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# Direct oral anticoagulants in patients with chronic thromboembolic pulmonary hypertension and the presence of recent thrombus during pulmonary endarterectomy

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## Abstract

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) require lifelong anticoagulant therapy. The safety and efficacy of direct oral anticoagulant (DOAC) in the chronic and transitional management of CTEPH has not been investigated. We performed a retrospective analysis of 405 consecutive pulmonary endarterectomy (PEA) cases at the University of California, San Diego, from July 2015 through July 2017. PEA specimen was reviewed for the presence of acute or subacute thrombotic material distinct from the expected chronic disease removed at the time of PEA by two investigators blinded to the patient information. Of 405 PEA cases, 166 patients (41.0%) were anticoagulated with one of three available DOACs; 239 (59.0%) presented on either oral vitamin-K antagonist or chronic injectable therapy. There were no significant differences in baseline characteristics between DOAC and non-DOAC groups. Evidence of recent thrombus was observed in 22 (13.3%) in the DOAC group versus 16 (6.7%) within the non-DOAC group. The odds ratio of DOACs usage and evidence of recent thrombus was 2.34 (95% confidence interval: 1.1–5.0, $p = 0.03$) after adjusting for age, gender, race, body mass index, and history of antiphospholipid antibody syndrome. CTEPH patients referred for PEA while on DOAC therapy were twice as likely to have associated acute or subacute thrombi present at the time of surgery compared with those on more traditional, non-DOAC anticoagulant therapies. This raises questions of the safety and efficacy of DOACs in the chronic management of CTEPH.

**KEYWORDS**
anticoagulation, chronic thromboembolic pulmonary hypertension, direct oral anticoagulant, pulmonary endarterectomy, vitamin-K antagonist

## INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of pulmonary embolism resulting in the formation of chronic, fibrotic organized thrombi within the pulmonary arteries leading to pulmonary hypertension.[1] Pulmonary thromboendarterectomy, also referred to as pulmonary endarterectomy (PEA), is the treatment of choice to remove these obstructive defects from the pulmonary arteries. Lifelong anticoagulation therapy is also recommended for all patients with CTEPH. The rationale for anticoagulation in CTEPH is to prevent both recurrent venous thromboembolism as well as in situ pulmonary artery thrombosis.[2] Traditionally, oral vitamin-K antagonist (VKA) was the principal option for chronic oral anticoagulation in CTEPH.[3,4] In recent years, there has been increased use of new classes of direct oral anticoagulants (DOACs) for anticoagulation therapy including patients referred with CTEPH. The data supporting the use of the DOACs in acute pulmonary embolism is robust (AMPLIFY, EINSTEIN, RECOVER trials),[5–7] leading to their use in CTEPH. However, the data are lacking regarding the safety and efficacy of DOACs specifically in CTEPH.[3] Accordingly, we conducted a retrospective analysis of the method of anticoagulation in patients with CTEPH before PEA and assessed the surgical specimens for the presence of recent thrombus to determine if there were differences between patients treated with conventional anticoagulants versus DOACs.

## METHOD

### Patient selection

The study population included all patients who had been diagnosed as CTEPH and underwent PEA at UCSD hospital between July 1, 2015, and July 1, 2017. The diagnosis of CTEPH was established according to current guidelines.[3] Surgical candidacy and operability were evaluated and established by a multidisciplinary CTEPH team. Patients who had PEA but were finally diagnosed as sarcoma, tissue-proven primary or metastatic cancer at the pulmonary vessel, septic embolus due to infection, and chronic kidney disease (estimated glomerular filtration rate less than 60 ml/min/1.73 $m^2$) were excluded. Antiphospholipid antibody syndrome (APS) was defined as anticardiolipin immunoglobulin positive or lupus anticoagulant test positive using dilute Russell viper venom test—either documented in the past or confirmed before surgery. At the time, beta-2-glycoprotein was not checked routinely on all PEA cases. All patients were bridged from either VKAs or DOACs before surgery with subcutaneous low molecular weight heparin (LMWH) regardless of their chronic anticoagulation therapy. All patients on oral anticoagulation therapy were instructed to stop 5 days before intervention. For patients on a DOAC, LMWH started the next day after stopping DOAC; for VKA patients, LMWH was started on the second day after stopping VKA.

