

Original

Prospective Randomized Study of the Safety and Efficacy of Interrupted Anticoagulant's Therapy in the Perioperative Period of Catheter Ablation for Atrial Fibrillation: The SEACOAST Rhythm AF Trial

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Abstract : No prospective, randomized study has been conducted to date in Japan comparing the use of warfarin and rivaroxaban for preventing thrombotic and bleeding events in the perioperative period of catheter ablation (CA) for atrial fibrillation (AF). This was a prospective, open-label randomized study assessing the safety and efficacy of warfarin and rivaroxaban in the perioperative period of CA for AF. Thrombotic events including silent cerebral lesion (SCL) detected by magnetic resonance imaging (MRI), bleeding events, and coagulation test results were assessed in correlation with interrupted warfarin or rivaroxaban in the perioperative period of CA for AF. Finally, thirty-six patients (18 men; aged 65 ± 9.4 years) who underwent CA for AF were prospectively enrolled. No instance of symptomatic cerebral infarction occurred, but 12 of 36 patients (33.3%) showed new SCLs during the postprocedural cerebral MRI examination (8/21 in the rivaroxaban group and 4/15 in the warfarin group; $P = 0.47$). The duration of hospitalization was significantly shorter in the rivaroxaban group than in the warfarin group (6 vs. 8 days; $P = 0.0135$). The incidence of minor bleeding was significantly lower in the rivaroxaban group than in the warfarin group (0% vs. 26.6%; $P = 0.078$). D-dimer concentration was significantly higher in the SCL group than in the no-SCL group ($P = 0.024$) under warfarin, while the values of protein S ($P = 0.017$) and prothrombin time ($P = 0.018$) were significantly lower in the SCL group than in the no-SCL group under rivaroxaban. Rivaroxaban usage in CA is safer than warfarin usage with respect to the incidence of minor bleeding. In patients receiving rivaroxaban therapy, a lower protein S level may be correlated with the incidence of SCL in CA.

Key words : rivaroxaban, warfarin, ablation, atrial fibrillation, coagulation tests

Introduction

Patients with atrial fibrillation (AF) have a high mortality risk with an incidence of 1.5% to

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1.9% in both men and women across a wide range of ages¹). Currently, catheter ablation (CA) for AF is a useful and important treatment for rhythm control therapy²). Furthermore, patients undergoing CA were reported to have a lower stroke rate than those not undergoing CA in spite of a high CHADS score and a stroke rate similar to that of those without AF in a large cohort³). Directorial anticoagulants (DOACs) have been widely adopted in the perioperative period of CA for AF and appear to be safe and effective^{4, 5}).

Meanwhile, using warfarin and rivaroxaban to prevent thrombotic events in the perioperative period of CA for AF has similarly been prospectively reported to be safe and effective⁶). Several retrospective studies comparing the use of warfarin and rivaroxaban in the perioperative period of CA for AF have been published to date^{6, 7}); however, few prospective and randomized studies examining the use of warfarin and rivaroxaban with coagulation testing have been conducted in Japan.

This study—referred to as the SEACOAST Rhythm AF (Safety and Efficacy of AntiCOagulant'S Therapy—Rhythm Control for Atrial Fibrillation) trial—therefore sought to prospectively examine the incidence of cerebral infarction, including silent cerebral lesions (SCL) detected by magnetic resonance imaging (MRI), systemic embolization, heart vascular events, and major bleeding events, using coagulation testing and to evaluate the safety and efficacy of interrupting warfarin or rivaroxaban therapy in the perioperative period of CA for AF.

Methods

SEACOAST Rhythm AF was a prospective randomized study of two interrupted anticoagulation therapies (warfarin and rivaroxaban) during CA of AF ablation designed in accordance with the guidelines of the Declaration of Helsinki, approved by the SHOWA University Clinical Research Review Board (permission no. 1429), and registered with UMIN (trial registration no. R000014015 at <http://www.umin.ac.jp/>).

Informed consent was written from all the included patients.

