Insufficient Warfarin Therapy Is Associated With Higher Severity of Stroke Than No Anticoagulation in Patients With Atrial Fibrillation and Acute Anterior-Circulation Stroke

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Background: Insufficient anticoagulant intensity on admission is common in stroke patients with atrial fibrillation (AF) on vitamin K antagonist (VKA) therapy. Nevertheless, the effects of VKA under-treatment on stroke severity or arterial occlusion are not well known. The aim of the present study was to investigate the relationship between insufficient VKA therapy and stroke severity, or the site of arterial occlusion in patients with acute ischemic stroke (AIS) and AF.

Methods and Results: From March 2011 through July 2016, 446 consecutive patients with AF and AIS were recruited. Of the 446 patients, 364 (167 women; median age, 79 years; IQR, 71–86 years) with anterior-circulation stroke were assessed to investigate the effects of insufficient VKA. Of these, 281 were on no anticoagulant, 53 were undertreated with a VKA, and 30 were sufficiently treated with VKA on admission (PT-INR ≥2.0 for patients <70 years and PT-INR ≥1.6 for ≥70 years old). On multivariate analysis, insufficient VKA was independently associated with severe stroke (i.e., initial NIHSS score ≥10; OR, 2.70, P=0.022) and higher prevalence of proximal artery occlusion (OR, 1.91; P=0.039) compared with no anticoagulant therapy.

Conclusions: Insufficient VKA therapy on admission was associated with higher severity of stroke and higher prevalence of proximal artery occlusion in patients with AF and acute anterior-circulation stroke compared with no anticoagulant medication.

Key Words: Anterior circulation; Arterial occlusion; Atrial fibrillation; Severity; Vitamin K antagonist

Patients with atrial fibrillation (AF) often develop severe ischemic stroke and have poor outcomes after stroke, even with thrombolytic therapy. Sufficient anticoagulant treatment with a vitamin K antagonist (VKA) has been proven to reduce the incidence of ischemic stroke for patients with AF. Moreover, VKA therapy, especially with sufficient anticoagulation, has been reported to reduce the severity and improve clinical outcomes of ischemic stroke in AF patients, compared with no anticoagulation. Decreasing clot size, with the resulting avoidance of major artery occlusion and hence small infarct volume, is the suggested main mechanism by which VKA alleviates initial symptoms in acute ischemic stroke (AIS) patients.

In the clinical setting, however, fewer than half of known AF patients are prescribed anticoagulant medication at stroke onset, and, even when treated with VKA, more than two-thirds of such stroke patients are on insufficient anticoagulation at admission. Insufficient VKA therapy has a limited prophylactic effect for thromboembolism in patients with AF, but the influence of insufficient VKA therapy on stroke severity or the site of arterial occlusion is not well known. The aims of the present study were therefore to investigate the relationships between insufficient VKA anticoagulant intensity at stroke onset and initial stroke severity or the site of arterial occlusion in patients with AIS and AF.

Methods

Subjects
From March 2011 through July 2016, consecutive AIS or transient ischemic attack (TIA) patients with AF who were admitted to the present stroke unit ≤7 days from symptom onset were retrospectively recruited from the prospective registry. In order to compare stroke severity between patients...
with prior insufficient VKA therapy and those with no anticoagulation or sufficient VKA therapy, patients pretreated with direct oral anticoagulants (DOAC) were excluded from the present study. This study was approved by the institutional ethics committee. Written, informed consent was obtained from all patients or their next-of-kin.

### Clinical Characteristics

Clinical background characteristics, including sex, age, cardiovascular risk factors, and past medical history, were recorded on admission. Cardiovascular risk factors were defined as follows: (1) hypertension, history of anti-hypertensive agents, systolic blood pressure $\geq 140$ mmHg, or diastolic blood pressure $\geq 90$ mmHg before or $\geq 2$ weeks after stroke onset; (2) hyperlipidemia, use of anti-hyperlipidemic agents, or serum total cholesterol $\geq 220$ mg/dL; (3) diabetes mellitus, use of hypoglycemic agents, random glucose $\geq 200$ mg/dL, or glycosylated hemoglobin $\geq 6.5\%$ on admission; and (4) current smoker. Pre-stroke CHADS$_2$ or CHA$_2$DS$_2$-VASc score was calculated for each patient based on the published guideline. Aortic plaque, however, was not assessed as a component of the score, because transesophageal echocardiography was performed for only approximately one-quarter of the present patients. The index stroke was not counted in the history of ischemic stroke. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Routine blood biochemistry was analyzed on admission.

