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Please cite this article as: Lachant DJ, Bach C, Fe A, *et al*. DOAC Therapy in Patients With Morbid Obesity After Intermediate or High Risk Pulmonary Emboli. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00554-2020).

DOAC Therapy in Patients With Morbid Obesity After Intermediate or High Risk Pulmonary Emboli

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Take Home: Direct oral anticoagulants appear to be safe and effective in the management of acute pulmonary embolism in morbidly obese patients.

DJL, CB, AF, RJW, NAL all contributed to the study design, analysis of the results, writing the manuscript, and approved the manuscript.

There was no funding for this study and none of the authors have any conflict of interests.

Abstract: 248 words
Main Text: 2,795 words

DOAC Therapy in Patients With Morbid Obesity After Intermediate or High Risk Pulmonary Emboli

Abstract

Background:

There is little reported on the efficacy and safety of direct oral anticoagulants (DOAC) in morbid obesity after venous thromboembolism (VTE).

Methods:

This was an observational study of patients after intermediate- or high- risk pulmonary embolus (PE) who followed up in the University of Rochester Pulmonary Hypertension Clinic 2-4 months after the initial event with echocardiogram and V/Q imaging regardless of symptoms. Rates of recurrent VTE, thrombus resolution, and development of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with morbid obesity treated with a DOAC compared to vitamin K antagonists and non-morbidly obese patient after PE. Using the electronic medical record, recurrent events were assessed out to 12 months.

Results:

107 patients (32, BMI>40; 39, BMI 30-39.9; and 36, BMI<30) followed up after treatment for PE. A DOAC was used in 70 patients (19, BMI>40; 27, BMI 30-39.9; and 24, BMI<30). There were no recurrent events within the first 12 months of initial diagnosis based on symptoms and imaging in any patient. There was no difference in rate of residual unmatched perfusion defect with DOAC or conventional anticoagulation, 49% vs. 49%. This finding remained in the subset of morbidly obese patients at 47% vs 50%. For the overall cohort, there was no difference in the rate of CTEPH development based on anticoagulation with DOAC having a rate of 5% (vs. 8% with warfarin). There were no major bleeding complications with DOAC.

Conclusion:

DOAC therapy appears to be effective and safe in morbid obesity even after intermediate- or high- risk PE.

Introduction

Direct oral anticoagulants (DOAC) used for the treatment of venous thromboembolism (VTE) have been available for almost a decade and are favorably recommended over vitamin K antagonist therapy in the treatment of VTE[1,2]. There are two classes of DOACs currently approved for treatment of VTE: direct thrombin inhibitors (dabigatran[3]) and direct Xa inhibitors (rivaroxaban[4], apixiban[5], and edoxapan[6]). However, despite the clear advantages, DOACs are not often used in morbidly obese patients. The International Society of Thrombosis and Haemostasis (ISTH) recommends against DOAC use in patients with a BMI $\geq$40 kg/m^2 or weight >120 kg because of the lack of available safety and efficacy data. Further, if they are used, the ISTH recommends checking anti-Xa levels[7], even though therapeutic ranges have not been established for any DOAC. Interestingly, neither BMI nor weight were exclusionary criteria in any of the DOAC trials, and there is no evidence that DOAC therapy is ineffective in the morbidly obese. Unfortunately, this ISTH consensus has led many providers to avoid DOAC therapy in morbid obesity, and these patients are frequently warfarin treated despite the significant challenges in achieving therapeutic levels[8].

With the growing obesity epidemic, almost 40% of United States adults are considered obese [9] and ~7% are considered morbidly obese with a BMI $\geq$40 kg/m^2 [10]. Obesity is not only an independent risk factor for VTE [11-13] but is also associated with an increased risk for recurrent VTE[14]. Morbid obesity is even more prevalent among hospitalized patients (one estimate of 16%[15]), many of whom are likely to require some anticoagulation therapy during hospitalization. Therefore, an effective and easy to manage anticoagulation strategy in this population is critical to decrease their risk for long-term complications, including recurrent VTE. Our institutional approach to intermediate- and high-risk pulmonary embolism (PE)[16] includes programmatic follow-up for the majority of patients, many of whom were morbidly obese. We thus had an opportunity to address disease recurrence among people treated with DOAC and performed a single-center study observing the efficacy and

safety of DOAC and warfarin therapy. In particular, we explicitly compared morbidly obese to obese and non-obese patients.

