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ORIGINAL ARTICLE

Long-term outcome of chronic thromboembolic pulmonary hypertension using direct oral anticoagulants and warfarin: a Japanese prospective cohort study

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Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) requires lifelong anticoagulation. Long-term outcomes of CTEPH under current anticoagulants are unclear.

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Objectives: The CTEPH AC registry is a prospective, nationwide cohort study comparing the safety and effectiveness of direct oral anticoagulants (DOACs) and warfarin for CTEPH.

Patients/Methods: Patients with CTEPH, both tre atment-naïve and on treatment, were eligible for the registry. Inclusion criteria were patients aged ≥20 years and those who were diagnosed with CTEPH according to standard guidelines. Exclusion criteria were not specified. The primary efficacy outcome was a composite morbidity, and mortality outcome comprised all-cause death, rescue reperfusion therapy, initiation of parenteral pulmonary vasodilators, and worsened 6-minute walk distance and WHO functional class. The safety outcome was clinically relevant bleeding, including major bleeding.

Results: Nine hundred twenty-seven patients on oral anticoagulants at baseline were analyzed: 481 (52%) used DOACs and 446 (48%) used warfarin. The 1-, 2-, and 3-year rates of composite morbidity and mortality outcome were comparable between the DOAC and warfarin groups (2.6%, 3.1%, and 4.2% vs 3.0%, 4.8%, and 5.9%, respectively; P = .52). The 1-, 2-, and 3-year rates of clinically relevant bleeding were significantly lower in DOACs than in the warfarin group (0.8%, 2.4%, and 2.4% vs 2.5%, 4.8%, and 6.4%, respectively; P = 0.036). Multivariable Cox proportional-hazards regression models revealed lower risk of clinically relevant bleeding in the DOAC group than the warfarin group (hazard ratio: 0.35; 95% CI: 0.13-0.91; P = .032).

Conclusion: This registry demonstrated that under current standard of care, morbidity and mortality events were effectively prevented regardless of anticoagulants, while the clinically relevant bleeding rate was lower when using DOACs compared with warfarin.

KEYWORDS
anticoagulants, hypertension, pulmonary, observational study, registries, venous thromboembolism

1 | INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of preceding pulmonary thromboembolism and develops in approximately 3% to 4% of patients with acute pulmonary thromboembolism [1,2]. The annual incidence of CTEPH per 100 000 people is reported to be 5.1 in the US, 3.3 to 5.0 in Europe, and 1.9 in Japan [3], and the number of patients with CTEPH has been increasing worldwide. Although specific treatments such as pulmonary endarterectomy, balloon pulmonary angioplasty, and pulmonary vasodilators have improved the hemodynamics and long-term survival of these patients [4–8], lifelong anticoagulation remains essential. Vitamin K antagonists (VKAs) are the first-line anticoagulants used in patients with CTEPH because of the abundant data and historical experience supporting the prevention of recurrent pulmonary embolism and worsening of CTEPH [9,10]. Four direct oral anticoagulants (DOACs) comprising dabigatran, rivaroxaban, apixaban, and edoxaban are currently available for the treatment of venous thromboembolism.

Essentials

- The efficacy and safety of direct oral anticoagulants (DOACs) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) remain unclear.
- This is the first report from the Japanese prospective nationwide CTEPH registry, aiming to assess the safety and effectiveness of DOACs in patients with CTEPH.
- Half of the patients with CTEPH in Japan use DOACs.
- DOACs are as effective as warfarin in preventing morbidity and mortality events, with a lower risk of clinically relevant bleeding (hazard ratio: 0.35; 95% CI: 0.13, 0.91; P = .032) under current clinical practice.

The safety and efficacy of the 4 DOACs in nonvalvular atrial fibrillation and venous thromboembolism have been established in large

clinical trials [11–21]. Notably, these trials provide evidence that DOACs have a lower risk of major bleeding than VKAs. Thus, major guidelines have currently recommended DOACs as the treatment of choice for venous thromboembolism, rather than VKAs [22,23]. Despite a lack of definite evidence supported by clinical trials, DOACs are increasingly being used for anticoagulation in patients with established CTEPH. Two CTEPH registries—the Turkish national database (sample size: n = 493) and the UK multicentre registry (sample size: n = 1000) reported use of DOACs in 21% and 36% of patients with CTEPH, respectively [24,25]. It is imperative to clarify whether DOACs are as safe and effective in patients with CTEPH as in patients with venous thromboembolism.

The CTEPH AntiCoagulants registry (CTEPH AC registry) is a nationwide registry started on August 20, 2018, in Japan. The current report presents the first results, as prespecified in the protocol, of this prospective nationwide cohort study aimed to compare the long-term safety and efficacy between DOACs and warfarin for the treatment of CTEPH under current clinical practice.

2 | METHODS

2.1 | Study design and setting

This prospective, observational, cohort study was conducted from August 2018 to December 2021, in compliance with the principles of the World Medical Association Declaration of Helsinki regarding investigations involving human subjects. The institutional review board of each participating institution approved this study. The study was registered at UMIN Clinical Trials Registry, which is an open access database (UMIN000033784). Thirty-three Japanese institutions nationwide participated in the study. The investigators obtained written informed consent from all registered subjects before participation according to the Patient Consent Form. Study oversight including source data verification was conducted by an independent clinical research organization (Soiken Corp) during the study. A full list of the institutions, personnel including the investigators, and the numbers and distribution of registered patients are provided in the Supplementary material.

