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Full Length Article

Clinical outcomes of patients with pulmonary embolism versus deep vein thrombosis: From the COMMAND VTE Registry

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ABSTRACT

Introduction: Pulmonary embolism (PE) and deep vein thrombosis (DVT) can be considered as one clinical entity, venous thromboembolism (VTE). However, the potential differences between PE and DVT might have to be taken into consideration for the decision-making of the optimal treatment strategies.

Materials and methods: The COMMAND VTE Registry is a multicenter registry enrolling 3027 consecutive patients with acute symptomatic VTE. The current study population consisted of 1715 PE patients with or without DVT and 1312 DVT only patients.

Results: The adjusted risk for recurrent VTE was not significantly different between the PE and DVT only groups (HR 1.22, 95%CI 0.93–1.60, P = 0.15). PE patients developed recurrent VTE events more often as PE than as DVT only (62% and 38%). The adjusted excess mortality risk of PE patients relative to DVT only patients was

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HR, hazard ratio; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism

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significant (HR 1.29, 95%CI 1.11–1.50, P < 0.001), with markedly higher cumulative 30-day incidence of all-cause death in PE patients (6.4% and 1.4%, P < 0.001). The most frequent cause of deaths was cancer death in both groups, and second most frequent cause of deaths in PE patients was fatal PE, most of which developed within 30 days.

Conclusions: The risk for recurrent VTE was not significantly different between PE and DVT, although PE was more likely to develop recurrent VTE as PE. The mortality risk of PE seemed to be higher than that of DVT, which was more remarkable in the short term due to PE death, and less remarkable in the long term due to cancer death.

1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major health problem in the world [1,2]. Historically, PE and DVT had been considered as different diseases, but they became collectively called VTE, because there was much overlap in their etiology, occurrence, and prognosis [3]. According to the concept that PE and DVT can be considered as one clinical entity, the current VTE guidelines recommend mostly identical treatment strategies beyond the acute phase, including anticoagulation therapy for both PE and DVT [4–6]. These management strategies would be reasonable, because PE and DVT are thought to be different manifestations of the pathophysiologically same disease.

However, a previous study reported that patients with PE had higher risks for fatal PE and overall mortality in the acute phase than patients with DVT [7]. Another study reported that a risk of recurrence was not different between PE and DVT, although types of recurrence were different [8]. Considering these potential differences in the prognosis between PE and DVT, the difference between PE and DVT might have to be taken into consideration for the decision making of the optimal treatment strategies. However, there is still limited information on the clinical characteristics, and long-term outcomes including causes of mortality comparing PE and DVT. Therefore, we sought to evaluate the clinical characteristics, management strategies, and outcomes of patients with PE and DVT in a large observational database of VTE in Japan.

2. Materials and methods

2.1. Study population

The COMMAND VTE (COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism) registry is a physician-initiated, retrospective, multicenter cohort study enrolling consecutive patients with acute symptomatic VTE objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography) or by autopsy among 29 centers in Japan between January 2010 and August 2014. The design of the registry was previously reported in detail [9–11]. The relevant review boards or ethics committees in all 29 participating centers (Supplementary Appendix 1) approved the research protocol.

In the current study, not only symptomatic PE patients but also asymptomatic PE patients were regarded as PE patients, and similarly, not only symptomatic DVT patients but also asymptomatic DVT patients were regarded as DVT patients. Consistent with the previous report [12], we classified patients who had PE with or without DVT as PE group. We compared the clinical characteristics, management strategies and outcomes between the 2 groups with a median follow-up period of 1218 (interquartile range [IQR]: 847–1764) days for surviving patients (95.1% follow-up rate at 1 year).

2.2. Definitions for patient characteristics

Patients with active cancer were defined as those on treatment for cancer such as chemotherapy or radiotherapy, those scheduled to undergo cancer-surgery, those with metastasis to other organs, and/or those with terminal cancer (expected life expectancy of 6 months or less) at the time of the diagnosis. Initial parenteral anticoagulation therapy was defined as parenteral anticoagulation therapy in the acute phase (heparin or fondaparinux) for ≤10 days after the diagnosis, while anticoagulation therapy beyond the acute phase was defined as anticoagulation therapy (warfarin, direct oral anticoagulant (DOAC), or heparin) continued beyond 10 days after the diagnosis. The detailed definitions of patient characteristics are described in Supplementary Appendix 2.

2.3. Clinical follow-up and clinical 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 regarding vital status, recurrent VTE, bleeding, invasive procedure, acute myocardial infarction, stroke and status of anticoagulation therapy. In this retrospective cohort study, data collection for follow-up events was performed between July 2016 and March 2017.

