Table 2. Baseline demographics and clinical characteristics of the intention-to-treat population who underwent primary total knee arthroplasty

Characteristic	Placebo ($n = 79$)	Enoxaparin 20 mg qd ($n = 78$)	Enoxaparin 40 mg qd ($n = 74$)	Enoxaparin 20 mg bid ($n = 84$)
Female (no.)	64 (81.0%)	63 (80.8%)	63 (85.1%)	79 (94.0%)
Age (years), mean (SD)	68.7 (9.5)	68.8 (9.0)	70.0 (9.4)	68.3 (8.7)
Height (cm), mean (SD)	150.1 (7.9)	151.8 (7.6)	150.7 (8.0)	149.0 (6.7)
Weight (kg), mean (SD)	57.2 (9.5)	59.0 (10.3)	57.6 (10.5)	54.0 (8.3)
BMI (kg/m^2) mean (SD)	25.4 (3.7)	25.7 (4.5)	25.3 (4.0)	24.0 (4.0)
BMI > 25 kg/m^2 (no.)	40 (50.6%)	40 (51.3%)	44 (59.4%)	35 (41.7%)
Systolic BP (mmHg), mean (SD)	133.1 (18.0)	132.9 (16.5)	132.1 (16.5)	129.1 (17.5)
Orthopedic disease (no.)				
Osteoarthritis	52 (65.8%)	56 (71.8%)	50 (67.6%)	57 (67.9%)
Rheumatoid arthritis	27 (34.2%)	22 (28.2%)	24 (32.4%)	27 (32.1%)
Osteonecrosis	0	0	0	0
Other	0	0	0	0
History of smoking (no.)	11 (13.9%)	9 (11.5%)	7 (9.5%)	6 (7.1%)
Previous major disease/complications/surgery (no.)	5 (6.3%)	12 (15.4%)	7 (9.5%)	1 (1.2%)
Previous minor disease/complications/surgery (no.)	79 (100%)	77 (98.7%)	74 (100%)	84 (100%)
Use of cement (no.)	62 (78.5%)	61 (78.2%)	57 (77.0%)	71 (84.5%)
Type of anesthesia (no.)				
Regional	0	0	0	0
General	10 (12.7%)	13 (16.7%)	14 (18.9%)	18 (21.4%)
Both	69 (87.3%)	65 (83.3%)	60 (81.1%)	66 (78.6%)
Duration of surgery (h), mean (SD)	2.11 (0.65)	2.03 (0.55)	2.21 (0.78)	2.12 (0.62)

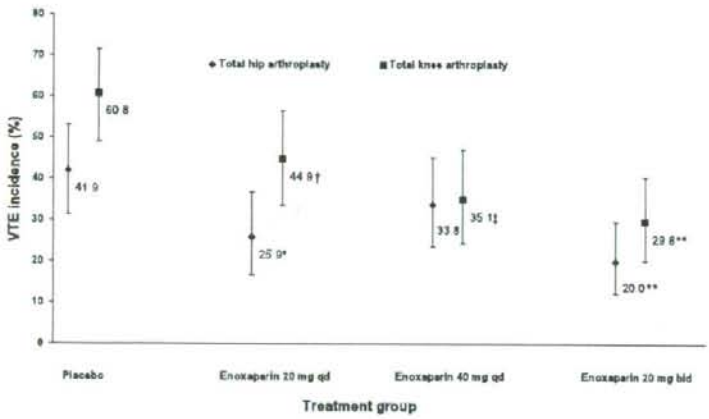

Fig. 3. Incidence (95% confidence intervals) of venous thromboembolism (*VTE*) in all groups. *P = 0.022, placebo vs. enoxaparin 20 mg qd (Dunnett test); **P = 0.001, placebo vs. enoxaparin 20 mg bid (Fisher's exact test); †P = 0.039, placebo vs. enoxaparin 20 mg qd (Dunnett test); ‡P = 0.001, placebo vs. enoxaparin 40 mg qd (Dunnett test)

the between-group difference in the incidence of VTE. A dose–response relation was detected for the placebo, enoxaparin 20 mg qd, and 40 mg qd groups ($P = 0.001$, Cochran–Armitage test).

Three patients experienced a PE; one patient in the placebo group had both DVT and PE, and one patient in the enoxaparin 20 mg qd group and one in the enoxaparin 40 mg qd group had a PE only. There was no statistically significant difference between these enoxaparin groups and placebo regarding the incidence of PE. At the 90-day follow-up visit, no further cases of VTE were reported. The incidence of proximal DVT was 7.6% in patients treated with placebo compared with 7.7%, 4.1%, and 0% in the enoxaparin 20 mg qd, 40 mg qd, and 20 mg bid groups.

Safety

The incidences of major and minor bleeding are presented in Table 4. The rejection criterion for the recommended dose of the study drug in the safety analysis was if any bleeding events occurred in >30% of patients. This criterion was not met for any of the enoxaparin doses used in either study.

Table 3. Incidence of VTE, DVT, proximal DVT, and PE in the mITT populations of the THA and TKA studies

Endpoint	Placebo		Enoxaparin 20 mg qd		Enoxaparin 40 mg qd		Enoxaparin 20 mg bid		*P*		
	n/*N*	% (95% CI)	*n*/*N*	% (95% CI)	*n*/*N*	% (95% CI)	*n*/*N*	% (95% CI)	Cochran–Armitage*	Dunnett**	Fisher's exact
THA study											
VTE (DVT + PE)	36/86	41.9 (31.3–53.0)	21/81	25.9 (16.8–36.9)	27/80	33.8 (23.6–45.2)	18/90	20.0 (12.3–29.8)	0.112	0.022[a] 0.188[c]	0.001[b]
DVT	36/86	41.9 (31.3–53.0)	21/81	25.9 (16.8–36.9)	27/80	33.8 (23.6–45.2)	18/90	20.0 (12.3–29.8)	0.112	0.022[a] 0.188[c]	0.001[b]
Proximal DVT	9/86	10.5 (4.9–18.9)	3/81	3.7 (0.8–10.4)	6/80	75 (2.8–15.6)	3/90	3.3 (0.7–9.4)	0.199	0.062[a] 0.314[c]	
TKA study											
VTE (DVT + PE)	48/79	60.8 (49.1–71.6)	35/78	44.9 (33.6–56.6)	26/74	35.1 (24.4–47.1)	25/84	29.8 (20.3–40.7)	0.001	0.039[a] 0.001[c]	0.001[b]
DVT	48/79	60.8 (49.1–71.6)	34/78	43.6 (32.4–55.3)	25/74	33.8 (23.2–45.7)	25/84	29.8 (20.3–40.7)	0	0.026[a] 0.001[c]	0.001[b]
Proximal DVT		7.6 (2.8–15.8)	6/78	7.7 (2.9–16.0)	3/74	4.0 (0.8–11.4)	0/84	0 (0.0–4.3)	0.147	0.676[a] 0.239[c]	

CI, confidence interval; DVT, deep vein thrombosis; mITT, modified intention-to-treat; PE, pulmonary embolism; THA, total hip arthroplasty; TKA, total knee arthroplasty; VTE, venous thromboembolism

[a]Placebo vs. enoxaparin 20 mg qd

[b]Placebo vs. enoxaparin 20 mg bid

[c]Placebo vs. enoxaparin 40 mg qd

* One-sided significance level 5%; ** one-sided significance level 2.5%

Table 4. Incidence of hemorrhage in the safety population of the THA and TKA studies

Endpoint	Placebo		Enoxaparin 20 mg qd		Enoxaparin 40 mg qd		Enoxaparin 20 mg bid		*P* (χ^2 test)
	n/N	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)	
THA study									
Any bleeding	2/101	2.0 (0.2–7.0)	2/100	2.0 (0.2–7.0)	9/102	8.8 (4.1–16.1)	7/104	6.7 (2.8–13.4)	0.031[a] 0.033[b]
Major bleeding	0/101	0 (0.0–3.6)	1/100	1.0 (0.0–5.4)	2/102	2.0 (0.2–6.9)	3/104	2.9 (0.6–8.2)	NS
Minor bleeding	2/101	2.0 (0.2–7.0)	1/100	1.0 (0.0–5.4)	7/102	6.9 (2.8–13.6)	4/104	3.8 (1.1–9.6)	NS 0.033[b]
TKA study									
Any bleeding	8/89	9.0 (4.0–17.0)	5/89	5.6 (1.8–12.6)	7/91	7.7 (3.2–15.2)	13/95	13.7 (7.5–22.3)	NS
Major bleeding	4/89	4.5 (1.2–11.1)	0/89	0 (0.0–4.0)	1/91	1.1 (0.0–6.0)	3/95	3.2 (0.7–9.0)	0.043[c]
Minor bleeding	4/89	4.5 (1.2–11.1)	5/89	5.6 (1.8–12.6)	6/91	6.6 (2.5–13.8)	10/95	10.5 (5.2–18.5)	NS

NS, no significant difference for any comparisons
[a] Enoxaparin 40 mg qd vs. placebo
[b] Enoxaparin 40 mg qd vs. enoxaparin 20 mg qd
[c] Enoxaparin 20 mg qd vs. placebo

THA study

In the safety population, 20 patients (4.9%) who underwent THA experienced at least one bleeding event (Table 4). There was no statistically significant difference between treatment groups for this composite endpoint ($P = 0.051$, χ^2 test). In paired comparisons, the incidence of any bleeding was greater in the enoxaparin 40 mg qd group than in the placebo ($P = 0.031$) and enoxaparin 20 mg qd ($P = 0.033$) groups. Of note, there was no statistically significant difference between the enoxaparin 20 mg bid and placebo groups for any bleeding. No between-group differences in major bleeding events were detected ($P = 0.354$, χ^2 test), and the incidence of bleeding events requiring treatment discontinuation in all enoxaparin treatment groups did not exceed that in the placebo group.