2.2 | Study population

The inclusion and exclusion criteria are provided in Supplementary Table S1. The inclusion criteria were patients aged ≥20 years who were diagnosed with CTEPH. The diagnosis of CTEPH was based on imaging studies (ventilation-perfusion scan and CT pulmonary angiogram) and hemodynamic criteria (mean pulmonary arterial pressure ≥ 25 mm Hg and pulmonary artery wedge pressure ≤ 15 mm Hg at rest) [26]. Patients who had been treated with pulmonary endarterectomy, balloon pulmonary angioplasty, and/or pulmonary vasodilators were eligible, even though their mean pulmonary arterial pressure was lower than 25 mm Hg at registration. Thus, this registry included both treatment-naïve patients and patients on treatment. No specific exclusion criteria were defined. The registry was elaborated to collect a wide range of cases and information on real-world clinical practice of CTEPH, and to be a national database of CTEPH in Japan. Thus, the number of cases registered during the study period determined the sample size.

2.3 | Baseline characteristics and outcomes

After obtaining written informed consent, the investigators documented baseline characteristics. As baseline data, the most recent data available up to 12 months prior to registration were collected. Follow-up data were electronically recorded by the investigators in November of each year during the observation period. When the prespecified efficacy (primary and secondary) and safety outcomes occurred, the investigators input additional follow-up data to the registry. No independent clinical endpoint adjudication committee was organized. The investigators at each site reported clinical outcomes according to the prespecified definitions.

The primary efficacy outcome was the first occurrence of morbidity and mortality events, a composite endpoint composed of the following:

1. All-cause death,
2. Lung transplantation,
3. CTEPH worsening–related rescue pulmonary endarterectomy, rescue balloon pulmonary angioplasty, or start of parenteral pulmonary vasodilator, and/or
4. Reduction (≥15%) in 6-minute walk distance accompanied by worsening of WHO functional class.

The secondary efficacy outcome was the first occurrence of symptomatic venous thromboembolism.

The safety outcome was the first occurrence of clinically relevant bleeding, a composite endpoint composed of major bleeding and/or clinically relevant nonmajor bleeding. Major bleeding and clinically relevant nonmajor bleeding were determined according to the International Society on Thrombosis and Haemostasis (ISTH) definitions in nonsurgical patients [27,28].

2.4 | Statistical analysis

The full analysis set (FAS) was defined as patients taking oral anticoagulants. Demographics and CTEPH-related characteristics are presented as mean and standard deviation or percentage unless otherwise noted. Morbidity and mortality events, symptomatic venous thromboembolism, and clinically relevant bleeding were aggregated to identify the time from registration to the first occurrence of these events. The FAS was used for analyses of the primary, secondary, and/or safety outcomes. These patients, irrespective of the length of follow-up, were grouped according to the type of anticoagulants used

TABLE Demographic and baseline clinical data of patients with chronic thromboembolic pulmonary hypertension on oral anticoagulation therapy at baseline, classified into the DOAC and warfarin groups.

	DOACs (n = 481)	Warfarin (n = 446)	*P* value
Demographics			
Age, years	67 ± 13	67 ± 13	.74
Male, no. (%)	132 (27.4)	138 (30.9)	.25
Time from diagnosis to registration, median days (IQR)	352 (30-1123)	1113 (219-2449)	<.001
Disease severities			
WHO functional class, I/II/III/IV (no. [%])	80 (16.6)/238 (49.5)/156 (32.4)/7 (1.5)	77 (17.3)/253 (56.7)/110 (24.7)/6 (1.4)	.06
6-min walk distance, m	386 ± 122	395 ± 127	.32
Mean PAP, mm Hg	31.4 ± 11.7	28.8 ± 11.2	<.001
PVR, dyn·s·cm^{-5}	487 ± 339	426 ± 331	.006
Cardiac index, L/min/m^2	2.7 ± 0.7	2.7 ± 0.7	.93
Mixed venous oxygen saturation, no. (%)	66.7 ± 7.5	67.8 ± 7.7	.05
BNP, pg/mL	88 ± 154	115 ± 273	.08
Comorbidities/past medical histories			
Active cancer/history of cancer, no. (%)	26 (5.4)	28 (6.3)	.58
Thyroid disease or hormone replacement therapy, no. (%)	21 (4.4)	20 (4.5)	1.00
Intravenous device, no. (%)	18 (4.0)	19 (4.0)	1.00
COPD/ILD, no. (%)	20 (4.2)	17 (3.8)	.87
History of acute VTE, no. (%)	191 (39.7)	146 (32.7)	.03
Hemiplegia/paraplegia, no. (%)	5 (1.0)	2 (0.5)	.45
Use of antipsychotic, no. (%)	56 (11.6)	34 (7.6)	.04
Inflammatory bowel disease, no. (%)	1 (0.2)	3 (0.7)	.36
Comorbid ovarian/uterine disease, no. (%)	54 (11.2)	55 (12.3)	.61
Hypercoagulable disorder, no. (%)[a]	28 (5.8)	48 (10.8)	.008
Chronic kidney disease (eGFR ≤ 30 mL/min), no. (%)	2 (0.5)	8 (2.2)	.04
Use of antiplatelet agent, NSAIDs, no. (%)	5 (1.0)	11 (2.5)	.13
History of major bleeding, no. (%)	8 (1.7)	7 (1.6)	1.00
History of CTEPH-specific treatment			
Pulmonary endarterectomy, no. (%)	36 (7.5)	74 (17.0)	<.001
Balloon pulmonary angioplasty, no. (%)	252 (52.4)	269 (60.3)	.02
No reperfusion treatment, no. (%)	207 (43.0)	139 (31.2)	<.001
Anticoagulants			
Dabigatran, no. (%)	6 (1.3)		
Rivaroxaban, no. (%)	164 (34.1)		
Apixaban, no. (%)	154 (32.0)		
Edoxaban, no. (%)	157 (32.6)		
Prothrombin time-INR 2.0-3.0, no. (%)[b]		187 (42.8)	