Study population

Between March 2012 and April 2014, a total of 41 patients undergoing CA for AF were randomly assigned in a 1 : 1 ratio to rivaroxaban or warfarin. The Japanese Circulation Society guidelines recommend maintaining an international normalized ratio (INR) of 2.0 to 3.0 in patients aged younger than 70 years and that of 1.6 to 2.6 in patients aged 70 years or older.

Patients who were 18 years or older and scheduled for their first CA for paroxysmal and/or persistent AF were eligible for enrollment. Patients with implanted rhythm devices, mechanical valves, and those not undergoing magnetic resonance imaging (MRI) were excluded.

Catheter ablation protocol

Prior to CA for AF, all eligible consecutive patients who were scheduled to undergo CA had taken warfarin or rivaroxaban (1 : 1) for at least three weeks. All patients also underwent thorough cardiologic assessments, including medical history-taking, a physical examination, electro-

cardiography, transthoracic echocardiography, and transesophageal echocardiography. Anticoagulant therapies were recommended to be discontinued before CA and replaced with unfractionated heparin (10,000–15,000 IU/day) if possible. The INR was checked one day before CA to evaluate warfarin efficacy (INR ≥ 1.6 was defined as an adequate effect) when warfarin was administered. Blood samples were collected immediately after inserting the sheaths used to insert catheters.

A bolus dose of unfractionated heparin (100 u/kg) was administered before the first transseptal puncture. Additional boluses were administered as required to maintain an activated clotting time (ACT) of more than 350 seconds, which was assessed every 20 minutes.

Deep sedation was achieved using intravenous fentanyl and dexmedetomidine. A steerable 8.5-French sheath (Agilis; St. Jude Medical, St. Paul, MN, USA) and a nonsteerable 8.5-French sheath (SL 0; St. Jude Medical, St. Paul, MN, USA) were introduced into the left atrium (LA) after transseptal puncture. In the LA, we placed an open irrigated-tip ablation catheter and a ring catheter, while in the coronary sinus and right ventricle, we placed a decapolar catheter. All CA procedures were performed using the open irrigated-tip ablation catheter and the ring catheter in the LA together with the aid of a three-dimensional mapping system. Irrigated ablation with pulsed radiofrequency energy was conducted with a target temperature of 43°C and maximum energy output of 35 W (but 20 W only in the posterior wall). CA was performed by adopting a dragging ablation method with a steerable sheath.

Patients with both paroxysmal and persistent AF were treated solely with pulmonary vein (PV) isolation (PVI). Briefly, a circumferential lesion pattern was created around the ipsilateral pulmonary veins (PVs) simultaneously. PVI was defined by the elimination or dissociation of PV potential as recorded using a ring catheter placed in the PVs. Electrical cardioversion was performed if AF persisted after PVI.

Discontinuance and restart of warfarin and rivaroxaban: The occurrence of major (i.e., need for blood transfusion and medical treatments, decrease in hemoglobin of less than 2 g/dl, bleeding in the vital organs, and death by bleeding) and minor (i.e., rebleeding of puncture sites in the perioperative CA period) bleeding, medical history, CA procedure data, heart ultrasound data, and blood test values were collected from medical charts.

Anticoagulant therapy protocol

Warfarin was discontinued for the two days before and on the day of the CA procedure, while rivaroxaban was discontinued only on the day of the CA procedure. Unfractionated heparin (10,000–15,000 IU/day) was administered by continuous intravenous injection during the discontinuance of anticoagulants and stopped at 6 o'clock on the morning of the day of CA in both groups, if possible. Warfarin or rivaroxaban administration was restarted on the night after CA.

Blood coagulation test

Coagulation tests [prothrombin time (PT), PT-PT-INR, activated partial thromboplastin time, fibrin/fibrinogen-degradation products, thrombin-antithrombin complex (TAT), plasmin- $\alpha 2$ plas-

min inhibitor complex (PIC), prothrombin fragment 1+2 (PTF1+2), and plasminogen activator inhibitor (PAI-1)] were conducted prior to the bolus infusion of heparin from the sheaths inserted at the beginning of CA.