The incidence of minor bleeding events in the enoxaparin 40 mg qd group was sevenfold greater than that in the enoxaparin 20 mg qd group ($P = 0.033$, χ^2 test). There were no serious bleeding events (e.g., retroperitoneal, intracranial, and intraocular hemorrhage) that were judged as being possibly related to treatment.

The incidence of all AEs was 98% in the placebo group and 100% in all enoxaparin groups, there being no statistical separation between groups for this comparison ($P = 0.107$, Cochran–Mantel–Haenszel test). The high incidence of AEs was expected in a population that had recently undergone major surgery and received polypharmacy. Most AEs were considered by the study investigators to be unrelated to study treatments. No class of serious AEs occurred with higher incidence in any one treatment group, and there was no statistical or clinical difference between the enoxaparin dosage groups. Five patients in the placebo and enoxaparin 40 mg qd groups discontinued treatment because of AEs compared with three patients in the enoxaparin 20 mg qd group and seven patients in the enoxaparin 20 mg bid group. Severe AEs occurred in three patients in the enoxaparin 40 mg qd group (increased hepatic enzymes, luxation of the hip, PE) and one patient in the placebo group (laryngeal cancer). Increased plasma levels of glutamic pyruvic transaminase were observed in each group: placebo ($n = 1$), enoxaparin 20 mg qd ($n = 1$), enoxaparin 40 mg qd ($n = 2$), and enoxaparin 20 mg bid ($n = 5$).

TKA study

In the safety population, 33 patients (9%) experienced a bleeding event (Table 4). Similar to patients in the THA study, there was no statistically significant difference among treatment groups for any bleeding event ($P = 0.267$, χ^2 test). For all other comparisons (see above), no statistically significant differences in event rates were detected within or between the enoxaparin and placebo groups. In particular, there were no episodes of severe bleeding events in the TKA study.

The incidence of all AEs in the TKA study was as high as that in the THA study, with 98.9% of patients in the placebo group and 100% in all enoxaparin groups reporting one or more AEs ($P = 0.377$, Cochran–Mantel–Haenszel test). Most AEs were considered unrelated to the study treatment. No class of serious AEs occurred with higher incidence in any one treatment group, and there were no major differences between different doses of enoxaparin. The incidences of treatment discontinuations due to AEs were (in rank order): enoxaparin 40 mg qd 8.8% (eight patients); enoxaparin 20 mg bid 6.3% (six patients); enoxaparin 20 mg qd 4.5% (four patients); and placebo 0%. Five patients experienced a severe AE, comprising one patient each from the placebo (bladder fistula), enoxa-

parin 40 mg qd (cancer of the renal pelvis), and enoxaparin 20 mg bid (heart failure) groups and two patients from the enoxaparin 20 mg qd group (amyloid enteritis and dermatitis). An increased plasma level of glutamic pyruvic transaminase was observed in one patient in the enoxaparin 20 mg qd group and in three patients each in the enoxaparin 40 mg qd and 20 mg bid groups.

Discussion

Orthopedic procedures such as THA and TKA can improve the mobility of patients with debilitating joint diseases such as osteoarthritis; however, patients undergoing these operations are at high risk of VTE, which can be fatal. Therefore, safe and effective measures to prevent VTE should be utilized. Whereas the approved dosage regimen of enoxaparin in North America has been well studied,[8,15] to our knowledge there have been no prospective randomized controlled studies describing its exclusive use in Japanese patients undergoing primary elective hip or knee surgery. We demonstrate here that enoxaparin is an effective treatment for the prevention of VTE after major orthopedic surgery of the lower limbs in Japanese patients, with a favorable safety profile.

The THA and TKA studies showed that administration of enoxaparin 20 mg bid, starting 24–36 h postoperatively, was associated with an approximately 50% lower incidence of postoperative VTE than placebo. The reduction in venous thromboembolic risk was entirely due to a reduction in the incidence of DVT, as there were few episodes of PE in either study. When administered according to the same protocol, enoxaparin 20 mg bid was associated with a 52% reduction in the incidence of VTE in TKA patients relative to placebo, and no proximal DVT was observed in this group. In patients undergoing THA, however, the incidence of VTE with enoxaparin 40 mg qd was not significantly different from that with placebo. We also found that the absolute incidence of any bleeding was higher after TKA than after THA. Importantly, administration of enoxaparin 20 mg bid did not increase the incidence of any bleeding compared with placebo after either type of surgery. Enoxaparin 40 mg qd was associated with an increased incidence of any bleeding relative to placebo in patients undergoing elective THA, primarily due to a greater incidence of minor bleeding. Enoxaparin was not associated with any bleeding events considered to be clinically significant, and its AE profile was similar to that of placebo. Based on these results, we recommend that Japanese patients undergoing major orthopedic surgery receive enoxaparin 20 mg bid as an effective regimen for reducing the risk of VTE while at the same time minimizing the risk of associated bleeding events. There are pharmacokinetic and pharmacodynamic differences between the enoxaparin 20 mg bid and 40 qd dosage regimens, which clinicians may consider before prescribing. Specifically, while total systemic exposure over the 24 h following administration of enoxaparin bid 20 mg is higher than that after administration of enoxaparin 40 mg qd, the peak activity of factor Xa inhibitor is higher after administration of enoxaparin 40 mg qd.[12]

The incidences of DVT in the placebo arms of our studies fell within the range of those reported previously in Western studies[2] but were >25% higher than those observed in a prospective epidemiological study involving Japanese patients who were not treated with anticoagulants.[3] Small sample sizes and patient heterogeneity may account for the differences in the incidences of DVT across the Japanese studies, but they support our finding that DVT was far more likely after TKA than THA.[3] Comparing data across our studies is justified because they used an identical design and methodology, the only difference being the type of joint replaced. Overall, our findings suggest that Japanese subjects have a high level of thromboembolic risk after major orthopedic surgery.

It is not possible to compare the efficacy of enoxaparin in our study directly with that reported in other studies owing to major methodological differences, particularly in dosage regimens. Recently, a synthetic selective factor Xa inhibitor has been studied in Japanese patients undergoing THA or TKA.[4] Patients in this study were administered fondaparinux qd for at least 10 days starting 24 h after surgery. This study showed a similar incidence of VTE in the placebo group compared with those in our studies. Because of differences in the definitions of major and minor bleeding, it would be inappropriate to attempt any comparison of AEs between these two studies.

The 95% CI of the mean DVT incidence in Japanese patients who received enoxaparin 20 mg bid after THA in our study (12.3%–29.8%) is consistent with the mean incidences reported in two systematic reviews of approximately 5000 patients who received a LMWH and also underwent THA (13.8%–17.8%).[16,17] Methodologically, our THA study resembles the randomized, double-blind international PENTATHLON study, in which enoxaparin 30 mg bid was compared with fondaparinux and VTE was assessed to day 11 in 1584 patients.[8] Fondaparinux qd was not significantly more effective than enoxaparin 30 mg bid at reducing the risk of VTE.[8] Furthermore, although the incidence of any bleeding was similar between the enoxaparin and fondaparinux groups, fondaparinux was associated with a greater risk of major bleeding ($P = 0.11$).[8] The incidences of objectively confirmed VTE and DVT (both 8%) associated with enoxaparin on day 11 of that study were lower than

that reported in our population (20%). However, there were a number of differences between the studies, such as the type and frequency of venous thrombosis risk factors, sex balance, age and ethnicity of the patients, dosing strategy, and the days on which venography was performed.