### Neuroimaging

Magnetic resonance imaging (MRI) including diffusion-weighted imaging (DWI) and time-of-flight MR angiography (MRA) were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Echelon Oval, Hitachi Medical Systems, Tokyo, Japan). DWI was obtained using the following parameters: TR/TE, 6,000/65 ms; $b$-values, 0 and 1,000 m$^2$/s; field of view, 24 cm; acquisition matrix, 128$\times$128; and slice thickness, 4.5 mm, with a 2.5-mm intersection gap. The site of arterial occlusion was determined on initial MRA. Major artery occlusion was defined as internal carotid artery (ICA), middle cerebral artery (MCA) horizontal segment (M1), or basilar artery occlusion. When analyzing patients with anterior-circulation stroke, the site of arterial occlusion was divided into 4 categories based on initial MRA: at the ICA; at the M1; at the MCA insular segment (M2); and occlusion at another site or no identifiable occlusion. Although almost all ($97\%$) of the patients were evaluated on MRI on admission, patients with a contraindication to MRI were evaluated on computed tomography angiography or conventional angiography.
Insufficient Warfarin Leads to Severe Stroke

PT-INR $\geq 1.6$ for patients $\geq 70$ years old). The cut-off for sufficient VKA anticoagulation was based on previous studies in Japan and on a domestic guideline. Renal function was assessed using estimated glomerular filtration rate (eGFR) instead of creatinine clearance on admission.

First, univariate analysis was performed for all included patients using the chi-squared test, Fisher’s exact test, or the Kruskal-Wallis test, as appropriate. The data are given as median (IQR) or n (%). Next, the independent variables were identified on backward selection. Abbreviations as in Table 1.

Table 2. Multivariate Indicators of Severe Stroke (NIHSS Score $\geq 10$): Total Cohort

| Variable† | OR     | 95% CI   | P-value |
|-----------|--------|---------|---------|
| Hypertension | 1.65   | 0.97–2.80 | 0.066 |
| Congestive heart failure | 1.94   | 1.00–3.76 | 0.049 |
| Pre-admission mRS score (per 1 point) | 1.55   | 1.28–1.88 | $<0.001$ |
| Anterior-circulation stroke | 3.31   | 1.70–6.44 | $<0.001$ |
| Major artery occlusion | 18.12  | 9.75–33.66 | $<0.001$ |
| Chronic AF (vs. paroxysmal) | 2.01   | 1.14–3.54 | 0.017 |
| BNP (per 100 pg/mL) | 1.18   | 1.05–1.33 | 0.004 |

†Identified on backward selection. Abbreviations as in Table 1.

Table 3. Anterior-Circulation Stroke: Clinical Background Characteristics vs. AC Status

| Variables | No AC (n=281) | Insufficient VKA (n=53) | Sufficient VKA (n=30) | P-value |
|-----------|---------------|------------------------|----------------------|---------|
| Female    | 127 (45)      | 22 (42)                | 18 (60)              | 0.238   |
| Age (years) | 79 (71–86)   | 78 (72–86)          | 81 (74–89)          | 0.398   |
| Risk factor |                     |                       |                     |         |
| Hypertension | 175 (62)     | 33 (62)               | 21 (70)             | 0.703   |
| Dyslipidemia | 83 (30)       | 20 (38)               | 16 (53)             | 0.021   |
| Diabetes mellitus | 41 (15) | 10 (19)               | 4 (13)              | 0.699   |
| Current smoker | 49 (17)      | 8 (15)                | 2 (7)               | 0.305   |
| Congestive heart failure | 52 (19) | 20 (38)               | 8 (27)              | 0.007   |
| Prior embolism† | 42 (15)       | 21 (40)               | 9 (30)              | $<0.001$ |
| History of vascular disease‡ | 37 (13) | 12 (23)               | 1 (3)               | 0.042   |
| CHADS2 score | 2 (1–3)       | 3 (2–4)               | 2 (1–3)             | $<0.001$ |
| CHA2DS2-VASc score | 3 (2–5) | 4 (3–5)               | 4 (3–5)             | 0.001   |
| Chronic AF | 199 (71)      | 41 (77)               | 22 (73)             | 0.614   |
| Pre-admission antiplatelet use | 86 (31) | 12 (23)               | 3 (10)              | 0.038   |
| Pre-admission mRS score | 0 (0–1) | 0 (0–3)               | 0 (0–2)             | 0.011   |
| Onset to arrival (h) | 4.0 (2.0–11.9) | 3.0 (2.0–10.5) | 8.5 (2.0–23.5) | 0.561   |
| NIHSS score on admission | 11 (3–22) | 18 (8–26)           | 7 (3–19)           | 0.022   |
| Arterial occlusion at admission |                     |                       |                     | 0.010   |
| ICA | 41 (15) | 16 (30) | 2 (7) |
| M1 | 63 (22) | 5 (9) | 5 (17) |
| M2 | 34 (12) | 9 (17) | 2 (7) |
| None or other artery | 143 (51) | 23 (43) | 21 (70) |

