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Direct Oral Anticoagulants and Warfarin Safety in Rural Patients with Obesity

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Abstract

Background: Direct oral anticoagulants (DOACs) are often used in patients with atrial fibrillation or flutter instead of warfarin and, although supporting evidence is limited, available studies suggest this may be an acceptable route of care. Our study assessed the question: are DOACs as effective and safe as warfarin in patients with atrial fibrillation and class III obesity specifically in a rural population?

Methods: A retrospective analysis was conducted by examining the first 6-12 months of therapy with a DOAC (apixaban or rivaroxaban) or warfarin in patients with weight >120kg or class III obesity. Events of interest, thrombosis and bleeding, were documented for analysis. The risk and odds of an event of interest for both groups were calculated and compared.

Results: Characteristics of both arms were similar (DOAC n=42; warfarin n=43). A lack of thrombosis events limited efficacy analysis. A total of 22 bleeds occurred with 8 in patients prescribed a DOAC (7 minor; 1 major) and 14 in those prescribed warfarin (12 minor; 2 major). Weight in kg ($p<0.001$), BMI ($p=0.013$) and HAS-BLED score ($p=0.035$) were predictive of a first bleeding event in patients prescribed warfarin. The odds ratio for any type of bleed on DOAC vs warfarin was 0.55 (0.180-1.681; 95% CI).

Conclusions: In patients with atrial fibrillation and class III obesity, regarding safety, DOACs appear to be non-inferior to warfarin during the first six to 12 months of therapy in our rural population – consistent with other analyses; however, the lack of thrombosis events limited the efficacy analysis.

Keywords

Obesity; atrial fibrillation; anticoagulants; factor Xa inhibitors; rural

1. Introduction

Individuals with obesity, defined as body mass index (BMI) greater than 30kg/m^2,[1] are at an increased risk for atrial fibrillation, an irregular heart rhythm that can lead to cardioembolic stroke.[2] Guideline directed medical therapy for the prevention of thromboembolic (TE) events such as stroke in patients with atrial fibrillation or flutter remains anticoagulation.[3] Warfarin remains one of the most widely prescribed anticoagulants for patients with atrial fibrillation but comes with a number of challenges including the need for regular international normalized ratio (INR) testing to ensure levels fall within the therapeutic range.[4] Direct oral anticoagulants (DOACs), such as the factor Xa inhibitors (i.e. apixaban and rivaroxaban), are relatively new medications that have become attractive alternatives to warfarin as they have fewer monitoring and follow-up requirements, a more rapid on-set and off-set, and fewer medication and dietary interactions.[5] Despite these advantages, data on factor Xa inhibitors' efficacy and safety in individuals with atrial fibrillation and concurrent obesity are limited and in some cases, such as in patients with class III obesity (BMI greater than 40kg/m^2), guidelines advise against their use.[6,7,8]

Despite this limitation, studies evaluating warfarin in individuals with obesity have illustrated it can be used safely and effectively although higher doses and additional monitoring may be required.[9,10] For the DOACs, only half of the large phase 3 approval studies investigated the medications' safety and efficacy by weight categories.[11] In a review of available studies, it was determined that data were of

insufficient quality while evidence of venous TE event prevention was lacking compared to stroke prevention in the subgroup of patients with Class 3 obesity treated with DOAC therapy.[12] Finally, DOAC medication use has been found to be lower amongst rural Medicare beneficiaries compared to their urban counterparts.[13] While the described advantages of DOACs warrant their use in all areas of the country, rural areas are most commonly associated with higher rates of obesity,[14] which could at least partially explain hesitancy on their use in these regions.

Given the current, growing incidence of atrial fibrillation and trends in obesity for the US, more studies are needed to verify the efficacy and safety of DOAC medications compared to warfarin and particularly in rural populations.[15,16] The current study was designed to evaluate the question: In atrial fibrillation patients with concurrent class III obesity, is DOAC anticoagulation, specifically apixaban and rivaroxaban, as effective and safe in terms of TE and bleeding events, respectively, as warfarin anticoagulation during the first 6-12 months of therapy in a rural community?