The observation that only one patient in the THA study and three patients in the TKA study experienced a PE should be interpreted with caution. Not only were our studies not powered to detect between-group differences in PE event rates, early venographic screening captured all patients with a DVT who then received appropriate anticoagulant therapy. However, it is generally accepted that asymptomatic thrombi, as detected by venography, are a valid marker for downstream symptomatic events.[18] As the enoxaparin 20 mg bid dose was associated with a halved risk of VTE compared with placebo and no proximal DVT in the TKA study, we believe that this dosage regimen can also reduce the likelihood of symptomatic outcomes such as PE.

Conclusion

These findings support the use of enoxaparin 20 mg bid up to 24–36 h postoperatively in Japanese patients, a protocol that demonstrated clear advantages over placebo with respect to venographically confirmed DVT. Furthermore, enoxaparin 20 mg bid was not associated with an increased propensity to induce any bleeding (minor or major hemorrhage) and was as well tolerated as a placebo. Enoxaparin is an effective treatment in Japanese patients for the prevention of VTE in patients undergoing major orthopedic surgery of the lower limbs.

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ORIGINAL PAPER

Fondaparinux prevents venous thromboembolism after joint replacement surgery in Japanese patients

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Abstract Venous thromboembolism (VTE) is an important complication of major orthopaedic surgery of the lower limbs. Fondaparinux, a synthetic pentasaccharide and highly selective inhibitor of activated Factor Xa, is the first in a new class of antithrombotic agents. To determine the optimal dose in Japanese patients, double-blind, placebo-controlled, dose-ranging studies of fondaparinux were conducted in patients undergoing total knee replacement (TKR) or total hip replacement (THR) surgery. Patients were randomly assigned to receive a once-daily subcutaneous injection of fondaparinux (0.75, 1.5, 2.5, or 3.0 mg) or placebo in Study 1 (TKR) and Study 2 (THR). In Study 1, the incidence of VTE was 65.3% in the placebo group and was 34.2%, 21.3%, 16.2%, and 9.5% in the groups receiving 0.75, 1.5, 2.5, and 3.0 mg fondaparinux respectively. In Study 2, the incidence of VTE was 33.8% in the placebo group and was 24.2%, 4.6%, 7.4%, and 14.4% in the 0.75, 1.5, 2.5, and 3.0 mg fondaparinux groups respectively. Dose–response effects were observed in both studies; however, no statistically significant differences in major bleeding events were found among any groups. Fondaparinux proved to be a potent anticoagulant with a favourable benefit-to-risk ratio in the prevention of VTE in these study patients.

Résumé Les complications thromboemboliques sont nombreuses dans la plupart des interventions de chirurgie orthopédique au niveau des membres inférieurs. Le fondaparinux (pentas saccharide synthétique) est un élément important parmi tous les agents anti-thrombotiques. De façon à déterminer la dose optimale de ce produit, une étude en double aveugle avec placebo a été conduite chez des patients devant bénéficier d'une prothèse totale du genou ou d'une prothèse totale de hanche. Les patients ont été randomisés de façon à recevoir une fois par jour une injection sous cutanée de fondaparinux (0.75, 1.5, 2.5, ou 3 mg) ou de placebo. L'incidence de la thrombose veineuse a été de 65.3% dans le groupe placebo et de 34.2%, 21.3%, 16.2% et 9.5% dans les groupes recevant respectivement 0.75, 1.5, 2.5 et 3 mg de fondaparinux, pour le groupe prothèse du genou. Pour le groupe prothèse de hanche l'incidence des complications thromboemboliques a été de 33.8% dans le groupe placebo et a été respectivement de 24.2%, 4.6%, 7.4% et 14.4% dans les groupes ayant reçu 0.75, 1.5, 2.5 et 3 mg de fondaparinux. Il n'y a pas de différence significatives en terme de saignement, dans chaque groupe. le fondaparinux est un anti-coagulant actif avec un bénéfice/risque important dans la prévention des thromboses veineuses et des accidents thromboemboliques dans cette étude de patients.

For the Steering Committee of the Japan Fondaparinux Study in Arthroplasty.

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Introduction

Fondaparinux is the first synthetic, selective Factor Xa inhibitor. Factor Xa is an important coagulation factor located at the junction of the extrinsic and intrinsic coagulation pathways [11]. Consequently, inhibition of Factor Xa results

in effective inhibition of the coagulation cascade and inhibition of thrombin generation. Unlike unfractionated heparin (UFH) and low molecular weight heparin (LMWH), fondaparinux is a single chemical entity (1728 Dalton) comprising five saccharides designed specifically to bind to antithrombin [8]. In experimental animal models, fondaparinux was associated with less bleeding than was UFH, at an equivalent antithrombotic concentration [8]. In humans, a therapeutic dose of fondaparinux did not prolong bleeding time [2].

A dose-ranging study in total hip replacement (THR) [16] demonstrated a statistically significant dose-response for the prevention of venous thromboembolism (VTE) in the range from 0.75 mg to 8.0 mg. Moreover, the results suggested that fondaparinux had the potential to improve significantly the risk-benefit ratio for VTE prophylaxis compared with LMWH. Based on the results, a 2.5 mg, once-daily dosage of fondaparinux was selected for the following four phase 3 studies. And these studies [1, 3, 10, 17] demonstrated that a once-daily fondaparinux 2.5 mg significantly improved the risk–benefit ratio for VTE prophylaxis in major orthopaedic surgery of the lower limbs. Eriksson BI et al. [4] reported that 4-week fondaparinux treatment was superior to 1-week fondaparinux in VTE prophylaxis for the patients with hip fracture surgery.

In the United States and Europe, a once-daily subcutaneous dose of 2.5 mg fondaparinux is indicated and used as VTE prophylaxis in fracture surgery, hip/knee replacement surgery and abdominal surgery [12, 15]. In the Seventh American College of Chest Physicians (ACCP) Guidelines on Prevention of VTE [7], fondaparinux, along with LMWH and vitamin K antagonists, was recommended with a Grade 1A rating for VTE prophylaxis in TKR and THR. Fondaparinux were the only anticoagulant recommended with a Grade 1A rating for hip-fracture surgery.

In Japan, UFH and warfarin are indicated for VTE prophylaxis, but there is no randomised clinical trial (RCT) in Japanese patients. LMWH has no indication for VTE prophylaxis. Therefore, no established active control is available in Japan.

These studies was conducted to compare the efficacy and safety of fondaparinux with a placebo, and to evaluate the dose-response relationship between 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux and the incidence of VTE, in TKR or THR surgery.

Methods

Patients

Patients of either gender were eligible if their age was 20 years or greater, and they were scheduled for TKR or THR surgery or revision surgery for TKR or THR. Exclusion criteria were: (a) active, clinically significant bleeding, (b) bleeding tendency/disorder (e.g., ulcer of the digestive tract, diverticulitis of the digestive tract, colitis, acute bacterial endocarditis, severe hypertension, or severe diabetes), (c) severe hepatic disorder, (d) hypersensitivity to UFH or LMWH, (e) requirement of an indwelling intrathecal or epidural catheter during the treatment period (after the first dose of test drug, until the completion of venography), or (f) brain, spine, or ophthalmologic surgery within the 3 months preceding enrollment. Patients with: (g) a body weight less than 40 kg (88 lb), or (h) severe renal disorder (serum creatinine concentration >2.0 mg/dL [180 μmol/L]) were also excluded.

The use of UFH, LMWH, heparinoids, antithrombin agents (argatroban), oral anticoagulants (warfarin), fibrinolytic agents and dextrans was prohibited, beginning 1 week before the first dose of study drug and study period. Nonsteroidal anti-inflammatory drugs (NSAIDs) and antiplatelet medications were also strongly discouraged during the treatment period, but were allowed, if necessary, in a condition of unchanged regimen. During the study, the use of intermittent pneumatic compression or a venous foot pump was prohibited during surgery, and continuous spinal and epidural anaesthesia (intrathecal or epidural catheterisation) were prohibited, beginning 2 hours before the first dose of study drug and study period.

Study design

There are two studies described in this paper, Study 1 for TKR and Study 2 for THR, both of which are multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose–response studies of subcutaneous fondaparinux.

The studies were conducted according to the provisions of the revised Declaration of Helsinki and the guidelines for Good Clinical Practice. The study protocols were approved by the institutional review board (IRB) at each centre. Written informed consent was obtained from each patient before enrollment in the trial. A Central Independent Adjudication Committee for Efficacy (CIACE) evaluated diagnostic images in a blind manner for the incidence of VTE. A Central Independent Adjudication Committee for Safety (CIACS) evaluated all reported bleeding events and adverse events (AEs), also in a blind manner.

