Current Venous Thromboembolism Management and Outcomes in Japan

– Nationwide The Japan Venous Thromboembolism Treatment Registry Observational Study –

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Background: Epidemiology and clinical management of acute venous thromboembolism (VTE) are not readily available in Japan.

Methods and Results: The Japan VTE Treatment Registry (JAVA) is a multicenter cohort study of consecutive patients with an objectively confirmed, symptomatic acute pulmonary embolism (PE), symptomatic acute deep vein thrombosis (DVT), or asymptomatic acute proximal DVT. Of the 1,076 patients enrolled with acute VTE, 68.7% presented with an isolated DVT; 17.0% had PE alone; and 14.4% had both. VTE management was characterized by a high rate of inferior vena cava filter insertion (40.6%), frequent thrombolysis (21.1%), and sub-therapeutic unfractionated heparin-based anticoagulation, followed by warfarin prescription, mostly targeting an international normalized ratio of 2.0 (range, 1.5–2.5). During a mean observation period of 252.5 days, 29 recurrent cases of VTE were documented, yielding an incidence rate of 3.9 per 100 patient-years. A total of 123 patients died during the study period, corresponding to a rate of 16.6 deaths per 100 patient-years. The incidence of major bleeding was 3.2% per patient-year, including 2 fatal hemorrhages and 7 intracranial hemorrhages.

Conclusions: VTE management in Japan is characterized by a highly aggressive strategy in the acute phase, in contrast to protocols that use low-level anticoagulation. The VTE recurrence rates in Japan and Western countries are similar, but mortality is higher in Japan, with significant variability depending on patient and management characteristics. (*Circ J* 2014; **78**: 708–717)

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In November 2004, the first Japanese guidelines for the diagnosis, treatment, and prevention of pulmonary embolism (PE) and deep vein thrombosis (DVT) were issued, and, in January 2010, an updated version was posted on the website of the Japanese Circulation Society and later published.¹

Editorial p 597

The approach to anti-thrombotic therapy should take into account the balance between the benefit and the risk of each treatment strategy. Depending on the severity of the clinical presentation and the bleeding risk, recommended management of acute-phase venous thromboembolism (VTE) may combine thrombolysis, parenteral anticoagulation, and insertion of an inferior vena cava (IVC) filter. In Japan, standard anticoagulation treatment during the acute phase of VTE involves i.v. unfractionated heparin (UFH), with routine monitoring of activated partial thromboplastin time (aPTT) for dose adjustment. Low-molecular-weight heparin (LMWH) has not been approved for the treatment of acute VTE. Fondaparinux is the sole approved alternative to UFH for the treatment of acute VTE in Japan, but the Japanese Circulation Society 2010 guidelines do not include a recommendation for use of fondaparinux. To prevent recurrent VTE, vitamin K antagonists (VKA) are recommended for a minimum of 3 months in most cases, and a longer duration can be considered in patients with cancer. The recommended target international normalized ratio (INR) for PE and DVT in the Japanese guidelines is 2.0 (range, 1.5–2.5), lower than the target value (INR, 2.5; range, 2.0–3.0) used in Western countries.² New oral anticoagulants such as rivaroxaban and dabigatran have not yet been approved for the treatment of VTE in Japan.

Most of the recommendations are not supported by clinical evidence in Japanese patients, and data related to real-world practice and compliance with the guidelines are lacking. Epidemiological data regarding the early and long-term outcomes of acute DVT or PE in Asian subjects in general, and Japanese patients in particular, are absent.

With regard to recurrence rates, a study conducted by another academic group in Taiwan concluded that the incidence of VTE was lower in Taiwanese than in Western populations, but that the recurrence rate was similar (9.4% at 12 months).³ The same Taiwanese academic group indicated that the overall short-term mortality rate 1 month after VTE was not negligible in the Taiwanese population, with 7.1% and 12.9% mortality rates after DVT and PE, respectively.⁴

Using data from a national database established by the Japanese Society of Pulmonary Embolism Research (JaSPER), we also previously reported that the in-hospital mortality rate after PE remains high, with a mean mortality rate of 14–30% in PE complicated by shock.⁵ In this study we therefore investigated the spectrum of VTE management in Japan and assessed the short- and long-term prognoses of patients with VTE using a nationwide patient record-based cohort.

