Table 3 Appopriate cut-off value of SF, D-dimer and FDP for the diagnosis of VTE

Marker	Cut off value (μg/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Odds ratio
Highest odds ratio						
SF	5.9	98.5	80.1	36.3	99.8	265.7
D-Dimer	4.8	28.4	96.6	48.7	92.1	11.1
FDP	2.1	98.5	68.1	26.2	99.7	140.9
Highest NPV (100%)						
SF	5.2	100	76.0	32.4	100	
D-Dimer	0.5	100	34.3	14.9	100	
FDP	1.3	100	56.1	20.7	100	

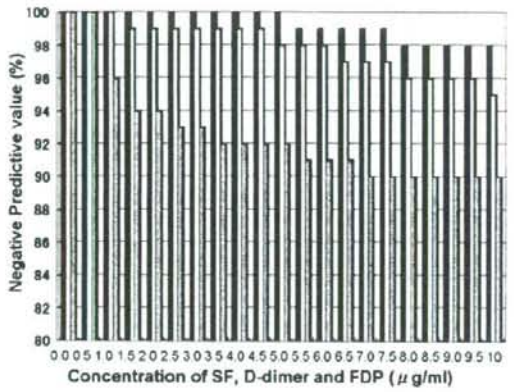

Fig. 5 Negative predictive value for the diagnosis of VTE. *Closed bar* SF, *shaded bar* D-dimer, *open bar* FDP

The plasma levels of SF tended to be high in all subjects, especially those with infectious diseases, those with trauma and burn and those without underlying disease, suggesting that these diseases have a hypercoagulable state or thrombosis. The plasma levels of D-dimer also tended to be high in those with orthopaedic conditions and those without underlying disease, indicating that D-dimer levels might be high in orthopaedic conditions without thrombosis, and that D-dimer may therefore not be useful for the diagnosis of thrombosis under those conditions.

The ROC analysis showed that SF, FDP and D-dimer are useful markers for the diagnosis of VTE; in particular, SF was the best marker of the FRMs. An appropriate cut-off value for the diagnosis of VTE was 5.9 μg/ml in SF, 2.1 μg/ml in FDP and 4.8 μg/ml in D-dimer. Except in the D-dimer, these cut-off values were close to the normal range and a slight increase of the SF and FDP from the normal range shows a high risk of thrombosis. At a value of 5.9 μg/ml for SF, both the sensitivity and specificity were sufficiently high, thus suggesting that SF is the best marker for the diagnosis of thrombosis at the onset. At the value of 4.8 μg/ml for D-dimer, the specificity was highest, suggesting that the diagnosis of VTE might be confirmed by high D-dimer levels.

In 100% of NPV for the diagnosis of VTE, SF was less than 5.2 μg/ml, FDP was less than 1.3 μg/ml and D-dimer was less than 0.5 μg/ml. In Europe and North America, D-dimer concentrations of less than 0.5 μg/ml are considered to exclude DVT/PE [17]. However, some D-dimer kits, which are frequently used in Japan have different cut-off values for the exclusion of DVT/PE [28]. These findings for D-dimer were similar to previous reports [28]. However, this study is the first to show that the SF level is a valuable indicator for the exclusion of DVT/PE.

Finally, the FRMs such as D-dimer, FDP and SF are considered to be useful for the diagnosis of thrombosis, and the SF level reflects the early phase of DVT/PE while D-dimer reflects the secondary fibrinolysis after clot formation [2]. By establishing an early diagnosis of thrombosis by FRM, we might improve the outcome in various underlying diseases, which carry a risk for the development of thrombosis.

Acknowledgments This study was supported in part by research grants from the Japanese Ministry of Health, Labour and Welfare, from the Japanese Ministry of Education, Science, Sports and Culture and the Mie University COE Fund.

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Elevated Levels of Prothrombin Fragment 1 + 2 Indicate High Risk of Thrombosis

Satoshi Ota, MD, PhD, Hideo Wada, MD, PhD, Yasunori Abe, Eri Yamada, Akane Sakaguchi, Junji Nishioka, PhD, Tsuyoshi Hatada, MD, PhD, Ken Ishikura, MD, PhD, Norikazu Yamada, MD, PhD, Akihiro Sudo, MD, PhD, Atsumasa Uchida, MD, PhD, and Tsutomu Nobori, MD, PhD

Prothrombin fragment 1 + 2 (F1 + 2) is considered to be useful for diagnosis of thrombosis. However, the evidence for a diagnosis of thrombosis by F1 + 2 is still not well established. The plasma concentrations of F1 + 2, soluble fibrin, D-dimer, and thrombin-antithrombin complex were measured in 694 patients suspected of having thrombosis and then were correlated with thrombosis. Plasma concentrations of F1 + 2, soluble fibrin, D-dimer, and thrombin-antithrombin complex were significantly higher in patients with thrombosis, compared with patients without thrombosis. When cutoff values of more than 300 pmol/L for F1 + 2 were used for the diagnosis, more than 50% of the patients were thus found to have thrombosis. The findings showed that F1 + 2, soluble fibrin, D-dimer, and thrombin-antithrombin complex have similar diagnostic ability. The plasma concentration of F1 + 2 closely was well correlated with thrombin-antithrombin complex, soluble fibrin, and D-dimer. Finally, F1 + 2 is one of the most useful parameters for the diagnosis of thrombosis.

Keywords: thrombosis; F1 + 2; SF, D-dimer; TAT

The prothrombin fragment 1 + 2 (F1 + 2) is cleaved from the aminoterminal end of human prothrombin when this zymogen is activated by factor Xa to yield thrombin.[1] The determination of human F1 + 2 in plasma with an antibody against a synthetic peptide has been reported.[2] Monitoring of F1 + 2 in patients treated with oral anticoagulants[3,4] and elevated plasma levels of F1 + 2 in patients with disseminated intravascular coagulation (DIC)[5,6] have been reported. Increased plasma level of thrombin-antithrombin complex (TAT)[7] also reflected with thrombin generation such as enhanced F1 + 2 levels.

From the Departments of Cardiology (SO, NY, TN), Molecular and Laboratory Medicine (HW, JN), Central Laboratory (YA, EY, AS), Emergency Medicine (TH, KI), and Orthopaedic Surgery (AS, AU), Mie University Graduate School of Medicine, Tsu, Mie-ken, Japan.