Outcome measures

The primary efficacy outcome was assessed by the rate of VTE [defined as deep vein thrombosis (DVT), pulmonary

Table 1 Summary of demographic characteristics: all-treated-patients population

						n (%)
Study 1 (TKR)						
Parameter	**Placebo**			**Fondaparinux**		
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=87	*n*=86	*n*=85	*n*=84	*n*=84	*n*=426
Gender						
Female	72 (82.8)	71 (82.6)	67 (78.8)	67 (79.8)	74 (88.1)	351 (82.4)
Age, y ± (SD)						
	70.4±7.9	71.4±8.7	70.5±8.0	71.2±7.8	71.5±7.6	71.0±8.0
Weight, kg ± (SD)						
	58.94±9.80	57.87±10.71	59.99±10.16	59.14±9.88	59.30±8.43	59.05±9.81
Height, cm (SD)						
	150.51±7.59	150.91±7.55	151.45±6.96	150.15±6.85	150.04±6.45	150.61±7.09
BMI, kg/m²						
<30	79 (90.8)	73 (84.9)	70 (82.4)	69 (82.1)	71 (84.5)	362 (85.0)
>=30	8 (9.2)	13 (15.1)	15 (17.6)	15 (17.9)	13 (15.5)	64 (15.0)
Baseline creatinine clearance, mL/min						
<30	2 (2.3)	1 (1.2)	1 (1.2)	1 (1.2)	0	5 (1.2)
30 – 50	7 (8.0)	10 (11.6)	12 (14.1)	12 (14.3)	10 (12.0)	51 (12.0)
50 – 80	44 (50.6)	44 (51.2)	43 (50.6)	37(44.0)	41 (49.4)	209 (49.2)
>=80	34 (39.1)	31 (36.0)	29 (34.1)	34 (40.5)	32 (38.6)	160 (37.6)
Missing	0	0	0	0	1	1
Type of surgery						
Primary	82 (94.3)	85 (98.8)	84 (98.8)	84 (100)	80 (95.2)	415 (97.4)
Revision	5 (5.7)	1 (1.2)	1 (1.2)	0	4 (4.8)	11 (2.6)
Study 2 (THR)						
Parameter	**Placebo**			**Fondaparinux**		
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=82	*n*=80	*n*=80	*n*=81	*n*=83	*n*=406
Gender						
Female	64 (78.0)	69 (86.3)	60 (75.0)	74 (91.4)	66 (79.5)	333 (82.0)
Age, y ± (SD)						
	62.3±12.4	60.8±9.8	60.9±10.1	61.5±10.8	62.7±11.4	61.6±10.9
Weight, kg ± (SD)						
	56.31±9.40	55.81±9.61	60.21±9.73	54.19±8.61	56.20±11.28	56.54±9.92
Height, cm (SD)						
	153.20±8.24	152.38±7.55	154.58±7.92	150.96±6.88	152.35±7.00	152.69±7.59
BMI, kg/m²						
<30	77 (93.9)	73 (91.3)	73 (91.3)	79 (97.5)	78 (94.0)	380 (93.6)
>=30	5 (6.1)	7 (8.8)	7 (8.8)	2 (2.5)	5 (6.0)	26 (6.4)
Baseline creatinine clearance, mL/min						
30 – 50	7 (8.9)	6 (7.6)	1 (1.3)	5 (6.2)	5 (6.0)	24 (6.0)
50 – 80	30 (38.0)	28 (35.4)	27 (34.6)	36 (44.4)	31 (37.3)	152 (38.0)
>=80	42 (53.2)	45 (57.0)	50 (64.1)	40 (49.4)	47 (56.6)	224 (56.0)
Missing	3	1	2	0	0	6
Type of surgery						
Primary	76 (92.7)	72 (90.0)	76 (95.0)	74 (91.4)	79 (95.2)	377 (92.9)
Revision	6 (7.3)	8 (10.0)	4 (5.0)	7 (8.6)	4 (4.8)	29 (7.1)

BMI: body mass index; THR: total hip replacement; TKR: total knee replacement

embolism (PE), or both] up to day 11. Patients were examined for deep-vein thrombosis by systematic bilateral ascending venography of the legs between day 11 and day 17, but no more than 2 days after the last injection of study drug, or earlier if thrombosis was clinically suspected. Symptomatic PE was confirmed by a lung scan indicating a high probability of PE, pulmonary angiography, or helical computed tomography, or at autopsy.

The primary safety outcome was the incidence of major bleeding, which included fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more. The bleeding index was calculated as the number of units of packed red cells or whole blood transfused plus the haemoglobin values before the bleeding episode minus the haemoglobin values after the episode (in grams per decilitre).

Treatment and regimen

Patients were assigned to receive a once-daily subcutaneous injection of fondaparinux (0.75 mg, 1.5 mg, 2.5 mg, or 3.0 mg) or placebo. Treatment was scheduled from Day 2 to Days 11–15 (at least 10 days, with the day of surgery defined as Day 1).

The first dose of study drug was administered at 24±2 h after surgery, before 11:00 pm on Day 2; subsequent doses were administered at 9:00 am ± 2 h, from Days 3 to 15. The first dose on Day 2 and the second dose on Day 3 were at least 12 hours apart.

Disposable pre-filled syringes containing 0.75 mg, 1.5 mg, 2.5 mg, or 3.0 mg of fondaparinux or placebo were supplied by Sanofi-Winthrop Industrie (Notre Dame de Bondeville, France). Fondaparinux and placebo were provided as isotonic solutions in 0.25 ml, and placebo was isotonic sodium chloride. All pre-filled syringes were indistinguishable from one another.

Results

Disposition of patients

Study 1

Study 1 was conducted from October 2001 to August 2003 at 56 centres in Japan. A total of 432 patients were enrolled and randomised. Six of the 432 patients did not receive any study drug and were excluded from further analyses, with 426 patients remaining in the "all treated patients" (ATP) population (339 in the fondaparinux groups and 87 in the placebo group). A total of 29 (6.8%) withdrew. There were no statistically significant differences in values for demographic variables (Table 1) among the five treatment groups. The physical prophylaxis during the study is summarised in Table 2.

Study 2

Study 2 was conducted from October 2001 to June 2003 at 57 centers in Japan. A total of 411 patients were enrolled and randomised. Five out of 411 patients did not receive any

Table 2 Summary of patients who used physical methods for DVT prophylaxis from surgery to end of treatment: all-treated-patients population

						n (%)
Study 1 (TKR)						
Parameter	**Placebo**			**Fondaparinux**		
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=87	*n*=86	*n*=85	*n*=84	*n*=84	*n*=426
Elastic stocking/bandage (%)						
No elastic stocking/bandage	26 (29.9)	28 (32.6)	33 (38.8)	26 (31.0)	31 (36.9)	144 (33.8)
Used elastic stocking/bandage 1–10 days	33 (37.9)	36 (41.9)	31 (36.5)	35 (41.7)	34 (40.5)	169 (39.7)
Used elastic stocking/bandage 11 days or more	28 (32.2)	22 (25.6)	21 (24.7)	23 (27.4)	19 (22.6)	113 (26.5)
Study 2 (THR)						
Parameter	**Placebo**			**Fondaparinux**		
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=82	*n*=80	*n*=80	*n*=81	*n*=83	*n*=406
Elastic stocking/bandage (%)						
No elastic stocking/bandage	40 (48.8)	40 (50.0)	40 (50.0)	41 (50.6)	38 (45.8)	199 (49.0)
Used elastic stocking/bandage 1–10 days	20 (24.4)	24 (30.0)	21 (26.3)	25 (30.9)	29 (34.9)	119 (29.3)
Used elastic stocking/bandage 11 days or more	22 (26.8)	16 (20.0)	19 (23.8)	15 (18.5)	16 (19.3)	88 (21.7)

DVT: deep vein thrombosis; THR: total hip replacement; TKR: total knee replacement

study drug and were excluded from further analyses, with 406 patients remaining in the ATP population (324 in the fondaparinux groups and 82 in the placebo group). A total of 25 (6.2%) withdrew. There were no statistically significant differences in the values for demographic variables (Table 1) among the five treatment groups. The use of physical prophylaxis is summarised in Table 2.

Efficacy

Study 1 (TKR)

In the intent to treat (ITT) population, 65.3%, 34.2%, 21.3%, 16.2% and 9.5% of the patients showed VTE in the groups given placebo, 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux respectively. The Cochran-Armitage trend test demonstrated a statistically significant difference ($P<0.001$) in VTE incidence by fondaparinux, compared with placebo (Fig. 1). VTE incidence in all groups receiving fondaparinux was significantly lower ($P<0.001$) than in the group receiving placebo, by Fisher's exact probability tests. The calculated relative risk reductions (RRR) of VTE with 0.75 mg, 1.5 mg, 2.5 mg and 3.0 mg of fondaparinux, compared with placebo, were 47.6%, 67.4%, 75.2%, and 85.5% respectively.