Methods

Subjects

The Japan VTE Treatment Registry (JAVA) Study was a nationwide, observational, multicenter, Japanese cohort study of consecutive patients with an objectively confirmed, acute VTE treated between April 2009 and March 2010. From an initial list of 100 institutions across Japan that were deemed representative of VTE management practices by the steering com-

mittee, 80 were approached, and 63 agreed to participate in the JAVA Study.

Inclusion criteria, baseline data and outcomes were obtained retrospectively from patient records and were subsequently reported on a standardized case report form. Inclusion criteria were acute, symptomatic PE; symptomatic DVT; or asymptomatic, acute, proximal DVT. Confirmed diagnosis implied that PE was documented in the patient's hospital records during the hospital stay using an objective method such as computed tomography (CT), magnetic resonance imaging, or other relevant imaging methods. Asymptomatic proximal DVT was defined as a DVT documented as a thrombus above the popliteal vein on a scan. An investigator classified each PE into the pre-specified severity grade (non-massive, submassive, or massive).

Patients of all ages were enrolled, but only the data for patients >18 years were included in the primary analysis. Patients with a distal DVT and those with a chronic or residual VTE were excluded.

Objectives and Outcomes

The primary objective was to assess the recurrence rate of VTE 12 months after the index event. The secondary objective included estimation of all-cause and VTE-related death rates, and the assessment of all types of bleeding, including major bleeding. Another aim of the study was to determine the current characteristics of Japanese VTE management strategies, in order to investigate the relationship between any events and treatment.

All outcomes were validated by 1 local investigator without double reading or central adjudication of the events. Recurrent VTE was defined as symptomatic PE, symptomatic DVT, or asymptomatic proximal DVT confirmed on the basis of an objective imaging method, using the same criteria as those for inclusion and without specific requirements in terms of timing of occurrence from the index event. Major bleeding was defined as life-threatening bleeding requiring transfusion of at least 2 units of whole blood or platelets, associated with a decrease in hemoglobin ≥ 2 g/dL, or the presence of retroperitoneal, intracranial, or intraocular bleeding. Early mortality was defined as death within 1 month after the index event.

The diagnoses of the primary cause of death and long-term complications (post-thrombotic syndrome and pulmonary hypertension) were based on evaluation by each investigator.

Statistical Analysis

The recurrence rates of symptomatic VTE at 3 months in the heparin/warfarin-treated patients were 4.1% in the Matisse DVT trial⁶ and 5.0% in the Matisse PE trial, which were conducted before the JAVA Study.⁷ In the THRIVE study, the recurrence rate in the LMWH/warfarin-treated group was lower, reaching 2.0% at 6 months.⁸ Because the number of reported VTE cases among Japanese patients was lower than that among Western patients in a real-life setting, we chose a conservative recurrence rate estimate of 4% at 12 months. Assuming an 85% completion rate for the primary outcome, and limiting the standard error to 20%, the target sample size was set at 800 patients, including a minimum of 300 patients with PE.

Incidence rates were calculated as cumulative incidence and person-time (events/100 patient-years). The Kaplan-Meier method was used for estimating event-free and cumulative recurrence curves, and the curves were compared using log-rank test. The chi-squared test was used to analyze the effect of specified risk factors on the recurrence of VTE or death within 1 year of diagnosis. Statistical analysis was done using

Table 1. Subject Characteristics

Baseline clinical characteristics	Overall n=1,076 (100%)	PE with or without DVT n=338 (31.4%)	DVT alone n=738 (68.6%)
Age (years)	65.3±15.1	66.2±14.7	65.0±15.2
Female	633 (58.8)	212 (62.7)	421 (57.0)
Weight (kg)	58.30±12.73	59.25±13.51	57.82±12.30
BMI (kg/m ²)	23.30±4.21	23.80±4.44	23.05±4.08
Hypertension	383 (35.6)	137 (40.5)	246 (33.3)
Stroke	84 (7.8)	23 (6.8)	61 (8.3)
Ischemic heart disease	53 (4.9)	21 (6.2)	32 (4.3)
Diabetes mellitus	150 (13.9)	40 (11.8)	110 (14.9)

Data given as mean±SD or n (%).

BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 2. Risk Factors of VTE

Risk factor	Overall n=1,076 (100%)	PE with or without DVT n=338 (31.4%)	DVT alone n=738 (68.6%)
Obesity (BMI ≥30)	59 (5.5)	23 (6.8)	36 (4.9)
Recent surgery (within 3 months)	192 (17.8)	56 (16.6)	136 (18.4)
Cancer	290 (27.0)	78 (23.1)	212 (28.7)
Heart disease	72 (6.7)	22 (6.5)	50 (6.8)
Respiratory disease	49 (4.6)	19 (5.6)	30 (4.1)
Severe infection	30 (2.8)	8 (2.4)	22 (3.0)
Severe injury	7 (0.7)	3 (0.9)	4 (0.5)
Fracture	49 (4.6)	14 (4.1)	35 (4.7)
Cesarean delivery (within 14 days)	3 (0.3)	3 (0.9)	0 (0.0)
History of VTE	66 (6.1)	21 (6.2)	45 (6.1)
Thrombophilia	44 (4.1)	12 (3.6)	32 (4.3)
Lower limb paresis	32 (3.0)	10 (3.0)	22 (3.0)
Varicosis	45 (4.2)	11 (3.3)	34 (4.6)
Estrogen and/or HRT	28 (2.6)	8 (2.4)	20 (2.7)
Central venous catheter	43 (4.0)	8 (2.4)	35 (4.7)
Immobilization	225 (20.9)	65 (19.2)	160 (21.7)

Data given as n (%).

HRT, hormone replacement therapy; VTE, venous thromboembolism. Other abbreviations as in Table 1.

SAS, and statistical significance was set at $P<0.05$.

Ethics

The study was approved by the steering and ethics committees of each institution.

Results

Cohort

We conducted a database search for records between April 2009 and March 2010, and obtained 1,087 consecutive patient records for screening. Among patients fulfilling the inclusion criteria, 1,076 were aged ≥18 years, thus considered for primary analysis. The patient records were collected from 63 institutions, including university-based hospitals that accounted for 48% of the centers and 48.3% of the inclusions. The remaining patient records were collected from community hospitals. Patients with acute VTE were enrolled from medical wards (35 sites: cardiology, cardiovascular, pulmonary, internal medicine, and hematology departments) in 56.0% of cases and from surgical wards (25 sites: cardiovascular and vascular surgery) or other departments (3 sites: emergency and intensive care units) in 37.5% and 6.4% of cases, respectively. The

mean observation period after the index event was 252 days, yielding a cohort of 742 patient-years.

VTE and Patient Characteristics

Among the 1,076 patients with acute VTE, one-third (33.7%) were inpatients and two-thirds (66.3%) were outpatients. Patients presented with isolated DVT in 68.6%, PE alone in 17%, and both PE and DVT in 14.4% of cases. In the present cohort, 633 (58.8%) were women and 443 (41.2%) were men. The mean±SD age was 65.3±15.1 years, ranging from 19 to 95 years, with 7.7% of the patients <40 years and 32.2% of the patients aged ≥75 years. Mean body weight and body mass index were 58.3±12.7 kg and 23.3±4.2 kg/m², respectively (Table 1).

A history of recent surgery (within 3 months) was reported in 17.8% of cases. Among the risk factors for VTE, a medical history of cancer was found to be most prevalent, accounting for 27.0% of the patients. A concomitant acute medical illness was found in approximately 20%. A history of VTE was reported in only 6.1% of the patients (Table 2). Overall, of the 1,076 VTE cases, 465 (43.2%) could be considered “idiopathic” without an associated trigger or chronic risk factor.