Cerebral magnetic resonance imaging

All patients underwent cerebral MRI one month before and one day after the procedure, using a 1.5-Tesla scanner (Magnetom Avanto; Siemens, Erlangen, Germany). The MRI protocol included a sagittal T1/T2-weighted spin-echo sequence, an axial fluid-attenuated inversion recovery sequence, and a diffusion-weighted sequence. Post-CA, an acute SCL was defined as a new focal hyperintense lesion detected by MRI without neurological findings. The incidence of new SCLs was analyzed. MRI scans were reviewed by two certified radiologists with in-depth knowledge of the CA technique. Patients who developed SCLs were referred to the neurology department for follow-up.

Study endpoints

Primary endpoints included cerebral infarction, systemic embolization, cardiovascular (acute coronary syndrome and death associated with cardiovascular events), and major bleeding events (i.e., need for blood transfusion and medical treatments, decrease in hemoglobin of less than 2 g/dl, bleeding in the vital organs, and death by bleeding). Separately, secondary endpoints included adverse events brought on by CA and/or anticoagulation therapy, the duration of hospitalization, the duration of discontinuance and restart of anticoagulation therapy, MRI findings including SCL, the incidence of minor bleeding defined as the rebleeding of puncture sites, and the values of coagulation tests.

Statistical analysis

Continuous variables with a normal distribution are presented as means \pm standard deviations, while medians and interquartile ranges (IQRs) were used when the distribution was biased. Between-group differences were analyzed using analysis of variance for continuous variables. Categorical variables are presented as counts and percentages and were compared using the chi-squared test (Fischer's exact test). Results with $P < 0.05$ were considered to be statistically significant. All statistical analyses were conducted using commercially available software (JMP SAS 12.0; SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the study population

Forty-one patients (21 men; aged 65 ± 8.5 years) who underwent CA for AF were prospectively enrolled. The protocol included cerebral MRI after CA for AF; as such, five initially eligible patients were later excluded from the study because they did not undergo MRI. Eventually, 36 patients (15 in the warfarin group and 21 in the rivaroxaban group) were analyzed in the study. The baseline characteristics of patients in each group are shown in Table 1. There

Table 1. Patient characteristics and procedure data

	Warfarin (n=15)	Rivaroxaban (n=21)	<i>P</i> -value
Age (years)	66.3±8.1	65.5±9.1	NS
Gender (male)	4 (26.7%)	14 (66.7%)	0.016
Weight (kg)	59.0±14.2	61.7±1.0	NS
Type of AF (paroxysmal AF)	8 (53.3%)	11 (52.4%)	NS
Duration of AF (month)	32.8±32.2	32.7±33.9	NS
Left atrial diameter (mm)	42.5±4.1	42.0±8.0	NS
Cerebral vascular disease	0 (0%)	0 (0%)	NS
Hypertension	10 (66.7%)	9 (47.4%)	NS
Diabetes mellitus	3 (21.4%)	1 (5.26%)	NS
Chronic heart failure	3 (23.1%)	4 (21.1%)	NS
Vascular disease	0 (0%)	1 (5.3%)	NS
CHADS score	1.1±0.7	1.2±1.2	NS
CHA ₂ DS ₂ -VASc score	1.9±1.4	1.7±1.7	NS
Dyslipidemia	6 (42.9%)	6 (31.6%)	0.05
Mean ACT (s)	407.8±53.1	373.7±42.0	0.052
Procedure time (min)	245.4±61.0	223.0±45.9	NS
Ablation time (s)	3407.7±1486.1	3165.1±1521.2	NS
Maximum power (W)	34.7±2.9	35.3±2.00	NS
Cardioversion during CA	8 (53.3%)	13 (65.0%)	NS
Heart rhythm during ablation (AF)	5 (32.3%)	8 (40%)	NS
Total unit of heparin during CA (units)	12461.5±2145.4	13105.3±3619.3	NS
Heparin replacement	6 (42.9%)	3 (16.7%)	0.08
Duration of anticoagulant discontinuance (days)	1±1.03	0.5±0.23	0.019

ACT : activated clotting time, AF : atrial fibrillation, CA : catheter ablation, NS : not significant, Values are given as mean ± standard deviation.

were significant differences in sex and the incidence of dyslipidemia between the two groups. Only one patient in the rivaroxaban group took an antiplatelet drug.