The outcomes measured were recurrent VTE, major bleeding and all-cause death. The 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 [13]. Major bleeding was defined as International Society of Thrombosis and Hemostasis (ISTH) major bleeding, which consisted of a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ [14].

The independent clinical event committee (Supplementary Appendix 3) unaware of the patient characteristics reviewed all study outcomes, and classified the cause of death as due to PE, due to cancers, due to bleeding events, due to cardiac events, due to other non-cardiac events, or due to unknown causes [15]. Death was judged to be due to PE (fatal PE), if it was confirmed by autopsy or if death followed a clinically severe PE, either initially or after recurrent PE events. Death from end-stage cancer without a specific cause of death was regarded as of cancer origin. Death was judged to be bleeding-related, if it followed an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration. Death was judged due to cardiac events, if it followed acute myocardial infarction, heart failure, or ventricular arrhythmia. Final classifications for causes of deaths were made on the basis of the full consensus of the independent clinical event committee.

Anticoagulation therapy cessation was classified into discontinuation and interruption according to the pre-specified definitions. Discontinuation of anticoagulation was defined as withdrawal of anticoagulation therapy lasting > 14 days for any reasons such as bleeding events, physicians' judgment in the absence of adverse events, and others. Interruption of anticoagulation was defined as temporary cessation of anticoagulation therapy with reinstitution within 14 days for any reasons including invasive procedure and bleeding events, etc. Scheduled switch from one anticoagulation therapy to another anticoagulation therapy was not regarded as interruption of anticoagulation.

Data for international normalized ratio (INR) during follow-up in patients receiving warfarin were collected from the hospital charts of the centers where the index VTE was diagnosed. Time in therapeutic range (TTR) was calculated by the Rosendaal method [16], according to a therapeutic INR range of 1.5 to 2.5, which is recommended in the Japanese guidelines [6], as well as according to a therapeutic INR range of 2.0 to 3.0, which is recommended in the Western guidelines [4,5,17].

2.4. Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and IQR based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using the Student's *t*-test or Wilcoxon's rank sum test based on their distributions. We used the Kaplan-Meier method to estimate the cumulative incidences of the clinical outcomes and assessed the differences with the log-rank test. To adjust for the clinically relevant confounders, we used the multivariable Cox proportional hazard model to estimate the hazard ratio (HR) and their 95% confidence interval (CI) for the risk of PE group relative to DVT only group for the clinical outcomes. Based on the previous reports [4–6,17] and consideration of clinical relevance, we selected 8 risk-adjusting variables for recurrent VTE, 9 risk-adjusting variables for major bleeding, and 16 risk-adjusting variables for all-cause death (Table 1). To evaluate all-cause death within and beyond 30 days after diagnosis, we conducted the landmark analysis at 30 days. In the analyses within 30 days after diagnosis, all patients who were alive at 30 days were censored at 30 days. In the analyses beyond 30 days after diagnosis, we excluded patients who died within 30 days. All statistical analyses were conducted using JMP version 10.0.2 (SAS Institute Inc., Cary, NC, USA). All reported P-values were 2-tailed, and P-values < 0.05 were considered statistically significant.

3. Results

We enrolled 3027 consecutive patients with acute symptomatic VTE after screening of the consecutive 19,634 patients with suspected VTE for eligibility through chart review by the physicians at each institution. The current study population consisted of 381 patients who had PE only, 1312 patients who had DVT only, and 1334 patients who had both PE and DVT (Fig. 1). PE group accounted for 1715 patients, and DVT only group accounted for 1312 patients.

3.1. Patient characteristics

In the entire study population, mean age was 67 years, 61% were women, and mean body weight and body mass index were 57.9 kg and 23.2 kg/m^2, respectively. The baseline patient characteristics were different in several aspects between the 2 groups (Table 1). PE group more often had hypertension, chronic lung disease, history of stroke, and history of major bleeding than DVT only group, whereas there were no significant differences in mean age, proportions of chronic kidney disease, active cancer, and history of VTE. Detailed imaging examinations at diagnosis between the 2 groups are shown in the Supplementary Table 1. Among all 2646 DVT patients, 2041 patients (77%) were examined by contrast-enhanced computed tomography, and 1294 patients were diagnosed as PE.

