Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Imaging

Multidetector-Row Computed Tomography-Based Clinical Assessment of Fondaparinux for Treatment of Acute Pulmonary Embolism and Acute Deep Vein Thrombosis in Japanese Patients

Mashio Nakamura, MD, PhD; Yoshiaki Okano, MD, PhD; Hiroki Minamiguchi, MD, PhD; Mitsuru Munemasa, MD, PhD; Masahiro Sonoda, MD, PhD; Norikazu Yamada, MD, PhD; Kazuhiko Hanzawa, MD, PhD; Narumi Aoyagi; Hiroshi Tsujimoto; Nobuaki Sarai, MD, PhD; Hiromu Nakajima, MD, PhD; Takeyoshi Kunieda, MD, PhD

Background: Unfractionated heparin (UFH) is the standard drug for the initial treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT) in Japan, whereas fondaparinux is the standard drug in Europe and the United States. Here, we examine the efficacy and safety of fondaparinux in Japanese patients.

Methods and Results: In 2 randomized, open-label, multicenter studies, 80 Japanese patients with acute PE or DVT received either subcutaneous fondaparinux or intravenous UFH as a non-comparative reference, in a 3:1 ratio, for 5–10 days. Concomitant warfarin therapy was continued until Day 90. Multidetector-row computed tomography-based assessment showed that 57.9% and 45.9% of the patients with acute PE and acute proximal DVT had proximal DVT and PE as a complication, respectively. There was no recurrence of symptomatic venous thromboembolism. In the fondaparinux group, the respective improvement rates at the end of the initial treatment and follow-up periods were 71.4% and 86.8% for 42 patients with PE, and 57.8% and 83.3% for 46 patients with DVT; similar results were noted in the UFH group. One patient in the fondaparinux group experienced major bleeding during the initial treatment, but no such episode in the UFH group.

Conclusions: Once-daily, subcutaneous fondaparinux is as effective and safe without monitoring as adjusted-dose intravenous UFH for the initial treatment of acute PE and DVT in Japanese patients. (*Circ J* 2011; **75:** 1424–1432)

Key Words: Deep vein thrombosis; Fondaparinux; Multidetector-row computed tomography; Pulmonary embolism; Venous thromboembolism

Pulmonary embolism (PE) and deep vein thrombosis (DVT) have been thought to be less common in Japan than in Europe and the United States (USA). Approximately 8,000 patients are annually diagnosed with PE in Japan,[1] which is much lower than the approximately 200,000 patients annually diagnosed in the USA,[2] especially considering the population disparity of these nations. Similarly, approximately 15,000 patients are annually diagnosed with DVT in Japan,[1] which is also lower than the approximately 116,000–250,000 patients annually diagnosed in the USA.[3,4] In recent years, however, the prevalence of PE and DVT in Japan has been increasing for various reasons, includ-

Received October 11, 2010; revised manuscript received December 29, 2010; accepted February 7, 2011; released online April 22, 2011 Time for primary review: 21 days

Department of Cardiology, Mie University Graduate School of Medicine, Tsu (M.N., N.Y.); Department of Internal Medicine, Hanwa Daini Senboku Hospital, Sakai (Y.O.); Department of Radiology, Wakayama Medical University, Wakayama (H.M.); Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama (M.M.); Second Department of Cardiology, National Hospital Organization Kagoshima Medical Center, Kagoshima (M.S.); Division of Thoracic and Cardiovascular Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata (K.H.); Development and Medical Affairs Division, GlaxoSmithKline K.K., Tokyo (N.A., H.T., N.S., H.N.); Department of Cardiovascular Medicine, Kaken Hospital, Clinical Medicine Research Center, International University of Health and Welfare, Ichikawa (T.K.), Japan

A part of these studies was reported at Chest 2010: The American College of Chest Physicians (ACCP) Annual Meeting held in Vancouver, BC, Canada, in October 30–November 4, 2010.

Name of grant: The studies were sponsored by GlaxoSmithKline K.K. (Tokyo, Japan).

Mailing address: Mashio Nakamura, MD, PhD, Department of Cardiology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu 514-8507, Japan. E-mail: mashio@clin.medic.mie-u.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-10-1036

ing westernization of dietary habits, population aging, and improved diagnosis.[5,6] Considering this, the first Japanese venous thromboembolism (VTE) treatment guidelines were published in 2004.[5] Acute PE often develops suddenly and has an associated mortality of 14%[7] in Japanese cases. In severe cases associated with shock, the mortality increases to 30%,[7] with more than 40% of the deaths reportedly occurring within 1 h of the onset of symptoms.[8]

PE is mostly caused by DVT in the legs or pelvis. Proximal DVT causes serious PE, which is fatal in over 20% of cases unless adequately treated.[9] In approximately 20% of the cases of distal DVT, the thrombus extends proximally unless treated with anticoagulants, and 40–50% of these patients develop PE.[10] Thus, acute PE and DVT form a disease continuum and are collectively termed as VTE, which should be prevented, diagnosed early, and adequately treated.

