Low-Dose Intravenous Recombinant Tissue-Type Plasminogen Activator Therapy for Patients With Stroke Outside European Indications

Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry

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Background and Purpose—The purpose of this study was to determine the safety and efficacy of intravenous recombinant tissue-type plasminogen activator (0.6 mg/kg alteplase) within 3 hours of stroke onset in Japanese patients outside the indications in the European license.

Methods—Of the 600 patients who were treated with recombinant tissue-type plasminogen activator, 422 met the inclusion criteria of the European license (IN group) and 178 did not (OUT group).

Results—The OUT group was inversely associated with any intracerebral hemorrhage (adjusted OR, 0.50; 95% CI, 0.29–0.84), positively associated with an unfavorable outcome (2.48; 1.55–3.94) and mortality (2.04; 1.02–4.04), and not associated with symptomatic intracerebral hemorrhage (0.53; 0.11–1.79) or complete independency (0.65; 0.40–1.03) after multivariate adjustment.

Conclusions—Functional and vital outcomes 3 months after low-dose recombinant tissue-type plasminogen activator in patients outside the European indications were less favorable compared with those included in the indications; however, the risk of intracerebral hemorrhage was not. (***Stroke.* 2012;43:253-255.**)

Key Words: acute stroke ■ diabetes mellitus ■ elderly patients ■ intracerebral hemorrhage ■ outcomes ■ thrombolysis

Patients with severe stroke as indicated by a baseline National Institutes of Health Stroke Scale (NIHSS) score of ≥25, those >80 years old, and those with any history of prior stroke and concomitant diabetes were excluded from a European postmarketing monitoring study for intravenous recombinant tissue-type plasminogen activator (rtPA) therapy (the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy [SITS-MOST] registry) without sufficient rationale.[1] European regulatory agencies do not advocate rtPA therapy for patients having such exclusion items. Using our multicenter registry,[2] this study documented the safety and efficacy of low-dose intravenous rtPA (0.6 mg/kg) in patients with stroke outside the European indications as compared with those who fulfilled the SITS-MOST criteria.

Patients and Methods

Patients were derived from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry.[2] Patient eligibility for alteplase was determined based on the Japanese guideline[3] stating that patients ≥75 years old, those with NIHSS score ≥23, those with a history of prior stroke, and those with poorly controlled diabetes are to be carefully considered but not excluded. Other exclusion criteria are almost identical between the European and Japanese indications. Each patient received alteplase (0.6 mg/kg) intravenously with 10% given as a bolus within 3 hours of stroke onset and the remainder delivered through continuous intravenous infusion over 1 hour. Patients not meeting the inclusion criteria of the European license were categorized into the OUT group and those who did were categorized into the IN group.

Outcomes included: any and symptomatic intracerebral hemorrhage (ICH) within the initial 36 hours, complete independence

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Table. Safety and Efficacy Outcomes

			Age		NIHSS		Prior Stroke Plus Diabetes	
	IN Group (N=422)	OUT Group (N=178)	≤80 Y (N=471)	>80 Y (N=129)	<25 (N=560)	≥25 (N=40)	Absent (N=575)	Present (N=25)
Any ICH within 36 h, no. (%)	93 (22.0)	26 (14.6)	96 (20.4)	23 (17.8)	113 (20.2)	6 (15.0)	116 (20.2)	2 (8.0)
Multivariate OR (95% CI)	1	0.50 (0.29–0.84)*	1	0.83 (0.46–1.46)	1	0.62 (0.22–1.46)	1	0.32 (0.05–1.16)
Symptomatic ICH, no. (%)	13 (3.1)	3 (1.7)	15 (3.2)	1 (0.8)	15 (2.7)	1 (2.5)	15 (2.6)	1 (4.0)
Multivariate OR (95% CI)	1	0.53 (0.11–1.79)	1	0.27 (0.01–1.47)	1	1.17 (0.06–6.88)	1	1.32 (0.07–7.70)
mRS 0–1, no. (%) (N=532)§	161 (40.5)	35 (26.1)	173 (39.4)	23 (24.7)	191 (38.2)	5 (15.6)	189 (36.8)	7 (38.9)
Multivariate OR (95% CI)	1	0.65 (0.40–1.03)	1	0.58 (0.31–1.04)	1	0.40 (0.13–1.05)	1	0.97 (0.32–2.91)
mRS 5–6, no. (%)	68 (16.1)	69 (38.8)	86 (18.3)	51 (39.5)	117 (20.9)	20 (50.0)	128 (22.3)	9 (36.0)
Multivariate OR (95% CI)	1	2.48 (1.55–3.94)‡	1	2.36 (1.36–4.09)†	1	3.23 (1.51–6.97)†	1	2.35 (0.81–6.44)
Mortality, no. (%)	20 (4.7)	23 (12.9)	25 (5.3)	18 (14.0)	34 (6.1)	9 (22.5)	41 (7.1)	2 (8.0)
Multivariate OR (95% CI)	1	2.04 (1.02–4.04)*	1	2.00 (0.93–4.24)	1	3.75 (1.45–9.09)†	1	1.54 (0.23–6.24)

NIHSS indicates National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; CI, confidence interval; OR, odds ratio.
*$P<0.05$.
†$P<0.01$.
‡$P<0.001$.
§Assessed for patients who had premorbid mRS 0–1.