3.2. Treatment strategies

PE group more often received initial parenteral anticoagulation therapy than DVT only group, whereas PE group received anticoagulation therapy beyond the acute phase as often as DVT only group (Table 2). Median TTR among warfarin users was higher in PE group than in DVT only group. Among patients who received anticoagulation therapy beyond the acute phase, discontinuation of anticoagulation therapy was less frequent in PE group (PE group: 38.0% and DVT only group: 48.9% at 3-year, $P < 0.001$) (Fig. 2). At 1 year, 946 patients (71%) of 1326 PE patients received anticoagulation therapy, and 681 patients (64%) of 1065 DVT patients received anticoagulation therapy. The most dominant reason for discontinuation of anticoagulation was physician's judgment in both groups (Table 2). The prevalence of interruption of anticoagulation therapy during follow-up period was not

Table 1
Patient characteristics.

	PE group (N = 1715)	DVT only group (N = 1312)	P-value
Baseline characteristics			
Age (years)[a,b,c]	66.7 ± 15.0	67.8 ± 15.7	0.06
Women[a,b,c]	1062 (62%)	796 (61%)	0.48
Body weight (kg)	58.8 ± 14.2	56.7 ± 13.0	< 0.001
Body mass index (kg/m^2)	23.4 ± 4.6	22.9 ± 4.2	0.004
Body mass index ≥ 30 kg/m^2[a]	111 (6.5%)	58 (4.4%)	0.01
Comorbidities			
Hypertension[c]	700 (41%)	461 (35%)	0.002
Diabetes mellitus[c]	196 (11%)	190 (14%)	0.01
Dyslipidemia	362 (21%)	246 (19%)	0.11
Chronic kidney disease[b,c]	304 (18%)	268 (20%)	0.06
Dialysis	7 (0.4%)	14 (1.1%)	0.03
History of cancer	523 (31%)	415 (32%)	0.50
Active cancer at diagnosis[a,b,c]	393 (23%)	302 (23%)	0.95
Chronic lung disease	179 (10%)	92 (7.0%)	0.001
Heart failure	51 (3.0%)	50 (3.8%)	0.20
History of myocardial infarction	26 (1.5%)	27 (2.1%)	0.26
History of stroke[c]	170 (9.9%)	100 (7.6%)	0.03
Atrial fibrillation	83 (4.8%)	46 (3.5%)	0.07
Liver cirrhosis[a,b]	11 (0.6%)	15 (1.1%)	0.14
Connective tissue disease[c]	108 (6.3%)	136 (10%)	< 0.001
Varicose Vein[a,c]	63 (3.7%)	76 (5.8%)	0.006
History of VTE[a,c]	90 (5.3%)	88 (6.7%)	0.09
History of major bleeding[b,c]	148 (8.6%)	83 (6.3%)	0.02
Transient risk factors for VTE[a,b,c]	584 (34%)	502 (38%)	0.02
Unprovoked VTE	840 (49%)	602 (46%)	0.09
Laboratory tests at diagnosis			
Anemia[b,c]	814 (47%)	813 (62%)	< 0.001
Thrombocytopenia (platelet count $< 100 \times 10^9/L$)[b,c]	102 (6.0%)	65 (5.0%)	0.24
D-dimer (μg/mL) (N = 2852)	12.3 (6.6–23.2)	7.5 (3.7–16.3)	< 0.001
Thrombophilia[a,c]	101 (5.9%)	46 (3.5%)	0.003

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using the Student's *t*-test or Wilcoxon's rank sum test based on distribution.

Chronic kidney disease was diagnosed if there was persistent proteinuria or if estimated glomerular filtration rate (eGFR) was < 60 mL/min/1.73 m^2 for > 3 months. The values of eGFR were calculated based on the equation reported by Japan Association of Chronic Kidney Disease Initiative [man: $194 * Scr^{-1.094} * age^{-0.287}$, woman: $194 * Scr^{-1.094} * age^{-0.287} * 0.739$].

Unprovoked VTE was defined as VTE without active cancer or transient risk factors for VTE. Anemia was diagnosed if the value of hemoglobin was < 13 g/dL for men and < 12 g/dL for women. Thrombophilia included protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Risk adjusting variables for the multivariable Cox regression model to estimate the risk for recurrent VTE.

[b] Risk adjusting variables for the multivariable Cox regression model to estimate the risk for major bleeding.

[c] Risk adjusting variables for the multivariable Cox regression model to estimate the risk for all-cause death.