In Japan, unfractionated heparin (UFH) is the current standard anticoagulant drug for the initial treatment of PE and DVT. Guidelines in Japan[5] and the USA[11] recommend UFH administration followed by long-term administration of a vitamin K antagonist such as warfarin. The initial treatment is continued until the prothrombin time/international normalized ratio (PT-INR) achieves the therapeutic window, and vitamin K antagonist therapy is recommended for at least 3 months. UFH, derived from swine small intestine, comprises a heterogeneous mixture of varying molecular weights and its pharmacokinetics displays much interindividual variability, so administration necessitates frequent dose adjustment based on coagulation tests. In addition, the use of UFH is associated with the risk of heparin-induced thrombocytopenia (HIT).[12]

Fondaparinux sodium (hereafter fondaparinux) is a synthetic inhibitor of coagulation Factor Xa. It acts by specifically binding to antithrombin to inhibit Factor Xa activity selectively; unlike UFH, fondaparinux does not inhibit thrombin activity. This selective inhibition of Factor Xa upstream of thrombin enables efficient inhibition of the coagulation response without increasing the bleeding risk. Fondaparinux is administered subcutaneously once daily and does not require dose adjustments or monitoring of coagulation parameters. In Europe and the USA, 2 large, randomized clinical trials of fondaparinux (MATISSE PE, an open-label trial involving patients with acute PE, and MATISSE DVT, a double-blinded trial involving those with acute DVT) demonstrated the noninferiority of fondaparinux to UFH and low-molecular-weight heparin, respectively.[13,14] Their primary endpoint was the incidence of recurrent symptomatic VTE during the 90-day study period.

We conducted 2 randomized, open-label, multicenter studies to confirm the efficacy and safety of fondaparinux in Japanese patients with acute PE and acute DVT.

Methods

The study of acute PE (PE study) was conducted from July 2007 through December 2008 at 27 medical institutions, and that of symptomatic acute DVT (DVT study) was conducted from June 2008 through November 2009 at 24 medical institutions; in total, 34 institutions, including multiple departments at one site, participated. Each institutional review board approved the study protocol, which complied with the guidelines of the Declaration of Helsinki (South Africa 1996 for the PE study; Edinburgh 2000, Washington 2002, and Tokyo 2004 for the DVT study). Written informed consent was obtained from each patient prior to the screening test.

Study Population

Both studies involved patients aged ≥20 years. Acute PE patients (symptomatic PE or asymptomatic PE in patients with symptomatic proximal DVT) who were hemodynamically stable and those with symptomatic acute proximal DVT without symptomatic PE in the PE and DVT studies, respectively, were diagnosed by contrast-enhanced multidetector-row computed tomography (MDCT). The use of UFH before randomization was allowed if the therapeutic dosage was not administered for longer than 24 h. Patients receiving thrombolytic therapy, surgical thrombectomy, or catheter intervention, or those treated by inferior vena cava filter placement were excluded. Other exclusion criteria were previous history of HIT, complications associated with bleeding risk, serum creatinine level at screening >2.0 mg/dl, platelet count <100,000/μl, systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg, possible pregnancy, and expected survival <3 months.

Because fewer patients with PE or DVT are clinically diagnosed in Japan than in Europe or the USA, the target sample size was set at 30 in the fondaparinux group and 10 in the UFH group in each study, totaling 80 patients. In the MATISSE PE and MATISSE DVT studies, the incidence of recurrent symptomatic VTE was 3.8% and 3.9%, respectively.[13,14] Assuming that the incidence is similar in Japan, recurrent symptomatic VTE was expected to be detectable in at least one of 30 patients in the fondaparinux group (assuming an efficacy-analysis population of 27 and a safety-analysis population of 29) with a probability of 64.9–65.8%. As the incidence of bleeding (major or minor bleeding) in the MATISSE PE and MATISSE DVT studies was 4.5% and 3.7%, respectively,[13,14] bleeding was expected to be detectable in at least 1 patient with a probability of 66.5–73.7%.

Design

Both studies had the same treatment method and duration. As the patients in these studies had a serious disease and it is ethically problematic to use a placebo group in clinical studies, a placebo group was not included. The duration of the entire treatment period was set at 90 days (±7 days), including the initial treatment period of 5–10 days and the follow-up period. Each study included a UFH group as the reference group, and in both studies the patients were assigned to receive either fondaparinux or UFH in a ratio of 3:1 during the initial treatment period.

Initial Treatment Period

Eligible patients were randomly assigned to each treatment group. Randomization was performed at a central location by computer algorithm. In the fondaparinux group, the drug was administered subcutaneously once daily according to the patient's body weight (<50 kg, 5 mg; 50–100 kg, 7.5 mg; >100 kg, 10 mg). In the UFH group, the dosage was according to the Japanese Treatment Guideline,[5] which is intravenous bolus injection followed by drip infusion, adjusted so that the activated partial thromboplastin time (APTT) is between 1.5- and 2.5-fold the control level. UFH available at each study center was administered. Concomitant warfarin therapy was initiated no later than 72 h after the start of fondaparinux or UFH administration. The fondaparinux or UFH for initial treatment was administered until the PT-INR was ≥1.5 on 2 consecutive days, and the usual period of administration was set at 5–10 days. If the PT-INR did not reach 1.5 within 10 days, the period of administration was prolonged at the discretion of the investigator.