(modified Rankin Scale score 0–1), unfavorable outcome (modified Rankin Scale score 5–6) at 3 months, and death within 3 months. Symptomatic ICH was defined as that associated with neurological deterioration corresponding to an increase of ≥4 points from the baseline NIHSS score.

To evaluate the independent effect of the OUT group and each exclusion criterion on the clinical outcomes, a multivariate logistic regression model was estimated adjusting for sex, hypertension, dyslipidemia, atrial fibrillation, onset-to-treatment time, Alberta Stroke Programme Early CT Score, and internal carotid artery occlusion. The model was adjusted for: patients >80 years using NIHSS score, prior stroke, and diabetes; patients with NIHSS score ≥25, using age, prior stroke, and diabetes; and patients with prior stroke plus diabetes using age and NIHSS score.

Results

Of the 600 patients, 178 (85 men; age, 81.7±8.6 years) were categorized into the OUT group and the remaining 422 (292 men; 67.7±10.5 years) into the IN group. A higher percentage of patients in the OUT group were female, older, hypertensive, diabetic, and had higher initial NIHSS scores and internal carotid artery occlusion compared with the IN group (Supplemental Table I; http://stroke.ahajournals.org). Of the OUT group, 129 patients were >80 years old, 40 had severe stroke with an NIHSS score ≥25, and 25 had prior stroke plus diabetes.

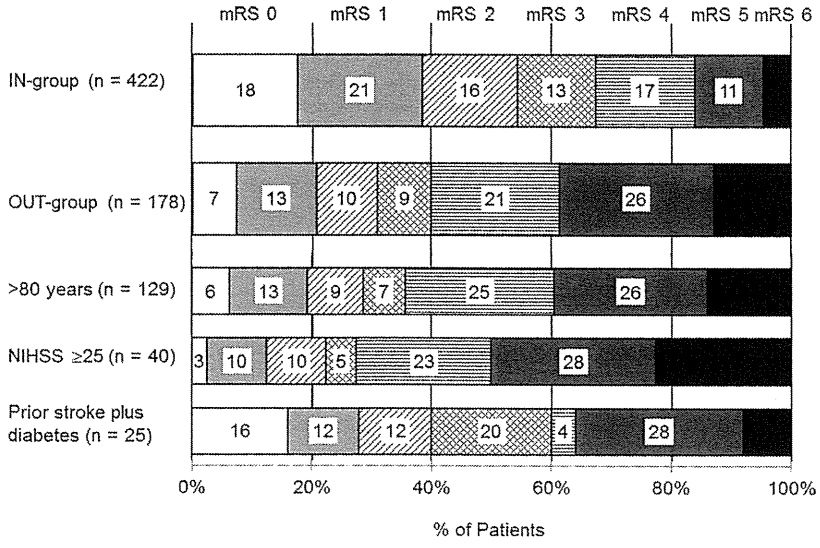

Figure. Modified Rankin Scale (mRS) distribution at 3 months.

After multivariate adjustment, any ICH was less common in patients in the OUT group than those in the IN group, but the frequency of symptomatic ICH did not differ significantly between the groups. Unfavorable outcome and death were more common in the OUT group than in the IN group and in patients with a NIHSS score ≥25 compared with those <25. Unfavorable outcome was also more common in patients >80 years than those ≤80 years (Table). The Figure shows the distribution of patients and their modified Rankin Scale scores at 3 months.

Discussion

More than 25% of ischemic strokes occur in patients ≥80 years old in Japan.[4] Advanced age was reported to be a strong predictor of poor outcomes and mortality independent of other clinical characteristics.[5] Randomized trials on rtPA did not include a sufficient number of patients with advanced age.[6–9] In the National Institute of Neurological Disorders and Stroke trial,[6] rtPA treatment was associated with increased likelihood of favorable outcome 3 months after stroke even in 49 patients aged >75 years with a NIHSS score >20 as compared with the placebo group. Risk of symptomatic ICH after thrombolysis did not increase, although clinical outcomes were worse in patients >80 years old as compared with younger patients in several studies.[10–13] An adjusted, controlled comparison based on 3472 patients >80 years old showed a better distribution of the modified Rankin Scale in thrombolysis patients than nonthrombolysis patients.[14] In this study, 0.6 mg/kg of alteplase may have caused the relatively small number of symptomatic ICH both in patients older than and ≤80 years old.

