Journal of the American Heart Association

ORIGINAL RESEARCH

Selection of Home Treatment and Identification of Low-Risk Patients With Pulmonary Embolism Based on Simplified Pulmonary Embolism Severity Index Score in the Era of Direct Oral Anticoagulants

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BACKGROUND: The simplified Pulmonary Embolism Severity Index (sPESI) score could help identify low-risk patients with pulmonary embolism for home treatment. However, the application of the sPESI score and selection for home treatment have not been fully evaluated in the direct oral anticoagulants era.

METHODS AND RESULTS: The COMMAND VTE (Contemporary Management and Outcomes in Patients With Venous Thromboembolism) Registry-2 is a multicenter registry enrolling consecutive patients with acute symptomatic venous thromboembolism. The current study population consists of 2496 patients with hemodynamically stable pulmonary embolism (2100 patients [84%] treated with direct oral anticoagulants), who were divided into 2 groups: sPESI scores of 0 and ≥1. We investigated the 30-day mortality, home treatment prevalence, and factors predisposing to home treatment using the Kaplan-Meier method and logistic regression model. Patients with an sPESI score of 0 accounted for 612 (25%) patients, and only 17% among 532 patients with out-of-hospital pulmonary embolism were treated at home. The cumulative 30-day mortality was lower in patients with an sPESI score of 0 than the score of ≥1 (0% and 4.8%, log-rank P<0.001). There was no patient with 30-day mortality with an sPESI score of 0. Independent factors for home treatment among out-of-hospital pulmonary embolism patients with an sPESI score of 0 were no transient risk factors for venous thromboembolism, no cardiac biomarker elevation, and direct oral anticoagulants use in the acute phase.

CONCLUSIONS: The 30-day mortality rate was notably low in an sPESI score of 0. Nevertheless, only a minority of patients with an sPESI score of 0 were treated at home between 2015 and 2020 after the introduction of direct oral anticoagulants for venous thromboembolismin Japan.

Key Words: home treatment ■ mortality ■ pulmonary embolism ■ risk stratification ■ sPESI score

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This article was sent to Yen-Hung Lin, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.034953

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We investigated the association between a low simplified Pulmonary Embolism Severity Index (sPESI) score and 30-day mortality, home treatment strategies among patients with a low sPESI score in the real world, and factors related to home treatment in the direct oral anticoagulants era.

What Are the Clinical Implications?

- The sPESI score can be used to predict 30-day mortality even in the era when direct oral anticoagulants were primarily used for venous thromboembolism.
- A minority of patients with an sPESI score of 0 were treated at home, and home treatment could have been determined based on other factors besides sPESI score.

Nonstandard Abbreviations and Acronyms

COMMAND VTE	Contemporary Management and Outcomes in Patients With Venous Thromboembolism
DOAC	direct oral anticoagulant
sPESI	simplified Pulmonary Embolism Severity Index

Venous thromboembolism (VTE), consisting of pulmonary embolism (PE) and deep vein thrombosis (DVT), is widely encountered in daily clinical practice,[1] and PE is a potentially life-threatening disease. Previous studies reported that the 30-day mortality rate of PE was still high at ≈10%.[2–4] However, the mortality rate of PE has been decreasing over time, which suggests the impact of increased awareness of PE, the easy availability of computed tomography, and improved therapeutic strategies in the current era.[5–7] According to previous reports and the current guidelines, some patients with PE can be treated safely at home if selected appropriately.[8–16] Thus, appropriate selection of low-risk patients with PE has become more clinically relevant.

Several risk stratification models have been proposed to assess the acute mortality risk in patients with PE.[17] Among them, the Pulmonary Embolism Severity Index score and its simplified version (simplified Pulmonary Embolism Severity Index [sPESI]) score might be the most practical score for predicting 30-day mortality, which have undergone extensive validation in previous studies.[18–20] The sPESI score has been validated not only in the vitamin K antagonist era but also in the direct oral anticoagulant (DOAC) era,[21,22] although there have been limited data on the validation in large-scale databases. In addition, there have been limited data on how to select patients with PE for home treatment in current daily clinical practice. Therefore, we sought to investigate the usefulness of predicting low 30-day mortality in patients with a low sPESI score, home treatment strategies among patients with a low sPESI score in the real world, and factors related to home treatment in the DOAC era using a large observational VTE database in Japan.

METHODS

Data Availability

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, if the relevant review board or ethics committee approves the data sharing and all investigators of the COMMAND VTE (Contemporary Management and Outcomes in Patients With Venous Thromboembolism) Registry-2 give consent, the deidentified participant data will be shared on a request basis through the principal investigator. Study protocol will also be available. The data will be shared as Excel files via email during the proposed investigation period.

Study Population

COMMAND VTE Registry-2 is a physician-initiated, multicenter, retrospective cohort study enrolling consecutive patients with acute symptomatic VTE objectively confirmed by imaging examination or by autopsy among 31 centers in Japan between January 2015 and August 2020 after the introduction of DOACs for VTE in Japan. In Japan, edoxaban was approved in September 2014, rivaroxaban in September 2015, and apixaban in December 2015 for the treatment of VTE and prevention of recurrent VTE. The design of the registry was previously reported in detail.[23] We searched the hospital databases for clinical diagnosis or imaging examinations in patients on an outpatient basis and in hospitalized patients, and enrolled consecutive patients who met the definitions of acute symptomatic VTE diagnosed within 31 days from symptom onset during the study period.[24] All of the potential patients with suspected VTE based on the hospital databases were evaluated through chart review by a physician at each institution. The relevant review board or ethics committee in all 31 participating centers (Data S1) approved the research protocol. Because of the retrospective enrollment, written informed consent from the patients was waived; however, we excluded those patients who refused participation in the study when contacted for follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor, and Welfare.

After screening of 51 313 patients with suspected VTE for eligibility through chart review by the physicians at each institution, a total of 5197 consecutive patients with acute symptomatic VTE were enrolled in the registry. After excluding 2410 patients with DVT only, 136 patients with cardiopulmonary arrest, and 155 patients with cardiogenic shock, the current study population consisted of 2496 patients with PE but without hemodynamic instability, who were divided into 2 groups based on an sPESI score of 0 and ≥1 (Figure 1). The index date (day 0) in the current study was the date of diagnosis. We compared the baseline characteristics, management strategies, and 30-day clinical outcomes between the 2 groups of patients with an sPESI score of 0 and ≥1. In addition, after excluding patients in whom PE occurred during hospitalization, we further divided the patients with an sPESI score of 0 into 2 groups: patients with home treatment and those with in-hospital treatment. We compared the baseline characteristics, management strategies, and 30-day clinical outcomes between the 2 groups of patients with home treatment and with in-hospital treatment.