Study endpoints

Regarding the primary endpoints, no cerebral infarction, systemic embolization, heart vascular events, or major bleeding events occurred in either group. Concerning the secondary endpoints, no adverse events prompted by CA or anticoagulation therapy occurred. After CA, one patient in the warfarin group had sick sinus syndrome and one patient in the rivaroxaban group had pneumothorax after CA. The duration of hospitalization for CA was eight days (IQR: 7–9.75

days) in the warfarin group and 6 days (IQR: 6–8 days) in the rivaroxaban group. As such, the duration of hospitalization in the rivaroxaban group was significantly shorter than that in the warfarin group ($P = 0.0135$), regardless of a heparin replacement. The incidence rates of minor bleeding were 26.6% (4/15) in the warfarin group and 0% (0/21) in the rivaroxaban group; such was significantly decreased in the rivaroxaban group as compared with in the warfarin group ($P = 0.0078$) (Figure 1). Concerning the perioperative usage of anticoagulant therapies, the mean duration of anticoagulant discontinuation was one day in the warfarin group and 0.5 days in the rivaroxaban group, revealing that the duration of discontinuation in the rivaroxaban group was significantly shorter than that in the warfarin group ($P = 0.019$). Conversely, the duration of restart in the warfarin group was significantly shorter than that in the rivaroxaban group ($P = 0.011$). The incidence rates of SCL were 33.3% (12/36) in all patients, with 26.7% (4/15) in the warfarin group, and 38.1% (8/21) in the rivaroxaban group. There was no significant difference in the incidence of SCL between the warfarin and rivaroxaban groups, even following adjustments for gender and dyslipidemia.

Coagulation tests

The results of coagulation testing before CA were compared between the warfarin and rivaroxaban groups and the values of protein C, protein S, PT F1+2, and D-dimer measured before CA under warfarin therapy were significantly decreased relative to those under rivaroxaban

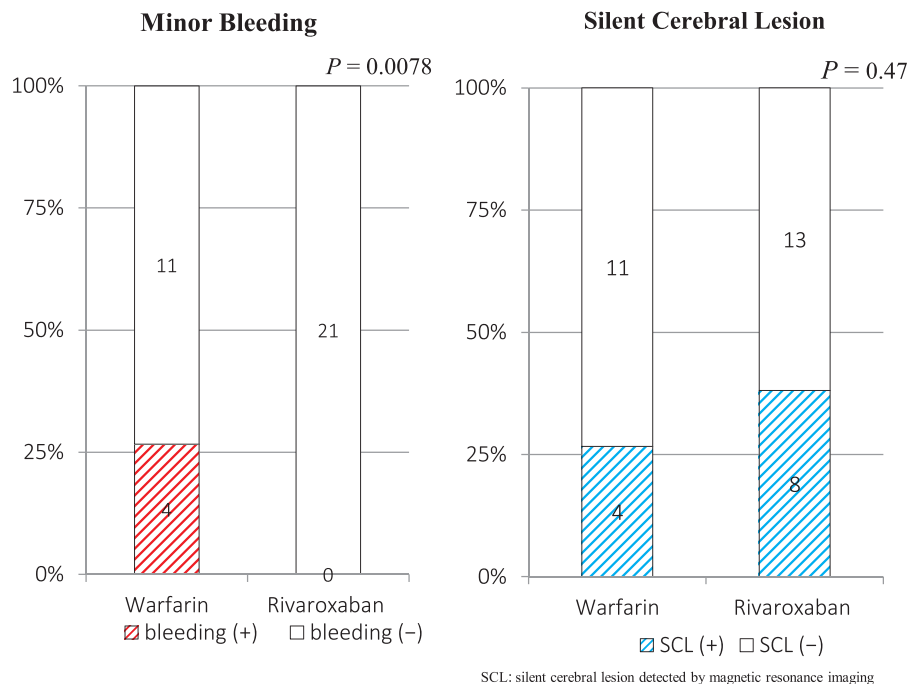


Fig. 1. Incidence rates of minor bleeding and SCL. Minor bleeding was defined as the rebleeding of puncture sites. No minor bleeding occurred in the rivaroxaban group. SCLs were detected by MRI.

therapy (Table 2).

