Research Article

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Real-life data of direct anticoagulant use, bleeding risk and venous thromboembolism recurrence in chronic thromboembolic pulmonary hypertension patients: an observational retrospective study

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Abstract

Introduction: Lifelong anticoagulation is the cornerstone of the chronic thromboembolic pulmonary hypertension (CTEPH) treatment regardless of the additional pulmonary endarterectomy, balloon pulmonary angioplasty, or medical treatment alone. Aim of this study was to evaluate the rate of oral anticoagulant preferences and document direct oral anticoagulants' (DOACs') safety, efficacy in the CTEPH population.

Methods: Patients' demographic data obtained from database between September 2011 and April 2018. In-hospital events, death, venous thromboembolism (VTE) recurrence, bleeding events and anticoagulant therapy transition were recorded.

Results: We reviewed 501 CTEPH patients who observed 9.0 ± 8.5 years. All-cause death, all bleeding, recurrent VTE was observed in 15.6%, 31% and 12%. Forty-one patients (8.2%) were diagnosed as inoperable. Of all, 15.2% of operable patients remained as residual. All-cause mortality rates were 13.8% (57 pts.) in the warfarin group as compared with 9.7% (13 pts.) in rivaroxaban group (HR: 1.61, 95% CI, 0.89–2.99; *p*: 0.11). Higher bleeding events occurred with warfarin group (27.1%) as compared with rivaroxaban (24.6%; HR: 1.28, 95% CI, 0.86–1.88; *p*: 0.22). Major bleeding was significantly higher with warfarin group (HR: 1.94, 95% CI, 1.05–3.62; *p*: 0.03). Subgroup analysis of all-cause death revealed that this significance dominated by the rate of death according to bleeding events; warfarin versus those seen with rivaroxaban (4.85% vs. 2.2%; HR: 4.75, 95% CI: 1.12–20.16; $p = 0.03$). The rate of recurrent VTE was found 8.9% in the rivaroxaban group, 10.9% in warfarin group (HR: 1.21, 95% CI, 0.64–2.23; *p*: 0.55).

Conclusion: DOACs could be a safe and effective alternative for lifelong anticoagulant therapy in CTEPH patients. Rivaroxaban produced similar rates of thromboembolism and non-relevant bleeding compared to those associated with warfarin. The main difference was found with major bleeding that it was mainly associated with the death rate according to major bleeding. Using DOACs might be a more reasonable way to prevent bleeding events without increasing thromboembolic risk.

Keywords

chronic thromboembolic pulmonary hypertension, direct oral anticoagulant, warfarin, haemorrhage, thromboembolism

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is the consequence of unresolved organized thrombi within pulmonary vessels. This event triggers the

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progressive vascular remodelling and a gradual increase in pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), and right ventricular overload that can be manifested as right heart failure with associated death. CTEPH diagnosis can be made after three months of effective anticoagulant treatment.[1] Pulmonary endarterectomy (PEA) is the first-line treatment for CTEPH patients although it depends on a patient's characteristics, co-morbidities, and surgical accessibility.[2] Balloon pulmonary angioplasty (BPA) is an alternative approach that has been proven to increase the efficacy of exercise capacity and haemodynamics in inoperable/ recurrent or residual CTEPH patients.[3,4] However, lifelong anticoagulation is the cornerstone of the CTEPH treatment regardless of the additional PEA, BPA, or medical treatment alone. There is a lack of evidence concerning the effectiveness of anticoagulant treatment in the CTEPH population. There have only been a few studies dedicated to direct oral anticoagulant (DOAC) use in with CTEPH patients. Neither drug preference nor duration has been comprehensively evaluated. Our clinical practice and dedicated guidelines are based on data accumulated from acute or recurrent pulmonary embolism (PE) studies.[5–8] The increasing number of CTEPH patients has given rise to investigations on the use of DOACs in a dedicated population beyond the previously mentioned trials that involved acute PE patients. The aim of this study was to evaluate the rate of oral anticoagulant treatment preferences, and anticoagulant-associated bleeding risk, venous thromboembolism (VTE) recurrence, and death; to document DOACs' safety and efficacy in the CTEPH population.

Materials and methods

We identified the CTEPH patients between September 2011 and April 2018 by requesting for access to the hospital informatics database. Baseline characteristics, right heart catheterization (RHC) findings, echocardiographic data, in-hospital events, such as death and its cause, VTE recurrence, bleeding events, any need for anticoagulant therapy transition, and additional pulmonary arterial hypertension (PAH)-specific medical treatment usage were recorded. A connection was established with the patients who reside in another region by communicating with the expert centre of the related region to obtain these patients' latest medical records. If a patient did not attend a follow-up session, the patient or the patient's caregiver was interviewed by telephone. The participants of this study provided written informed consent.