We classified patients as either conventional anticoagulation group (non-DOACs group) who were anticoagulated with either oral VKA or chronic subcutaneous LMWH versus DOACs group who used apixaban, dabigatran, or rivaroxaban as their oral anticoagulation therapy leading up to PEA. Clinical data were compared between these two groups. This study has been granted an exemption from the UCSD IRB to be conducted using our internal quality improvement database.

### Definition of acute or subacute thrombus

Two investigators (T. M. F., N. H. K.) who were blinded to patients independently reviewed the photos of specimens for evidence of recent thrombus. Recent thrombus was defined as a fresh, red-appearing blood clot formation inside or along the pulmonary artery and not seen in the setting of a pouch defect (Figure 1A,B). Figure 1C is an example of an endarterectomy specimen without recent thrombus. In cases of discrepant adjudication, the respective surgeon who performed the PEA (M. M., V. P.) made the final ruling.

### Statistical analysis

Continuous variables were expressed as mean ± standard deviation of the mean or as median values (interquartile range, IQR). Categorical variables are expressed as numbers and percentages and were analyzed by $\chi^2$ or Fisher exact test analysis. The student's *t*-test was used to compare means from normally distributed variables. All statistical tests were two-sided and used a significance level of 0.05. To identify the factors with recent thrombus formation in CTEPH specimens, univariate and multivariate logistic regression analyses were used. Multivariate logistic regression analysis was conducted adjusting factors not only significant in univariate analysis such as gender, body mass index (BMI), history of an indwelling catheter, splenectomy, hypertension, total number of risk factors for CTEPH and use of DOACs but also considered as potential risk factors for venous thromboembolism such as age, race, and history of APS. Results of logistic regression are reported as odds ratio

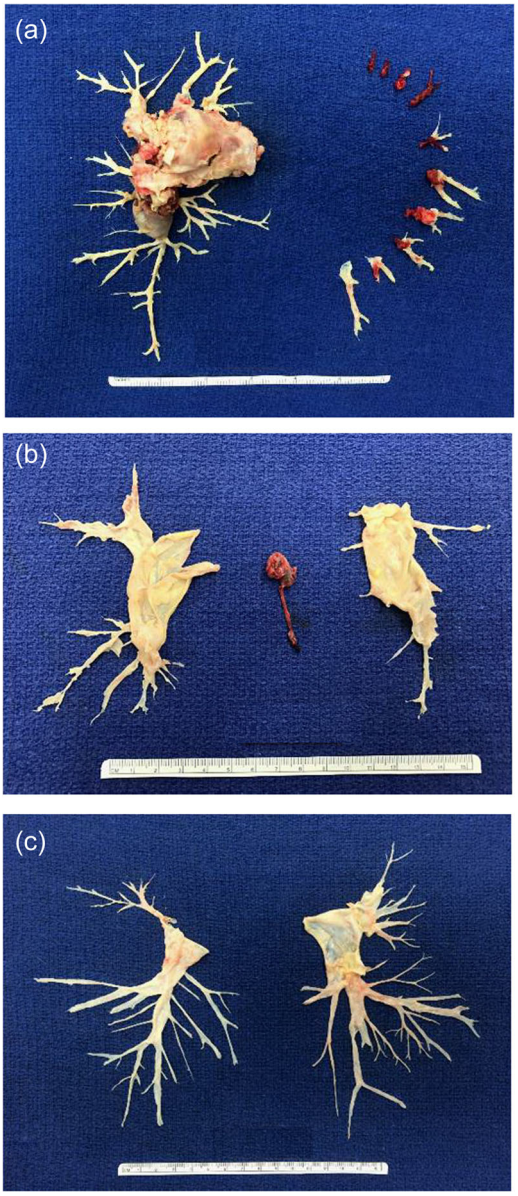


**FIGURE 1** Pulmonary endarterectomy specimen. Presence of recent thrombi removed in addition to chronic material (a, b), versus only chronic organized material without recent thrombus (c).

(OR) estimates with 95% confidence intervals (CIs). All statistical analyses were performed using SPSS v18.0 (SPSS).