Methods

This was an initially retrospective and subsequently prospective observational cohort study evaluating imaging and clinical outcomes after inpatient management for an intermediate- or high-risk PE at the University of Rochester Medical Center between November 2016 and June 2019. The study protocol (00003058) was approved by the University of Rochester Medical Center Institutional Review Board. Beginning in August, 2017, at the time of hospital discharge for an acute intermediate- or high risk- PE[16], all patients with estimated survival >1 year (based on the assessment of the discharging physician) were offered follow up at our Pulmonary Hypertension Association accredited Comprehensive Care Center. We scheduled a V/Q scan, echocardiogram, and office visit to assess for PE resolution or recurrent thrombosis. PE on initial CT angiogram was classified as saddle, main, lobar, or segmental depending on location of the most proximal clot. Ventilation perfusion scans were performed using 30 mCi of aerosolized Tc-99m-DTPA followed by intravenous administration of 2-4 mCi Tc-99m-MAA. Six standard projections were obtained for both sets of images using a large FOV dual head gamma camera fitted with general purpose parallel hole collimators, for a minimum of 100k counts per ventilation image and 500k counts per perfusion image. Residual unmatched perfusion defect at follow-up was defined as mismatched or partly mismatched segmental ventilation-perfusion defects. Board certified cardiologists using standardized criteria[17] interpreted echocardiograms. The pulmonary hypertension physicians (D.J.L and R.J.W.) made clinical and functional assessments. Once patients were optimized in regards to apparent volume status, we referred those in whom we expected pre-capillary pulmonary hypertension (PH) for right heart catheterization (RHC) with angiography to assess for CTEPH after at least three months of appropriate anticoagulation. Patients were classified as having confirmed CTEPH based on the hemodynamic definition from the 5th World Symposium[18] in the presence of

perfusion defects with angiography. Patients were classified as having "suspected CTEPH" if the clinical assessment strongly suggested CTEPH but patients declined catheterization for sensible reasons like advanced neurologic disease (dementia).

Statistical Analysis

Variables are expressed as mean +/- SD or median and interquartile range. Non parametric testing was performed with Mann-Whitney and Kruskal-Wallis testing using SAS 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was defined as $p<0.05$.

Results

One hundred and seven out of 122 patients followed up in our pulmonary hypertension clinic 2-4 months after management of acute intermediate- or high- risk PE with the demographics and presentation shown in Tables 1 and 2. Of the 15 that did not follow up, 2 died before their scheduled appointment because of complications related to malignancy (not VTE or bleeding mediated), 8 were never scheduled, and 5 did not show up. For these 13 patients not seen in clinic, electronic medical record evidence showed them to be alive and without evidence of recurrent pulmonary emboli or major bleeding. The majority of patients who followed up were obese with an average BMI of 35.7 (table 1); 32 patients had a BMI $\geq$40 kg/m^2 (morbid obesity) and 39 patients had a BMI between 30-39 kg/m^2 (obese, Table 1). The most common treatment during hospitalization was anticoagulation with heparin (either unfractionated or low molecular weight), while 28% received advanced therapies (e.g., thrombolytics; Table 2). At discharge, 67% of patients were prescribed a DOAC and 26% were prescribed warfarin (Table 2).