2. Methods

The present study was designed as a retrospective chart review. Data was extracted between the dates January 1st, 2015 to April 16th, 2021 from the Seaside Hospital Anticoagulation Clinic roster located along the Northwest Coast of Oregon serving patients in the towns of Astoria, Warrenton, Gearheart, and Seaside. The areas qualify as "rural" under the definition provided by the Oregon Office of Rural Health: "any geographic areas in Oregon ten or more miles from the centroid of a population center of 40,000 people or more."[17] The project's protocol was reviewed and approved by the health facility's Institutional Review Board (IRB). All patient data was deidentified prior to analysis and Good Research Principles were followed throughout. To ensure proper reporting, the Strengthening the

Reporting of Observational Studies in Epidemiology (STROBE) process was followed (Supplemental Table 1).[18]

For chart review, patients who routinely take a DOAC or warfarin for stroke prevention in the setting of a history of atrial fibrillation or atrial flutter were included. Patients must have either a recorded BMI greater than 40 kg/m^2 or weight above 120 kg; both parameters were followed given the mixed use of each in previous studies on this topic.[19,20,21] Included patients were required to be above 18 years of age and taking the respective anticoagulant for at least six to 12 months. Patients with active metastatic cancer were excluded.

Data was extracted through retrospective chart review with key characteristics transferred to a deidentified spreadsheet. Characteristics retrieved from patient charts included the variables for age, sex, weight, and concurrent antiplatelet use. Patients' BMIs were also included given the mixed findings related to anticoagulants' efficacy and safety in persons with obesity.Error! Bookmark not defined.,Error! Bookmark not defined.,[22] For each subject, a CHA_2DS_2VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score was calculated given the score's ability to estimate the risk of stroke in patients with atrial fibrillation.[23] A HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage) score was calculated based on the score's power to predict the one-year risk of major bleeding in atrial fibrillation patients prescribed anticoagulant medications.[24] Finally, in those patients' prescribed warfarin a time in therapeutic range (TTR) was calculated as the percentage of time within therapeutic range during investigative period.[25]

Primary endpoints were evaluated within the first six months to one year of starting therapy and measured as the incidence of a TE event (efficacy) and the incidence of major and minor bleeding as

defined by the International Society on Thrombosis and Haemostasis (ISTH).[26] No sample size power calculation was completed; all available patient files that met inclusion criteria were included.

Analysis was conducted using Microsoft Excel and SPSS version 27. Counts and frequencies were calculated and reported for categorical variables. Means and standard deviations (SD) were calculated for numerical values. Between group testing was performed via independent samples t-tests with an alpha set at 0.05 for significance.

Both efficacy and safety endpoints were analyzed in a stepwise fashion. First, the risk and odds for thrombosis and bleeds during the study period were calculated for patients on warfarin or one of the DOACs (apixaban or rivaroxaban). Non-inferiority of the DOACs would be established if the point estimate for the risk and odds of thrombosis and bleeds were within, or below, the pre-specified range of 80% (lower-bound) to 120% (upper-bound) of those using warfarin. If the prespecified non-inferiority margin was met and the point-estimate for the DOACs was below the lower-bound of calculated risk and odds for warfarin, a one-sided test of superiority (Chi-square and Fisher's exact test), with an alpha of 0.025, would be conducted.

Two by two contingency tables were created for this non-inferiority to superiority calculation of risk[27] and odds[28] as well as the statistics for Chi-square and one-sided Fisher's exact test.[29] "Risk" was considered the probability of an event, such as thrombosis or bleeding occurring, divided by all possible outcomes while "odds" was defined as the probability of the event occurring divided by the probability of the event not occurring.[30,31]

Utilizing regression guided by correlations, patient characteristics were used to find a predictive model that could be used in efficacy and safety analyses. Multiple regression was used to identify predictors of thrombosis and bleeds. The process began with identifying significant bivariate correlates and entering

variables into the model. Items that do not add to the explanatory power of the multivariate model were removed until the optimal predictive model was achieved. After the model was selected, statistics for multicollinearity were reviewed. Although no exact cutoffs for variance inflation factors (VIF) or tolerance were pre-assigned, a VIF above 4 and/or a tolerance below 0.25 would lead to further investigation and correction if warranted.

