Comparison of Direct Oral Anticoagulants and Warfarin in the Treatment of Deep Venous Thrombosis in the Chronic Phase

A Large, Single-Center, Observational Study

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Summary

We assessed the efficacy and safety of direct oral anticoagulants (DOACs) for the treatment of deep venous thrombosis (DVT) in the chronic phase through comparison with conventional warfarin therapy.

A total of 807 consecutive patients who were diagnosed with having DVT in the chronic phase were included (484 patients to warfarin therapy and 323 patients to DOAC therapy). The condition of leg veins was assessed 3 to 6 months after starting the therapies by ultrasound examination. Major bleeding and mortality during the therapies were followed-up.

There was no significant difference between the two groups in the thrombosis improvement rate (DOAC group: 91.2% versus warfarin group: 88.9%). There was no significant difference between the two groups in major bleeding (DOAC group: 1.8% versus warfarin group: 1.8%). In patients with active cancer, the DOAC group had a borderline higher thrombosis improvement rate than the warfarin group (92.1% versus 80.0%, $P = 0.05$). The proportion of major bleeding in the patients with active cancer was slightly higher in the warfarin group than in the DOAC group (4.3% versus 2.8%; $P = 0.71$). Active cancer was not an independent risk factor for major bleeding and recurrence in the DOAC group (OR 2.68, 95% CI 0.51-14.1; $P = 0.24$ and OR 0.65, 95% CI 0.20-2.07; $P = 0.47$).

In treatment using oral anticoagulants for DVT in the chronic phase, DOACs exhibited equal efficacy and safety as warfarin did. Particularly DOACs appear to be an attractive therapeutic option for cancer-associated DVT in chronic phase, with relatively low anticipated rates of recurrence and major bleeding.

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The number of cases of deep vein thrombosis (DVT) is increasing in Japan, as well as other countries, because of the aging population, westernized diets, and advanced diagnostic technology.^{1,2)} For the treatment of DVT, warfarin therapy was highly effective.^{3,4)} However, warfarin administration in the chronic phase has many disadvantages, such as food and drug interactions, varying responses among individuals, regular monitoring of the international normalized ratio (INR), and maintaining the INR within the therapeutic range of 1.5-2.5.^{5,6)} Thus, warfarin therapy for DVT in the chronic phase is a burden for patients and is very costly.

Recently, direct oral anticoagulants (DOACs) have been developed because they require no monitoring and have few drug and food interactions. DOACs have been shown to be effective in phase 3 randomized trials for acute and long-term treatment of DVT.⁷⁻¹⁴⁾ However, the qualitative evaluation of the effect and the data of the safety evaluation in the chronic phase in routine clinical

practice are not sufficient.

Patients with active cancer are prone to developing and having recurrent DVT. Low-molecular weight heparin (LMWH) has been more effective and safer than vitamin K antagonists in patients with cancer-related DVT.¹⁵⁻¹⁸⁾ Current guidelines recommend a 6-month course of LMWH as the first line of anticoagulation for cancer patients with DVT.¹⁹⁾ However, LMWH for DVT is not covered by public health insurance in Japan, and, therefore, warfarin has been continued to be used. If we could prove the efficacy and safety of long-term administration of DOACs for cancer-related DVT, DOACs might become used instead of warfarin.

The aim of the present study was to assess the efficacy and safety of DOACs for the treatment of DVT in the chronic phase by comparison with conventional warfarin therapy. Furthermore, the efficacy and safety for cancer-related DVT were assessed.

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Methods

Study population: A total of 807 consecutive patients (male: 184, mean age: 68.1 ± 13.8 years) who were diagnosed with having DVT by ultrasound examinations between January 2009 and December 2014 were included in the present study; 484 patients were assigned to warfarin therapy, and 323 patients were assigned to DOAC therapy in the chronic phase by each physician's decision. We defined the cases, where a thrombosis was remained after the thrombolytic therapy or parenteral anticoagulant therapy in the acute phase and where a thrombosis was remained more than one month, as chronic phase. The DOAC used was apixaban in 36 cases (11.1%), rivaroxaban in 154 cases (47.7%), dabigatran in 104 cases (32.2%), and edoxaban in 29 cases (9.0%). Patients were excluded if they had a high risk of bleeding, active bleeding, or other contraindication to treatment with DOACs or warfarin. The patients were further classified according to whether they had active cancer. Patients with active cancer were defined as those with cancer who were receiving any treatment for cancer, including surgery, radiation, hormonal therapy, chemotherapy, palliative care, or combined modality therapy within the past 6 months.