# RESULTS

## Patient characteristics

Of the 419 PEA cases included in the study population, 14 cases were excluded from the analysis based on exclusion criteria (12 cases of sarcoma, 1 metastatic carcinoma, 1 septic emboli case) (Figure 2). Among 405 included cases, 239 (59.0%) presented on either oral VKA or injectable LMWH (34 patients); 166 patients (41.0%) were anticoagulated with DOACs. In DOACs treated group, most of the patients were prescribed direct factor Xa inhibitors rivaroxaban (114, 68.7%), and apixaban (40, 24.1%). Dabigatran, a direct thrombin inhibitor, was prescribed in 12 (7.2%) patients. There were no significant differences in the preoperative characteristics of the patients treated with conventional anticoagulation compared to those treated with DOACs (Tables 1–3). The reason reported for prescribing DOACs was mainly due to relative convenience of DOACs. One patient could not tolerate warfarin. There were no significant differences in baseline characteristics, past histories of thromboembolic disease, and severity of CTEPH between DOACs and non-DOACs groups (Tables 1 and 2). Also, the incidence of bleeding history before and in the perioperative period was not significantly different between the groups: 17 (7.1%) in non-DOACs group versus 10 (6%) in DOACs group, $p$ value = 0.67. The prevalence of APS as well as other CTEPH risk factors was similar in both groups (Table 2). There were 44 (18.4%) of conventional anticoagulation group and 21 (12.7%) of DOACs group patients who had APS, respectively ($p$ value = 0.12). Of the 65 patients with APS, 30 patients had used DOACs at least once during the disease course, and 21 patients were still on DOACs before PEA referral.

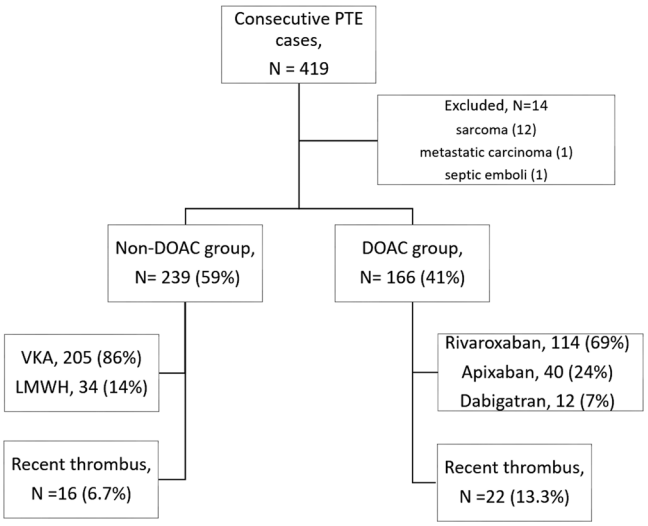


**FIGURE 2** Patient flow chart.

## Thrombus detection

Overall, 38 patients had evidence of recent thrombus found in the postoperative specimen. In univariate

