Analysis of recurrent stroke volume and prognosis between warfarin and four NOACs (non-vitamin K antagonist oral anticoagulants) administration for secondary prevention of stroke.

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Abstract

Objective. We investigated recurrent stroke volume with nonvalvular atrial fibrillation (NVAF) patients treated with non-vitamin K antagonist oral anticoagulants (NOACs) about clinical backgrounds and number of recurrent stroke. **Methods.** We administered four NOACs, dabigatran, rivaroxaban, apixaban and edoxaban in 101 post cardioembolic stroke with NVAF. In retrospective study, we measured recurrent stroke volume with MRI volumetric soft and compared them between 10 vitamin K anticoagulant (VKA: warfarin) cases and 13 NOACs cases under anticoagulant therapy. **Results.** Of 101 cases, 31 cases were started with VKA and switched to NOACs after 10 recurrent strokes. Other 70 cases were directly started with NOACs and 13 cases with NOACs as first anticoagulants had recurrent stroke. The frequency of recurrent stroke during anticoagulant therapy are not different among VKA group and three NOACs group. Recurrent stroke volume is significantly larger in VKA group (26.4 cm^3) than in NOACs group (3.8cm^3). **Conclusions.** Secondary prevention with NOACs after stroke might be more beneficial by reducing recurrent infarct volume than VKA.

1. Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) have gradually changed anticoagulant therapy with non-inferiority to vascular event and decreasing major bleeding in atrial fibrillation and venous thrombosis (1-4). We have treated post stroke patients with four types of NOACs for 4 years. However, there is no clear consensus for selection of NOACs. A meta-analysis showed that dabigatran 300mg daily (Odds Ratio: OR 0.66) and apixaban 5mg daily (OR 0.78) were more effective to prevent stroke and systemic embolism than other NOACs. It also showed that edoxaban 30mg daily (OR0.46) and apixaban 5mg daily (OR 0.69) were more effective to prevent major bleedings than other NOACs (5). We selected 101 post stroke cases with NOACs for prevention of recurrent ischemic strokes in retrospective study. Although some studies revealed patients taking NOACs appeared to present lower risk of intracranial hemorrhage and inhibit increasing of hemorrhage volume, ischemic stroke have not been fully examined (6-10). We examined the recurrent stroke volumes and clinical outcome under taking NOACs and compared with recurrent cases under vitamin K anticoagulant (VKA: warfarin).

2. Subjects and Method

101 post embolic stroke patients with nonvalvular atrial fibrillation (NVAF) (mean age 80±9 years) were treated with four types of NOACs for 4 years from October 2011

to September 2016. NVAF was diagnosed by atrial fibrillation within 14 days after admission without rheumatic mitral valve disease, history of prosthetic mitral valve replacement and infectios endocarditis. During the study period, the direct thrombin inhibitor, dabigatran (March 2011), the factor Xa inhibitors, rivaroxaban (April 2012), apixaban (February 2013) and edoxaban (October 2015) were clinically available in Japan. The eligibility for anticoagulant drugs and selection of NOACs have been freely determined by each stroke neurological physician without any definite intervention. NOACs administration in cardioembolic stroke cases due to NVAF were divided into two arms (Figure). Our enrolled 101 patients with NOACs contains 15 cases with dabigatran (DA), 43 cases with rivaroxaban (RI), 33 cases with apixaban (AP) and 10 cases with edoxaban (ED) as using NOACs finally. We divided 101 post stroke patients with four NOACs into two groups which first anticoagulant therapy with VKA or NOACs as prevention therapy of cardioembolic stroke onset.

Basic clinical characteristics included age, gender, body weight (kg) and type of atrial fibrillation (chronic or paroxysmal). To stratify risk factors of stroke event, we calculated $CHADS_2$ score, CHA_2DS_2-VASc score and HAS-BLED score after the onset of first cardioembolic stroke and before administration of VKA and NOACs. Hypertension was defined as blood pressure levels $\geq$ 140/90mmHg or by use of antihypertensive drugs. Diabetes mellitus was defined as hemoglobin A1c (HbA1c NGSP) level $\geq$ 6.5% or by use of oral antidiabetic drugs or insulin. Dyslipidemia was defined as a serum cholesterol level $\geq$ 220mg/dl or by use of lipid-lowering drugs including statin. CKD was defined as either positive proteinuria or eGFR<60ml/min/1.73m^2. The data of blood chemistry were noted with the prothrombin time-international normalized ratio (PT-INR), d-dimer, creatinine clearance and brain natriuretic peptide (BNP). The number of cases with recombinant tissue plasminogen activator (rt-PA) on acute stroke therapy was also counted retrospectively.

