Circ J 2017; 81: 855–861
doi:10.1253/circj.CJ-16-1012

ORIGINAL ARTICLE
Peripheral Vascular Disease

Short-Term Subcutaneous Fondaparinux and Oral Edoxaban for Acute Venous Thromboembolism

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Background: No studies have compared treatment efficacy between subcutaneous (SC) fondaparinux and oral edoxaban, which are categorized as factor Xa inhibitors, for venous thromboembolism (VTE) in the acute phase, and only a limited number of imaging-based quantitative studies have evaluated treatment.

Methods and Results: In this open-label, randomized study, 50 patients with acute non-massive pulmonary embolism (PE) and/or deep-vein thrombosis (DVT) were assigned to fondaparinux or edoxaban groups. Lower-limb venous ultrasonography (US), and chest computed tomography (CT) were compared before and 7 days after treatment. Thrombus volume in DVT was calculated using quantitative ultrasound thrombosis (QUT) score on US. For evaluation of PE thrombus volume, lung perfused blood volume (PBV) on CT was calculated. The measurements before and after treatment, respectively, were as follows: QUT score: fondaparinux, 8.1±7.3 to 4.1±4.5; edoxaban, 7.7±6.3 to 4.4±4.3, both significant decreases (P=0.001, P<0.001, respectively); lung PBV: fondaparinux, 32.0±7.8 to 32.1±8.2 HU; edoxaban, 34.2±8.6 to 38.5±11.8 HU (P=0.732, P=0.426, respectively). On subjective CT-based evaluation, all pulmonary artery-related filling defects decreased/disappeared after treatment in both groups (P=NS).

Conclusions: Both SC fondaparinux and oral edoxaban are effective in acute VTE. Effects on thrombus regression on imaging-based quantitative measurement did not differ between the 2 drugs.

Key Words: Anticoagulation; Edoxaban; Factor Xa inhibitor; Fondaparinux; Venous thromboembolism

In recent years, the efficacy of initial treatment of acute, non-massive pulmonary embolism (PE)[1,2] or acute lower-limb deep-vein thrombosis (DVT) with fondaparinux has been established,[3,4] instead of the conventional treatment with unfractionated heparin (UFH).

In September 2014, edoxaban, categorized as a factor Xa inhibitor, one of the direct oral anticoagulants (DOAC), was approved in Japan for the treatment and recurrence prevention of venous thromboembolism (VTE),[5] under the expectation that an oral agent would be an effective initial treatment for VTE. All previous large-scale clinical trials of DOAC for VTE had evaluated treatment effects only in the chronic phase.[5–9]

So far, there have been no studies comparing the effects of subcutaneous (SC) fondaparinux monotherapy and DOAC monotherapy as initial treatment of acute non-massive PE and acute DVT in the clinical setting. Therefore, the aim of this study was to investigate the acute effects of 1-week monotherapy with fondaparinux or edoxaban as initial treatment for acute non-massive PE and acute DVT alone.

There have been only a limited number of imaging-based quantitative studies on the effects of medication on VTE. In the present study, we conducted a quantitative evaluation using lower-limb venous ultrasonography (US) and chest computed tomography (CT).[10–12]

Methods

Subjects

The present subjects consisted of 50 patients aged ≥20 years receiving inpatient treatment at Department of Cardiovascular Medicine, Toho University Hospital, Tokyo between February 2015 and September 2016, who were diagnosed with acute non-massive PE and/or acute DVT. These patients were symptomatic or asymptomatic, had elevated D-dimer on blood test during the perioperative periods or during hospitalization, and provided informed consent for study participation. PE was diagnosed on contrast-enhanced chest CT and DVT on lower-limb venous US.

Study Design

In this open-label, prospective study, we randomly assigned subjects to 2 treatment groups: SC fondaparinux or oral

Received October 5, 2016; revised manuscript received January 10, 2017; accepted January 23, 2017; released online February 25, 2017 Time for primary review: 23 days

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ISSN-1346-9843

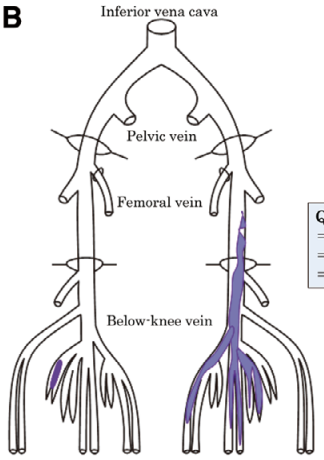
A

	Thrombus site (A)		Thrombus formation (B)		A×B
	Not exist	Exist	Not filling	Filling	
Inferior vena cava thrombosis	0	1	1	2	T1
Pelvic thrombosis	0	1	1	2	T2
Femoral vein thrombosis	0	1	1	2	T3
Below-knee vein thrombosis	0	1	1	2	T4

(When there are multiple below-knee vein thromboses, each is evaluated; i.e., T5 and thereafter are additionally described.)