Clinical endpoints and definition of outcomes

Patients were diagnosed as CTEPH according to European Society of Cardiology guidelines if they had a mean pulmonary arterial pressure (mPAP) of $\geq$25 mmHg, a wedge pressure of $\leq$15 mmHg that was demonstrated with RHC, and persistent pulmonary emboli as confirmed via lung perfusion /computed tomography pulmonary angiography (CTPA) scans, or the need for pulmonary angiography even after three months of effective anticoagulation.[1] Primary endpoints were death from any cause, recurrent VTE, major and minor bleeding, and residual CTEPH after medical or surgical treatment. Bleeding events were reviewed on the basis of the International Society of Thrombosis and Haemostasis criteria.[9] Major bleeding was defined as a reduction in haemoglobin levels to $>$2.0 g/dL, bleeding that requires transfusion of $>$2 U of blood, and bleeding in vital organs, for example, intracranial haemorrhage or a haemorrhage causing death. Minor bleeding was considered temporary haemorrhaging of the nose, gingiva, airway, gastrointestinal tract, muscle, or subcutaneous tissue. VTE recurrence was confirmed as new filling defects on a lung perfusion scan, PE via a CTPA scan, and deep venous thrombus on compression ultrasonography. HAS-BLED scoring system was utilized to assess a one-year risk of major bleeding in patients under anticoagulant treatment. The mean time in therapeutic range (TTR) indicates the effective warfarin treatment period, in which the International normalized ratio (INR) remains in the 2.0–3.0 range over time.

Statistical analysis

Statistical analyses were performed using the statistical package IBM-SPSS (Version 22.0; SPSS, NY). Continuous variables were expressed as mean $\pm$ standard deviation whereas categorical variables were expressed as frequencies (%). Comparisons between subgroups were performed by using the Wilcoxon signed-rank test for unpaired non-parametric variables and Fisher's exact test for frequencies. Median values were reported with the confidence intervals for non-parametric tests. The correlation was determined by using the Pearson's test. The significance of differences regarding categorical variables between groups was compared using χ^2 tests. A p value of $<$0.05 was considered statistically significant. Kaplan–Meier survival estimates were calculated. A separate log-rank test was used to determine the independent effect of anticoagulant therapy on survival. Cox regression was used for survival (time-to-event) analyses.

Results

We reviewed the medical records of 583 patients between 2011 and 2018. We excluded 36 chronic thromboembolic patients (6.2%) because this is a form of thromboembolism without pulmonary hypertension,[10] nine sarcomas (1.5%), and seven hydatid cyst patients (1.2%) from the registry because they will not require lifelong anticoagulation. Thirty patients (5.1%) were lost to follow-up (Fig. 1). Baseline demographics, RHC, and echocardiographic data are shown in Table 1.

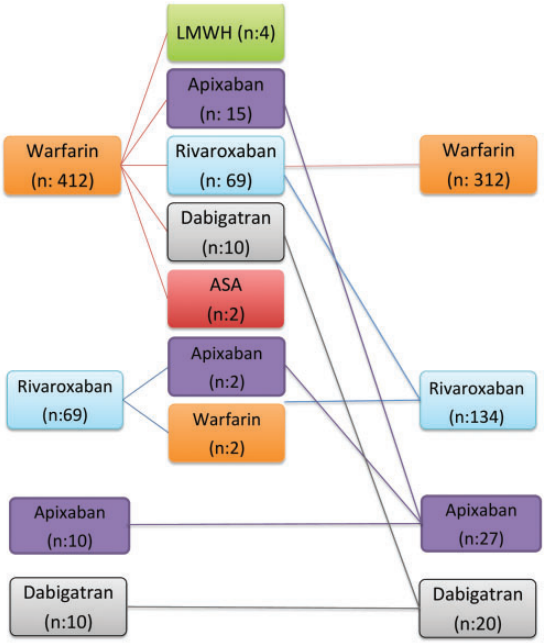

Fig. 1. Initial study population and excluded groups.

The total observation period was 9.0 ± 8.5 years. The rate of the primary endpoint of all-cause death, all bleeding, and recurrent VTE were found to be 15.6%, 31%, and 12%, respectively. The underlying reasons for death included several causes, namely, perioperative mortality, embolism recurrence, right heart failure, myocardial infarction, bleeding and respiratory failure in 19 (3.8%), 3 (0.6%), 24 (4.8%), 2 (0.4%), 24 (4.8%), and 6 (1.2%) patients, respectively (Fig. 2).

