



Letter to the Editors-in-Chief

Use of direct oral anticoagulants prevents increase in pulmonary vascular resistance and incidence of clinical worsening in patients with chronic thromboembolic pulmonary hypertension



1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) requires lifelong anticoagulation therapy to prevent thrombotic progression of the disease. Major guidelines have recommended the use of vitamin K antagonist (VKA) as an anticoagulant [1] [2]. On the other hand, there are few reports evaluating the safety or effectiveness of direct oral anticoagulants (DOACs) for the treatment of CTEPH. In contrast to venous thromboembolism (VTE), in situ thrombus formation in the pulmonary artery and/or abnormal coagulation and fibrinolytic conditions have also been suggested as possible pathogenetic mechanisms of CTEPH [3–5]. Therefore, it remains controversial whether DOACs would have a similar safety and efficacy as VKA in patients with CTEPH.

The purpose of this study was to clarify the safety and effectiveness of DOACs as anticoagulants in CTEPH patients. We evaluated the impact of DOACs on change in pulmonary vascular resistance (PVR), D-dimer level, and incidence of clinical worsening of CTEPH and clinically relevant bleeding.

2. Methods

2.1. Study design and patient selection

This retrospective observational study was conducted based on the medical records at Kyushu University Hospital. The protocol was approved by the Institutional Ethics Review Board (29-526). In our clinical practice, we continue DOACs if the patient had been administered with DOACs at the onset of VTE. In addition, if the patient had problems with VKA (e.g. bleeding concerns or labile INR), treatment was switched to DOACs depending on the physician's judgement. We extracted patient characteristics, type of anticoagulant, CTEPH/VTE risk and bleeding risk from the medical records. The change in PVR, D-dimer level, clinical worsening of CTEPH, and clinically relevant bleeding were collected as outcome measures.

2.2. Definition of outcome measures

Two PVR measurements satisfying the following criteria were extracted. PVR was measured by right heart catheterization:

1. Two PVR measurements at least 90 days apart without specific interventions (pulmonary endarterectomy, balloon pulmonary angioplasty, and/or changing/starting/discontinuing pulmonary vasodilators) between them. If there are three or more PVR measurements in a patient, two PVR measurements with the longest interval was adopted.

D-dimer level for spontaneous monitoring on regular outpatient visits was measured by latex agglutination immunoassay.

Clinical worsening in CTEPH was defined as a composite outcome of the following component endpoints using modified criteria described in a previous CHEST-1 trial [6]:

1. Death from any cause.
2. Lung transplantation.
3. Worsening pulmonary hypertension that resulted in hospitalization, start of new specific pulmonary hypertension treatment, rescue pulmonary endarterectomy or balloon pulmonary angioplasty (BPA).

Clinically relevant bleeding was defined as major bleeding under criteria described by the International Society on Thrombosis and Haemostasis or clinically relevant non-major bleeding, which was defined in Hokusai-VTE trial [7].

2.3. Statistical analysis

Descriptive statistics for categorical variables were reported as frequency and percentage. Continuous variables were reported as mean \pm standard deviation. A p value < 0.05 indicated statistical significance. A chi-square test and a t -test were used for categorical and continuous variables, respectively. Statistical tests were conducted using Microsoft Office Excel 2016 (Microsoft Corp., WA, USA).

3. Results

3.1. Patient baseline characteristics

Eighty-four CTEPH patients were classified into two groups, those treated with VKA and those treated with DOACs. There were 38 patients in the VKA group and 46 in the DOACs group. Thirteen out of 46 patients in the DOACs group were subjects who were changed from VKA to DOACs due to labile INR and/or bleeding concern. Table 1 shows the patients' background. Longer medical records were available in the VKA group than in the DOACs group. The DOACs group underwent more BPAs reflecting recent therapeutic trends and resultantly had lower pulmonary arterial pressure than the VKA group. Common risk factors for CTEPH/VTE and bleeding were not significantly different between those groups.

3.2. Efficacy outcome measures

3.2.1. Change in PVR

The full analysis set for PVR evaluation included 21 patients in the VKA group and 21 in the DOACs group. Baseline PVR was higher in the

Table 1
Patient characteristics at the beginning of the record.