Address correspondence to: Hideo Wada, MD, PhD, Department of Laboratory Medicine, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie-ken 514-8507, Japan; e-mail: wadahide@clin.medic.mie-u.ac.jp.

Disseminated intravascular coagulation[8,9] is often observed in patients with leukemia, solid cancers, infections, gynecological conditions, and aneurysms, and it is also frequently associated with severe bleeding and organ failure. Because DIC is frequently a fatal condition,[10] it is important to diagnose DIC at an early stage using hemostatic molecular markers.[11] Pulmonary embolism (PE) is a common, frequently undiagnosed, and potentially fatal cause of several common symptoms, for example, dyspnoea and chest pain.[12-14] Because PE is often a fatal disease caused by deep-vein thrombosis (DVT), the early evaluation of DVT[15] and PE[16] is therefore considered to be clinically important.

Fibrin-related markers such as D-dimer, fibrin and fibrinogen degradation products, and soluble fibrin (SF) are considered to be useful for the diagnosis of thrombosis. These markers are reported to be elevated in DVT/PE,[17-19] DIC,[20-22] acute myocardial infarction (AMI),[23,24] and thrombotic thrombocytopenic purpura.[25] In this regard, D-dimer has been

Table 1. Clinical Characteristics of the Patients Included in the Study

Underlying Diseases	Total	Without Thrombosis	With Thrombosis	Rate (%)
Solid cancer	191	167	24	12.5
Orthopedic diseases	178	150	28	16.0
Cardiovascular diseases	60	53	7	12.0
Collagen diseases	36	33	3	8.0
Digestive diseases	36	34	2	6.0
Infectious diseases	29	18	11	38.0
Hematological diseases	26	20	6	23.1
Diabetes mellitus	16	11	5	31.3
Without underlying diseases	15	0	15	100
Aneurysm and varicose	12	5	7	58.3
Trauma and burn	11	5	6	54.5
Obstetric diseases	6	6	0	0
Thrombophilia	4	2	2	50.0
Other diseases	11	11	0	0
Total	633	517	116	18.3

reported to be a negative predictor for DVT and less than 0.5 μg/mL of D-dimer is considered to exclude DVT in the most commonly used D-dimer assays in Europe and North America.[15] The International Society of Thrombosis and Haemostasis (ISTH) established the diagnostic criteria for overt-DIC using fibrin-related markers.[26] D-dimer is widely used to diagnose thrombosis as DVT, but many of the commercially available D-dimer assay kits contain different monoclonal antibodies and standard substances, and are based on different assay systems. The issue of standardization of D-dimer assays remains to be resolved, and several studies[27,28] have reported the basic data for standardization of D-dimer.

The present study was designed to evaluate the cutoff values of F1 + 2 in the diagnosis of thrombosis such as DVT, DIC, cerebral thrombosis, and AMI prospectively and to compare the findings to those for TAT, D-dimer, and SF. For this purpose, we determined the plasma concentrations of these molecules in 694 patients suspected of having thrombosis and also in 67 healthy volunteers.

Materials and Methods

Subjects

From June 1, 2003 to September 31, 2004, 694 patients (age range = 57.7 ± 17.8 years; mean = ±SD 398 females and 296 males) were suspected to have thrombosis (DVT, DIC, cerebral thrombosis or acute myocardial infarction) at hospitals affiliated with Mie University Graduate School of Medicine. The plasma concentrations of F1 + 2, SF, TAT, and D-dimer were examined in these patients and then were correlated with thrombosis. The study protocol was approved by the Human Ethics Review Committees of participating institutions, and a signed informed consent form was obtained from each subject. Thirty-four patients within 3 days after operation (OPE) and 29 patients who had undergone liver transplantation (LT) were excluded from analysis of the cutoff value. However, of the remaining 631 patients, 515 patients did not have any thrombosis, whereas 116 patients had thrombotic diseases, 66 with DVT, 27 with DIC, 10 with cerebral vascular accidents due to thrombosis (CVA), 5 with AMI, 4 with portal vein thrombosis, and 4 with arteriosclerosis obliterans. Deep-vein thrombosis was diagnosed by either ultrasonography or venography. Disseminated intravascular coagulation was diagnosed based on the ISTH overt-DIC diagnostic criteria.[26] Cerebral vascular accidents due to thrombosis were diagnosed either by computed tomography or by magnetic resonance imaging, and AMI was diagnosed by electrocardiograms and clinicolaboratory data. The underlying diseases of these patients are shown in Table 1.

Citrated blood samples were obtained from the peripheral veins of healthy subjects (see below) and from patients under fasting conditions. The blood samples were then centrifuged for 20 minutes at 3000 rpm. The supernatants (plasma) were analyzed within 4 hours. The plasma concentrations of F1 + 2, SF, TAT, and D-dimer were measured in patients with thrombosis at the onset and those without thrombosis at first consultation. The same parameters were also measured in 67 healthy subjects (age range = 38.6 ±

17.7-years-old; 58 males and 9 females) who were free of any diseases including thrombotic disease or hyperlipidemia, as confirmed by annual medical checkup.

Measurement of Plasma Concentrations of F1 + 2, TAT, D-Dimer, and SF

The plasma levels of F1 + 2 were measured by a new enzyme-linked immunosorbent assay (ELISA) for the determination of F1 + 2 (Dade Behring Marburg GmbH, Marburg, Germany). Two different monoclonal antibodies in this kit recognize the terminal end of N fragment 2. The plasma levels of TAT were measured using the TAT test (Sysmex, Kobe, Japan) by ELISA. The plasma D-dimer levels were measured by LPIA-ACE D-dimer (Mitsubishi Kagaku Iatron Inc, Tokyo, Japan) using JIF23 monoclonal antibody. The JIF23 monoclonal antibody, which recognizes plasmin-digested N-terminus of the γ chain on the D region, was used for latex agglutination.[29] Soluble fibrin was also determined by the latex agglutination method using IATRO SF (Mitsubishi Kagaku Iatron Inc) containing monoclonal antibody IF-43, which recognizes a segment of the fibrin Aa chain (Aα-17-78) residue segment exposed in the E region of fibrin monomer (FM) when the FM molecule binds to the D region of another FM or fibrinogen. The antibody is coated for the SF assay.[30]

Statistical Analysis

The data are expressed as mean ± SD. Differences between groups were examined for statistical significance using the Mann-Whitney *U* test, whereas the correlation between the 2 variables was evaluated by Pearson's correlation analysis. A *P* value of less than .05 denoted the presence of a statistically significant difference. The usefulness of D-dimer and SF for the diagnosis of thrombosis, DVT, and DIC were examined by a receiver operating characteristic (ROC) analysis.[31] The cutoff values were determined by an ROC analysis. All statistical analyses were performed using the SPSS II software package (SPSS, Tokyo, Japan).