The clinical outcomes were estimated with hospitalization period (days) of first stroke event without recurrence and the period of recurrent event. It also includes improvement in National Institute of Health Stroke Scale (NIHSS) between admission and discharge during VKA and NOACs, modified Rankin Scale (mRS) on discharge, tube feeding on discharge. We calculated total stroke volume which was measured with MRI Volumetry soft: MRIcron (http://www.cabiatl.com/mricro/mricron/install.html). Total stroke volume（cm^3）is Σ all slices of stroke lesions（cm^2）×slice thickness（cm） with diffusion weighted image (DWI) axial MR images with the intensity threshold used by our previous reports (11). Modified Rankin Scale (mRS) as a clinical outcome is estimated correlation with total stroke volume. Cerebral microbleeds and hemorrhagic

infarction were diagnosed with T2*-weighted MRI scans. The study protocol was approved by the ethics committees of Shimane University, Faculty of Medicine.

Statistical analysis: We compared clinical factors in two groups of patients with VKA or NOACs after the onset of cardioembolic stroke by Mann Whitney U test (nonparametric data). And we also compared recurrent stroke cases with VKA or NOACs, no recurrent stroke cases with VKA or NOACs and recurrent versus no recurrent stroke in each VKA and NOACs by Mann Whitney U test. We used χ^2 test between VKA group and NOACs group for evaluating several clinical factors including type of atrial fibrillation, risk factors, concurrent antiplatelet drugs, treatment by t-PA, tube feeding, and recurrent stroke during VKA or NOACs (nonparametric data). Analysis of covariance is used to assess the statistical significance of mean differences in recurrent stroke volumes and mRS between NOACs and VKA. P value of <0.05 was considered statistically significant.

3. Results

Of 101 cardiac embolic stroke cases due to NVAF, 31 cases were started with VKA and switched to NOACs after 10 recurrent strokes or without 21 recurrent events. Other 70 cases were directly started with three NOACs and 13 of 70 NOACs as first anticoagulant had recurrent stroke (Figure). In 31 (31%) of 101 cases with using VKA, 10 cases had been switched into NOACs with recurrent stroke, and 21 cases had been also switched into NOACs without any event. In table 1, we showed the clinical background of VKA group and four NOACs group. The NOACs group is significantly lower in $CHADS_2$ score, CHA_2DS_2-VASc score, HAS-BLED score, mRS on discharge and NIHSS score on admission and discharge than VKA group. VKA group is significantly higher rate of chronic kidney disease (CKD) with lower Ccr and higher BNP. Although recurrent stroke occurred in 10 of 31 (32.3%) patients in VKA group and in 13 of 70 (18.5%) in NOACs group, we could not find any difference between two groups.

In table 2, we can recognize the baseline characteristics of recurrent or no recurrent case with each anticoagulant, VKA or NOACs. In recurrent cases of the VKA group had lower body weight and higher risk score with stroke event predicted by CHA_2DS_2-VASc score and HAS-BLED score. The VKA group in recurrent case has significantly higher rate of CKD with lower value of Ccr as well as basic characteristics in table 1. NOACs group had a shorter period of hospitalization, lower mRS on discharge and lower rate of tube feeding. On two columns right end of table 2, we can recognize that low body weight, presence of CKD and tube feeding is characteristic of VKA in recurrent patients. And we could find increased D-dimer in recurrent patients with NOACs (=3.03 μg/ml)

compared to recurrent patients with VKA (=1.58 μg/ml). The mean value of PT-INR in 10 recurrent strokes under VKA was 1.55 with under therapeutic range. Of 10 recurrent strokes under VKA, 6 patients (60%) had been in therapeutic range less than 1.8. Of 31 VKA therapy after second prevention, only 8 (25%) had been in therapeutic range more than 1.8 with PT INR.