			VKA (n = 38)		DOACs (n = 46)		p value			
Time at the beginning of the medical record			Month-year, median	Q1 Mar-16	Q3 Apr-14 Apr-17	Aug-16 Apr-16 Jul-17	0.003			
Referred duration			Years per patient	2.92 ±	2.87	1.61 ±	1.01	0.01		
Age			Year-old	60 ±	14	62 ±	11	0.42		
Female/male			n	30 /	8	39 /	7	0.49		
Comorbidities or past medical history	CTEPH/VTE risk	History of VTE	n (%)	20	(53%)	28	(61%)	0.45		
		Intravenous device	n (%)	5	(13%)	6	(13%)	0.99		
		Ventriculoatrial shunt	n (%)	0	(0%)	0	(0%)	NA		
		Splenectomy	n (%)	0	(0%)	0	(0%)	NA		
		Hemostatic risk (antiphospholipid syndrome, protein C deficiency)	n (%)	1	(3%)	2	(4%)	0.67		
		Cancer-bearing	n (%)	2	(5%)	2	(4%)	0.84		
		Thyroid replacement therapy	n (%)	1	(3%)	2	(4%)	0.67		
		Inflammatory bowel disease	n (%)	0	(0%)	1	(2%)	0.36		
		Antipsychotic drug	n (%)	8	(22%)	5	(11%)	0.33		
		Steroid use	n (%)	2	(5%)	0	(0%)	0.12		
		Paraplegia/Hemiplegia	n (%)	2	(5%)	2	(4%)	0.84		
		HAS-BLED score without Labile INR (0–8 points)			Point	1.1 ±	1.1	1.0 ±	0.8	0.61
		Type and dose of DOACs	Dabigatran/Rivaroxaban/Apixaban/Edoxaban (standard dose, low dose ^a)		n	NA		1,0/11,1/9,2/4,18		NA
Time in therapeutic range	Target INR 1.5–2.5 (JCS 2017 ^b)		%	74 ± 16		NA		NA		
Hemodynamics	Mean pulmonary artery pressure		mm Hg	41 ± 13		34 ± 11		0.01		
	Pulmonary vascular resistance		wood units	6.6 ± 2.9		6.7 ± 4.2		0.82		
	Cardiac index		L/min/m ²	3.1 ± 0.7		2.8 ± 0.7		0.07		
Use of pulmonary vasodilator	PDE-5 inhibitors/sGC stimulators		n (%)	19 (50%)		14 (30%)		0.08		
	Endothelin receptor antagonists		n (%)	9 (24%)		5 (11%)		0.11		
	Prostacyclin analogues/receptor agonists		n (%)	9 (24%)		9 (20%)		0.64		
History of CTEPH specific intervention	Pulmonary endoarterectomy		n (%)	1 (3%)		3 (7%)		0.10		
	Balloon pulmonary angioplasty		n (%)	0 (0%)		22 (48%)		< 0.001		

DOACs: direct oral anticoagulants, JCS: Japanese Circulation Society [2], VKA: vitamin K antagonist, VTE: venous thromboembolism, PDE-5: phosphodiesterase type 5, Q1: first quartile, Q3: third quartile, sGC: soluble guanylate cyclase.

^a Dabigatran is not approved for the VTE prevention in Japan. Standard dose or low dose were Dabigatran, 150 mg or 110 mg BID; Rivaroxaban, 15 mg or 10 mg QD; Apixaban, 5 mg or 2.5 mg BID; Edoxaban, 60 mg or 30 mg QD, respectively, according to the indication for use in VTE prevention in Japan. Most reason for low dose Edoxaban is ≤ 60 kg of body weight.

^b Japanese Circulation Society, which is the major academic society in the field of cardiovascular medicine in Japan, states target INR as 1.5–2.5 in the treatment of VTE, based on Japanese real-world practice [11].