Forty-one patients (8.2%) were diagnosed as inoperable CTEPH after taking into account all of the patients' characteristics, co-morbidities, and lesions' surgical accessibility after a final review by the CTEPH team. Inoperable patients were older (mean age = 64), more female (70% vs. 50% with operable patients), higher rates of concomitant coronary artery disease (29.3% vs. 20% in operable patients), higher BMI (30 kg/m^2), and more NYHA Class IV patients (41.5%) than operable patients. PEA performed for the rest 460 patients. However, 15.2% ($n = 70$) of 460 operated CTEPH patients remained as residual PH after PEA and medical treatment. Residual PH patients have similar characteristics with operable patients (mean age = 55, 51% female gender, 27.1% NYHA Class IV patients, 20% concomitant coronary artery disease, BMI of 26 kg/m^2).

Univariate analysis showed that cardiac index, right atrial pressure, functional capacity, N-terminal pro-brain natriuretic peptide (NT pro-BNP levels), and PVR at diagnosis were associated with higher mortality (Table 2). Patients without coronary artery disease had lower risk for mortality (HR: 0.361; 95% CI: 0.179–0.730; $p = 0.005$).

The rates of recurrent VTE did not differ significantly between the DOAC and vitamin K antagonist (VKA) groups. Among all of the VTE events ($n = 60$), 50% of the DOACs were provided at non-recommended doses, and 55% of the VKA arm had untargeted INR values. Interestingly, recurrent VTE events have been observed less often in coronary artery disease patients (non-coronary artery disease: 71.2% vs. coronary artery disease: 28.8%, hazards ratio (HR): 4.35; 95% confidence interval (CI): 1.079–17.555; $p = 0.039$). Also, higher atrial pressures become significant in the patients with recurrent VTE ($p = 0.04$).

Table 1. Baseline demographics, right heart catheterization and echocardiographic data.

	CTEPH (n = 501)
Characteristic	
Age, years	53.54 ± 15.02
Gender, *n*; females (%)	254 (50.7%)
BMI, kg/m^2	28.15 ± 5.78
WHO FC, % (I/II/III/IV)	0/24.8/47.7/27.5
6MWD, m	278 ± 105
The median duration of observation, years	9.00 ± 8.5
NT pro-BNP (pg / ml)	722.33
mPAP, mmHg	47.06 ± 14.55
PVR, Wood Units, dyn·s^{-1}·cm^{-5}	9.16 ± 5.18
PCWP, mmHg	10.69 ± 2.93
Cardiac index, L/min/m^2	2.43 ± 0.95
RAP, mmHg	9.84 ± 4.19
Hypertension, *n* (%)	232 (46.3%)
Diabetes, *n* (%)	87 (17.4%)
Coronary artery disease (%)	95 (19.3%)
Time in therapeutic range at warfarin population (%)	50%
HAS-BLED score	3.31 ± 1.55
Echocardiographic parameters	
Peak tricuspid regurgitation velocity, m/s	3.85 ± 0.77
Ejection fraction (%)	62.86 ± 5.51
Estimated systolic pulmonary artery pressure, mmHg	72.16 ± 26.77
Tricuspid annular plane systolic excursion, mm	18.53 ± 4.37
Right ventricular systolic doppler velocity, cm/s	10.82 ± 2.05
E/A	1.00 ± 0.49
E/é	6.68 ± 2.42
Deceleration time, ms	186.18 ± 37.80
Right atrium area, cm^2	22.36 ± 6.60
Myocardial performance index	0.55 ± 0.11

CTEPH: chronic thromboembolic pulmonary hypertension; BMI: body mass index; WHO: World Health Organization; FC: functional capacity; 6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; RAP: right atrial pressure.

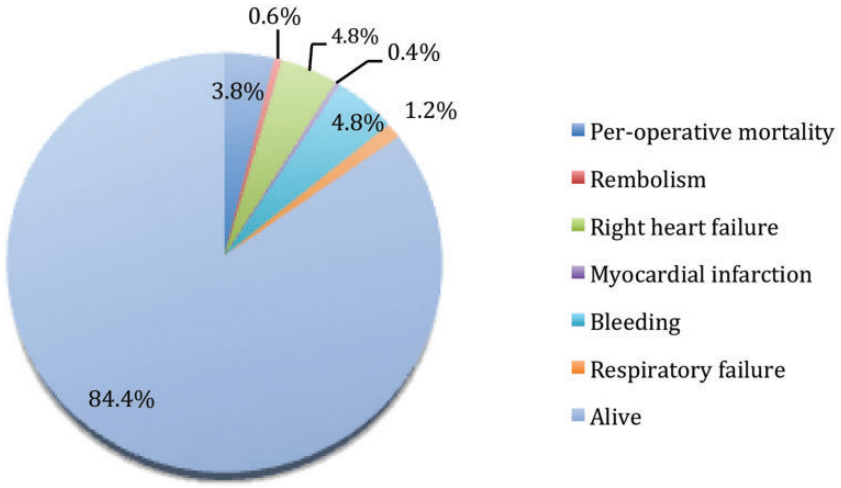

Fig. 2. Distribution of the underlying causes of death.

Table 2. Significant predictors of all-cause mortality.