Data Collection and Definitions for Patient Characteristics and Anticoagulation Therapies

Data for patient characteristics were collected from hospital charts or hospital databases according to the prespecified definitions, using an electronic case report form in a web-based database system. The physicians at each institution were responsible for data entry, and data were automatically checked for missing or contradictory input and values out of the expected range. Additional editing checks were performed at the general office of the registry.

The sPESI score consisted of several variables, including age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate of ≥110 bpm, systolic blood pressure <100 mm Hg, and arterial oxygen saturation <90% at the time of diagnosis.[19] The original data of the sPESI score component were collected from hospital charts, and the sPESI score was recalculated by the current investigators. If these variables were not documented in the medical record, we assumed that there was no score component of the variable. Chronic cardiopulmonary disease included heart failure or chronic lung disease. Heart failure was diagnosed if the patient had a history of hospitalization for heart failure, if the patient had symptoms due to heart failure (New York Heart Association functional class ≥2), or if the left ventricular ejection fraction was <40%. Chronic lung disease was defined as persistent lung disorders such as asthma, chronic obstructive pulmonary disease, and restrictive lung diseases.

Initial parenteral anticoagulation therapy included heparin (single or continuous injection) and fondaparinux within 10 days after the diagnosis.[25] Oral anticoagulation therapy included a vitamin K antagonist

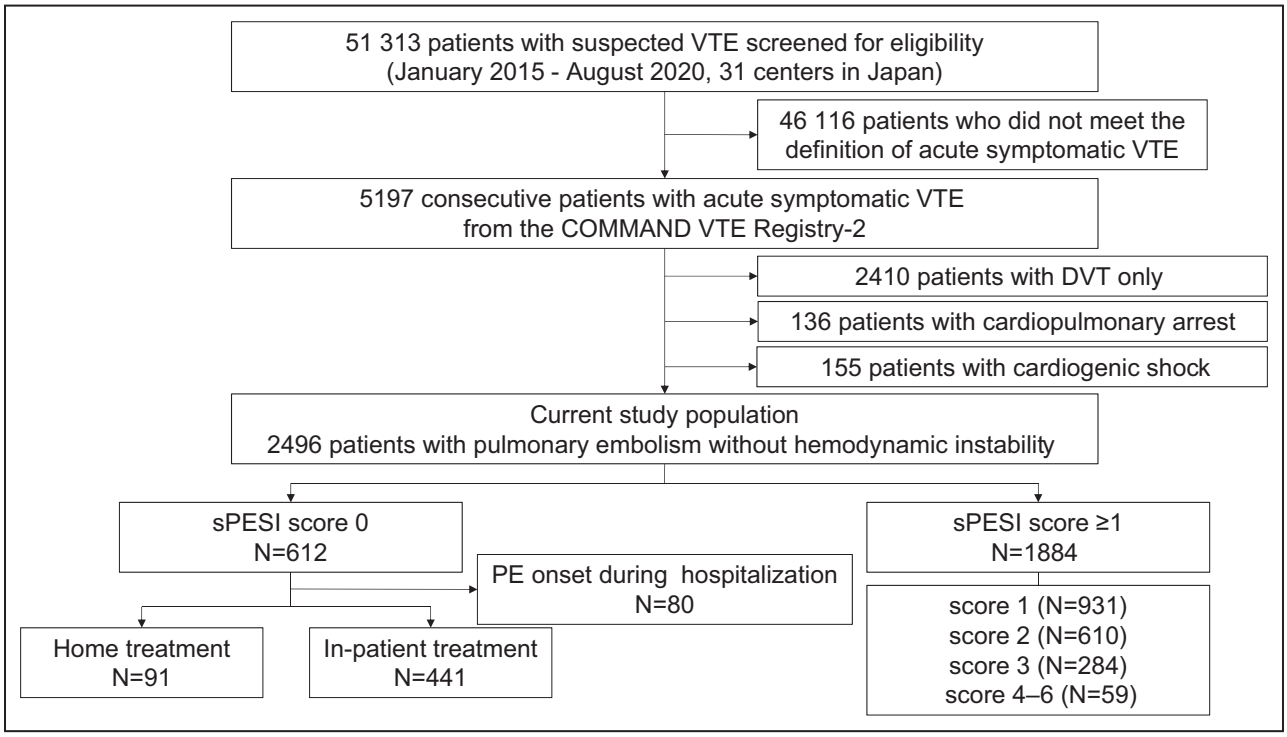


Figure 1. Study flowchart.
COMMAND VTE indicates Contemporary Management and Outcomes in Patients With Venous Thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; sPESI, simplified Pulmonary Embolism Severity Index; and VTE, venous thromboembolism.

(warfarin) and DOACs. DOACs included dabigatran, rivaroxaban, apixaban, and edoxaban. Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy (warfarin, DOACs, or heparin) that was continued beyond the acute phase of 10 days after the diagnosis.[25] The detailed definitions of other patient characteristics are described in Data S2.

Clinical Follow-Up and Outcomes

Collection of follow-up information was mainly conducted through review of hospital charts, and additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by phone and/or mail with questions on vital status, clinical events, invasive procedure, and status of anticoagulation therapy.

The primary outcome measure in the present study was all-cause death at 30 days after diagnosis. The secondary outcomes were recurrent VTE and major bleeding at 30 days after diagnosis. Recurrent VTE was defined as PE and/or DVT with symptoms accompanied by confirmation of new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy.[26] Major bleeding consisted of fatal bleeding, symptomatic bleeding in a critical area or organ, and bleeding causing a reduction in the hemoglobin level by at least 2 g/dL or leading to transfusion of at least 2 U of whole blood or red cells according to International Society of Thrombosis and Hemostasis definitions.[27]

The independent clinical event committee (Data S3), which was unaware of the patients' characteristics, reviewed all of the detailed clinical course and adjudicated the clinical events. If there was inconsistency, final adjudication for clinical events was made on the basis of the full consensus of the independent clinical event committee. The definitions of other clinical events are described in Data S4.

