MEDDOCS Open Access Publisher

ISSN: 2639-4383

Annals of Cardiology and Vascular Medicine

Open Access | Research Article

Comparative efficacy and safety associated with apixaban and rivaroxaban treatment in morbidly obese versus non-obese patients

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Received: Dec 30, 2019

Accepted: Jan 27, 2020

Published Online: Jan 30, 2020

Journal: Annals of Cardiology and Vascular Medicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Apixaban; Rivaroxaban; Factor Xa Inhibitor; Morbid Obesity; Pharmacology

Abstract

Background: Due to limited enrollment in landmark trials of patients with a BMI > 30 or weight > 100 kg for apixaban and rivaroxaban, the International Society of Thrombosis and Hemostasis (ISTH) recommends against the use of direct oral anticoagulants (DOACs) in those with a BMI > 40 or weight > 120 kg. The purpose of this study was to investigate the efficacy and safety of apixaban and rivaroxaban, prescribed in morbidly obese patients compared to non-obese patients.

Methods: This was a retrospective, single center analysis of morbidly obese (MO) compared to non-obese patients (NO) prescribed apixaban or rivaroxaban for VTE or NVAF between August 2016 and August 2017. The major outcome was the composite of new or recurrent VTE, stroke, and TIA. Minor outcomes included the incidence of major or minor ISTH-defined bleeding events. Data were assessed using Fisher's exact test; sub-analyses of the outcomes were stratified by BMI, weight, and DOAC; posthoc analyses controlled for baseline differences and assessed safety outcomes to weight and BMI.

Results: Two-hundred and ninety-one patients were included, 153 MO patients compared to 138 NO patients. No difference in the incidence of the composite efficacy outcome was observed between MO and NO arms (1.2% vs 2.2%; p=0.67). Major bleeding occurred less frequently in the MO arm (0.7% vs 5.1%; p=0.02) and no difference in minor bleeding was observed between arms (13.1% vs 20.3%, p=0.1).

Conclusion: In this relatively small analysis, patients with morbid obesity did not have an increased incidence of treatment failure or major bleeding compared to non-obese patients.

Cite this article: Duperreault MF, Stern G, Rimsans J, Connors JM. Comparative efficacy and safety associated with apixaban and rivaroxaban treatment in morbidly obese versus non-obese patients. Ann Cardiol Vasc Med.2020: 3(1); 1013

Background

America is amidst an obesity epidemic that is estimated to affect 39% of the adult population [1]. The Center of Disease Control and Prevention defines obesity as a body mass index (BMI) ≥ 30 kg/m^2, morbid or severe obesity as BMI ≥ 40 kg/m^2, and healthy weight as a BMI of 18 to < 25 kg/m^2. Obese patients have a 2-fold increased risk for development of venous thromboembolism (VTE), and a 1.5-fold increased risk for the development of new onset atrial fibrillation compared to normal weight patients [2,3].

Vitamin K antagonists (VKAs) have long been the cornerstone of oral anticoagulation, but since the approval of the first direct oral anticoagulant (DOAC) in 2010, there has been a gradual shift in prescribing patterns. DOACs are recommended as first-line agents for the treatment of VTE and prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) [4-6], as they were shown to reduce the risk of stroke and systemic embolic events by 20% [7] and recurrent VTE by 10% when compared to VKAs [8].

However, landmark trials of DOACs had limited enrollment of patients with a BMI > 30 kg/m^2 and weight > 100 kg [9-12]. Concerns for subtherapeutic levels in the obese population exist as observational pharmacokinetic (PK) studies have shown variable effects on drug concentrations for both apixaban and rivaroxaban [13,14]. It is unknown if these PK variances in obese patients compared to healthy weight patients are clinically relevant and, if so, whether the currently approved doses of apixaban and rivaroxaban are adequate to prevent stroke or recurrent VTE within the obese population. Currently, the International Society of Thrombosis and Hemostasis (ISTH) recommends against the use of DOACs in patients with a BMI > 40 kg/m^2 or weight > 120 kg due to limited evidence [15]. As such, there is an emphasized need for more data assessing safety and efficacy of DOACs in the obese population.