Results

The frequency of thrombotic diseases was high in patients with solid cancer, orthopedic diseases, hematological diseases, infectious diseases, cardiovascular diseases, diabetes mellitus, and aneurysm (Table 1). In healthy subjects, plasma concentrations of F1 + 2 were not distributed normally, with a maximum value of 214 pmol/L, minimum value 42 pmol/L, and median value of 121 pmol/L. The 95% confidence interval (95% CI) of F1 + 2 was from 56 to 213 pmol/L.

The plasma levels of F1 + 2, SF, D-dimer, and TAT (median; 25-75 percentile) were significantly higher in the patients with thrombosis (516 pmol/L; 349-709 pmol/L, 18.49 μg/mL; 8.68-35.24 μg/mL, 11.38 μg/mL; 6.58-19.06 μg/mL, and 15.87 ng/mL; 9.04-36.98 ng/mL, respectively), OPE (431 pmol/L; 331-520 pmol/L, 13.32 μg/mL; 8.17-22.10 μg/mL, 7.32 μg/mL; 3.04-12.78 μg/mL, and 17.38 ng/mL; 13.04-32.87ng/mL, respectively), and LT (590 pmol/L; 249-985 pmol/L, 16.03 μg/mL; 5.60-24.08 μg/mL, 6.54 μg/mL; 2.67-12.68 μg/mL, and 19.36 ng/mL; 12.69-32.51 ng/mL, respectively) than in those without thrombosis (192 pmol/L; 138-274 pmol/L, 2.79 μg/mL; 0.76-5.29 μg/mL, 0.88 μg/mL; 0.45-2.27 μg/mL, and 2.43 ng/mL; 1.58-5.50 ng/mL; $P < .01$, each; Figure 1). On other hand, the plasma concentrations of F1 + 2, SF, D-dimer, and TAT were significantly higher in patients without thrombosis than in healthy subjects ($P < .01$, each).

Figure 2 shows the positive predictive values (PPV) and negative predictive values (NPV) for several cutoff values of F1 + 2 in patients with thrombosis. When F1 + 2 levels of >300 pmol/L were used, more than 50% of the patients, excluding either those with LT or those who had undergone an operation, had some thrombosis and NPV for thrombosis was >95%. When the cutoff values were set at <100 pmol/L for F1 + 2, NPV for thrombosis was 100%, but PPV was <25%.

An ROC analysis showed the curves of F1 + 2, SF, D-dimer, and TAT to be similar and useful for the diagnosis of all thromboses (Figure 3). The area under the curve (AUC) of those markers was markedly high (Table 2). An ROC analysis provided adequate cutoff values of F1 + 2 (300 pmol/L), SF 6.8 (μg/mL), D-dimer (3.0 μg/mL), and TAT (7.8 ng/mL) for the diagnosis of all thromboses (Table 3). The sensitivity and specificity of F1 + 2 were 86.2% and 80.6%, respectively. These statistical values of F1 + 2 were similar to those of other molecular markers.

Table 4 shows the correlation between F1 + 2 and other hemostatic molecular markers. The plasma levels of F1 + 2 were closely correlated with SF, D-dimer, and TAT, and the correlation between F1 + 2 and TAT was the best.

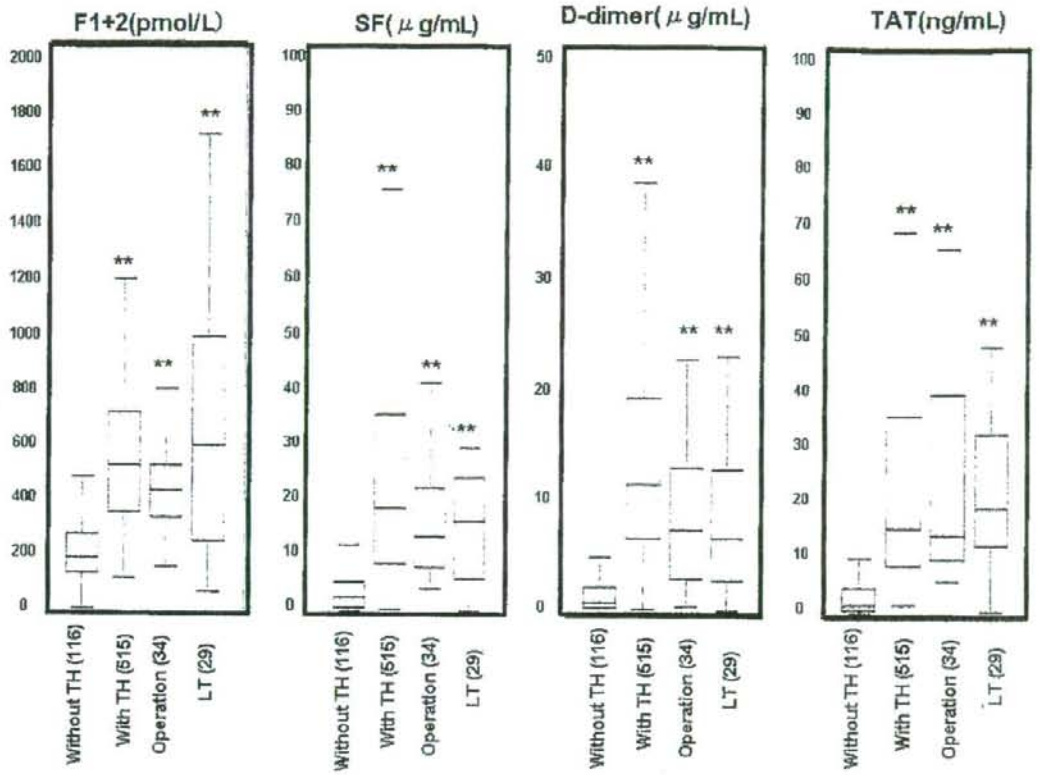

Figure 1. Plasma levels of F1 + 2, SF, D-dimer, and TAT in patients with or without thrombosis, those after the operation and those after LT. SF indicates soluble fibrin; TAT, thrombin-antithrombin complex; LT, liver transplantation. ** indicates $P < .01$ (comparison to without thrombosis). The box shows 25 percentile, median, and 75 percentile. Operation; patients within 3 days after operation, LT; patients after liver transplantation.