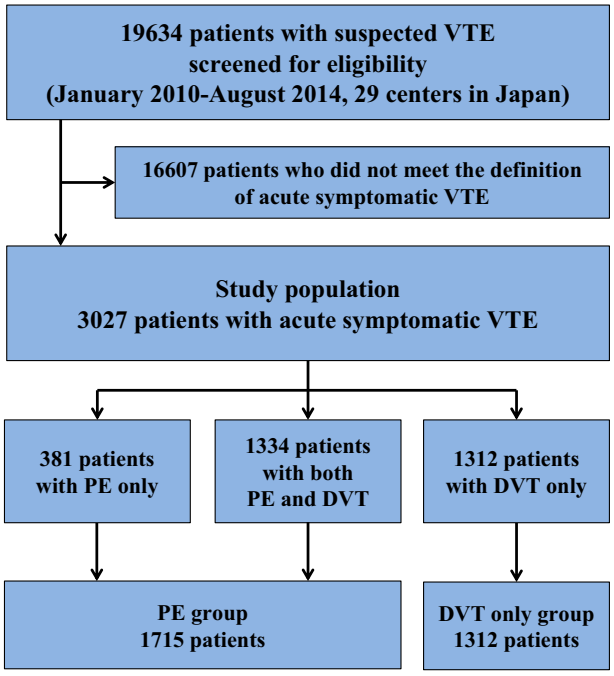


Fig. 1. Study flow chart.
VTE included PE and/or DVT.
DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

significantly different between the 2 groups.

3.3. Recurrent VTE and major bleeding outcomes

The median follow-up period was 1218 (IQR: 847–1764) days for surviving patients (95.1% follow-up rate at 1 year). The cumulative 5-year incidence of recurrent VTE was not significantly different between the 2 groups (PE group: 11.4% and DVT only group: 9.4%, P = 0.11) (Fig. 3A). After adjusting confounders, the risks of PE group relative to DVT only group for recurrent VTE remained insignificant (HR 1.22, 95%CI 0.93–1.60, P = 0.15) (Supplementary Table 2). PE group developed recurrent VTE events more often as PE than as DVT only (recurrent PE: 62% and recurrent DVT only: 38%), whereas DVT only group developed recurrent VTE events more often as DVT only than as PE (recurrent PE: 26% and recurrent DVT only: 74%) (Table 3). The recurrent VTE events during anticoagulation therapy and after discontinuation of anticoagulation therapy are shown in the Supplementary Table 3.

The cumulative 5-year incidence of major bleeding was not significantly different between the 2 groups (12.6% and 11.4%, P = 0.22) (Fig. 3B). After adjusting confounders, the risks of PE group relative to DVT only group for major bleeding remained insignificant (HR 1.24, 95%CI 0.97–1.59, P = 0.09) (Supplementary Table 2).

3.4. Mortality outcomes

The cumulative 5-year incidence of all-cause death was not significantly different between the 2 groups (PE group: 30.2% and DVT only group: 28.4%, P = 0.06) (Fig. 4A), although by the landmark analysis at 30 days, the cumulative 30-day incidence of all-cause death in PE group was markedly higher than that of DVT only group (6.4%

Table 2
Treatments.

	PE group (N = 1715)	DVT only group (N = 1312)	P-value
Treatment in the acute phase			
Initial parenteral anticoagulation therapy	1597 (93%)	937 (71%)	< 0.001
Thrombolysis	346 (20%)	84 (6.4%)	< 0.001
Vena cava filter use	494 (29%)	226 (17%)	< 0.001
Ventilator support	91 (5.3%)	1 (0.1%)	< 0.001
Percutaneous cardiopulmonary support	39 (2.3%)	0 (0.0%)	< 0.001
Concomitant medications at discharge			
Corticosteroids	181 (11%)	166 (13%)	0.07
Non-steroidal anti-inflammatory drugs	139 (8.1%)	158 (12%)	< 0.001
Proton pump inhibitors/H2-blockers	830 (48%)	506 (39%)	< 0.001
Statins	255 (15%)	182 (14%)	0.44
Antiplatelet agents	150 (8.8%)	157 (12%)	0.004
Anticoagulation therapy beyond the acute phase	1595 (93%)	1208 (92%)	0.33
Warfarin	1529 (89%)	1147 (87%)	0.51
Direct oral anticoagulant	40 (2.3%)	38 (2.9%)	
Heparin	26 (1.5%)	23 (1.8%)	
TTR for INR 1.5–2.5 (%) (N = 2509)	75.1 (47.9–93.3)	69.1 (41.9–88.5)	< 0.001
TTR for INR 2.0–3.0 (%) (N = 2509)	33.7 (10.8–57.9)	27.5 (4.8–52.7)	< 0.001
Duration of anticoagulation therapy			
− 3 months	254 (16%)	203 (17%)	0.03
3–6 months	167 (10%)	154 (13%)	
6–12 months	209 (13%)	192 (16%)	
12–24 months	240 (15%)	167 (14%)	
24 months	725 (45%)	492 (41%)	
Discontinuation of anticoagulation during follow-up	552/1595	537/1208	< 0.001
Reason for discontinuation			
Physician's judgment	300/552 (54%)	348/537 (65%)	0.002
Bleeding event	117/552 (21%)	84/537 (16%)	
Other	135/552 (24%)	105/537 (20%)	
Interruption of anticoagulation during follow-up period	204/1595 (13%)	138/1208 (11%)	0.27

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the median and interquartile range. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using Wilcoxon's rank sum test.
DVT, deep vein thrombosis; PE, pulmonary embolism; INR, international normalized ratio; TTR, time in therapeutic range.