VKA group than the DOACs group (VKA; 3.3 ± 1.0 wood units, DOACs; 4.1 ± 1.1 wood units, $p = 0.02$) (Supplemental Table). The intervals of 2-point PVRs were shorter in DOACs group than VKA group (VKA; 421 ± 273 days, DOACs; 271 ± 147 days, $p = 0.03$). The change in PVR was comparable between two groups (VKA; -0.17 ± 0.82 wood units/year, DOACs; -0.44 ± 0.89 wood units/year, $p = 0.32$) (Fig. 1).

3.2.2. D-dimer level

The full analysis set for D-dimer level included 34 patients in the VKA group and 39 in the DOACs group. D-dimer levels were not significantly different between two groups (VKA; 0.58 ± 0.22 $\mu\text{g/ml}$, DOACs; 0.67 ± 0.47 $\mu\text{g/ml}$, $p = 0.41$).

3.2.3. Clinical worsening of CTEPH

The incidence rate (density) for clinical worsening of CTEPH during the entire observation period was 1.8% per patient-year (2 events per 108.3 patient-year) in the VKA group and 0% per patient-year (0 events

per 71.6 patient-year) in the DOACs group with no statistical difference between the groups ($p = 0.24$). The 2 incidences in the VKA group were 1 worsening pulmonary hypertension, which required hospitalization and BPA, and 1 symptomatic VTE recurrence, resulting in hospitalization after prolonged insufficient INR.

3.3. Safety outcome measures

3.3.1. Clinically relevant bleeding

The incidence rate (density) for clinically relevant bleeding during the entire observation period was 2.8% per patient-year (3 events per 108.3 patient-year) in the VKA group and 2.8% per patient-year (2 events per 71.6 patient-year) in the DOACs group with no statistical difference between the groups ($p = 0.98$). There was also no statistical difference between the groups with respect to major bleeding ($p = 0.10$). This occurred at a rate of 0.9% per patient-year (1 event per 108.3 patient-year) in the VKA group and 2.8% per patient-year (2 events per 71.6 patient-year). The types of bleeding in the VKA group

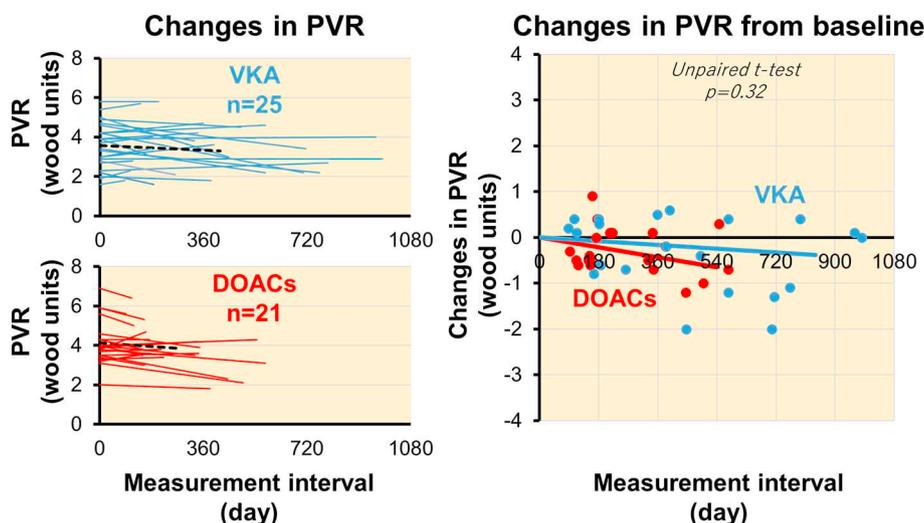


Fig. 1. Change in pulmonary vascular resistance.

Left panel shows the paired-PVR by patient. Right panel shows the changes in PVR from baseline.

DOACs: direct oral anticoagulants, PVR; pulmonary vascular resistance, VKA; vitamin K antagonist.

were 1 gastrointestinal bleeding, 1 huge subcutaneous hematoma requiring blood transfusion, and 1 prolonged hematuria. The bleeding events in DOACs group were associated with 2 excessive menstruations.