(Continues)

TABLE (Continued)

	DOACs (n = 481)	Warfarin (n = 446)	*P* value
Pulmonary vasodilators			
Any pulmonary vasodilators, no. (%)	261 (54.3)	248 (55.6)	.69
PDE5 inhibitors/sGC stimulators, no. (%)	244 (50.7)	222 (49.8)	.79
Prostacyclin analog, PGI2 receptor agonist, no. (%)	36 (7.5)	50 (11.2)	.05
Endothelin receptor antagonist, no. (%)	39 (8.1)	45 (10.1)	.30

BNP, brain natriuretic peptide; COPD/ILD, chronic obstructive pulmonary disease/interstitial lung disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drug; PAP, pulmonary artery pressure; PDE5, phosphodiesterase 5; PGI2, prostaglandin I2; PVR, pulmonary vascular resistance; sGC, soluble guanylate cyclase; VTE, venous thromboembolism; WHO, World Health Organization.

[a] Details of hypercoagulable disorders are shown in Supplementary Table S5.

[b] The distribution of prothrombin time-INR is shown in Supplementary Figure S1.

at the time of registration: DOAC and warfarin (VKA currently used in Japan) groups. Kaplan-Meier estimates were used to estimate the cumulative event rate. Separate univariable and multivariable Cox proportional-hazards regression models that included all available data of the FAS were used to estimate the overall risks of morbidity and mortality events, symptomatic venous thromboembolism, and clinically relevant bleeding for selected covariates. As a sensitivity analysis, for a given anticoagulant, we used propensity-score models that were adjusted for the following variables: age; sex; time from diagnosis to registration; WHO functional class; 6-minute walk distance; pulmonary vascular resistance; brain natriuretic peptide; history of cancer, hypercoagulable disorder, acute venous thromboembolism, chronic kidney disease, and major bleeding; previous reperfusion treatment; and use of pulmonary vasodilators. Propensity-score matching was implemented using the 1:1 nearest-neighbor strategy. Our goal was to rule out a clinically meaningful difference in risk, which we defined a priori as an absolute standardized difference of at least 0.25 points. After generating the matched cohorts for each anticoagulant, we computed Kaplan-Meier estimates for the primary and safety outcomes, as for the FAS. A *P* value of $< .05$ is considered significant. Missing data imputation was not performed. Analyses were performed with JMP software, version 16 (SAS Institute Inc).

3 | RESULTS

3.1 | Demographic and patient characteristics

The baseline characteristics of the cohort are summarized in Table. A total of 956 patients were registered. After excluding 29 patients (no informed consent form: n = 5; no oral anticoagulation: n = 24), the FAS consisted of 927 patients who took DOACs or warfarin (Figure 1). Approximately one-half of patients with CTEPH on anticoagulants at baseline were using DOACs: DOACs were used by 481 patients (52%), and warfarin by 446 patients (48%). The age and sex ratio were comparable between the 2 groups. The median observation period was 825 (IQR; 499-886) days in the DOAC group and 838 (IQR;