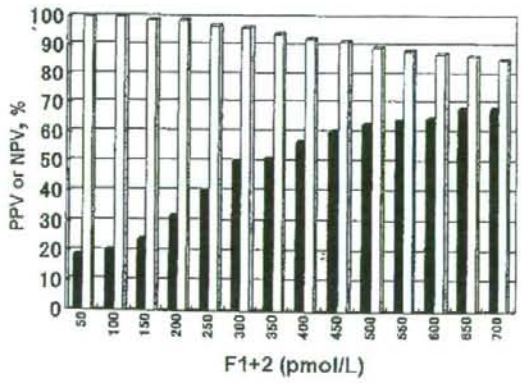

Figure 2. The PPV and NPV for plasma concentrations of F1 + 2 in thrombosis. PPV indicates positive predictive values; NPV, negative predictive values. Solid bar represents PPV and white bar represents NPV.

Discussion

The frequency of thrombotic diseases was high in patients with solid cancer, orthopedic diseases, hematological diseases, infectious diseases, cardiovascular diseases, diabetes mellitus, and aneurysm, suggesting that prevention of thrombosis will be important in these underlying diseases. Although the sample number was not ideal in this study, DVT was frequently associated with cancer and orthopaedic diseases, whereas DIC was frequently associated with cancer, infectious diseases, and aneurysm. Such frequencies were similar to those reported in previous studies.[9,12,13] Regarding the underlying diseases frequently associated with thrombosis (eg, DVT and DIC), the risk for thrombosis should be evaluated by a simple test. In the present study, we demonstrated the concentrations

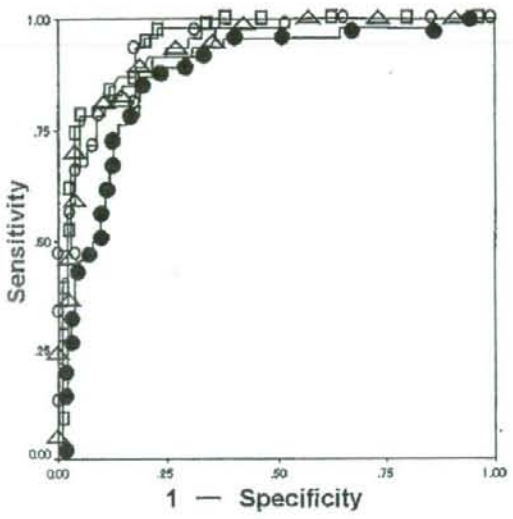

Figure 3. ROC analysis of F1 + 2, SF, D-dimer, and TAT for thrombosis. ROC indicates receiver operating characteristic; SF, soluble fibrin; TAT, thrombin-antithrombin complex. (□) TAT; (○) F1+2; (▯) SF; (•) D-dimer.

Table 2. Area Under the Curve of Receiver Operating Characteristic in F1 + 2, Soluble Fibrin, D-Dimer, and Thrombin-Antithrombin Complex

	AUC
F1 + 2	0.938
D-dimer	0.910
SF	0.901
TAT	0.940

NOTES: AUC = area under the curve; SF = soluble fibrin; TAT = thrombin-antithrombin complex.

of F1 + 2 to be significantly high in patients with thrombosis such as DIC, DVT, CVA, and AMI, and these findings were similar to those for SF, D-dimer, and TAT.

In healthy subjects, the plasma concentrations of F1 + 2 were not distributed normally, and the 95% CI of F1 + 2 ranged from 56 pmol/L to 213 pmol/L, thus indicating that the patients with more than 220 pmol/L of F1 + 2 may have a hypercoagulable state. In contrast, the plasma levels of F1 + 2 were significantly high in patients with thrombosis such as the plasma levels of SF, D-dimer, and TAT. As a result, high concentrations of SF, D-dimer, and TAT could thus be considered as markers of thrombosis, because these parameters were also reported to be elevated in DVT,[32,33] DIC,[20,34] and hyperlipidemia.[35] It should be noted, however, no prospective studies have previously evaluated the F1 + 2 assay including the cutoff value for the diagnosis of thrombosis. The plasma levels of F1 + 2 were significantly high in patients with all types of thrombosis although the levels were also high in some patients who were not found to have any thrombosis.

More than 50% of patients who had more than 300 pmol/L of F1 + 2 had some thrombosis, suggesting that these patients need anticoagulant therapy such as aspirin for atherosclerotic thrombosis or warfarin for venous thrombosis. It is considered that these patients with a high value of F1 + 2 have hypercoagulable state. D-dimer is also useful for the diagnosis of DVT, but the cutoff values of D-dimer should be mentioned in each measurement kit.[28]

An ROC analysis showed that the curves of F1 + 2, SF, D-dimer, and TAT to be similar. Because both AUC of these markers, especially F1 + 2 and TAT, were high in ROC analysis, we believe that these markers are useful for the diagnosis of either thrombosis or a hypercoagulable state. In particular, both F1 + 2 and TAT may be more useful than D-dimer and SF for the diagnosis of thrombosis by AUC. An ROC analysis provided adequate cutoff values of F1 + 2 (300 pmol/L), SF (6.8 μg/mL), D-dimer (3.0 μg/mL), and TAT (7.8 ng/mL) for the diagnosis of all types of thromboses. The sensitivity and specificity of F1 + 2 were 86.2% and 80.6%, respectively. These statistical values of F1 + 2 were similar to those observed for other molecular markers, thus suggesting that the ability to diagnose thrombosis is similar among F1 + 2, D-dimer, SF, and TAT. Soluble fibrin has also been reported to reflect the early phase of DVT/PE, whereas D-dimer reflects secondary fibrinolysis after clot formation and the measurements of both D-dimer and SF may be recommended.[36,37] Both F1 + 2 and TAT reflect an earlier phase of thrombosis. The plasma levels of F1 + 2 were closely correlated with those of SF, D-dimer, and TAT and the correlation between F1 + 2 and TAT was best, thus suggesting that both markers reflect thrombin formation. Specificity for thrombosis was better in F1 + 2 than in TAT, thus suggesting that F1 + 2 may be the most useful marker for the earlier phase of thrombosis.