In addition to stratifying by whether SCL occurred or not while taking warfarin or rivaroxaban, under warfarin therapy, the value of PT in both the SCL and no-SCL groups was higher, beyond the normal range (42.4 vs. 40.2), and there was a significant difference between the two. Meanwhile, the value of D-dimer in the SCL group was significantly higher than that in the no-SCL group, even within the normal range ($P = 0.024$) (Table 3). Under rivaroxaban therapy, the values of protein S ($P = 0.017$) and PT ($P = 0.018$) in the SCL group were significantly lower than those in the no-SCL group, even within the normal ranges. Finally, the values of TAT and PT F1+2 in both groups were beyond normal ranges (Table 4).

Discussion

Warfarin and direct anticoagulants

Warfarin exerts anticoagulant effects by inhibiting synthesizing prothrombin and factors II, VII, IX, and X. Therefore, it takes 24 to 72 hours to affect anticoagulant action and it is a very slow-acting medication⁸⁾, while rivaroxaban inhibits only factor X more quickly, taking just two to three hours to affect anticoagulant action⁹⁾.

Several retrospective studies have compared the use of warfarin and rivaroxaban (including

Table 2. Comparison of coagulation tests between warfarin and rivaroxaban at the beginning of CA

	Warfarin	Rivaroxaban	P-value	normal range
Number	15	21		
PT (%)	40.5±13.5	81.0±8.9	<0.001	>70
PT-INR	1.75±0.43	1.11±0.07	<0.001	
APTT (s)	52.2±50.1	38.1±27.4	NS	25.0-45.0
Fib (mg/ml)	307.1±81.4	304.2±63.6	NS	200-400
FDP (µg/ml)	1.73±0.41	2.06±0.53	0.07	<5.0
D-dimer (µg/ml)	0.49±0.10	0.46±0.07	0.04	≤1.0
TAT (ng/ml)	7.9±4.2	14.7±11.0	0.058	<4.0
PIC (µg/ml)	0.43±0.23	0.48±0.30	NS	≤0.8
PTF1+2 (pmol/l)	137.1±68.1	245.5±100.6	0.0035	69-229
Protein C (%)	68.0±15.6	86.3±17.6	0.0069	≥70%
Protein S (%)	45.3±4.0	80.3±10.1	<0.001	≥70%
thrombomodulin (FU/ml)	2.33±0.53	2.24±0.63	NS	2.1-4.1
PAI-1 (ng/ml)	20.8±10.1	26.6±9.7	NS	≤50

CA : catheter ablation, PT : prothrombin time, PT-INR : prothrombin time-international normalized ratio, APTT : activated partial thromboplastin time, FDP : fibrin-/fibrinogen-degradation products, TAT : thrombin-antithrombin complex, PIC : plasmin- α 2 plasmin inhibitor complex, PTF1+2 : prothrombin fragment 1+2, PAI-1 : plasminogen activator inhibitor, NS : not significant, Values are given as mean±standard deviation.

