

## Saddle Pulmonary Embolism in a Morbidly Obese Patient on Rivaroxaban

Young R Lee<sup>1\*</sup>, Lauren N Adams<sup>2</sup> and Hayley S Brazeale<sup>3</sup>

<sup>1</sup>Department of Pharmacy Practice, Texas Tech University Health Sciences Center School of Pharmacy, Abilene, Texas, USA

<sup>2</sup>Hendrick Medical Center, Abilene, Texas, USA

<sup>3</sup>Texas Tech University Health Sciences Center School of Pharmacy, Abilene, Texas, USA

Received: 12 September, 2017; Accepted: 16 October, 2017; Published: 23 October, 2017

\*Corresponding author: Young R Lee, Department of Pharmacy Practice, Texas Tech University Health Sciences Center School of Pharmacy, Abilene, Texas, USA, Tel: 325-696-0449; Email: young.lee@ttuhsc.edu

### Abstract

**Purpose:** To describe the case of an obese patient who presented with a saddle Pulmonary Embolism (PE) while being treated with rivaroxaban.

**Summary:** A 46-year-old female was admitted with bilateral PE and Deep Venous Thromboembolism (DVT) of the left lower extremity. She was treated and discharged on rivaroxaban (Xarelto<sup>®</sup>) 15mg twice daily for three weeks then 20mg daily. Five weeks later, she presented to the emergency department with dyspnea, chest pain, tachycardia and hypoxia. CT angiogram showed a new saddle pulmonary embolism. She was admitted and started on a heparin drip that was later switched to enoxaparin and warfarin. The decision was made to discontinue rivaroxaban and begin long-term treatment with warfarin.

**Discussion:** It has been reported that extremes of body weight do not alter rivaroxaban exposure, but the EINSTEIN-PE trial showed a trend of worse outcome with rivaroxaban in patients weighing > 90 kg. The etiology of saddle PE of this case may include not only obesity and previous DVT, but also possible inadequate rivaroxaban concentration.

**Conclusion:** This patient developed a saddle pulmonary embolism while receiving anticoagulation with rivaroxaban. Although she had previously been diagnosed with a PE and is morbidly obese, possible failure of Xarelto<sup>®</sup> may not be disregarded.

**Key words:** Xarelto<sup>®</sup>; Rivaroxaban; Obese; Venous Thromboembolism; Deep Vein Thrombosis; Pulmonary Embolism; Prophylaxis

### Introduction

For treatment of Deep Venous Thromboembolism (DVT) and Pulmonary Embolism (PE), the American College of Chest Physicians Guideline of Antithrombotic Therapy for VTE Disease recommends dabigatran, apixaban, edoxaban, or rivaroxaban (grade 2B) over vitamin K antagonist or low-molecular weight heparin therapy (grade 2C) for patients without cancer [1]. Therapy with a Direct Oral Anticoagulant (DOAC), such as rivaroxaban, should be continued for at least 3 months unless longer treatment duration is indicated [1]. The guideline does not evaluate use or recommend dosage change with DOAC therapy in obese patients.

Rivaroxaban (Xarelto<sup>®</sup>) is an oral factor Xa inhibitor which inhibits platelet activation and fibrin clot formation through a direct, selective, and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways [2]. Xarelto<sup>®</sup> was first approved in July 2011 for prevention of DVT and PE following knee or hip replacement surgery [3]. The trials that led to the approval of Xarelto<sup>®</sup> were the RECORD 1, 2, and 3 trials [3]. In November of 2011, Xarelto<sup>®</sup> was approved for the prevention of stroke in patients with non-valvular atrial fibrillation following the results of the ROCKET AF trial [4]. Xarelto<sup>®</sup> was then approved for the treatment and prevention of recurrent blood clots in November 2012 [5]. The dose for this indication is 15 mg twice daily with food for 3 weeks followed by 20 mg daily with food based on the EINSTEIN-DVT and EINSTEIN-PE trials [5].

Xarelto<sup>®</sup> use should be avoided in patients with renal impairment (CrCl < 30 mL/min) being treated for a DVT/PE [2]. Previous studies have shown that body weight > 120 kg did not significantly influence Xarelto<sup>®</sup> exposure, and postoperative thromboprophylaxis trials were not affected by weight up to 190 kg, so no dosage adjustment is recommended at this time [2]. DOACs such as Pradaxa<sup>®</sup> (dabigatran), Eliquis<sup>®</sup> (apixaban) and Xarelto<sup>®</sup> (rivaroxaban) have been approved for various indications to give patients an alternative to warfarin therapy. There are no case reports at this time involving possible Xarelto<sup>®</sup> failure in obese populations.