Diabetes mellitus was independently associated with symptomatic ICH after standard-dose rtPA therapy.[15] Infrequent development of ICH in our cohort and exclusion of patients with premorbid modified Rankin Scale ≥2 from the outcome analysis might weaken the impact of prior stroke plus diabetes on outcomes in this study. The small number of patients with prior stroke plus diabetes might also affect the statistical power.

This was not a randomized controlled study, subgroups were small, and physicians used judgment in selecting patients, all of which limit this study and introduce potential for error. In addition, data for patients with stroke who did not undergo thrombolysis were not collected and a comparison of patients with and without thrombolysis was not done.

In conclusion, 3-month outcomes after low-dose rtPA in patients outside the European indications were less favorable compared with those included in the indications. Low-dose intravenous rtPA therapy may be safely administered to patients outside the European indications without an increase of ICH by careful selection of patients. Patients with prior stroke and concomitant diabetes seem to be appropriate candidates for rtPA therapy.

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Original Article

Systolic blood pressure lowering to 160 mmHg or less using nicardipine in acute intracerebral hemorrhage: a prospective, multicenter, observational study (the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-Intracerebral Hemorrhage study)

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Objective: Optimal blood pressure (BP) control in acute intracerebral hemorrhage (ICH) remains controversial. We determined the effects of SBP lowering to 160 mmHg or more using intravenous nicardipine for acute ICH patients.

Methods: This is a prospective, multicenter, observational study conducted in Japan, with the lack of control groups. Patients with supratentorial ICH within 3 h of onset, admission SBP 180 mmHg or more, Glasgow Coma Scale (GCS) 5 or more, and hematoma volume less than 60 ml were initially treated with intravenous nicardipine to maintain SBP between 120 and 160 mmHg with 24-h frequent BP monitoring. The primary endpoints were neurological deterioration within 72 h [GCS decrement $\geq$2 points or National Institutes of Health Stroke Scale (NIHSS) increment $\geq$4 points; estimated 90% confidence interval (CI) on the basis of previous studies: 15.2–25.9%] and serious adverse effects (SAE) to stopping intravenous nicardipine within 24 h (1.8–8.9%). The secondary endpoints included hematoma expansion more than 33% at 24 h (17.1–28.3%), modified Rankin Scale (mRS) 4 or more (54.5–67.9%) and death at 3 months (6.0–13.5%).

Results: We enrolled 211 Japanese patients (81 women, 65.6 $\pm$ 12.0 years old). At baseline, BP was 201.8 $\pm$ 15.7/107.9 $\pm$ 15.0 mmHg. Median hematoma volume was 10.2 ml (interquartile range 5.6–19.2), and NIHSS score was 13 (8–17). Neurological deterioration was identified in 17 patients (8.1%), SAE in two (0.9%), hematoma expansion in 36 (17.1%), mRS 4 or more in 87 (41.2%), and death in four (1.9%). All the results were equal to or below the estimated lower 90% CI.

Conclusion: SBP lowering to 160 mmHg or less using nicardipine appears to be well tolerated and feasible for acute ICH.

Keywords: acute, antihypertensive treatment, blood pressure, hypertension, intracerebral hemorrhage, nicardipine, stroke

Abbreviations: ABC/2, (length $\times$ width $\times$ height)/2; AHA, American Heart Association; ASA, American Stroke Association; ATACH, Antihypertensive Treatment of Acute Cerebral Hemorrhage; BAT, Bleeding with Antithrombotic Therapy; BP, blood pressure; CI, confidence interval; CT, computed tomography; EUSI, European stroke initiative; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; INTERACT, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAE, serious adverse effect; SAMURAI, Stroke Acute Management with Urgent Risk-factor Assessment and Improvement

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INTRODUCTION

Chronic hypertension is a leading risk factor for intracerebral hemorrhage (ICH) [1–3], and high blood pressure (BP) is commonly observed in acute ICH on admission [4]. Acute high BP might enhance active intracerebral bleeding and hematoma growth, which could be determinants of poor clinical outcome [1,2,5–7]. In contrast, some investigators insist that high BP might work to maintain normal cerebral blood flow and prevent perihematomal ischemic damage [8,9].

Pilot phases of the Intensive Blood Pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT) [10] and the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) [11,12] studies supported the safety and feasibility of acute intensive BP lowering for ICH. Accordingly, the American Stroke Association (ASA) and American Heart Association (AHA) revised the guidelines for acute ICH to recommend that lowering of SBP to 140 mmHg is probably well tolerated in patients presenting with a SBP of 150–220 mmHg [13]. The INTERACT 2 [14] and ATACH II studies [15] are ongoing to confirm whether guideline-based SBP lowering less than 180 mmHg or intensive SBP lowering less than 140 mmHg is appropriate for acute ICH management.