Statistical Analysis

Categorical variables are presented as number and percentage. Continuous variables are presented as the mean±SD or the median and interquartile range based on their distributions. Categorical variables were compared with the χ^2 test when appropriate; otherwise, the Fisher exact test was used. Continuous variables were compared using the Student *t* test or Wilcoxon rank sum test based on their distributions. We calculated the sPESI score for each patient, and patients with a score of 0 were considered to be low risk. We compared baseline characteristics, management strategies, and 30-day clinical outcomes between the 2 groups of patients with sPESI scores of 0 and sPESI scores of ≥1, as well as between the 2 groups of home treatment and in-hospital treatment among the patients with out-of-hospital onset PE with sPESI scores of 0. We used the Kaplan-Meier method to estimate the cumulative incidences and assessed the differences with a log-rank test. To explore the temporal changes in penetration of home treatment over time, we evaluated the prevalence of home treatment among patients with sPESI scores of 0 in each year during the study period. We constructed a multivariable logistic regression model to explore the factors associated with the home treatment among the patients with out-of-hospital onset PE with an sPESI score of 0. Based on the clinical relevance, we first selected the following 13 variables as potential variables: age >65 years, sex, body mass index ≥30 kg/m^2, hypertension, diabetes, chronic kidney disease, history of VTE, transient risk factors for VTE, concomitant proximal DVT in the lower extremities at diagnosis, D-dimer levels, right ventricular dysfunction, cardiac biomarker elevation, and DOAC use in the acute phase. After that, we included variables with *P* values <0.2 in a univariate model. Moreover, we performed a multivariable logistic regression model to explore the factors associated with home treatment among the patients with out-of-hospital onset PE, including an sPESI score of 0 or ≥1 as independent variables. The odds ratios (ORs) and 95% CIs were calculated using the logistic regression model. Furthermore, to take the competing risk of all-cause death into account, we used the Gray method to estimate the cumulative incidence for recurrent VTE and major bleeding. All statistical analyses were conducted by physicians (R.N. and Y.Y.) and a statistician (T.M.) with the use of JMP version 16.1.0 (SAS Institute, Cary, NC). All reported *P* values were 2-tailed, and $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics According to the sPESI Score

In the current study population, the mean age was 66.6±15.3 years, 56% of the patients were women, and the mean body mass index was 23.9±4.7 kg/m^2. Among 2496 patients with PE, 2100 patients (84%) were treated with DOACs. Patients with an sPESI score of 0 accounted for 612 (25%) patients, whereas patients with an sPESI score of ≥1 accounted for 1884 (75%) patients (Figure 1). Patients with an sPESI score of 0 were younger and less frequently women, and had a higher body mass index compared with patients with an sPESI score of ≥1 (Table 1). Patients with an sPESI score of 0 less often had several comorbidities including hypertension, chronic kidney disease, and a history

Table 1. Baseline Characteristics, Laboratory Findings, and Treatment: sPESI Score of 0 Versus sPESI Score of ≥1

Variables	Total (N=2496)	sPESI score 0 (N=612)	sPESI score≥1 (N=1884)	*P* value
Baseline characteristics				
Age, y	66.6±15.3	58.3±15.0	69.2±14.4	<0.001
Age>65 y	1552 (62%)	261 (43%)	1291 (69%)	<0.001
Women	1388 (56%)	274 (45%)	1114 (59%)	<0.001
Body weight, kg	61.2±14.9	66.4±14.3	59.5±14.7	<0.001
Body mass index, kg/m^2	23.9±4.7	24.6±4.3	23.6±4.8	<0.001
Body mass index ≥30 kg/m^2	206 (8.3%)	66 (11%)	140 (7.4%)	0.009
Comorbidities				
History of cancer	926 (37%)	0 (0%)	926 (49%)	<0.001
Active cancer	717 (29%)	0 (0%)	717 (38%)	<0.001
History of heart failure	88 (3.5%)	0 (0%)	88 (4.7%)	<0.001
History of chronic lung disease	277 (11%)	0 (0%)	277 (15%)	<0.001
History of heart failure or chronic lung disease	353 (14%)	0 (0%)	353 (19%)	<0.001
Hypertension	1091 (44%)	216 (35%)	875 (46%)	<0.001
Diabetes	375 (15%)	78 (13%)	297 (16%)	0.07
Dyslipidemia	651 (26%)	155 (25%)	496 (26%)	0.62
Chronic kidney disease	421 (17%)	66 (11%)	355 (19%)	<0.001
Dialysis	11 (0.4%)	1 (0.2%)	10 (0.5%)	0.23
History of VTE	170 (6.8%)	51 (8.3%)	119 (6.3%)	0.09
History of major bleeding	176 (7.1%)	29 (4.7%)	147 (7.8%)	0.01
Transient risk factors for VTE	826 (33%)	205 (34%)	621 (33%)	0.81
Presentation				
Arterial oxyhemoglobin saturation level<90%	967 (39%)	0 (0%)	967 (51%)	<0.001
Heart rate≥110 bpm (N=2416)	344 (14%)	0 (0%)	344 (18%)	<0.001
Systolic blood pressure<100 mm Hg (N=2413)	135 (5.4%)	0 (0%)	135 (7.2%)	<0.001
Concomitant proximal DVT in the lower extremities at diagnosis	1490 (60%)	419 (68%)	1071 (57%)	<0.001
Laboratory tests and imaging examinations				
Anemia	1183 (47%)	188 (31%)	995 (53%)	<0.001
Thrombocytopenia (N=2495)	110 (4.4%)	19 (3.1%)	91 (4.8%)	0.07
D-dimer, μg/mL (N=2424)	10.6 (5.5–20.5)	8.5 (4.3–14.7)	11.6 (6.0–22.8)	<0.001
BNP, pg/mL (N=1336)	56.0 (19.9–186.8)	25.0 (9.7–67.3)	73.6 (25.4–244.0)	<0.001
NT-proBNP, pg/mL (N=321)	479 (111–1905)	97 (43–306)	662 (183–2653)	<0.001
High level of BNP or NT-proBNP (N=1621)	615 (38%)	74 (19%)	541 (44%)	<0.001
Troponin I, ng/mL (N=713)	0.040 (0.010–0.159)	0.010 (0.010–0.055)	0.053 (0.013–0.210)	<0.001
Troponin T, ng/mL (N=281)	0.024 (0.010–0.058)	0.010 (0.005–0.029)	0.030 (0.012–0.067)	<0.001
High level of troponin (N=965)	570 (59%)	77 (36%)	493 (66%)	<0.001
Right ventricular dysfunction	916 (37%)	135 (22%)	781 (41%)	<0.001
Treatment in the acute phase				
Initial parenteral anticoagulation therapy	1636 (66%)	373 (61%)	1263 (67%)	0.006
Heparin	1609 (64%)	366 (60%)	1243 (66%)	0.006
Fondaparinux	36 (1.4%)	6 (1.0%)	30 (1.6%)	0.27
Initial oral anticoagulation therapy with DOAC	2100 (84%)	533 (87%)	1567 (83%)	0.02
Dabigatran	3/2100 (0.1%)	0/533 (0%)	3/1567 (0.2%)	…