DOACs and warfarin therapy administration: The initial warfarin dose was determined by the investigator, based on the patient's clinical profile and local practice. The subsequent warfarin doses were adjusted to target an INR of 2.0 (range, 1.5-2.5). The DOAC dosages were determined by each physician's decision, depending on the patient's renal function, age, and body weight. Treatment with DOACs or warfarin was continued for at least 1 month in all patients. The duration was determined by the treating physician on the basis of the patient's clinical features and patient preference.

Diagnosis of DVT or PTE: The study included only acute DVT patients who were diagnosed with DVT for the first time at our institute, chronic DVT patients who had previously been diagnosed with DVT and took some kind of oral anticoagulants were excluded. Overall, 807 DVT cases were given parenteral or oral coagulants for an acute phase, oral anticoagulation was continued in a chronic stage. DVT was diagnosed by venous compression ultrasound, and PTE was diagnosed by spiral computed tomography or lung perfusion scintigraphy.

Surveillance and follow-up: All patients were followed-up in the outpatient clinic 1 to 3 months after the oral medication started, and then further followed-up either in the outpatient clinic or contacted by telephone every 12 months. During these contacts, the patient's treatment, clinical course, and laboratory tests for safety were evaluated. All patients were to have a safety follow-up visit 1 month after the last dose following permanent discontinuation of the study drug.

Study outcomes: The primary efficiency outcome was to assess the efficacy of thrombus regression by leg vein ultrasound after 3 to 6 months. The area of thrombosis was classified into four areas as the "iliac vein area," "femoral vein area," "popliteal vein area," and "calf vein area." Initial leg vein ultrasound was performed at the start of administering warfarin or DOAC. For the cases on whom

was performed thrombolytic therapy or parenteral anticoagulant therapy in the acute phase, the ultrasound as of change to oral anticoagulant was set as baseline. The efficacy of thrombus regression was classified into three groups as "improvement," "deteriorated," and "unchanged" by leg vein ultrasound at follow-up after 3 to 6 months. Reduction of the diameter of the blood thrombosis by more than 50% compared with the baseline was defined as "improvement"; expansion of the blood thrombosis of more than 4 mm in diameter compared with the baseline was defined as "deteriorated," and where none of the above two definitions was applicable, it was defined as "unchanged."

The primary safety outcome was to assess major bleeding, defined as bleeding associated with a decrease in hemoglobin ≥ 2.0 g/dL, blood transfusion of 2 or more units, or hemorrhage that was intracranial, spinal cord, intraocular, pericardium, intra-articular, intramuscular (accompanied by compartment syndrome), retroperitoneal, or lethal.²⁰ The predefined secondary safety outcome was death from any cause, or death related to venous thromboembolism plus major bleeding. Early mortality was defined as death within 3 months after the index event.

Statistical analysis: Continuous variables are expressed as means $\pm$ standard deviation, medians (quartile: 25%-75%), or numbers (%). Comparisons between groups were analyzed by univariate analyses (unpaired *t*-test, Fisher's exact test, or the Mann-Whitney test) and multivariate analysis using a logistic regression analysis.

The relationships of the administration of DOACs or warfarin therapy and the major bleeding complication rate were analyzed using the Kaplan-Meier method, and the curves were compared using the log-rank test. A *P* value < 0.05 (2-tailed) was considered to indicate significance. All statistical analyses were performed using R commander software (ver. 1.24).²¹

Ethical considerations: This study was approved by our institutional review board (number 27-247). All patients provided informed consent for the study protocol that was approved by the institutional review board.

Results

Patients' characteristics: The characteristics of the two study treatment groups are shown in Table I. The ratio of males was lower than of females in both groups; it was significantly lower in the warfarin group. The proportion of renal impairment was slightly higher in the warfarin group compared with the DOAC group. There were no significant differences in age and mean body mass index between the groups. There were no significant differences in hemoglobin, platelets, and the fibrinolytic system before treatment. There was more left leg thrombosis than right leg thrombosis in both groups. In addition, many thromboses were confined to the calf vein site, while the distribution of others was almost the same. Thrombus on both sides of the lower limb was seen in 39.0% of the DOAC group and 39.0% of the warfarin group. Pulmonary embolism was seen in 30.2% of the DOAC group and 30.3% of the warfarin group. Approximately 80% were non-massive PTEs in both groups.