QUT score = T1 + T2 + T3 + T4 (+ T5 and so on)

B



QUT score
= T1 + T2 + T3 + T4 (+ T5 and so on)
= (0) + (0) + (1×1) + (1×1) + (1×1) + (1×2) + (1×2) + (1×2) + (1×1) + (1×2)
= 12

Figure 1. (**A**) Calculation of quantitative ultrasound thrombosis (QUT) score. (**B**) Schematic illustration of QUT score in the case of bilateral lower-limb deep vein thrombosis.

edoxaban. The subjects did not receive any anticoagulants, such as UFH, before being assigned to the groups. Fondaparinux and edoxaban dose were determined in accordance with the package inserts, according to body weight and estimated creatinine clearance (CrCL) calculated using the Cockcroft-Gault formula.[13] The fondaparinux subjects received a once-daily SC dose depending on body weight (body weight <50 kg, 5 mg; 50–100 kg, 7.5 mg; >100 kg, 10 mg). The edoxaban group received a once-daily oral dose, depending on estimated CrCL and body weight (estimated CrCL ≤50 mL/min, 30 mg; estimated CrCL >50 mL/min, body weight ≤60 kg, 30 mg; >60 kg, 60 mg). After 7 days of treatment with either drug, the subjects underwent blood test, lower-limb venous US, and chest CT, and the results before and 7 days after treatment were compared.

Patients who met any of the following criteria were excluded from the study: receiving other anti-thrombotic drugs or the P-glycoprotein inhibitors quinidine, verapamil, erythromycin, or cyclosporine; estimated CrCL <30 mL/min; sub-massive, massive, or collapse-type PE according to the clinical severity classification;[1,2] indwelling inferior vena cava filter; medical history of hypersensitivity to any of the ingredients of fondaparinux or edoxaban; intracranial hemorrhage, retroperitoneal hemorrhage, or bleeding in other vital organs; acute bacterial endocarditis; hepatic disorders accompanied by coagulopathy; pregnancy, either established or possible; and judgement of inappropriate for study participation by the responsible doctors.

The primary endpoint of this study was the efficacy of initial treatment of acute, non-massive PE and/or DVT with fondaparinux or edoxaban. The efficacy was evaluated on CT for PE, and on US for DVT.

Subjects were treated in accordance with the Declaration of Helsinki and provided informed consent before study participation. The study protocol was approved by the Ethics Committee of Toho University Omori Hospital, Japan (application number 27-191).

Blood Sampling

Serum creatinine and plasma D-dimer were measured.

US

All patients underwent US with an Aplio™ 500 (Toshiba Medical Systems, Tochigi, Japan) with linear probe. By observing the inferior vena cava and its peripheral regions on compression US (CUS),[14] the site of venous thrombosis and whether it was the venous filling type or not were identified, and the DVT thrombus volume calculated (**Figure 1**), using the quantitative ultrasound thrombosis (QUT) score,[15] according to the scoring system developed in-house.

CT

All patients were examined with a dual-source CT scanner (Somatom Definition Flash; Siemens Healthcare, Forchheim,