All-cause mortality					$p < 0.05$
WHO functional class	Class I 0.0%	Class II 11.2%	Class III 40.2%	Class IV 48.6%	0.000†
NT-proBNP plasma levels	NT-proBNP <300 ng/l 10.5%	NT-proBNP 300–1400 ng/l 25.4%	NT-proBNP >1400 ng/l 37.1%		0.000†
RA area	RA area <18 cm^2 13.1%	RA area 18–26 cm^2 21%	RA area >26 cm^2 32.7%		0.02†
Cardiac index	CI ≥2.5 l/min/m^2 17.4%	2.4 l/min/m^2 ≥ CI ≥ 2 l/min/m^2 17.5%	CI >2 l/min/m^2 30.3%		0.006†
RA pressure	RAP <8 mmHg 9.6%	RAP 8–14 mmHg 18.4%	RAP >14 mmHg 30.3%		0.000†

†p-values of <0.05, that was accepted statistically significant. WHO: World Health Organization; CI: cardiac index; NT-proBNP: N-terminal pro-brain natriuretic peptide; RA: right atrium.

The rate of the bleeding events was higher among the patients with systemic hypertension, and higher HAS-BLED scores were significantly related to high bleeding risk. Major bleeding events showed a similar pattern with respect to all bleeding events, whereas the rate of minor bleeding events was significantly higher solely in the systemic hypertensive population (Table 3).

The majority of the patients were initially discharged with VKAs ($n = 412$, 82.2%). In the VKA group, 24.2% ($n = 100$) of the patients had transitioned to other treatments during the follow-up period. Four patients transitioned to low-molecular weight heparin (LMWH) owing cancer-associated VTE events. Sixteen patients switched their anticoagulant therapy to DOACs because of major or minor bleeding, 10 patients because of re-embolism despite therapeutic drug doses, and 70 patients because of out-of-range INR levels. Major bleeding events (intracranial and gastrointestinal) were recorded in two patients receiving VKA treatment, which was repeated after switching to a different

Table 3. The rate of significant predictor incidence at each bleeding event.

The rate of significant predictor incidence at each bleeding event	$p < 0.05$
Systemic hypertension	
All bleeding events 59.7%	**0.000**†
Major bleedings 69.4%	**0.000**†
Minor bleedings 56.1%	**0.012**†
HAS-BLED score ≥3	
All bleeding events 51.9%	**0.001**†
Major bleedings 62.9%	**0.000**†
Minor bleedings 48%	0.570

kind of DOAC or LMWH. Therefore, off-label acetylsalicylic acid administration was initiated. Two patients stopped their medication on purpose. In the DOAC group, 0.79% ($n=4$) of patients who were treated with 20 mg of rivaroxaban changed their initial treatment to VKA ($n=2$) and apixaban ($n=2$) therapy because of underlying major bleeding events. Twenty-eight major and 77 minor bleeding events were recorded in patients undergoing VKA therapy with the average TTRs of 50% and 49.9%, respectively. One hundred three patients (25.4%) continued warfarin therapy despite bleeding caused by a decrease in creatinine clearance (<35 ml/min). After switching the initial therapy, the redistribution of oral anticoagulant preferences was demonstrated as shown in Fig. 3.

Notably, the majority of the prescribed anticoagulants were mainly, warfarin and rivaroxaban. Edoxaban was not yet approved during the study period. For dabigatran or apixaban, the reduced sample sizes and end-points limited the ability to draw definitive conclusions. Thus, comparison was made between warfarin and rivaroxaban. The clinical outcomes are listed in Table 4. All-cause mortality rates were 13.8% (57 pts.) in the warfarin group as compared with 9.7% (13 pts.) in the rivaroxaban group (HR: 1.61; 95% CI: 0.89–2.99; $p=0.11$). Higher rates of bleeding events were observed in the warfarin group (27.1%) than in the rivaroxaban (24.6%) (HR: 1.28; 95% CI: 0.86–1.88; $p=0.22$). The rate of major bleeding was significantly higher in the warfarin group (HR: 1.94; 95% CI: 1.05–3.62; $p=0.03$). Subgroup analysis of all-cause death revealed that this significance dominated the death rate according to bleeding events: warfarin versus those seen with rivaroxaban (4.85% vs. 2.2%; HR: 4.75; 95% CI: 1.12–20.16; $p=0.03$). The rates of recurrent VTE were found to be 8.9% in the rivaroxaban group, 10.1% in warfarin group (HR: 1.21; 95% CI: 0.64–2.23; $p=0.55$). The Kaplan–Meier survival analysis and hazard functions were demonstrated in Fig. 4.

The most of the recurrent VTE events occurred in the VKA group (89.8%) followed by 8.5% in the rivaroxaban group, and 5% in the dabigatran group without any significant differences. No recurrent VTE was experienced with apixaban in our study population. We detected 155 bleeding events, including 72.2% with warfarin, 21.3% with rivaroxaban, 3.9% with dabigatran and 2.6% with apixaban (Table 5).

