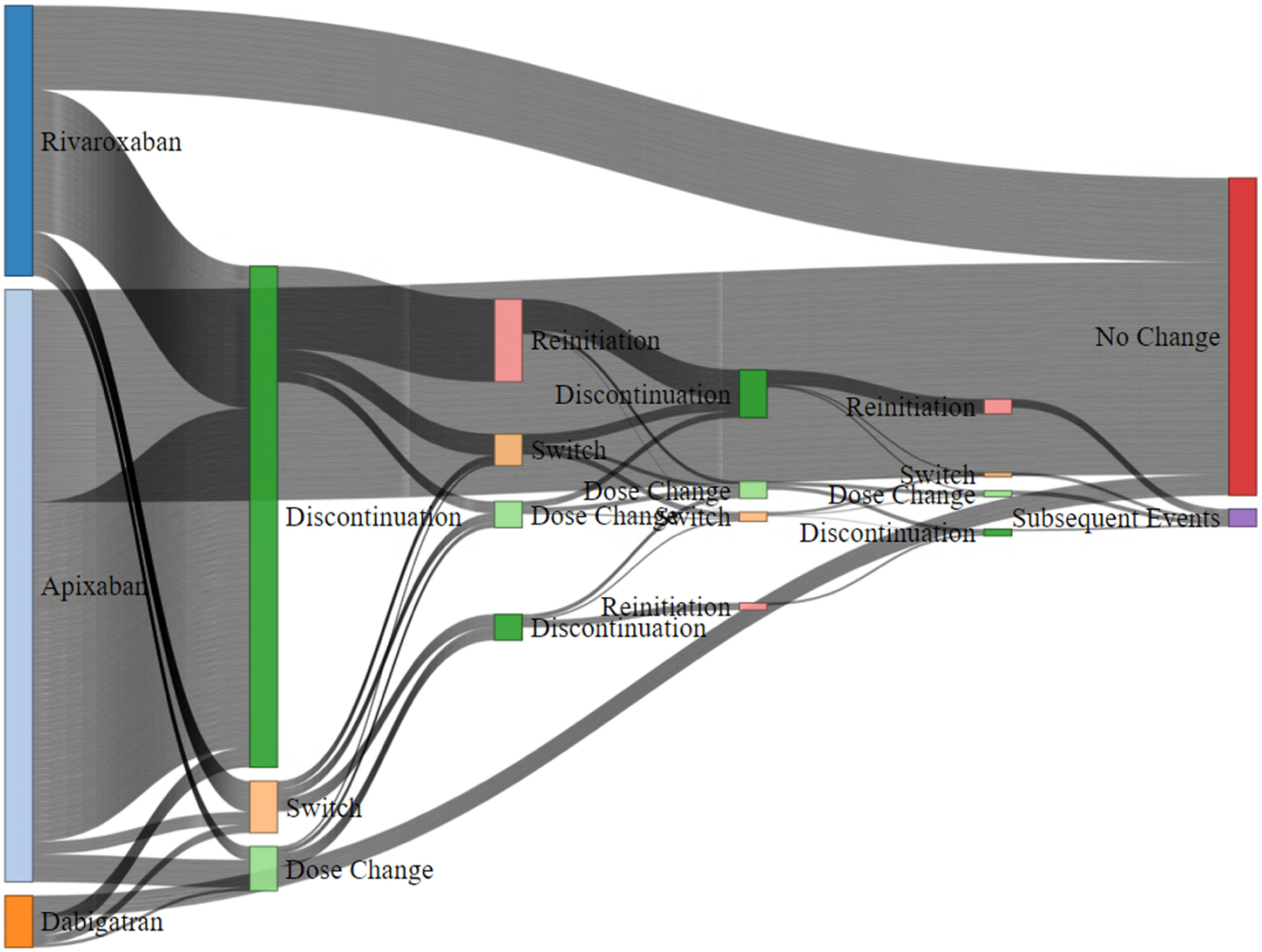


Table 1: Baseline Characteristics of Study Population

Characteristics	**Bleed Group (N= 2,087)**	**Matched Cohort (N= 6,261)**	**Standardized Mean Difference**
Age at index year, mean (SD)	73.39 (12.15)	73.62 (11.78)	0.021
Sex Male, n (%)	1,173 (56.2)	3,534 (56.4)	0.015
Region, n (%)	--	--	0.036
Northeast	612 (29.3)	1901 (30.4)	--
North Central	523 (25.1)	1532 (24.5)	--
South	753 (36.1)	2251 (36.0)	--
West	193 (9.2)	571 (9.1)	--
Unknown	6 (0.3)	6 (0.1)	--
Insurance Type, n (%)	--	--	0.025
Medicare	1,519 (72.8)	4,595 (73.4)	--
Commercial	568 (27.2)	1,666 (26.6)	--
Quan-Charlson Comorbidity Index, n (%)	--	--	0.029
0	255 (12.2)	679 (10.8)	--
1	173 (8.3)	506 (8.1)	--
2	376 (18.0)	1,310 (20.9)	--
3+	1,283 (61.5)	3,766 (60.2)	--
CHA_2DS_2-VASc Score, mean (SD)	4.60 (1.74)	4.62 (1.81)	0.001
Stroke Risk, n (%)	--	--	0.009
High	1,957 (93.8)	5,855 (93.5)	--
Low	130 (6.2)	406 (6.5)	--