Table 1. Baseline Demographics

	BMI <30 (n=36)	**BMI 30-39 (n=39)**	**BMI $\geq$40 (n=32)**

Age (yrs)	69 (28, 93)	62 (29, 85)	50 (25, 75)
Male	23 (64%)	21 (54%)	14 (44%)
Caucasian	28 (78%)	32 (82%)	25 (78%)
BMI (kg/m^2)	27 (23, 29)	34 (30, 39)	46 (40, 68)
Active Smoking	3 (8%)	5 (13%)	4 (13%)
HFpEF	9 (25%)	15 (38%)	28 (88%)
CAD	4 (11%)	2 (5%)	4 (13%)
CKD >II	1 (3%)	2 (5%)	2 (6%)
Atrial Fibrillation	3 (8%)	4 (10%)	3 (9%)
Diabetes	6 (17%)	10 (26%)	9 (28%)
Hypertension	14 (39%)	25 (64%)	23 (72%)
Splenectomy	2 (6%)	2 (5%)	2 (6%)
Hypothyroidism	5 (14%)	8 (21%)	32 (6%)
Obstructive Sleep Apnea*	7 (19%)	11 (28%)	20 (63%)
Provoked	14 (39%)	11 (28%)	9 (28%)
Post-Operative	6 (17%)	9 (23%)	6 (28%)
Active Malignancy	6 (17%)	1 (3%)	0
Prior VTE	10 (28%)	7 (18%)	5 (16%)
Prior Gastric Bypass Surgery (Rou-En-Y)	1 (3%)	2 (5%)	2 (6%)

*Diagnosis made prior to presentation or after.

Table 2. Clinical Information at Presentation and During Hospitalization

	BMI <30 (n=36)	**BMI 30-39 (n=39)**	**BMI ≥40 (n=32)**
Pulmonary Embolus			
High Risk	4 (11%)	7 (18%)	1 (3%)
Intermediate Risk	32 (89%)	32 (82%)	31 (97%)
Duration of Symptoms (Days)	3 (1, 15)	1 (1, 4)	3 (1, 7)
Signs/Symptoms at Presntation			
Cardiac Arrest	1 (3%)	2 (5%)	0
Chest Pain	13 (36%)	19 (49%)	12 (38%)
Syncope	9 (25%)	7 (18%)	5 (16%)

Presyncope	6 (17%)	14 (36%)	9 (28%)
Dyspnea	29 (81%)	36 (92%)	29 (91%)
Hypoxia	20 (56%)	29 (74%)	18 (56%)
Admission NT-pro BNP (pg/ml)	1,698 (485, 4,497)	908 (473, 2,540)	1,161 (224, 3,564)
CT Imaging			
Saddle	12 (33%)	20 (51%)	6 (28%)
Main	10 (28%)	9 (23%)	12 (38%)
Lobar	11 (31%)	7 (18%)	11 (31%)
Right Heart Enlargement	30 (83%)	31 (79%)	23 (72%)
Echocardiogram			
Moderate/Severe Right Ventricular Enlargement	23 (63%)	24 (62%)	22 (69%)
Moderate/Severe Right Ventricular Dysfunction	20 (56%)	25 (64%)	20 (63%)
Confirmed DVT on Ultrasound	20 (56%)	22 (56%)	19 (59%)
Treatment			
Anticoagulation Only	26 (72%)	23 (59%)	28 (88%)
Advanced Therapies*	10 (28%)	16 (41%)	4 (12%)
Hospitalization Duration	5 (2, 8)	5 (3, 11)	4 (3, 7)
Anticoagulation on Discharge			
DOAC	24 (67%)	27 (69%)	19 (59%)
Apixaban	14 (39%)	15 (38%)	8 (25%)
Rivaroxaban	10 (28%)	12 (31%)	11 (34%)
Vitamin K antagonist	8 (22%)	10 (26%)	10 (31%)

*Systemic thrombolysis, catheter directed lysis, surgical embolectomy

Recurrent Events and Residual Perfusion Defect

Between hospital discharge and 6 months after the index event, no patients had diagnostic evidence for recurrent pulmonary embolus or DVT. At follow up, 68 patients who were taking DOAC and 35 taking warfarin or low-molecular weight heparin had V/Q testing regardless of symptoms (we evaluated four patients without V/Q imaging). 50 patients (49%) had residual unmatched perfusion defects. There was no difference whether patients were treated with DOAC or conventional

anticoagulation [33 out of 68 (49%) vs. 17 out of 35 (49%), p=0.99]. Similarly, there was no difference in the rate of residual unmatched perfusion defects in the subset of morbidly obese patients treated with a DOAC or conventional anticoagulation [9 (47%) vs 6 (50%) p=0.99, Table 3].