Laboratory data at admission

| Variable | No AC (n=281) | Insufficient VKA (n=53) | Sufficient VKA (n=30) | P-value |
|---------|---------------|------------------------|----------------------|---------|
| aPTT (s) | 28.7 (26.2–31.8) | 30.4 (26.9–35.1) | 35.7 (33.4–38.7) | $<0.001$ |
| PT-INR | 1.08 (1.00–1.17) | 1.36 (1.16–1.47) | 2.07 (1.72–2.45) | $<0.001$ |
| Blood glucose (mg/dL) | 115 (102–144) | 117 (99–134) | 113 (98–142) | 0.503   |
| Creatinine (mg/dL) | 0.83 (0.66–1.04) | 0.82 (0.72–1.10) | 0.91 (0.72–1.18) | 0.448   |
| eGFR (mL/min) | 60 (48–75) | 58 (43–73) | 51 (34–68) | 0.124   |
| D-dimer (μg/mL) | 1.8 (0.9–3.3) | 1.6 (1.1–3.2) | 1.2 (0.7–2.7) | 0.093   |
| BNP (pg/mL) | 195 (111–389) | 235 (135–407) | 188 (63–335) | 0.313   |

Data given as n (%) or median (IQR). †Including ischemic stroke and systemic embolism; ‡including ischemic heart disease and peripheral artery disease. ICA, internal carotid artery; M1, middle cerebral artery horizontal segment; M2, middle cerebral artery insular segment. Other abbreviations as in Table 1.

Statistical Analysis

The patients were divided into 3 groups based on anticoagulant status on admission: no prior anticoagulant medication; undertreated with VKA (corresponding to warfarin treatment and prothrombin time-international normalized ratio [PT-INR] on admission $<2.0$ for patients $<70$ years old and PT-INR $<1.6$ for patients $\geq 70$ years old); and sufficient VKA (corresponding to warfarin treatment and PT-INR on admission $\geq 2.0$ for patients $<70$ years old and PT-INR $\geq 1.6$ for patients $\geq 70$ years old).
SAKAMOTO Y et al.

years; IQR, 71–85 years; n=346, 78% ≥70 years old; median NIHSS score, 10; IQR, 3–21; median onset to arrival, 4.5 h; IQR, 2.0–13.3 h) were enrolled in the present study. Of these 446 patients, 353 (79%) were on no anticoagulant medication, 58 (13%) were undertreated with VKA, and 35 (8%) were on sufficient VKA on admission.

Table 1 lists the patient clinical background characteristics. The proportions of patients with a history of dyslipidemia (P=0.009), congestive heart failure (P=0.011), and prior embolism (P<0.001); CHADS2 (P<0.001), CHA2DS2-VASc (P<0.001), and pre-admission modified Rankin scale (mRS, P=0.005) scores; and aPTT (P<0.001), PT-INR (P<0.001), eGFR (P=0.037), and D-dimer (P=0.031) were significantly different between the 3 groups. Although the initial NIHSS score was also significantly different between groups (median 9 in patients with no anticoagulation; 14 in insufficient VKA; and 7 in sufficient VKA; P=0.035, Table 1), on multivariate logistic regression analysis with backward stepwise selection there was no independent relationship between anticoagulant status on admission and severe stroke (anticoagulant status had been removed from the regression model after backward stepwise selection; Table 2).