3. Results

A total of 85 individuals were included in the study with 43 individuals on warfarin and 42 on a DOAC (apixaban=37; rivaroxaban=5). Prior to pooling both DOACs into a single group, between group differences for apixaban and rivaroxaban were completed with no differences found (Supplemental Table 2). After pooling, no significant differences between those prescribed DOACs and those prescribed warfarin were found (Table 1).

For the full sample (N=85), the average age was 68.4 years (SD=9.1; range: 46 to 86 years of age). The average weight was found to be 133 kg (SD=19.5; range: 93.8 to 212.3 kg) corresponding to an average BMI of 44 kg/m^2 (SD=6.9; range: 31.2 to 71.2 kg/m^2). The mean CHA_2DS_2VASc score was 4 (SD=1.4; range: 1 to 7) while HAS-BLED was found to be 1.4 (SD=1; range 0 to 4).

During the study period there were no TE events, and due to this lack of occurrence, no efficacy endpoint could be analyzed.

There was a total of 22 bleeding events recorded during the study period (Figure 1). During the study period individuals taking warfarin experienced 14 total bleeds (12 minor and two major bleeds). In this same group, a total of 10 patients accounted for the 14 bleeds. As for individuals utilizing a DOAC, there was a total of eight bleeds during the study period with seven being considered minor and one major bleeding event. All of the minor bleeds (n=7) were documented in patients prescribed apixaban

with the one major bleed occurring in an individual treated with rivaroxaban. Six individuals accounted for the eight total bleeds reported in those prescribed a DOAC.

The absolute risk of a bleed occurring during the study period in individuals prescribed warfarin was found to be 23.3% (lower-bound: 18.6%; upper-bound: 28%) while the absolute risk of a bleed in those prescribed a DOAC was 14.3%. The absolute risk reduction for DOACs compared to warfarin was 9%. The odds of any type of bleed occurring during the study in those taking warfarin was found to be 30.3% (lower-bound: 24.2%; upper-bound: 36.4%) while the odds for the same event occurring in those on a DOAC was 16.7%. The absolute reduction in the odds of a bleed was found to be 13.6%.

The risk ratio of a bleed occurring in those prescribed a DOAC compared to warfarin was found to be 0.614 (95% confidence interval: 0.245 to 1.539) which corresponded with a 38.6% relative reduction in the risk of a bleed occurring. The odds ratio for a DOAC compared to warfarin was found to be 0.55 (95% confidence interval: 0.18 to 1.681) which corresponded with a 45% relative reduction in the odds of any bleed. Table 2 illustrates the contingency table used for the calculation of this safety endpoint.

The risk and odds of any type of bleed occurring in those patients utilizing a DOAC for anticoagulation therapy was below the prespecified lower-bound which allowed for superiority testing. The Pearson Chi-squared value between the two groups was found to be 1.12 (p=0.29) while the results of the one-tailed Fisher's exact probability test was 0.218.

The absolute risk of a major bleed in individuals prescribed warfarin was found to be 4.7% (lower-bound: 3.8%; upper-bound: 5.6%) while it was 2.4% in those prescribed a DOAC. The absolute risk reduction was calculated as 2.3%. The odds of a major bleed occurring in individuals prescribed warfarin was found to be 4.9% (lower-bound: 3.9%; upper-bound: 5.9%) compared to 2.4% in those

taking a DOAC. The absolute reduction in the odds of a major bleed for those prescribed a DOAC compared to warfarin was 2.5%.