Table I. Patient and Clinical Characteristics

	Overall (n = 807)	DOACs (n = 323)	Warfarin (n = 484)	P value
Age (years)	69.4 ± 13.6	69.8 ± 12.7	69.4 ± 14.2	0.75
Age group, years				
< 75 (%)	476 (58.9)	206 (63.8)	270 (55.8)	0.090
≥ 75 (%)	237 (29.3)	123 (38.1)	214 (44.2)	0.090
Male (%)	184 (22.8)	103 (31.9)	81 (16.7)	< 0.05
Weight (kg)	56.7 ± 13.2	57.5 ± 14.5	56.2 ± 12.1	0.20
< 50 (%)	245 (30.6)	95 (29.4)	150 (31.0)	0.27
≥ 50 (%)	568 (70.4)	234 (72.4)	334 (69.0)	0.27
Height (m)	1.55 ± 0.10	1.56 ± 0.10	1.54 ± 0.09	0.68
BMI (kg/m ²)	23.6 ± 4.62	23.4 ± 4.96	23.8 ± 4.37	0.35
BUN (mg/dL)	16.9 ± 11.0	15.4 ± 6.4	17.8 ± 13.1	< 0.05
S-Cr (mg/dL)	0.84 ± 0.87	0.72 ± 0.24	0.91 ± 1.06	< 0.05
CrCl (mL/minute)	71.5 ± 28.4	75.4 ± 28.5	68.8 ± 27.9	< 0.05
< 60 (%)	251 (31.1)	92 (28.5)	159 (32.6)	0.061
≥ 60 (%)	562 (69.6)	237 (73.4)	325 (67.4)	0.061
Hemoglobin (g/dL)	11.2 ± 1.9	11.2 ± 2.1	11.2 ± 1.8	0.79
Platelets (10 ³ /μL)	238 ± 101	247 ± 107	230 ± 94	0.56
PT-INR (%)	1.18 ± 0.39	1.12 ± 0.32	1.20 ± 0.46	< 0.05
APTT (seconds)	33.26 ± 17.7	30.83 ± 9.17	34.79 ± 21.35	< 0.05
D-dimer (ng/mL)	16.32 ± 23.48	15.11 ± 15.91	17.16 ± 27.52	0.23
FDP (ng/mL)	28.56 ± 43.21	26.46 ± 27.89	29.95 ± 50.93	0.30
Right limb (%)	496 (61.5)	198 (61.3)	298 (61.6)	0.71
Iliac vein (%)	55 (6.8)	19 (5.9)	36 (7.4)	0.39
Femoral vein (%)	100 (12.4)	30 (9.2)	70 (14.5)	< 0.05
Popliteal vein (%)	124 (15.4)	47 (14.6)	77 (15.9)	0.55
Calf vein (%)	442 (54.8)	177 (54.8)	265 (54.8)	0.83
Left limb (%)	615 (76.2)	250 (77.4)	365 (75.4)	0.87
Iliac vein (%)	73 (9.0)	28 (8.7)	45 (9.3)	0.95
Femoral vein (%)	124 (15.4)	38 (11.8)	86 (17.8)	< 0.05
Popliteal vein (%)	145 (18.0)	52 (16.1)	93 (19.2)	0.94
Calf vein (%)	552 (68.4)	237 (73.4)	315 (65.1)	< 0.05
Both limbs (%)	315 (39.0)	126 (39.0)	189 (39.0)	0.38
Inferior vena cava (%)	26 (3.2)	5 (1.5)	21 (4.3)	< 0.05
Pulmonary embolism (%)	244 (30.2)	98 (30.3)	146 (30.2)	0.53
Non-massive (%)	188/244 (77.0)	79/98 (80.6)	109/146 (74.7)	0.54
Sub-massive (%)	40/244 (16.4)	13/98 (13.3)	27/146 (18.5)	0.30
Massive (%)	16/244 (6.6)	6/98 (6.1)	10/146 (6.8)	0.87
IVC filter (%)	53 (6.6)	9 (2.8)	44 (9.1)	< 0.05
Follow-up period (days)	287 ± 126	256 ± 134	301 ± 119	0.094
Oral administration period (days)	198 ± 152	187 ± 144	206 ± 157	0.12

Data are expressed as means ± SD or numbers (%). P values were determined by an unpaired *t*-test, Fisher's exact test, or Mann-Whitney test. BMI indicates body mass index; S-Cr, serum creatinine; CrCl, Creatinine clearance; INR, international normalized ratio; APTT, activated partial thromboplastin time; and IVC, inferior vena cava.

The risk factors for DVT are shown in Table II. We defined the disease, medication, and medical practice that cause venous reflux disorder or coagulation disorder as risk factors of DVT.

The proportion of subjects with active cancer was higher in the DOAC group (33.4%) than in the warfarin group (19.2%). The common sites in patients with active cancer in the DOAC group were lung (15.7%), uterus (13.8%), blood (12.0%), ovary (10.1%), colon (10.1%), urinary tract (9.2%), stomach (2.7%), and other cancers (25.9%); in the warfarin group, they were lung (17.2%), ovary (17.2%), colon (11.8%), blood (11.8%), uterus (8.6%), urinary tract (7.5%), stomach (3.2%), and other cancers (21.5%). A history of recent surgery (within 3 months) was reported in 39.6% of cases in the DOAC

group and 30.8% of cases in the warfarin group. The ratios of autoimmune disorder patients and oral steroid-taking patients were significantly higher in the warfarin group than in the DOAC group.