Of the included patients, 364 (82%) had ischemic lesions in the anterior-circulation territory (167 women; median age, 79 years; IQR, 71–85 years; n=346, 78% ≥70 years old; median NIHSS score, 10; IQR, 3–21; median onset to arrival, 4.5 h; IQR, 2.0–13.3 h) were assessed on multivariate logistic regression analysis with a backward stepwise selection procedure. Then, the same analyses were performed for those with anterior-circulation stroke (developed in the anterior and middle cerebral artery territories). Variables available on admission (except for CHADS2 and CHA2DS2-VASc scores, activated partial thromboplastin time [aPTT], and PT-INR) were included in the models (Table 1). Backward selection was carried out using P>0.1 of the likelihood ratio test for exclusion. The relative risks of severe stroke are expressed as OR with 95% CI. Finally, multivariate ordinal logistic regression analysis was performed to identify independent factors associated with higher prevalence of proximal arterial occlusion in patients with anterior-circulation stroke. This model allows the outcome variable to have >2 categories and estimates proportional OR for each predictor of shifting to a more proximal arterial occlusion category (e.g., no occlusion vs. M2, M1, and ICA occlusion; no and M2 occlusion vs. M1 and ICA occlusion; and no, M2, and M1 occlusion vs. ICA occlusion). Sex, age, and all clinical characteristics identified on univariate analysis at P<0.1 were entered into the model. In the multivariate ordinal regression model, CHADS2 and CHA2DS2-VASc scores were excluded due to duplication of variables, and initial NIHSS score was also excluded, because this parameter is a consequence of, rather than a factor associated with, arterial occlusion. All statistical analysis was performed using PASW for Windows version 17.0 (SPSS, Chicago, IL, USA). Results were considered significant at P<0.05.

Results

Overall, 489 consecutive patients with AF and AIS were admitted to the stroke center during the study period. Of these, 43 patients were excluded due to prior DOAC treatment. Finally, 446 patients (189 women; median age, 79 years; IQR, 71–85 years; n=346, 78% ≥70 years old; median NIHSS score, 10; IQR, 3–21; median onset to arrival, 4.5 h; IQR, 2.0–13.3 h) were enrolled in the present study. Of these 446 patients, 353 (79%) were on no anticoagulant medication, 58 (13%) were undertreated with VKA, and 35 (8%) were on sufficient VKA on admission.

Table 1 lists the patient clinical background characteristics. The proportions of patients with a history of dyslipidemia (P=0.009), congestive heart failure (P=0.011), and prior embolism (P<0.001); CHADS2 (P<0.001), CHA2DS2-VASc (P<0.001), and pre-admission modified Rankin scale (mRS, P=0.005) scores; and aPTT (P<0.001), PT-INR (P<0.001), eGFR (P=0.037), and D-dimer (P=0.031) were significantly different between the 3 groups. Although the initial NIHSS score was also significantly different between groups (median 9 in patients with no anticoagulation; 14 in insufficient VKA; and 7 in sufficient VKA; P=0.035, Table 1), on multivariate logistic regression analysis with backward stepwise selection there was no independent relationship between anticoagulant status on admission and severe stroke (anticoagulant status had been removed from the regression model after backward stepwise selection; Table 2).

Of the included patients, 364 (82%) had ischemic lesions in the anterior-circulation territory (167 women; median age, 79 years; IQR, 71–86 years; n=289, 79% ≥70 years old; median NIHSS score, 12; IQR, 3–22; median onset to arrival, 4.0 h; IQR, 2.0–12.0 h). Table 3 lists the clinical background characteristics of these patients. Prevalence of history of dyslipidemia (P=0.021), congestive heart failure (P=0.007), prior embolism (P<0.001), vascular disease (P=0.042), and pre-admission antiplatelet use (P=0.038), and the CHADS2 (P<0.001) and CHA2DS2-VASc (P<0.001) scores, pre-admission mRS (P=0.011) score, site of arterial occlusion on admission (P=0.010, Figure), and aPTT (P<0.001) and PT-INR (P<0.001) were significantly different between the 3 groups: stroke patients with insufficient VKA on admission tended to have a higher prevalence of...
Insufficient Warfarin Leads to Severe Stroke

stroke severity in patients with AIS and AF compared with no anticoagulant therapy.\(^5\)\(^7\) There have been few reports, however, on the effects of insufficient VKA on stroke severity or the site of arterial occlusion, especially in the setting of a relatively lower PT-INR target (≥1.6 for patients ≥70 years old).\(^20\) Insufficient VKA treatment was independently associated with higher severity of stroke and higher prevalence of proximal artery occlusion in the present study, and this seems pharmacokinetically plausible: the functional activity of protein C — the protein that has the anticoagulant effect — is decreased even in the subtherapeutic PT-INR range.\(^22\) Insufficient VKA therapy may lead to larger thrombus formation than in those without anticoagulant medication through insufficient suppression of coagulation factors plus suppression of functional activity of protein C, and it may be associated with more severe stroke via proximal artery occlusion. This association was found only in patients with anterior-circulation stroke, probably because the relationship between vessel occlusion and NIHSS score in posterior-circulation stroke patients was relatively weaker than in anterior-circulation stroke.\(^10\) The present study showed that insufficient VKA on admission was independently associated with higher severity of stroke and higher prevalence of proximal artery occlusion in patients with AF and acute anterior-circulation stroke, compared with no anticoagulant before the index stroke.