The risk ratio of a major bleed in those taking a daily DOAC compared to daily warfarin was found to be 0.512 (95% confidence interval: 0.048 to 5.435) which corresponds to a 48.8% relative risk reduction. The odds ratio for a major bleed in those prescribed a DOAC compared to warfarin was found to be 0.5 (95% confidence interval: 0.044 to 5.732) which translates to a 50% reduction in the relative odds of a major bleed occurring. Table 3 illustrates the contingency table used for the calculation of this safety endpoint.

Although the risk and odds of a major bleed occurring in those patients taking a DOAC allowed for superiority testing, below the prespecified lower-bound, the relatively small number of major bleeding events limited the value of calculating a Pearson Chi-squared statistic. The one-sided Fisher's exact test between the two groups was calculated at 0.51.

Due to the relatively small number of patients that experienced any bleeding event (n=6) in those on a DOAC (n=42), no correlates were identified, and no predictive equation created.

As for those prescribed warfarin (n=43), modeling was conducted via multiple regression analysis to predict first bleeding event (n=10). While all documented patient characteristics were considered as predictors of bleeds (age, sex, BMI, weight, CHA_2DS_2VASc, HAS-BLED, TTR, and concurrent antiplatelet use), the strongest predictive model included weight in kilograms ($p<0.001$), BMI ($p=0.013$) and HAS-BLED score ($p=0.035$) (Table 4): $F(3, 39) = 4.459$ ($p=0.009$)

This regression model accounted for 25.5% of the variance in bleeds for this patient group.

To ensure all components of the calculation were valid, the model's tolerance and VIF were also calculated. All tolerance statistics were above 0.25 (weight=0.343; BMI=0.452; and HAS-BLED=0.668) while all VIFs were below 4 (weight=2.918; BMI=2.211; HAS-BLED=1.497). These findings suggest that multicollinearity was not present and no adjustment to the model was needed. A post hoc sample size power calculation was also calculated. The post-hoc power calculation for bleeding risk (safety) was calculated to be 29.3% based on the sample size and bleeding incidence along with 0.05 alpha. Again, since there were no thrombotic events, we cannot calculate a post-hoc power for efficacy.

4. Discussion

Anticoagulation therapy in patients with obesity presents unique challenges for healthcare providers due to differences in pharmacokinetic parameters (administration, distribution, metabolism and excretion).Error! Bookmark not defined. Despite the limited evidence, DOACs continue to be used in atrial fibrillation patients with all categories of obesity because of the ease of use, lack of interactions, and rapid on-set/off-set. The results of this retrospective chart review indicate that regarding safety, patients being treated for atrial fibrillation with obesity, apixaban and rivaroxaban are, at worst, non-inferior to warfarin. There were no thrombotic events during the study period for any of the patients evaluated, which resulted in an inability to perform statistical analysis for efficacy. This is an unfortunate limitation, particularly for the analysis of Apixaban, given a study on pharmacokinetics noted lower average peak concentrations and half-life of this drug in patients with elevated body weight compared to the reference group.Error! Bookmark not defined.

Baseline characteristics did not differ significantly among the anticoagulant groups. The average TTR, while having a large standard deviation, was within the typical acceptable range for warfarin efficacy and higher than other contemporary registries.[32] This indicates improper dosing was not a strong factor when considering variation in bleeding rates between warfarin and the DOACs.

During regression analysis it was noted that weight, BMI, and HAS-BLED score are key determinants for the risk of a bleed occurring in patients prescribed warfarin. It is unsurprising that a well-validated tool for bleed prediction remains relatively valid in this study, and although weight and BMI are related, there does not appear to be multicollinearity between each component of the model. It is notable that weight and BMI are not predictive of bleeds in the DOAC-prescribed stratum. This is consistent with recent studies suggesting DOAC use in patients with obesity is safe.[33] Regardless, individual patient risk factors should be considered when a clinician is considering anticoagulation with warfarin or a DOAC for stroke prevention in the setting of atrial fibrillation or atrial flutter and concurrent obesity.

There were no significant between group differences noted for subjects on apixaban or rivaroxaban but having a larger study population would be desirable and provided additional power to the statistical analysis. Also, the lack of any TE events impacted the statistical analysis that could take place. The single location setting limits the ability to apply the results to another patient population. Future studies should include additional patients at multiple locations and be prospective and longitudinal in order to capture more efficacy and safety events.