In Table 3, 13 recurrent stroke cases (first dosage NOACs of 5 DA, 5 RI and 3 AP) under treatment of NOACs and 10 patients with VKA with their clinical backgrounds are presented. They have high age, low adherence, under dose of NOACs, malignancy and systemic atheromatous disease. Especially case number 11 patient in NOACs group showed small hemorrhage of left thalamus and hematoma had gradually disappeared after 20 days from stroke onset. After adjusting for age, concurrent antiplatelet, NIHSS on admission, microbleeds on MRI and complicated hemorrhage, the recurrent stroke volume is larger in VKA group (26.4 cm^3) than in NOACs group (3.8cm^3) ($p<0.05$, $F=5.35$). After adjusting for age, concurrent antiplatelet, NIHSS on admission and complicated hemorrhage, the mRS on discharge is lower in NOACs group (2.0) than in VKA group (3.7) ($p<0.05$, $F=3.88$).

4. Discussion

Antithrombotic therapy is recommended on the basis of assessment of risk factor of cerebral infarction with NVAF. Suitable anti-coagulate drugs could be selected by both of $CHADS_2$ scores and CHA_2DS_2-VASc scores (12, 13). The incidence of cerebral infarction is ≥4% among patients with the score of $CHADS_2 \geq 2$, so all of four NOACs and VKA are recommended (12, 14). CHA_2DS_2-VASc score considering over 65 years of age, sex category, vascular diseases including prior myocardial infarction of ≥ 1 is also recommended with all of four NOACs and VKA (13, 14). However we have no definite consensus for selection of NOACs. Our eligibility for anticoagulant drugs and selection of NOACs which had been freely determined by each physician is equal to recent multicenter prospective cohort study (da Vinci study) (15).

RE-LY trial showed that the rate of hemorrhagic stroke was 0.38% per year in the VKA group, as compared with 0.12% per year with 110 mg of dabigatran ($P<0.001$) and 0.10% per year with 150 mg of dabigatran ($P<0.001$) (1). ROCKET-AF trial showed that rivaroxaban group showed significant reduction in intracranial hemorrhage as compared with VKA group (0.5% vs. 0.7%, $P=0.02$) (4). ARISTOTLE trial showed that the rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the VKA group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; $P<0.001$)(3). All of three NOACs have lower rate in major bleeding and intracranial hemorrhage in these major

studies and superior to VKA in prevention of bleeding events. Patients with HAS-BLED score ≥ 3 have high risk for major bleeding, so all of our three NOACs groups with mean HAS-BLED score ≥ 3 might been adequate to use NOACs (16).

Our NOACs group is significantly lower in $CHADS_2$, CHA_2DS_2–VASc, HAS-BLED, NIHSS on admission and discharge than VKA group. And our VKA group in recurrent case has significantly higher rate of CKD with lower value of Ccr. Toyoda et al and SAMURAI Study Investigators reported that post stroke patients taking NOACs due to NVAF had more frequently lower scores for $CHADS_2$, CHA_2DS_2–VASc, HAS-BLED, admission NIHSS and discharge mRS (17). Fujimoto et al reported that NOACs were preferentially chosen for the patients with lower severity and better renal function in current status of choice of oral anticoagulants (18). Our results equal to these reports in Japan. Our results showing the rate of stroke recurrence with 32.2% in VKA group and 18.6% in NOACs group without significant difference between two groups also equals to mega trial in ROCKET-AF and sub analysis in ARISTOTLE trial (3, 4, 19). The reason for the characteristic of dabigatran could not be not crushed and were not fitted with a nasogastric tube in severe stroke patients with dysphagia. So our group might be tend to choice dabigatran for patients with milder neurological symptom (6, 15). Following oral administration of apixaban, urinary excretion is approximately 27% of the total clearance in healthy subjects, and it is lowest elimination in kidney among four NOACs (20-22). Relative low renal excretion could make us choice apixaban in subjects with renal dysfunction. Exactly our patients treated with apixaban was 54.5(mL/min) in creatinine clearance and is not significantly lower than two other NOACs.

