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Early View

Research letter

Use of direct oral anticoagulants for acute pulmonary embolisms in obesity: a propensity matched multicenter case-control study

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Use of direct oral anticoagulants for acute pulmonary embolisms in obesity: a propensity matched multicenter case-control study.

Short title: Direct oral anticoagulants for pulmonary embolisms in obesity

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Take home message: We assessed efficacy and safety of DOACs in treatment of pulmonary embolisms in obese patients. The findings provide reassurance that treatment with DOACs carries similar rates of recurrent VTE and bleeding complications compared to warfarin.

Keywords: Pulmonary embolism, Venous Thromboembolism, Obesity, Anticoagulants Factor Xa Inhibitors.

Direct oral anticoagulants (DOACs) are widely used as first-line treatment for pulmonary embolism (PE) in patients without contraindications,[1] however limited data exists on the efficacy and safety in obesity. The most recent International Society of Thrombosis and Haemostasis (ISTH) guidelines recommend avoiding DOACs in individuals with body mass index (BMI) >40 kg/m^2 or a body weight >120kg, due to lack of robust clinical efficacy data. Obtaining serum drug levels for therapeutic monitoring in this population has been suggested, however testing of DOAC levels is neither widely available nor well validated in real-world clinical settings.[2] Given the ongoing uncertainty regarding the clinical outcomes with DOACs in treating acute PE in obese patients, this study aimed to evaluate the efficacy and safety of DOACs compared to warfarin in this population.

We conducted a multisite propensity scores matched case-control study combining databases from three hospitals in Queensland, Australia. The Venous Thromboembolism (VTE) database at Princess Alexandra Hospital (January 2015 to January 2020) and Patient Admission Records databases from Logan Hospital (January 2018 to January 2020) and Sunshine Coast University Hospital (January 2018 to January 2020) were screened to identify consecutive patients admitted with acute PE. Patients discharged directly from the emergency department were excluded as follow-up data was less reliable. Patients aged >18 years who had a BMI >30 kg/m^2 and were initiated on any oral anticoagulant (DOACs or warfarin) during the hospital admission were eligible. Patients who had other indications for anticoagulation or recurrent VTE were excluded. Demographic, clinical characteristics at diagnosis and outcome data were collected for eligible patients from the state-wide Electronic Medical Record. Ethical approval for this study was granted by the local Research Ethics Committee (HREC/2019/QMS/57882).

The primary outcome was the rate of recurrent VTE within six months of commencing anticoagulation, confirmed on diagnostic imaging. Secondary outcomes included I) rate of major, clinically relevant non-

major and minor bleeding as defined by the International Society of Thrombosis and Haemostasis guidelines[3], II) all-cause mortality at 30-days and six months following the PE and III) length of hospital stay.

Propensity scores were generated for eligible patients using a logistical regression model with pre-specified variables. Propensity score analysis is a statistical method used to control for selection bias in observational studies.[4] Anticoagulation type (DOAC vs warfarin) was used as the dependent variable and the covariates included age, gender, pulmonary embolism severity index (PESI) score, BMI, estimated glomerular filtration rate (eGFR) and raised cardiac troponin. Propensity scores were matched to generate a DOAC group and a warfarin group at a 2:1 ratio using caliper width equal to 0.3 of the standard deviation of the propensity score. It was estimated that a target sample size of 58 patients per group were required, with rate of VTE recurrence of 5% at six-months in both groups, and a clinically significant difference set at 10% (80% power and 5% significance), using the principles of two-sample equivalence tests for proportions.[5] Outcome measures were determined on an intention-to-treat basis. The non-parametric continuous variables were compared between the two groups using the Mann-Whitney test. The analysis was performed on SPSS Statistics V27 with the Python based extensions Fuzzy and PSM (IBM Corp.,Armonk, NY, USA).

There were 1682 hospital presentations with acute PE during the study period across the three sites, and 848 were discharged directly from emergency department. A total of 271 adult obese patients with a median age of 59 years (IQR 41 to 78) met inclusion criteria, and 231 underwent propensity score matching to the DOAC group (N=154) and warfarin group (N=77). No appropriate match found for 40 patients. The mean body weight of the study group was 123kg (range 87 to 235kg). The study population included 150 (64.9%) patients who were morbidly obese (BMI >40 kg/m^2 or weight >120kg), of which 36 (15.6%) patients had a body weight >160kg. The two groups were well matched at baseline (Table 1.0). The intended duration of anticoagulation was ≥6 months in all patients. Nine patients were lost to follow-up: 7 (4.5%) in the DOAC group and 2 (2.6%) in the warfarin group.