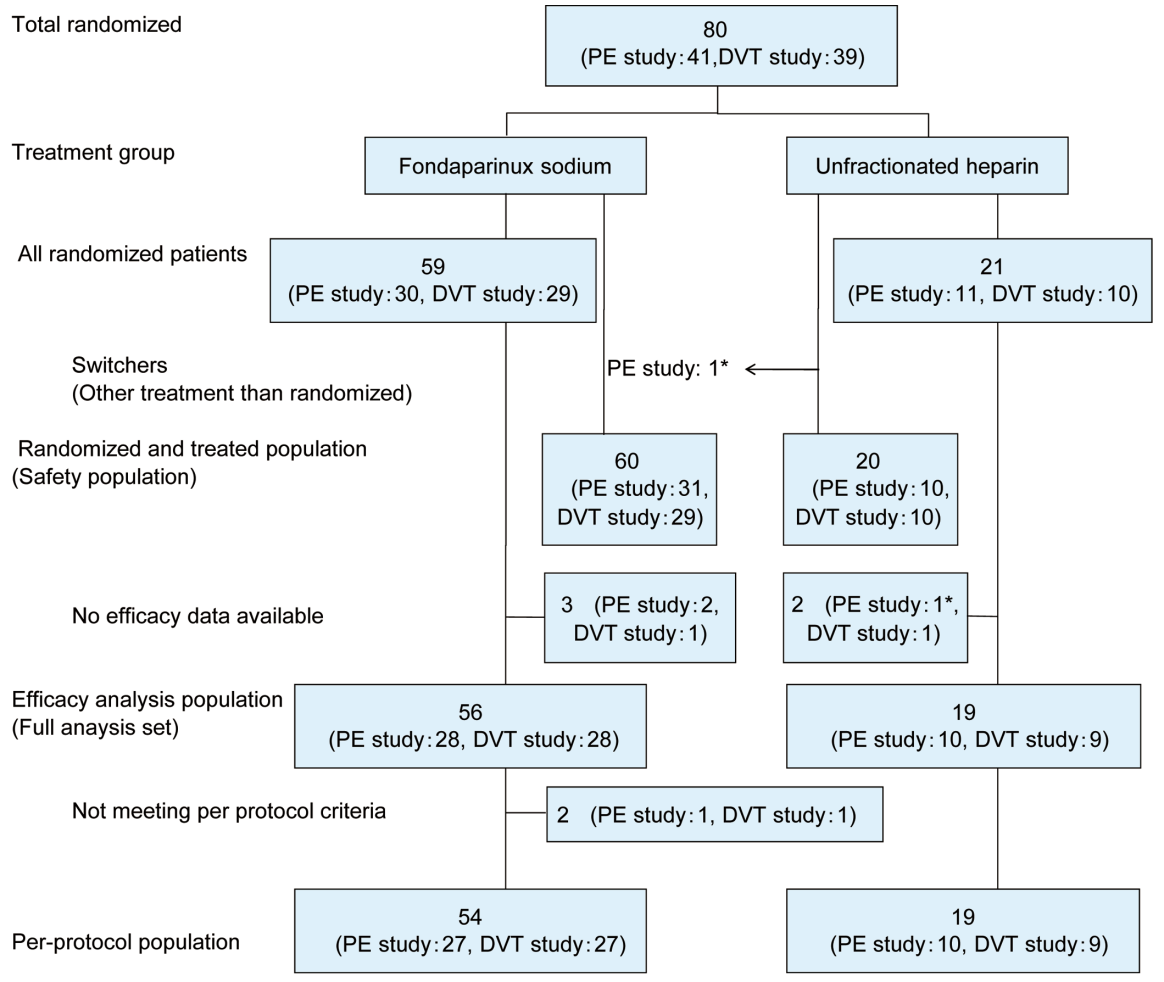

Figure. Distribution of participants.

Follow-up Period

Warfarin therapy was continued up to 90 (±7) days. The dose of warfarin was adjusted to maintain the PT-INR in the range 1.5–3.0 with a 2.0–2.5 target.

Prohibited and Restricted Concomitant Drugs

The use of drugs such as thrombolytic agents, UFH (excluding that administered during the initial treatment), low-molecular-weight heparin, heparinoids, antithrombin agents, dextrans, and antithrombotic peripheral circulation-improving drugs were prohibited from the start of the initial treatment until the end of the follow-up period. The use of antiplatelet agents was prohibited from the start until up to 24 h after the end of the initial treatment. When an antiplatelet agent was initiated before the study to manage other medical conditions, the patient was enrolled and allowed to continue using the drug provided that the dosing regimen remained unchanged. During the initial treatment period, the use of nonsteroidal anti-inflammatory drugs was kept to a minimum.

Evaluation Methods

Efficacy Endpoint Analyses Full analysis set (FAS) was the population for the efficacy analysis. The primary efficacy endpoint of the studies was the incidence of recurrent symptomatic VTE, which was evaluated by contrast-enhanced MDCT (scan range: pulmonary artery and iliac to popliteal vein) at baseline, end of the initial treatment period (Days 5–10 [±1 day]), end of the follow-up period (Day 90 [±7 days]), and any time of suspected VTE recurrence. The presence or absence of recurrent VTE was assessed by the Central Independent Adjudication Committee of Efficacy (CIACE) (2 members) blinded to the treatment groups.

The incidence of recurrent symptomatic nonfatal PE, symptomatic DVT without concomitant PE, fatal VTE, and all VTEs, including asymptomatic PE and asymptomatic DVT, was evaluated as the secondary efficacy endpoint. The response (improved or unchanged) to treatment in the patients without recurrent PE and DVT relative to the baseline contrast-induced MDCT data was also assessed by the CIACE. Contrast-enhanced MDCT, with a CT scanner having 4 or more rows, was conducted under the same scanning conditions at all institutions: ≤2.5 mm per slice for the chest and ≤5 mm per slice for the lower extremity; image reconstruction thickness same as the scanning slices; same field of view

Table 1. Baseline Characteristics of the Japanese Patients With Acute PE or DVT (Safety Population)