The purpose of this study was to investigate the efficacy and safety of apixaban and rivaroxaban, prescribed for NVAF or VTE in morbidly obese (MO: BMI ≥ 40 kg/m^2) patients compared to non-obese (NO: BMI ≤ 30 kg/m^2) patients.

Methods

In this retrospective, observational study, patients who were prescribed apixaban or rivaroxaban for NVAF or VTE between August 2016 and August 2017 were evaluated for inclusion. Patients were identified using a report that captured oral factor Xa inhibitor (FXai) prescriptions originating from outpatient clinics via electronic medical records. Patients who received follow-up care at an affiliated outpatient clinic and were prescribed either apixaban or rivaroxaban using FDA-approved dosing (including renal adjustment per package-insert recommendations, if necessary) were included in the analysis. Exclusion criteria included inactive prescriptions, loss to follow up, chart duplication, pregnancy, completion of < 90 days of anticoagulation therapy for VTE, and/or therapy interruption of > 30 days according to refill history or documented non-compliance during follow-up. Patients with a BMI > 30 kg/m^2 to < 40 kg/m^2 were excluded to compare specifically NO patients to MO patients.

Patients with a BMI ≥ 40 kg/m^2 were assigned to the MO group and patients with a BMI between 18 kg/m^2 to ≤ 30 kg/m^2 were assigned to the NO comparator group. NO patients were randomly selected by a computer-generated algorithm to obtain a similar cohort size for a comparator group. Demographics including weight, BMI, and age were collected at the time of FXai initiation, or if previously on a FXai, they were recorded from the earliest documented encounter. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation using the patient's baseline serum creatinine and actual body weight.

The efficacy outcome was defined as the composite occurrence of stroke or transient ischemic attack (TIA) in patients with NVAF or the recurrence of VTE if verified via computerized tomography or doppler ultrasound in VTE patients. Safety outcomes evaluated the occurrence of ISTH-defined major bleeding and minor bleeding events. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a reduction in hemoglobin of ≥ 20 g/L, or leading to transfusion of ≥ 2 units of whole blood or red cells. Minor bleeding was defined as all other non-major bleeding events [15]. Thrombotic events were collected if documented in the electronic health record and confirmed by computerized tomography and doppler ultrasound. This study was Institutional Review Board approved.

Statistical analysis

Efficacy and safety endpoints were counted as binary outcomes (did not assess for multiple events per patient) and analyzed using Fisher's exact test. Patient characteristics are presented as mean (±SD) for normally-distributed data and median (interquartile range, IQR) for non-parametric distributed data. Patient characteristics were compared using chi-squared test for categorical data, and Student's *t*-test for continuous data. Statistical significance was defined as $p < 0.05$. Post-hoc logistic regressions were completed to assess the association between weight and BMI with composite safety (major and minor bleeding) outcomes after controlling for differences in baseline characteristics using STATA/IC 15.1.

Results

Between August 2016 to August 2017, we evaluated 392 records with a BMI ≥ 40 kg/m^2, of which 153 patients satisfied inclusion criteria for the MO group. One-hundred and thirty-eight patients with a BMI between 18 kg/m^2 to ≤ 30 kg/m^2 were included in the NO group. The median BMI in the MO arm was 44.6 kg/m^2 (42.1 kg/m^2 - 48.6 kg/m^2) compared to 25.8 kg/m^2 (23.8 kg/m^2 - 27.9 kg/m^2) in the NO arm ($p < 0.001$). MO patients were younger, had better baseline renal function, and tended to be mostly female compared to NO patients (Table 1). Most patients were on a FXai for NVAF, and prescriptions for FXai type were proportional between groups. Incidence of active cancer, presence of a thrombotic disorder and concomitant use of aspirin, P2Y12 inhibitor, or both were not significantly different between groups.

Stroke/TIA or VTE recurrence occurred in two (1.2%) MO patients and three (2.2%) NO patients (Table 2; p=0.672). Both events in the MO arm were pulmonary emboli (PE) in patients being treated for a previous VTE, with one patient receiving apixaban and one patient on rivaroxaban (Table 2). Stroke/TIA represented all three treatment-failure events in the NO arm of NVAF patients, with one patient in the NO group receiving rivaroxaban that developed a TIA less than 48 hours after the medication was held for a procedure. No patients with a thromboembolic event had cancer.