On intention to treat analysis, recurrent VTE at six-months occurred in 5.8% (n=9) of patients in the DOAC group compared to 6.6% (n=5) in the warfarin group (OR 0.89; 95%CI 0.3-2.8, p=0.85). The

sensitivity analysis excluding patients lost to follow-up or deceased within the study period showed similar rates of recurrent VTE (6.3% in DOAC group vs 7.1% in warfarin group, OR 0.90; 95%CI 0.3-2.7). The overall rate of bleeding events was 14.3% (n=22) in the DOAC group and 16.9% (n=13) in the warfarin group (OR 0.82; 95%CI 0.4–1.7, p = 0.60). The rate of 30-day mortality was 1.3% (n=2) in the DOAC group compared to 3.9% (n=3) in the warfarin group (OR 0.32; 95%CI 0.1-2.0, p = 0.22). Amongst the patients who had a BMI >40 kg/m^2 or weight >120kg, the rate of recurrent VTE was 5.8% (n=6) in the DOAC group compared to 6.8% (n=3) in the warfarin group, and bleeding events occurred in 9.6% (n=10) in the DOAC group compared to 15.2% (n=7) in the warfarin group. In patients who had intermediate or high-risk PE, the rate of recurrent VTE was 4.3% (n=5) in the DOAC group compared to 6.6% (n=4) in the warfarin group.

This case control study assessed outcomes at six-months in obese patients with acute PE requiring hospital admission who received treatment with DOACs compared to warfarin. Treatment with DOACs carries similar rates of recurrent VTE and overall bleeding complications compared to warfarin. As none of the patients in the DOAC group had treatment adjustments based on therapeutic drug monitoring, our findings are directly applicable to real-world clinical settings where serum DOAC level measurements may not be routinely available.

Major bleeding events were rare and clinically relevant non-major bleeding events were similar between the two groups. Most of these bleeding events occurred within the first two months of discharge from hospital. Previous studies comparing DOACs to warfarin have indicated a trend towards lower bleeding with DOACs, and is evident in patients who have both normal and elevated BMI.[6-8]. However, there is also evidence indicating that each DOAC may have differences in outcomes when used in obese patients,[9] and studies comparing different DOACs in this patient population are needed. An increased average length of hospital stay following PE was observed in the warfarin group (7.9 days vs 5.1 days in the DOAC group, p=0.01), mostly due to patients awaiting therapeutic INR levels prior to discharge. The longer length of hospital stay in patients initiated on warfarin for VTE compared to DOACs has been shown in previous studies [10, 11], and is associated with higher healthcare costs.[12]

A strength of our study is the propensity score matched study groups, which reduces bias associated with the case-controlled design. Furthermore, the patients were well phenotyped at baseline and extensively risk stratified. Our results are concordant with the findings of a recent meta-analysis combining observational studies on DOACs for treatment of VTE.[7] Coons et al, also reported similar recurrent VTE rates of 6.5% with DOACs compared to 6.4% with warfarin at 12-months in patients with a body weight >100kg who had any form of VTE.[13] In a large registry based retrospective study of obese patients with all forms of VTE, Spyropoulos et al also showed similar efficacy between rivaroxaban and warfarin with recurrent VTE rates of 16.8% and 15.9% at 12 months retrospectively.[12] Recent evidence also suggests that's DOACs may have similar risks of long-term complications including chronic thromboembolic pulmonary hypertension compared to warfarin in morbidly obese patients with intermediate or high-risk PE.[14]

This study has several limitations. INR monitoring and warfarin dose adjustments were carried out in the community in line with routine clinical practice, and we were therefore unable to account for the effect of sub- or supratherapeutic INR on outcome measures. The number of patients who received apixaban was very small, therefore meaningful comparison of DOAC subtypes could not be performed. As majority of the patients received rivaroxaban, the applicability of the findings to other DOACs is limited. The impact of different initial high dose administration durations (3 weeks for rivaroxaban and 7 days for apixaban) may be an important consideration in this patient group in the event of potential underdosing related to bodyweight. The study excluded patients discharged directly from the emergency department, which may impact on generalisability of the results, particularly in patients with lower risk PE. Few patients in our study had extreme obesity, and the management of such patients (e.g body weight >160 kg) requires further research.

In summary, our study adds to the emerging evidence regarding the efficacy and safety of treating PE with DOACs in obese patients in a real-world clinical setting without anti-factor-Xa or serum DOAC level measurements guiding treatment. The rate of recurrent VTE and bleeding complications at six-months were similar between DOACs and warfarin. Larger studies are needed to assess for differences in outcome according to subtype of DOAC in this patient population.

