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A multicenter, prospective, observational study of warfarin-associated intracerebral hemorrhage: The SAMURAI-WAICH study

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ABSTRACT

Background: Because patients with warfarin-associated intracerebral hemorrhage (WAICH) have a high risk of ongoing bleeding, disability, and death, urgent coagulopathy reversal should be considered. On the other hand, thromboembolism may occur with reversal or withholding of anticoagulant therapy. The current status of acute hemostatic treatments and clinical outcomes in WAICH patients was investigated.
Methods: WAICH patients admitted within 3 days of onset were prospectively enrolled in 10 stroke centers. Thromboembolic and hemorrhagic complications and functional outcomes were followed-up for one year.
Results: Of 50 WAICH patients (31 men, 73 ± 9 years old) enrolled, all stopped warfarin on admission. Elevated prothrombin time-international normalized ratios (PT-INR) were normalized in 43 (86%). Anticoagulant therapy was resumed with intravenous full-dose unfractionated heparin followed by warfarin in 9 (18%), intravenous low-dose unfractionated heparin followed by warfarin in 14 (28%) and warfarin alone in 14 (28%) at a median of 2.5 (IQR 1.25–9), 4 (2–5.5) and 6 (3–11) days after onset, respectively, after emergent admission. Onset-to-admission time (per 1-hour increase; OR 0.55, 95% CI 0.19–0.84) was inversely associated with hematoma expansion. Anticoagulant therapy was resumed with intravenous full-dose unfractionated heparin in 9 (18%), low-dose heparin in 14 (28%) and warfarin alone in 14 (28%) at a median of 2.5, 4 and 6 days after onset, respectively. During one-year follow-up (n = 47), 11 thromboembolic and 6 hemorrhagic complications were documented. Twenty four patients showed unfavorable outcomes, corresponding to a modified Rankin Scale score of 4–6. Thromboembolic complications (OR, 10.62; 95% CI, 1.05–227.85), as well as advanced age (per 1 year; OR, 1.27; 95% CI, 1.10–1.61) and higher National Institutes of Health Stroke Scale (NIHSS) score (per 1 point; OR, 1.24; 95% CI 1.07–1.55), were independently associated with unfavorable outcome.
Conclusions: PT-INR normalization on admission and early anticoagulant resumption were common in WAICH patients. Thromboembolic complications were independently associated with unfavorable outcome.
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1. Introduction

Warfarin is widely used for the prevention of thromboembolism. Warfarin-associated intracranial bleeding occurs in 0.62–0.85% per year [1–5]. Although non-vitamin K antagonist oral anticoagulants

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(NOACs) have recently become available as alternatives to warfarin for patients with nonvalvular atrial fibrillation (NVAF), warfarin is still an important anticoagulant for patients without NVAF and those who are ineligible for NOACs because of renal dysfunction and swallowing disturbance. Patients with warfarin-associated intracerebral hemorrhage (WAICH) are at high risk of large hemorrhage [6] and hematoma expansion [7]. When WAICH occurs, the mortality rate is exceedingly high, estimated at nearly 50% [8]. Therefore, emergent discontinuation of anticoagulant therapy and normalization of PT-INR are consistently included in several recommendations and guidelines [9–12]. However, guidelines for resumption of anticoagulant therapy are not entirely clear due to a lack of data. The European Stroke Organization (ESO) does not mention a clear guidance about the necessity and the timing of resuming anticoagulant therapy in WAICH [12]. The American Heart Association (AHA)/American Stroke Association (ASA) recommend use of low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin for prevention of venous thromboembolism in patients with lack of mobility 1 to 4 days after onset [10]. However, the guidelines did not include long-term prophylaxis against atrial fibrillation (AF) in patients with WAICH. Japanese guidelines recommend resumption of anticoagulant therapy with heparin in patients who have a high risk for cerebral embolism, but there is no description of the timing of heparinization nor the subsequent anticoagulant therapy [11].

Bleeding risk scores (e.g. HAS-BLED, HEMORR$_2$HAGES) are useful in the management of patients with a high risk for bleeding, and thromboembolism risk scores (e.g. CHADS$_2$, CHA$_2$DS$_2$-VASc) are useful when considering the use of anticoagulant therapy, although the usefulness of these risk stratifications has not been well assessed in patients following WAICH. Physicians often wonder whether and when their patients should resume anticoagulant therapy, because risk factors for thromboembolism and bleeding are partially overlapping, and both risk scores are occasionally high in most WAICH patients.

According to our nationwide survey [13], most Japanese physicians interrupt warfarin and perform normalization of PT-INR, and they resume anticoagulant therapy in patients with WAICH. However, the strategies to normalize PT-INR and to resume anticoagulant therapy varied by physician.