Table 3. Anti-Thrombotic Management (Acute and Chronic Phases)

	Overall (n=1,076)	PE with or without DVT (n=338)	DVT alone (n=738)
Thrombolytic	225 (20.9)	87 (25.7)	138 (18.7)
Urokinase	163 (71.8)	41 (47.1)	122 (87.1)
tPA	63 (27.8)	47 (54.0)	16 (11.4)
Parenteral anticoagulant	908 (84.4)	302 (89.3)	606 (82.1)
UFH	864 (80.3)	293 (86.7)	571 (77.4)
aPTT			
<1.5	268 (37.6)	91 (35.4)	177 (38.8)
1.5–3	438 (61.4)	166 (64.6)	272 (59.6)
>3	7 (1.0)	0 (0.0)	7 (1.5)
LMWH	45 (4.2)	10 (3.0)	35 (4.7)
Warfarin	956 (88.8)	305 (90.2)	651 (88.2)
Duration (months)	7±4.8	6.4±5.0	7.3±4.7
Target INR			
<1.5	65 (6.8)	19 (6.2)	46 (7.1)
1.5–2.5	812 (84.9)	253 (83.0)	559 (85.9)
>2.5	49 (5.1)	22 (7.2)	27 (4.1)
NA	30 (3.1)	11 (3.7)	19 (2.9)

Data given as n (%) or mean±SD.

aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NA, not available (INR performed but unknown or not measured); tPA, tissue plasminogen activator; UFH, unfractionated heparin. Other abbreviations as in Table 1.

VTE Management

VTE was confirmed using CT for PE (92.6% of patients) and a combination of ultrasonography and CT for DVT (75.4% and 69.2%, respectively).

Most VTE patients (91.9%) were initially treated in hospital. In the acute phase of VTE management (Table 3), systemic thrombolysis was used in 20.9% of the patients (25.7% of the initial PE patients and 18.7% of the initial isolated DVT patients); treatment mostly (71.8%) involved urokinase followed by tissue plasminogen activator (27.8%). No significant difference was found in the rate of use of thrombolytics between the university-based (18.0%) and community hospitals (23.6%). In contrast, thrombolysis was performed more frequently in surgical wards (29.7%) than in medical wards (16.5%).

Early parenteral anticoagulation was initiated in 914 patients (84.9%) and was most often performed with i.v. UFH (83.6%) rather than s.c. UFH (13.6%) or LMWH (4.9%). Among patients who underwent UFH-based treatment, a substantial proportion of patients (14.5%) did not undergo monitoring of aPTT. For those who had aPTT-based dose adjustment, the level of anticoagulation was subtherapeutic in approximately 40% of cases (aPTT ≤1.5-fold higher than the control; 37.6%). VTE type did not have a substantial impact on the early anticoagulant strategy, although heparin and its derivatives were more frequently used in patients with PE with or without DVT (89.3%) than in those with an initial diagnosis of isolated DVT (82.1%). Warfarin-based anticoagulation therapy was prescribed in 88.8% of the patients for a mean duration of 7 months, targeting a low INR in the range 1.5–2.5 in most cases (84.9%). The treatment duration was paradoxically longer in the patients with isolated DVT (mean, 7.3 months) than in those with DVT+PE (mean, 6.6 months) or isolated PE (mean, 6.3 months).

Many patients received an IVC filter, inserted in 40.7% of all patients, ranging from 28.4% for PE alone, 39.2% for DVT alone, and up to 62.6% for PE was associated with DVT. No

difference in insertion rate was observed either between the university-based (39.3%) and community hospitals (42.0%) or between the surgical (36.9%) and medical wards (43.5%). In 5.8% of the patients, an endovascular treatment approach was selected, which consisted of catheter-directed thrombolysis in most cases (83%), with or without other techniques such as thromboaspiration (29%). Surgical thrombectomy/embolectomy was deemed necessary in only 1.7% of cases. Graduated compression stockings (GCS) were used in 69.5% of cases. Fewer than half of the patients with isolated PE and three-quarters of those with DVT alone were prescribed GCS.

Outcomes

VTE Recurrence During a mean observation period of 252.2 days (range, 1–365 days), 29 cases of recurrent VTE were reported, of which 51.7% were isolated DVTs, 24.1% were PEs alone, and 24.1% both PE and DVT. This yielded an estimated annual incidence of 3.6% and an incidence rate of 4.0 per 100 patient-years, as determined using the Kaplan-Meier method (Figure 1A). The risk of PE recurrence (with or without DVT) was 7.0% per patient-year and was significantly lower in those patients with an initial diagnosis of isolated DVT (2.8% per patient-year; Figure 1B). The patients with PE were >2-fold more likely to experience a recurrent event compared with those with isolated DVT (hazard ratio, 2.39; 95% confidence interval: 1.15–4.96, $P=0.016$, log-rank test). Half (15/29) of the events occurred within 3 months (median, 85 days) and they became rarer after 6 months (third interquartile range, 203 days). Apart from the initial clinical presentation (DVT or PE), the patients who had recurrent DVT did not differ significantly from those who had a recurrent VTE, except patients with an initial, symptomatic PE (Table 4).