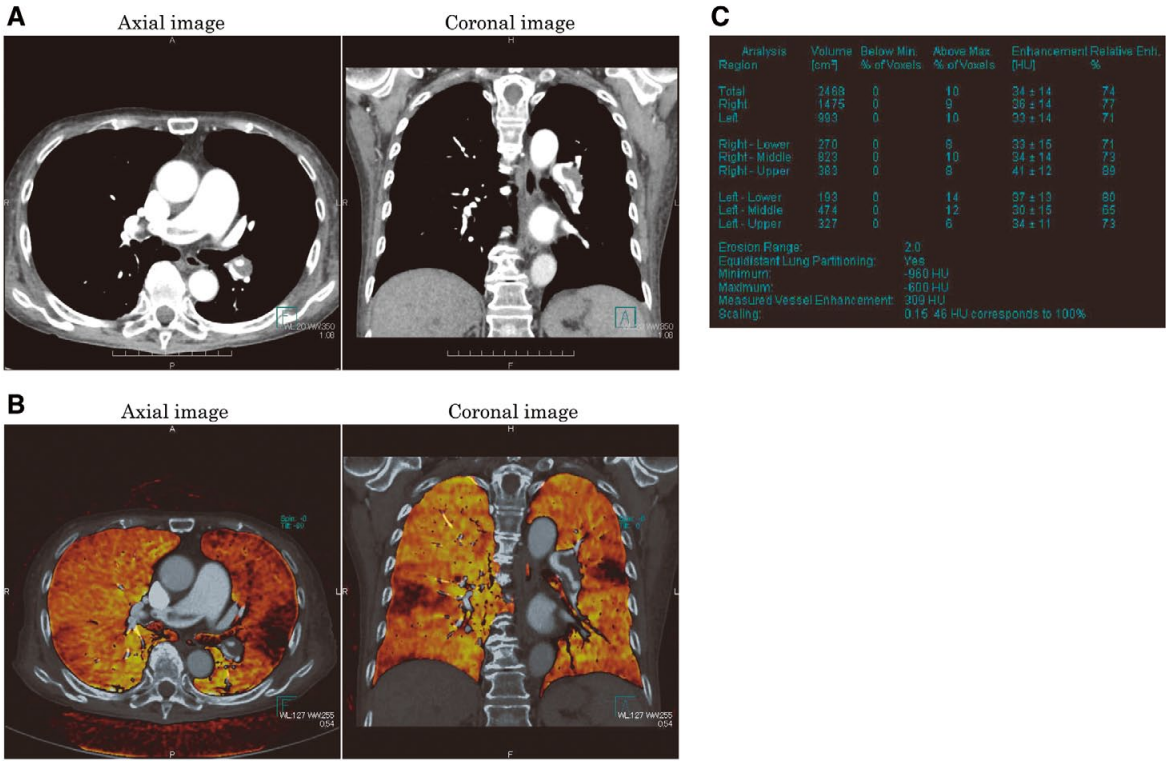


Figure 2. Lung perfused blood volume (PBV) calculation in a patient with bilateral central pulmonary embolism. (**A**) General view (axial image and coronal image). (**B**) Fusion with iodine distribution maps (axial image and coronal image). (**C**) Perfused blood volume (PBV) analysis (screen shot from the automated analysis).

Germany) in dual-energy mode. CT parameters were as follows: 64×0.6-mm collimation; 80 and 140 kV at 280 and 119 effective mAs; and 0.28-s rotation time. Images were acquired in a single breath-hold from the lung apex to the costophrenic angles. Imaging was carried out in the caudocranial direction so that the chaser bolus was being injected by the time that the scanner reached the upper chest to avoid streak artifacts because of contrast material in the subclavian vein or the superior vena cava.

The examinations were performed using an adapted contrast injection protocol aimed at displaying both angiograms of the pulmonary arteries and parenchymal iodine distribution. In all patients, a fixed dose of contrast medium was given using a dual-phase approach. Injection was carried out through a 20-G cannula in the antecubital vein. The usual practice is to inject a standard dose of 70 mL of high-concentration iodine-based contrast material, that is, iopamidol (Oypalomin 370; Konica Minolta, Tokyo, Japan) at a flow rate of 4 mL/s followed by a 30-mL saline chaser bolus at a flow rate of 5 mL/s. Early phase CT acquisition was started using a bolus tracking technique with a threshold of 50 Hounsfield units (HU) in the pulmonary trunk and an additional delay of 6 s; late phase acquisition was started 60 s from the start of injection.

CT Data Analysis

Color-coded iodine distribution maps were generated using the lung perfused blood volume (PBV) application of the workstation software according to the 3-material decomposition method (Syngo MMWP DE Lung PBV; Siemens Healthcare; **Figure 2**).