Study 2 (THR)

In the ITT population, 33.8%, 24.2%, 4.6%, 7.4% and 14.3% of the patients showed VTE in the groups receiving placebo, 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux respectively. The Cochran-Armitage trend test demonstrated a statistically significant reduction ($P<0.001$) in VTE incidence by fondaparinux, compared with placebo (Fig. 1). The groups receiving 1.5 mg, 2.5 mg, or 3.0 mg fondaparinux were significantly lower ($P<0.01$, $P<0.01$ and $P=0.007$ respectively) from the placebo group by Fisher's exact probability tests. RRR of VTE with 0.75 mg, 1.5 mg, 2.5 mg and 3.0 mg of fondaparinux were 28.4%, 86.4%, 78.1%, and 57.7% respectively, compared with placebo.

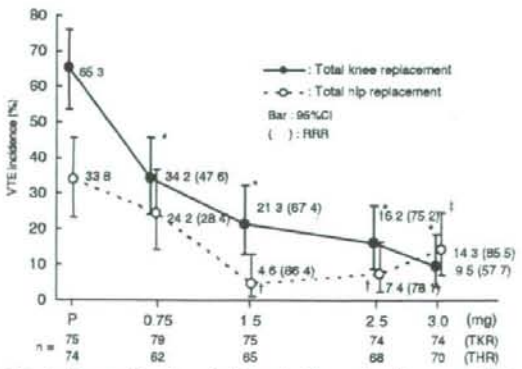

Fig. 1 Venous thromboembolism: incidence in all groups. *VTE*: venous thromboembolism; *TKR*: total knee replacement; *THR*: total hip replacement; *RRR*: relative risk reduction * $P<0.001$, † $P<0.01$, ‡ $P=0.007$ (Fisher's exact probability test)

Safety evaluation

The incidences of major and minor bleeding are presented Table 3. In the studies, major bleeding during the treatment period was the primary safety endpoint.

In Study 1 (TKR), the incidence of major bleeding was 1.1% with placebo and 0%, 0%, 1.2%, and 1.2% with 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux respectively. The incidences of major or minor bleeding among the treatment groups were not statistically significant; there was no fatal bleeding, bleeding in a critical organ, or bleeding leading to re-operation. All of the patients who experienced major bleeding received >2 units of blood. Two patients treated with fondaparinux had bleeding at the surgical site. One patient in the placebo group had major bleeding in the gastrointestinal tract.

There were no deaths during the study; three severe AEs were reported in two patients. One patient (receiving fondaparinux 3.0 mg) experienced skin necrosis that was not considered by the investigator to be related to the study drug; another patient (receiving placebo) developed a gastric ulcer and had a gastrointestinal hemorrhage. Both patients recovered without sequelae from these events.

There was no statistically significant difference in drug-related AEs among treatment groups.

In Study 2 (THR), there were no statistically significant differences in major or minor bleeding events between the fondaparinux groups and the placebo group. The incidences of major and minor bleeding events by fondaparinux were not dose-dependent. Three cases of major bleeding included a reduction in haemoglobin of >2 g/dL in one patient (receiving fondaparinux 2.5 mg) and transfusion of more than two units of blood in two patients (receiving fondaparinux 0.75 mg, 2.5 mg). No fatal bleeding occurred. Furthermore, although clinically abnormal blood loss occurred in more patients in the 2.5 mg fondaparinux group, all abnormal blood loss in this group was considered to be associated with surgery and not related to fondaparinux treatment.

There were no deaths during the study; however, three severe AEs were reported in two patients. One patient (0.75 mg fondaparinux) had hepatic dysfunction on Day 4 that was not related to test drug. The second patient (0.75 mg fondaparinux) experienced a cerebral infarction and supra-

Table 3 The proportion of patients with bleeding by treatment group: all-treated-patients population, Study 1 (TKR)

Study 1 (TKR)					
Types of bleeding (%)	**Placebo**	**Fondaparinux**			
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**
	n=87	*n*=86	*n*=85	*n*=84	*n*=84
Major bleeding	1 (1.1)	0	0	1 (1.2)	1 (1.2)
	[0.0 – 6.2]	[0.0 – 4.2]	[0.0 – 4.2]	[0.0 – 6.5]	[0.0 – 6.5]
Minor bleeding only	3 (3.4)	0	5 (5.9)	2 (2.4)	3 (3.6)
	[0.7 – 9.7]	[0.0 – 4.2]	[1.9 – 13.2]	[0.3 – 8.3]	[0.7 – 10.1]
Any bleeding	4 (4.6)	0	5 (5.9)	3 (3.6)	4 (4.8)
	[1.3 – 11.4]	[0.0 – 4.2]	[1.9 – 13.2]	[0.7 – 10.1]	[1.3 – 11.7]
***Any bleeding Cochran-Armitage (P)*[a]**			***0.57***		
Study 2 (THR)					
Types of bleeding (%)	**Placebo**	**Fondaparinux**			
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**
	n=82	*n*=80	*n*=80	*n*=81	*n*=83
Major bleeding	0	1 (1.3)	0	2 (2.5)	0
	[0.0 – 4.4]	[0.0 – 6.8]	[0.0 – 4.5]	[0.3 – 8.6]	[0.0 – 4.3]
Minor bleeding only	0	3 (3.8)	2 (2.5)	4 (4.9)	0
	[0.0 – 4.4]	[0.8 – 10.6]	[0.3 – 8.7]	[1.4 – 12.2]	[0.0 – 4.3]
Any bleeding	0	4 (5.0)	2 (2.5)	6 (7.4)*	0
	[0.0 – 4.4]	[1.4 12.3]	[0.3 – 8.7]	[2.8 – 15.4]	[0.0 – 4.3]
***Any bleeding Cochran-Armitage (P)*[a]**			***0.54***		

n (%), [95% CI]
A significant dose-response relationship in bleeding was not observed with the 0.75 mg to 3.0 mg fondaparinux dose range in either of the studies.
[a] Comparisons across all 5 treatment populations, using the values of the doses as score (0, 0.75, 1.5, 2.5, and 3.0)
*P=0.013 vs placebo group
THR: total hip replacement; TKR: total knee replacement

ventricular tachycardia on Day 5 but recovered; both events were considered possibly related to the test drug.

Discussion

In both studies, fondaparinux groups demonstrated significant dose-dependent effect in VTE incidence. 1.5 mg and 2.5 mg fondaparinux respectively reduced risk of VTE by 67.4% and 75.2% in the THR study, and that of VTE by 86.4% and 78.1% in the TKR study, compared with placebo. Fondaparinux also showed a good safety profile, in terms of bleeding complication, and the incidences of bleeding events by fondaparinux were not dose-dependent in both the TKR and THR studies.

In the United States, VTE is recognised as a silent, life-threatening disease and VTE prophylaxis is considered critical in a variety of medical settings, not only in postsurgical patients but also in acutely ill medical patients [7]. It is estimated that there are approximately 2 million cases of DVT and 600,000 cases of PE—including 60,000 fatal cases—per year in the United States [9]. In contrast, in Japan, 3,492 PE cases were estimated in 1996, based on surveillance by the Japanese Government [13, 14]. Because of the reported lower incidence of VTE in Japan, the importance of VTE prophylaxis has not been well-recognised by Japanese physicians.

Recently, Fujita et al. reported that, similar to Western data, VTE incidences of 48.6% and 22.6% followed TKR and THR surgery respectively, in Japanese patients [5].

According to the Sixth ACCP Guidelines [6], overall RRR of VTE following TKR surgery was 33% with low-dose UFH (two studies) and 52% with LMWH (13 studies), and the overall RRR of VTE following THR surgery was 45% with low dose UFH (11 studies) and 70% with LMWH (30 studies).

In Study 2 for THR, the incidence of VTE in both the 2.5 mg and 3.0 mg fondaparinux groups was slightly higher than that of the 1.5 mg group. However, there were no statistically significant differences among these groups; therefore, these differences could be observed by chance. There were no differences in demographic or VTE risk factors among the groups; however, there were more patients with ischaemic heart disease or diabetes in the 3.0 mg group, and it is speculated that these disorders may affect the efficacy of anticoagulant therapy. The incidences of VTE with 1.5 mg to 2.5 mg of fondaparinux in Study 2 for THR are similar to those in other published reports [1, 3, 10, 17].

The efficacies of these studies were completely equal to that in the United States and Europe. Major bleeding associated with fondaparinux was reported in 2.1% (11/517) of patients undergoing TKR [1], and 1.8% [17] and 4.1% [10] in THR; however, fatal bleeding or critical organ bleeding was not reported in Western studies. In the present studies, major bleeding occurred in one patient (0.6%) in the placebo group, one patient (0.6%) at 0.75 mg, 3 (1.8%) at 2.5 mg, and one patient (0.6%) at 3.0 mg of fondaparinux. The incidences of major bleeding in Japanese studies were somewhat lower than in the United States and Europe. It is considered that lower incidence of major bleeding could be due to the initial administration fondaparinux 24 hours after operation. Compared with overseas data, the efficacy and safety findings in this study support a once-daily dose of 2.5 mg fondaparinux is favorable for VTE prophylaxis in Japanese patients undergoing TKR or THR.