Mortality During the 252.5-day observation period, 123 patients died, corresponding to an incidence rate of all-cause death of 16.6 per 100 patient-years. The mortality was 13.6% per patient-year in those patients who presented with DVT alone, compared with 24.4% per patient-year in those with PE

Figure 1. Kaplan-Meier curves for (A) cumulative incidence of recurrent venous thromboembolism (VTE; black line), recurrent pulmonary embolism (PE) with or without deep vein thrombosis (DVT; red line), and recurrent DVT alone (blue line). (B) Cumulative incidence of recurrent VTE according to the entry diagnosis: symptomatic PE with or without DVT (red line) or DVT alone (blue line). The risk of recurrence was significantly higher in patients with an initial diagnosis of PE (with or without DVT) than in those with isolated DVT (Cox proportional hazard analysis).

(with or without DVT; **Figure 2**). The mortality rate had high variability among subgroups: during the course of the study, 88 (30.3%) of 290 patients with cancer died vs. 28 (3.7%) of the 750 without cancer. The rate of all-cause death was also higher in patients with respiratory failure (28.6% vs. 10.6%) and in those with severe infection (23.3% vs. 11.1%). The patients who died were also more likely to be male, to be non-obese, and to have a history of stroke, but neither age nor the presence of concomitant ischemic heart or peripheral arterial disease seemed to influence the prognosis (**Table 5**).

Of the 123 deaths, 36 (29.3%) were early deaths that occurred 1 month after the index event. The time course varied markedly depending on the entry diagnosis; for instance, early mortality accounted for 19.2% of the all-cause deaths in patients with DVT alone as compared with 58.3% in those with PE alone. Of the 36 early deaths, 17 (47.2%) were directly attributed to VTE, according to the investigator's assessment.

Bleeding Events During the observation period, 59 cases of bleeding of all types were encountered, corresponding to an

incidence rate of 8.2% per patient-year. Half ($n=24$) of the bleeds were considered major, including 2 fatal hemorrhages and 7 intracranial hemorrhages. The subsequent incidence rate for major bleeding was 3.3% per patient-year, which was higher in patients who presented with symptomatic PE with or without DVT (6.0% per patient-year, with PE) than in those with isolated DVT (2.2% per patient-year). As shown in **Figure 3**, the peak onset for bleeding events was observed during the acute phase of VTE management, within the first week. Major bleeding events occurred earlier in those patients with PE than in those with DVT alone, with a median time of occurrence of 6 and 91 days, respectively.

Other Long-Term Outcomes After the index event and 12-month observation period, 851 patients (79.1%) were considered cured, whereas approximately 7% had chronic complications such as post-thrombotic syndrome (5.9%) or pulmonary hypertension (1.2%).

Table 4. Baseline Characteristics vs. VTE Recurrence

Explanatory variable		VTE recurrence			P-value†
		No	%	Yes	
Symptomatic PE	No	723		15	0.047
	Yes	324	30.9	14	
Age (years)	<75	722		7	0.794
	≥75	336	31.8	11	
Sex	Male	433		10	0.458
	Female	614	58.6	19	
BMI	<25	623		20	0.733
	≥25	288	31.6	8	
Surgery	No	854		22	0.630
	Yes	186	17.9	6	
Cancer	No	733		17	0.642
	Yes	282	27.8	8	
Respiratory failure	No	999		28	0.772
	Yes	48	4.6	1	
Severe infection	No	1,017		29	0.355
	Yes	30	2.9	0	
Previous VTE	No	982		28	0.541
	Yes	65	6.2	1	
Thrombophilia	No	1,006		26	0.085
	Yes	41	3.9	3	
Lower limb paresis	No	1,015		29	0.339
	Yes	32	3.1	0	
Varicosis	No	1,004		27	0.459
	Yes	43	4.1	2	
Central vein catheter	No	1,006		27	0.419
	Yes	41	3.9	2	
Immobilization	No	827		24	0.622
	Yes	220	21.0	5	
Warfarin	No	116		4	0.647
	Yes	931	88.9	25	
UFH	No	206		6	0.965
	Yes	841	80.3	23	
IVC filter	No	623		15	0.400
	Yes	424	40.5	14	
Thrombolysis	No	828		23	0.976
	Yes	219	20.9	6	

†Chi-squared test.