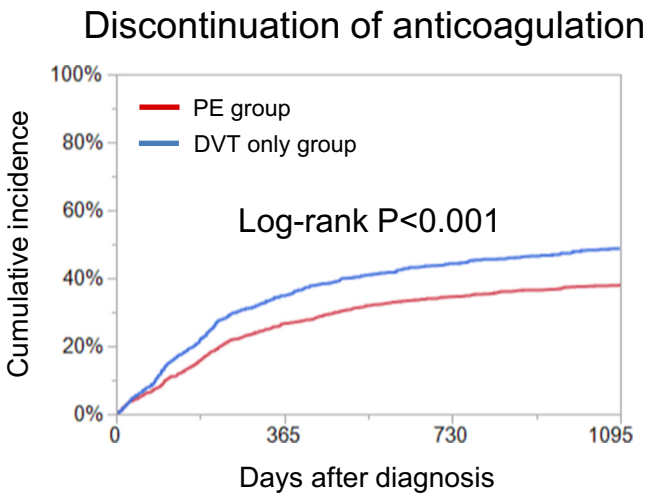
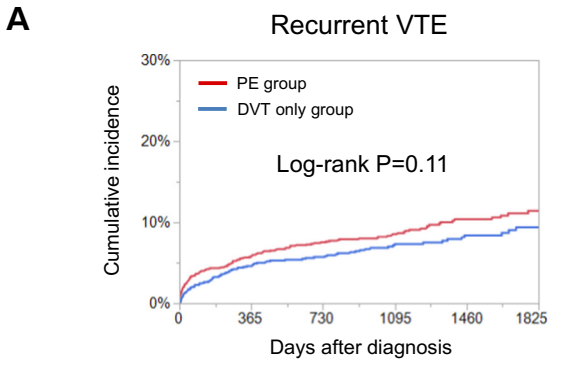
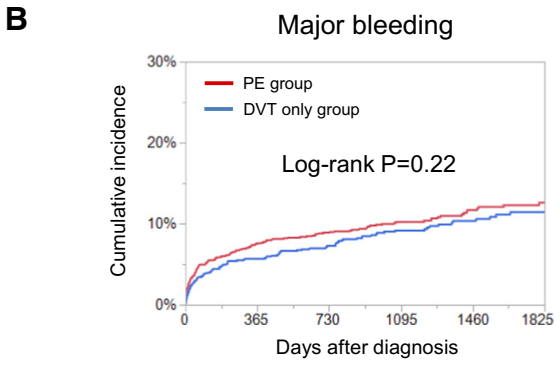


Fig. 2. Kaplan-Meier curves for discontinuation of anticoagulation therapy comparing PE group versus DVT only group.
The discontinuation of anticoagulation was estimated in patients who received anticoagulation therapy beyond the acute phase, and defined as withdrawal of anticoagulation therapy lasting > 14 days for any reasons.
DVT, deep vein thrombosis; PE, pulmonary embolism.

	0-day	90-day	180-day	1-year	3-year
PE group					
N of patients with discontinuation		119	230	380	511
N of patients at risk	1595	1344	1175	966	508
Cumulative incidence		7.8%	15.6%	26.7%	38.0%
DVT only group					
N of patients with discontinuation		127	241	384	511
N of patients at risk	1208	1007	852	660	335
Cumulative incidence		10.9%	21.2%	34.8%	48.9%





	0-day	90-day	1-year	3-year	5-year
PE group					
N of patients with event		59	89	120	136
N of patients at risk	1715	1444	1256	741	264
Cumulative incidence		3.7%	5.8%	8.6%	11.4%
DVT only group					
N of patients with event		29	55	78	86
N of patients at risk	1312	1187	1013	585	217
Cumulative incidence		2.3%	4.6%	7.3%	9.4%

	0-day	90-day	1-year	3-year	5-year
PE group					
N of patients with event		80	117	146	159
N of patients at risk	1715	1426	1243	732	267
Cumulative incidence		4.9%	7.6%	10.2%	12.6%
DVT only group					
N of patients with event		46	70	101	111
N of patients at risk	1312	1177	1015	593	221
Cumulative incidence		3.6%	5.7%	9.2%	11.4%

Fig. 3. Kaplan-Meier curves for (A) recurrent VTE and for (B) major bleeding comparing PE group versus DVT only group.
VTE included PE and/or DVT.
VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

and 1.4%, P < 0.001) (Fig. 4B). After adjusting the confounders, the excess long-term mortality risk of PE group relative to DVT only group was significant (HR 1.29, 95%CI 1.11–1.50, P < 0.001) (Supplementary Table 2).