The lung parenchyma was color-coded with 16-bit color coding with different optimal color scales available depending on user performance. A color-coded iodine image was used for perfusion imaging. Lung PBV was calculated automatically in HU. For the automated quantification of pulmonary PBV, the software measures the enhancement in the reference vessel such as the pulmonary trunk. In the standard setting, a 15% enhancement of the reference vessel is defined as 100% enhancement of the pulmonary parenchyma (%PBV). The software then displays pulmonary parenchymal enhancement relative to this reference vessel for the entire pulmonary parenchyma, the right and left lungs separately, as well as the lower, middle, and upper zones of each lung separately. Contrast-enhanced chest CT data underwent not only quantitative evaluation but also qualitative evaluation according to visual interpretation by 2 independent radiologists. In cases of discrepancy, they reviewed the dataset to reach a consensus.

Bleeding

Major bleeding was defined as follows: (1) fatal bleeding; (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or i.m. bleeding with compartment syndrome; and (3) bleeding causing a fall in the hemoglobin requiring a transfusion of ≥2 units whole blood or red cells, in accordance with the International

Table 1. VTE Patient Clinical Characteristics

	Total			PE			DVT		
	Fondaparinux group	Edoxaban group	P value	Fondaparinux group	Edoxaban group	P value	Fondaparinux group	Edoxaban group	P value
No. patients	25	25		11	6		14	19	
Age (years)	72±13	67±17	0.242	69±13	60±17	0.227	74±13	69±17	0.371
Sex (M/F)	11/14	9/16	0.573	5/6	3/3	0.868	6/8	6/13	0.521
Body weight (kg)	54±13	55±16	0.806	56±17	64±22	0.428	53±10	52±13	0.938
Serum creatinine (mg/dL)	0.63±0.22	0.65±0.16	0.647	0.67±0.27	0.58±0.16	0.479	0.59±0.18	0.67±0.17	0.187
Estimated creatinine clearance (mL/min)	78±30	87±48	0.435	79±26	122±68	0.183	78±33	76±34	0.863
Qualifying diagnosis									
DVT	14	19	0.141	0	0		14	19	0.141
PE	1	0	0.327	1	0	0.327	0	0	
PE with DVT	10	6	0.234	10	6	0.234	0	0	
PESI score	101.8±12.0	96.7±19.8	0.512	101.8±12.0	96.7±19.8	0.512			
Simplified PESI score	1.09±0.30	1.00±0.63	0.690	1.09±0.30	1.00±0.63	0.690			
IMPROBE bleeding risk score	2.9±1.4	2.6±1.3	0.460	3.2±1.5	2.0±1.1	0.101	2.6±1.3	2.8±1.3	0.704
Symptom									
Leg pain or leg edema	10	12	0.578	5	1	0.232	5	11	0.220
Dyspnea or chest pain	2	0	0.161	2	0	0.167	0	0	
None	14	13	0.782	7	2	0.259	7	11	0.665
Recent surgery or trauma	6	8	0.538	4	1	0.426	2	7	0.141
Active malignant disease	10	10	1.000	5	1	0.232	5	9	0.518
Prior malignant disease	1	0	0.327	1	0	0.478	0	0	
Diabetes mellitus	3	4	0.691	2	1	0.942	1	3	0.468
Previous VTE	0	2	0.161	0	0		0	2	0.163
Thrombophilia	0	0		0	0		0	0	
Protein S deficiency	0	0		0	0		0	0	
Protein C deficiency	0	0		0	0		0	0	
Anti-phospholipid antibody syndrome	0	0		0	0		0	0	
Plasma D-dimer (μg/mL)	8.6±6.0	10.7±10.8	0.419	12.2±6.7	13.2±16.4	0.866	5.8±3.5	9.9±8.7	0.080
QUT score	8.1±7.3	7.7±6.3	0.837	11.5±9.5	13.2±9.5	0.728	5.4±3.6	6.0±3.7	0.690
Lung PBV (HU)	32.0±7.8	34.2±8.6	0.357	30.9±8.6	35.2±10.0	0.380	32.9±7.3	33.9±8.3	0.716
Fondaparinux daily dose 5 mg/7.5 mg/10 mg	9/16/0			4/7/0			5/9/0		
Edoxaban daily dose 30 mg/60 mg		18/7			3/3			15/4	

Data given as n or mean±SD. DVT, deep vein thrombosis; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; PBV, perfused blood volume; PE, pulmonary embolism; PESI, pulmonary embolism severity index; QUT, quantitative ultrasound thrombosis; VTE, venous thromboembolism.