HAS-BLED2 score, mean (SD)	2.29 (0.93)	2.29 (0.93)	0.003
Prior warfarin use, n (%)	267 (12.8)	690 (11.0)	0.063
DOAC agent, n (%)	--	--	0.076
Apixaban	1,352 (64.8)	4,252 (67.9)	--
Rivaroxaban	617 (29.6)	1,680 (26.8)	--
Dabigatran	118 (5.7)	329 (5.3)	--
Follow-up Time in Days , mean (SD)	219.28 (121.85)	270.77 (137.30)	0.412

Figure 3: Treatment Patterns of AF Patients After a Major Bleed



*first 4 events experienced stratified by initial DOAC agent

*Subsequent events = more than 4 events experienced

Table 2: Frequency Table of Most Common First Switches of Bleed Group

Index DOAC	**Switch Agent**	**N (%)**
Apixaban (n= 53)	Warfarin	36 (67.9%)
	Enoxaparin	10 (18.9%)
	Rivaroxaban	7 (13.2%)
Rivaroxaban (n= 88)	Apixaban	65 (73.9%)
	Warfarin	16 (18.2%)
	Enoxaparin	7 (8.0%)
Dabigatran (n= 25)	Apixaban	18 (72.0%)
	Rivaroxaban	6 (24.0%)
	Warfarin	1 (4.0%)

*includes patients whose first outcome is not switch but switch later

* n = number of patients with at least one switch at any time

Table 3: Bleed Versus Control Cox Proportional-Hazards Regression Model – Any Change to Treatment

	Hazard Ratio	**95% CI**
Bleed	3.84	(3.56 to 4.14)
Age	0.89	(0.87 to 0.92)
Age^2	1.00	(1.00 to 1.00)
Female	1.00	(0.92 to 1.08)
Region		
North Central	1.18	(1.07 to 1.39)
South	1.19	(1.08 to 1.30)
West	1.18	(1.03 to 1.35)
Unknown	1.39	(0.57 to 3.41)
Commercial Insurance	1.07	(0.93 to 1.24)
Quan-Charlson Comorbidity Index		
1	1.15	(1.05 to 1.26)
2	1.13	(1.02 to 1.24)
3+	1.04	(0.93 to 1.16)
HAS-BLED2	1.09	(1.04 to 1.15)
CHA_2DS_2-VASc	1.00	(0.97 to 1.03)
Prior Warfarin Use	0.98	(0.87 to 1.09)
Initial DOAC		
Dabigatran	0.88	(0.75 to 1.04)
Rivaroxaban	1.07	(0.99 to 1.16)

Table 4: Warfarin Exposure Analysis Cox Proportional-Hazards Regression Model - Switch (Bleed Group)

	Hazard Ratio	**95% CI**
Prior Warfarin Use	2.93	(1.83 to 4.68)
Age	1.21	(0.96 to 1.52)
Age^2	1.00	(1.00 to 1.00)
Female	0.80	(0.53 to 1.20)
Region		
North Central	0.87	(0.52 to 1.45)
South	0.90	(0.57 to 1.42)
West	0.88	(0.45 to 1.73)
Unknown	5.78	(2.22 to 15.01)
Commercial Insurance	2.25	(1.00 to 5.04)
Quan-Charlson Comorbidity Index		
1	1.18	(0.75 to 1.88)
2	1.01	(0.60 to 1.71)
3+	0.80	(0.44 to 1.43)
HAS-BLED2	1.21	(0.92 to 1.60)
CHA_2DS_2-VASc	1.02	(0.88 to 1.18)
Initial DOAC		
Dabigatran	10.15	(5.14 to 20.03)
Rivaroxaban	5.45	(3.54 to 8.38)

Table 5: Warfarin Exposure Analysis Cox Proportional-Hazards Regression Model - Discontinuation (Bleed Group)

	Hazard Ratio	**95% CI**
Prior Warfarin Use	0.87	(0.73 to 1.03)
Age	0.90	(0.87 to 0.94)
Age^2	1.00	(1.00 to 1.00)
Female	1.02	(0.90 to 1.16)
Region		
North Central	1.19	(1.02 to 1.40)
South	1.25	(1.08 to 1.45)
West	1.29	(1.04 to 1.60)
Unknown	1.79	(0.39 to 8.20)
Commercial Insurance	1.25	(0.99 to 1.57)
Quan-Charlson Comorbidity Index		

1	1.15	(0.99 to 1.34)
2	1.18	(1.01 to 1.39)
3+	1.02	(0.85 to 1.21)
HAS-BLED2	1.12	(1.03 to 1.22)
CHA_2DS_2-VASc	0.95	(0.91 to 1.00)
Initial DOAC		
Dabigatran	0.73	(0.54 to 0.99)
Rivaroxaban	0.94	(0.83 to 1.07)

Table 6: Stroke Risk Analysis Cox Proportional-Hazards Regression Model – Discontinuation (Bleed Group)

	Hazard Ratio	**95% CI**
High Stroke Risk	0.71	(0.55 to 0.92)
Age	0.90	(0.87 to 0.94)
Age^2	1.00	(1.00 to 1.00)
Female	0.97	(0.86 to 1.09)
Region		
North Central	1.19	(1.01 to 1.40)
South	1.26	(1.08 to 1.46)
West	1.31	(1.05 to 1.62)
Unknown	1.86	(0.41 to 8.37)
Commercial Insurance	1.25	(0.99 to 1.58)
Quan-Charlson Comorbidity Index		
1	1.16	(1.00 to 1.34)
2	1.15	(0.98 to 1.35)
3+	1.01	(0.85 to 1.21)
Warfarin	0.87	(0.73 to 1.03)
HAS-BLED2	1.11	(1.03 to 1.20)
Initial DOAC		
Dabigatran	0.73	(0.54 to 0.99)
Rivaroxaban	0.95	(0.84 to 1.08)

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