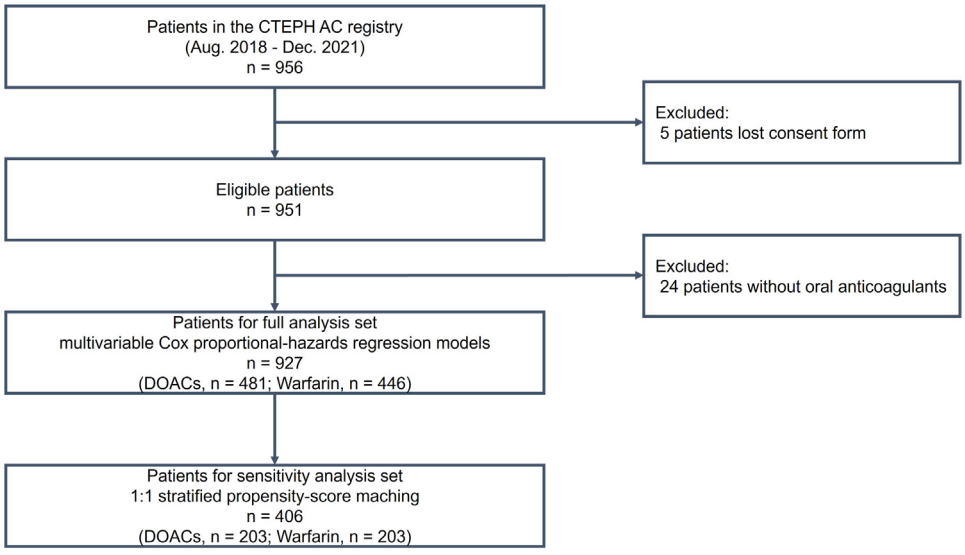

FIGURE 1 Patient disposition. CTEPH, chronic thromboembolic pulmonary hypertension; DOACs, direct oral anticoagulants.

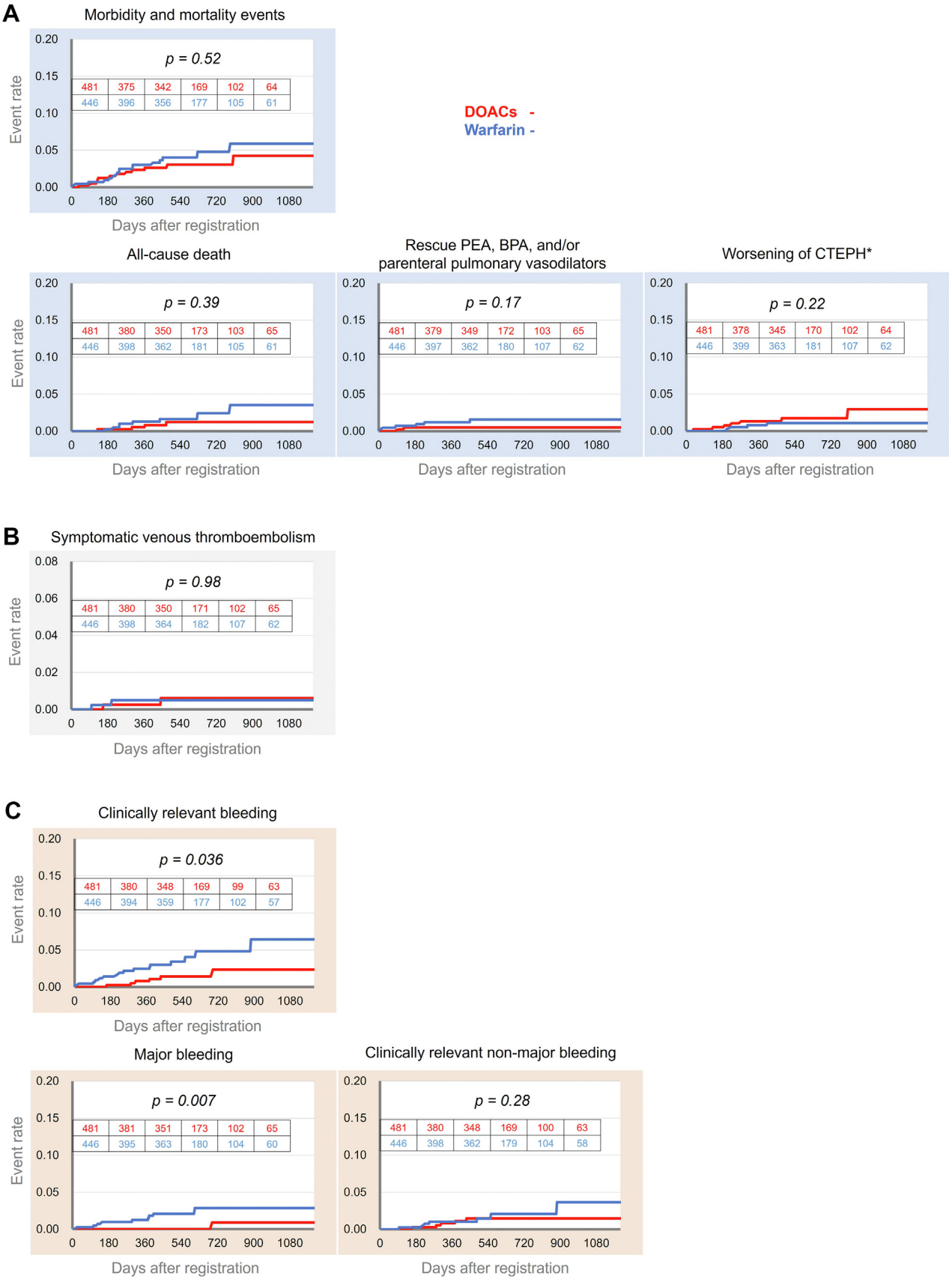

FIGURE 2 Kaplan-Meier analyses for the primary, secondary, and safety outcomes. Red indicates the DOAC group, and blue indicates the warfarin group. The table in each graph shows the numbers at risk. (A) Primary efficacy outcome: morbidity and mortality events defined as a