Hereditary and acquired prothrombotic traits in patients with CTEPH were evaluated according to recurrent and non-recurrent VTE patients. Antiphospholipid antibodies (APA) is the most frequent coagulopathy among our CTEPH population (n: 74, 14.8%, n: 12 with recurrent VTE, n: 62 with non-VTE population) followed by lupus anticoagulant (LA; $n=48$, 9.6%, $n=12$ with recurrent VTE, $n=36$ with non-VTE population), Factor V Leiden mutation ($n=26$, 5.1%, $n=9$ with recurrent VTE, $n=17$ with non-VTE population), antithrombin (AT) deficiency ($n=10$, 1.2%, $n=2$ with recurrent VTE, $n=8$ with non-VTE population), protein C deficiency ($n=2$, 0.4%, $n=0$ with recurrent VTE, $n=2$ with non-VTE population) and protein S deficiency (0%). There were no significant differences in the frequencies of AT, protein C, and protein S deficiencies between the recurrent VTE and non-recurrent VTE groups ($p>0.05$). With regard to the acquired thrombotic risk factors, we have found no significant difference in the frequencies of APA between the two groups of patients ($p=0.22$). When we cumulate all coagulopathies and compare the recurrent VTE ratio among all CTEPH population, recurrent VTE incidence increased accompanied by coagulopathies ($n=35$, 58.3%, HR: 2.78; CI: 1.47–5.28, $p=0.02$). Most of the prothrombotic patients were on VKA treatment, the small amounts of non-VKA group inhibited us to perform comprehensive statistical analysis.

The average TTR level of patients who have experienced bleeding events while undergoing warfarin treatment was 49.6% ± 17.1%. Effective TTR levels (≥70%) were found

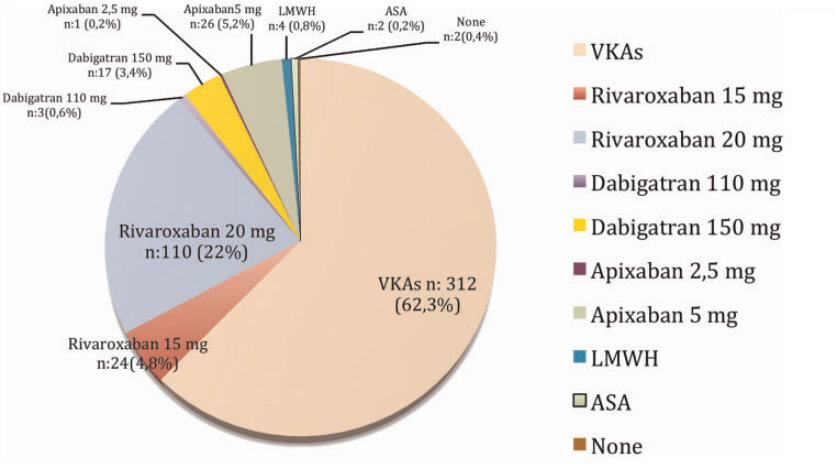

Fig. 3. Final distribution of oral anti-coagulant preferences. LMWH: low molecular weight heparin; ASA: acetylsalicylic acid; VKAs: vitamin K antagonists.

Table 4. Clinical outcomes, comparing warfarin with rivaroxaban.

Outcome	Warfarin	Rivaroksaban	Hazard ratio (95% CI)*	*p* value
	n: 412	*n*: 134		
Recurrent venous thromboembolism, no. (%) (*n*: 60)	42 (10.1%)	12 (8.9%)	1.21 (0.64–2.23)	0.55
Major or clinically relevant nonmajor bleeding during treatment, no. (%)	112 (27.1%)	33 (24.6%)	1.28 (0.86–1.88)	0.22
Major bleeding episode, no. (%)	**61 (14.8%)**	**12 (8.9%)**	**1.94 (1.05–3.62)**	**0.03†**
Clinically relevant nonmajor bleeding episode, no. (%)	51 (12.3%)	24 (17.9%)	1.30 (0.80–2.12)	0.27
Death during intended treatment period, no. (%)	57 (13.8%)	13 (9.7%)	1.61 (0.89–2.99)	0.11
Peri-operative mortality	16 (3.8%)	3 (2.2%)		
Re-embolism	2 (0.5%)	1 (0.7%)		
Right heart failure	14 (3.4%)	5 (3.7%)		
Myocardial infarction	2 (0.5%)	0 (0%)		
Bleeding	**20 (4.85%)**	**3 (2.2%)**	**4.75 (1.12–20.16)**	**0.03†**
Respiratory failure	3 (0.7%)	1 (0.7%)		
Inoperable CTEPH patients (n: 41)	*n*: 10	*n*: 26		
Recurrent venous thromboembolism, no. (%)	2 (20%)	3 (11.5%)		0.34
Major or clinically relevant nonmajor bleeding during treatment, no. (%)	2 (20%)	4 (15.3%)		0.17
Major bleeding episode, no. (%)	1 (10 %)	1 (3.8%)		0.5
Clinically relevant nonmajor bleeding episode, no. (%)	1 (10%)	3 (11.5%)		0.27
Death during intended treatment period, no. (%)				
Right heart failure	1 (10%)	2 (7.7%)		0.68
Residual PH patients (n: 70)	*n*: 35	*n*: 21		
Recurrent venous thromboembolism, no. (%)	7 (20%)	3 (14.3%)		0.12
Major or clinically relevant nonmajor bleeding during treatment, no. (%)	10 (28.5%)	5 (23.8%)		0.79
Major bleeding episode, no. (%)	4 (11.4%)	2 (9.5%)		0.79
Clinically relevant non-major bleeding episode, no. (%)	6 (17.1%)	3 (14.3%)		0.13
Death during intended treatment period, no. (%)	6 (17.1%)	3 (14.3%)		0.74