Chronic Thromboembolic Pulmonary Hypertension

At follow up, 59 patients (55%) reported self-limited activity because of breathlessness. Based on symptoms and imaging concerning for CTEPH, we diagnosed CTEPH in 8/11 patients that underwent RHC after the requisite 3 months of anticoagulation. One patient was directly referred for CTEPH surgery after index hospitalization without being seen in clinic, giving a total of 9 patients diagnosed with CTEPH (Table 3). We also recommended RHC and angiography in 11 patients who declined testing because of preference or severe cognitive impairment. If we include these patients who declined testing, we estimate a prevalence of >15% (15-20 patients) with confirmed or suspected CTEPH after intermediate- or high- risk PE (Table 3).

Table 3 Clinical Assessment 2-4 Months After Pulmonary Embolus

	BMI <30 (n=36)	**BMI 30-39 (n=39)**	**BMI ≥40 (n=32)**
Self-Limiting Activity	15 (42%)	22 (56%)	22 (69%)
New York Heart Association Functional Class	34	35	29
I	16 (47%)	18 (51%)	5 (17%)
II	16 (47%)	15 (43%)	19 (66%)
III	2 (6%)	2 (6%)	5 (17%)
6-Minute Walk Distance (meters)	395 (308, 496)	408 (351, 482)	338 (219, 407)
Decompensated Heart Failure*	6 (17%)	13 (33%)	22 (69%)

Iron Deficiency**	7 (19%)	10 (26%)	14 (44%)
New OSA Diagnosis at Follow Up	3 (8%)	12 (31%)	6 (19%)
Sleep Study Recommended but not completed	8 (22%)	9 (23%)	7 (22%)
Echocardiogram	35	39	32
RV Size			
Normal	23 (66%)	29 (74%)	14 (44%)
Mild Enlargement	8 (23%)	7 (18%)	16 (50%)
RV Dysfunction			
None	24 (69%)	26 (67%)	23 (72%)
Mild	10 (29%)	13 (33%)	6 (19%)
Residual Unmatched Perfusion Defects ***	18 (50%)	17 (44%)	15 (47%)
Recurrent VTE**	1 (3%)	0	0
Confirmed CTEPH	5 (14%)	2 (5%)	2 (6%)
Suspected CTEPH	2 (5%)	4 (10%)	5 (16%)
Total CTEPH	7 (19%)	6 (15%)	7 (22%)

*clinical diagnosis

**Criteria from FAIR-HF

***100 patients underwent V/Q testing. (3 patients in the heparin group and 1 embolectomy patient did not have testing).

**** Recurrent VTE occurred >1 year after the index event.

There was no difference in the rate of confirmed CTEPH whether patients were treated with DOAC or conventional anticoagulation [4 (6%) vs. 4 (11%), p=0.45]. There was no difference in the rate of confirmed CTEPH in morbid obesity when comparing DOAC with conventional anticoagulation [1 (5%) vs 1 (8%), p =0.99, Table 3]. Even if we assume that all patients for whom we recommended further testing had CTEPH, patients with morbid obesity treated with a DOAC did not have a higher rate of CTEPH compared to conventional anticoagulation therapy [2 (11%) vs 5 (41%), p=0.06].

There was no difference in the rate of CTEPH in the obese and non-obese patients based on type of anticoagulation.

Right Ventricular Recovery

At the time of acute presentation, the majority (63%) of patients had moderate or severe RV enlargement without differences between obese and non-obese patients (Table 2). At follow up, 106 patients had an echocardiogram, 69 treated with a DOAC (19 morbidly obese) and 37 treated with conventional warfarin or enoxaparin anticoagulation (13 morbidly obese, Table 3). In total, 97 patients had a normal or mildly enlarged right ventricle, and 9 had a moderately enlarged right ventricle (Table 3). 102 patients had a normal or mildly reduced right ventricular function, and 4 had moderately reduced function (Table 3).