(*Continued*)

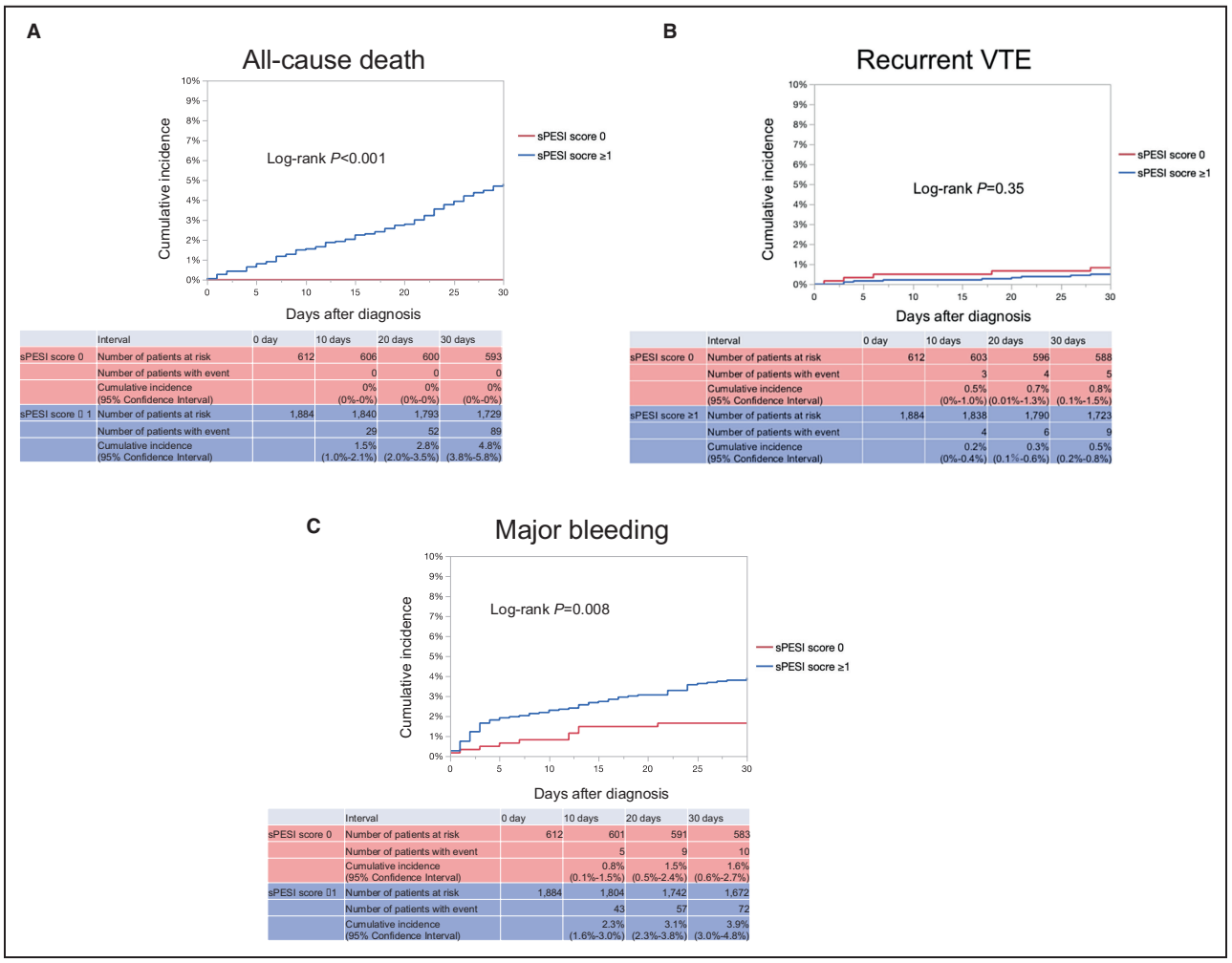
Table 1. Continued

Variables	Total (N=2496)	sPESI score 0 (N=612)	sPESI score ≥1 (N=1884)	*P* value
Initial parenteral anticoagulation therapy	2/3 (67%)	0 (0%)	2/3 (67%)	…
Rivaroxaban	716/2100 (34%)	213/533 (40%)	503/1567 (32%)	…
Initial parenteral anticoagulation therapy	398/716 (56%)	118/213 (55%)	280/503 (56%)	…
Apixaban	513/2100 (24%)	129/533 (24%)	384/1567 (25%)	…
Initial parenteral anticoagulation therapy	252/513 (49%)	55/129 (43%)	197/384 (51%)	…
Edoxaban	868/2100 (41%)	191/533 (36%)	677/1567 (43%)	…
Initial parenteral anticoagulation therapy	646/868 (74%)	134/191 (70%)	512/677 (76%)	…
Ventilator support	21 (0.8%)	0 (0%)	21 (1.1%)	0.009
Percutaneous cardiopulmonary support	3 (0.1%)	0 (0%)	3 (0.2%)	0.32
Prolonged anticoagulation therapy	2419 (97%)	605 (99%)	1814 (96%)	0.001
Vitamin K antagonist (warfarin)	299 (12%)	70 (11%)	229 (12%)	0.64
DOAC	2100 (84%)	533 (87%)	1567 (83%)	0.02
Concomitant medications at discharge				
Corticosteroids	306 (12%)	47 (7.7%)	259 (14%)	<0.001
Nonsteroidal anti-inflammatory drugs	181 (7.3%)	27 (4.4%)	154 (8.2%)	0.002
Proton pump inhibitors/H2-blockers	1364 (55%)	297 (49%)	1067 (57%)	<0.001
Statins	448 (18%)	108 (18%)	340 (18%)	0.82
Antiplatelet agents	152 (6.1%)	28 (4.6%)	124 (6.6%)	0.07
Onset				
In-hospital onset with recent surgery	243 (9.7%)	39 (6.4%)	204 (11%)	<0.001
In-hospital onset without recent surgery	311 (12%)	41 (6.7%)	270 (14%)	
Out-of-hospital onset	1942 (78%)	532 (87%)	1410 (75%)	
Home treatment	273/1942 (14%)	91/532 (17%)	182/1410 (13%)	0.02
In-hospital treatment	1669/1942 (86%)	441/532 (83%)	1228/1410 (87%)	
Length of hospital stay, d	14 (10–21)	13 (9–18)	15 (10–22)	<0.001