*Hazard ratios are for rivaroxaban as compared with warfarin.

in 28.5% of the major bleeding group and 40% in the minor bleeding group. Overall, in the warfarin-bleeding group, only 38.6% of the patients had effective TTR levels. Bleeding event distribution according to the bleeding site and oral anticoagulation are shown in Table 4. The PAH-specific drug utilization rate was 42%. The distributions of the preferences were 9% bosentan, 75.2% riociguat, 8.6% iloprost, 1.4% ambrisentan, 2.5% sildenafil, 0.95% tadalafil, 1.4% bosentan + iloprost + sildenafil, and 0.95% bosentan + iloprost + riociguat. There were no statistically significant differences among all PAH-specific drugs based on bleeding events.

Discussion

To the best of our knowledge, this study is the largest retrospective study investigating the safety and efficacy of DOACs in the CTEPH population. We demonstrated that rivaroxaban is a safe alternative to VKAs without any evidence of an increase in recurrent VTE or relevant bleeding. Besides, warfarin has been associated with significantly higher major bleeding rates as compared with rivaroxaban, especially death related to bleeding.

Notably, in our study, warfarin was the most favoured anticoagulant among the oral anticoagulants. The prescription rate of all DOACs was about 36%. Our rate of DOAC prescription was below the rates that were observed in the French[11] and XALIA registries.[12] These were the first and last published registries investigating the DOACs for treating acute PE episodes, respectively. Whereas the French registry demonstrated that the prescription rate of DOACs was >70%, in the XALIA registry, 51% of patients received DOACs upon discharge. The sparse data on DOACs in the CTEPH population may have discouraged physicians from prescribing DOACs as an initial treatment.