Major bleeding occurred more frequently in NO patients relative to the MO patients (Table 2; 7 [5.1%] vs 1 [0.7%]; p=0.021). One patient in the MO arm with a BMI of 45.5 kg/m^2 and weight

of 128 kg receiving rivaroxaban experienced a major bleeding event due to an accidental overdose. No difference in minor bleeding was detected between the MO and NO patients (20 [13.1%] vs 28 [20.3%], p = 0.098). More overall bleeding occurrences were associated with the NO arm (35 [25.4%]) compared to the MO arm (21 [13.7%]), p = 0.012.

Post-hoc logistic regressions for safety outcomes controlled for baseline characteristics (sex, age and CrCl) and demonstrated BMI ≥ 40 kg/m^2 was not associated with bleeding occurrences (OR = 0.653 [95% CI 0.269 – 1.589], p = 0.348), however each kg increase in weight was associated with a decreased risk of bleeding occurrences (OR = 0.983 [95% CI 0.967 – 0.999], p = 0.048). In this analysis, there were 108 patients ≥ 120kg, and 36 patients ≥ 150kg, with weights ranging from 54 kg-208 kg.

Table 1: Baseline Characteristics

Characteristic	MO (BMI ≥40 kg/m2)(N=153)	NO (BMI 18 - ≤30 kg/m2) (N=138)	*p-value*
Age (mean ± SD)	60.6 ± 12.9	71.8 ± 11.6	< 0.001
Sex (female) - n (%)	97 (63.40)	56 (40.58)	< 0.001
BMI kg/mg^2 (median, IQR)	44.6 (42.1-48.6)	25.8 (23.8-27.9)	< 0.001
Apixaban Rivaroxaban	76 (49.67) 77 (50.33)	73 (52.90) 65 (47.10)	0.639
CrCl - n (%) < 30 mL/min 30-50 mL/min > 50 mL/min	 0 (0) 2 (1.31) 151 (98.69)	 1 (0.72) 24 (17.39) 113 (81.88)	 < 0.001 < 0.001
Indication - n (%) NVAF VTE	 104 (67.97) 49 (32.03)	 102 (73.91) 36 (26.09)	0.370
Medications - n (%) Aspirin P2Y12 inhibitor Both	 32 (20.92) 3 (1.24) 4 (2.61)	 34 (23.19) 3 (2.17) 3 (2.17)	 0.485 1.0 1.0
Active cancer - n (%)	12 (7.84)	18 (13.04)	0.177
Thrombotic disorder - n (%)[ϕ] Factor V Leiden Lupus anticoagulant	9 (5.88) 4 (2.61) 2^ (1.31)	8 (5.80) 2 (1.45) 1 (0.72)	1.0 0.687 1.0

^One patient had both Factor V Leiden and Lupus anticoagulant

[ϕ]Other types of thrombotic disorders included antiphospholipid syndrome, heterozygous prothrombin gene mutation, monoclonal gammopathy of undetermined significance, and protein C deficiency.

BMI: Body mass index; CrCl: creatinine clearance; NVAF: Non-valvular atrial fibrillation; VTE: Venous thromboembolism

Table 2: Sub-analysis by FXai and BMI

	Rivaroxaban (n = 142)				Apixaban (n = 149)			
BMI (units)	18-25 (n = 23)	>25-30 (n = 42)	40-45 (n = 41)	>45 (n = 36)	18-25 (n = 29)	>25-30 (n = 44)	40-45 (n = 39)	>45 (n = 37)
Thrombotic event	0	1 (2.4)	1 (2.4)	0	1 (3.5)	1 (2.3)	1 (2.6)	0
Stroke	0	1	0	0	1 (3.5)	1 (2.3)	0	0
PE	0	0	1 (2.4)	0	0	0	1 (2.6)	0
DVT	0	0	0	0	0	0	0	0
Bleed event	7 (30.4)	14 (33.3)	7 (17.1)	8 (22.2)	10 (34.5)	8 (18.2)	4 (10.3)	3 (8.1)
Major	2 (8.7)	1 (2.4)	0	1 (2.8)	2 (6.9)	3 (6.8)	0	0
Minor	5 (21.7)	13 (31)	7 (17.1)	7 (19.4)	8 (27.6)	5 (11.4)	4 (10.3)	3 (8.1)