	Fondaparinux group (n=60)	UFH group (n=20)	Total (n=80)
Sex			
Female	31 (51.7)	16 (80.0)	47 (58.8)
Male	29 (48.3)	4 (20.0)	33 (41.3)
Age (years)			
Mean (SD) (years)	66.9 (15.8)	69.0 (14.2)	67.4 (15.4)
Median (years)	71.0	70.5	71.0
Range (years)	22–92	28–90	22–92
<65	21 (35.0)	5 (25.0)	26 (32.5)
65–<75	17 (28.3)	8 (40.0)	25 (31.3)
≥75	22 (36.7)	7 (35.0)	29 (36.3)
Body weight (kg)			
<50	14 (23.3)	4 (20.0)	18 (22.5)
50–100	46 (76.7)	16 (80.0)	62 (77.5)
>100	0	0	0
Creatinine clearance (ml/min)			
<30	1 (1.7)	1 (5.0)	2 (2.5)
30–<50	8 (13.3)	3 (15.0)	11 (13.8)
50–<80	31 (51.7)	5 (25.0)	36 (45.0)
≥80	20 (33.3)	11 (55.0)	31 (38.8)

All data represent the number of patients (%), unless indicated otherwise.
PE, pulmonary embolism; DVT, deep vein thrombosis; UFH, unfractionated heparin.

setting during the entire treatment period. The standard scanning procedure involved injection of a contrast agent via the cubital vein followed by breath-hold scanning of the chest 20–30 s after the injection and scanning of the lower extremities 3–4 min after the injection. At the time of the evaluation, the scanned image data from contrast-enhanced MDCT was the DICOM standard, and the axial images were assessed.

As another secondary efficacy endpoint, perfusion lung scanning was performed at baseline, end of the initial treatment period (Days 5–10 [±1 day]), and any time of suspected VTE recurrence. The scan data were assessed in terms of the improvement effects (improved, unchanged, or worsened relative to the baseline perfusion lung scan). The improvement effects were adjudicated by the CIACE.

Safety Endpoint Analyses Safety population (SP) was the population for the safety analysis. The primary safety endpoint in the studies was the incidence of major bleeding during the initial treatment period. In both studies, bleeding events considered as clinically unusual bleeding by the investigators were classified as "major", "minor", or "no bleeding" by the Central Independent Adjudication Committee of Safety (1 member) blinded to the treatment groups.

The events were classified according to the following criteria: major bleeding was clinically overt bleeding associated with a decrease in hemoglobin ≥2 g/dl from the prebleeding value within 48 h of onset, transfusion of 2 or more units of red blood cells or whole blood, bleeding involving a critical organ (retroperitoneum, intracranial, intraocular, adrenal gland, pericardium, spine, etc), or fatal bleeding; minor bleeding included all unusual clinically overt bleeding episodes reported by an investigator as an adverse event and not considered as major bleeding. The events that did not meet the major or minor bleeding definition were adjudicated as "no bleeding".

Because fondaparinux is excreted by the kidney, safety was assessed mainly in the initial treatment period, consisting of the drug administration period and an additional observation period, on the basis of the patient's renal function. Adverse events judged by an investigator to be related to fondaparinux or UFH were considered as adverse drug reactions.

In the fondaparinux group, blood samples were collected before drug administration and at 2±1 h after administration on any day between Days 5–7 during the initial treatment period, and the plasma fondaparinux concentration was determined by measuring the anti-Factor Xa activity of antithrombin. The plasma fondaparinux concentrations were measured by adding antithrombin III to plasma samples containing fondaparinux to cause the formation of fondaparinux–antithrombin III complexes, then adding a certain excessive amount of Factor Xa to cause the formation of fondaparinux–antithrombin III–Factor Xa complexes, and determining the remaining Factor Xa activity as absorbance of p-nitroaniline (405 nm) generated from a chromogenic substrate (peptide-p-nitroaniline).

Statistical Analysis

For the incidences of recurrent VTE and bleeding, the pooled data of both studies were used to calculate the point estimates and 95% confidence intervals by treatment group. Because the UFH group was used as a reference to examine the efficacy and safety of the standard treatment for VTE, statistical comparison between the groups was not performed. The improvement effects on VTE determined by contrast-enhanced MDCT and perfusion lung scanning were calculated as the percentage of patients with improvement or no change and assessed by the CIACE. The plasma fondaparinux concentration at each evaluation point was calculated according to the dosage group determined by body weight.

Results

Distribution of the Patients

Of the 80 randomized patients, 59 and 21 were assigned to the fondaparinux and UFH groups, respectively. One pa-

Table 2. Patients With PE or Proximal DVT at Enrollment (Full Analysis Set)

Disease	Fondaparinux group (n=56)	UFH group (n=19)	Total (n=75)
PE			
PE study			
n	28	10	38
Patients with PE	28 (100)	10 (100)	38 (100)
DVT study			
n	28	9	37
Patients with proximal DVT complicated by PE	14 (50.0)	3 (33.3)	17 (45.9)
Total			
n	56	19	75
Patients with PE	42 (75.0)	13 (68.4)	55 (73.3)
Proximal DVT			
PE study			
n	28	10	38
Patients with PE complicated by proximal DVT	18 (64.3)	4 (40.0)	22 (57.9)
DVT study			
n	28	9	37
Patients with proximal DVT	28 (100)	9 (100)	37 (100)
Total			
n	56	19	75
Patients with proximal DVT	46 (82.1)	13 (68.4)	59 (78.7)

All data represent the number of patients (%).
PE and proximal DVT were diagnosed at the start of the respective studies.
Abbreviations see in Table 1.