The acute and chronic phases of DVT management are shown in Table III. There were no differences in the rates of use of urokinase between the DOAC group (2.4%) and the warfarin group (5.0%) and of t-PA between the DOAC group (0.6%) and the warfarin group (0.6%). The rate of use of unfractionated heparin was significantly higher in the warfarin group (59.8%) than in the DOAC group (16.8%), while the rate of use of fondaparinux was significantly higher in the DOAC group (39.0%) than in the warfarin group (3.9%). Among patients who underwent UHF therapy, 39.3% of patients in

Table II. Risk Factors for DVT

	Overall (n = 807)	DOACs (n = 323)	Warfarin (n = 484)	P value
Active cancer (%)	202 (25.0)	108 (33.4)	94 (19.2)	< 0.05
Recent surgery (within 3 months) (%)	277 (34.3)	128 (39.6)	149 (30.8)	< 0.05
Autoimmune disorder (%)	69 (8.6)	16 (5.0)	53 (11)	< 0.05
Mental disorder (%)	59 (7.3)	32 (9.9)	27 (5.6)	< 0.05
Gynecological disorder (%)	68 (8.4)	29 (9.0)	39 (8.1)	0.70
Orthopedic disorder (%)	183 (22.7)	76 (23.5)	107 (22.1)	0.79
Immobilization (%)	55 (6.8)	24 (7.4)	31 (6.4)	0.67
Thrombophilia (%)	17 (2.1)	4 (1.2)	13 (2.7)	0.21
Central venous catheter (%)	10 (1.2)	4 (1.2)	6 (1.2)	1
Taking steroid (%)	93 (11.5)	27 (8.4)	64 (13.2)	< 0.05
Taking oral contraceptives (%)	7 (0.9)	1 (0.3)	6 (1.2)	0.25
Economy class syndrome (%)	6 (0.7)	0 (0)	6 (1.2)	0.086

Data are expressed as n (%). P values were determined by an unpaired t-test or Fisher's exact test.

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

	Overall (n = 807)	DOACs (n = 323)	Warfarin (n = 484)
Thrombolytic			
Urokinase (%)	32 (3.9)	8 (2.4)	24 (5.0)
t-PA (%)	23 (2.8)	20 (0.6)	3 (0.6)
Parenteral anticoagulant			
Fondaparinux (%)	149 (18.3)	130 (39.0)	19 (3.9)
UFH (%)	345 (42.4)	56 (16.8)	289 (59.8)
APTT			
< 45 or missing (%)	180/345 (52.2)	32/56 (57.2)	148/289 (51.2)
45-90 (%)	153/345 (44.3)	22/56 (39.3)	131/289 (45.3)
> 90 (%)	12/345 (3.5)	2/56 (3.5)	10/289 (3.5)
Target PT-INR			
< 1.5 or missing (%)	NA	NA	198 (40.9)
1.5-2.5 (%)	NA	NA	208 (43.0)
> 2.5 (%)	NA	NA	78 (16.1)

Data are expressed as n (%). t-PA indicates tissue plasminogen activator; UFH, unfractionated heparin; APTT, activated partial thromboplastin time; INR, international normalized ratio; and NA, no available.

the DOAC group were within the therapeutic range of activated partial thromboplastin time ($1.5 \leq \text{APTT} \leq 3$), compared to 45.3% in the warfarin group. In the warfarin control group, only 43.0% patients were within the therapeutic range of PT INR 1.5-2.5, 16.1% had a PT INR > 2.5, and the rest, 40.9%, did not reach the therapeutic range nor have their levels measured. Moreover, cancer patients in the warfarin control group, 51/94 (54.3%) were within the therapeutic range, 6/94 (6.3%) had exceeded the therapeutic range, and the rest, 37/94 (39.4%), did not reach the therapeutic range.

Outcomes of efficacy: During a mean observational period of 287 days (range, 8-365 days), 69.2% of patients underwent ultrasound follow-up. The average time to the follow-up ultrasound examination was 183 days (range, 38-242 days). Each follow-up period of the DOAC group and the warfarin group was 256 ± 134 days and 301 ± 119 days, respectively, ($P = 0.094$). Each oral administration period of the DOAC group and the warfarin group was 187 ± 144 and 206 ± 157 , respectively, ($P = 0.12$; Table I).