In conclusion, our findings suggest that high concentrations of hemostatic molecular markers,

Table 3. Cutoff Values of F1 + 2, Soluble Fibrin, D-Dimer, and Thrombin-Antithrombin Complex

	Cutoff Values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Odds Ratio
F1 + 2	300 pmol/L	86.2	80.6	50.0	96.3	26.07
SF	6.8 μg/mL	89.7	88.0	62.7	97.4	63.01
D-dimer	3.0 μg/mL	82.8	82.4	51.3	95.5	22.47
TAT	7.8 ng/mL	82.4	82.4	72.4	90.4	24.79

NOTE: PPV = positive predictive values; NPV = negative predictive values; SF = soluble fibrin; TAT = thrombin-antithrombin complex.

Table 4. Correlation Between F1 + 2 and Other Hemostatic Molecular Markers[a]

	F1 + 2	SF	D-Dimer	TAT
F1+2	1.0	0.543 ($P < .001$)	0.681 ($P < .001$)	0.760 ($P < .001$)
SF	0.543 ($P < .001$)	1.0	0.588 ($P < .001$)	0.691 ($P < .001$)
D-dimer	0.681 ($P < .001$)	0.588 ($P < .001$)	1.0	0.710 ($P < .001$)
TAT	0.760 ($P < .001$)	0.691 ($P < .001$)	0.710 ($P < .001$)	1.0

NOTE: SF = soluble fibrin; TAT = thrombin-antithrombin complex.
[a]The numbers show the correlation coefficients.

especially F1 + 2 which is also known as a marker for a hypercoagulable state, reflect a high risk for thrombosis.

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Original article

Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin

TAKESHI FUJI[1], TAKAHIRO OCHI[2], SHIGEO NIWA[3], and SATORU FUJITA[4]

[1]Department of Orthopedic Surgery, Osaka Koseinenkin Hospital, 4-2-78 Fukushima, Fukushima-ku, Osaka 553-0003, Japan
[2]Osaka Police Hospital, Osaka, Japan
[3]Aichi Medical University, Aichi, Japan
[4]Department of Orthopaedic Surgery, Takarazuka Dai-ichi Hospital, Hyogo, Japan

Abstract

Background. Enoxaparin is a low-molecular-weight heparin indicated in Europe and North America for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery. Registration trials of enoxaparin have been conducted primarily in Caucasian populations, and the efficacy and safety of enoxaparin in Japanese patients have not been demonstrated. We evaluated three dosage regimens of postoperative enoxaparin in Japanese patients undergoing elective total hip or knee arthroplasty.

Methods. Two multicenter, randomized, double-blind studies enrolled 436 and 396 Japanese adults undergoing total hip or knee arthroplasty, respectively. The dosage regimens of enoxaparin were 20 mg once daily (qd), 40 mg qd, 20 mg twice daily (bid), or placebo for 14 consecutive days. The primary efficacy endpoint was the incidence of VTE in the modified intention-to-treat (mITT) population up to 15 days after surgery. VTE was defined as a composite of deep vein thrombosis (determined by venography) and symptomatic pulmonary embolism (confirmed by appropriate objective methods). Patients were also followed up at 90 days for VTE events. The primary safety outcome was the incidence of any bleeding during treatment and the follow-up period.

Results. In the mITT populations, the incidence of VTE was 41.9% and 60.8% in the placebo groups after hip or knee arthroplasty, respectively, 25.9% and 44.9% in the enoxaparin 20 mg qd groups, 33.8% and 35.1% in the enoxaparin 40 mg qd groups, and 20.0% and 29.8% in the enoxaparin 20 mg bid groups. Only enoxaparin 20 mg bid significantly lowered the risk of VTE relative to placebo (by 52.2% and 51.0% after hip and knee arthroplasty, respectively). At the 90-day follow-up, no further cases of VTE were reported. In both the hip and knee studies, the four treatment groups did not differ significantly regarding the incidence of patients with any bleeding.

Conclusions. Our findings support the use of enoxaparin (20 mg bid daily, commencing 24–36 h postoperatively) in Japanese patients undergoing total hip or knee arthroplasty.

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Introduction

Patients undergoing hip or knee arthroplasty are at particularly high risk of postoperative venous thromboembolism (VTE).[1] If no antithrombotic measures are taken, the prevalence of total deep vein thrombosis (DVT) is in the range of 42%–57% for total hip arthroplasty (THA) and 41%–85% for total knee arthroplasty (TKA).[1,2] Thrombi involving the proximal deep veins, which are considered as the most likely to become symptomatic and to result in pulmonary embolism (PE), also occur in up to 36% of patients after joint arthroplasty surgery.[1] In Western countries, nearly all arthroplasty patients are treated with anticoagulants, leading to a paucity of recent data on PE in the absence of prophylaxis. The rate of PE in early trial s was 3%–28% in arthroplasty patients, and 0.1%–2.0% of these events were fatal.[1] The absolute risk for VTE in Japanese patients is comparable to that observed in European and North American studies: The risk indicated 23% and 49% in a prospective epidemiological study,[3] 33.8% and 65.3% after THA and TKA, respectively, in the placebo arm of a recent randomized clinical trial.[4]

In North American trials, enoxaparin 30 mg twice daily (bid) reduced the risk of total DVT by more than 70% compared with placebo after both THA and TKA, without increasing the bleeding risk.[5,6] Findings from a systematic review of 19 randomized controlled trials involving approximately 7000 patients undergoing elective hip arthroplasty showed that treatment with a low-molecular-weight heparin (LMWH) resulted in a 24% reduction in the incidence of both DVT and minor bleeding (both $P < 0.05$) compared with treatment with unfractionated heparin.[7] Routine use of such thromboprophylactic measures in the management of hip or knee arthroplasty has greatly reduced the likelihood of PE[8] without increasing the risk of

major bleeding.[7] Use of LMWH in patients undergoing THA or TKA has become standard practice in Western countries.[1]

The improved efficacy and safety of LMWH relative to unfractionated heparin for major surgery have been established, but the optimum dose and duration of therapy have not yet been determined for all patient populations.[9,10] Usual practice in Europe is to administer LMWH preoperatively, whereas in the United States these agents are administered postoperatively.[8,11] The approved enoxaparin dosage regimen in Europe is 40 mg once daily (qd) (administered 12 h preoperatively), whereas in North America a regimen of 30 mg bid (administered 12–24 h postoperatively) is recommended.[9]

Among Japanese patients, less information is available regarding the dosage and timing of initiation of enoxaparin treatment to maximize efficacy while minimizing hemorrhagic risk. To address this issue, we conducted two randomized, double-blind, Phase IIB/III trials that compared the clinical efficacy and safety versus placebo of three dosage regimens of enoxaparin initiated postoperatively in Japanese patients undergoing primary THA or TKA.

