The anticoagulant effects of warfarin and the bleeding risk associated with its use in patients with chronic thromboembolic pulmonary hypertension at a specialist center in Japan: a retrospective cohort study

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Abstract

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) require lifelong anticoagulation therapy. However, the bleeding risk and recurrence of venous thromboembolism (VTE) in CTEPH patients who are administered warfarin have not been adequately evaluated. The purpose of this study was to evaluate the risk of clinically relevant bleeding, recurrent VTE, and clinical worsening in patients with CTEPH who were administered warfarin.

The clinical records of 72 patients with CTEPH who regularly visited our institution and were administered warfarin were retrospectively reviewed between 1 January 2011 and 31 December 2015. We investigated the incidence of clinically relevant bleeding events, recurrent VTE, and hospitalization for the deterioration of pulmonary hypertension or right heart failure (RHF) during the observation period.

The mean observation period for the 72 patients was 3.60 ± 1.60 person-years. Clinically relevant bleeding, RHF, and recurrent VTE occurred in 21 (29.2%), eight (11.1%), and three (4.2%) of 72 patients, respectively, and the incidence rates for these events were 8.1%/person-year, 3.1%/person-year, and 1.2%/person-year, respectively. The incidence rates for the major and non-major bleeding events were 5.0%/person-year and 3.9%/person-year, respectively. The incidence of clinically relevant bleeding events was 20.8%/person-year during medical treatment with a soluble guanylate cyclase stimulator. One of 35 patients (2.9%) during the post-pulmonary endarterectomy period experienced hemoptysis during observation period (>6 months after pulmonary endarterectomy). No bleeding events occurred during the post-balloon pulmonary angioplasty period.

In conclusion, warfarin effectively prevents VTE recurrence in CTEPH patients, but its effects may be associated with a considerable bleeding risk.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a type of pulmonary hypertension (PH) characterized by chronic pulmonary obstruction caused by organized thrombi.[1–3] Following its definitive diagnosis at specialist

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institutions, specific treatments for CTEPH are considered. Pulmonary endarterectomy (PEA), which is a surgical procedure that removes organized thrombi from the pulmonary arteries,[4] is recommended for CTEPH patients who have surgically accessible thrombi and low risk/benefit ratios.[2] For patients diagnosed with inoperable CTEPH or those who have symptomatic residual PH after PEA, balloon pulmonary angioplasty (BPA) and/or medical treatment using pulmonary vasodilators are considered.[2] The findings from the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial (CHEST) showed that riociguat, which is a soluble guanylate cyclase (sGC) stimulator, improves the hemodynamics and exercise capacity of patients with CTEPH.[5] Prior to disease-specific therapy, lifelong anticoagulation is essential,[2] because venous thromboembolism (VTE) with repeated acute pulmonary thromboembolism[1,6] may cause or trigger CTEPH. Warfarin, a vitamin K antagonist, is commonly used for anticoagulation in CTEPH patients. Recently, direct oral anticoagulants (DOACs) have become widely available for VTE, and they may become available for the treatment of CTEPH in the future. However, the recurrence of VTE and the bleeding risk in CTEPH patients while taking warfarin have not been investigated. We believe that the risks associated with warfarin use in CTEPH patients should be elucidated in a clinical practice setting before undertaking a study to investigate the transition from warfarin to DOAC therapy. Hence, with the above in mind, the purpose of this study was to evaluate the risk of clinically relevant bleeding, recurrent VTE, and clinical worsening in patients with stable CTEPH who were administered warfarin, and to investigate the relationships between the effects of the bleeding risk associated with warfarin and specific treatments for CTEPH.

Methods

Patient inclusion and exclusion criteria

This study was approved by the Ethics Committee of Chiba University (Approval number: 826). Written informed consent was provided by all patients.