We can see several studies about stroke volume and anti-coagulant therapy. Hagii et al reported that rivaroxaban-associated intracranial hemorrhage (ICH) had relatively small hematoma and no expansion of hematoma compared with VKA-associated ICH (7). Matsumoto M et al reported that therapeutic anticoagulation by VKA (PT-INR>1.6) reduces infarct volume and improves neurological outcome after ischemic stroke in patients with NVAF (23). Hakan et al reported that patients who were on therapeutic PT-INR (>2.0) had smaller infarcts compared with patients without preadmission VKA use ($p<0.001$). Preadmission VKA use associated with therapeutic level of anticoagulation can offer a benefit in limiting the extent of ischemic injury and volume in an event of acute stroke (24). NOACs could act as neuro-protectors by inhibiting the activation of matrix metalloproteinase-9 which significantly reduces brain infarct size in early inhibition (25, 26). We hypothesized that NOACs might contribute stroke volume at minimum because of decreased ischemic stroke events (5). Coagulation Factor X is an

important amplifier of both the intrinsic and extrinsic activation pathways. Under-dose of VKA with sub-therapeutic PT-INR values were found in 74% of first ischemic stroke with NVAF and 68% of those with recurrent stroke (27, 28). Of our 10 recurrent ischemic strokes with VKA 6 patients (60%) were under sub-therapeutic PT-INR value, and its percentage is near the previous reports. Direct Factor Xa inhibitor, rivaroxaban cause more permeable to flow in fibrin network and decreased degradation of plasma clots being formed with a looser structure in the presence of rivaroxaban (29).

Thrombin acts as the agonist for platelet activation and aggregation on the vascular endothelium. It generates fibrin formation and deposition on the cerebral vessel wall during focal ischemia and induces increasing vascular permeability within micro vessels in the territory at risk (30). Thrombin inhibitor, dabigatran has antiplatelet effect with blocking platelet signaling pathways (30, 31). Otherwise Factor Xa initiates intracellular protease activated receptor mediated signaling which contributes to the production of interleukin-6, interleukin-8, chemokine ligand and expression of cell-adhesion molecules (32). FXa inhibitors have a possibility to inhibit progression of atherosclerotic plaque by suppress these proatherogenic cellular responses. The efficacy of stable blood concentration, the direct thrombin inhibitor or the factor Xa inhibitors as specific and narrow blockers in coagulating pathways with NOACs also might contribute to less stroke event and smaller volume in ischemic stroke.

The superiority of NOACs to VKA is still controversial, because Japanese prospective survey of patients with atrial fibrillation, the Fushimi AF registry showed any significant difference in stroke events or major bleeding between VKA and NOACs for five years. In real clinical status, patients treated by oral anticoagulant (OAC) have gone through several transitions of drug status (VKA, NOACs and no OAC)(33). It is not easy exact evaluation for anticoagulant drugs because of these changes of prescription with OAC.
Study limitations: Our study may have been influenced by relatively small sample size and retrospective study. Randomized control trial will be needed to make anticoagulant treatment definitively.

5. Conclusion

Secondary prevention with NOACs after stroke might be more beneficial by reducing infarct volume and modified Rankin Scale in recurrent stroke compared to VKA, warfarin.

Conflict of Interests

The authors have the scholarship donations from Bayer Yakuhin, Ltd and Pfizer Japan Inc.

Legend

Figure

Two arms of NOACs administration.

NVAF: nonvalvular atrial fibrillation

NOACs: non-vitamin K antagonist oral anticoagulants

Table 1

Clinical characteristics of the cardioembolic patients under each anticoagulant therapy with VKA or NOACs as first prevention post cardioembolic stroke.

VKA: vitamin K antagonists, warfarin, NOACs: non-vitamin K antagonist oral anticoagulants, CKD: chronic kidney disease, PT-INR: prothrombin time-international normalized ratio, rt-PA: recombinant tissue plasminogen activator, NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale

Table 2

The baseline characteristics of patients who had recurrent stroke and those who had no recurrent stoke in VKA group and NOACs group.

VKA: vitamin K antagonists, warfarin, NOACs: non-vitamin K antagonist oral anticoagulants , CKD: chronic kidney disease, PT-INR: prothrombin time-international normalized ratio, rt-PA: recombinant tissue plasminogen activator, NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale

Table 3

13 recurrent stroke cases with NOACs and 10 recurrent stroke cases with VKA.