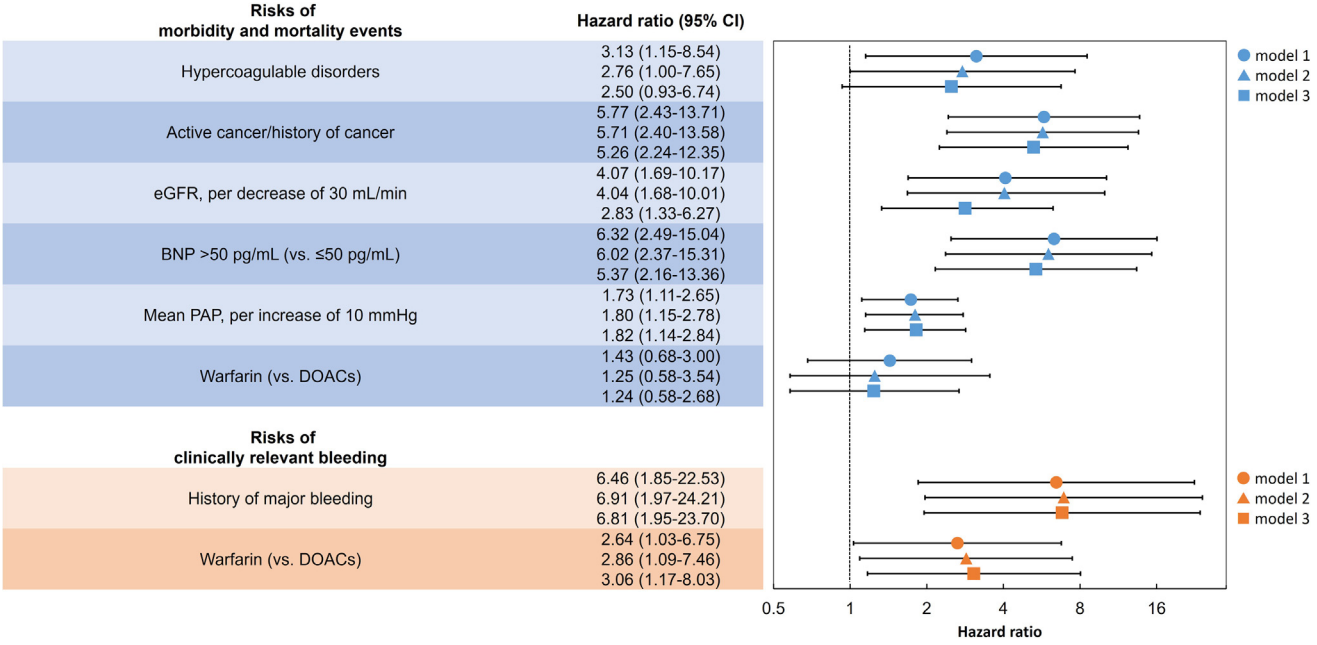

FIGURE 3 Independent risks of morbidity and mortality events and clinically relevant bleeding by multivariable Cox proportional-hazards regression models. Model 1: adjusted for age, sex, and pulmonary vascular resistance. Model 2: adjusted for age, sex, pulmonary vascular resistance, and time from diagnosis to registration. Model 3: adjusted for pulmonary vascular resistance, time from diagnosis to registration, history of acute venous thromboembolism, history of reperfusion treatment, and use of pulmonary vasodilators. Morbidity and mortality events are a composite endpoint comprising all-cause death; lung transplantation; CTEPH worsening–related rescue pulmonary endarterectomy, rescue balloon pulmonary angioplasty, or start of parenteral pulmonary vasodilators; and/or worsening of CTEPH defined as ≥15% reduction in 6-minute walk distance accompanied by worsening of the WHO functional class. Symbols and bars indicate hazard ratios and 95% confidence intervals, respectively. BNP, brain natriuretic peptide; CTEPH, chronic thromboembolic pulmonary hypertension; DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; PAP, pulmonary artery pressure; WHO, World Health Organization.

755-893) days in the warfarin group (P = .003). The time from diagnosis to registration (i.e., duration of disease) was significantly longer in the warfarin group [352 (IQR; 30-1123) days vs 1113 (IQR; 219-2449) days, P < .001]. The proportion of patients with a history of acute venous thromboembolism was significantly higher in the DOAC group (39.7% vs 32.7%; P = .03) than in the warfarin group. The proportion of patients with no history of reperfusion treatment (pulmonary endarterectomy or balloon pulmonary angioplasty) at baseline was significantly higher in the DOAC group (43.0% vs 31.2%; P < .001). The proportion of patients who used pulmonary vasodilators was comparable between the DOAC group and the warfarin group (54.3% vs 55.6%, P = .69). The mean pulmonary artery pressure and pulmonary vascular resistance were significantly higher in the DOAC group (mean pulmonary artery pressure: 31.4 ± 11.7 mm Hg vs 28.8 ± 11.2 mm Hg, respectively, P < .001; pulmonary vascular resistance, 487 ± 339 dyn·s·cm^{-5} vs 426 ± 331 dyn·s·cm^{-5}, respectively, P = .006).