### Case Presentation

A 46-year-old female was hospitalized with dyspnea, tachycardia, hypoxia, bilateral leg swelling and pain. A doppler of the left lower extremity revealed a Deep Venous Thromboembolism (DVT) of the popliteal vein. CT angiogram showed multiple, bilateral pulmonary emboli extending from the hilar portions of the left and right main pulmonary arteries to the upper and lower lobes. There were no pleural or pericardial

effusions noted. She was treated with Xarelto® 15mg twice daily with food for three weeks followed by 20mg once daily. Five weeks later, she presented to the emergency department with increasing shortness of breath and chest pain when breathing deep. She also stated she experienced some nausea, vomiting, and lightheadedness that morning which resolved after oxygen delivery via nasal cannula was started in the emergency department. CT angiogram showed a new saddle embolus and the patient was admitted to the intensive care unit. When asked about her compliance, the patient stated that she had not missed any doses of Xarelto® and took it with meals. Her past medical history included Coronary Artery Disease (CAD) with stent placement 10 months prior, hypertension, type 2 diabetes mellitus, hyperlipidemia, and morbid obesity. Her family history was significant for CAD. There was no known family history of clots. Social history was negative for tobacco, alcohol, and illicit drug use. Patient's home medications included aspirin, atenolol, acetaminophen-hydrocodone, atorvastatin, clopidogrel, glyburide, isosorbide mononitrate ER, metformin, metoprolol tartrate, niacin, nitroglycerin, omeprazole, rivaroxaban, and sio-mag.

Vital signs at admission are available in Table 1. Laboratory results at admission can be found in Table 2. Upon admission, physical exam revealed bilateral edema in the left lower extremity greater than the right. Chest x-ray revealed mild to moderate vascular congestion. CT angiogram of the chest showed multiple pulmonary artery filling defects including a saddle embolus. The patient received oxygen at 4 L/min via nasal cannula, and unfractionated heparin drip per hospital protocol for Venous Thrombo Embolism (VTE) and was admitted to the intensive care unit. A venous doppler that afternoon revealed a DVT of the left popliteal vein.

**Table 1:** Vital signs at admission

Heart rate	104 bpm
Blood pressure	122/95 mmHg
Respiratory rate	20 - 33 breaths/min
O <sub>2</sub> saturation	87% on room air
Temperature	97.9°F
Height	165.1 cm
Weight	149.5 kg
BMI	54.8 kg/m <sup>2</sup>

**Table 2:** Laboratory results at admission

Glucose	363 mg/dL	T-Bili	0.68 mg/dL
Troponin	0.01 mcg/L	ALP	133 U/L
D-dimer	2.66 mcg/L	ALT	28 U/L
BUN	16 mg/dL	AST	15 U/L
SCr	1.0 mg/dL	PT	14.1 sec
Na	141 mmol/L	INR	1.1
K	4.2 mmol/L	Hemoglobin	14.6 g/dL
Cl	106 mmol/L	Hematocrit	42.9%
CO <sub>2</sub>	23 mmol/L	Platelets	131 X 10 <sup>9</sup> /L

On day two the patient's oxygen was decreased to 2 liters and an IVC filter was placed. Also, unfractionated heparin was replaced with enoxaparin 150 mg (1mg/kg) subcutaneous twice daily. The patient education regarding warfarin therapy was completed by a clinical pharmacist and pharmacy students and the patient received one dose of warfarin 10 mg by mouth. That evening the patient was moved to the general medical floor.

On day six the patient was discharged on warfarin 12.5 mg by mouth daily and enoxaparin 150 mg (1 mg/kg) subcutaneously twice daily. The patient was to follow up with the Coumadin clinic 2 days after discharge. At a follow-up visit six months later, warfarin dose was 20 mg on Monday, Tuesday and Wednesday and 15 mg on Thursday, Friday, Saturday and Sunday (total 120 mg/week) and a chest CT did not identify any remaining thrombus.

### Discussion

PE is a common disease with about 70 cases per 100,000 patients in the population [6]. Previously, the standard of therapy for patients with PE was administration of low molecular weight heparin (LMWH) and warfarin, though warfarin has many disadvantages making maintenance therapy more difficult [6]. Direct Oral Anticoagulants (DOACs) are now recommended first line for treatment of VTE [1]. The advantages of DOACs include a rapid onset of action, wide therapeutic range, fewer interactions, predictable therapeutic effect with fixed or weight based dosing, and routine coagulation monitoring is not required [7]. Though fewer than warfarin, there are some disadvantages to DOACs such as lack of a coagulation assay available to measure anticoagulation effects, no available antidotes (except for dabigatran), and they are more expensive.

For VTE treatment, the International Society on Thrombosis and Haemostasis (ISTH) recommends standard dosing in patients with a body weight ≤ 120 kg and BMI of ≤ 40 kg/m<sup>2</sup> [8].