**TABLE 1** Patient characteristics

| | Non-DOACs group | DOACs group | *p* Value |
|---|---|---|---|
| Number, (%) | 239 (59) | 166 (41) | |
| Age, Median (years) | 54.8 ± 15.5 | 54.5 ± 15.0 | 0.846 |
| Gender, male, *n* (%) | 136 (56.9) | 93 (56) | 0.861 |
| Body mass index (kg/m$^2$) | 30.9 ± 8.0 | 30.0 ± 7.6 | 0.269 |
| Race, *n* (%) | | | 0.994 |
| White | 169 (70.7) | 119 (70.5) | |
| African American | 40 (16.7) | 30 (18.1) | |
| Hispanic | 17 (7.1) | 11(6.6) | |
| Asian | 3 (1.3) | 2 (1.2) | |
| Mixed, Arabic | 10 (4.2) | 6 (3.6) | |
| Smoking, *n* (%) | | | 0.325 |
| Never smoker | 147 (61.5) | 112 (67.5) | |
| Current smoking | 11 (4.6) | 4 (2.4) | |
| Past smoking | 81 (33.9) | 50 (30.1) | |
| Smoking, py | 25.9 ± 29.7 | 18.6 ± 19.8 | 0.127 |
| Comorbidities, *n* (%) | | | |
| Diabetes | 38 (15.9) | 18 (10.8) | 0.147 |
| Hypertension | 99 (41.4) | 70 (42.2) | 0.881 |
| Coronary artery disease | 39 (16.3) | 27 (16.3) | 0.989 |
| Atrial fibrillation | 19 (7.9) | 23 (13.9) | 0.055 |
| Dyslipidemia | 63 (26.4) | 38 (22.9) | 0.428 |
| History of DVT, *n* (%) | 126 (52.7) | 85 (51.2) | 0.764 |
| History of DVT, multiple, *n* (%) | 41 (17.2) | 21 (12.7) | 0.216 |
| History of pulmonary embolism, *n* (%) | 233 (97.5) | 159 (95.8) | 0.338 |
| History of pulmonary embolism, multiple, *n* (%) | 55 (23) | 37 (22.3) | 0.463 |
| History of thrombolysis, *n* (%) | 12(5.0) | 12 (7.2) | 0.355 |
| History of IVC filter, *n* (%) | 69 (29%) | 41 (24.7) | 0.340 |
| Supplemental oxygen, *n* (%) | 116 (48.5) | 74 (44.6) | 0.433 |
| Preoperative PH medication | 117(49%) | 95 (57.2%) | 0.101 |
| Preoperative NYHA functional class, *n* (%) | | 0.725 | |
| I | 5 (2.1) | 3 (1.8) | |
| II | 44 (18.4) | 29 (17.5) | |
| III | 167 (69.9) | 123 (74.1) | |
| IV | 23 (9.6) | 11 (6.6) | |

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; IVC, inferior Vena Cava; NYHA. New York Heart Association; PH, pulmonary hypertension; py, pack year.

**TABLE 2** Associated conditions

| Risk factors | Non-DOACs group, *n* (%) | DOACs group, *n* (%) | *p* Value |
|---|---|---|---|
| Antiphospholipid syndrome | 44 (18.4) | 21 (12.7) | 0.120 |
| Obstructive sleep apnea | 74 (31) | 46 (27.9) | 0.505 |
| COPD | 15 (6.3) | 11 (6.6) | 0.887 |
| History of congenital heart disease, ASD or PFO | 41 (17.2) | 28 (16.9) | 0.940 |
| History of illicit drug | 17 (7.1) | 13 (7.8) | 0.786 |
| History of anorexic drug | 6 (2.5) | 3 (1.8) | 0.743 |
| History of splenectomy | 6 (2.5) | 7 (4.2) | 0.338 |
| Hypothyroidism | 29 (12.1) | 19 (11.4) | 0.833 |
| Indwelling catheter | 10 (4.2%) | 6 (3.6%) | 0.772 |
| Hematologic disorder | 13 (5.4) | 11 (6.6) | 0.619 |
| Coagulopathy | 18 (7.5) | 22 (13.3) | 0.058 |
| History of malignancy | 31 (13) | 13 (7.8) | 0.099 |
| Trauma/Immobilization | 9 (3.8) | 8 (4.8) | 0.603 |
| Oral contraceptive | 12 (5) | 8 (4.8) | 0.927 |
| Systemic lupus erythematosus | 7 (2.9) | 0 | 0.045 |
| Heparin induced thrombocytopenia | 7 (2.9) | 3 (1.8) | 0.537 |

Abbreviations: ASD, atrial septal defect; COPD, chronic obstructive pulmonary disease; PFO, patent foramen ovale.

logistic regression, male gender, BMI, history of splenectomy, indwelling catheter, the total number of CTEPH risk factors, and use of DOACs were significant risk factors for thrombus detection. History of hypertension showed a negative association with likelihood of observing a qualifying thrombus. Age or history of APS were not associated with thrombus detection (Table 4). APS as