Society on Thrombosis and Haemotosis.[16] Minor bleeding was defined as all unusual clinically overt bleeding episodes reported by an investigator as an adverse event and not considered as major bleeding.[3]

Symptomatic VTE

Symptomatic VTE recurrence was evaluated on contrast-enhanced CT and/or lower-limb venous US when symptoms (i.e., appearance of dyspnea, worsening leg edema, or leg pain) suspected to be associated with recurrent VTE were observed.

Statistical Analysis

All data are expressed as mean±SD. Unpaired t-test was used to compare baseline characteristics between the fondaparinux and edoxaban groups. Paired t-test was used to compare pre-treatment and post-treatment D-dimer, QUT score, and lung PBV. For pulmonary artery filling defects on CT-based visual evaluation, chi-squared test was used to analyze differences between the fondaparinux group and edoxaban group. $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was carried out using SPSS ver. 20.0 (SPSS, Chicago, IL, USA).

Results

Baseline Characteristics

The VTE patient clinical characteristics are listed in **Table 1**. There were no differences between the 2 groups in age, sex, body weight, serum creatinine, estimated CrCL, qualifying diagnosis, presence or absence of symptoms, recent surgery or trauma, active malignant disease, prior malignant disease, diabetes mellitus, previous VTE, thrombophilia,

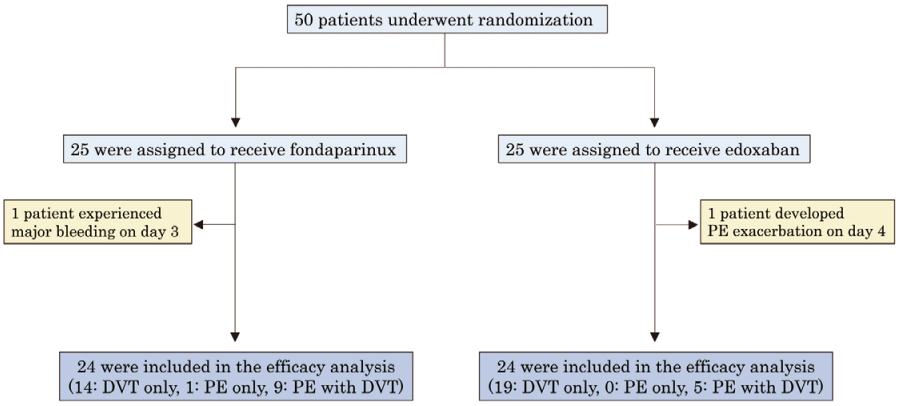


Figure 3. Patient enrollment and outcomes. DVT, deep-vein thrombosis; PE, pulmonary embolism.

Table 2. Bleeding Events and Recurrent VTE in Treatment Period

	Fondaparinux group	Edoxaban group	P value
Bleeding			
Major bleeding	1 (gastrointestinal hemorrhage)	0	0.327
Minor bleeding	0	0	
Any bleeding	1	0	0.327
Symptomatic VTE			
PE only	0	1 (massive PE)	0.327
DVT only	0	0	
Fatal VTE	0	0	
Asymptomatic VTE			
PE only	0	0	
DVT only	0	0	

Data given as n. Abbreviations as in Table 1.

protein S deficiency, protein C deficiency, or antiphospholipid antibody syndrome, PE severity index (PESI),[17] simplified PESI,[18] International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) bleeding risk score,[19] plasma D-dimer, QUT score on US, or lung PBV on CT. Fondaparinux and edoxaban daily dose used are also listed in **Table 1**.

The final efficacy analysis consisted of 48 patients of the 50 enrolled who could complete the 7-day treatment with either active drug (**Figure 3**); 1 patient in the fondaparinux group discontinued treatment on day 3 because of gastrointestinal hemorrhage, and 1 in the edoxaban group discontinued treatment on day 4 because of PE exacerbation (**Table 2**).

Blood Data

Post-treatment changes in plasma D-dimer are shown in **Figure 4**. Statistically significant decreases in D-dimer were observed after treatment in both the fondaparinux and edoxaban groups (P<0.001, P=0.001, respectively): 8.6±6.0 to 3.4±2.4 μg/mL, and 10.7±10.8 to 4.9±5.4 μg/mL, respectively.