Between March 1986 and December 2015, 268 patients were diagnosed with CTEPH at Chiba University Hospital. The CTEPH diagnostic criteria were as follows: (1) a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and a normal pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, which was confirmed using right heart catheterization (RHC); (2) symptoms, including dyspnea, which had persisted for > 6 months; and (3) a persistent pulmonary embolism that was resistant to effective anticoagulation (>3 months) and was confirmed by a lung perfusion scan, a computed tomography (CT) scan, or pulmonary angiography.[3] We reviewed the clinical records of 268 patients and excluded 196 patients. The exclusion criteria were
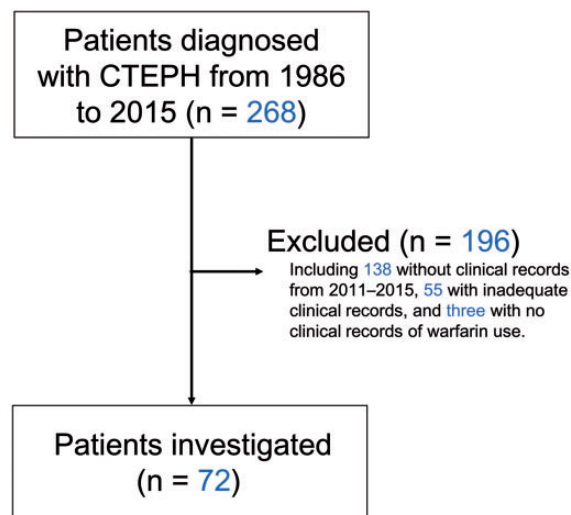

Fig. 1. Flow diagram showing the inclusion and exclusion of patients. CTEPH, chronic thromboembolic pulmonary hypertension.

as follows: (1) the absence of clinical records from 2011 to 2015; (2) too few visits to our institution during the observation period to generate sufficient clinical data to enable evaluations of clinical worsening and bleeding; and (3) patients who did not take warfarin from 2011 to 2015. Finally, 72 CTEPH patients were retrospectively investigated in this study (Fig. 1).

Definitions and exclusion criteria associated with the observation period

The entire observation period spanned from 1 January 2011 to 31 December 2015 (five years). For a patient who was diagnosed between 2011 and 2015, the start date was defined as the date of the definitive diagnosis at our institution. For a patient who was transferred to another hospital during the observation period, the end date was defined as the last day on which they visited our institution. For a patient who died during the observation period, the end date was defined as the date of death. The targets of this study were CTEPH patients in the stabilized period, and the confounding effects of other anticoagulants or interventional treatments were eliminated. Therefore, the following time periods were excluded from the observation periods: (1) the periods before a definitive diagnosis at our institution; (2) the six-month period after PEA or BPA; (3) treatment periods involving the use of DOACs or heparin including changes to heparin before and after interventional procedures; (4) periods associated with double-blind clinical trials, for example, those involving riociguat or selexipag.

Assessment of anticoagulation control

CTEPH patients require lifelong anticoagulation therapy. However, there is no evidence supporting an appropriate

warfarin dose.[2] According to the 2014 European Society of Cardiology and the Japanese VTE guidelines, the target ranges for the prothrombin time (PT)-international normalized ratio (INR) for patients with acute pulmonary embolism are 2–3 and 1.5–2.5, respectively.[7,8] Therefore, we aimed to use warfarin doses that achieved a PT-INR therapeutic range of 1.5–3.0. Anticoagulation control was assessed as a percentage of the INR value (%INR) using the method described by Nakatani et al.[9] The %INR was defined as the ratio of the number of PT-INRs within the target range to the total number of PT-INR measurements, and was correlated positively with the time within the therapeutic INR range ($R^2 = 0.917$, $P < 0.01$).[9]

Definition of clinically relevant bleeding events

To rigorously evaluate bleeding events, we adopted the bleeding events criteria used in previous clinical trials involving DOACs.[10] Clinically relevant bleeding comprised major bleeding and clinically relevant non-major bleeding. Major bleeding included hemorrhage associated with a reduction in hemoglobin level of $>2.0 \, g/dL$, bleeding requiring a red blood cell or whole blood transfusion of >2 units, hemorrhage in a vital organ, such as intracranial bleeding, or a hemorrhage that led to death. Clinically relevant non-major bleeding, or non-major bleeding, was defined as a mild-to-moderate temporary hemorrhage that originated from the gingiva, nose, airway, gastrointestinal tract, muscle, or subcutaneous tissue ($>25 \, cm^2$), and persistent bleeding after catheter insertion or surgery.

Definition of clinical worsening events

We defined clinical worsening events as hospitalization caused by exacerbations of PH or right heart failure (RHF) or recurrent symptomatic VTE, although regular check-up hospitalizations for RHC were excluded. We defined VTE events as symptomatic pulmonary embolism or deep vein thrombosis,[10] confirmed by CT or leg echo. We excluded asymptomatic in situ rethrombosis or growing thrombosis of the pulmonary artery after PEA, which were incidentally found at follow-up CT.