**TABLE 3** Hemodynamic data

| | Non-DOACs group | DOACs group | *p* Value |
|---|---|---|---|
| Preoperative cardiac output | 4.8 ± 1.3 | 4.7 ± 1.3 | 0.493 |
| Preoperative cardiac index | 2.3 ± 0.6 | 2.3 ± 0.6 | 0.853 |
| Preoperative PVR | 617 ± 364 | 590 ± 327 | 0.459 |
| Preoperative RA pressure | 10.1 ± 5.4 | 9.0 ± 4.9 | 0.047 |
| Preoperative RV pressure | 74 ± 21 | 72 ± 21 | 0.278 |
| Preoperative PAWP | 12.3 ± 4.9 | 11.6 ± 4.6 | 0.155 |
| Preoperative mPAP | 44 ± 12 | 42 ± 11 | 0.155 |
| Preoperative PA saturation (%) | 65 ± 9 | 66 ± 9 | 0.464 |
| Postoperative cardiac output | 5.6 ± 1.3 | 5.4 ± 1.3 | 0.255 |
| Postoperative PVR | 273 ± 117 | 281 ± 132 | 0.561 |
| Postoperative PAWP | 12.3 ± 3.8 | 12.2 ± 3.9 | 0.759 |
| Postoperative mPAP | 29 ± 8 | 28 ± 7 | 0.277 |

Abbreviations: mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAWP, Pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle.

**TABLE 4** Univariate and multivariate logistic regression results

| Factor | Univariate *p* value | OR (95% CI) | Multivariate, adjusted[a] *p* value | OR (95% CI) |
|---|---|---|---|---|
| Age[b] | 0.772 | 1.00 (0.98–1.03) | 0.839 | 1.00 (0.97–1.03) |
| Male gender | 0.005 | 3.17 (1.41– 7.09) | 0.002 | 4.34(1.73–10.86) |
| BMI | 0.001 | 0.91 (0.86– 0.96) | 0.002 | 0.89 (0.82–0.96) |
| Race (Black) | 0.055 | 2.13 (0.99–4.61) | 0.003 | 3.814 (1.56–9.32) |
| Splenectomy | 0.014 | 4.68 (1.37– 16.01) | 0.065 | 3.79 (0.92–15.58) |
| Indwelling catheter | 0.001 | 6.69 (2.29– 19.61) | 0.001 | 8.07 (2.24–29.09) |
| DOACs | 0.029 | 2.13 (1.08– 4.19) | 0.028 | 2.34 (1.09–5.01) |
| Total number of risk factors | 0.008 | 1.46 (1.10– 1.92) | 0.002 | 1.71 (1.23–2.39) |
| Hypertension[b] | 0.047 | 0.467 (0.22–0.99) | 0.14 | 0.51 (0.21–1.24) |
| Antiphospholipid antibody syndrome | 0.162 | 0.42 (0.13–1.41) | 0.051 | 0.24 (0.05–1.01) |

Abbreviations: BMI, body mass index; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; DOACs, direct oral anticoagulant; OR, odds ratio.

[a]Adjusted for gender, race, BMI, history of indwelling catheter, history of splenectomy, history of APS, and total number of risk factors for CTEPH and current DOACs use.

[b]Excluded from final multivariate analysis model.

a thrombus formation risk had a $p$ value = 0.162, (OR 0.42 [95% CI: 0.13–1.41]).

Next, we investigated potential risk factors for thrombus detection in a multivariate logistic regression analysis. It included not only significant factors in the univariate analysis but also age, gender, race, BMI, and history of APS, and the type of anticoagulation therapy. The final multivariate analysis model selected included: male gender, low BMI, black race, history of an indwelling catheter, splenectomy, APS, the number of CTEPH risk factors, and anticoagulation with DOACs (Table 4). Interestingly, APS status as a thrombus risk in the multivariate analysis had a $p$ value = 0.051 (OR 0.24, [95% CI: 0.05–1.01]). Indwelling catheter-related CTEPH (16 patients, 3.9% overall) had the largest estimated association with thrombus detection (OR 8.1; 95% CI:

**TABLE 5** Type of DOACs and recent thrombus detection at time of PEA

| Type of DOACs, $N = 166$ | Thrombus present, $N = 22$ | No thrombus, $N = 144$ |
|---|---|---|
| Rivaroxaban, 114 (68.7%) | 19 (86.4%) | 95 (66%) |
| Apixaban, 40 (24.1%) | 2 (9.1%) | 38 (26.4%) |
| Dabigatran, 12 (7.2%) | 1 (4.5%) | 11 (7.6%) |

*Note*: $p$ value 0.15, $\chi^2 = 3.78$, by Pearson $\chi^2$.

Abbreviation: DOACs, direct oral anticoagulant; PEA, pulmonary endarterectomy.