Table 3. Incidence of Recurrent VTE in the Overall Treatment Period (Full Analysis Set)

Disease	Fondaparinux group (n=56)	UFH group (n=19)
Symptomatic VTE	0 [0.0, 6.4]	0 [0.0, 17.6]
Symptomatic DVT (nonfatal) only	0 [0.0, 6.4]	0 [0.0, 17.6]
Symptomatic PE (nonfatal)	0 [0.0, 6.4]	0 [0.0, 17.6]
Fatal VTE	0 [0.0, 6.4]	0 [0.0, 17.6]
Asymptomatic VTE	1 (1.8) [0.0, 9.6]	0 [0.0, 17.6]
Asymptomatic DVT only	1 (1.8) [0.0, 9.6]	0 [0.0, 17.6]
Asymptomatic PE	0 [0.0, 6.4]	0 [0.0, 17.6]

All data represent the number of patients (%) or [95% confidence intervals]. Overall treatment period=Day 90 (±7).
Abbreviations see in Table 1.

tient was assigned to the UFH group but actually received fondaparinux. Patients with no available efficacy data (n=5) were excluded. The remaining 75 patients (fondaparinux group, n=56; UFH group, n=19) were included in the FAS. All the 80 patients who received fondaparinux or UFH (fondaparinux group, n=60 [including the wrongly assigned patient]; UFH group, n=20) were included in the SP (Figure).

Baseline Characteristics of the Patients

In the studies together, women accounted for 51.7% of the fondaparinux group and 80% of the UFH group (Table 1). The mean age was 66.9 years in the fondaparinux group and 69.0 years in the UFH group. In both groups, approximately 80% of the patients weighed 50–100 kg, and none weighed over 100 kg (Table 1). In the individual studies, the mean age and mean body weight were similar, although the proportion of women was slightly higher in the DVT study (64.1%) than in the PE study (53.7%). In addition, the creatinine clearance rate was less than 50 ml/min in 7.3% of the patients in the PE study, compared with 25.7% in the DVT study. In the FAS, proximal DVT was a complication in 57.9% of the patients with acute PE in the PE study, and asymptomatic PE was a complication in 45.9% of the patients with acute proximal DVT in the DVT study (Table 2).

Duration of Drug Administration

The mean (SD) and median duration were 7.5 (2.7) days and 7 days, respectively, in the case of fondaparinux administration, and 9.1 (3.0) days and 8 days, respectively, for UFH administration. Fondaparinux and UFH were administered for 5–10 days in 88.3% and 85.0% of the patients, respectively, and for a maximum of 16 and 17 days, respectively.

Efficacy

Incidence of Recurrent VTE No recurrence of symptomatic VTE was observed until Day 90 in either treatment group (Table 3). Asymptomatic DVT recurred in 1 patient in the fondaparinux group during the follow-up period. This patient showed improvement in the DVT in the initial treatment period but was withdrawn from the study during follow-up

Table 4. Contrast-Enhanced MDCT-Based Assessment of Improvements in the Patients With PE and Proximal DVT (Full Analysis Set)

Outcome	Effect on PE		Effect on DVT	
	Fondaparinux group (n=42)	UFH group (n=13)	Fondaparinux group (n=46)	UFH group (n=13)
End or discontinuation of initial treatment (Days 5–10)				
n	42	13	45	11
No recurrence				
Improved	30 (71.4)	10 (76.9)	26 (57.8)	5 (45.5)
Unchanged	12 (28.6)	3 (23.1)	19 (42.2)	6 (54.5)
Recurrence	0	0	0	0
End or discontinuation of follow-up (Day 90)				
n	38	13	42	13
No recurrence				
Improved	33 (86.8)	10 (76.9)	35 (83.3)	8 (61.5)
Unchanged	5 (13.2)	3 (23.1)	6 (14.3)	5 (38.5)
Recurrence	0	0	1 (2.4)	0

All data represent the number of patients (%) but excluding those without assessment, because it was either not evaluated or not performed.
PE and proximal DVT were diagnosed at the start of the respective studies.
Abbreviations see in Table 1.

because of treatment of concomitant lung cancer and bone metastasis; the contrast-enhanced MDCT scan conducted on the day of discontinuation (Day 23) showed recurrence of asymptomatic DVT.

Improvement Effects on PE and DVT Based on Contrast-Enhanced MDCT Data Among the patients with any PE at the start of the study, 71.4% and 86.8% in the fondaparinux group and 76.9% and 76.9% in the UFH group showed an improvement in PE at the end of the initial treatment and follow-up periods, respectively (Table 4). Among the patients with any proximal DVT at the start of the study, 57.8% and 83.3% in the fondaparinux group and 45.5% and 61.5% in the UFH group showed an improvement in DVT at the end

Table 5. Bleeding Events in the Initial Treatment Period (Safety Population)

	Fondaparinux group (n=60)	UFH group (n=20)
Major bleeding	1 (1.7) [0.0, 8.9]	0 [0.0, 16.8]
Minor bleeding only	4 (6.7) [1.8, 16.2]	0 [0.0, 16.8]
Any bleeding	5 (8.3) [2.8, 18.4]	0 [0.0, 16.8]

All data represent the number of patients (%) or [95% confidence intervals].
UFH, unfractionated heparin.