In the Japanese Guidelines for the Management of Stroke 2009, the recommendation for SBP for acute ICH was less than 180 mmHg [16]. The Japanese official label prohibited nicardipine use during hyperacute ICH [17]. In contrast, our nationwide survey on antihypertensive treatment strategies for ICH revealed inconsistencies with the recommendations [17]. The target SBP was 160 mmHg or less from 82% of Japanese respondents and 57% of respondents named intravenous nicardipine as the first choice antihypertensive drug. However, there is little data to support the validity of these choices. In this study, we aimed to elucidate the safety and feasibility of SBP lowering to 160 mmHg or less in acute ICH using nicardipine. We compare our data with previous studies.

PATIENTS AND METHODS

The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-ICH Study is a prospective, multicenter, observational study designed to determine the safety and feasibility of early SBP reduction within 3 h from symptom onset 160 mmHg or less with intravenous nicardipine for acute hypertension in patients with spontaneous ICH (see supplemental Appendix, http://links.lww.com/HJH/A200). As this was an observational study, we did not set control groups. Most protocols for patient selection and nicardipine injection were similar with those of ATACH or ATACH II [11,12,15]. Use of the same basic design allows us to assess the noninferiority comparisons with those from previous studies. All study procedures were reviewed and approved by the local Ethics Committee.

Patient enrollment

We planned to enroll 200 patients who met following criteria: age 20 years or more, clinical signs consistent with the diagnosis of stroke; total Glasgow Coma Scale (GCS) score 5 or more, initial SBP more than 180 mmHg on two repeat measurements at least 5 min apart; computed tomography (CT) scan less than 2.5 h of onset, demonstrating a supratentorial intraparenchymal hematoma with manual volume measurement less than 60 ml, capable of initiating intravenous nicardipine less than 3 h after symptom onset, and informed consent being obtained from the patient, legally authorized representative or next of kin. We excluded patients who met the following criteria: uncertain time of symptom onset; previously known cerebral neoplasms, arteriovenous malformation, or aneurysms; intracerebral hematoma considered to be related to trauma; ICH located in infratentorial regions such as the pons or cerebellum; isolated intraventricular hemorrhage; extensive intraventricular hemorrhage associated with intraparenchymal hemorrhage; candidates for immediate surgical intervention for ICH; current pregnancy, parturition within previous 30 days or active lactation; any history of bleeding diathesis or coagulopathy; use of warfarin with prothrombin time international normalized ratio (INR) 1.7 or more; a platelet count less than 50 000/μl; or inappropriate candidate judged by attending neurologist (or neurosurgeon).

Blood pressure management and monitoring

BP and pulse rate were taken using manual or automated cuff measurement under established guidelines. The arm must be horizontal and at the level of the heart as denoted by the midsternal level in a recumbent position. Levels of BP and pulse rate were measured every 15 min during 2 h after the initiation of titrating nicardipine (or during dose adjustments, which ever lasts longer), and every 60 min during the remainder of the first 24 h, as well as at 48 and 72 h, respectively.

Bolus infusion of 1 mg nicardipine was allowed prior to the titrating infusion. Titrating of intravenous nicardipine was started within 3 h of symptom onset and continued for 24 h to achieve and maintain the target SBP level below 160 mmHg and above 120 mmHg. Intravenous nicardipine was initiated at a rate of 5 mg/h. If SBP was not reduced to 160 mmHg or less after 15 min, the infusion dose was increased by another 2.5 mg/h. The 2.5 mg/h increments continued every 15 min until the maximum dose of 15 mg/h was reached. If SBP was more than 160 mmHg despite infusion of the maximum nicardipine dose for 30 min, other antihypertensive drugs including intravenous nitroglycerin and diltiazem were used additionally or alone. Once the target SBP was reached, the infusion rate was adjusted by 1–2.5 mg/h to maintain SBP in the target range. If SBP fell below 120 mmHg, nicardipine was reduced until the rate of infusion was 0 mg/h, and was not restarted unless SBP rose above 160 mmHg. BP management after the first 24 h was at the primary neurologist's discretion. Basically oral antihypertensive agents were introduced after the first 24 h.

Hematoma evaluation

Noncontrast head CT was mandatorily performed on admission and at 24 (±6) h after the initiation of nicardipine infusion. Additionally, brain imaging studies were repeated

at the discretion of the treating physician as a part of routine care. The hematoma was classified on the basis of the location of its major component. Hematoma volume was determined with the length × width × height/2 method at bedside by the neurologist on admission and again 24 h after the initiation of nicardipine. If the patient underwent surgical intervention or died within 24 h, the hematoma volume on CT just prior to the event was used as follow-up data.