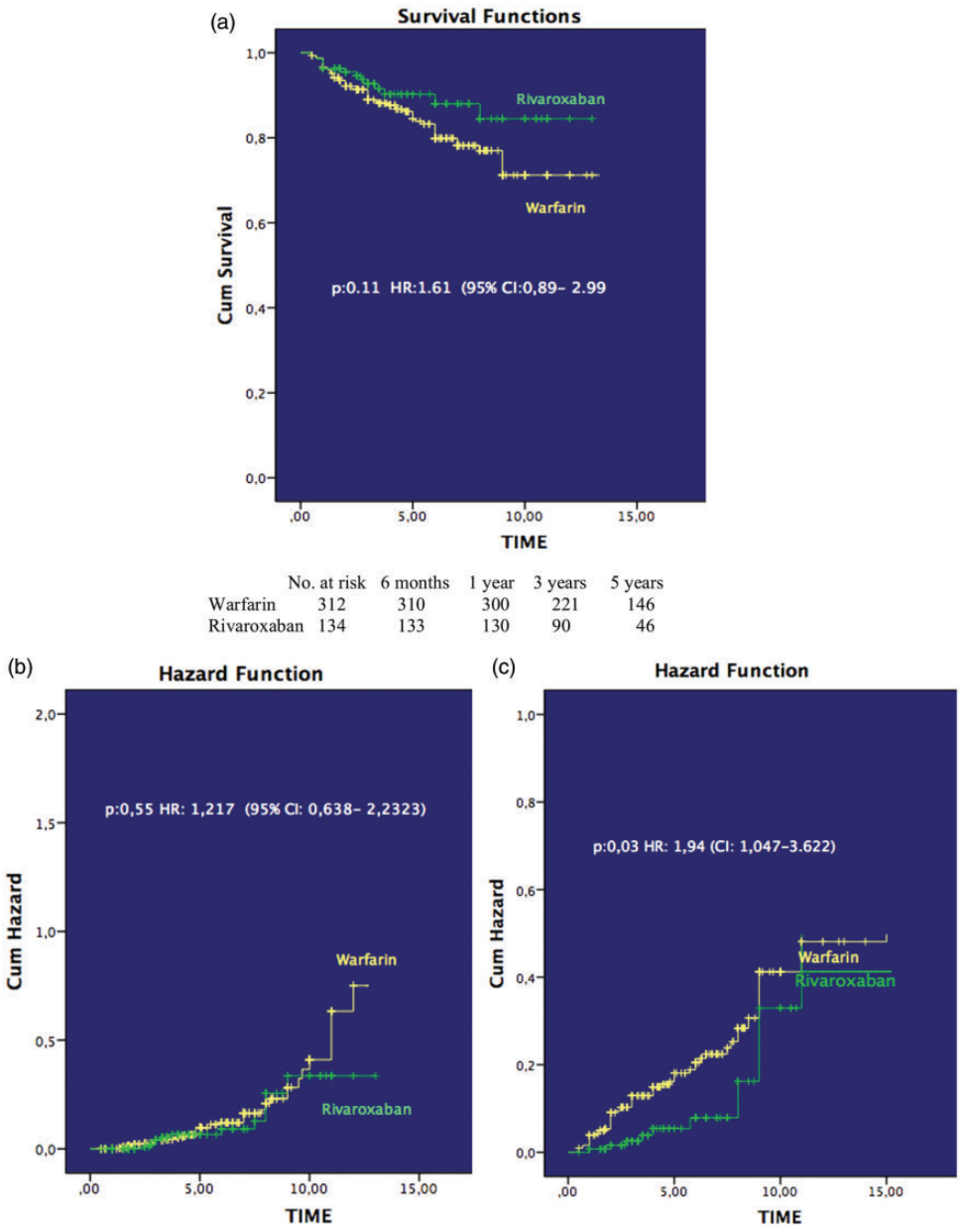

Fig. 4. Kaplan–Meier; (a) survival analysis, (b) hazard functions for recurrent VTE, (c) hazard functions for major bleeding when comparing warfarin with rivaroxaban.

DOACs were prescribed at the recommended dose in 84.7% of the patients in our study. Care was taken in order to prevent severe renal insufficiency and cancer-associated VTE patients from receiving DOACs. Cancer-associated patients were directed to LMWH prescription since randomized controlled trials demonstrated that LMWH reduced VTE recurrence better than warfarin.[13] The additional need for antiplatelet drugs, renal insufficiency and advanced age may cause a physician to be reluctant in prescribing the recommended dose.[14]

When we compared the HAS-BLED scores of each anticoagulant treatment group; higher (HAS-BLED $\geq$3) scores were observed with the warfarin group (71.4%) than with the rivaroxaban group (67.8%) without a major difference. In the warfarin group, the TTR was 60.4% and that INR exceeding 3.0 was 28.1%; meanwhile in the EINSTEIN-PE[5] study, similar rate (62.7%) of TTR was observed, with lower rates for INR exceeding 3.0 (15.7%). Unfavoured INR levels and higher HAS-BLED scores may facilitate the bleeding events in our study. Similar to our results, major bleeding was observed with higher rates with warfarin (2.2%) than with rivaroxaban (1.1%; HR: 0.49; 95% CI: 0.31 to 0.79; $p = 0.003$) in EINSTEIN-PE study.[5] We considered that the difference between the rates of bleeding events was associated with a longer observation time in our study with a more frail population in a chronic process

Table 5. Major and minor bleeding sites according to oral anticoagulants.

	Warfarin	Rivaroxaban 15 mg	Rivaroxaban 20 mg	Dabigatran 110 mg	Dabigatran 150 mg	Apixaban 2.5 mg	Apixaban 5 mg	Total
All bleeding	112	9	24	2	4	0	4	155
Major bleeding	61	3	9	1	2	0	1	77
Gastrointestinal	13	2	2	1				
Intracranial	6				2			
Hemopericardium	9							
Genito-urinary	4		1				1	
Hemoptysis	25	1	5					
Nasal	1							
Retroperitoneal	3		1					
Minor bleeding	51	6	15	1	2	0	3	78
Nasal	9	2	2					
Oral & gingival	13	3	3	1	1		2	
Genito-urinary	12	1	6				1	
Gastrointestinal	7		2		1			
Subcutaneous	3		2					
Hemoptysis	7							

LMWH: low molecular weight heparin; UFH: unfractionated heparin.