Finally, our study demonstrated that fondaparinux effectively prevents VTE without increasing the risk of bleeding or other AEs in patients undergoing TKR or THR. Fondaparinux could be a promising option for the prevention of VTE major orthopedic surgery of the lower limbs.

Conclusion

1) The incidence of VTE in Japanese TKR and THR patients are similar to Western data.
2) Once-daily, subcutaneous doses of 1.5 mg to 2.5 mg fondaparinux have a favourable risk (bleeding and other AEs) to benefit (VTE prevention) ratio in these patients.
3) Fondaparinux, the first in a new class of anticoagulants, could be one of the best options for managing the risk of VTE in patients at major orthopaedic surgery of the lower limbs.

In order to define optimal daily dose of fondaparinux for Japanese patients, further clinical study is needed.

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Gender Differences in Chronic Thromboembolic Pulmonary Hypertension in Japan

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Background The predominance of chronic thromboembolic pulmonary hypertension (CTEPH) in females and association of HLA-B*5201 with CTEPH have been reported in Japan. However, the clinical characteristics of female CTEPH remain uncertain. The purpose of the present study is to clarify the clinical phenotype of female CTEPH in Japan.

Methods and Results The 150 consecutive patients (female 103, male 47; age 52.8±12.4 years SD) were admitted to Chiba University Hospital, and diagnosis was confirmed using right cardiac catheterization and pulmonary angiography. Among these patients, 78 underwent pulmonary endarterectomy. Clinical characteristics, pulmonary hemodynamics, extent of central disease and surgical outcome in females were compared with those in males. The female patients were elderly and had less deep vein thrombosis, less acute embolic episodes, better cardiac function, lower arterial oxygen tension and more peripheral thrombi, and showed less improvement through surgery than males. When the patients were identified using HLA-B*5201, HLA-B*5201-positive female patients had less embolic episodes and better cardiac function with lower operative mortality. In contrast, HLA-B*5201-negative female patients had less embolic episodes, and more peripheral thrombi, resulting in less improvement by surgery.

Conclusion The clinical phenotype of female CTEPH differed from that of male CTEPH. Additionally, gender differences of HLA-B*5201-positive type were dissimilar to those of HLA-B*5201-negative type. (*Circ J* 2008; **72:** 2069–2074)

Key Words: Chronic thromboembolic pulmonary hypertension; Gender difference; HLA; Pulmonary embolism

Chronic thromboembolic pulmonary hypertension (CTEPH) has been considered to be caused by single or recurrent pulmonary emboli arising from deep vein thrombosis (DVT)[1,2] However, the incidence of DVT in this disease is only 35 to 45% in the USA and 12 to 38% in Japan[2–6] It was reported that the risk of recurrent venous thromboembolism was higher in men than women[7] The female-to-male ratio in CTEPH was 2.1 in Japan, which is much higher than that of 0.7 in the USA[3,8] However, the incidence of DVT in females was similar to that in males, even in Japan[9] Jamieson reported a female predominance in type 3 disease (distal segmental arteries only type)[10] In addition, we previously reported that female predominant CTEPH without DVT exists in Japan, and that the disease was associated with HLA-B*5201 and HLA-DPB1*0202. HLA-B*5201-positive patients were predominantly female, and this was unrelated to DVT[11]

It remains uncertain whether the clinical phenotype in female CTEPH differed from male CTEPH, especially in the Japanese series.

The purpose of the present study is to clarify the clinical phenotype in female CTEPH in Japan. We also examined the clinical phenotype of female CTEPH when patients were analysed according to HLA-B*5201 status because the HLA-B*5201-positive type could indicate a female-predominant Japanese-specific type, while the HLA-B*5201-negative type could indicate a DVT-related type similar to Western countries. Because of the female predominance in HLA-B*5201 patients, gender differences in the clinical parameters might be more related to the HLA-B*5201-positive type than the female gender itself. We added multivariate analysis to clarify whether female gender or HLA-B*5201 had the main effects on clinical parameters.

Methods

Study Subjects

We studied 150 patients, 103 females and 47 males, with CTEPH, diagnosed at Chiba University Hospital, Chiba, Japan. CTEPH was defined as mean pulmonary arterial pressure (Ppa) >25 mmHg with normal wedge pressure in patients with symptoms for >6 months. Chronic thromboembolic findings were confirmed using pulmonary angiography. All patients were examined using blood gas examination, right-heart catheterization, pulmonary angiography and computed tomographic angiography. Seventy-eight of the patients underwent pulmonary endarterectomy.

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Table 1 Clinical Characteristics of All Patients With CTEPH (n=150)

Age (years)	*52.8±12.4*
F/M (n)	*103/47*
Acute embolic episodes (%)	*45.3*
Underlying disease	
DVT (%)	*38.7*
Pelvic surgery (%)	*13.3*
Coagulopathy (%)	*31.3*
(Anti-cardiolipin antibody) (%)	*24.7*
Malignancy (%)	*4.0*
Heart disease (%)	*7.3*
*HLA-B*5201 (%)*	*31.3*
Cardiorespiratory variables	
Mean Pra (mmHg)	*5.2±4.4*
Mean Ppa (mmHg)	*44.2±11.1*
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	*2.54±0.63*
PVR ($dynes \cdot s \cdot cm^{-5}$)	*827±382*
PaO_2 (Torr)	*58.6±9.8*
WHO functional classification I/II/III/IV	*2/37/97/14*

Values are mean±SD or n (%).
CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; Pra, right atrium pressure; Ppa, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PaO_2, arterial oxygen tension.

Measurements

At least 3 months after an acute episode, pulmonary hemodynamics, cardiac output (using thermodilution technique) and blood gases were measured in the supine position while breathing normally. The cardiac index was calculated as cardiac output divided by body surface area. Pulmonary vascular resistance (PVR) was calculated conventionally as the ratio of the difference between mean Ppa and pulmonary wedge pressure to cardiac output. Cardiorespiratory variables were also measured after surgery. To evaluate the effectiveness of surgery, the % decrease in PVR was calculated using [preoperative PVR−postoperative PVR]×100 (%)/preoperative PVR.

HLA Typing

HLA typing was analyzed in 126 patients. Serological HLA typing of A and B antigens was done using a standard microcytotoxicity test[12] Genomic DNA was obtained from peripheral blood leukocytes using a QIAamp DNA blood minikit (Qiagen). DNA typing of HLA-B and –DPB1 genes was performed using a RELI-typing kit (Dynal) and/or using SSO probes as previously reported[13,14]

Assessment of Central Extent of Thrombi

Using the Bergin's method, central arteries were defined as vessels proximal to the segmental branches and were divided into 4 portions. These portions included the right and left main pulmonary arteries proximal to the upper lobe branches and the right and left descending portions of the central arteries between the upper lobes and the segmental branches. The central disease score was quantified by adding up the number of abnormal central portions in each patient up to a maximum score of 4[15] Two investigators retrospectively calculated the scores independently by workstation, and if the score differed, it was changed to either one score up or down by consensual agreement of the 2 investigators.

During the operation, thromboembolic disease was visualized and each patient was classified into one of 4 groups as reported by Thistlethwaite (intraoperative classification): type 1, fresh thrombus in the main-lobar pulmonary arteries; type 2, intimal thickening and fibrosis proximal to the segmental arteries; type 3, disease within distal segmental arteries only; and type 4, distal arteriolar vasculopathy without visible thromboembolic disease[16]

Pulmonary Endarterectomy

The selection criteria for pulmonary thromboendarterectomy were slightly modified from those defined by Moser[17] Our criteria were: (1) mean Ppa >30 mmHg, resulting in calculated PVR >300 $dynes \cdot s \cdot cm^{-5}$ even after oral anticoagulant therapy for >6 months; (2) WHO functional class ≥3; (3) thrombi defined as accessible to current surgical techniques (presence at main, lobar, segmental arteries); and (4) absence of severe associated disease[4,18] Although we have used a lateral thoracotomy in 16 previous cases, since 1990 we used median sternotomy with the application of deep hypothermia and circulatory arrest in 62 cases[4,19]

The Human Subject Committee of Chiba University approved the study, written informed consent was obtained from all patients and the study protocol for HLA typing was approved by the Research Ethics Committee of Chiba University School of Medicine.

Clinical characteristics were compared between males and females in all patients, and in patients with or without HLA-B*5201, respectively.