Data analysis

All of the data were combined using Microsoft Excel 2013. Unless otherwise stated, the data are presented as means and standard deviations. To account for exposure to each specific CTEPH therapy, an event incidence was calculated as a ratio obtained by dividing the number of patients with that event by the mean exposure period to each treatment, and it is expressed as %/person-year. Comparisons between two groups were analyzed by Student's t-test using EZR (ver. 1.29, Saitama Medical Center, Jichi Medical University, Saitama, Japan).[11]

Results

Patients' characteristics

The mean age of the 72 patients on the start date of the observation period was 59.7 ± 11.9 years; 11 patients were men. At diagnosis, the mPAP, pulmonary vascular resistance (PVR), and cardiac index were $43.5 \pm 10.9 \, mmHg$, $694 \pm 270 \, dyne \cdot s \cdot cm^{-5}$, and $2.96 \pm 0.82 \, L/min/m^2$, respectively. The number of days from diagnosis to the start of the observation period was 1663 ± 2121 days. At the last catheterization before the observation periods the mPAP, PVR, and cardiac index were $41.4 \pm 13.6 \, mm \, Hg$, $656 \pm 321 \, dyne \cdot s \cdot cm^{-5}$, and $2.77 \pm 0.56 \, L/min/m^2$, respectively. Sixty-two (86.1%) of the 72 patients had PH at the start of the observation period, and 39 (54.2%) and ten (13.9%) patients underwent PEA and BPA, respectively, from the date of their diagnosis to the end of the observation period.

Bleeding events, right heart failure, and recurrent thrombosis

The total observation period was 258.9 person-years (94,500 person-days) and the mean observation period was 3.60 ± 1.60 person-years. Clinically relevant bleeding, RHF or PH exacerbation, and recurrent pulmonary embolism occurred in 21 (29.2%), eight (11.1%), and three (4.2%) patients, respectively and the number of these events was 36, 14, and three, respectively. All three VTE events were symptomatic pulmonary embolism detected by enhanced CT. One RHF event was associated with recurrent pulmonary embolism. The incidence rates for patients with these events were 8.1%/person-year, 3.1%/person-year, and 1.2%/person-year, respectively (Fig. 2a).

Characteristics of the clinically relevant bleeding events

All of the clinically relevant bleeding events occurred in women. The numbers of patients with major and non-major bleeding events were 13 (18.1%) and ten (13.9%), respectively, which included two patients who experienced both major and non-major bleeding events. The incidence rates for the major and non-major bleeding events were 5.0%/person-year and 3.9%/person-year, respectively (Fig. 2a). Table 1 presents the bleeding sources and the numbers of patients and bleeding events associated with each source. The incidence rates for clinically relevant bleeding in each year were 6.5%/person-year in 2011, 7.8%/person-year in 2012, 11.2%/person-year in 2013, 13.2%/person-year in 2014, and 14.8%/person-year in 2015 (Fig. 2b and Supplementary Table 1).

Anticoagulation control and bleeding events

The 72 patients had a mean %INR of 81.1 ± 13.3% and the 21 patients with clinically relevant bleeding had a

mean %INR of 75.5 ± 12.4%. Thirty-one of 36 clinically relevant bleeding events (86.1%) were not associated with hyperanticoagulation (PT-INR > 3.0) (Table 1).
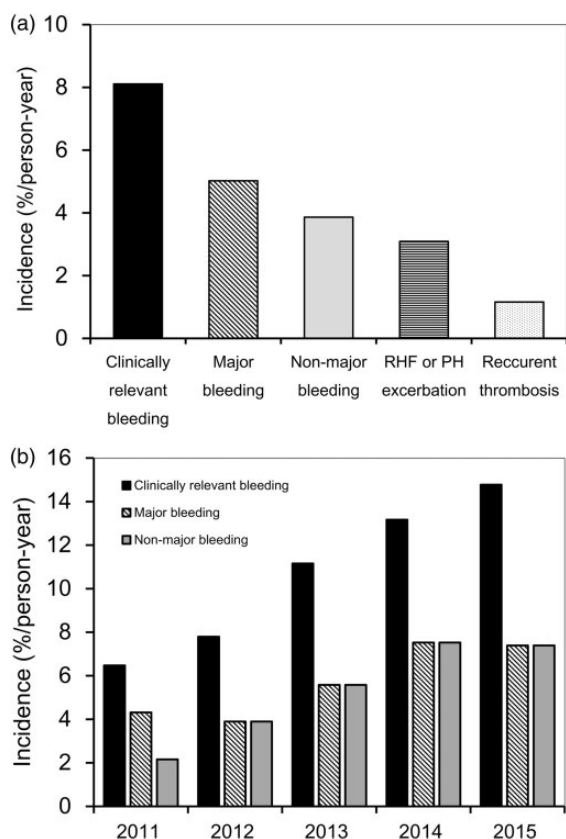