Patients and methods

Two randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase IIb/III clinical studies were conducted between 1999 and 2002 among patients undergoing primary THA and TKA at 51 medical institutions in Japan. Both studies were approved by the appropriate institutional review board and were undertaken in full compliance with the principles of Article 14-3 and Article 80-2 of the Pharmaceutical Affairs Law, the Ministry of Health and Welfare Ordinance on Good Clinical Practice, and the Declaration of Helsinki. Written informed consent was obtained from all patients before their participation in the study according to the guidelines at each institution.

Patient selection

Patients aged ≥20 years (no upper age limit was applied) undergoing elective primary THA or TKA were eligible for enrollment in the studies. Patients requiring revision THA or TKA were excluded. Other exclusion criteria were contraindication to heparin therapy; positive clinical evidence of chronic (postphlebitic syndrome) or acute DVT within 12 months of the study drug treatment; documented allergy to iodine or contrast medium; impaired renal function (creatinine clearance <30 ml/min or plasma creatinine level >1.5 mg/dl); severe hepatic disease; uncontrolled hypertension; illicit drug use or alcohol abuse; treatment with other investigational agents within 3 months of surgery; failure to achieve postoperative hemostasis; and female subjects if pregnant or breast-feeding. Use of the following medications or interventions was prohibited from 2 days before surgery until the end of the study drug treatment: low-dose aspirin and other antiplatelet agents, dextran, anticoagulants, thrombolytics, and nonsteroidal antiinflammatory drugs (within 72 h of surgery). In addition, use of intermittent pneumatic compression devices was not allowed from the end of surgery to the completion of venography; and postoperative epidural or spinal analgesia was prohibited from 2 h before the first dose of the study drug until completion of venography. The use of compression bandages and stockings was allowed.

Treatment regimens

Patients were randomized in a 1:1:1:1 ratio to receive a subcutaneous injection of enoxaparin 20 mg qd, enoxaparin 40 mg qd, enoxaparin 20 mg bid, or placebo (saline) into the anterolateral or posterolateral abdominal wall for 14 consecutive days (Fig. 1). The enoxaparin dosages used in this study were determined based on the approved dosage regimen in the United States (i.e., 30 mg bid)[12] and scaled to account for the difference in mean body weight between Japanese and Caucasian patients. Specifically, the mean body weight of Japanese patients who participated in a prospective epidemiological study of enoxaparin for DVT prophylaxis was approximately two-thirds that of their Caucasian counterparts (54 kg vs. 80 kg, respectively).[3] Therefore, in a postoperative regimen in Japanese patients, an enoxaparin dosage of 20 mg bid was thought to be equivalent to that prescribed in the United States. Once-daily regimens of enoxaparin 40 mg and 20 mg were also evaluated, as this protocol may be more acceptable to patients and medical staff.

Treatment was started 24–36 h after surgery. A postoperative regimen was used in all patients (including those with an epidural tube) because of published reports describing spinal hematomas in association with concurrent use of spinal or epidural anesthesia and heparin or LMWH in Western countries.[13,14] In Japan, spinal or epidural anesthesia is frequently used for patients undergoing surgery to the lower extremities. Treatment was scheduled to last for 14 days. Patients were followed up at 90 days after surgery to determine whether VTE events had occurred.

Analysis of populations

Patients were included in the safety population if they had provided written informed consent, had received

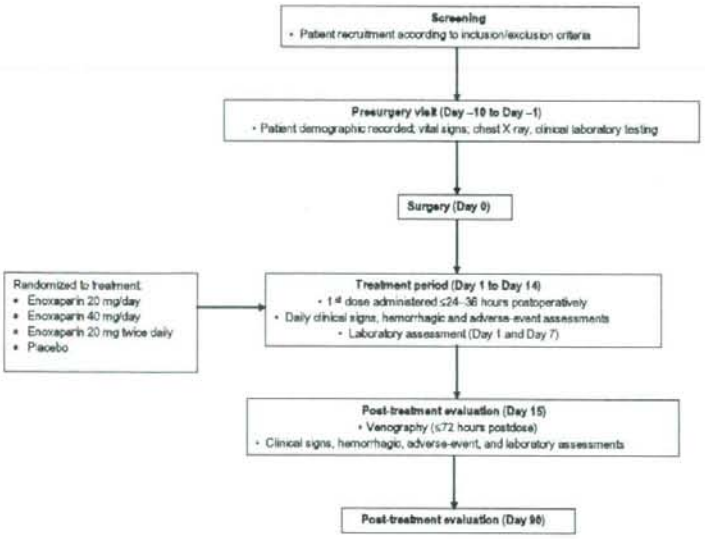

Fig. 1. Study time line, portraying scheduled observations, tests, evaluations, and interventions

at least one dose of the study medication, and there were no violations of good clinical practice in their management. Those in the safety populations who had clearly interpretable VTE imaging tests were included in the modified intention-to-treat (mITT) populations.

Assessments and outcome definitions

Patients underwent routine laboratory tests, physical examinations, vital signs, and chest radiography at preoperative screening, during surgery, and throughout the postoperative period (Fig. 1).

The primary efficacy endpoint was the incidence of VTE (DVT or PE) in the mITT populations objectively confirmed within 72 h after completion or discontinuation of treatment. Mandatory venography (or ultrasonography when venography was difficult to perform due to extensive swelling of the lower extremity caused by thrombi in the deep veins) was performed in all patients to detect any DVTs at the end of the study. Suspicion of a symptomatic PE was objectively confirmed by ventilation perfusion lung scans or pulmonary angiography. All objective tests, including venography, ventilation perfusion lung scans, and pulmonary angiography, were centrally adjudicated by an independent expert panel blinded to the treatment group of the patient.