They also suggest avoidance of newer oral anticoagulants with a body weight > 120 kg and BMI > 40 kg/m<sup>2</sup> due to lack of clinical data for use in this population [8]. If the agents are used in these patients, the ISTH recommends monitoring anti-Xa levels or mass spectrometry for efficacy. When the level falls below the expected range for the drug in use, they suggest changing therapy to a vitamin K antagonist rather than dose adjusting the agent [8].

The results of the EINSTEIN-PE trial are available in Table 3 [9]. Xarelto® was non-inferior to warfarin in recurrent VTE and superior to standard therapy with regard to major bleeding (NNT=91) [9]. The subgroup analysis looked at efficacy in BMI ≥ 30 kg/m<sup>2</sup> and weight > 90 kg and found no statistically significant difference between groups; however, BMI > 30 kg/m<sup>2</sup> is not morbidly obese [10]. The trend was in favor of enoxaparin plus warfarin rather than rivaroxaban in patients > 90 kg. With low power in the subgroup analysis, true difference between standard therapy and rivaroxaban cannot be indisputable [10]. The EINSTEIN-DVT trial was similar comparing Xarelto® to VKA bridged with subcutaneous enoxaparin in patients with symptomatic DVT. The results of this trial were similar to the EINSTEIN-PE trial, detailed results are available in Table 4 [11]. Due to the small number of obese patients in each of these studies, it may not be easy to extrapolate the results of this study to an obese population.

**Table 3:** Comparison of rivaroxaban and enoxaparin plus VKA in the based on weight and BMI in the EINSTEIN-PE trial

EINSTEIN-PE <sup>9</sup> (n=4832)	Recurrence on rivaroxaban (n=2419)	Recurrence on enoxaparin +VKA (n=2413)	P value
Total patient population	2.1%	1.8%	
≤ 70kg	2.6%	1.6%	> 0.05
> 70-90kg	1.9%	2.1%	> 0.05
> 90kg	1.9%	1.5%	> 0.05
BMI < 30 kg/m <sup>2</sup>	2.3%	1.9%	> 0.05
BMI ≥ 30 kg/m <sup>2</sup>	1.5%	1.5%	> 0.05

**Table 4:** Comparison of rivaroxaban and enoxaparin plus VKA based on weight in the EINSTEIN-DVT trial

EINSTEIN-DVT11 (n=3449)	Recurrence on rivaroxaban (n=1731)	Recurrence on enoxaparin +VKA (n=1718)
Total patient population	2.1%	3.0%
≤ 70kg	2.4%	4.0%
> 70-90kg	1.8%	2.7%
> 90kg	2.2%	2.3%

In 2007, Kubitzka, et al. looked at the influence of body weight on pharmacokinetics and pharmacodynamics of Xarelto®. Results of this study are available in Table 5 [12]. The average BMI in the > 120 kg group was 43.5 kg/m<sup>2</sup> [12]. This study showed that Xarelto® was well tolerated and its pharmacokinetics and pharmacodynamics were not influenced by body weight to an extent considered likely to be clinically relevant [12]. However, this study did show the maximum effect of anti-Xa activity was slightly lower in the > 120 kg group, though not considered clinically significant [12]. Based on these results, the author concluded that Xarelto® is unlikely to need dose adjustment in subjects with extreme body weight. However, given the small number of patients, there may not have been a large enough sample size to detect a difference in pharmacokinetic or pharmacodynamics properties [12]. The patient in the presenting case had a BMI of 54.8 kg/m<sup>2</sup> which is higher than the average BMI (43.5 kg/m<sup>2</sup>) in this study. This indicates that the results in this study may not apply to morbidly obese patients with larger BMI values. The pharmacokinetic properties and pharmacodynamics of patients with higher BMIs remains unknown.

**Table 5:** Results of max pharmacodynamics effect of the dose in the trial by Kubitzka, et al. [12]

Kubitzka, et al. <sup>12</sup> (n=48)	Max pharmacodynamic effect of the dose
Patient population	
≤ 50kg	46.80
> 70-80kg	45.80
> 120kg	41.70

There is evidence that change in volume of distribution due to extremes of body weight can affect the exposure and efficacy of rivaroxaban. Mueck, et al. found that a lower body weight was correlated with a decrease of 0.8% in clearance of rivaroxaban per 1 kg, therefore increasing the exposure [13]. In theory, a higher body weight with a larger volume of distribution would reduce the exposure and efficacy. A 2001 study by Douketis revealed a 5.5% recurrence rate of VTE during the initial three months of anticoagulant therapy [14]. The incidence of recurrence increases in studies with longer follow up periods [15]. This particular patient's VTE recurrence could be due to suboptimal therapy, but could also be due to the fact that VTEs recur in the general population. As demonstrated in this case report, standard doses may not prevent a recurrent VTE in larger patients. Studies should be performed in obese populations to determine if an adjusted Xarelto® dose is needed for therapeutic efficacy in clinical practice.