Fig. 2. Incidence rates of events. (a) Overall incidence of events. (b) Incidence of bleeding events from 2011 to 2015. RHF, right heart failure.

PT-INR on clinical worsening events

Anticoagulation control in patients who had deterioration of PH or RHF and VTE events is shown in Table 2. The PT-INR values on 9/14 events of deterioration of PH or RHF (64.3%) were within the target range. The PT-INR values of three events of recurrent VTE were 1.54, 1.55, and 1.76.

Pulmonary vasodilators and bleeding events

Fig. 3 illustrates the use of pulmonary vasodilators for CTEPH patients at our institution. Table 3 summarizes the medical therapies used for CTEPH and the incidence of bleeding events during each exposure period. The incidence of clinically relevant bleeding events during the periods when pulmonary vasodilators were not used was 9.2%/person-year (Table 3). Five (21.7%) of 23 patients who were treated with an sGC stimulator experienced clinically relevant bleeding events and the incidence was 20.8%/person-year. Two major bleeding events occurred during sGC stimulator treatment that required blood transfusions: one was gastrointestinal; and one was genital. Three non-major bleeding events occurred: one was nasal; one comprised hemoptysis; and one was subcutaneous. The incidence of clinically relevant bleeding events during monotherapy with an sGC stimulator was 22.2%/person-year. The incidence rates for clinically relevant bleeding events during dual and triple combination therapy were 9.5%/person-year and 0%/person-year, respectively (Supplementary Table 2).

The incidence of hemoptysis after pulmonary endarterectomy and balloon pulmonary angioplasty

One of 35 patients (2.9%) after PEA had hemoptysis and this patient was administered a pulmonary vasodilator

Table 1. Bleeding site or cause and prothrombin time-international normalized ratio.

	Patients (n)	Events (n)	Mean %INR	Mean PT-INR on bleeding events	PT-INR on event (number of events)		
					< 1.5	1.5–3.0	≥3.0
Clinically relevant bleeding	21	36	75.5 ± 12.4	2.58 ± 2.00	5	26	5
Major bleeding	13	19	74.4 ± 11.0	2.79 ± 2.49	4	12	3
Gastrointestinal	4	4	65.3 ± 5.1	6.08 ± 4.20	0	2	2
Genital	2	8	85.0 ± 17.1	1.73 ± 0.36	3	5	0
Intracranial bleeding	1	1	64.2	1.47	1	0	0
Hemopericardium	1	1	81.2	1.89	0	1	0
Intraarticular	1	1	79.3	1.60	0	1	0
Surgery/trauma	4	4	82.7 ± 9.9	2.48 ± 0.60	0	3	1
Non-major bleeding	10	17	76.8 ± 14.5	2.22 ± 0.80	1	14	2
Hemoptysis	6	13	80.7 ± 12.9	2.00 ± 0.37	0	13	0
Nasal	2	2	61.9 ± 22.2	2.10 ± 1.34	1	0	1
Urinary tract	1	1	83.3	2.68	0	1	0
Subcutaneous	1	1	76.9	4.77	0	0	1

%INR, percentage of the international normalized ratio; PT-INR, prothrombin time-international normalized ratio.

Table 2. Prothrombin time-international normalized ratio on clinical worsening events.