Although properly powered prospective, longitudinal randomized control studies directly comparing DOACs to warfarin in patients with atrial fibrillation and obesity would be beneficial, it is unlikely to occur. The current regulatory climate does not require manufacturers to provide proof of superiority to a reference product, only that the new medication is “safe” and “effective” often based on surrogate endpoints.[34] Despite the clinical need for head-to-head comparisons, manufacturers rely on studies against placebo or non-inferiority to an active agent.[35] Even with the described limitations, observational studies, such as the present report, can help guide clinical decisions when other evidence is lacking.[36,37,38]

5. Study Limitations

Our study has several limitations. For starters, it is a retrospective study, meaning the researchers cannot control exposures or outcomes and there is bound to be some degree of selection bias. Our analysis was also limited by a small sample size of 85 subjects in the same relative geographic area which limits the applicability of this research to the national population. The researchers had hoped to perform efficacy analysis for the DOAC medications in this patient population as this is the main question driving the associated literature base, but no thrombotic events occurred and so this study was limited to safety analysis – thereby failing to help answer this ongoing clinical question. Finally, the Xarelto arm contained only five subjects and so no significant conclusions can be drawn about this medication in patients with class III obesity, and the analysis was otherwise limited to the Apixaban and Warfarin use with no consideration for the use of other oral anticoagulants, Edoxaban and Pradaxa.

6. Conclusion

Along with other published research in this area, this study's results increase the overall understanding of the safety profile for DOAC medications in individuals with atrial fibrillation and concurrent class III obesity. The results contribute to literature suggesting that the factor Xa inhibitors (mainly Apixaban) are not off limits for use in this subset of patients especially if there is a concern for the initiation or continuation of warfarin therapy such as an increased risk of bleeding or patient-specific contraindication. These findings, paired with additional results, can be used along with clinical experience and expertise to advance the understanding and the treatment of this group of patients to ensure optimal outcomes particularly in rural populations.

Conflict of Interest

No authors or collaborators have any conflicts of interest to report.

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Author Contributions

Zachary R. Caverley: Principal investigator, data collection & tabulation, writing – review and editing.

Ross Bindler: Data analysis, writing – original draft, review, and editing.

Sherri G. Mendelson- Data analysis support, review, editing.

Pamela Soh: Literature review, data extraction and tabulation, writing – review

Ethical Standards

The described research project was conducted in accordance with the Declaration of Helsinki. Prior to initiation, the study protocol was approved by the Providence Seaside IRB on March 9th, 2021, with study ID number 2021000217. All Good Research Principles were followed throughout execution of the project's protocol.

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Table 1. Patient Characteristics by Medication Group*

Characteristic**	Warfarin (n=43)	DOAC (n=42)
Age (years); mean (SD)	68.3 (8.2)	68.4 (10.1)

Sex category; n (%) *Male* *Female*	 25 (58.1%) 18 (41.9%)	 25 (59.5%) 17 (40.5%)
BMI (kg/m^2); mean (SD)	45.2 (8.4)	42.8 (4.9)
Weight (kg); mean (SD)	136.2 (21.9)	129.8 (16.4)
CHA_2DS_2VASc; mean (SD)	3.9 (1.4)	4.1 (1.5)
HAS-BLED; mean (SD)	1.4 (1)	1.5 (1)
TTR (percent of days); mean (SD)	63.2% (19.1)†	--
Concurrent Antiplatelet; n (%) *Yes*	 9 (20.9%)	 6 (14.3%)

Abbreviations: Direct Oral Anticoagulant (DOAC); Standard Deviation (SD); Number (n); Percent (%); Body Mass Index (BMI); Kilogram per meter-squared (kg/m^2); Kilogram (kg); Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 65 to 74 years, Sex category (CHA_2DS_2VASc); Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage (HAS-BLED); Time in therapeutic range (TTR).

*No significant between group differences were found.