Data presented as n (%); Percentage per BMI bracket

Table 3: Sub-analysis by FXai and Weight of 120 kg

	Weight ≥120 kg (n = 108)		Weight <120 kg (183)	
	Apixaban (n = 54)	Rivaroxaban (n = 54)	Apixaban (n = 95)	Rivaroxaban (n = 88)
Thrombotic event	1 (1.8)	0	2 (2.1)	2 (2.3)
Stroke/TIA	0	0	2 (2.1)	1(1.1)
PE	1 (1.8)	0	0	1(1.1)
DVT	0	0	0	0
Bleed event	2 (3.7)	11 (20.4)	23 (24.2)	25 (28.4)
Major	0	1 (1.8)	5 (5.3)	3 (3.4)
Minor	2 (3.7)	10 (18.5)	18 (18.9)	22 (25)

Data presented as n (%); Percentage per oral factor Xa inhibitor bracket

Discussion

Obesity is a known risk factor for increased thrombotic complications [16], and the use of anticoagulation in this patient population remains challenging, particularly with heparin, low molecular weight heparin, and the use of DOACs. Given the landmark trials had limited representation of obese patients, PK data and case reports, aimed at filling the gaps in knowledge, drive clinicians when choosing therapy.

Previously published PK data of the DOACs in the obese population have demonstrated variable results. A PK study of apixaban comparing healthy weight (65-86 kg), low weight and high weight (≥ 120 kg) subjects showed that compared to healthy subjects, high weight subjects had a C_{max} and area under the curve (AUC) that were 31% and 23% lower respectively [13]. Additionally the half-life of apixaban was decreased by three hours in the high body weight group. For healthy patients receiving rivaroxaban, a PK study observed the C_{max} and AUC were not affected by subjects with a weight > 120 kg when compared to subjects with a weight between 70-80 kg [14].

However, recent safety and efficacy analyses have supported the use of apixaban and rivaroxaban in obese patients [17-19]. A sub-analysis of the clinical trials investigating rivaroxaban for the treatment of VTE observed a BMI of ≥ 35 kg/m^2 was not a risk factor for the recurrence of VTE while receiving therapy [20]. When apixaban was retrospectively compared to warfarin in 341 morbidly obese patients, no statistically significant differences were found for the incidence of stroke in patients with NVAF or recurrence of VTE [17]. In a large retrospective study of 3563 propensity matched patients taking rivaroxaban or warfarin for AF, ischemic stroke/thrombotic embolism and major bleeding was similar between groups [21]. Moreover, a retrospective analysis of 795 MO patients taking both apixaban and rivaroxaban for NVAF and VTE demonstrated similar efficacy and safety as compared to warfarin [22]. Most recently, Netley et al published a retrospective study including 3458 patients taking apixaban, rivaroxaban or dabigatran and assessed for differences in safety and efficacy between the following BMI subgroups: BMI < 30, BMI 30 – 40, and BMI > 40. They found no difference in thrombotic (1.3%, 1.0% and 1.5% respectively, p = 0.598) or overt bleeding (2.6%, 1.7% and 1.2% respectively, p = 0.065) events between groups [23].

In our patient population of 291 patients, thrombotic events were observed in two (1.31%) MO patients and three (2.17%) NO patients (p=0.672). Due to the small sample size and low event occurrence, our efficacy results are at risk of type II error and regression analysis could not be performed to balance baseline risks between NO and MO groups. Both events in the MO arm were PE, and neither event stemmed from the same FXai. Both FXais were appropriately prescribed, and there were no additional risk factors for VTE. Of the patients who experienced a stroke/TIA, all were prescribed a FXai for NVAF, with CHA_2DS_2-VASc scores ranging from 3 to 6, inferring a 4.6-13.6% risk of developing stroke/TIA or systemic embolism [24]. In the NO arm, no patients experienced a VTE. Overall, thrombotic events were low and comparable to incidence of treatment failure seen in landmark trials (1.3-2.3%) [9-12].