Table 6. Adverse Drug Reactions in the Initial Treatment Period (Safety Population)

Adverse event	Fondaparinux group (n=60)	UFH group (n=20)
Adverse event related to the initial treatment	13 (21.7)	6 (30.0)
Subcutaneous hemorrhage	4 (6.7)	0
Skin hemorrhage	1 (1.7)	0
Drug eruption	1 (1.7)	0
Abnormal hepatic function	1 (1.7)	4 (20.0)
Aspartate aminotransferase increased	0	1 (5.0)
Alanine aminotransferase increased	0	1 (5.0)
Coagulation time prolonged	1 (1.7)	0
Blood alkaline phosphatase increased	1 (1.7)	0
White blood cell count decreased	0	1 (5.0)
Gastrointestinal hemorrhage	1 (1.7)	0
Hematochezia	1 (1.7)	0
Heparin-induced thrombocytopenia	0	1 (5.0)
Anaemia	1 (1.7)	0
Hemoptysis	1 (1.7)	0
Operative hemorrhage	1 (1.7)	0
Injection site hemorrhage	1 (1.7)	0

All data represent the number of patients (%).
UFH, unfractionated heparin.

of the initial treatment and follow-up periods, respectively (Table 4).

Perfusion Lung Scan Data Among the patients with confirmed PE at the start of the study, 61.9% in the fondaparinux group and 76.9% in the UFH group showed an improvement in PE by perfusion lung scanning at the end of the initial treatment period.

Safety

Bleeding Events In the initial treatment period, major bleeding due to gastrointestinal hemorrhage was reported in one patient on Day 6 in the fondaparinux group (Table 5). The PT-INR was 2.72 and the patient received multiple antiplatelet agents. In addition, minor bleeding occurred in 4 patients in the fondaparinux group during the initial treatment period. None of these events was considered serious and all subsequently resolved. No bleeding event was observed in the UFH group during the initial treatment period.

Adverse Drug Reactions In the initial treatment period, adverse drug reactions occurred in 21.7% of the patients in the fondaparinux group and 30.0% of those in the UFH group (Table 6). The adverse drug reactions reported in at least 2 patients were subcutaneous hemorrhage in the fondaparinux group (6.7%) and abnormal hepatic function in the UFH group (20.0%). In addition, HIT occurred in 1 patient (5.0%) in the UFH group.

Pharmacokinetics of Fondaparinux

On the basis of the pooled pharmacokinetic data of the fondaparinux groups in both studies, the mean±SD plasma fondaparinux concentration was similar in the patients who received 5 mg (pre-dose, 0.422±0.132 mg/L; 2 h post-dose, 1.020±0.260 mg/L; n=12 in both cases) or 7.5 mg (pre-dose, 0.504±0.169 mg/L [n=39]; 2 h post-dose, 1.227±0.331 mg/L [n=44]). No patient received 10 mg fondaparinux.

Discussion

More than 90% of acute PE cases are caused by DVT in the legs or pelvis, and 50–80% of patients with PE in Western countries also have DVT;[15,16] reportedly, 50–60% of patients with DVT in Western countries have PE as a complication.[17,18] In our studies, diagnosis of PE and proximal DVT at enrollment indicated that 57.9% of the patients with acute PE had proximal DVT as a complication, and 45.9% of those with acute proximal DVT also had PE (Table 2). These results confirm that the incidence of the complications of PE and DVT is comparable in Japan.

On the basis of the MATISSE PE and MATISSE DVT studies,[13,14] the dose of fondaparinux for the initial treatment of acute PE and acute DVT in Japanese patients is set according to body weight. The pharmacokinetics after a single dose of subcutaneously administered fondaparinux up to 8 mg was similar in Japanese and Western subjects in a phase I study.[19,20] The optimal prophylactic dose of fondaparinux for Japanese patients undergoing lower limb orthopedic surgery and abdominal surgery is 2.5 mg once daily, which is the same dose used in Europe and the USA. The guidelines in Japan and other countries indicate that the target of anticoagulation therapy and the usage of UFH are similar.[5,11] Thus, we expected that the therapeutic dose for acute VTE in Japanese patients would be about the same as that used in other countries. In our studies of Japanese patients, therefore, the dose of fondaparinux depended on body weight, as in other countries. Analysis of the drug concentration in these studies revealed that the plasma fondaparinux concentration was similar in the patients who received 5 mg of fondaparinux and those who received 7.5 mg. These results indicate that the exposure to fondaparinux can be appropriately controlled by dose adjustment based on body weight, as applied in Europe and the USA.

Although symptomatic VTE recurrence was expected in at least one of 30 patients in the fondaparinux group with a probability of 64.9–65.8%, according to the MATISSE PE and MATISSE DVT studies,[13,14] there was no case of symptomatic VTE recurrence in either the fondaparinux or UFH group in our studies. Moreover, contrast-enhanced MDCT-based evaluation of the efficacy for PE and DVT revealed that the improvement rates in the fondaparinux group for PE were 71.4% at the end of the initial treatment period and 86.8% at the end of the follow-up period; the respective improvement rates for DVT were 57.8% and 83.3% (Table 4). The perfusion lung scan-based assessment of the improvement effects at the end of the initial treatment showed comparable results with those by contrast-enhanced MDCT assessment. The risk of VTE recurrence was possibly reduced to a similar level by fondaparinux and UFH, although statistical comparison of the groups was not performed because of the noncomparative study design. The results also indicate that efficacy evaluation of PE and DVT based on contrast-enhanced MDCT is effective, especially for studies with a relatively small sample size.