**Race/ethnicity not included as all patients identify as “white” or “Caucasian”.

†TTR range: 21.7 to 100%

Table 2. Occurrence of First Bleed (major and minor) in Atrial Fibrillation Patients with Obesity Prescribed Warfarin or a DOAC (apixaban or rivaroxaban).

	Any First Bleed		Risk of Bleed	Odds of Bleed
	Yes	No		
Warfarin (n=43)	10	33	23.3%	30.3%
DOAC (n=42)	6	36	14.3%	16.7%

Total (N=85)	16	69	

Abbreviations: Direct Oral Anticoagulant (DOAC); Number in subgroup (n); Number if full sample (N)

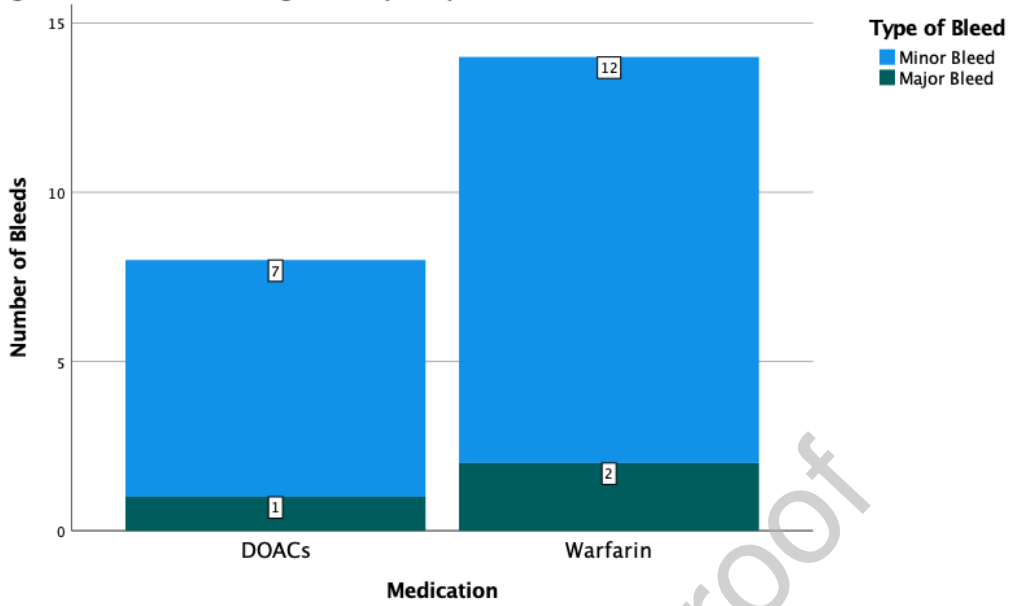
Table 3. Occurrences of a Major Bleed in Atrial Fibrillation Patients with Obesity Prescribed Warfarin or a DOAC (apixaban or rivaroxaban)

	Major Bleed		Risk	Odds
	Yes	No		
Warfarin (n=43)	2	41	4.7%	4.9%
DOAC (n=42)	1	41	2.4%	2.4%
Total (N=85)	3	82		
Abbreviations: Direct Oral Anticoagulant (DOAC); Number in subgroup (n); Number if full sample (N)				

Table 4. Multivariate Regression Model Predicting First Bleed in Atrial Fibrillation Patients with Obesity Prescribed Warfarin (n=43)

	B	Standard Error B	Beta	Significance
Weight (kg)	0.017	0.005	0.862	p<0.001
BMI	-0.027	0.01	-0.538	p=0.013
HAS-BLED	0.158	0.072	0.369	p=0.035
R^2=0.255 (p=0.009)				

Figure 1: Number of Bleeding Events by Study Arm



A total of 22 bleeds occurred during the study period; 14 in those prescribed warfarin (12 minor and two major) and eight in individuals prescribed a DOAC (seven major and one minor; all minor bleeds were with apixaban, and the one major bleed was with rivaroxaban).

Abbreviations: Direct Oral Anticoagulant (DOAC)