The most frequent cause of deaths during the follow-up period was cancer death in both groups (Table 3). Second most frequent cause of deaths in PE group was fatal PE, whereas only 1 patient died due to recurrent fatal PE in DVT only group. Vast majority of fatal PE

Table 3
Clinical outcomes and causes of deaths.

	PE group (N = 1715)	DVT only group (N = 1312)
Recurrent VTE	137 (11.4%)	89 (9.4%)
Recurrent PE	85/137 (62%)	23/89 (26%)
Recurrent DVT only	52/137 (38%)	66/89 (74%)
Major bleeding	162 (12.6%)	113 (11.4%)
All-cause death	449 (30.2%)	315 (28.4%)
Fatal PE	84/449 (18.7%)	1/315 (0.3%)
Cancer	219/449 (48.8%)	190/315 (60.3%)
Bleeding events	21/449 (4.7%)	14/315 (4.4%)
Other non-cardiac events	75/449 (16.7%)	62/315 (19.7%)
Cardiac events	20/449 (4.5%)	17/315 (5.4%)
Unknown	30/449 (6.7%)	31/315 (9.8%)

Number of patients with event was evaluated throughout the entire follow-up, while the cumulative incidence in the parenthesis was assessed at 5-year. Variables for the types of recurrent VTE and causes of death are presented as number of patients with event and proportions (%). Death was judged due to cardiac events if it followed acute myocardial infarction, heart failure, or ventricular arrhythmia.
DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

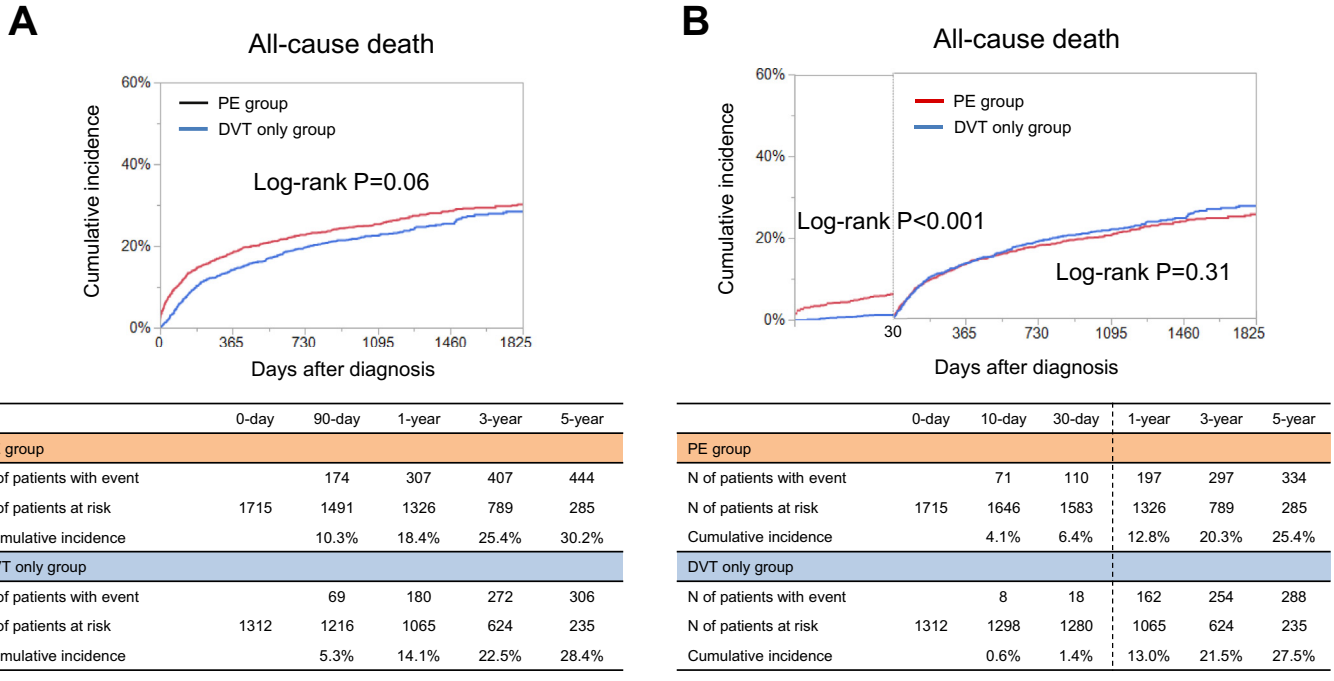
developed in the acute phase within 30 days, whereas the predominant cause of deaths beyond 31 days was cancer death (Table 4).