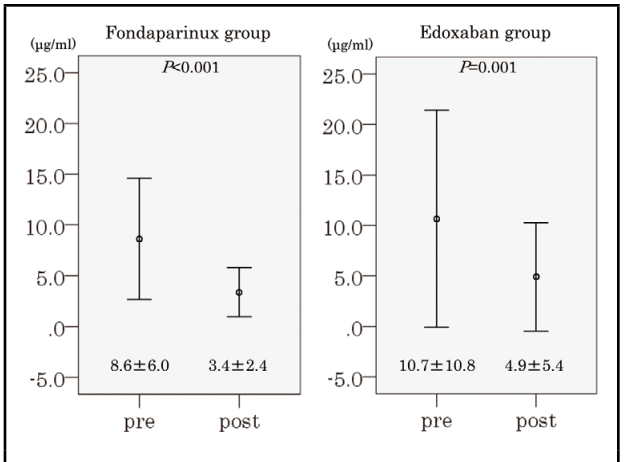


Figure 4. Plasma D-dimer level. A statistically significant decrease was observed after treatment in both the fondaparinux and edoxaban groups.

QUT Score

Post-treatment changes in QUT score, which represents US-based quantitative evaluation of DVT thrombus volume, are shown in **Figure 5**. Statistically significant decreases in QUT score were observed after treatment in

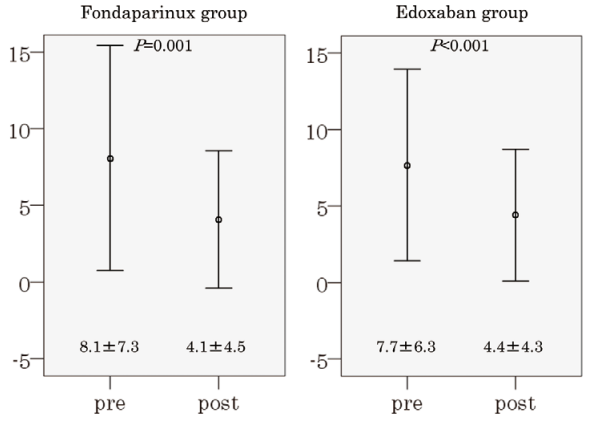


Figure 5. Quantitative ultrasound thrombosis score in patients with deep vein thrombosis. A statistically significant decrease was observed after treatment in both the fondaparinux and edoxaban groups.

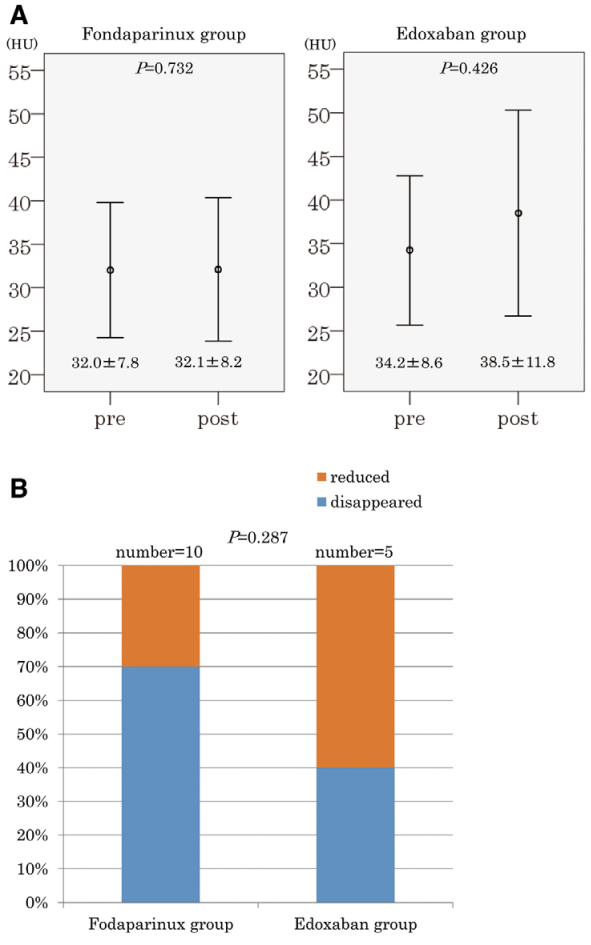


Figure 6. (**A**) Lung perfused blood volume (PBV) and (**B**) visual analysis based on post-treatment contrast-enhanced chest computed tomography (CT) in patients with pulmonary embolism. (**A**) No statistically significant differences were observed between pre-treatment and post-treatment lung PBV, in both the fondaparinux and edoxaban groups, despite slight increases. (**B**) Pulmonary artery filling defects decreased or disappeared in both groups.

both the fondaparinux and edoxaban groups (P=0.001, P<0.001, respectively): 8.1±7.3 to 4.1±4.5, and 7.7±6.3 to 4.4±4.3, respectively.