**Discussion**

The present study showed that insufficient VKA on admission was independently associated with higher severity of stroke and higher prevalence of proximal artery occlusion in patients with AF and acute anterior-circulation stroke, compared with no anticoagulant before the index stroke. Sufficient VKA on admission has been shown to reduce

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### Table 4. Multivariate Indicators of Severe Stroke (NIHSS Score ≥10) in Anterior-Circulation Stroke Patients

| Variable† | OR    | 95% CI      | P-value |
|-----------|-------|-------------|---------|
| Hypertension | 1.80  | 0.94–3.44  | 0.078   |
| Pre-admission mRS score (per 1 point) | 1.54  | 1.24–1.92  | <0.001  |
| Arterial occlusion on admission | | | |
| No occlusion | 1.00  | Ref.        |         |
| M2          | 5.59  | 2.53–12.4  | <0.001  |
| M1          | 35.4  | 13.9–90.0  | <0.001  |
| ICA         | 45.1  | 12.6–161.3 | <0.001  |
| Chronic AF (vs. paroxysmal) | 2.02  | 1.03–3.98  | 0.042   |
| Glucose (per 10 mg/dL) | 1.07  | 0.99–1.16  | 0.087   |
| BNP (per 100 pg/mL) | 1.21  | 1.05–1.39  | 0.007   |
| AC status prior to the event | | | |
| No AC | 1.00  | Ref.        |         |
| Insufficient VKA | 2.70  | 1.15–6.34  | 0.022   |
| Sufficient VKA | 0.92  | 0.31–2.70  | 0.880   |

†Identified on backward selection. Abbreviations as in Tables 1,3.

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### Table 5. Multivariate Indicators of Proximal Artery Occlusion

| Variable | OR    | 95% CI      | P-value |
|----------|-------|-------------|---------|
| Female sex | 1.09  | 0.69–1.71  | 0.723   |
| Age (per 10 years) | 1.52  | 1.19–1.94  | 0.001   |
| Dyslipidemia | 0.57  | 0.36–0.90  | 0.017   |
| Congestive heart failure | 1.32  | 0.79–2.21  | 0.293   |
| Prior embolism | 0.43  | 0.24–0.77  | 0.004   |
| BNP (per 100 pg/mL) | 1.10  | 1.04–1.16  | 0.001   |
| D-dimer (per 1 μg/mL) | 1.07  | 0.98–1.16  | 0.120   |
| AC status prior to the event | | | |
| No AC | 1.00  | Ref.        |         |
| Insufficient VKA | 1.91  | 1.03–3.51  | 0.039   |
| Sufficient VKA | 0.46  | 0.20–1.06  | 0.070   |

Abbreviations as in Table 1.
therapy. Such deleterious effects of insufficient VKA therapy, however, were not found in previous studies in which the cut-off level of PT-INR for insufficient VKA therapy was <2.0. Because nearly 80% of the present patients were ≥70 years old (and hence a lower PT-INR target was adopted), insufficient VKA therapy, especially with PT-INR <1.6, may be associated with severe stroke, and better anticoagulant control with VKA can achieve not only a lower probability of developing stroke, but also less severe stroke when it does occur.

There are several limitations to be addressed in the present study. First, because this was a retrospective study from a prospective registry of consecutive patients, the present results should be treated with caution. Causes of low PT-INR in the insufficient VKA therapy group and the usual indicators of warfarin control, such as time in the therapeutic range (TTR) before stroke, were not clear. Moreover, detailed examinations of various coagulation markers were unavailable. Second, because the present anterior-circulation stroke patients were old (median age, 79 years) and arrived at hospital in a short time (median, 4.0 h) from onset, the present results may not be generalizable. The present findings should be confirmed in a prospective cohort with detailed information about TTR before stroke and coagulation markers on admission.

Conclusions

Insufficient VKA on admission was associated with higher severity of stroke and higher prevalence of proximal artery occlusion in patients with AF and acute anterior-circulation stroke compared with no anticoagulant medication prior to the index stroke. Appropriate PT-INR control seems to be critical not only for preventing ischemic stroke, but also for preventing severe stroke.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1
Table S1. Background characteristics vs. site of arterial occlusion
Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-17-1110