Clinical and laboratory assessment

Patient characteristics such as sex, age, height, body weight, BMI, vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, alcohol intake, histories of ischemic and hemorrhagic stroke, comorbidities such as liver cirrhosis and chronic renal dysfunction on hemodialysis, use of antithrombotic medication, and premorbid modified Rankin Scale (mRS) score were collected. Hypertension was defined as SBP 140 mmHg or more or DBP 90 mmHg or more before stroke onset or in the chronic stage of stroke or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose 126 mg/dl or more or the use of oral antidiabetic agents or insulin. Dyslipidemia was defined as a total plasma cholesterol level 220 mg/dl or more, low-density lipoprotein cholesterol level 140 mg/dl, or the use of antihypercholesterolemic medication. Alcohol intake was defined as daily consumption of alcohol 40 g or more. Neurological status was assessed using the National Institutes of Health Stroke Scale (NIHSS) by the treating neurologist just before (as baseline) and at 72 (±12) h after the initiation of nicardipine infusion. Neurological deterioration, including the level of consciousness and new or worsening focal neurological deficits were frequently (at least hourly) monitored by an attending nurse or neurologist for 24 h. Adverse events such as extensive BP lowering, ischemic stroke, transient ischemic attack, recurrent ICH, convulsion, tachycardia, phlebitis, pneumonia, and other adverse events within 72 h were also recorded, regardless of potential causal relationships with nicardipine. Routine laboratory surveillance including activated partial thromboplastin time, INR, a complete blood count, glucose, liver enzymes, and lipid profiles were measured at baseline, 24 and 72 h, respectively. Patients underwent a follow-up evaluation at 3 months after ICH onset to assess mRS score, cardiovascular events including newly developed stroke, and acute coronary syndrome in person or by telephone.

Clinical outcome measures

Clinical outcome measures are summarized in Table 1. Primary outcomes included: neurological deterioration corresponding to a decrease of 2 points or more from the baseline GCS score or an increase of 4 points or more from the baseline NIHSS score at 72 h after the initiation of treatment and serious adverse event (SAE) to stop intravenous nicardipine within 24 h. Patients who received surgical intervention for ICH within the initial 72 h were regarded as having neurological deterioration regardless of GCS or NIHSS scores. Secondary endpoints were as follows: time to reach target SBP range; frequency of time in the target range of SBP, once within the range; ICH volume expansion over 33% from baseline to 24 h; unfavorable outcome corresponding to patients with mRS of 4–6 at 3 months after ICH onset; and death at 3 months of onset. Patients who received surgical intervention for ICH were regarded as having unfavorable outcome regardless of the mRS score.

Safety and feasibility regarding primary outcomes were assessed whether the proportion of outcomes was at least less than the upper limit of the 90% confidence interval (CI) for the predicted proportion based on the weighted average of cited studies in the protocol study for the ATACH [11, 18–23], and main results of the INTERACT [10]. Finally, the weighted average of 588 patients was used for outcome 1 and that of 225 patients were used for the outcome 2. Secondary outcomes (5–7) were assessed whether their proportion was at least less than the upper limit of the 90% CI for the proportion of 445 patients who were registered in the Bleeding with Antithrombotic Therapy (BAT) Retrospective Study and had the same inclusion criteria as the present study [24], and patients in the INTERACT study for the assessment of outcomes 5–7. Finally, the weighted average of 549 patients within 3 h from onset was used for outcome 5, that of 445 patients were used for outcome 6, and that of 849 patients were used for outcome 7. The differences of confounding factors between our study and previous studies are shown in Appendix Table 1, http://links.lww.com/HJH/A200. Patients' background features were generally similar among the studies.

TABLE 1. Clinical endpoints

Endpoints	90% CI of predictive proportion for 211 patients	Present results number [% (95% CI)] (211 patients)
Primary		
Neurological deterioration within 72 h	15.2–25.9%	17 [8.1% (5.1–12.5)]
Serious adverse event to stop intravenous nicardipine within 24 h	1.8–8.9%	2 [0.9% (0.3–3.4)]
Secondary		
Time to reach the target SBP range	N/A	Median 30 min (IQR 15–45)
Frequency of time in the target SBP range	N/A	77.6% (75.3–79.9)
Hematoma expansion (>33%) at 24 h	17.1–28.3%	36 [17.1% (12.6–22.7)]
Modified Rankin Scale 4–6 at 3 months	54.5–67.9%	87 [41.2% (34.8–48.0)]
Death at 3 months	6.0–13.5%	4 [1.9% (0.7–4.8)]

CI, confidence interval; IQR, interquartile range.