Although symptomatic VTE did not recur in either the fondaparinux group or the UFH group, recurrent asymptomatic DVT was noted in one patient in the fondaparinux group at discontinuation (Table 3). The patient was withdrawn during the follow-up period because of treatment of concomitant lung cancer and bone metastasis. The patient had exhibited asymptomatic PE and symptomatic DVT at the start of the study. The assessment of the contrast-enhanced MDCT images of DVT by the CIACE revealed that the thrombi observed extending from the common femoral vein to the popliteal vein of the left leg at screening were reduced to the femoral vein on the image taken at the end of the initial treatment (Day 8), considered as an improvement. However, the image taken 16 days after switching to the follow-up period (Day 23) (at the withdrawal from the study) exhibited the extension of the thrombi to the external iliac vein. The assessment of the contrast-enhanced MDCT images of PE revealed that the thrombi were reduced at the end of the initial treatment and withdrawal from the study, showing an improvement (no recurrent PE). The PT-INR during concomitant warfarin therapy remained slightly below the lower limit of the target range (2.0–2.5) during the follow-up period. Thus, the duration of the initial treatment and the range of the PT-INR during follow-up should be examined further in relation to the size of remaining thrombi and the severity of the risk factors for VTE.

Regarding safety, major bleeding during the initial treatment period occurred in 1 patient in the fondaparinux group (Table 5). At the onset of gastrointestinal hemorrhage in this patient, the PT-INR was 2.72 and the patient received multiple antiplatelet agents other than fondaparinux and warfarin. Considering the risk factors, the patient was hospitalized 9 days before the start of fondaparinux administration because of hematemesis, which was diagnosed as Mallory-Weiss syndrome by gastrointestinal endoscopy. The investigator, however, evaluated that the patient had a low bleeding risk after in-hospital treatment, when the patient was enrolled in the DVT study. When using fondaparinux, thorough consideration

of the concomitant bleeding risks, including complications and other medications used, is required. In the initial treatment period, 4 (6.7%) episodes of subcutaneous hemorrhage were reported as adverse drug reactions in the fondaparinux group (Table 6): bleeding possibly developed because of subcutaneous injection in 3 cases, in contrast to the intravenous injection of UFH. Among the adverse drug reactions, abnormal hepatic function was observed in 4 patients (20.0%) in the UFH group (Table 6): 1 case (1.7%) of abnormal hepatic function occurred in the fondaparinux group.

Although only UFH is available for the initial treatment of VTE in Japan, frequent monitoring of the platelet count is necessary for early detection of HIT during continuous administration of UFH through intravenous infusion, in addition to dose adjustment by monitoring the APTT. In our studies, HIT occurred in 1 of the 20 patients (5.0%) in the UFH group but never in the fondaparinux group. In this patient, the platelet count markedly reduced after the start and until the end of UFH administration. The risk of HIT type II during UFH administration is between 1% and 5%,[12,21,22] which is comparable to that in our studies. Theoretically, fondaparinux is less likely to produce thrombocytopenia probably because it poorly complexes with platelet Factor 4, the antigen recognized by HIT antibodies, and does not cross-react with the serum of patients with HIT type II.[23–25]

Conclusions

1) Recurrent symptomatic VTE was not observed in either the fondaparinux group or the UFH group. Evaluation of PE and DVT based on contrast-enhanced MDCT imaging data demonstrated that the improvement rate after fondaparinux administration in the initial treatment period was 71.4% for patients with PE and 57.8% for those with DVT.
2) During the initial treatment period, major and minor bleeding events occurred in 1 and 4, respectively, of the 60 patients in the fondaparinux group.
3) About half of the patients with acute PE also had proximal DVT (57.9%) and 45.9% of those with acute proximal DVT also had PE, which is similar to the results from Western countries.

We conclude that the synthetic Xa inhibitor, fondaparinux, is as effective and safe as the standard drug, UFH, used for the initial treatment of acute PE and acute DVT in hemodynamically stable Japanese patients. As fondaparinux is less likely to produce thrombocytopenia and can be subcutaneously administered once daily without the need for anticoagulation-system monitoring, it could be a suitable alternative treatment for patients with acute VTE in Japan.

Declaration of Funding

Funding for these studies was provided by GlaxoSmithKline (NCT00981409 and NCT00911157).

Disclosures

M.N. has received consulting fees from GlaxoSmithKline, Daiichi Sankyo Company Limited and Astellas Pharma Inc. Y.O., H.M. and T.K. have received consulting fees from GlaxoSmithKline. N.A., H.T., N.S. and H.N. are employees of GlaxoSmithKline.

M.M., M.S., N.Y. and K.H.: No conflict of interest to report.