than acute PE population. The rates of recurrent VTE were found to be 8.9% in the rivaroxaban group, 10.1% in the warfarin group (HR: 1.21, 95% CI: 0.64–2.23; $p = 0.55$) whereas in EINSTEIN-PE[5] study these rates were found to be 2.1% in the rivaroxaban group while 1.8% in the warfarin group (HR: 1.12, 95% CI: 0.75–1.68; $p = 0.003$) for acute PE patients. The prothrombotic tendency might have a role in facilitating the development of the thromboembolic period. The current results confirm that as the most frequent coagulopathy in our study, APAs along with LA were two thrombophilic factors associated with recurrent thrombosis. The incidence of APA in our study (14.8%) is consistent with the findings that have been previously pronounced between 10% and 24%.[15,16] Factor V Leiden deficiency can be detected in 4–6.5%[16,17] while inherited deficiencies of coagulation inhibitors such as antithrombin III (AT III), protein C, and protein S are rare with prevalence approximately 5%.[18] We noticed that in over half of recurrent VTE patients (58.3%) had an underlying prothrombotic deficiency. We suggest that these acquired or inherited deficiencies are associated with high rates of recurrent VTE. But the coagulation deficiencies involved in CTEPH is a comprehensive topic and a detailed investigation will be the subject of a separate publication. For coronary artery disease patients, low rates of VTE recurrence can be explained by additive anti-platelet drugs on anticoagulants.

On the other hand, the preference for DOACs over VKAs was associated with a lack of concern about drug and food interactions, no continuous monitoring, and expected better compliance among patients with low TTR levels. Our results indicate that rivaroxaban was the leading drug (26.8%) among the DOACs as it was the first approved DOAC on the national market followed by apixaban (5.4%) and dabigatran (4%). The small patient sample size using dabigatran and apixaban restricted the utility of the statistical analysis. Thus, we have analyzed the outcomes between rivaroxaban and warfarin groups. The rate of major bleeding events was significantly higher in the warfarin group (HR: 1.94, 95% CI: 1.05–3.62; $p = 0.03$). Subgroup analysis of all-cause death revealed that, for death related to bleeding events, warfarin demonstrated a higher risk than rivaroxaban (4.85% vs. 2.2%; HR: 4.75, 95% CI: 1.12–20.16; $p = 0.03$).

As it is well known that, PEA is associated with an excellent long-term survival and a marked improvement in clinical status and hemodynamics. On the other hand, long-term survival is poor in inoperable and residual CTEPH patients with severe functional limitations and poor quality of life.[19,20] The factors influencing short- and long-term mortality are numerous as operative complications, post-operative PH, need for additional cardiac surgery concomitantly with the PEA, and a history of cancer or other morbidities, also preoperative level of PVR.[21,22] mPAP,[23] NYHA functional class, RAP,[24] preoperative use of PAH-specific medical treatment,[25] and associated medical conditions that Bonderman et al. demonstrated.[26] Thus it seemed to be difficult to design a real-life study to determine the pure effect of DOACs on mortality and morbidity by ignoring the underlying factors influencing short- and long-term mortality. We demonstrated that the main difference between VKAs and rivaroxaban was at major bleeding and death

related to bleeding without any significant difference in all-cause or perioperative mortality. These results represent the increased bleeding risk attributed to VKAs in comparison with rivaroxaban. Having said that in randomized trials of DOACs versus VKAs for the treatment of acute PE, DOACs were associated with significantly less bleeding risk.[5–8] Therefore we suggest that prescription of DOACs rather than VKAs reduce the risk of bleeding in CTEPH patients as same as acute PE patients. We emphasize the physicians' concerns about DOACs in CTEPH population due to the absence of robust data from randomized, controlled trials. But the only study dedicated to DOAC use in CTEPH patients was a case series report involving 20 patients.[27] Case series reports have a similar pattern with respect to age, body mass index, and gender when compared with our study, whereas functional capacity, 6 min walking distance, and NT pro-BNP levels at the initial presentation, introduced a higher mortality risk in our study population.[28] Similarly, in this study rivaroxaban was the leading DOAC (16 of 20 patients). One patient died after trauma-related bleeding. No VTE episodes were observed during the follow-up period. It is difficult to compare the primary endpoints owing to the small sample size, short follow-up duration, and absence of a VKA group. There is an urgent need for additional prospective, randomized, multicenter trials in order to establish routine DOAC use in CTEPH patients.

The strength of this study was its largest population with the longest follow-up period, to the best of our knowledge. The follow-up period was also a limitation of this study, which could favour adverse events in the warfarin population because of its earlier release to the national market. The other limitation of this study was its retrospective nature, in addition to the use of patient data from a single centre only.

Conclusion

DOACs could be a safe and effective alternative to lifelong anticoagulant therapy in CTEPH patients. Rivaroxaban produced similar rates of thromboembolism and non-relevant bleeding similar to those associated with VKAs. The main difference was found with major bleeding that was mainly associated with the death rate related to major bleeding. Using DOACs would be a more reasonable way of preventing bleeding events without increasing thromboembolic risk. However, we hope that prospective, randomized, and multicenter studies will be carried out to help us to fill the gaps on DOAC usage in CTEPH patients.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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