Categorical variables are presented as number and percentage, and continuous variables are presented as mean±standard deviation or median and interquartile range based on their distributions. Categorical variables were compared using the χ^2 test. Continuous variables were compared using the Student *t* test or Wilcoxon rank sum test based on their distributions. Chronic lung disease was defined as persistent lung disorders such as asthma, chronic obstructive pulmonary disease, and restrictive lung diseases. History of major bleeding was diagnosed if the patient had a history of International Society of Thrombosis and Hemostasis major bleeding. Proximal DVT in the lower extremities was defined as venous thrombosis that was located in popliteal, femoral, or iliac veins. Anemia was defined as hemoglobin level<13 g/dL for men and<12 g/dL for women. Thrombocytopenia was defined as platelet count $<100\times10^9$/L. Right ventricular dysfunction was defined as interventricular septum flattening and estimated systolic pulmonary artery pressure >40 mm Hg, as determined by transthoracic echocardiography. Interventricular septum flattening was evaluated qualitatively in the short-axis parasternal view to determine whether it caused a D-shaped short-axis left ventricular cavity profile predominantly during systole. Additionally, right ventricular dysfunction was defined as an obstruction index >50% and right ventricular dilatation with an RV/LV ratio >0.90 by contrast-enhanced computed tomography. Initial parenteral anticoagulation therapy included heparin and fondaparinux within 10 d after the diagnosis. Oral anticoagulation therapy included vitamin K antagonist (warfarin) and DOACs. Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy (warfarin, DOAC, or heparin) that was continued beyond the acute phase of 10 d after the diagnosis. Antiplatelet agents included aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor, and cilostazol. BNP indicates B-type natriuretic peptide; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; H2-blockers, histamine type 2 receptor agonists; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; sPESI, simplified Pulmonary Embolism Severity Index; and VTE, venous thromboembolism.

of major bleeding, and more often had concomitant proximal DVT in the lower extremities at diagnosis compared with patients with an sPESI score of ≥1.

Of 1942 patients with out-of-hospital onset of PE, 1669 (86%) patients were admitted to the hospital, and the median length of hospital stay was 14 days. Patients with an sPESI score of 0 were less often admitted to the hospital (83% and 87%, *P*=0.02) and had a shorter length of stay than those with an sPESI score of ≥1 (13 and 15 days, *P*<0.001) (Table 1). Patient characteristics in all of the categories based on the sPESI score are shown in Table S1.



	Interval	0 day	10 days	20 days	30 days
sPESI score 0	Number of patients at risk	612	606	600	593
	Number of patients with event		0	0	0
	Cumulative incidence (95% Confidence Interval)		0% (0%-0%)	0% (0%-0%)	0% (0%-0%)
sPESI score ≥1	Number of patients at risk	1,884	1,840	1,793	1,729
	Number of patients with event		29	52	89
	Cumulative incidence (95% Confidence Interval)		1.5% (1.0%-2.1%)	2.8% (2.0%-3.5%)	4.8% (3.8%-5.8%)

	Interval	0 day	10 days	20 days	30 days
sPESI score 0	Number of patients at risk	612	603	596	588
	Number of patients with event		3	4	5
	Cumulative incidence (95% Confidence Interval)		0.5% (0%-1.0%)	0.7% (0.01%-1.3%)	0.8% (0.1%-1.5%)
sPESI score ≥1	Number of patients at risk	1,884	1,838	1,790	1,723
	Number of patients with event		4	6	9
	Cumulative incidence (95% Confidence Interval)		0.2% (0%-0.4%)	0.3% (0.1%-0.6%)	0.5% (0.2%-0.8%)

	Interval	0 day	10 days	20 days	30 days
sPESI score 0	Number of patients at risk	612	601	591	583
	Number of patients with event		5	9	10
	Cumulative incidence (95% Confidence Interval)		0.8% (0.1%-1.5%)	1.5% (0.5%-2.4%)	1.6% (0.6%-2.7%)
sPESI score ≥1	Number of patients at risk	1,884	1,804	1,742	1,672
	Number of patients with event		43	57	72
	Cumulative incidence (95% Confidence Interval)		2.3% (1.6%-3.0%)	3.1% (2.3%-3.8%)	3.9% (3.0%-4.8%)

Figure 2. Kaplan-Meier curves for clinical outcomes between patients with an sPESI score of 0 and those with an sPESI score of ≥1.
A, All-cause death. **B**, Recurrent VTE. **C**, Major bleeding. sPESI indicates simplified Pulmonary Embolism Severity Index; and VTE, venous thromboembolism.

Clinical Outcomes According to the sPESI Score

The cumulative 30-day incidence of all-cause death was lower in patients with an sPESI score of 0 compared with patients with an sPESI score of ≥1 (0.0% and 4.8%, *P*<0.001) (Figure 2A). The cumulative 30-day incidence of all-cause death was incrementally higher with increasingly higher sPESI score categories (sPESI score of 0, N=0, 0%; sPESI score of 1, N=22, 2.4%; sPESI score of 2, N=36, 6.0%; sPESI score of 3, N=26, 9.3%; sPESI score of 4–6, N=5, 8.8%) (Figure S1).

There was no significant difference in the cumulative 30-day incidence of recurrent VTE between the 2 groups of patients with sPESI scores of 0 and those with sPESI scores of ≥1 (0.8% and 0.5%, *P*=0.35) (Figure 2B). The cumulative 30-day incidence of major bleeding was lower in patients with an sPESI score of 0 compared with patients with a score of ≥1 (1.6% and 3.9%, *P*=0.008) (Figure 2C). Even after accounting for the competing risk of all-cause death, the cumulative incidence of recurrent VTE and major bleeding was consistent with the main analysis (Table S2).