This analysis demonstrated BMI ≥ 40 kg/m^2 was associated with a decreased risk of major and composite bleeding compared to patients with a BMI of 18 kg/m^2 to ≤ 30 kg/m^2. The HAS-BLED score is a validated tool for assessing the risk of bleeding in patients prescribed an anticoagulant for NVAF but does not consider obesity within the risk assessment. When bleeding risks for the FXai, edoxaban, and VKA were compared for NVAF, obesity did not impact bleeding risk [25]. The recent study by Netley et al also found no difference between BMI subgroups, however observed a trend towards more bleeding with the lower BMI subgroup [23]. In this analysis, significantly more major bleeding events occurred in the NO arm, however, after controlling for baseline characteristics which are known bleeding risk factors (age, renal function) and sex, logistic regression demonstrated no association with BMI and composite bleeding events. The singular major bleeding event that occurred in the MO arm was due to an accidental overdose by the patient despite being prescribed the correct package insert dosing. In the comparator arm, one patient with a BMI of 25 kg/m2 and weight of 86 kg receiving apixaban for VTE experienced two major bleeding events on two different occasions. The patient's HAS-BLED score was 3 on first occasion and 4 on second occasion (aspirin use, age > 65, hypertension, and prior major bleed), suggesting this patient had a high risk of bleeding compared to most patients. The results from our analysis reflect similarly to the landmark trials with respect to incidence of major bleeding from 0.6-5.6% [9-12].

Most data available that evaluate DOAC use in obese patients utilize BMI cutoffs, though the best tool to define obesity or a direct measurement of body fat is unclear, as BMI is a poor dosing metric and can often represent dissimilar body compositions [26]. After data collection was completed, we chose to evaluate the association of safety outcomes with weight using logistic regressions. We found that although BMI ≥ 40 kg/m^2 was not associated with a difference in safety outcomes, weight, as a continuous outcome, was inversely associated with composite bleeding outcomes. The inconsistency between BMI and weight

associations for outcomes may suggest one characteristic could be more accurate in risk assessment. Unfortunately, the nature of our study did not allow for us to accurately assess which marker of obesity was better correlated with the outcomes of interest, and the exclusion of patients with BMI > 30 and < 40 may decrease the ability to make accurate assumptions about weight as a continuous outcome.

This study is limited by its retrospective design and small sample size originating from a single-center. As such, we were unable to obtain power and avoid potential for a type II error in our efficacy outcome. Without CHA_2DS_2-VASc scores for all patients taking a FXai for NVAF, we cannot be sure the baseline stroke risk was balanced between groups. As such, differences in baseline risk may have contributed to the stroke/TIA events thus clouding the ability to observe differences between the MO and NO groups. Drug concentrations of apixaban and rivaroxaban are more than 95% cleared 72 hours after the last dose, thus undocumented non-compliance may have occurred in our sample population [27]. When interpreting safety outcomes, renal function is a constituent of the HAS-BLED risk assessment and our choice to report renal function using the Cockcroft-Gault calculation likely overestimated renal function in obese patients [28]. However, the choice to use actual body weight in all patients for the Cockcroft-Gault calculation was made to be consistent with the landmark studies investigating apixaban and rivaroxaban for stroke prevention in patients with NVAF and VTE treatment [9-12]. This may explain the significantly larger population of MO patients with healthier renal function. Lastly, there was a potential for underreporting of efficacy and safety outcomes due to patients presenting to out-of-network hospitals during emergent situations.

Conclusion

In this analysis of 291 patients, apixaban and rivaroxaban were not associated with an increased incidence of treatment failure or major bleeding in MO patients, compared to NO patients. While results should be cautiously interpreted due to low event occurrences, apixaban and rivaroxaban may be safe to use for prevention of recurrent VTE or stroke in NVAF in the MO population based upon our sample. In the future, novel anticoagulants should be assessed with a larger spectrum of BMIs and weights to reflect use in the obese population in North America.

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