Statistical Analysis

Comparison of males and females was performed using unpaired Student's t-test when data were continuous variables, and by chi-square test or Mann-Whitney test when data were categorical, where appropriate. We performed a 2-way factorial analysis of variance (ANOVA) for parametric data and multiple regression analysis for categorized data, using gender and HLA-B*5201 as independent variables, and other clinical parameters as dependent variables. A p-value<0.05 was considered significant.

Results

Patient Characteristics

Characteristics of the patients are shown in Table 1. There were more female (n=103) than male patients (n=47). Age at catheterization varied from 18 to 78 years, with a mean±SD of 52.8±12.4. Sixty-eight patients (45.3%) had a history of acute embolic episodes. Fifty-eight patients (38.7%) had a history of DVT. Forty-seven patients (31.3%) revealed abnormalities in the screening for coagulopathy. Thirty-seven patients (24.7%) were diagnosed with antiphospholipid syndrome. Mean Ppa, cardiac index, PVR and PaO_2 were 44.2±11.1 mmHg, 2.54±0.63 $L \cdot min^{-1} \cdot m^{-2}$, 827±382 $dynes \cdot s \cdot cm^{-5}$ and 58.6±9.8 Torr, respectively. The patients were classified as WHO functional class I (n=2), class II (n=37), class III (n=97) and class IV (n=14).

Comparison of Clinical Characteristics Between Males and Females

As shown in Table 2, female patients were significantly older than males (54.3±11.3 vs 49.6±14.1 years, p=0.03). Female patients showed significantly less acute embolic episodes (34.0 vs 70.2%, p<0.001) and less history of DVT (31.1 vs 55.3%, p=0.005) compared with males. Female patients had a significantly greater history of pelvic surgery compared with males (19.4 vs 0.0%, p=0.012), while females had significantly less heart disease than males (3.9 vs 14.9%, p=0.016).

The cardiac index was significantly higher in females than in males (2.65±0.62 vs 2.36±0.66 $L \cdot min^{-1} \cdot m^{-2}$, p=0.01), and

Table 2 Gender Differences of Clinical Characteristics in CTEPH Patients

	Female (n=103)	Male (n=47)	p value
Age (years)	54.3±11.3	49.6±14.1	0.03
Acute embolic episodes (%)	34.0	70.2	<0.001
Underlying disease			
DVT (%)	31.1	55.3	0.005
Pelvic surgery (%)	19.4	0.0	0.012
Coagulopathy (%)	27.1	40.4	0.105
(Anti-cardiolipin antibody) (%)	23.2	30.4	0.35
Malignancy (%)	1.9	8.5	0.057
Heart disease (%)	3.9	14.9	0.016
HLA-B*5201 (%)	41.6	27.0	0.124
Haemodynamics			
Pra (mmHg)	4.3±3.5	7.1±5.5	0.0002
Mean Ppa (mmHg)	44.8±11.1	43.0±11.3	0.36
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.65±0.62	2.36±0.66	0.01
PVR ($dynes \cdot s \cdot cm^{-5}$)	850±393	777±357	0.28
PaO_2 (Torr)	56.4±9.8	61.7±9.8	0.005
Location of thrombi			
Central disease score	1.09±1.01	1.83±1.27	0.0002
Intra-operative classification			
Type 1/2/3/4	29/10/8/0	28/0/2/1	
Non-type 1 (%)	38.3	9.7	0.005
WHO functional classification I/II/III/IV	1/23/69/10	1/14/28/4	0.71

Values are mean±SD or n (%).
Abbreviations see in Table 1.

Table 3 Gender Differences for Surgical Outcome by Pulmonary Endarterectomy

	Female (n=47)	Male (n=31)	p value
Operative mortality (%)	11	23	0.15
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	406±282	257±119	0.02
% decrease in PVR (%)	51.9±25.4	65.2±21.4	0.04

Values are mean±SD or n (%).
% decrease in PVR, [preoperative PVR-postoperative PVR]×100(%)/preoperative PVR. Other abbreviation see in Table 1.

mean right atrial pressure (Pra) was significantly lower in females than in males (4.3±3.5 vs 7.1±5.5 mmHg, p=0.0002). However, PaO_2 in females was significantly lower than in males (56.4±9.8 vs 61.7±9.8 Torr, p=0.005).

With regard to the WHO functional classification, there was no significant difference between females and males.

Central disease score in females was significantly lower than in males, indicating a peripheral type (1.09±1.01 vs 1.83±1.27, p=0.0002). With regard to intra-operative classification, female patients showed significantly more non-type 1 disease compared with male patients (38.3 vs 9.7%, p=0.005).

Surgical Outcome and Gender

Although there was no significant difference in mortality between males and females, postoperative PVR in females was significantly higher than in males (406±282 vs 257±119 $dynes \cdot s \cdot cm^{-5}$, p=0.02), and the percentage decrease in PVR in females was significantly less than in males (51.9±25.4 vs 65.2±21.4%, p=0.04) (Table 3).

*Association With Gender Differences in Clinical Characteristics and HLA-B*5201*

As shown in Table 4, in HLA-B*5201-positive patients, females showed less embolic episodes (27.0 vs 80.0%, p=0.002). The cardiac index in females was significantly higher than in males (2.77±0.61 vs 2.23±0.38 $L \cdot min^{-1} \cdot m^{-2}$, p=0.001), and mean Pra in females was significantly lower than in males (3.9±3.7 vs 8.2±5.9 mmHg, p=0.0006). The surgical mortality was significantly lower in females than in males (0 vs 40%, p=0.0098).

In contrast, as shown in Table 5, in HLA-B*5201-negative patients, female CTEPH patients had less embolic episodes (40.4 vs 66.7%, p=0.03), lower central disease score (0.93±0.98 vs 2.04±1.32, p<0.0001) and more non-type 1 disease (48.0 vs 0.0%, p=0.0005), indicating the peripheral type of emboli. As a result, female patients showed higher postoperative PVR (405±303 vs 234±115 $dynes \cdot s \cdot cm^{-5}$, p=0.05) and a modest percentage decrease in PVR compared with males (55.6±21.3 vs 69.9±18.3%, p=0.04).

Two-way factorial ANOVA and multiple regression analysis revealed that the HLA-B*5201-positive type was significantly correlated with the absence of DVT (p=0.005), but female gender was not correlated with the absence of DVT (p=0.06). HLA-B*5201 did not show any correlation with any other clinical parameters (p>0.10). In contrast, female gender correlated with the absence of acute embolic episodes (p=0.0007), higher cardiac index (p=0.01), lower mean Pra (p<0.0001), lower central disease score (p=0.03) and non-type 1 disease (p=0.01).

Differences of Clinical Phenotype in Female CTEPH Based on HLA Types

To identify the differences of clinical phenotype of female

Table 4 Characteristics of Gender Difference in HLA-B*5201-Positive Type

	Female (n=37)	Male (n=10)	p value
Age (years)	53.9±10.5	50.4±18.9	0.45
DVT (%)	13.5	40.0	0.06
Embolic episode (%)	27.0	80.0	0.002
Pra (mmHg)	3.9±3.7	8.2±5.9	0.0006
Mean Ppa (mmHg)	43.7±11.3	44.6±12.2	0.79
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.77±0.61	2.23±0.38	0.001
PVR ($dynes \cdot s \cdot cm^{-5}$)	837±460	857±396	0.86
PaO2 (Torr)	57.1±10.5	63.2±9.8	0.04
Central disease score	1.24±0.98	1.50±1.08	0.48
Intraoperative classification			
Type 1/2/3/4	13/1/1/0	4/0/0/1	
Non-type 1	13.3	20.0	0.72
Operative mortality (%)	0.0	40.0	0.0098
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	365±223	232±112	0.34
% decrease in PVR (%)	53.7±25.5	65.6±23.2	0.46

Values are mean±SD or n (%).
Abbreviations see in Tables 1,3.

Table 5 Characteristics of Gender Difference in HLA-B*5201-Negative Type

	Female (n=52)	Male (n=27)	p value
Age (years)	54.2±11.6	53.1±11.4	0.71
DVT (%)	42.3	55.6	0.26
Embolic episode (%)	40.4	66.7	0.03
Pra (mmHg)	4.6±3.3	6.3±5.1	0.07
Mean Ppa (mmHg)	45.8±10.9	41.9±10.6	0.12
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.59±0.56	2.46±0.73	0.38
PVR ($dynes \cdot s \cdot cm^{-5}$)	862±316	717±319	0.06
PaO2 (Torr)	57.1±9.8	61.7±9.8	0.06
Central disease score	0.93±0.98	2.04±1.32	<0.0001
Intraoperative classification			
Type 1/2/3/4	13/8/4/0	18/0/0/0	
Non-type 1	48.0	0.0	0.0005
Operative mortality (%)	4.0	5.6	0.81
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	405±303	234±115	0.05
% decrease in PVR (%)	55.6±21.3	69.9±18.3	0.04

Values are mean±SD or n (%).
Abbreviations see in Tables 1,3.