	Patients (n)	Events (n)	Mean %INR	Mean PT-INR on bleeding events	PT-INR on event (number of events)		
					<1.5	1.5–3.0	≥3.0
Deterioration of PH or RHF	8	14	74.5 ± 9.0	2.53 ± 0.87	1	9	4
Recurrent VTE	3	3	74.9 ± 6.5	1.62 ± 0.12	0	3	0

%INR, percentage of the international normalized ratio; PT-INR, prothrombin time-international normalized ratio; PH, pulmonary hypertension; RHF, right heart failure; VTE, venous thromboembolism.
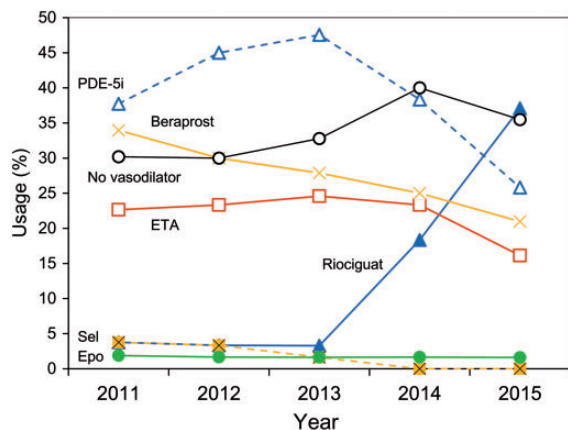

Fig. 3. Usage of pulmonary vasodilators for CTEPH patients at our institution.
Epo, epoprostenol; Sel, selexipag; ERA, endothelin receptor antagonist; PDE-5i, phosphodiesterase-5 inhibitor.

(riociguat) (Table 4). None of seven patients after BPA had any hemoptysis nor bleeding events in the stabilized periods.

Discussion

In this study, we evaluated the occurrence of bleeding, RHF, and VTE events in patients with CTEPH treated with warfarin. We found that while anticoagulation therapy using warfarin was effective at preventing recurrent VTEs in CTEPH patients, it was associated with a considerable bleeding risk.

With the exception of a study reported by Henkens et al.,[12] the bleeding risk associated with anticoagulation in CTEPH patients has not been comprehensively evaluated until now. The incidence of major bleeding events in the current study was higher than that reported by Henkens et al. (2.4%/person-years) (Table 5).[12] While the definition of major bleeding events used in this study was similar to that used by Henkens et al.,[12] differences between the studies with respect to the participants' backgrounds could explain the discrepancies in bleeding risk. The study by Henkens et al.[12] focused on inoperable CTEPH patients during 1997–2009, and while the use of pulmonary vasodilators was not described in detail in this previous report, the time interval studied contained years in which the choice

of pulmonary vasodilators was extremely limited. In our study, half of the patients underwent PEA and two-thirds were administered pulmonary vasodilators.

Some selective pulmonary vasodilators might be associated with increases in the bleeding risk during anticoagulation by warfarin. The present study revealed that the frequency of bleeding events was higher during combined sGC stimulator and warfarin therapy than that during treatment with warfarin alone. The findings of the present study also showed that the incidence of clinically relevant bleeding events increased during the observation period, and that the use of sGC stimulators increased during the latter half of the study period. The findings from the CHEST-2 study showed that hemoptysis or pulmonary hemorrhage occurred in 5% of patients over a two-year period.[13,14] The findings from clinical studies of CTEPH patients treated with bosentan or sildenafil showed that nasal hemorrhage occurred in 5.2% and 7.5% of patients, respectively.[15,16] Epoprostenol and beraprost may increase the bleeding risk,[17] but the precise bleeding incidence has not yet been evaluated in any study, including clinical trials investigating epoprostenol[18,19] and beraprost[20] in the treatment of patients with CTEPH. In a clinical trial of selexipag, which is a prostacyclin receptor agonist, it was reported that 2.4% of patients treated with selexipag experienced major bleeding events, and the occurrence was similar to that of the placebo group.[14] Bleeding events were neither primary nor secondary endpoints, nor were the bleeding event criteria clearly defined in any of the clinical studies that have investigated the use of pulmonary vasodilators in CTEPH patients.[5,15,18–20] It is possible that the investigators might have failed to report the bleeding events and that the bleeding risk might have been underestimated in previous clinical studies. Hence, the hemodynamic changes as well as detailed assessments of bleeding risk should be included in future clinical trials.