NOACs: non-vitamin K antagonist oral anticoagulants ,VKA: vitamin K antagonists, warfarin, mRS: modified Rankin Scale, DA: dabigatran, RI：rivaroxaban, AP：apixaban, Re: recurrent, 1^{st}: first event

Type of stroke: CE：cardioembolic stroke, AT：atherothrombotic brain infarction, TIA：transient ischemic attack, CH：cerebral hemorrhage * $p<0.05$

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Figure

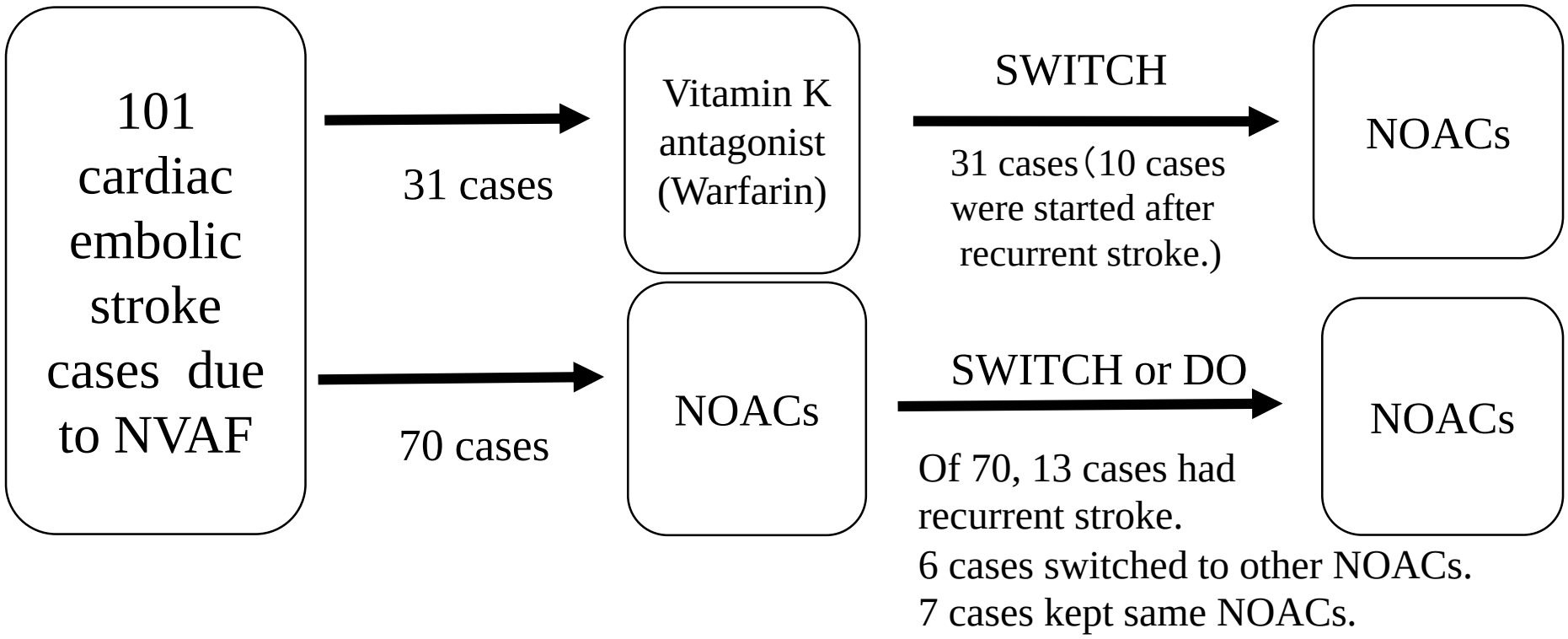
101 cardiac embolic stroke cases due to NVAF
31 cases
Vitamin K antagonist (Warfarin)
SWITCH
31 cases（10 cases were started after recurrent stroke.)
NOACs
70 cases
NOACs
SWITCH or DO
Of 70, 13 cases had recurrent stroke.
6 cases switched to other NOACs.
7 cases kept same NOACs.
NOACs