Lung PBV

Lung PBV, which reflects CT-based quantitative evaluation of PE thrombus volume, is shown in **Figure 6**. No statistically significant differences were observed between the pre-treatment and post-treatment lung PBV levels, in both the fondaparinux and edoxaban groups, despite slight increases (P=0.732, P=0.426, respectively): 32.0±7.8 HU to 32.1±8.2, and 34.2±8.6 to 38.5±11.8 HU, respectively.

Qualitative Contrast-Enhanced Chest CT

On visual qualitative evaluation of pulmonary artery filling defects on contrast-enhanced chest CT, the filling defects had decreased or disappeared in both groups after treatment (**Figure 6**). There were no statistically significant differences in such effects between the 2 groups.

Bleeding Events

In the fondaparinux group, 1 patient had major bleeding due to gastrointestinal hemorrhage after 3 days of treatment (**Table 2**). The pre-treatment IMPROVE bleeding risk score of this patient was 3.

Recurrent VTE

Only 1 patient in the edoxaban group developed exacerbation of PE after 4 days of treatment (**Table 2**).

Discussion

Plasma D-dimer and QUT score were significantly reduced after 1 week of treatment compared with before treatment, in both drug groups, confirming the efficacy of the 2 anticoagulants for short-term treatment of DVT.

Nakamura et al previously reported on the short-term efficacy of fondaparinux for the treatment of acute VTE.[3] The present results also support the short-term efficacy of treatment with fondaparinux.

The short-term efficacy of edoxaban monotherapy as initial treatment for acute DVT has also been confirmed. In addition, because no premedication with anticoagulants such as UFH was used in this study, this is the first report to show the short-term efficacy of edoxaban monotherapy starting from the acute phase. In this study, only one patient in the edoxaban group developed exacerbation of PE after 4 days of treatment. This patient, who had DVT complicated by PE, had maintained a pulmonary blood flow with pretreatment lung PBV at 37±17 HU, but had a very large DVT (QUT score=30). This patient was the only one in this study to have a large thrombus volume. It is crucial to more carefully choose treatment options in the case of PE with relatively large DVT thrombus volume, even if the effects on hemodynamics seem to be minimal.

In the fondaparinux group, 1 patient had hematemesis because of gastrointestinal hemorrhage after 3 days of treatment. Emergency upper gastrointestinal endoscopy showed active bleeding from the duodenal papilla of Vater. The underlying disease was terminal pancreatic cancer, with invasion into the common bile duct. Before treating that patient with fondaparinux, approval was obtained from the consulting gastroenterologist for anticoagulants, but this case shows that it is necessary to be even more careful to determine whether or not anticoagulants should

be used in the case of terminal malignant disease.

In this study, we used a novel method of evaluating DVT thrombus volume. The QUT score system uses CUS test, a standard test method for DVT, and is considered highly useful for evaluation of thrombus volume because of its ease of use and highly objective, quantified results.

Although no statistically significant differences were observed between the pre-treatment and post-treatment lung PBV in PE, on visual qualitative evaluation the PE decreased or disappeared in all patients in both groups. This suggests that there may be limitations in lung PBV evaluation of pulmonary blood flow in mild cases of non-massive PE.

Also, one study has reported that there were no significant differences in lung PBV between mild PE and no PE.[20] This seems to support the limitations of lung PBV-based quantitative evaluation of mild PE used in the present study. The reasons for the absence of statistically significant differences between the pre-treatment and post-treatment lung PBV in the present PE patients are as follows. First, comparison of pre-treatment and post-treatment lung PBV can be inaccurate even in the same patient, because pulmonary artery contrast timing may vary, depending on cardiac function and heart rate at the time of testing. Furthermore, %PBV can change, depending on how the region of interest in the pulmonary artery trunk is defined.