Table 6 Characteristics of Female in HLA-B*5201-Positive or -Negative Type

	HLA-B*5201 positive (n=37)	HLA-B*5201 negative (n=52)	p value
Age (years)	53.9±10.5	54.2±11.6	0.90
DVT (%)	13.5	42.3	0.0036
Embolic episode (%)	27.0	40.4	0.19
Pra (mmHg)	3.9±3.7	4.6±3.3	0.25
Mean Ppa (mmHg)	43.7±11.3	45.8±10.9	0.08
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.77±0.61	2.59±0.56	0.15
PVR ($dynes \cdot s \cdot cm^{-5}$)	837±460	862±316	0.14
PaO2 (Torr)	57.1±10.5	57.1±9.8	0.35
Central disease score	1.24±0.98	0.93±0.98	0.11
Intraoperative classification			
Type 1/2/3/4	13/1/1/0	13/8/4/0	
Non-type 1	13.3	48.0	0.02
Operative mortality (%)	0.0	4.0	0.43
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	365±223	405±303	0.68
% decrease in PVR (%)	53.7±25.5	55.6±21.3	0.81

Values are mean±SD or n (%).
Abbreviations see in Tables 1,3.

CTEPH based on HLA types, we compared the clinical characteristics of HLA-B*5201-positive and -negative females. As shown in Table 6, HLA-B*5201-positive females had less history of DVT (13.5 vs 42.3%, p=0.0036) and less non-type 1 disease (13.3 vs 48%, p=0.02) compared with HLA-B*5201-negative females.

Discussion

The incidence of pulmonary thromboembolism in Japan in 2004 (4,106 patients) was much lower than in the USA (630,000)[20] The absence of factor V leiden and prothrombin mutation, and low lipid levels in the Japanese might be involved in the difference between Japanese and Caucasian populations with this disease[21,22] However, female predominance and a higher incidence ratio of chronic to acute pulmonary thromboembolism in Japan as compared to those in the USA were recently reported[1–3] From an annual report in Japan, the total number of CTEPH patients in Japan was 800 in 2006[23] It was reported that the risk of recurrent venous thromboembolism was higher in men than women, but the female-to-male ratio in CTEPH is 2.1 in Japan, much higher than that of 0.7 in the USA[3,7,8] In addition, we previously reported that HLA-B*5201-positive patients with Japanese CTEPH were predominantly females and were unrelated to DVT[11] The frequency of HLA-B*5201 among the normal population in Japan was reported to be 20%, much higher than 2% in western countries[24–26] Then we considered that the HLA-B*5201-positive type indicates Japanese-specific CTEPH, and that HLA-B*5201-negative type could indicate CTEPH related to DVT, similar to Western countries.

We investigated whether the clinical phenotype in female CTEPH differs from male CTEPH, especially in the Japanese series.

Female patients were elderly and had less DVT, less acute embolic episodes, a higher cardiac index, lower mean Pra, lower PaO_2, more peripheral thrombi and less improvement through surgery than males. When the patients were divided according to HLA-B*5201 status, in HLA-B*5201-positive patients, females showed less embolic episodes, higher cardiac index and lower mean Pra with lower operative mortality. In contrast, in HLA-B*5201-negative patients, females showed less embolic episodes and more peripheral thrombi, resulting in less improvement through surgery.

This is the first report to reveal gender differences in the clinical characteristics of CTEPH, and that gender differences in the HLA-B*5201-positive type were dissimilar to those in HLA-B*5201-negative type.

Several issues need to be considered in the interpretation of these results. First, female CTEPH showed peripheral thrombi according to the central disease score and intra-operative classification. These findings were similar to those of Jamieson et al, who reported that females predominate in type 3 disease (distal segmental arteries only type)[10] When the patients were divided according to HLA-B*5201 status, only in HLA-B*5201-negative patients did females show more peripheral type than males, but in HLA-B*5201-positive patients such difference could not be observed. It remains uncertain why female CTEPH showed more of the peripheral type that in the USA as well as in HLA-B*5201-negative type in Japan. Although distal small DVT could induce peripheral type CTEPH, it is possible that peripheral pulmonary arteriopathy, similar to pulmonary arterial hypertension, in situ thrombosis might cause peripheral type CTEPH? As shown in Table 6, in females, the frequencies of non-type 1 in intra-operative classifications were significantly higher in HLA-B*5201-negative than in -positive type patients. We have already shown that the frequencies of HLA-B*5201 were higher in CTEPH with central predominant type[10] It seems that the existence of HLA-B*5201 might be related to a more proximal location of thrombi only in females.

Second, female patients showed less history of DVT. However, there was no significant difference in DVT between males and females when the patients were divided by HLA-B*5201 status. Additionally, multiple regression analysis revealed that the HLA-B*5201-positive type significantly correlated with the absence of DVT, but female gender did not show significant correlation with DVT. It is likely that a significant correlation with female gender might be related to female predominance in the HLA-B*5201-positive type. Takayasu arteritis is epidemiologically known for its female predominance, and the association of HLA-B*5201 with this disease has been well documented in Japan[13,14,27] Takayasu arteritis is a chronic vasculitis, mainly involving the aorta and its major branches, as well as the coronary and pulmonary arteries[28] The frequency of HLA-B*5201 in CTEPH was similar to that reported in Takayasu arteritis[27] We previously reported that the HLA-B*5201-positive type showed female predominance and was unrelated to DVT, and that this Japanese-specific type might include underdiagnosed pulmonary arteritis secondary to thrombi, although Takayasu arteritis was clinically excluded by CT angiographies. In our series, the frequency of HLA-B*5201-positive type (27.0%) in male CTEPH was not dissimilar to that in the normal Japanese population (20.0%), while that in female CTEPH (41.6%) was much higher. Only female CTEPH in HLA-B*5201-positive type could be a specific Japanese type unrelated to DVT, caused by underdiagnosed arteritis secondary to thrombi.

Third, univariate analysis showed that female patients had less history of acute embolic episode regardless of the existence of HLA-B*5201. The results obtained by multiple logistic regression also showed that acute embolic episode was influenced by gender more strongly than the existence of HLA-B*5201. The peripheral type of CTEPH and lower frequency of DVT might be related to less embolic episodes.

Fourth, female patients showed higher cardiac index and lower mean Pra, indicating preserved right ventricular function. Although preserved right ventricular function in females was significant only in HLA-B*5201-positive type, 2-way factorial ANOVA revealed that female gender had the main effect on higher cardiac index and lower mean Pra independent of the existence of HLA-B*5201. Several studies of the left ventricle have suggested that female gender is associated with more favorable myocardial adaptations to hemodynamic overload, including a better preserved contractile response and a greater adaptive hypertrophic reserve[29–31] Our data for the right ventricle were consistent with these data. The use of diuretics did not differ between males and females (62.5 vs 62.7%, p=0.99). Only fifteen patients had systemic hypertension, with 3 of them taking an angiotensin converting enzyme inhibitor. Therefore, it is unlikely that such medications might have strong effects on gender difference in terms of right ventricular function.

Female patients had less heart disease compared with males. After excluding patients with heart disease, females still showed higher cardiac index and lower mean Pra. In

addition, there was no significant differences in pulmonary capillary wedge pressure (7.3 vs 6.1 mmHg, p=0.83) between male and female CTEPH. Further studies on gender differences regarding right ventricular function will be needed.

Fifth, female patients showed higher postoperative PVR and a modest percentage decrease in PVR in all patients as well as in the HLA-B*5201-negative type. In contrast, the mortality of female patients was lower than that of males in only the HLA-B*5201-positive type despite similar postoperative PVR and percentage decrease in PVR. The peripheral type of emboli in females could be related to less improvement using surgery in all patients as well as in the HLA-B*5201-negative type. In contrast, it is likely that better right ventricular function in females contributes to lower mortality in HLA-B*5201-positive type. We previously reported that the female HLA-B*5201-positive type had a tendency to be the central predominant type![1] In the present study, HLA-B*5201-positive females showed more type 1 disease compared with HLA-B*5201-negative females, although there was no significant difference in central disease score. More type 1 disease in HLA-B*5201-positive females could be related to lower mortality.

Finally, the present study is based on the results from a single institution, and the number of patients in each group subcategorized according to gender and HLA type was small. Nonetheless, it will be important to manage patients while taking into account gender differences and HLA type. Larger studies are needed to confirm the relationship of gender difference and clinical phenotype.

In conclusion, to our knowledge, this is the first study to report that clinical phenotype in female CTEPH differed from that in males, and that gender differences in HLA-B*5201-positive type were dissimilar to those in HLA-B*5201-negative type.

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Disclosure

The authors have no conflicts of interest to disclose.

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