2.2–29.1; $p < 0.01$). Overall, thrombus was detected in 22 (13.3%) patients in the DOACs group and 16 (6.7%) patients in the non-DOACs group, respectively. Anticoagulation with DOACs was an independent risk factor of thrombus detection, regardless of other factors, the odds ratio [OR] of DOACs usage and evidence of thrombus was 2.3 (95% CI: 1.1–5.0; $p = 0.03$) after adjustment of other significant factors. The distribution of specific DOACs and thrombus detection is shown in Table 5.

## DISCUSSION

To the best of our knowledge, this is the first study investigating the PEA specimen for concurrent thrombus and correlating that finding with the type of chronic anticoagulation therapy. DOAC treated CTEPH patients undergoing PEA were more likely to have concomitant thrombus removed at the time of PEA. The clinical implications of this finding is unclear—whether the presence of more recent thrombi at the time of PEA would make the surgery more challenging or affect outcomes. However, it raises the question of whether DOACs are safe and effective in patients with CTEPH. DOACs are known to have several practical advantages over VKAs in both prevention and treatment of venous thromboembolism—such as minimal food and drug interactions, more predictable pharmacokinetics and pharmacodynamics, rapid onset and offset of action, a short half-life, and the convenience of not requiring regular laboratory monitoring.[8] The popularity of DOACs use in CTEPH was demonstrated in this (41%) and other reports.[9]

VKAs inhibits the gamma-carboxylation of the vitamin K-dependent factors, including factor II, VII, IX, X in the clotting cascade as opposed to DOACs inhibit only factor Xa or factor IIa. VKAs also limit the effect of anticoagulant proteins, protein C, and protein S.[8,10] The efficacy and safety of VKAs are related to the level of anticoagulation, as expressed by the international normalized ratio (INR) of the prothrombin time. Although it is difficult to maintain the therapeutic range throughout the whole course of treatment,[11] VKAs have been time-tested and represent the traditional anticoagulant of choice in CTEPH. VKAs have a slower onset of action and longer clinical half-life compared to DOACs. On the other hand, rapid offset and short half-life of DOACs may be a potential disadvantage under lifelong anticoagulation conditions. Poor adherence to DOACs such as missed doses may pose risk of breakthrough thromboembolic events.

Our findings regarding the status of antiphospholipid syndrome—either historical diagnosis or detected from one of two routine testing conducted before PEA—should be interpreted with caution as we did not control for intensity of anticoagulation (INR range or DOAC dose). There was a trend toward lower rate of thrombus detection within the APS subgroup in multivariate analysis. Although the association is unclear, one plausible explanation is better adherence to anticoagulation therapy and transition instructions in this known higher thrombosis-risk cohort.

Reports on the safety and efficacy of DOACs in patients with CTEPH are limited.[12–14] One case series reported the successful use of DOACs in CTEPH patients, but the duration of exposure and follow-up period, were relatively short ($20 \pm 14$ months).[12] Another observational study noted no differences in intraoperative and postoperative complications, or in midterm survival when comparing patients on DOACs versus conventional anticoagulation.[9] A more recent multicenter study reported 10 years data reviewing CTEPH patients treated with DOACs. Compared to the non-DOACs group, bleeding events were lower but pulmonary embolism recurrence rates were significantly higher in the DOACs group: 4.62%/person-year versus 0.76%/person-year.[13] There was no difference reported in survival.

The current study has several limitations. In this retrospective review, the details on adherence rates and clinical decisions leading to choice in anticoagulation are unknown. Inherent bias may exist if nonadherent VKA patients were switched to DOACs to improve treatment

adherence and those remaining on VKA tended to be more compliant with medications. Second, although all patients were bridged with LMWH, this transition aspect was not controlled and individual adherence to bridging was not captured. Lastly, the specific dosage of each DOACs, chronic LMWH, or the INR ranges for those on VKA were not analyzed to address adequacy of each anticoagulation method.

In conclusion, use of DOACS was an independent risk factor for the concomitant finding of recent thrombus during PEA, raising the concern for the use of DOACs in the prevention of recurrent thromboembolism in patients with CTEPH. Further studies are needed to assess the safety and efficacy of DOACs in CTEPH.

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Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ETHICS STATEMENT

The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local requirements.

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