This study examined patients with DVT alone and those with non-massive PE, the groups most likely to be encountered in actual clinical practice. The study analyzed, using a highly objective, quantitative evaluation method, the effects of initial monotherapy with SC fondaparinux and oral edoxaban on thrombus regression.

Study Limitations

This study was conducted in a single center with a relatively small number of patients; therefore, the results should be interpreted with caution. PBV is considered highly useful as a quantitative method of PE evaluation, because it may eliminate the need for pulmonary blood flow scintigraphy, but further development in data collection and analysis is required.

Conclusions

One-week monotherapy with SC fondaparinux or oral edoxaban is effective for inpatient treatment of acute non-massive PE or acute DVT alone. The 2 drugs had similar regressive effects on thrombus volume.

Acknowledgments

This manuscript was supported in part by Grants-in-Aid (24591074 and 15K09103 to T.I.) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Disclosures

T.I. has received grant support through his institution from Bristol-Myers Squibb and Daiichi Sankyo; and honoraria for lectures from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Tanabe-Mitsubishi, and Ono Pharmaceutical. The other authors declare no conflicts of interest.

References

1. JCS Joint Working Group. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009): Digest version. *Circ J* 2011; **75:** 1258–1281.
2. Task Force on Pulmonary Embolism, European Society of Cardiology. Guidelines on diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2000; **21:** 1301–1336.
3. Nakamura M, Okano Y, Minamiguchi H, Munemasa M, Sonoda M, Yamada N, et al. Multidetector-row computed tomography-based clinical assessment of treatment of acute pulmonary embolism and acute deep vein thrombosis in Japanese patients. *Circ J* 2011; **75:** 1424–1432.
4. Mastroiacovo D, Sala G, Dentali F. The safety of fondaparinux sodium for the treatment of venous thromboembolism. *Expert Opin Drug Saf* 2016; **15:** 1259–1265.
5. Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; **369:** 1406–1415.
6. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363:** 2499–2510.
7. EINSTEIN-PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366:** 1287–1297.
8. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014; **129:** 764–772.
9. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; **369:** 799–808.
10. Sueyoshi E, Tsutsui S, Hayashida T, Ashizawa K, Sakamoto I, Uetani M. Quantification of lung perfusion blood volume (lung PBV) by dual-energy CT in patients with and without pulmonary embolism: Preliminary results. *Eur J Radiol* 2011; **80:** e505–e509.
11. Nagayama H, Sueyoshi E, Hayashi T, Ashizawa K, Sakamoto I, Uetani M. Quantification of lung blood volume (lung PBV) by dual-energy CT in pulmonary embolism before and after treatment: Preliminary results. *Clin Imaging* 2013; **37:** 493–497.
12. Meinel FG, Graef A, Bamberg F, Thieme SF, Schwarz F, Sommer WH, et al. Effectiveness of automated quantification of pulmonary perfused blood volume using dual-energy CTPA for the severity assessment of acute pulmonary embolism. *Invest Radiol* 2013; **48:** 563–569.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16:** 31–41.
14. Dauzat M, Laroche JP, Deklunder G, Ayoub J, Quére I, Lopez FM, et al. Diagnosis of acute lower limb deep venous thrombosis with ultrasound: Trends and controversies. *J Clin Ultrasound* 1997; **25:** 343–358.
15. Kabuki T, Nakanishi R, Hisatake S, Fujii T, Dobashi S, Wakakura S, et al. A treatment strategy using subcutaneous fondaparinux followed by oral rivaroxaban is effective for treating acute venous thromboembolism. *J Cardiol*, doi:10.1016/j.jjcc.2016.10.013.
16. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* 2010; **8:** 202–204.
17. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005; **172:** 1041–1046.
18. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010; **170:** 1383–1389.
19. Hostler DC, Marx ES, Moores LK, Petteys SK, Hostler JM, Mitchell JD, et al. Validation of the International Medical Prevention Registry on venous thromboembolism bleeding risk score. *Chest* 2016; **149:** 372–379.
20. Sakamoto A, Sakamoto I, Nagayama H, Koike H, Sueyoshi E, Uetani M. Quantification of lung perfusion blood volume with dual-energy CT: Assessment of the severity of acute pulmonary thromboembolism. *AJR* 2014; **203:** 287–291.