Table 3. Comparison of coagulation tests under warfarin with respect to the incidence of SCL at the beginning of CA

	SCL (+)	SCL (-)	<i>P</i> -value	Normal range
N	4	11		
PT (%)	42.4±13.1	40.2±12.1	NS	>70
PT-INR	1.67±0.36	1.73±0.40	NS	
APTT (sec)	34.4±12.7	51.0±49.9	NS	25.0–45.0
Fib (mg/ml)	347.4±72.1	305.7±76.1	NS	200–400
FDP (µg/ml)	1.82±0.45	1.71±0.40	NS	<5.0
D-dimer (µg/ml)	0.59±0.13	0.46±0.07	0.024	≤1.0
TAT (ng/ml)	8.1±4.2	14.7±11.0	NS	<4.0
PIC (µg/ml)	0.52±0.24	0.41±0.24	NS	≤0.8
PTF1+2 (pmol/l)	134.0±72.2	124.0±71.1	NS	69–229
Protein C (%)	59.0±14.0	64.8±16.5	NS	≥70%
Protein S (%)	43.8±7.8	46.2±10.1	NS	≥70%
thrombomodulin (FU/ml)	2.26±0.15	2.39±0.55	NS	2.1–4.1
PAI-1 (ng/ml)	28.0±19.4	22.7±12.2	NS	≤50

CA : catheter ablation, SCL : silent cerebral lesion, PT : prothrombin time, PT-INR : prothrombin time–international normalized ratio, APTT : activated partial thromboplastin time, FDP : fibrin-/fibrinogen-degradation products, TAT : thrombin–antithrombin complex, PIC : plasmin- α 2 plasmin inhibitor complex, PTF1+2 : prothrombin fragment 1+2, PAI-1 : plasminogen activator inhibitor, NS : not significant, Values are given as mean±standard deviation.

using both interrupted and uninterrupted anticoagulant protocols) in the perioperative period of CA for AF^{6, 7)}. In a meta-analysis of the efficacy and safety of rivaroxaban and vitamin K antagonists¹⁰⁾, the risks of thromboembolism, major bleeding, and minor bleeding were not significantly different between the rivaroxaban and vitamin K antagonist groups. Thus, among patients undergoing CA for AF, rivaroxaban was suggested to be an effective and safe alternative to vitamin K antagonists.

In our study, the incidence of SCL was similar between the rivaroxaban and warfarin groups, whereas the incidence of minor bleeding was decreased in the rivaroxaban group relative to the warfarin group (0% vs. 26.6%), which may be due to the difference in the duration of anticoagulant effect between the two drugs, indicating that rivaroxaban is similarly effective for anticoagulation and may be safer when considering the tendency for bleeding in comparison with warfarin.

The VENTURE-AF study was the first prospective, randomized trial performed using uninterrupted rivaroxaban in preprocedural CA¹¹⁾, and sought to evaluate the efficacy and safety of uninterruptedly using vitamin K agonists and rivaroxaban while having an evening meal in the perioperative period of CA for AF. Here, the incidence rates of major bleeding,

Table 4. Comparison of coagulation tests under rivaroxaban with respect to the incidence of SCL at the beginning of CA

	SCL (+)	SCL (-)	P-value	Normal range
	8	13		
PT (%)	77.7±5.2	84.7±6.4	0.018	>70
PT-INR	1.13±0.03	1.08±0.03	0.0112	
APTT (s)	49.5±46.6	32.5±6.7	NS	25.0–45.0
Fib (mg/ml)	277.5±75.5	321.8±54.6	NS	200–400
FDP (µg/ml)	2.03±0.19	2.13±0.59	NS	<5.0
D-dimer (µg/ml)	0.62±0.1	0.73±0.34	NS	≤1.0
TAT (ng/ml)	13.7±6.6	15.5±13.6	NS	<4.0
PIC (µg/ml)	0.44±0.32	0.48±0.29	NS	≤0.8
PTF1+2 (pmol/l)	258.7±95.0	240.8±110.9	NS	69–229
Protein C (%)	85.3±11.7	88.9±19.5	NS	≥70%
Protein S (%)	72.5±6.6	87.1±13.6	0.017	≥70%
thrombomodulin (FU/ml)	2.37±0.73	2.19±0.62	NS	2.1–4.1
PAI-1 (ng/ml)	22.4±6.9	28.4±10.8	NS	≤50