Baseline Characteristics and Clinical Outcomes Compared Between Home Treatment and In-Hospital Treatment

Among 532 patients with out-of-hospital PE with an sPESI score of 0, only 91 (17%) patients were treated at home, whereas 441 (83%) patients were treated in the hospital (Figure 1). During the study period between 2015 and 2020, the proportion of home treatment slowly increased over time, ranging from 7% to 24% (Figure 3). Patients treated at home had lower D-dimer

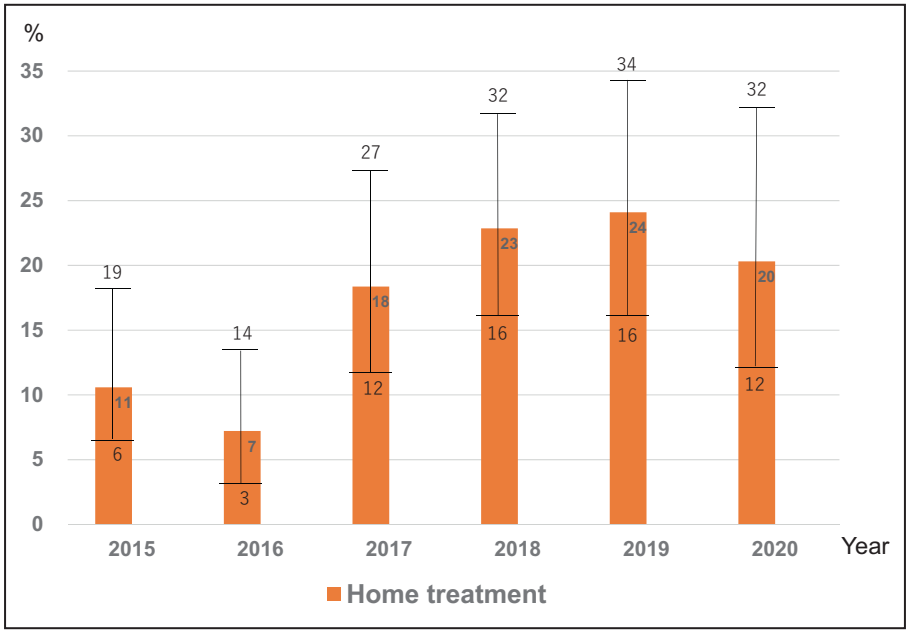


Figure 3. Temporal change in the prevalence of home treatment during the study period between 2015 and 2020.
We evaluated those patients with an sPESI score of 0 who developed an out-of-hospital pulmonary embolism. sPESI, indicates simplified Pulmonary Embolism Severity Index.

levels and cardiac biomarkers levels such as B-type natriuretic peptide, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and troponin T, and less frequently had right ventricular dysfunction than those treated in the hospital (Table 2).

The cumulative 30-day incidences of all-cause death, recurrent VTE, and major bleeding were low and not different between the in-hospital and home treatment groups (0.0% and 0.0%, 0.9% and 0.0%, *P*=0.36; 1.8% and 1.1%, *P*=0.63) (Table S3).

Factors Predisposing to Home Treatment Among Patients With Out-of-Hospital PE With an sPESI Score of 0

The multivariable logistic regression model revealed that transient risk factors for VTE (OR, 0.54 [95% CI, 0.31–0.97]; *P*=0.04) and cardiac biomarker elevation (OR, 0.19 [95% CI, 0.07–0.58]; *P*=0.003) were independently and negatively associated with home treatment, whereas only DOAC use in the acute phase (OR, 3.33 [95% CI, 1.16–9.58]; *P*=0.03) was independently and positively associated with home treatment (Table 3). The multivariable logistic regression model among patients with out-of-hospital onset PE also showed that patients with an sPESI score of 0 were not independently associated with home treatment compared with patients with an sPESI score ≥1 (Table S4).

DISCUSSION

The main findings of the current study were as follows: (1) Patients with an sPESI score of 0 represented about 25% of patients with PE without hemodynamic instability, and most of them were treated in the hospital even in the DOAC era. (2) There was no patient with a 30-day mortality among patients with an sPESI score of 0. (3) Transient risk factors for VTE and cardiac biomarker elevation were independently and negatively associated with home treatment, whereas only DOAC use in the acute phase was independently and positively associated with home treatment.

The Pulmonary Embolism Severity Index score and sPESI score were originally designed to predict the risk of 30-day mortality in patients with acute PE.[18,19] The 30-day mortality rates in patients with an sPESI score of 0 were reported to be a low of 1.0% in the derivation study cohort and 1.1% in the validation cohort.[19] In addition, a recent meta-analysis reported the 30-day mortality rate in patients with an sPESI score of 0 was 1.5% (95% CI, 0.9%– 2.5%),[20] suggesting that they were potential candidates for outpatient treatment. The proportions of sPESI scores of 0 in the present study were similar to the previous studies in the vitamin K antagonist era.[25,26] The current guidelines recommend that appropriately selected low-risk patients can be treated completely at home.[28] Moreover, treatment of acute PE with some DOACs,

Table 2. Baseline Characteristics, Laboratory Findings, and Treatment: Home Versus In-Hospital Treatment Among Patients With Out-of-Hospital Onset Pulmonary Embolism With a Simplified Pulmonary Embolism Severity Index Score of 0

Variables	In-hospital treatment (N=441)	Home treatment (N=91)	*P* value
Baseline characteristics			
Age, y	58.5±14.6	55.3±15.9	0.06
Age >65 y	191 (43%)	31 (34%)	0.10
Women	192 (44%)	36 (40%)	0.49
Body weight, kg (N=513)	67.1±14.3	66.6±14.4	0.80
Body mass index, kg/m^2 (N=501)	24.7±4.2	24.7±4.8	0.91
Body mass index ≥30 kg/m^2	48 (11%)	10 (11%)	0.98
Comorbidities			
Hypertension	154 (35%)	29 (32%)	0.58
Diabetes	52 (12%)	8 (8.8%)	0.41
Dyslipidemia	119 (27%)	14 (15%)	0.02
Chronic kidney disease	47 (11%)	9 (9.9%)	0.83
Dialysis	1 (0.2%)	0 (0%)	0.65
History of VTE	37 (8.4%)	10 (11%)	0.43
History of major bleeding	14 (3.2%)	3 (3.3%)	0.95
Transient risk factors for VTE	119 (27%)	18 (20%)	0.15
Presentation			
Concomitant proximal DVT in lower extremities at diagnosis	308 (70%)	58 (64%)	0.25
Laboratory tests and imaging examinations			
Anemia	117 (27%)	17 (19%)	0.12
Thrombocytopenia	12 (2.7%)	2 (2.2%)	0.78
D-dimer, μg/mL (N=526)	8.5 (4.2–14.6)	6.3 (3.8–11.5)	0.03
BNP, pg/mL (N=318)	30.5 (11.0–82.1)	13.0 (7.6–25.9)	<0.001
NT-proBNP, pg/mL (N=70)	116 (42–479)	65 (23–104)	0.04
High level of BNP or NT-proBNP (N=377)	70 (22%)	1 (1.6%)	<0.001
Troponin I, ng/mL (N=145)	0.010 (0.010–0.068)	0.010 (0.010–0.016)	0.16
Troponin T, ng/mL (N=61)	0.010 (0.005–0.030)	0.005 (0.003–0.005)	0.03
High level of troponin (N=200)	68 (40%)	4 (14%)	0.01
Right ventricular dysfunction	119 (27%)	9 (9.9%)	<0.001
Treatment in the acute phase			
Initial parenteral anticoagulation therapy	300 (68%)	21 (23%)	<0.001
Heparin	295 (67%)	21 (23%)	<0.001
Fondaparinux	3 (0.7%)	0 (0%)	0.43
Oral anticoagulation therapy	434 (98%)	90 (99%)	0.73
Vitamin K antagonist (warfarin)	53 (12%)	3 (3.3%)	0.01
DOAC	381 (86%)	87 (96%)	0.01
Dabigatran	0/381 (0%)	0/87 (0%)	0.96
Rivaroxaban	164/381 (43%)	37/87 (43%)	
Apixaban	91/381 (24%)	22/87 (25%)	
Edoxaban	126/381 (33%)	28/87 (32%)	
Prolonged anticoagulation therapy	435 (99%)	90 (99%)	0.84
Concomitant medications at discharge			
Corticosteroids	30 (6.8%)	5 (5.5%)	0.65
Nonsteroidal anti-inflammatory drugs	17 (3.9%)	2 (2.2%)	0.44
Proton pump inhibitors/H2-blockers	228 (52%)	22 (24%)	<0.001