3.2 | Primary outcome: morbidity and mortality events

The cumulative rates of morbidity and mortality events were comparable between the DOAC group and the warfarin group [1-, 2-, and 3-year event rates (95% CI): 2.6% (1.4%-4.8%), 3·1% (1.7%-5.5%), and 4.2% (2.1%-8.3%) in the DOACs group vs 3.0% (1.7%-5.3%), 4.8% (2.8%-8.0%), and 5.9% (3.4%-10.1%) in the warfarin group, respectively; P = .52] (Figure 2A). The cumulative rates of all-cause death, rescue reperfusion therapy and/or parenteral vasodilator use, and worsening of CTEPH were also comparable between the DOAC and

composite endpoint of all-cause death; lung transplantation; CTEPH worsening–related rescue pulmonary endarterectomy, rescue balloon pulmonary angioplasty, or start of parenteral pulmonary vasodilators; and/or worsening of CTEPH. Worsening of CTEPH is defined as ≥15% reduction in 6-minute walk distance accompanied by worsening of WHO functional class. No lung transplantation was reported. (B) Secondary efficacy outcome: symptomatic venous thromboembolism. (C) Safety outcome: clinically relevant bleeding comprising major bleeding and/or clinically relevant nonmajor bleeding. The definitions of major bleeding and clinically relevant nonmajor bleeding are in accord with the ISTH definitions [27,28]. BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; DOACs, direct oral anticoagulants; PEA, pulmonary endarterectomy.

warfarin groups (all $P > .05$). There was no case of lung transplantation. Parenteral vasodilator was started on day 1 after registration in only 1 patient in the warfarin group.

3.3 | Secondary outcomes: symptomatic venous thromboembolism

Four patients developed symptomatic venous thromboembolism. The cumulative rate of symptomatic venous thromboembolism was similar between the DOAC and warfarin groups ($P = .98$; Figure 2B). Two patients who developed symptomatic venous thromboembolism in the warfarin group had risks of active cancer/history of cancer. One of the 2 patients that took DOACs developed venous thromboembolism 12 days after a clinically relevant nonmajor bleeding event.

3.4 | Safety outcomes: major bleeding and/or clinically relevant nonmajor bleeding

The cumulative rate of clinically relevant bleeding was significantly lower in the DOAC group than in the warfarin group [1-, 2-, and 3-year event rates (95% CI): 0.8% (0.3%-2.5%), 2.4% (0.9%-5.9%), and 2.4% (0.9%-5.9%) in the DOACs group vs 2.5% (1.3%-4.5%), 4.8% (2.8%-8.3%), and 6.4% (3.4%-11.9%) in warfarin group, respectively; $P = .036$] (Figure 2C). The rate of major bleeding was also significantly lower in the DOACs group than in the warfarin group ($P = .007$), whereas the rate of clinically relevant nonmajor bleeding was not significantly different ($P = .28$).

3.5 | Independent risks for morbidity and mortality events and clinically relevant bleeding

To identify the independent risk factors for morbidity and mortality events as well as for clinically relevant bleeding in all patients with CTEPH regardless of the type of oral anticoagulant used, we analyzed the demographics and baseline patient characteristics by Cox proportional-hazards regression models. Univariable analyses identified active cancer/history of cancer, higher brain natriuretic peptide level, higher mean pulmonary arterial pressure, higher pulmonary vascular resistance, and lower estimated glomerular filtration rate as significant risk factors of morbidity and mortality events. Hypercoagulable disorder was identified as a potential risk factor of morbidity and mortality events (Supplementary Table S2). A history of major bleeding, use of warfarin, and higher pulmonary vascular resistance were identified as significant risk factors of clinically relevant bleeding (Supplementary Table S3). Three models adjusting for different sets of covariates identified these factors as independent risks: model 1 (adjusted for age, sex, and pulmonary vascular resistance); model 2 (adjusted for age, sex, pulmonary vascular resistance, and time from diagnosis to registration); and model 3 (adjusted for pulmonary vascular resistance, time from diagnosis to registration, history of acute venous thromboembolism, history of reperfusion treatment, and use of pulmonary vasodilators; Figure 3). The choice of warfarin or DOACs was a significant risk factor of clinically significant bleeding, but not of morbidity and mortality events in patients with CTEPH.

3.6 | Sensitivity analysis: Kaplan-Mayer analysis of propensity-score–matched patients

Propensity-score matching for 14 covariates measured in this study generated a matched DOAC cohort (n = 203) and warfarin cohort (n = 203) with unbiased baseline characteristics (Supplementary Table S4). Kaplan-Mayer analysis of the matched cohorts demonstrated a lower risk of clinically relevant bleeding in the DOAC group than in the warfarin group ($P = .037$), while the risk of morbidity and mortality events was comparable between the DOAC and warfarin groups (Supplementary Figure S2).

4 | DISCUSSION

This first large-scale prospective cohort study from the CTEPH AC registry reveals that one-half of the patients with CTEPH on oral anticoagulation therapy use DOACs in real-world clinical practice in Japan. In this registry, DOACs were comparable in efficacy to warfarin for the prevention of morbidity and mortality events as well as symptomatic venous thromboembolism. On the other hand, DOACs were superior in safety to warfarin in terms of clinically relevant bleeding.