The primary safety endpoint was the incidence of any bleeding — a composite of the incidence of major and minor bleeding. Bleeding was assessed daily during the 14-day treatment period, within 24 h after completion or discontinuation of treatment, and at day 15 at a follow-up consultation (Fig. 1). A bleeding episode was classified as major if it was retroperitoneal, intracranial, or intraocular or if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction in the hemoglobin level of ≥2 g/dl; or a serious or life-threatening clinical event that required medical intervention. Suspicion of intraabdominal or intracranial bleeding was confirmed by ultrasonography, computed tomography, or magnetic resonance imaging. Minor bleeding episodes were defined as having at least one of the following features: epistaxis lasting >5 min or requiring intervention; ecchymosis or hematoma with a maximum size of >5 cm; hematuria not associated with urinary catheter trauma; gastrointestinal hemorrhage not related to intubation or a nasogastric tube; wound hematoma or hemorrhagic wound complications not associated with major hemorrhage; or subconjunctival hemorrhage requiring cessation of medication.

Secondary safety endpoints were assessed over a similar time frame and included the incidence, type, and severity of generalized adverse events (AEs) based on clinical and biochemical evaluations.

Statistical analyses

For the THA study, VTE event rates were expected to be 30% in the placebo group, 20% in the enoxaparin 20 mg qd group, and 10% in the enoxaparin 40 mg qd group. With a one-sided type I error rate of 0.05 and a type II error of 0.1, a total of 72 patients were required

per treatment arm to a show a dose–response relation by the Cochran–Armitage trend test. To demonstrate a statistically significant difference between treatment with placebo and enoxaparin 40 mg qd with a one-sided type I error of 0.025 and a type II error of 0.1, a total of 92 patients per arm were needed. With the anticipated rate of patients who could not be evaluated at approximately 15%, the study plan was to enroll 110 patients per treatment arm.

For the TKA study, it was assumed that the type I and type II error rates would be the same as for the THA study; VTE event rates were expected to be 50% in the placebo group, 35% in the enoxaparin 20 mg qd group, and 25% in the enoxaparin 40 mg qd group. Therefore, 62 patients per treatment arm were required to show a dose–response relation (Cochran–Armitage trend test), and 85 patients per arm were required for pairwise comparison. With the anticipated rate of patients who could not be evaluated at approximately 15%, the study plan was to enroll 100 patients per treatment arm. If these assumptions were met, two-sided tests at the 0.025 level of statistical significance would have 90% power.

The χ^2 test was used to determine if there was a difference between groups for all baseline characteristics except age and the body mass index (BMI), for which an analysis of variance test was used. The Cochran–Armitage test was used to examine whether the incidence of thromboembolism was reduced in a dose-dependent fashion and to explore the relation between the incidence of VTE across groups. A Dunnett test was performed to test differences in the incidence of thromboembolism between the placebo and enoxaparin 20 mg qd/enoxaparin 40 mg qd groups. Fisher's exact test was performed to confirm statistically significant differences between the placebo and enoxaparin 20 mg bid groups.

Major and minor bleeding categories were analyzed combined, as any bleeding event, and separately; pairwise comparisons of the incidence of bleeding events were made using the χ^2 test. Each bleeding event was identified as bleeding from surgical or other sites.

Results

Patient disposition and analysis populations

A total of 407 THA and 364 TKA patients were randomized and received one or more doses of the study medication (safety population), among whom 337 and 315 patients, respectively, were included in the mITT population for each study (Fig. 2). The most common reason for withdrawal from the mITT population was a missing or defective evaluation of VTE imaging test data (due to protocol violations during their assessment).

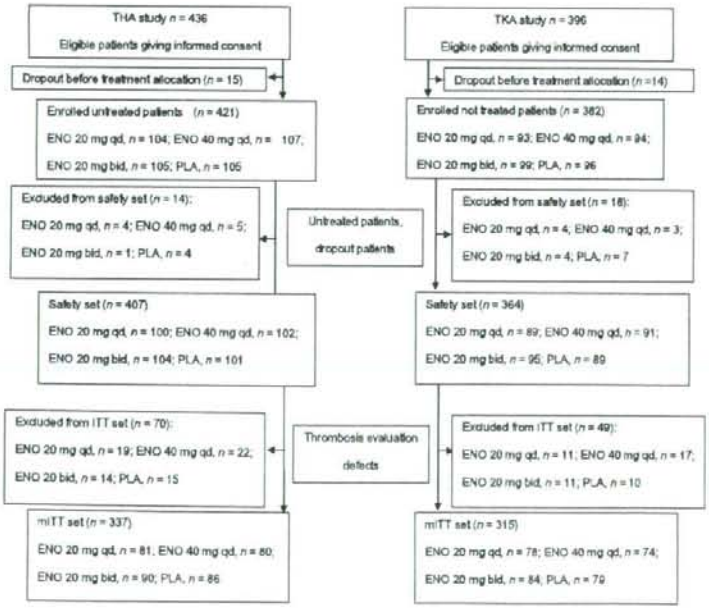

Fig. 2. Disposition of Japanese patients in two studies comparing three enoxaparin dosage regimens versus placebo as thromboprophylaxis for total hip or knee arthroplasty. *bid*, twice daily; *ENO*, enoxaparin; *ITT*, intention to treat; *mITT*, modified intention to treat; *PLA*, placebo; *qd*, once daily; *THA*, total hip arthroplasty; *TKA*, total knee arthroplasty

Table 1. Baseline demographics and clinical characteristics of the intention-to-treat population who underwent primary total hip arthroplasty