(*Continued*)

Table 2. Continued

Variables	In-hospital treatment (N=441)	Home treatment (N=91)	*P* value
Statins	85 (19%)	9 (9.9%)	0.03
Antiplatelet agents	19 (4.3%)	3 (3.3%)	0.66

Categorical variables are presented as number and percentage, and continuous variables are presented as mean±SD or median and interquartile range based on their distributions. Categorical variables were compared using the χ^2 test. Continuous variables were compared using the Student *t* test or Wilcoxon rank sum test based on their distributions. History of major bleeding was diagnosed if the patient had a history of International Society of Thrombosis and Hemostasis major bleeding. Proximal DVT in the lower extremities was defined as venous thrombosis, which was located in popliteal, femoral, or iliac veins. Anemia was defined as hemoglobin level<13 g/dL for men and<12 g/dL for women. Thrombocytopenia was defined as platelet count <100×10^9/L. Right ventricular dysfunction was defined as interventricular septum flattening and estimated systolic pulmonary artery pressure >40 mm Hg, as determined by transthoracic echocardiography. Interventricular septum flattening was evaluated qualitatively in the short-axis parasternal view to determine whether it caused a D-shaped short-axis left ventricular cavity profile predominantly during systole. Additionally, right ventricular dysfunction was defined as an obstruction index >50% and right ventricular dilatation with an RV/LV ratio >0.90 by contrast-enhanced computed tomography. Initial parenteral anticoagulation therapy included heparin and fondaparinux within 10 d after the diagnosis. Oral anticoagulation therapy included vitamin K antagonist (warfarin) and DOACs. Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy (warfarin, DOAC, or heparin) that was continued beyond the acute phase of 10 d after the diagnosis. Antiplatelet drugs included aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor, and cilostazol. BNP indicates B-type natriuretic peptide; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; H2-blockers, histamine type 2 receptor agonists; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; and VTE, venous thromboembolism.

including apixaban and rivaroxaban, without administering intravenous anticoagulant would be more suitable for home treatment.[29,30] Thus, the introduction of DOACs for PE was supposed to increase the proportion of home treatment. However, the present study showed only 17% were treated at home among patients with an sPESI score of 0, although the proportion of home treatment slowly increased over time. The previous study from the Registro Informatizado de la EnfermedadTromboEmbólica registry reported that only 5% of the entire population of PE and approximately 7% of the low-risk patients with PE were treated at home.[31] The prevalence of home treatment was reported to vary from 0.99% to 21% across different

Table 3. Logistic Regression Model for the Factors Associated With Home Treatment Among Patients With Out-of-Hospital Onset Pulmonary Embolism With a Simplified Pulmonary Embolism Severity Index Score of 0

	Univariate models		Multivariate model	
Variables	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age>65 y	0.68 (0.42–1.08)	0.10	0.72 (0.44–1.19)	0.20
Women	0.85 (0.54–1.35)	0.49	…	…
Body mass index ≥30 kg/m^2	1.01 (0.49–2.08)	0.98	…	…
Hypertension	0.87 (0.54–1.41)	0.58	…	…
Diabetes	0.72 (0.33–1.57)	0.41	…	…
Chronic kidney disease	0.92 (0.43–1.95)	0.83	…	…
History of VTE	1.35 (0.64–2.82)	0.43	…	…
Transient risk factors for VTE	0.67 (0.38–1.16)	0.15	0.54 (0.31–0.97)	0.04
Proximal DVT in lower extremities	0.76 (0.47–1.22)	0.25	…	…
D-dimer per 1 ug/mL	0.98 (0.95–1.004)	0.10	0.98 (0.96–1.01)	0.19
Right ventricular dysfunction	0.30 (0.14–0.61)	<0.001	0.47 (0.22–1.03)	0.06
Cardiac biomarkers elevation	0.14 (0.05–0.39)	<0.001	0.19 (0.07–0.58)	0.003
DOAC use in the acute phase	3.43 (1.21–9.68)	0.02	3.33 (1.16–9.58)	0.03

Transient risk factors included major surgery with general anesthesia for >30 min and within 2 mo before VTE, confinement to bed in the hospital with only bathroom privileges for at least 4 d with an acute illness within 2 mo before VTE, cesarean section within 2 mo before VTE, minor surgery with general anesthesia for <30 min and within 2 mo before VTE, admission to hospital without confinement to bed due to acute illness within 2 mo before VTE, estrogen therapy within 2 mo before VTE, pregnancy or puerperium within 2 mo before VTE, confinement to bed out of the hospital for at least 4 d within 2 mo before VTE, leg injury associated with reduced mobility for at least 4 d within 2 mo before VTE, long-distance travel lasting >6 hours in the previous 3 weeks, and central venous catheter use and infection of COVID-19 within 3 mo before VTE. Proximal DVT in the lower extremities was defined as venous thrombosis that was located in popliteal, femoral, or iliac veins. Right ventricular dysfunction was defined as interventricular septum flattening and estimated systolic pulmonary artery pressure >40 mm Hg, as determined by transthoracic echocardiography. Interventricular septum flattening was evaluated qualitatively in the short-axis parasternal view to determine whether it caused a D-shaped short-axis left ventricular cavity profile predominantly during systole. Additionally, right ventricular dysfunction was defined as an obstruction index >50% and right ventricular dilatation with an RV/LV ratio >0.90 by contrast-enhanced computed tomography. Cardiac biomarkers elevation was defined as BNP ≥100 pg/mL, NT-proBNP ≥600 pg/mL, troponin I ≥0.0262 ng/mL, or troponin T ≥0.014 ng/mL. Values were missing for cardiac biomarker elevation in 144 patients. The missing values for these variables were imputed as normal in the binary classification, because the data should have been available if abnormalities were suspected. BNP indicates B-type natriuretic peptide; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; and VTE, venous thromboembolism.