Table 1

	VKA(warfarin) n = 31	NOACs n = 70	P value
Basic characteristics			
Age(y)	81 (77-87)	81 (73-87)	0.21
Male gender (%)	16 (52)	34 (48)	0.95
Body weight (kg)	53 (43-60)	55 (44-63)	0.64
Type of atrial fibrillation (chronic/paroxysmal)(%)	28(90)/3(10)	43(61)/27(39)	0.01
Risk stratification			
$CHADS_2$ score	5 (4-5)	4 (3-5)	<0.001
CHA_2DS_2-VASc score	6 (6-7)	5 (4-6)	<0.0001
HAS-BLED score	4 (3-4)	3 (2-3)	<0.01
Hypertension (%)	26 (84)	59 (84)	0.99
Diabetes mellitus (%)	8 (26)	14 (20)	0.69
Dyslipidemia (%)	9 (29)	22 (31)	0.99
CKD (%)	19 (61)	17 (24)	<0.001
Concurrent antiplatelet (%)	4 (13)	15 (21)	0.46
Blood chemistry			
PT-INR on admission	1.32 (1.12-1.80)	1.03 (0.97-1.10)	<0.0001
D-dimer （μg/ml)	1.60 (0.60-3.00)	0.90 (0.50-2.32)	0.19
Ccr (mL/min)	48.0 (36.0-62.0)	62.0 (43.0-81.0)	<0.05
BNP (pg/ml)	297 (180-439)	171 (121-265)	<0.01
Treatment			
rt-PA thrombolysis (%)	3(10)	8(11)	0.99
Outcomes			
Period of hospitalization (days)	25 (11-33)	23 (10-31)	0.55
NIHSS on admission	8.0 (4.0-14.0)	4.0 (2.0-10.5)	<0.05
NIHSS on discharge	5.0 (2.0-14.0)	2.0 (1.0-6.3)	<0.05
Improvement in NIHSS	-2.0 (-4.0- -1.0)	-1.0 (-3.0- -1.0)	0.53
mRS on discharge	4.0 (1.0-5.0)	2.0 (1.0-4.0)	<0.05
Tube feeding (%)	10 (32)	8 (11)	<0.05
Recurrent stroke (%)	10 (32)	13 (19)	0.21

Table 2

	Recurrent case with anticoagulant			No recurrent case with anticoagulant			Recurrent vs no recurrent	
	VKA (warfarin)	NOACs		VKA (warfarin)	NOACs		VKA (warfarin)	NOACs
	n = 10	n = 13	P value	n = 21	n = 57	P value	P value	P value
Basic characteristics								
Age(y)	82 (79-88)	80 (71-87)	0.29	81 (77-87)	82 (73-87)	0.62	0.21	0.95
Male gender (%)	4 (40)	7 (54)	0.79	12 (57.1)	27 (47.4)	0.61	0.60	0.91
Body weight (kg)	43 (39-52)	56 (51-65)	<0.01	57 (50-64)	54 (43-62)	0.25	<0.01	0.23
Type of atrial fibrillation (chronic/paroxysmal)(%)	10(100)/0(0)	10(77)/3(23)	0.11	18(86)/3(14)	33(58)/24(42)	<0.05	0.53	0.33
Risk stratification								
$CHADS_2$ score	4 (4-5)	4 (3-5)	0.14	5 (4-5)	4 (3-5)	<0.01	0.88	0.56
CHA_2DS_2-VASc score	6 (6-7)	6 (4-7)	<0.05	6 (5-7)	5 (4-6)	<0.01	0.13	0.67
HAS-BLED score	4.0 (3.7-4.0)	3 (3-4)	<0.05	3 (3-4)	3 (2-3)	0.06	0.11	0.43
Hypertension (%)	9 (92)	12 (90)	0.99	17 (81)	47 (83)	0.99	0.89	0.64
Diabetes mellitus (%)	2 (20)	2 (15)	0.99	6 (29)	12 (21)	0.69	0.93	0.64
Dyslipidemia (%)	2 (20)	6 (46)	0.37	7 (33)	16 (28)	0.86	0.72	0.35
CKD (%)	9 (90)	4 (31)	<0.05	10 (48)	13 (23)	0.06	0.06	0.81
Concurrent antiplatelet (%)	1 (10)	3 (23)	0.77	3 (14)	12 (21)	0.72	0.99	0.99
Blood chemistry								
PT-INR on admission	1.36 (1.22-1.86)	1.10 (1.03-1.15)	<0.001	1.29 (1.06-1.65)	1.02 (0.97-1.08)	<0.0001	0.18	<0.05
D-dimer （μg/ml)	1.35 (0.5-3.12)	0.60 (0.15-1.65)	0.17	1.9 (0.7-3.0)	1.10 (0.57-2.75)	0.19	0.30	<0.05
Ccr (mL/min)	42.5 (27.7-52.5)	76.0 (57.5-94.5)	<0.05	51.0 (38.2-69.5)	58.0 (42.0-79.0)	0.43	0.09	0.24
BNP (pg/ml)	276 (216-384)	165 (116-230)	<0.05	331 (159-453)	176 (134-265)	<0.05	0.98	0.98
Treatment								
rt-PA thrombolysis (%)	0 (0)	1 (8)	0.99	3 (10.0)	7 (9)	0.99	0.53	0.99
Outcomes								
Period of hospitalization (days)	29 (16-48)	18 (6-30)	0.07	23 (10-31)	24 (11-32)	0.56	0.11	0.24
NIHSS on admission	8.5 (6.0-15.5)	5.0 (2.0-18.0)	0.09	8.0 (3.2-13.0)	4.0 (2.0-10.0)	0.08	0.55	0.86
NIHSS on discharge	5.5 (2.7-9.5)	4.0 (1.0-4.5)	<0.05	4.5 (2.0-15.3)	2.0 (0.7-8.0)	0.15	0.48	0.76
Improvement in NIHSS	-2.0 (-4.7- -0.7)	-2.0 (-7.0- -1.0)	0.87	-2.0 (-3.7- -1.0)	-1.0 (-3.0 - -0.8)	0.47	0.93	0.48
mRS on discharge	4.0 (2.8-4.3)	2.0 (0.5-4.0)	<0.05	3.0 (1.0-5.0)	4.0 (1.0-5.0)	0.26	0.48	0.55
Tube feeding (%)	6 (60)	1(8)	<0.01	4 (19)	7 (12)	0.69	0.06	0.99
Recurrent stroke volume (cm^3)	26.4 (4.7-41.9)	1.2 (0.2-7.2)	<0.01					