IVC, inferior vena cava. Other abbreviations as in Tables 1,2,3.

VTE Management Features and Outcome

On post-hoc analysis, we investigated the relationship between duration of anticoagulant therapy and clinical outcome. Patients were categorized into 2 groups: the first group included patients with no prescription of VKA, or treatment duration <3 months; the second group consisted of patients who received at least 3 months (minimal length as per Japanese Guidelines) of VKA treatment. More than one-third of patients (n=384, 38.6%) received no therapy, or therapy that lasted <3 months. These patients, who were prescribed a sub-therapeutic treatment duration, tended to be 3-fold more likely to experience VTE recurrence (relative risk, 3.03, P=0.0525, log-rank test). The propensity to receive a suboptimal duration of VKA was not correlated with institution type (academic vs. community hospitals, P=0.733, chi-squared test). Conversely, patients diagnosed with VTE in a surgical ward had significantly more chance of receiving >3 months' VKA treatment than those

hospitalized in the medical wards. In addition, patients with a higher baseline risk were more prone to not receive the recommended VKA treatment of ≥3 months. This included patients with cancer, who were 1.65-fold more likely to be prescribed treatment for <3 months; those with a concomitant baseline condition also had a lower likelihood of VTE treatment for the recommended duration. This practice was not justified by the baseline risk of bleeding, which was similar between the 2 groups (P=0.947, chi-squared test). Cancer patients who were prescribed a >3-month VKA treatment had a 44% significantly lower mortality risk (odds ratio, 0.56, P=0.028) as compared to those who received a <3-month therapy. Similarly, patients with higher overall risk (concomitant disease) had both a higher mortality risk and a lower chance to receive per-recommended-length and INR target VKA treatment.

Explanatory variable		All-cause death				P-value†
		No	(%)	Yes	(%)	
Age (years)	<75	644		85		0.733
	≥75	309	32.4	38	30.9	
Sex	Male	380		63		0.016
	Female	573	60.1	60	48.9	
BMI	<25	552		91		0.002
	≥25	275	33.3	21	18.8	
Surgery	No	776		100		0.691
	Yes	172	18.1	20	16.7	
Cancer	No	722		28		<0.001
	Yes	202	21.9	88	75.9	
Respiratory failure	No	918		109		<0.001
	Yes	35	3.7	14	11.4	
Severe infection	No	930		116		0.038
	Yes	23	2.4	7	5.7	
Stroke	No	884		108		0.054
	Yes	69	7.2	15	12.2	
IHD	No	906		117		0.979
	Yes	47	4.9	6	4.9	
PAD	No	938		121		0.965
	Yes	15	1.5	2	1.6	
Warfarin	No	76		44		<0.001
	Yes	877	92.0	79	64.2	
UFH	No	181		31		0.103
	Yes	772	81.0	92	74.8	
IVC filter	No	569		69		0.443
	Yes	384	40.3	54	43.9	
Thrombolysis	No	743		108		0.012
	Yes	210	22.0	15	12.2	

†Chi-squared test.

IHD, ischemic heart disease; PAD, peripheral arterial disease. Other abbreviations as in Tables 1,3,4.