4.1 | Choice of anticoagulants in real-world clinical practice

According to Japanese national statistics [29], currently, the number of patients with CTEPH is approximately 4000, with an annual increase of approximately 300. The CTEPH AC registry registered more than 900 patients, estimated to be around 25% of all Japanese patients with CTEPH. The rate of DOAC use was significantly higher in patients with a history of venous thromboembolism (Table), probably because DOACs are recommended as first-line anticoagulants for initial treatment and medium- to long-term prevention of venous thromboembolism [22,23]. In this study, DOACs were more frequently used than warfarin in patients with higher mean pulmonary arterial pressure, higher pulmonary vascular resistance, and no history of reperfusion therapy. This trend reflects that DOACs are more likely to be selected for newly diagnosed patients and is supported for a shorter time from diagnosis to registration in the DOAC group than in the warfarin group. On the other hand, the brain natriuretic peptide level was significantly higher in the warfarin group. The brain natriuretic peptide level increases during renal failure. Some patients with impaired renal function who used warfarin had brain natriuretic peptide levels exceeding 4000 pg/mL in the present study. DOACs are

contraindicated for patients with severe renal function impairment. This selection bias could have caused the difference in brain natriuretic peptide levels between the DOAC and warfarin groups. The proportion of comorbid hypercoagulable disorders was higher in the warfarin group than in the DOAC group. Recent clinical guidelines for pulmonary embolism recommend VKAs instead of DOACs for patients with high-risk triple-positive antiphospholipid syndrome [23] based on the increased events associated with the use of rivaroxaban in this condition [30]. This recommendation might have led to the preference for warfarin in patients with CTEPH and hypercoagulable disorders.

4.2 | Previous studies on anticoagulation therapy for CTEPH

The safety and efficacy of DOACs in nonvalvular atrial fibrillation and venous thromboembolism have been established in large clinical trials [11–21]. However, DOACs failed to show superiority or noninferiority to VKAs under some other conditions. In a randomized controlled trial of patients with rheumatic heart disease–associated atrial fibrillation, vitamin K antagonist therapy led to a lower rate of cardiovascular events or death than rivaroxaban therapy, with no difference in the rate of bleeding between the 2 groups [31]. A randomized controlled trial in patients with high-risk antiphospholipid syndrome reported unacceptable rates of thromboembolic events, particularly ischemic stroke, with the use of rivaroxaban compared to warfarin [30].

Recently, the Turkish CTEPH database demonstrated a higher risk of major bleeding in patients taking warfarin compared to rivaroxaban (hazard ratio [HR]: 1.94; 95% CI: 1.05-3.62; P = .03) [24], while the UK CTEPH registry showed a higher recurrence rate of venous thromboembolism in DOAC users (4.62%/person-year for DOACs vs 0.76%/person-year for VKAs; P = .008) [25]. The international registry EXPERT (EXPosurE Registry RiociguaT in patients with pulmonary hypertension; sample size: n = 956) aiming to monitor the long-term safety of riociguat from 2014 to 2018 also demonstrated higher embolic and/or thrombotic event rates in patients who took DOACs than in those who took VKAs after adjusting for drug-exposure period (4.6%/person-year for DOACs vs 1.7%/person-year for VKAs; not statistically tested) [32]. The present study demonstrated the superiority of DOACs to warfarin in terms of bleeding risk in patients with CTEPH (Figure 3), which is similar to the report from the Turkish database [24]. On the other hand, in contrast to the results of the UK registry and EXPERT, our study found few cases of symptomatic venous thromboembolism overall and showed comparable efficacy of DOACs and warfarin for the prevention of symptomatic venous thromboembolism. The UK registry registered patients with operable CTEPH and retrospectively analyzed the entire observation period including the perioperative period. The perioperative period is associated with several risks for venous thromboembolism, such as cessation of anticoagulation and bed rest. In addition, the definition of venous thromboembolism in the UK registry included incidental asymptomatic venous thromboembolism. The outcome measures in EXPERT, which adopted all thrombotic/embolic events including venous thromboembolism, may have overestimated the event rate compared to the current study. The low cumulative rates of symptomatic venous thromboembolism (0.31%/person-year for DOACs vs 0.30%/person-year for warfarin) in the current registry might be associated with the different definitions of venous thromboembolism and the different study population. Similarly, there was no advantage of warfarin over DOACs in terms of morbidity and mortality events. All-cause mortality was worse in the VKA group compared with the DOACs group in the Turkish registry due to bleeding complications (HR, 1.61; 95% CI, 0.89-2.99; P = .11) [24]. The superiority of DOACs to VKAs regarding both risks of mortality and major bleeding has been confirmed in nonvalvular atrial fibrillation [33]. The current study showed apparently slightly lower all-cause mortality in the DOAC group than the warfarin group (P = .39; Figure 2A), although the risk-adjusted models did not demonstrate the superiority of DOACs in terms of mortality (HR, 1.63; 95% CI, 0.47-5.67; P = .44). The current results suggest that DOACs could be acceptable as an alternative to warfarin, given the safety of DOACs as well as the comparable efficacy and usability.