Subgroup analysis stratified by active cancer showed that among patients with active cancer, the cumulative 5-year incidence of all-cause death was not significantly different between the 2 groups (71.4% and 74.6%, P = 0.69), whereas among patients without active cancer, the cumulative 5-year incidence of all-cause death in PE group was significantly higher than that in DVT only group (17.6% and 14.0%, P = 0.007) (Supplementary Fig. 1). Among patients without active cancer, the most frequent cause of deaths in PE group was fatal PE, whereas among patients with active cancer, vast majority of deaths was cancer death in both PE group and DVT only group (Supplementary Table 4).

4. Discussion

The main findings of the current study were as follows; 1) The risk for recurrent VTE was comparable between PE patients and DVT only patients, although PE patients were more likely to develop recurrent VTE events as PE events, and DVT only patients were more likely to develop recurrent VTE events as DVT only events; 2) the adjusted mortality risk of PE patients was significantly higher than that of DVT only patients with remarkable difference in the short term; and 3) Vast majority of fatal PE events in PE patients developed in the acute phase within 30 days, whereas the predominant cause of deaths beyond 31 days was due to cancer in both PE patients and DVT only patients.

A previous meta-analysis study reported a similar risk for long-term recurrence between PE and DVT patients after anticoagulation therapy was discontinued [8]. In line with the previous study, the current study showed the comparable risk for recurrent VTE between PE and DVT patients after VTE diagnosis. The previous study also reported that patients presenting with a first episode of PE were 3-fold more likely to suffer PE than DVT as a recurrence [8]. Consistent with the previous report, the current study also showed that PE patients were more likely to develop recurrent VTE events as PE events. The current several VTE guidelines recommend that VTE patients should receive anticoagulation therapy for at least 3 months, followed by prolonged anticoagulation therapy depending on risks for recurrence and bleeding [4–6,17]. However, not only a risk of recurrence but also types of recurrence could be clinically important, because a risk for mortality could be different between PE and DVT patients. Considering a higher likelihood of recurrent PE events in PE patients than in DVT patients, PE patients might derive more benefit by prolonged anticoagulation therapy through prevention of recurrent PE events. Furthermore, a risk for development of chronic thromboembolic pulmonary hypertension was reported to be markedly higher in patients with PE than in patients without PE [18]. Complete resolution of thrombus in pulmonary arteries through adequate duration of anticoagulation therapy might be beneficial for prevention of chronic thromboembolic pulmonary hypertension, although chronic thromboembolic pulmonary hypertension



	0-day	90-day	1-year	3-year	5-year
PE group					
N of patients with event		174	307	407	444
N of patients at risk	1715	1491	1326	789	285
Cumulative incidence		10.3%	18.4%	25.4%	30.2%
DVT only group					
N of patients with event		69	180	272	306
N of patients at risk	1312	1216	1065	624	235
Cumulative incidence		5.3%	14.1%	22.5%	28.4%

	0-day	10-day	30-day	1-year	3-year	5-year
PE group						
N of patients with event		71	110	197	297	334
N of patients at risk	1715	1646	1583	1326	789	285
Cumulative incidence		4.1%	6.4%	12.8%	20.3%	25.4%
DVT only group						
N of patients with event		8	18	162	254	288
N of patients at risk	1312	1298	1280	1065	624	235
Cumulative incidence		0.6%	1.4%	13.0%	21.5%	27.5%

Fig. 4. Kaplan-Meier curves for all-cause death (A) during the entire follow-up period comparing PE group versus DVT only group, and (B) landmark analysis of all-cause death within and beyond 30 days.
VTE included PE and/or DVT.
DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 4
Causes of deaths during the follow-up period.