4. Discussion

The present study demonstrated the safety and effectiveness of DOACs in patients with CTEPH in a real-world setting. Gavilanes-Oleas et al. recently reported a case series in CTEPH patients who use DOACs [8]. However, the current study is the first to demonstrate the impact of VKA and DOACs on PVR and clinically adverse incidence associated with CTEPH and anticoagulation. As compared with VKA, DOACs demonstrated similar effectiveness and safety with respect to thrombotic progression or bleeding.

4.1. Daily practice in the use of DOACs

To correctly interpret the results of the present study, it is important to understand our daily practice in the use of DOACs for the treatment of CTEPH. Most CTEPH patients visit the outpatient clinic in our hospital every 1 or 2 months. The dose of DOACs adapted from the preventive dose for VTE. The primary reason for the use of DOACs was continuation of the referral prescription (47%, 22/46 patients). Other frequent reasons for the use of DOACs were labile INR (22%, 10/46 patients) and bleeding concerns (e.g. excessive menstruation) (6%, 3/46 patients).

Pivotal trials in the use of DOACs for the prevention of VTE recurrence consistently showed a lower risk of major bleeding compared to VKA [9]. In the present study, we found 1 instance of major bleeding in the VKA group and 2 in the DOACs group, but the difference was not statistically significant. Two patients in the DOACs group who presented excessive menstruation accompanied with reduced hemoglobin > 2 g/dl, were those who had switched from VKA to DOAC due to repeated menorrhagia. It is possible that these patient backgrounds influenced the occurrence of major bleeding during our study.

4.2. Patient characteristics of the present CTEPH survey

Table 1 shows patient characteristics. Gender distributions are female dominant in both groups (VKA; 79%, DOACs; 85%). This is consistent with the occurrence of CTEPH in Japan being higher among females, in contrast to Western countries where the occurrence is equal among the sexes [3]. In the current survey, the number of patients

taking an antipsychotic drug was remarkably high regardless of the type of anticoagulants (Overall 15%, 13/84 patients; VKA 22%, 8/38 patients; DOACs 11%, 5/46 patients). Based on the Japanese national survey, the usage of antipsychotics or anti-depressants among the general population is much lower (< 3% of the elderly population). Antipsychotic medications are known to be associated with an increased risk of VTE [10]. However, no report has indicated the association between antipsychotic drugs and development of CTEPH. Potential side effects of these drugs including clot formation and/or sedative effect of these drugs on physical activity may contribute to repeated VTE and subsequent CTEPH.

4.3. Impact of DOACs on outcome measures

We evaluated the change in PVR as an efficacy outcome to clarify the impact of DOACs on preventing thrombotic progression. The aim of the present study was to verify the preventive effect of DOACs on the progression of pulmonary hypertension, including asymptomatic pulmonary thromboembolism and in situ thrombus formation in the pulmonary artery, in addition to symptomatic VTE. The change in PVR was comparable between the DOACs and VKA groups (Fig. 1), indicating DOACs and VKA have similar efficacy on prevention of thrombotic progression in CTEPH. Comparable D-dimer levels and rates of clinical worsening of CTEPH among the groups supported this conclusion. Therefore, it is reasonable to consider that DOACs are effective in our clinical setting. However, in this study, approximately half of the patients in the DOACs group had undergone BPA treatment at baseline. Lower pulmonary arterial pressure may reduce the risk of lung hemorrhage and attenuate the development of small vessel arteriopathy. Further investigation is needed to clarify our conclusions.

4.4. Study limitations

The present report is a preliminary result of the use of DOACs in CTEPH treatment. Because the present work is a retrospective observational study, selection bias, duration of follow-up and historical differences in therapeutic strategies (e.g. BPA) between the 2 groups were unavoidable. In addition, the sample size was not sufficient to detect statistical differences between the groups, especially in the incidence of clinical worsening of CTEPH and bleeding events. To ensure the safety and the efficacy of DOACs in patients with CTEPH, a larger-scale registry and eventually a prospective randomized controlled trial are required.

5. Conclusion

The use of DOACs in patients with CTEPH for the treatment of thrombotic disease progression resulted in similar PVR change and rates of clinical worsening of CTEPH and clinically relevant bleeding as compared with VKA in our clinical practice.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2019.05.018>.

Declaration of Competing Interest

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