There was no difference in the rate of having a normal or mildly enlarged right ventricle at follow up when comparing DOAC to conventional therapy, 63 (92%) vs 34 (92%) (Table 3). Eighteen (95%) morbidly obese patients treated with a DOAC had a normal or mildly enlarged RV at follow-up compared to 12 (92%) warfarin or enoxaparin treated morbidly obese patients (Table 3). Similarly, there were no differences between the obese and non-obese groups.

There was no difference in the rate of recovery in right ventricular function (normal or mildly reduced at follow up) comparing DOAC to conventional anticoagulation, 68 (99%) vs. 34 (92%). Eighteen of nineteen (95%) morbidly obese patients treated with DOAC therapy had normal or mildly impaired right ventricular function while 11/13 (84%) treated with conventional anticoagulation had a normal or mildly impaired right ventricle, p=0.55.

NT-pro BNP and 6-Minute Walk (6MW) Assessment

At follow up, 55 patients had a NT-pro BNP checked because of breathlessness or signs of heart failure, 22 morbidly obese (13 on DOAC therapy and 9 on conventional therapy), 18 obese (10 on DOAC and 8 on conventional therapy), and 15 non-obese (10 on DOAC and 5 on conventional

therapy). Due to staffing limitations, only 58 patients completed a 6MW regardless of symptoms, 16 of whom were morbidly obese (9 on a DOAC and 7 on conventional therapy).

There was no difference in NT-pro BNP when comparing patients treated with a DOAC to conventional therapy (97 pg/ml vs 167 pg/ml, p=0.13), for the entire cohort. There was no difference in NT-pro BNP based on DOAC vs conventional therapy in morbid obesity (97 pg/ml vs 183 pg/ml, p=0.19). There was no difference in 6MW distance based on DOAC vs conventional therapy (399 m vs 338 m p=0.09), for the entire cohort or for the 3 subgroups based on BMI.

Bleeding

There were two patients on non-DOAC therapy with bleeding complications requiring intervention. One morbidly obese patient treated with warfarin developed hematuria in the setting of an elevated INR and required hospitalization. Another morbidly obese patient developed a spontaneous retroperitoneal bleed on low-molecular weight heparin requiring hospitalization. No patients on DOAC therapy were hospitalized due to bleeding complications. One morbid obesity patient required dose reduction from 20 mg to 10 mg of rivaroxaban because of gingival bleeding in the setting of poor dentition. The bleeding stopped and there were no further complications at this dose.

Discussion

In an observational cohort of higher-risk pulmonary embolus patients, we report that 1) DOAC therapy in morbidly obese patients was not associated with an increased risk of recurrent VTE compared to warfarin anticoagulation therapy within 6 months of management of acute PE, and 2) these higher risk patients had recovery of RV function on DOAC therapy similar to those treated with warfarin (even among morbidly obese). This work is strengthened by the rigorous follow up and imaging acquisition in almost all patients regardless of symptoms.

Fixed dose DOAC therapies have greatly simplified management of acute pulmonary embolus by preventing recurrent VTE without the need for laboratory monitoring and the associated effort to make warfarin dose adjustments. For patients, the 'real-world' rates of bleeding are low[19], and there's relatively little concern for drug-diet or drug-drug interactions [20]. The initial concern about using fixed dose DOAC therapy in morbid obesity was understandable. Both unfractionated and low-molecular weight heparin are weight based drugs, and vitamin K antagonist doses are typically higher in morbid obesity[8]. Theoretically, it would make sense that morbidly obese patients would require higher doses of DOAC therapy based on a fixed dose diluted in a larger volume of distribution, but limited pharmacokinetic and pharmacodynamic studies evaluating DOAC in morbid obesity suggest weight does not influence dosing [21-25]. Furthermore, there is no clear relationship between drug levels and clinical outcomes like VTE recurrence or bleeding[3-6]. No therapeutic range of Xa inhibition is established for DOAC. Given the difficulty in achieving therapeutic levels with warfarin[8], having a simplified option could decrease recurrent events.