	Within 30 days	31 days–90 days	91 days–365 days	Beyond 366 days
PE group (N = 1715)				
All-cause death (N = 449)	110	64	133	142
Fatal PE	72/110 (65.5%)	5/64 (7.8%)	4/133 (3.0%)	3/142 (2.1%)
Cancer	26/110 (23.6%)	44/64 (68.8%)	88/133 (66.2%)	61/142 (43.0%)
Bleeding events	5/110 (4.6%)	3/64 (4.7%)	4/133 (3.0%)	9/142 (6.3%)
Other non-cardiac events	5/110 (4.6%)	9/64 (14.1%)	21/133 (15.8%)	40/142 (28.2%)
Cardiac events	2/110 (1.8%)	0/64 (0.0%)	7/133 (5.3%)	11/142 (7.8%)
Unknown	0/110 (0.0%)	3/64 (4.7%)	9/133 (6.8%)	18/142 (12.7%)
DVT group (N = 1312)				
All-cause death (N = 315)	18	51	111	135
Fatal PE	1/18 (5.7%)	0/51 (0.0%)	0/111 (0.0%)	0/135 (0.0%)
Cancer	10/18 (55.6%)	39/51 (76.5%)	80/111 (72.1%)	61/135 (45.2%)
Bleeding events	2/18 (11.1%)	1/51 (2.0%)	3/111 (2.7%)	8/135 (5.9%)
Other non-cardiac events	5/18 (27.8%)	6/51 (11.8%)	15/111 (13.5%)	36/135 (26.7%)
Cardiac events	0/18 (0.0%)	3/51 (5.9%)	2/111 (1.8%)	12/135 (8.9%)
Unknown	0/18 (0.0%)	2/51 (3.9%)	11/111 (9.9%)	18/135 (13.3%)

Variables are presented as numbers of events and proportions (%). Death was judged due to cardiac events if it followed acute myocardial infarction, heart failure, or ventricular arrhythmia.
DVT, deep vein thrombosis; PE, pulmonary embolism.

is considered a relatively rare complication of PE.

Another previous study reported that PE patients showed worse mortality at 3 month than DVT patients [7]. Consistent with the previous report, the current study showed markedly worse short-term mortality in PE patients than in DVT patients. This might be mainly driven by a high prevalence of fatal PE within 30 days in PE patients. The current study also showed that the adjusted long-term mortality risk of PE patients was significantly higher than that of DVT patients, although the risk difference trended to be decreasing with longer follow-up. This was partly because during the long-term follow-up period, a few patients died due to PE and majority of patients died due to other reasons than PE such as cancer. In terms of VTE-related mortality, appropriate management of PE patients in the acute phase would be especially important. Although the current guidelines recommend treating low-risk PE patients with early discharge, those patients should be carefully selected because a prognosis of PE was worse than that of DVT in the first 30 days. On the other hand, only 1 patient died due to fatal PE in DVT only patients. Considering the low risk of DVT only patients for VTE-related mortality, these patients could be good candidates for home treatment. In the era of DOACs for VTE, some of the DOACs have been used as a single drug approach without administering intravenous anticoagulants, which would be more suitable for early hospital discharge or home treatment [19,20]. Furthermore, the current subgroup analysis stratified by active cancer suggested potential difference in the impact of PE and DVT on overall mortality depending on the presence or absence of active cancer. Vast majority of VTE patients with active cancer died due to cancer, and mortality impact of PE and DVT in patients with active cancer seemed to be less important, suggesting needs for different management strategies in patients with active cancer.

4.1. Study limitations

The current study has several limitations. First, this was a retrospective cohort study with the limitations inherent to observational study design. The therapeutic decision-making was left to the discretion of the attending physicians, which could have some influence on clinical outcomes. Second, the treatment strategies in the acute phase including initial parenteral anticoagulation therapy and thrombolysis were different between the 2 groups. These differences could have some influence on bleeding events, although there was no significant difference in the incidence of major bleeding between the 2 groups. Third, some DVT patients could have been misclassified as DVT only, because 545 patients were not examined by imaging examinations for PE. Fourth, because there could be difficulty in determining the cause of death in PE patients, the case fatality rate of recurrent PE could be overestimated. Finally, the current study was conducted before introduction of DOACs for VTE in Japan. Thus, it should be interpreted with caution whether the present results could be extrapolated to patients treated with DOACs.

5. Conclusions

The risk for recurrent VTE was not significantly different between PE and DVT, although PE patients were more likely to develop recurrent VTE events as PE events. The mortality risk of PE seemed to be higher than that of DVT, which was more remarkable in the short term due to predominance of PE death, and less remarkable in the long term due to predominance of cancer death.

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Declaration of competing interest

Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Bayer Healthcare. Dr. Morimoto received lecture fees from Mitsubishi Tanabe Pharma and Pfizer Japan and consultant fees from Asahi Kasei, Bristol-Myers Squibb, and Boston Scientific. Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare and Daiichi-Sankyo. Dr. Kimura serves as an advisory board member for Abbott Vascular

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.10.029.

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