Discussion

During the 1-year study period, we recorded a total of only 1,076 VTE patients (338 PEs) at 63 institutions, corresponding to a mean enrollment of 17 patients per center (range, 2–73). This apparently low rate in the Japanese population possibly reflects an actual epidemiological characteristic of the Asian population. For instance, in a study conducted using the California Patient Discharge Data Set,⁹ the incidence of idiopathic VTE was significantly lower among Asian/Pacific Islander than among Caucasian or African-American subjects. The JAVA Study, however, was not designed to assess the incidence of DVT and PE in the Japanese population and the reported rates do not represent the actual burden of VTE in Japan. The methodology used in the JAVA Study did not consider all VTEs diagnosed at each hospital; at each institution a limited number of wards, considered by the steering committee to be most representative of hospital practice in terms of VTE management, were selected. Thus, a PE diagnosed and treated in another ward was not included in the JAVA Study. In addition, the present study was fully non-interventional, and the variation in inclusion rates also reflects the ward-specific practices as regards diagnostic protocols. For instance, in some surgical wards, all patients would be screened before discharge to rule out the presence of asymptomatic DVT. The prevalence of VTE would then be higher than that in a similar ward that does not conduct routine screening. Epidemiologically, the retrospective collection of data was the major limitation of the JAVA Study but was also its strength with regard to the assessment of practices: the protocol and implementation of the study did not influence VTE management in the selected wards. But, because we did not use random selection of the participating centers, we cannot

warrant that the observed practice was fully representative of general VTE management practice in Japan. All academic regions, however, were represented and university-based hospitals accounted for a significant proportion of the included institutions. Therefore, we believe that the findings of the JAVA Study reliably depict contemporary VTE management in Japan, albeit with a lower accuracy than would a study with a prospective cohort and examination of long-term clinical outcomes of VTE.

A remarkably large number of patients in Japan had IVC filters inserted, and thrombolytics were used more frequently than in other countries. In the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE), which is a collection of data mostly from Spain and other European countries, IVC filters were inserted in only 2.1% of cases.¹⁰ In the Taiwanese registry, the rate of insertion (2.2%)⁴ was similar to that in the RIETE. The main reported indication for use of filters in the RIETE was bleeding (high risk of bleeding or bleeding during treatment), followed by VTE recurrence under treatment and need for surgery.¹¹ In contrast, in the current JAVA Study, IVC filters were used in 40% of VTE patients, with overall rates increasing up to 60% in the case of PE+DVT. Although the investigators in the JAVA Study were not asked to report the reasons for insertion, it is interesting to note that only 9.9% of patients were at a high risk of bleeding according to the investigator's assessment; thus, bleeding did not seem to be the main reason for IVC filter insertion, according to the JAVA Study. Likewise, in another study conducted in a small series of Japanese patients, the reasons for filter insertion were also markedly different from those in other countries: the most frequently reported indications were perioperative VTE prophylaxis (84.8%), followed by other prophylactic indications, thrombolytic therapy, and pregnancy

with DVT. Contraindications to anticoagulation therapy were reported only in 9.1% of cases.¹²

Similarly, thrombolysis was performed at a high rate (20.9%), which contrasts with the infrequent application of this technique in Western countries, as indicated in the RIETE (1.2%); this finding deviates from the recommendations of international and Japanese guidelines.

In the latest consensus guidelines of the American College of Chest Physicians (ACCP), the recommended anti-thrombotic treatment for patients with acute proximal DVT is anticoagulant therapy alone, preferred over combination with thrombolysis (grade 2C) in those with PE.¹³ Systemic thrombolytics can be considered in the case of hypotension (eg, systolic blood pressure <90 mmHg), but the ACCP recommends against thrombolytic therapy in the absence of hypotension (grade 1C). The Japanese guidelines are more flexible, suggesting that systemic thrombolysis can be considered in PE with persistent shock, unstable hemodynamics, or hypotension, and for treatment of acute DVT (grade 2a), unless contraindicated.¹

The JAVA Study also confirmed that parenteral anticoagulation in the acute phase was almost exclusively performed with UFH (94.5%), whereas in Europe, LMWH was already the treatment of choice 10 years ago, according to the RIETE study (LMWH, 88% vs. UFH, 11%).¹¹ In addition, the aPTT-based dose adjustment was subtherapeutic (aPTT ≤ 1.5) in almost 40% of cases, although this practice is not supported by the Japanese guidelines, which recommend a therapeutic range of aPTT 1.5–2.0 (optimal, 1.9–2.7).¹ With regard to chronic anticoagulation, the JAVA Study showed that practices were in line with the Japanese guidelines, targeting an INR of 2.0 (range, 1.5–2.5) for 85% of patients, that is, a lower level of anticoagulation than that recommended in Western countries, where the target INR is 2.5 (range, 2.0–3.0) for most patients and 3.0 with VTE recurrence or additional risk factors.