countries.[31] The selection of home treatment might be influenced by the medical system and facility policies of each country in addition to the patient factors. Notably, in the HOME-PE trial, which aimed to triage acute PE for home treatment using Hestia or sPESI criteria, among 477 patients with an sPESI score of 0, 136 (28.5%) patients were switched from home treatment to inpatient treatment; 96 patients had another illness requiring hospitalization, 13 patients had social reasons for hospitalization, 13 patients needed specific PE treatment (like reperfusion therapy or vena cava filter insertion), 11 patients rejected home treatment, and 3 had reasons against using low-molecular-weight heparin or DOACs.[32]

The reported 30-day mortality rate among patients with an sPESI score of 0 ranged between 0.4% and 1.6%.[19,33,34,35] Consistent with the previous studies, the present study showed that the 30-day mortality rate of patients with an sPESI score of 0 was as low as 0%, suggesting that these patients could be potential candidates for home treatment. In the HoT-PE trial, which aimed to investigate the efficacy and safety of early discharge and home treatment with rivaroxaban in patients with low-risk PE, the rate of symptomatic recurrent VTE was 0.6%, and the rate of all-cause death was only 0.4%, without any PE-related deaths within 3 months of enrollment.[36] The mortality rate of low-risk patients with PE, including an sPESI score of 0, was reasonably low, and home treatment with DOACs might be a good treatment option for these patients.

There were several independent factors predisposing to home treatment in the current study, such as no transient risk factors for VTE, no cardiac biomarker elevation, and DOAC use in the acute phase. In addition, no right ventricular dysfunction also showed a tendency to choose home treatment. The transient risk factors for VTE included many factors that would consider recommending hospitalization. The Hestia rule was proposed as an alternative approach, which consisted of medical and social criteria that discouraged home treatment.[37] Pregnancy was one of the transient risk factors covered by the Hestia rule,[37] and might have been taken into consideration when choosing home treatment. Some reports suggested that right ventricular dysfunction or cardiac biomarker elevation were associated with a higher risk of a severe state, and European Society of Cardiology guidelines recommended that these factors be taken into account when deciding on a treatment strategy.[16] The Hot-PE trial excluded patients with right ventricular dysfunction.[36] In the HOME-PE trial, the proportion of patients with right ventricular dysfunction or cardiac biomarker elevation was considerably low.[34] Among 361 patients with home treatment using the sPESI strategy, 44 (12.2%) patients had right ventricular dysfunction, 37 (10.2%) patients had a high level of troponin, and 11 (3.0%) patients had a high level of B-type natriuretic peptide or NT-proBNP.[34] Thus, right ventricular dysfunction or cardiac biomarker elevation might play an important role in selecting home treatment. Further research would be needed to develop a specific score for selecting good candidates for home treatment.

The present study clearly showed that patients with an sPESI score of 0 could be at a considerably lower risk of mortality in the DOAC era, which suggests that there may be patients who can be treated at home among patients with an sPESI score of 0. Whereas, a certain number of patients with an sPESI score of 0 are treated in the hospital even in the DOAC era. There might be some concerns for home treatment among patients with several characteristics that are not included in the sPESI score component, including right ventricular dysfunction and cardiac biomarker elevation, which should be further investigated in the future.

Study Limitations

The current study has several limitations. First, this study was an observational study, which inherently carried various biases associated with an observational study design. The decision-making process for treatments, including the selection for home treatment, was guided by the attending physicians' judgment, introducing the possibility of impacting clinical outcomes. Second, demographic characteristics, treatment approaches, and clinical outcomes among individuals with VTE in Japan might differ from those in other regions. Third, there could be important differences in the health care system and medical care insurance among different countries. The longer duration of hospital stay in Japan than in other countries could have some influence on outcomes.[38] The low copayment rate with the Japanese public health insurance system makes patients who are not inclined to shorten their length of hospital stay remain as long as possible. Fourth, the current study was an observational study. Therapeutic management, including the use of DOACs, was left to the discretion of the attending physicians, and there could be various potential biases. The results of multivariable analysis could not provide causal relationship, but only association. Fifth, we could not fully adjust for all potential confounders due to sample size, and thus there was the possibility of residual confounding. Finally, social variables that are included in the Hestia rule were not evaluated in the present study.

CONCLUSIONS

The 30-day mortality rate of acute PE was notably low among patients with an sPESI score of 0, which suggested that these patients could be good candidates

for home treatment. Nevertheless, only a minority of patients with an sPESI score of 0 were treated at home even in the DOAC era. Further prospective clinical trials would be warranted to popularize home treatment for low-risk PE patients.

ARTICLE INFORMATION

Received February 21, 2024; accepted August 22, 2024.

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Acknowledgments

The authors appreciate the support and collaboration of the coinvestigators participating in the COMMAND VTE Registry-2.

Sources of Funding

The COMMAND VTE Registry-2 is partly supported by Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research grant number JP 21K16022. The research funding had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article.

Disclosures

Dr Yamashita received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo, and grant support from Bayer Healthcare and Daiichi-Sankyo. Dr Morimoto reports lecturer's fees from Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Kyocera, Novartis, and Toray; article fees from Bristol-Myers Squibb and Kowa; and advisory board participation for Sanofi. Dr Kaneda received lecture fees from Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo. Dr Nishimoto received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo. Dr N. Ikeda received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, and Daiichi-Sankyo. Dr S. Ikeda received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, and Daiichi-Sankyo. Dr Ogihara received research funding from Bayer Healthcare. Dr Koitabashi received lecture fees from Bayer Healthcare and grant support from Pfizer. The remaining authors have no disclosures to report.

Supplemental Material

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