References

1. Sakuma M, Nakamura M, Yamada N, Ota S, Shirato K, Nakano T, et al. Venous thromboembolism: Deep vein thrombosis with pulmonary embolism, deep vein thrombosis alone, and pulmonary embolism alone. *Circ J* 2009; **73:** 305–309.
2. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. *Arch Intern Med* 1998; **158:** 585–593.
3. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: The Worcester DVT Study. *Arch Intern Med* 1991; **151:** 933–938.
4. Coon WW, Willis PW III, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation* 1973; **48:** 839–846.
5. Japanese Circulation Society. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2004). *Circ J* 2004; **68**(Suppl)**:** IV1079–IV1134 (in Japanese).
6. Ota S, Yamada N, Tsuji A, Ishikura K, Nakamura M, Ito M. Incidence and clinical predictors of deep vein thrombosis in patients hospitalized with heart failure in Japan. *Circ J* 2009; **73:** 1513–1517.
7. Nakamura M, Fujioka H, Yamada N, Sakuma M, Okada O, Nakanishi N, et al. Clinical characteristics of acute pulmonary thromboembolism in Japan: Results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. *Clin Cardiol* 2001; **24:** 132–138.
8. Ota M, Nakamura M, Yamada N, Yazu T, Ishikura K, Hiraoka N, et al. Prognostic significance of early diagnosis in acute pulmonary thromboembolism with circulatory failure. *Heart Vessels* 2002; **17:** 7–11.
9. Zilliacus H. On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to the post-thrombotic sequelae: The results of five years' treatment of thrombosis and pulmonary embolism at a series of Swedish hospitals during the years 1940–1945. *Acta Med Scand* 1946; **171:** 1–221.
10. Kakkar VV, Howe CT, Flanc C, Clarke MB. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969; **294:** 230–232.
11. Hirsh J, Guyatt G, Albers GW, Harrington R, Schünemann HJ; American College of Chest Physicians. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133:** 71S–109S.
12. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: Recognition, treatment, and prevention: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; **126:** 311S–337S.
13. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al; Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; **349:** 1695–1702.
14. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al; Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: A randomized trial. *Ann Intern Med* 2004; **140:** 867–873.
15. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 1983; **98:** 891–899.
16. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: Are we detecting enough deep vein thrombosis? *J R Soc Med* 1989; **82:** 203–205.
17. Huisman MV, Büller HR, Ten Cate JW, van Royen EA, Vreeken J, Kersten MJ, et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. *Chest* 1989; **95:** 498–502.
18. Moser KM, Fedullo PF, LitteJohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. *JAMA* 1994; **271:** 223–225.
19. Package insert. Arixtra injection, 2009, GlaxoSmithKline K.K. (in Japanese).
20. Donat F, Duret JP, Santoni A, Cariou R, Necciari J, Magnani H, et al. The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet* 2002; **41:** 1–9.
21. Dager WE, White RH. Treatment of heparin-induced thrombocytopenia. *Ann Pharmacother* 2002; **36:** 489–503.
22. Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. *N Engl J Med* 2006; **355:** 809–817.
23. Warkentin TE. Fondaparinux versus direct thrombin inhibitor therapy for the management of heparin-induced thrombocytopenia

(HIT): Bridging the River Coumarin. *Thromb Haemost* 2008; **99:** 2–3.
24. Warkentin TE, Cook RJ, Marder VJ, Sheppard JA, Moore JC, Eriksson BI, et al. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. *Blood* 2005; **106:** 3791–3796.
25. Amiral J, Lormeau JC, Marfaing-Koka A, Vissac AM, Wolf M, Boyer-Neumann C, et al. Absence of cross-reactivity of SR90107A/ORG31540 pentasaccharide with antibodies to heparin-PF4 complexes developed in heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis* 1997; **8:** 114–117.

Appendix

The following institutions and investigators participated in these studies, in no particular order.

Yoshiro Matsui and Ichizo Tsujino, Hokkaido University Hospital; Kazufumi Tsuchihashi, Sapporo Medical University Hospital; Shuichi Taguchi and Masanori Koizumi, National Hospital Organization Mito Medical Center; Kazutaka Aonuma, Tsukuba University Hospital; Toyoshi Sasaki, National Hospital Organization Takasaki General Medical Center; Masahiko Kurabayashi, Gunma University Hospital; Masahiro Suzuki, National Hospital Organization Saitama National Hospital; Nobuhiro Tanabe, Chiba University Hospital; Tetsuro Miyata and Atsushi Yao, The University of Tokyo Hospital; Keiji Tanaka, Nippon Medical School Hospital; Yutaro Nishi, St. Luke's International Hospital; Koichi Sayama, Keio University Hospital; Toru Obayashi, Japan Red Cross Musashino Hospital; Kazuhiko Hanzawa, Niigata University Medical and Dental Hospital; Uichi Ikeda, Shinshu University Hospital; Koji Matsumoto, Koichi Yokoya and Tsuneo Tanaka, National Hospital Organization Toyohashi Medical Center; Norikazu Yamada, Mie University Hospital; Yoshio Yasumura, National Hospital Organization Osaka National Hospital; Kunihiko Nagai, Kitano Hospital; Norifumi Nakanishi, National Cerebral and Cardiovascular Center; Masatoshi Shimizu, National Hospital Organization Kobe Medical Center; Mitsuru Munemasa, National Hospital Organization Okayama Medical Center; Hitoshi Yasumoto and Masashi Iwabuchi, Kokura Memorial Hospital; Kazuro Yoshida, National Hospital Organization Nagasaki Kawatana Medical Center; Kazuteru Fujimoto, National Hospital Organization Kumamoto Medical Center; Hisao Ogawa, Kumamoto University Hospital; Masahiro Sonoda, National Hospital Organization Kagoshima Medical Center; Hironori Murakami, Teine Keijinkai Hospital; Kazunori Iwade, National Hospital Organization Yokohama Medical Center; Yoshikazu Yazaki, National Hospital Organization Matsumoto Medical Center; Masaaki Koide, Seirei Hamamatsu General Hospital; Kazunori Inuzuka, Iwata City Hospital; Yutaka Kajikawa, National Hospital Organization Fukuyama Medical Center; Hitoshi Fujiwara, National Hospital Organization Hiroshima-Nishi Medical Center.

Central Independent Adjudication Committees (Efficacy)

Yoshiaki Okano, Hanwa Daini Senboku Hospital; Hiroki Minamiguchi, Wakayama Medical University.

Central Independent Adjudication Committees (Safety)

Takeyoshi Kunieda, Kaken Hospital, Clinical Medicine Research Center, International University of Health and Welfare.

Research and Development

Development and Medical Affairs Division, GlaxoSmithKline K.K.: Hiroshi Tsujimoto, Narumi Aoyagi, Nobuaki Sarai, Mika Nariyama, Ryuichiro Okuda, Yuri Shida, Hiroyuki Yoshizaki, Hiromu Nakajima.