Table 3

	Case	Age	Initial amount of NOACs	Type of Stroke	Switched NOACs	Stroke volume (cm^3)	Discharge mRS	Hemorrhagic infarction
NOACs group (n=13)	1	67	DA 300mg	CCE Re	DA 300mg	0.481	1	none
	2	71	DA 220mg	AT Re	DA 300mg	0.325	0	none
	3	67	RI 15mg	CCE 1st	DA 300mg	1.161	2	none
	4	86	RI 10mg	CCE Re	RI 10mg	15.950	1	none
	5	74	DA 220mg	CCE 1st	DA 220mg	0.051	3	none
	6	89	RI 10mg	AT Re	AP 5mg	0.075	0	none
	7	72	RI 15mg	CCE Re	AP 10mg	1.275	2	none
	8	80	AP 5mg	TIA	AP 5mg	0	0	none
	9	92	DA 220mg	CCE Re	AP 5mg	7.692	4	none
	10	78	DA 220mg	CCE Re	RI 10mg	6.710	4	positive
	11	88	AP 5mg	CH Re	AP 5mg	1.020	4	none
	12	84	AP 5mg	AT Re	AP 5mg	12.020	5	positive
	13	74	RI 15mg	CCE Re	ED 60mg	2.688	2	none
	Median (IQR)	80 (71-87)				**1.161 (0.200-7.201)***	**2.0 (0.5-4.0)**	
Warfarin group (n=10)	1	82		CCE Re	RI 10mg	24.843	5	none
	2	71		CCE Re	DA 300mg	1.226	0	none
	3	82		CCE Re	RI 10mg	62.654	4	none
	4	81		CCE Re	RI 10mg	12.771	5	none
	5	90		CCE Re	API 5mg	59.092	4	none
	6	83		CCE Re	RI 15mg	3.280	4	positive
	7	88		CCE Re	API 5mg	28.071	4	none
	8	92		CCE Re	API 5mg	5.229	2	none
	9	78		CCE Re	ED 30mg	36.174	3	none
	10	80		CCE Re	ED 30mg	31.050	4	none
	Median (IQR)	82 (79-88)				**26.457 (4.742-41.903)***	**4.0 (2.8-4.3)**	