Given that DOACs do not require monitoring, it is difficult to assess if the levels of rivaroxaban were actually subtherapeutic due to increased BMI or if there was another cause to this

patient's recurrent VTE. Based on Kubitza's trial, the 12 patients > 120 kg on rivaroxaban showed a slight decrease in the maximum anti-Xa activity [12] (Table 5). The maximum pharmacodynamics effect results demonstrate that it is theoretically possible to have subtherapeutic activity in morbidly obese patients, especially with a BMI greater than 50 kg/m<sup>2</sup>. The patient was morbidly obese as well, which is itself an independent predictor of VTE and VTE recurrence [16, 17]. Based on the Padua VTE Prediction Score, this patient had a total score of 4 from previous VTE history and obesity which led to a high risk for VTE [18, 19].

When warfarin education was delivered, the patient's compliance to Xarelto<sup>®</sup> was assessed. It seems the patient was compliant with her regimen. Possible drug interactions between the patient's home meds and Xarelto<sup>®</sup> were assessed and no significant interactions were found. The initial PE was not a saddle embolism; the different placement could mean this is not the same PE. However, her previous DVT could have migrated and led to her saddle embolism. Her initial therapy was in line with 2016 CHEST guidelines, which states that rivaroxaban is appropriate for the treatment of acute PE [1]. There were no hypercoagulability test results available for review. Despite the limitations of this case report, there remains a high possibility of treatment failure being the cause of her saddle embolus.

## Conclusion

A morbidly obese patient presents with a recurrent PE 5 weeks after initiating rivaroxaban therapy for treatment of DVT and PE. While it is not currently recommended to dose adjust according to body weight, this case may open a question of whether a fixed dose of rivaroxaban ensures therapeutic efficacy in the morbidly obese population (BMI > 40 kg/m<sup>2</sup>) and whether more extensive monitoring should be employed in obese patients on rivaroxaban to better detect PE or DVT symptoms. Further studies are needed to assess differences in pharmacokinetics and pharmacodynamics of obese patients on rivaroxaban.

## References

1. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149(2):315-352. doi: 10.1016/j.chest.2015.11.026
2. Kubitza D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol*. 2010;70(5):703-712. doi: 10.1111/j.1365-2125.2010.03753.x
3. FDA approves Xarelto to reduce risk of blood clots after hip, knee replacements. U.S. Food and Drug Administration. 2014.
4. FDA approves Xarelto to prevent stroke in people with common type of abnormal heart rhythm. U.S. Food and Drug Administration. 2014.
5. FDA expands use of Xarelto to treat, reduce recurrence of blood clots. U.S. Food and Drug Administration. 2014.
6. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297. doi: 10.1056/NEJMoa1113572
7. Ansell J. New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. *Circulation*. 2012;125(1):165-170. doi: 10.1161/CIRCULATIONAHA.111.031153
8. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(6):1308-1313. doi: 10.1111/jth.13323
9. The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287-1297. doi: 10.1056/nejmoa1113572
10. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi: 10.1056/NEJMoa1007903
11. The EINSTEIN Investigators. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi: 10.1056/nejmoa1007903
12. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban in healthy subjects. *J Clin Pharmacol*. 2007;47(2):218-226.
13. Mueck W, Lensing AW, Agnelli G, Decousus H, Prandoni P, Misselwitz F. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure to simulations in patients with atrial fibrillation treated for stroke prevention. *Clin Pharmacokinet*. 2011;50(10):675-686. doi: 10.2165/11595320-000000000-00000
14. Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? *Am J Med*. 2001;110(7):515-519.
15. Hansson PO, Sörbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med*. 2000;160(6):769-774.
16. Palareti G. Recurrent venous thromboembolism: what is the risk and how to prevent it. *Scientifica (Cairo)*. 2012;2012:391734. doi: 10.6064/2012/391734
17. Patel JP, Roberts LN, Arya R. Anticoagulating obese patients in the modern era. *Br J Haematol*. 2011;155(2):137-149. doi: 10.1111/j.1365-2141.2011.08826.x
18. Eichinger S, Hron G, Bialonczyk C, Hirschl M, Minar E, Wagner O, et al. Overweight, obesity, and the risk of recurrent venous thromboembolism. *Arch Intern Med*. 2008;168(15):1678-1683. doi: 10.1001/archinte.168.15.1678
19. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8(11):2450-7. doi: 10.1111/j.1538-7836.2010.04044.x