Table 1.0: Baseline characteristics and outcomes of study participants

Characteristics		DOAC N = 154	Warfarin N = 77	P
Baseline characteristics				
Demographics				
Age / years (median/ IQR)		60.1 (36.2-84.1)	59.0 (35.4-82.3)	0.83
Gender female (n/ %)		83 (53.9)	41 (53.2)	0.92
Anthropometrics				
Height in cm (mean/ SD)		170.9 (9.3)	170.8 (9.0)	0.91
Weight in kg (mean/ SD)		122.4 (22.6)	125.9 (33.5)	0.82
BMI kg/m^2 (mean/ SD)		42.0 (7.5)	43.3 (11.8)	0.74
BMI > 40 kg/m^2 or weight > 120kg (n/ %)		104 (67.5)	46 (59.7)	0.24
Clinical parameters on presentation				
First recorded SBP in mmHg (mean/ SD)		128.1 (21.5)	124.5 (25.7)	0.31
First recorded heart rate (mean/ SD)		96.5 (19.1)	96.6 (18.1)	0.89
SpO2 < 94% on presentation (n/ %)		73 (47.4)	40 (51.9)	0.51
History of malignancy (n/ %)		16 (10.4)	6 (7.8)	0.43
PESI score (mean/ SD)		86.1 (29.9)	88.7 (33.7)	0.56
PESI score	Class V - Very high risk (n/ %)	14 (9.1)	7 (9.1)	-

	Class IV – High risk (n/ %)	19 (12.3)	11 (14.3)	0.24
	Class III – Moderate risk (n/ %)	49 (31.8)	24 (31.2)	0.89
	Class II – Low risk (n/ %)	29 (18.8)	15 (19.5)	0.78
	Class I – Very low risk (n/ %)	43 (27.9)	20 (26.0)	0.67
CTPA characteristics				
Most proximal clot location	Saddle/ Main PA (n/ %)	36 (23.4)	13 (16.7)	0.47
	Lobar arteries (n/ %)	66 (42.9)	36 (46.8)	0.78
	Segmental (n/ %)	25 (32.5)	46 (30.0)	0.81
Clot number	Bilateral	133 (86.3)	62 (80.5)	0.50
RHS on CTPA (n/ %)		97 (63.3)	51 (66.2)	0.83
Echocardiographic parameters				
LV impairment (n/ %)		16 (12.7)	7 (11.3)	0.76
RV impairment (n/ %)		78 (61.9)	39 (60.0)	0.89
RV dilatation (n/ %)		92 (73.1)	41 (66.1)	0.46
RVSP in mmHg (mean/ SD)		43.5 (12.4)	43.9 (10.5)	0.85
Laboratory markers				
Elevated troponin (n/ %)		72 (62.6)	29 (64.4)	0.88
Lactate on presentation mmol/L (mean/ SD)		2.3 (1.4)	2.5 (1.6)	0.52
eGFR / mL/min/1.73m^2 (mean/ SD)		68.1 (15.5)	67.3 (20.2)	0.78
Pulmonary embolism risk category				
Low risk		39 (25.3)	16 (20.8)	0.45
Intermediate-low risk		45 (29.2)	30 (39.0)	0.14
Intermediate-high risk		57 (37.0)	22 (28.6)	0.24
High risk		13 (8.4)	9 (11.7)	0.48
Initial treatment				
Intravenous heparin infusion (n/ %)		66 (42.9)	40 (51.9)	0.11
Low molecular weight heparin (n/ %)		53 (34.4)	28 (36.4)	0.69
Thrombolysis and heparin (n/ %)		13 (8.4)	9 (11.7)	0.62
Upfront DOAC		22 (14.3)	-	-
Type of DOAC and maintenance dose				
Rivaroxaban 20mg daily (n/ %)		141 (91.6)	-	-
Apixaban 5mg twice a day (n/ %)		13 (8.4)	-	-
Outcomes at follow-up				
Recurrent VTE within six months (n/ %)				
All recurrent VTE (n/ %)		9 (5.8)	5 (6.5)	0.85
Recurrent PE (n/ %)		4 (2.6)	3 (3.9)	0.59
Bleeding within 6 months				

Major bleeding (n/ %)	1 (0.6)	2 (2.6)	0.25
CRNM bleeding (n/ %)	7 (4.5)	6 (7.8)	0.22
Minor bleeding (n/ %)	14 (9.1)	5 (6.5)	0.58
Mortality			
30-day all-cause mortality (n/ %)	2 (1.3)	3 (3.9)	0.22
Six-months all-cause months (n/ %)	4 (2.6)	5 (6.5)	0.16
Length of hospital stay in days (mean / SD)	5.1 (3.8)	7.9 (4.1)	**0.01**

DOAC = direct oral anticoagulant; IQR = Interquartile range; SD = standard deviation; BMI = body mass index; PA = pulmonary artery; RHS = right heart strain; CTPA = computed tomography pulmonary angiogram; SBP = systolic blood pressure; SpO2 = oxygen saturation; PESI = pulmonary embolism severity index; LV = left ventricle; RV = right ventricle, RVSP = right ventricular systolic pressure; CRNM = clinically relevant non-major

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