The number of subjects with DVT whose thrombus was considered improved on leg vein ultrasound was 197/

216 (91.2%) in the DOAC group and 305/343 (88.9%) in the warfarin group (RR 1.25, 95% confidence interval (CI) 0.69-2.35, $P = 0.48$) (Figure 1A). In overall patients, the number of subjects with DVT whose thrombus was considered improved on leg vein ultrasound was 502/559 (89.8%), unchanged was 43/559 (7.7%), and deteriorated was 14/559 (2.5%). The number of subjects with DVT whose thrombus was considered unchanged on leg vein ultrasound was 15/216 (6.9%) in the DOAC group and 28/343 (8.2%) in the warfarin group (RR 0.87, 95% CI 0.43-1.72, $P = 0.62$) (Figure 1A). The number of subjects with DVT whose thrombus was considered deteriorated on leg vein ultrasound was 4/216 (1.9%) in the DOAC group and 10/343 (2.9%) in the warfarin group (RR 0.61, 95% CI 0.13-2.15, $P = 0.58$) (Figure 1A). There were no significant differences in the anticoagulant effect between the two groups.

Outcomes of major bleeding: During the six months of treatment, major bleeding occurred in 15 of 807 patients (1.8%). There was no significant difference between the two groups in major bleeding (DOAC group: 1.8% versus warfarin group: 1.8%, RR 0.97, 95% CI 0.28-3.07; $P = 1.0$). As for bleeding in the DOAC group, gastrointestinal

Figure 1. Thrombotic burden assessments by follow-up leg vein ultrasound examination. **A:** All patients. **B:** Active cancer patients. **C:** No active cancer patients.

hemorrhage was seen in 2 cases, subdural hemorrhage in 2 cases, muscular hemorrhage in 1 case, and hemarthrosis in 1 case; in the warfarin group, gastrointestinal hemor-

rhage was seen in 7 cases, and alveolar hemorrhage was seen in 2 cases. The Kaplan-Meier curves for the first major bleeding episode are shown in Figure 2A. The Kaplan-

Figure 2. Kaplan-Meier cumulative event rates. Kaplan-Meier curves are shown for the first event of major bleeding. **A:** All patients. **B:** Active cancer patients.

Maier curves suggest that the risk of major bleeding was similar during therapy. In the first month, major bleeding had occurred in 4 patients (66.7%) in the DOAC group and in 6 (66.7%) patients in the warfarin group; the rates of early major bleeding were similar in the two groups.

Outcomes of Mortality: During the follow-up period, all-cause mortality was 7.4% (24/323) with DOACs and 10.3% (50/484) with warfarin. There was no venous thromboembolism-related or major bleeding-related death

in the DOAC group. There was no major bleeding-related death in the warfarin group also, but 3 patients died from venous thromboembolism. Of the 74 deaths, 56 (75.6%) were early deaths that occurred 3 months after the index event.

Multivariable Analysis in overall patients: Multivariable analysis was performed among all study subjects to determine the predictors of major bleeding and recurrence with the following variables; age, body weight, renal function,

Table IV. Multivariable Analysis for Predictors of Major Bleeding and Recurrence in Overall Patients (Logistic Regression Analysis)

Variable	Major bleeding		Recurrence	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Age ≥ 75 years	1.37 (0.47-4.00)	0.57	0.85 (0.47-1.52)	0.59
BW < 50 kg	1.36 (0.44-4.15)	0.59	0.62 (0.32-1.21)	0.16
CrCl < 60 mL/minute	0.49 (0.13-1.83)	0.29	1.25 (0.70-2.23)	0.44
Male	1.19 (0.34-4.14)	0.78	0.94 (0.48-1.83)	0.86
Active cancer	2.70 (0.91-8.02)	0.07	2.01 (1.10-3.67)	< 0.05
DOACs administration	0.59 (0.16-2.17)	0.43	0.61 (0.31-1.19)	0.14
Warfarin administration	0.96 (0.86-6.49)	0.21	0.86 (0.72-3.22)	0.56
Fondaparinux	1.64 (0.38-7.01)	0.50	0.65 (0.26-1.51)	0.30
UFH	0.83 (0.24-2.97)	0.78	0.54 (0.29-1.02)	0.06

OR indicates odds ratio; and CI, confidence interval. Other abbreviations as in Table I and III.

Table V. Major Bleeding with DOACs and Warfarin for Selected Patient Subgroups

	DOACs <i>n</i> / <i>N</i> (%)	Warfarin <i>n</i> / <i>N</i> (%)	Hazard ratio (95% CI)	<i>P</i> value
Weight (kg)				
< 50	1/95 (1.1)	5/150 (3.3)	0.31 (0.01-2.86)	0.41
≥ 50	5/228 (2.2)	4/334 (1.2)	1.67 (0.35-8.56)	0.50
Age (years)				
< 75	3/200 (1.5)	5/270 (1.9)	0.78 (0.12-4.08)	1
≥ 75	3/123 (2.4)	4/214 (1.9)	1.27 (0.18-7.60)	0.71
CrCl (mL/minute)				
< 60	0/86 (0)	3/159 (1.9)	0 (0.00-4.32)	0.55
≥ 60	6/237 (2.5)	6/325 (1.8)	1.32 (0.35-5.02)	0.77
Active cancer				
Yes	3/108 (2.8)	4/94 (4.3)	0.64 (0.09-3.91)	0.71
No	3/215 (1.3)	5/390 (1.3)	1.04 (0.16-5.39)	1