Statistical analysis

Data are presented as mean ± SD or median [interquartile range (IQR)]. ICH volumes at baseline and at 24 h, and NIHSS scores at baseline and at 72 h were compared by Wilcoxon's signed rank test. For each primary outcome (1 and 2) and secondary outcomes (5–7), independent predictors were assessed from sex, age, BMI, vascular risk factors, history of stroke, comorbidities, prior antithrombotic medication, onset to treatment time, initial levels of SBP, pulse rate and hematoma volume, hematoma location (putamen versus other sites), and initial NIHSS by backward stepwise logistic regression analysis using $P > 0.10$ of the likelihood ratio test as the exclusion criterion. Outcomes were considered statistically significant if $P < 0.05$.

RESULTS

We enrolled 211 patients (81 women, 65.6 ± 12.0 years old) with acute supratentorial ICH from July 2009 to June 2011. Baseline characteristics are shown in Table 2. Figure 1 shows the trends for SBP, DBP, and pulse rate during the initial 24 h, at 48 and 72 h, respectively. SBP was 201.8 ± 15.7 mmHg at baseline, and steeply lowered to the target SBP range between 120 and 160 mmHg within 1 h for most patients. The median time to reach the target range was 30 min (15–45 min) (Table 1). For seven patients, nicardipine was not strong enough, and additional intravenous antihypertensive drugs (diltiazem in three, nitroglycerin in three, isosorbide nitrate in one) were started at a median of 110 min (97.5–120 min) from the initiation of nicardipine. The proportion of time in the target SBP range once within the range was 77.6% (75.3–79.9%). DBP was 107.9 ± 15.0 mmHg at baseline and was steeply lowered to less than 90 mmHg in most patients within 1 h. Pulse rate was 81.8 ± 16.1/min at baseline and mildly increased up to 90/min until 105 min, and thereafter gradually returned to the initial rate after about 10 h.

TABLE 2. Baseline characteristics

Total, number	211
Women, number (%)	81 (38.4)
Age (year)	65.6 ± 12.0
Body height (cm)	160.4 ± 9.9
Body weight (kg)	61.6 ± 14.9
BMI (kg/m^2)	23.7 ± 4.2
Risk factors, number (%)	
Hypertension	176 (83.4)
Diabetes mellitus	29 (13.7)
Dyslipidemia	87 (41.2)
Alcohol intake	57 (27.0)
Comorbidity	
Liver cirrhosis	10 (4.7)
Renal failure on hemodialysis	23 (10.9)
History of stroke/TIA	26 (12.3)
Ischemic stroke or TIA	19 (9.0)
Hemorrhagic stroke	10 (4.7)
Prior medication, number (%)	
Antiplatelet	22 (10.4)
Anticoagulant	2 (0.9)
SBP (mmHg)	201.8 ± 15.7
DBP (mmHg)	107.9 ± 15.0
Pulse rate (per min)	81.8 ± 16.1
Hematoma volume (ml) median (IQR)	10.2 (5.6–19.2)
Hematoma location, number (%)	
Putamen	112 (53.1)
Thalamus	75 (35.5)
Subcortex	12 (5.7)
Mixed	10 (4.7)
Caudate nucleus	1 (0.5)
Internal capsule	1 (0.5)
Admission NIHSS score, median (IQR)	13 (8–17)

Data are mean ± SD unless otherwise stated. IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Figure 2a shows the change in the NIHSS scores during the initial 72 h. The median NIHSS score was 13 (8–17) at baseline and 10 (5–15) at 72 h ($P < 0.0001$). The average absolute change was −2 (−4 to 0). Six patients (2.8%) received surgical intervention for ICH (a hematoma evacuation in five and a ventriculoperitoneal shunting in one) within 72 h. Of the remaining 205 patients, 11 showed a decrease of 2 points or more from the baseline GCS score or an increase of 4 points or more from the baseline NIHSS score at 72 h. In total, neurological deterioration was identified in 17 patients (8.1%), and the proportion was low compared with the lower cutoff (15.2%) of 90% CI for the predicted proportion (Table 1). Crude odds ratios (ORs) of confounding factors to predict neurological deterioration are shown in Appendix Table 2, http://links.lww.com/HJH/A200. On multivariate logistic regression analysis with backward selection, the initial pulse rate (OR 1.47, 95% CI 1.08–2.03 per 10 beat increase) was positively related to neurological deterioration (Table 3).

As another primary outcome, SAEs to stop nicardipine were observed in two patients (0.9%) (Table 1). One experienced extensive SBP lowering to 84 mmHg and the other had tachycardia and heart rhythm change into atrial fibrillation. The proportion was also low compared with the lower cutoff (1.8%) and was too small to perform multivariate analysis. Additionally, five adverse events were identified within 24 h. There was recurrent ICH in two, tachycardia in one, and phlebitis in two. Another 16 events were identified between 24 and 72 h including tachycardia in three, phlebitis in eight, pneumonia in three, epilepsy in one, and elevated total bilirubin in one.