The aim of the present study was to elucidate the current status of acute hemostatic treatments and the impact of thromboembolic and hemorrhagic events on the clinical outcome after WAICH.

2. Methods

The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-WAICH study was a multicenter, hospital-based, prospective, observational, cohort study designed to examine the current status of acute treatments for WAICH and the impact of hemorrhagic or thromboembolic complications on clinical outcomes. Patients who developed intracerebral hemorrhage (ICH) during oral warfarin intake and were admitted within three days after onset were prospectively enrolled from 10 stroke centers between April 2010 and June 2011. Patients who met the following criteria were excluded: ICH that was caused by brain tumor, cerebral artery aneurysm, or cerebral arteriovenous malformation; traumatic ICH; and comatose or fatally ill patients who were likely to die within a few days. Written informed consent was obtained from all patients or their relatives. This study was approved by each institutional Ethics Committee.

Baseline data were collected on admission for all eligible patients, including sex, age, reason for warfarin, risk factors such as hypertension, diabetes and dyslipidemia, comorbidities, history of stroke, neurological severity using the National Institutes of Health Stroke Scale (NIHSS) score, prior concomitant drugs such as antiplatelet drugs, and laboratory data, including the prothrombin time-international normalized ratio (PT-INR).

Computed tomography (CT) was performed on admission and 24 h later. Hematoma volume was determined with the $(A \times B \times C)/2$ method at the bedside by the attending stroke specialist on both CT scans [14]. Hematoma expansion was defined as a > 33% increase in the volume on the CT scan 24 h from baseline.

Each attending physician decided on reversal and resumption of anticoagulant therapy at his or her individual discretion. Dose of intravenous unfractionated heparin was defined as full-dose when adjusted activated partial thromboplastin time (aPTT) between 1.5 and 2.0 times the baseline and low-dose when adjusted aPTT less than 1.5 times the baseline. According to our nationwide survey about WAICH with nonvalvular AF in Japan, recurrent ICH and poor functional condition were often chosen as contraindications for resuming anticoagulation. The major key finding on follow-up CT to restart anticoagulation was the absorption tendency of hematomas [13]. Absorption tendency of hematoma on CT indicates the density or size reduction trend of hematoma. Information including reversal timing of anticoagulant therapy, reversal methods, resumption timing of anticoagulant therapy, drug holidays, resumption methods, and thromboembolic and hemorrhagic complications was collected.

Patients were evaluated to check the functional outcomes and complications at one year after stroke onset. That evaluation was performed by outpatient examination, mailing questionnaire, or telephone interview. Thromboembolic or hemorrhagic complications were defined as events requiring hospital admission or requiring a change in medical anticoagulant therapy. Ischemic stroke was defined as a focal neurological deficit with documented ischemic lesions on CT or MRI. Hemorrhagic complications were intracranial hemorrhage such as ICH, subarachnoid hemorrhage, subdural hematoma, and extracranial hemorrhage that affect the continuation of anticoagulant therapy. Hematoma re-expansion within a month after onset was also regarded as a hemorrhagic complication. Unfavorable outcome was defined as mRS of 4–6 at one year after stroke onset.

Statistical analysis was performed using JMP 8.0 statistical software (SAS Institute Inc., Cary, NC). The chi-square test (without the Yates

Table 1
Patients' clinical characteristics.

	All patients (N = 50)
Men	31 (62)
Age (years)	73 ± 9
Hypertension	46 (92)
Diabetes	10 (20)
Dyslipidemia	21(42)
Drinking	21(42)
Smoking	3 (6)
Prior antiplatelet use	12 (24)
Onset to admission time (hours)	2.5 (0.9–10.8)
Initial systolic blood pressure (mm Hg)	161 ± 26
Baseline NIHSS	9 (3–18)
Laboratory data on admission	
PT-INR	2.02 (1.73–2.39)
Blood glucose (mmol/L)	7.3 ± 1.9
Creatinine (mg/dL)	0.9 ± 0.6
Aspartate aminotransferase (IU/L)	29 ± 16
Alanine aminotransferase (IU/L)	22 ± 16
Platelet (10^4/μL)	20 ± 6
Computed tomography findings	
Baseline hematoma volume (mL)	14 ± 16
Location of hematoma	
Putamen	12 (24)
Thalamus	14 (28)
Lobar	10 (20)
Cerebellar	5 (10)
Brainstem	6 (12)
Other	1 (2)
Multiple	2 (4)

Data are numbers of patients (%), medians (interquartile range) for onset to admission time, baseline NIHSS score, and PT-INR, or means ± standard deviation for initial systolic blood pressure, glucose, and hematoma volume.
NIHSS, National Institutes of Health Stroke Scale;
PT-INR, prothrombin time–international normalized ratio.

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