4.3 | Patients who switched anticoagulants during the study period

Since the current study was an observational study, the anticoagulants were switched in some patients during the study period. Thirty-three patients (6.9%) who took DOACs at registration switched to warfarin, and 48 patients (10.8%) treated with the warfarin at registration switched to DOACs or no anticoagulant. The warfarin group was more likely to switch anticoagulant than the DOAC group (DOACs vs warfarin, P = .04). Anticoagulants are often switched when adverse events occur or when conditions unsuitable for anticoagulation develop (such as labile INR). The patients who switched anticoagulants in the present study were associated with a higher incidence of clinically relevant bleeding than those who did not switch (8.6% vs 1.8%, P = .002).

4.4 | Independent risks of morbidity and mortality events and clinically relevant bleeding

Figure 3 shows multivariable Cox proportional-hazards regression models after risk adjustment for various covariates. The analysis identified higher brain natriuretic peptide and increased mean pulmonary arterial pressure at baseline as the independent risk factors of morbidity and mortality events, which is reasonable because these factors reflect a severe disease state. In addition, comorbid cancer/a history of cancer was an independent risk of morbidity and mortality events. Several risk factors for developing thromboembolism coexist in patients with cancer, such as chemotherapy and immobilization, which contribute to a hypercoagulable state in these patients [34]. Moreover, patients with cancer had an extremely high recurrence rate of venous thromboembolism during VKA treatment than patients

without cancer [35]. In CTEPH, cancer-associated thrombosis might cause in situ thrombosis in pulmonary arterial lesions or recurrent asymptomatic venous thromboembolism. In this study, when we analyzed the DOAC and warfarin groups separately, comorbid cancer/a history of cancer remained an independent risk factor of morbidity and mortality events for both anticoagulants (HR = 4.98, 95% CI = 1.37-18.11, and P = .01 for DOACs; HR = 5.14, 95% CI = 1.67-15.80, and P = .004 for warfarin). The adjusted models indicated a lower estimated glomerular filtration rate as an independent risk of morbidity and mortality events (Figure 3). A lower glomerular filtration rate significantly increased the risk of all-cause death (risk-adjusted models: eGFR, per decrease of 30 mL/min—HR = 18.58, 95% CI = 3.72-92.69) without increasing the risk of rescue reperfusion therapy or worsening of CTEPH (data not shown). Impaired kidney function may be associated with death unrelated to CTEPH.

Meanwhile, the use of warfarin and a history of major bleeding were identified as the independent risk factors of clinically relevant bleeding in the risk-adjusted models (Figure 3). The risk of warfarin for bleeding events remained after adjusting for the history of major bleeding in addition to age, sex, and pulmonary vascular resistance (HR, 2.84; 95% CI, 1.11-7.31; P = .030). In addition, the Kaplan-Mayer estimates after propensity-score matching (sensitivity analysis) supported a lower bleeding risk in DOACs than in warfarin (P = .037; Supplementary Figure S2B).

4.5 | Study limitations

The current study has several limitations. First, given the observational design of the study, in the analyses of the association between the types of anticoagulation and clinical outcomes, the possibility of residual confounding cannot be completely ruled out despite adjustment for the known, measured confounders. Second, in the current study, the principal investigator at each site evaluated the clinical events, but central adjudication was not performed, which could have impacted the accuracy of the clinical event classification. Third, this study was a single-country prospective observational cohort study. To establish the DOACs as anticoagulant therapy for CTEPH, a randomized controlled trial and a larger, longer-term international registry are needed.

5 | CONCLUSIONS

The CTEPH AC registry study demonstrated that under the current standard of care, morbidity and mortality events in CTEPH were effectively prevented up to 3 years regardless of using DOACs or warfarin, while the clinically relevant bleeding rate was lower when using DOACs compared with warfarin.

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AUTHOR CONTRIBUTIONS

K.H. initially drafted the manuscript and the writing committee further developed it. K.A., K. Funakoshi, K. Todaka, K. Tatsumi, Y. Tamura, T.O., H.M., K.F., N.N., and H.T. contributed substantially to the conception and design of the work. K.H., Y. Taniguchi, T.I., S.A., I.T., J.Y., S.M., N.I., H.S., T.K., H.O., Y.F., and N.T. contributed substantially to the acquisition of data. K.H., K.A., K. Funakoshi, K. Todaka, and H.T. contributed to the analysis or interpretation of data. K.H. and K.A. were responsible for the decision to submit the manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to data interpretation, critical review and revision of the manuscript, and read and approved the final paper.

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DATA AVAILABILITY

Collaborations with the CTEPH AC registry study are open to biomedical institutions, always after an accepted proposal for a scientific work. Depending on the nature of the collaboration, electronic data or hard-copy data should be provided. All collaborations will be made after a collaboration agreement. Terms of the collaboration agreement will be specific for each collaboration, and the extent of the shared documentation (i.e., identified participant data, data dictionary, hard copy, or other specified data sets) will be also specifically set on the light of each work.

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SUPPLEMENTARY MATERIAL

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