Characteristic	Placebo ($n = 86$)	Enoxaparin 20 mg qd ($n = 81$)	Enoxaparin 40 mg qd ($n = 80$)	Enoxaparin 20 mg bid ($n = 90$)
Female (no.)	75 (87.2%)	71 (87.7%)	74 (92.5%)	75 (83.3%)
Age (years), mean (SD)	62.0 (10.3)	63.3 (10.4)	60.6 (9.9)	63.0 (9.3)
Height (cm), mean (SD)	152.5 (7.9)	150.9 (7.6)	151.8 (6.6)	151.3 (7.3)
Weight (kg), mean (SD)	56.0 (10.0)	53.6 (9.3)	54.2 (9.8)	54.3 (9.4)
BMI (kg/m^2), mean (SD)	24.0 (3.4)	23.5 (3.4)	23.5 (3.7)	23.7 (3.6)
BMI > 25 kg/m^2 (no.)	34 (39.5%)	23 (28.4%)	26 (32.5%)	31 (34.4%)
Systolic BP (mmHg), mean (SD)	127.6 (17.2)	126.1 (16.4)	125.9 (17.5)	128.1 (16.2)
Orthopedic disease (no.)				
Osteoarthritis	76 (88.4%)	67 (82.7%)	66 (82.5%)	75 (83.3%)
Rheumatoid arthritis	2 (2.3%)	6 (7.4%)	5 (6.3%)	7 (7.8%)
Osteonecrosis	3 (3.5%)	3 (3.7%)	4 (5.0%)	2 (2.2%)
Other	5 (5.8%)	5 (6.2%)	5 (6.3%)	6 (6.7%)
History of smoking (no.)	14 (16.3%)	12 (14.8%)	10 (12.5%)	16 (17.8%)
Previous major disease/complications/surgery (no.)	7 (8.1%)	1 (1.2%)	3 (3.8%)	12 (13.3%)
Previous minor disease/complications/surgery (no.)	85 (98.8%)	81 (100%)	77 (96.3%)	86 (95.6%)
Use of cement (no.)	35 (40.7%)	32 (39.5%)	35 (43.8%)	42 (46.7%)
Type of anesthesia (no.)				
Regional	0	0	0	0
General	14 (16.3%)	14 (17.3%)	13 (16.3%)	19 (21.1%)
Both	72 (83.7%)	67 (82.7%)	67 (83.8%)	71 (78.9%)
Duration of surgery (h), mean (SD)	2.15 (0.78)	2.17 (0.64)	2.06 (0.65)	2.05 (0.66)

BP, blood pressure; bid, twice daily; BMI, body mass index; qd, once daily

Patient population: demographics and baseline medical characteristics

Patients in all treatment arms in each study had similar demographic characteristics, clinical diagnoses, disease etiologies, and disease histories except with regard to body weight in the TKA study (Tables 1, 2). The only exception was the TKA study in which patients in the enoxaparin 20 mg bid group had the highest mean weight ($P = 0.010$) (Table 1). Although osteoarthritis was the most common reason for joint arthroplasty in both studies, it affected more patients requiring THA than TKA (84% vs. 68%, respectively). Rheumatoid arthritis was the second most common reason for joint arthroplasty, affecting approximately one-third of patients in the TKA group. Fewer than 15% of patients in both studies had a history of tobacco use. Physical DVT prophylaxis with compression stockings or bandages was used by 53.7% of patients in THA study and 64.4% in the TKA study.

Clinical outcomes

THA study

The incidence of the primary efficacy endpoint (VTE objectively confirmed within 72 h of completing or discontinuing treatment) in the mITT population was 41.9% in the placebo group, 25.9% in the enoxaparin 20 mg qd group ($P = 0.022$, Dunnett test), 33.8% in the enoxaparin 40 mg qd group ($P = 0.188$, Dunnett test), and 20.0% in the enoxaparin 20 mg bid group ($P = 0.001$, Fisher's exact test) (Fig. 3, Table 3). There was no enoxaparin dose–response relation for the incidence of VTE ($P = 0.112$, Cochran–Armitage test).

One patient in the THA study treated with enoxaparin 40 mg qd had both DVT (confirmed by venography) and symptomatic PE (incidence 1.2%). At the 90-day follow-up visit, no additional episodes of VTE were reported. No episodes of PE occurred in the placebo, enoxaparin 20 qd, or enoxaparin 20 mg bid groups. Proximal DVT occurred in 10.4% of patients treated with placebo versus 3.7%, 7.5%, and 3.3% in the enoxaparin 20 mg qd, 40 mg qd, and 20 mg bid groups, respectively.

TKA study

The incidence of VTE was 60.8% in the placebo group, 44.9% in the enoxaparin 20 mg qd group, 35.1% in the enoxaparin 40 mg qd group, and 29.8% in the enoxaparin 20 mg bid group (Table 3, Fig. 3). The incidence of VTE was significantly lower, compared with the placebo group, in the enoxaparin 40 mg qd ($P = 0.001$, Dunnett test) and 20 mg bid groups ($P = 0.001$, Fisher's exact test) but not in the enoxaparin 20 mg qd ($P = 0.039$, Dunnett test; $P < 0.025$ was required for significance). Enoxaparin 20 mg bid was not inferior to enoxaparin 40 mg qd based on the 95% confidence interval (CI) of

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)

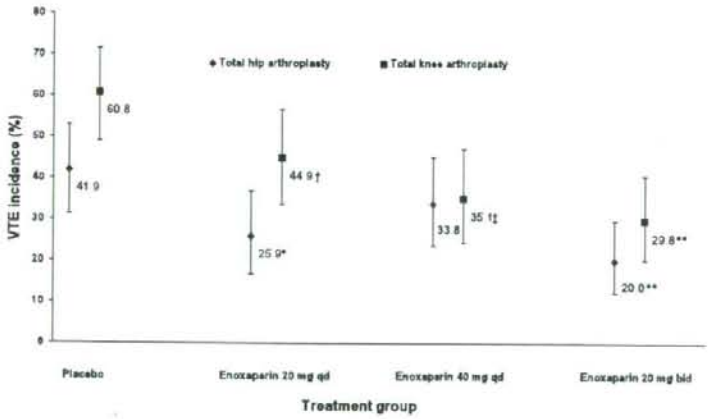

Fig. 3. Incidence (95% confidence intervals) of venous thromboembolism (*VTE*) in all groups. *P = 0.022, placebo vs. enoxaparin 20 mg qd (Dunnett test); **P = 0.001, placebo vs. enoxaparin 20 mg bid (Fisher's exact test); †P = 0.039, placebo vs. enoxaparin 20 mg qd (Dunnett test); ‡P = 0.001, placebo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

Takeshi Fuji · Satoru Fujita · Takahiro Ochi

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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.

T. Fuji (✉)
Department of Orthopaedic Surgery, Osaka Koseinenkin Hospital,
4-2-78 Fukushima, Fukushima-ku,
Osaka 553-0003, Japan
e-mail: fuji-th@umin.ac.jp

S. Fujita
Department of Orthopaedic Surgery, Takarazuka Daiichi Hospital,
19-5 Kogetsu-cho, Takarazuka-shi,
Hyogo-ken 665-0832, Japan

T. Ochi
National Hospital Organization Sagamihara National Hospital,
18-1 Sakuradai, Sagamihara-shi,
Kanagawa-ken 228-8522, Japan

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