The risk of hemoptysis during the post-PEA or BPA periods might not be high. The luminal structure of the pulmonary arteries can drastically change after PEA or BPA. After PEA, organized thrombi can be removed after PEA and media of pulmonary arteries can be exposed to blood flow.[4] It was reported that the microscopic dissection of pulmonary arteries occurred after BPA.[21] It is also thought that hemoptysis in CTEPH patients might be associated with the development bronchial arteries that may connect

Table 3. Medical therapy and the incidence of bleeding events.

| | | | Incidence of bleeding events | | | | | | | |
| | | | Clinically relevant bleeding | | Major bleeding | | Non-major bleeding | | Hemoptysis | |
	Cases (n)	Mean exposure period (years)	Cases (n)	%/person-year	Cases (n)	%/person-year	Cases (n)	%/person-year	Cases (n)	%/person-year
No vasodilator (warfarin only)	26	3.36 ± 1.82	8	9.2	5	5.7	3	3.4	2	2.3
sGC stimulator	23	1.04 ± 1.22	5	20.8	2	8.3	3	12.5	1	4.2
PDE-5i	35	2.41 ± 1.74	6	7.1	4	4.7	2	2.4	2	2.4
ETA	16	3.49 ± 1.52	3	5.4	3	5.4	1	1.8	1	1.8
Beraprost	26	2.36 ± 1.99	6	9.8	4	6.5	2	3.3	1	1.6
Selexipag	3	0.97 ± 0.07	1	34.4	0	0.0	1	34.4	1	34.4
Epoprostenol	1	4.23	0	0.0	0	0.0	0	0.0	0	0.0

sGC, soluble guanylate cyclase; PDE-5i, phosphodiesterase-5 inhibitors; ETA, endothelin receptor antagonists.

Table 4. Anticoagulation effect and bleeding risk of warfarin after interventional treatments.

| | Total | | Clinically relevant bleeding | | Hemoptysis | | PH exacerbation or RHF | | Recurrent VTE | |
	n	Observation period (years)	n	Incidence (%/person-year)	n	Incidence (%/person-year)	n	Incidence (%/person-year)	n	Incidence (%/person-year)
No intervention	54	2.5 ± 2.1	11	8.1	4	2.9	5	3.7	2	1.5
Post-PEA	35	3.2 ± 1.7	10	8.9	1	0.9	3	2.7	1	0.9
Vasodilators +	20	2.2 ± 1.9	4	9.0	1	2.3	2	4.5	0	0.0
Vasodilators −	20	3.3 ± 1.8	7	10.7	0	0.0	1	1.5	1	1.5
Post-BPA	7	0.8 ± 1.1	0	0.0	0	0.0	0	0.0	0	0.0

PH, pulmonary hypertension; RHF, right heart failure; VTE, venous thromboembolism; PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty.

with pulmonary arteries and organized thrombi.[22,23] We hypothesized that the risk of hemoptysis might be increased after PEA and BPA. The results suggested that the risk might be lower than expected. Simonneau et al. reported that hemoptysis occurred in 8% of patients who were treated with sGC stimulator riociguat for residual PH after PEA.[14] In the current study, hemoptysis occurred in one of 35 patients (2.9%) during the postoperative periods and in none of seven patients during the post-BPA period.[14] To the best of our knowledge, very little information is available regarding bleeding events during the periods of stabilization after PEA and BPA; hence, further investigations to address this gap in knowledge are required.

Hyperanticoagulation tends to be associated with an increase in the bleeding risk. Certain antibiotics, anti-inflammatory drugs, fruits (such as grapefruit and mango), and alcohol can increase the anticoagulant effect of warfarin, resulting in a high risk of bleeding.[24] In particular, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) have antiplatelet effects and can induce gastric erosion, which increases the risk of gastrointestinal bleeding.[24] In the present study, two patients with major gastrointestinal bleeding and prolonged PT-INRs had received NSAIDs (data not shown). However, 86% of the clinically relevant bleeding events were not associated with hyperanticoagulation in the current study. Bronchiectasis is a major cause of hemoptysis.[25] In the current study, three of six patients with hemoptysis had bronchiectasis. Both patients who experienced major genital bleeding had histories of repeated prolonged menstruation that was associated with uterine myomas and endometrial hyperplasia. We believe that a patient's co-morbidities are associated with the risk of bleeding risk.