CA : catheter ablation, SCL : silent cerebral lesion, PT : prothrombin time, PT-INR : prothrombin time-international normalized ratio, APTT : activated partial thromboplastin time, FDP : fibrin-/fibrinogen-degradation products, TAT : thrombin–antithrombin complex, PIC : plasmin- α 2 plasmin inhibitor complex, PTF1+2 : prothrombin fragment 1+2, PAI-1 : plasminogen activator inhibitor, NS : not significant. Values are given as mean±standard deviation.

thromboembolic, and any bleeding events in the rivaroxaban group were low (0.4%, 0.8%, and 7.2%, respectively), supporting that the safety and efficacy of uninterrupted rivaroxaban in the perioperative period of CA for AF. However, antidotes for rivaroxaban are not yet available on the market¹²⁾, so punctures to arteries and veins should be made carefully at a peak dose of rivaroxaban in cases receiving uninterrupted rivaroxaban therapy. Oral administration in the evening one day before the procedure like in VENTURE-AF¹¹⁾, which is not the maximum blood concentration of rivaroxaban, may be ideal for ensuring a good balance of efficacy and safety with uninterrupted rivaroxaban therapy.

We empirically suggest that CA should be performed in the context of a PT-INR of 2.0 or less if using warfarin or with skipping rivaroxaban entirely on the morning of CA if using rivaroxaban. If antidotes for rivaroxaban become available, CA could be performed more than three hours after the last dose of rivaroxaban is given.

Silent cerebral lesions associated with catheter ablation

The incidence of symptomatic cerebral thromboembolic events caused by CA for AF has been reported to range from 0.5% to 1.0%^{13, 14)} and the incidence of asymptomatic SCL detected by

MRI ranges from 11% to 50%¹⁵⁻¹⁷). In our study, no symptomatic embolic events occurred and the incidence rates of SCL were 26.6% in the warfarin group and 38.1% in the rivaroxaban group—almost the same as that stated in previous reports.

The relatively lower incidence rate of SCL in the warfarin group was due to the difference in PT-INR, which was longer in the warfarin group (1.75 ± 0.43) than that in the rivaroxaban group (1.11 ± 0.07).

Coagulation tests

PTF1+2, TAT, and D-dimer are markers of an active coagulating system, while PAI-1 and PIC are markers of an active fibrinolytic system. Proteins C and S affect the inactivation of factors VII and V, while thrombomodulin has a strong affinity for thrombin. Finally, thrombomodulin with thrombus lead to anticoagulant effect¹⁸).

To our knowledge, there is no report investigating thrombotic biomarkers such as PTF1+2, PAI-1, and TAT, and SCL during the circumstance of CA performed under warfarin or a DOAC.

The values of protein C, protein S, and PT in the warfarin group were significantly decreased relative to those in the rivaroxaban group because the anticoagulant effect of warfarin usually lingers for a few days. These results seem to be reasonable because vitamin K is critical for the synthesis of many coagulation factors including prothrombin, factors II, VII, IX, X and proteins C and S.

Moreover, there is no report available investigating the association with the incidence of SCL. Here, we could not find significant differences between the SCL and no-SCL groups under warfarin except regarding the value of D-dimer, which was significantly increased in the SCL group, even though it remained within the normal range. On the other hand, the value of protein S under rivaroxaban was decreased significantly in the SCL group, albeit similarly within the normal range. The deficiency of protein S is known to facilitate the formation of thrombus; therefore, a decrease in protein S may be correlated with the increased incidence of SCL under rivaroxaban administration.

Limitations

First, the number of patients in this study was small and a larger sample size is needed in the future. Second, the study was randomized but it included different proportions of the sexes between the warfarin and rivaroxaban groups. Third, heparin infusion was discontinued for three hours before CA but the effect of heparin may have remained during the procedure.

Conclusions

In this randomized study of Japanese patients, the usage of rivaroxaban in the perioperative period of CA for AF was safer when considering the incidence of minor bleeding as compared with warfarin. In patients taking rivaroxaban, a lower protein S level may be correlated with the incidence of SCL in CA.

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