Figure 2b shows the change in the hematoma volume during the initial 24 h. The volume was 10.2 ml [5.6–19.2 (IQR), 14.9 ± 13.2 ml] at baseline and 11.5 ml (6–24.9, 18.1 ± 19.0 ml) at 24 h ($P < 0.0001$). The absolute volume increment and relative volume increment were 0 ml (0–1, 3.2 ± 12.3 ml) and 0% (0–15.6, 22.5 ± 73.5%), respectively. Hematoma expansion greater than 33% at 24 h was found in 36 patients (17.1%), and the proportion was equal to the lower cutoff (17.1%) of 90% CI for predicted proportion (Table 1). Crude ORs of confounding factors to predict hematoma expansion are shown in Appendix Table 2, http://links.lww.com/HJH/A200. On multivariate regression analysis, prior antiplatelet medication (OR 4.69, 95% CI 1.51–14.20), and initial pulse rate (OR 1.36, 95% CI 1.07–1.74, per 10 beat increase) were independently related to hematoma expansion (Table 3).

A 3-month follow-up was completed for all 211 patients. The 3-month mRS score was 3 (2–4) (Fig. 3). Eighty-seven patients (41.2%) had unfavorable outcomes, including

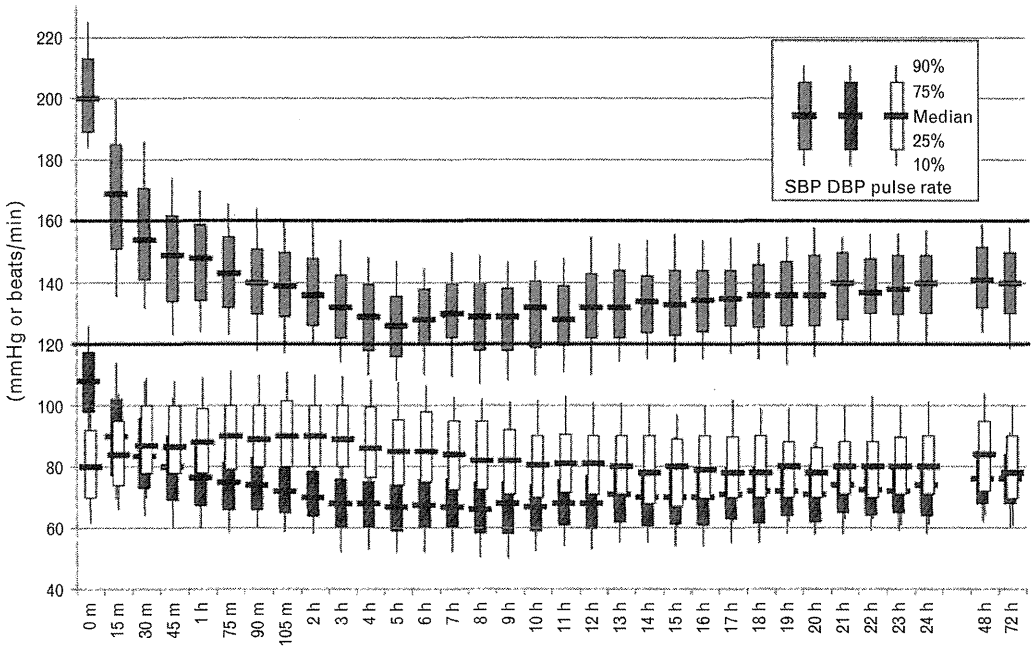

FIGURE 1 Trends of SBP, DBP, and pulse rate after the initiation of intravenous nicardipine.

three patients who received surgical intervention and recovered with an mRS score of 2 or 3. The proportion of unfavorable outcomes was low compared with the lower cutoff (54.5%) of the 90% CI for the predicted proportion (Table 1). Crude ORs of confounding factors to predict unfavorable outcomes are shown in Appendix Table 2, http://links.lww.com/HJH/A200. On multivariate regression analysis, men (OR 2.28, 95% CI 1.15–4.67), advanced age (OR 2.46, 95% CI 1.79–3.52, per 10-year increase), and higher initial NIHSS score (OR 4.45, 95% CI 2.53–8.25, per 10-point increase) were positively associated with unfavorable outcomes (Table 3). Four patients (1.9%) died within 3 months, one from the index ICH, two from pneumonia, and one from hepatoma. The proportion was low as compared with the lower cutoff (6.0%) of the 90% CI for the predicted proportion and was too small to perform multivariate analysis.