The incidence of recurrent VTE was 1.2%/person-year in this study. To the best of our knowledge, the incidence of recurrent VTE in CTEPH patients during anticoagulation therapy has not been clearly determined as yet. The findings from clinical trials of DOACs for the treatment of acute VTE showed that the incidence of recurrent VTE was 1.3–3.5% per half year in patients in the conventional treatment groups who were administered unfractionated or low-molecular-weight heparin followed by warfarin.[10,26–28]

Table 5. Comparison between the current study and a previous study.

	Current study	Henkens et al., 2007[12]
Study design	Retrospective	Retrospective
Study period	2011–2015	1997–2009
Vitamin K antagonists and number of patients receiving treatment	Warfarin: 72	Fenprocoumon: 14 Acenocoumarol: 46
Mean observation period (years)	3.60	4.85
Target range for PT-INR	1.5–3.0	N.A.
Background on start date		
Participants	CTEPH patients	Inoperable CTEPH patients
Patients (n)	72	60
Age (years)	59.7 ± 11.9	61 ± 14
Gender (n (male/female))	11/61	21/39
mPAP (mmHg)	41.4 ± 10.9	46 ± 11
PEA (n (%))	39 (54.1%)	0 (0%)
BPA (n)	10 (13.9%)	N.A.
Incidence of major bleeding (%/person-year)	5.1	2.4
Bleeding site		
Fatal bleeding (n (%))	0	0
CNS bleeding (n (%))	1 (1.4)	0
Hemopericardium (n (%))	1 (1.4)	0
Intra-articular bleeding (n (%))	1 (1.4)	0
Hemoptysis (n (%))	6 (8.3)	1 (1.7)
Gastrointestinal bleeding (n (%))	4 (5.6)	4 (6.7)
Urogenital hemorrhage (n (%))	3 (4.2)	0
Hematoma (n (%))	1 (1.4)	2 (3.3)
Nasal bleeding (n (%))	2 (2.8)	10 (16.7)
Bleeding associated with surgery or trauma (n (%))	4 (5.6)	N.A.

PT-INR, prothrombin time-international normalized ratio; mPAP, mean pulmonary arterial pressure; CNS, central nervous system; N.A., not analyzed; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty.

Three recurrent VTE events occurred when PT-INR values were < 2 in this study. It seems that the dose of warfarin in these cases might be sub-therapeutic. Further study to investigate the appropriate target dose of warfarin for CTEPH patients is needed.

In this study, the incidence of hospitalization due to the deterioration of PH or RHF was 3.1%/person-year. During the treatment of patients with inoperable CTEPH or those with residual PH after PEA with an sGC stimulator, the incidence of clinical worsening was 22% over an observation period of two years.[14] The present study included patients who did not have residual PH after PEA; hence, the discrepancy between the current study and the aforementioned study in relation to the incidence of deterioration of PH or RHF might be associated with differences in the characteristics of the participants.

The impact of polymorphisms of vitamin K epoxide reductase 1 (VKORC1) and cytochrome P450 2C9 (CYP2C9) on anticoagulant effect and bleeding risk was unclear. The polymorphisms of VKORC1 and CYP2C9 could be affected by the dose of warfarin.[29,30] However, it seems that the impact of polymorphisms of VKORC1 and CYP2C9 on anticoagulant effect and bleeding risk was unclear in the clinical setting. Kimmel et al. reported that there was no difference in the therapeutic range of PT-INR and the incidence of major bleeding or thromboembolism between genotype-guided and clinically guided groups.[31] In this study, the mean dose of warfarin in patients with or without clinically relevant bleeding at the end of observation period was 3.3 ± 1.0 or 3.8 ± 1.5 mg/day, respectively, and the difference was not significant ($P = 0.2$, data not shown).

The present study has several limitations. First, the study was retrospective and observational. Second, the study was performed at a single institution. Third, the sample size was relatively small. Therefore, precise evaluations of the bleeding event rates in large prospective studies are necessary. Finally, the polymorphisms of VKORC1 and CYP2C9 were not investigated in this study. However, the results of this study still shed light on the potential bleeding risk associated with anticoagulation in CTEPH patients.

In conclusion, warfarin effectively prevents VTE recurrence in CTEPH patients, but this may be associated with a considerable bleeding risk. Pulmonary vasodilators and co-morbidities might be associated with increases in the bleeding risk.

design, collection of data or their analysis, decision to publish, or the preparation of the manuscript.

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