Data are expressed as *n* (%). *P* values were determined by an unpaired *t*-test or Fisher's exact test. Abbreviations as in Table I.

sex, active cancer, DOAC or warfarin administration, and treatment in the acute phase (Fondaparinux or heparin) (Table IV). In recent studies,⁷⁻¹⁴⁾ recurrence is defined as follows: abnormal CUS where compression had been normal, a substantial thrombus diameter increase (4 mm or more) during full compression when incompressible during screening, an extension of an intraluminal filling defect, a new intraluminal filling defect, or an extend area of unvisualized veins in the presence of a sudden occlusion on venography. In our study, recurrence was defined as deteriorated cases or incompressible cases in ultrasound examination among no change regarding the thrombus regression response.

Among the clinical parameters, there were no significant factors for major bleeding in overall patients. Active cancer exhibited higher contribution to predict major bleeding, although it was not a significant factor (OR 2.70, 95% CI 0.91-8.02; *P* = 0.07). Active cancer was the only significant factor for recurrence in our multivariable analysis (OR 2.01, 95% CI 1.10-3.67; *P* < 0.05).

DOAC or warfarin administration in chronic phase treatment was not a significant factor for major bleeding and recurrence, neither the use of fondaparinux or heparin in acute phase treatment.

Subgroup analyses: Incidence rates for the primary outcomes of major bleeding are shown in Table V. Patient subgroup data showed no significant differences in the rates of major bleeding between treatments for body weight, age, renal function, or active cancer at baseline. Among the active cancer patients, major bleeding occurred in 3 of 108 patients (2.8%) in the DOAC group and in 4 of 94 patients (4.3%) in the warfarin group (RR 0.64, 95% CI 0.09-3.91; *P* = 0.71). Among the no-cancer patients, major bleeding occurred in 3 of 225 patients (1.3%) in the DOAC group and in 5 of 389 patients (1.3%) in the warfarin group (RR 0.96, 95% CI 0.18-6.26; *P* = 1). Multivariable Analysis for predictors of major bleeding in the DOAC and the warfarin groups are shown in Table VI. Among the clinical factors, only active cancer in the warfarin group was a significant factor for major bleeding (OR 6.12, 95% CI 1.47-51.6; *P* < 0.05). The Kaplan-Maier curves for the first major bleeding episode in cancer patients are shown in Figure 2B.

Among the total 202 patients with active cancer, 146 underwent follow-up by ultrasound examination. There were no significant differences in the ultrasound follow-up period between the DOAC group and the warfarin group in active cancer patients (157 ± 113 days versus 131 ±

Table VI. Multivariable Analysis for Predictors of Major Bleeding and Recurrence in the DOACs and the Warfarin Groups (Logistic Regression Analysis)

Variable	DOACs		Warfarin	
	OR (95% CI)	P value	OR (95% CI)	P value
Major bleeding				
Age $\geq$ 75 years	2.85 (0.54-15.1)	0.27	2.27 (0.20-7.15)	0.32
BW < 50 kg	0.29 (0.03-2.71)	0.28	0.34 (0.09-6.42)	0.22
CrCl < 60 mL/minute	0.18 (0.01-2.08)	0.19	0.69 (0.15-3.03)	0.62
Male	0.28 (0.03-2.61)	0.26	2.85 (0.57-14.3)	0.20
Active cancer	2.68 (0.51-14.1)	0.24	6.12 (1.47-51.6)	< 0.05
Recurrence				
Age $\geq$ 75 years	2.35 (0.01-2.03)	0.14	0.64 (0.30-1.36)	0.64
BW < 50 kg	0.96 (0.86-6.49)	0.21	0.76 (0.36-1.62)	0.22
CrCl < 60 mL/minute	1.73 (0.61-4.85)	0.50	1.03 (0.48-2.17)	0.95
Male	1.59 (0.57-4.37)	0.30	0.73 (0.28-1.91)	0.53
Active cancer	0.65 (0.20-2.07)	0.47	3.22 (1.45-7.15)	< 0.05

OR indicates odds ratio; and CI, confidence interval. Other abbreviations as in Table I.

100 days; $P = 0.15$).