The current consensus guidelines from ISTH[7] and the European Society of Cardiology [26] both caution against using DOAC therapy for a BMI >40 kg/m^2; if DOACs are used, these documents recommend measurement of anti-Xa activity despite the fact that no therapeutic range has been established. The American Society of Hematology does not address morbid obesity in their 2018 VTE guidelines[27]. Papers being published today still caution against DOAC use in morbidly obese patients due to lack of clinical data with calls for prospective trials to be completed before DOAC use can be recommended in this population[28-30]. However, at least one meta-analysis found no reduction in efficacy in the registration trials when looking at obese vs. non-obese patients[31]. To the best of our knowledge, there are no active clinical trials evaluating DOAC therapy for VTE in morbid obesity (clinicaltrials.gov October 2020).

The majority of the patients included in the original DOAC clinical trials were low risk VTE and not obese. However, it is important to note that neither BMI nor weight was an exclusionary criteria in

the registration trials. A meta-analysis determined that 20% of participants in the registration trials were 'high body weight' at randomization (either >100 Kg or >90 kg)[31]. None of the registration trials reported event rates specifically in morbid obesity, but they did report no differences in recurrent events in the high body weight groups treated with DOAC versus conventional therapy[3-6].

Recurrent VTE events often occur within 3-6 months at of a rate of 4-8% [32,33] and typically present in a similar manner as the index event[34,35]. With obesity being a risk factor for initial [11-13] and recurrent VTE[14], if effective anticoagulation was not provided, the observed VTE recurrence rate would likely be much higher than the reported baseline of ~4-8%. We did not observe an elevated recurrence rate in our cohort. There is evolving retrospective data on the efficacy of DOAC therapy in morbid obesity. Kushnir et al. used single center chart review and determined a 2% risk for recurrent VTE in 366 morbidly obese (BMI >40 kg/m^2) patients with any DOAC-treated VTE event [36]. Using two US claims databases, Spyropoulos et al. found similar rate of risk of recurrent thrombotic events in morbid obesity[37]. Although both studies relied on coding, their findings are real world evidence that DOAC are effective in morbid obesity. We don't know if some of their recurrent VTE could have been unrecognized CTEPH or chronic clot.

We complement these larger studies with rigorous clinical followup and detailed chart review including echocardiogram, V/Q scan, and right heart catheterization. We did not observe any recurrent PE within the first year in any of patients, regardless of weight group or type of anticoagulation. We were able to differentiate CTEPH from recurrent PE. Furthermore, we did not observe any difference in the resolution of thrombotic disease on perfusion lung scanning, and DOAC treated patients were just as likely to achieve RV recovery (an indirect measure that pulmonary circulation obstruction is no longer present) after higher risk PE. Our numbers are small, but DOAC did not appear to leave patients at higher risk for CTEPH. None of the registration clinical trials reported rates of CTEPH development, and given the large numbers of patients involved, CTEPH would be expected in some patients. Our data strengthens a growing body of literature

supporting the clinical efficacy of DOAC therapy in morbid obesity as none of the previously reported studies detail follow up data on imaging and physiologic recovery.

There are limitations to our study. We have a small number of morbidly obese patients on DOAC therapy which took 2 years to collect. However, given that this is a high risk group, DOAC failure with recurrent events should have been observed. Our data are observational and anticoagulation was chosen based on the preference of the discharging attending and patient. Peak and trough drug concentrations were not measured, and we have no measurements of anti- Xa levels. We only included patients who had an intermediate- or high-risk pulmonary embolus. We did not include atrial fibrillation in our analysis and therefore our results may not be applicable to patients with BMI >40 kg/m^2 and atrial fibrillation.

In conclusion, we found that DOAC therapy does not put patients with morbid obesity at higher risk for recurrent VTE after intermediate- or high- risk PE compared to warfarin anticoagulation; we observed similar outcomes in obese and non-obese patients. Perfusion lung scanning did not suggest a difference in the rate of thrombus resolution, and echocardiography suggested similar rates of right ventricular recovery regardless of anticoagulation choice. In patients with PE, we believe that the available evidence makes DOAC therapy a reasonable option even in morbid obesity; we propose prospective clinical trials to address this directly.

Acknowledgements: None

There was no financial support for this study.

Citation

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