We obtained a lower rate of VTE recurrence (3.9% per patient-year) in the present study than was found in a Taiwanese cohort (9.4% at 12 months)³ and in historical Western studies (between 7.7% and 12.9% at 1 year).¹⁴ These rates, however, varied widely depending on the type of VTE (DVT or PE), whether the VTE was idiopathic, and on the presence of concomitant risk factors.^{15–17} For instance, in the Baglin et al study, the cumulative incidence of recurrent VTE after 2 years was 11.0%, ranging from 0% in cases of postoperative VTE up to 19.4% after an unprovoked VTE.¹⁷ Given that the study design of the trials was different, we cannot tell whether the low recurrence rates observed in the JAVA Study actually correspond to the epidemiological characteristics of VTE in Japan or only reflect methodological and/or historical between-study differences. The Olmsted county registry, using data collected during a 25-year period, indicated that in addition to the traditional risk factors of VTE, the year of diagnosis was also a significant predictor of recurrence.¹⁸ It is also interesting to note that the recurrence rate in the JAVA Study was similar to that observed in the recently published MASTER registry of data collected from Italian patients (3.63% patient-years).¹⁹

We observed an all-cause mortality rate of 16.6% per patient-year, which is more favorable than the 1-month mortality rate of 8.8% found in the Taiwanese registry but is much higher than the fatality rate of 4.55% per patient-year found in the MASTER registry (without significant differences in mortality between patients included for PE and DVT). Cancer yielded the highest mortality risk in the JAVA Study (43.6% of cancer patients died, corresponding to an incidence rate of

30.3% per patient-year). In a post-hoc analysis of JAVA, we also observed that these patients were more likely to receive a subtherapeutic duration or level of anticoagulation and that VKA initiation was associated with an improved prognosis. Approximately three-quarters of deaths occurred in patients with a history of cancer at the time of VTE diagnosis, and although we could not adjust the results using propensity scoring, this suggests that improving VTE management in patients with cancer might translate into an overall decrease in all-cause deaths in patients diagnosed with VTE.

Long-term anticoagulation may play an important role in the overall prognosis given that, based on the JAVA Study, 76 patients did not receive the benefit of warfarin and mortality was significantly (5-fold) higher in this group than in the group who received VKA treatment. This high mortality rate might be related to confounding factors such as comorbidities that prompted the decision not to treat, but we should also note that in the MASTER registry, lack of anticoagulation was significantly associated with a 3.2-fold increase in mortality.

Improvement of acute-phase anti-thrombotic management might also influence clinical outcome: among all the fatalities in the JAVA Study, 29.3% occurred within 1 month, of which half were deemed VTE related. Most patients received parenteral anticoagulation, but the widespread practice of IVC insertion and use of thrombolytics may not always have been justified by the risk factors for bleeding or thromboembolism. This practice is not supported by clinical evidence. Moreover, in the multivariate analysis of the MASTER registry, neither IVC filter nor thrombolytics was associated with a better prognosis. In the JaSPER survey, on multivariate analysis for predictors of in-hospital mortality, thrombolysis was not associated with a better prognosis in all PE patients.⁵ The in-hospital mortality rate for PE without shock was 8% vs. 4%, for patients who received thrombolytics as compared to those who did not receive thrombolytics, respectively. The results, however, suggest that thrombolysis might improve the outcome in PE associated with cardiogenic shock. The in-hospital mortality rate was 30% vs. 50% in patients who received thrombolytics vs. those who did not receive thrombolytics, respectively.

Conclusions

In general, VTE management in Japan is characterized by highly aggressive strategies in the acute phase, which are not supported by international guidelines and are not clearly justified by the clinical presentation and associated risk factors. This contrasts with a low level of target INR in the chronic phase of anticoagulation with warfarin, which is aligned with the Japanese guidelines. The VTE recurrence rate appeared to be as high as in the latest Western registries, but mortality may be higher. We believe that there is room for optimization of VTE management practices, particularly in the acute phase and when VTE is associated with cancer.

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Supplementary Files

Supplementary File 1

Appendix. Participating institutions

Please find supplementary file(s);
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