The number of subjects with DVT whose thrombus was considered improved on leg vein ultrasound was 70/76 (92.1%) in the DOAC group and 56/70 (80.0%) in the warfarin group (RR 2.89, 95% CI 0.98-9.81; $P = 0.05$) (Figure 1B). The number of subjects with DVT whose thrombus was considered unchanged on leg vein ultrasound was 4/76 (5.3%) in the DOAC group and 8/70 (11.4%) in the warfarin group (RR 0.43, 95% CI 0.01-1.71; $P = 0.23$) (Figure 1B). The number of subjects with DVT whose thrombus was considered deteriorated on leg vein ultrasound was 2/76 (2.6%) in the DOAC group and 6/70 (8.6%) in the warfarin group (RR 0.29, 95% CI 0.03-1.69; $P = 0.15$) (Figure 1B). There was no significant difference between DOAC therapy and warfarin therapy in active cancer patients, but DOACs had a higher anticoagulant effect than warfarin. Otherwise, there were no significant differences in the anticoagulant effect among subgroups by body weight, age, or renal function. Figure 1C shows that there were no differences in the rates of thrombus regression between the DOAC group and the warfarin group in no active cancer patients. Among the clinical factors, only cancer in the warfarin group was a significant factor for recurrence (OR 3.22, 95% CI 1.45-7.15; $P < 0.05$) with multivariate analysis (Table VI).

Discussion

Main findings: The main findings of the present study were as follows: First, DOACs exhibited equal efficacy and safety as warfarin did in the treatment of chronic phase DVT. Second, DOACs were superior to warfarin in terms of DVT thrombus regression in active cancer patients, with fewer bleeding complications. The results of multivariate analysis showed that active cancer was a significant factor for recurrence in all subjects, with the most contribution to predict major bleeding. Moreover, active cancer was an independent risk factor for major bleeding and recurrence in the warfarin group, but not in the DOAC group.

The efficacy and safety outcome of DOACs and warfarin administration: Figure 1 indicated that the throm-

bus regression and recurrence prevention effect of DOACs were equivalent to that of warfarin. There was no significant difference in the rate of major bleeding between the DOAC therapy (1.8%) and the warfarin therapy (1.8%). Moreover, the rates of early major bleeding were the same between the two groups (66.7%), and the Kaplan-Maier curves were approximately similar. Figure 2 showed that two thirds of major bleeding occurred within the first month of anticoagulation. This increased risk could be a consequence of less well-controlled therapy at the start of treatment in combination with the presence of lesions predisposing patients to bleeding. Therefore, physicians have to monitor more carefully the intensity of anticoagulant therapy during the first treatment week, which has the greatest bleeding risk. However our research was a retrospective and observational study, with significantly different background between the DOAC group and the warfarin group. The ratio of active cancer in the DOAC group (32.8%) was higher than the ratio in the warfarin group (19.2%) (Table II). Moreover, there were also significant differences in parenteral anticoagulant therapy in acute phase between the two groups (Table III). Therefore, it was very difficult to simply compare the efficacy and safety in the two groups. Therefore we performed multivariable analysis to determine predictors of major bleeding and recurrence among overall patients, which revealed that the parenteral anticoagulant therapies in acute and chronic phase were not significant factors. Age, body weight, renal function, and sex were not independent risk factors either, for major bleeding and recurrence in both groups.

In recent randomized, controlled trials of the effects of DOACs for the treatment of acute venous thromboembolism, any type of DOACs reduced the incidence of major bleeding significantly compared with warfarin.⁷⁻¹⁴ The reason why the current study did not show differences in major bleeding between DOACs and warfarin in the overall population might be due to the difficulty in warfarin control in the chronic phase. The recommended target INR for PE and DVT in the Japanese guideline is 2.0 (target range 1.5-2.5), which is lower than that in Western countries (INR 2.0, target range 2.0-3.0). This difference

makes warfarin control in the chronic phase more complicated. In the present study, only 43.0% of patients reached the therapeutic range of INR 1.5-2.5, while more than 80% of patients obtained the therapeutic range in the Japan VTE treatment Registry (JAVA).²²⁾ To make a solid comparison between DOACs and warfarin in clinical settings, the quality of warfarin therapy should be proactively monitored throughout the study. However, in the real world, DVT is a disease that occurs in many medical departments, and thus, maintaining the INR within the therapeutic range of 1.5-2.5 is often difficult.

Association between DVT and active cancer: Generally, patients with active cancer have a 4-fold increased risk of developing DVT, with a 15% recurrence risk annually after discontinuation of anticoagulation.^{23,24)} They are also at a 3 to 6-fold higher risk of major bleeding during anticoagulation with a vitamin K antagonist (VKA), as compared to patients without cancer.²⁵⁻²⁷⁾ An enhanced vitamin K deficiency status is provoked by surgery, chemotherapy, hormone therapy, anti-cancer drugs, renal failure, and fluctuating dietary intake during the course of cancer therapy resulting in difficulties of anticoagulation during the management of cancer patients. Studies have reported that LMWH is more effective and safer than VKA in patients with malignancy-associated venous thromboembolism, and current guidelines suggest that LMWH therapy for 3 to 6 months is recommended as a first-line treatment to reduce recurrent VTEs in patients with active cancer.^{28,29)} However, LMWH therapy is expensive and with a possible risk of heparin-induced thrombocytopenia. Furthermore, public health insurance in Japan currently does not cover LMWH therapy for VTE.

Usefulness of DOACs for cancer-associated DVT in the chronic phase: In our institution, approximately 20% of DVT patients have active cancer at baseline. A leg vein ultrasound examination was performed if an activated fibrinolytic system or lower limb swelling was observed. In cancer patients, the incidence of major bleeding was 2.8% with DOAC therapy and 4.3% with warfarin therapy (Table V). This showed that DOACs were more effective than conventional warfarin therapy, with a clinically relevant reduction of 36% in major bleeding. These results are also similar to the pooled analysis of cancer patients treated with DOACs for the incidence of major bleeding.³⁰⁾ Moreover, the rate of improved thrombosis was higher in the DOAC group (92.1%) than in the warfarin group (80.0%), and the rate of deteriorated thrombosis was lower in the DOAC group (2.6%) than in the warfarin group (8.6%) (Figure 1). Thus, the DOAC group showed a higher tendency in terms of efficacy and safety than the warfarin group, but there was no statistical difference in the 2 groups. Furthermore, in multivariable logistic analysis, active cancer was the only independent predictor of recurrence (OR 2.01, 95% CI 1.10-3.67; $P < 0.05$) (Table IV), while conventional risk factors for bleeding, such as renal dysfunction, age, and weight, were not associated with major bleeding and thrombus regression. Active cancer was an independent risk factor for major bleeding and recurrence in the warfarin group (OR 6.12, 95% CI 1.47-51.6; $P < 0.05$ and OR 3.22, 95% CI 1.45-7.15; $P < 0.05$), but it was not an independent risk factor for major

bleeding and recurrence in the DOAC group (OR 2.68, 95% CI 0.51-14.1; $P = 0.24$ and OR 0.65, 95% CI 0.20-2.07; $P = 0.47$) (Table VI).

Cancer patients can be easily out of warfarin control especially during chemotherapy, due to significant change of diet therapy or antibiotics use. Also, it is known that the effect of warfarin is attenuated in cancer patients, and the recurrence rate is 3 times more than that of non-cancer patients even if PT INR is in the therapeutic range. It is suggested that warfarin itself has a large impact on the blood concentration of anti-cancer agent, increasing complications of major bleeding.³¹⁾ Therefore, in our study, active cancer was the only independent risk factor for recurrence and major bleeding in the warfarin group while there was no significant difference in the ratio of PT INR therapeutic range between cancer patients and non-cancer patients. DOAC does not have as much drug interaction as warfarin,³²⁾ and poor compliance impact of DOAC is also small, which may be the reason why active cancer did not become an independent risk factor of recurrence and major bleeding in the DOAC group.

Ross, *et al.*³³⁾ reported that there was no statistically significant difference between DOAC and LMWH with regard to recurrence and major bleeding of DVT in cancer patients. Patients at low risk of recurrence are recommended that anticoagulation be discontinued after 6 months in the absence of active malignancy (i.e., patients are cured or in complete remission), provided that no anti-cancer therapy is ongoing or planned. Patients at high risk of recurrence are recommended that anticoagulation be continued but with periodic re-evaluation of risks and benefits.³⁴⁾

This study was limited in a half year during the follow-up period, and the further efficacy and safety of DOACs may be shown by the observation in the longer term. The current data suggest that DOACs appear to be an attractive therapeutic option for cancer-associated DVT in chronic phase, with relatively low anticipated rates of recurrence and major bleeding.

Study limitations: This study has some potential limitations. First, it was a retrospective and observational study, and dabigatran were not approved for treatment of DVT in Japan. In this study, dabigatran was included in 32.2% of the whole patients. Second, the DOAC dosages were determined by each physician's decision. In the DOAC group except dabigatran, 144/219 (65.8%) were initiated with maintenance dose. 34.2% of patients were reduced dose without reduction criteria by each physician's decision. There are no patients who were administered with intensive dose.

Conclusion

DOACs exhibited equal efficacy and safety as warfarin did in the treatment of chronic phase DVT. Active cancer was an independent risk factor for major bleeding and recurrence in the warfarin group, but not in the DOAC group. DOACs appear to be an attractive therapeutic option for cancer-associated DVT in chronic phase, with relatively low anticipated rates of recurrence and major bleeding.

Disclosures

Conflicts of interest: None.

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