DISCUSSION

This study showed the safety and feasibility of major expert opinions in our nationwide survey that SBP should be lowered to 160 mmHg or less using intravenous nicardipine for acute ICH [17]. The first major finding was that neurological deterioration was relatively uncommon as compared with that from previous studies and neurological

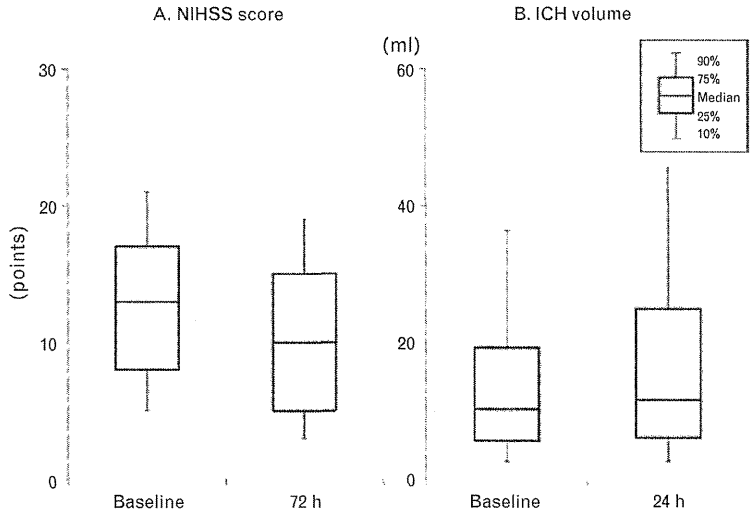

FIGURE 2 Changes in National Institutes of Health Stroke Scale score from baseline to 72 h and intracerebral hematoma volume from baseline to 24 h. ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale score.

TABLE 3. Independent predictors of primary and secondary clinical endpoints

	odds ratio	95% confidence interval	P
Neurological deterioration[a]			
Initial pulse rate (per 10 beat)	1.47	1.08–2.03	0.016
Hematoma expansion more than 33%[b]			
Prior antiplatelet medication	4.69	1.51–14.20	0.009
Initial pulse rate (per 10 beat)	1.36	1.07–1.74	0.012
Onset to treatment time (per 10 min)	1.10	0.99–1.23	0.082
Initial NIHSS score (per 10 point)	1.77	0.97–3.29	0.062
Unfavorable outcome at 3 months[c]			
Men	2.28	1.15–4.67	0.018
Age (per 10 year)	2.46	1.79–3.52	<0.0001
Initial NIHSS score (per 10 point)	4.45	2.53–8.25	<0.0001

Items with $P < 0.1$ are listed. NIHSS, National Institutes of Health Stroke Scale.
[a]Adjusted for age and prior antiplatelet medication.
[b]Adjusted for age.
[c]Adjusted for prior antiplatelet medication.

severity was rather ameliorated within the initial 72 h, showing an absolute 2-point decrease in the NIHSS score. These results suggest that the present antihypertensive therapy was protective toward the brain from acute insult by ICH. The second major finding was that intravenous nicardipine under tight BP monitoring lowered SBP to the target range within 1 h and kept SBP within the range in most patients with only a small chance of SAEs. Finally, early hematoma expansion, as well as 3-month unfavorable outcome, was relatively uncommon. Death was especially rare, occurring in only four patients in the present sample population.

As early neurological deterioration after ICH is thought to be common due to expansion of hematoma and perihematomal edema, it is impressive that the median NIHSS score was 2 points lower at 72 h than at baseline in the studied patients. A low percentage of hematoma expansion seems to cause neurological improvement, although edema volume was not measured. This improvement seems to contribute to relatively good outcomes at 3 months. One should note, however, that mortality after ICH was reported to be much lower in Japan than in other countries, [25] presumably partly due to the tendency of maintaining intensive therapy even for terminal patients. Thus, the contribution of BP lowering to reduced mortality should be underestimated to some extent. Prior antiplatelet medication and high pulse rate were associated with one or more of the above safety outcomes, as well as the established predictors such as male sex, advanced age, and severe initial neurological disability. Of these, antiplatelet medication was found to be independently related to hematoma expansion and mortality [24,26]. So far, there has been no evidence to show the association between the initial pulse rate and ICH outcomes. High pulse rate may reflect sympathetic hyperactivity, which resists BP lowering. Early hospital visit is a known predictor of hematoma expansion, [27] but late visit was marginally related to hematoma expansion in this study. Earlier initiation of BP lowering might prevent hematoma growth.

Intravenous nicardipine was revealed to be tolerable for the management of acute hypertension in several diseases [12,21,22,28]. The present study showed that nicardipine seldom brought early SAEs and was useful for prompt lowering and maintenance within the scheduled range of SBP. These findings were supportive of safe clinical use of nicardipine for Japanese ICH patients, although such a use was contraindicated in Japan as was explained in our previous study [17]. We submitted our study including the nationwide survey to the Ministry of Health, Labour, and Welfare of Japan, [17] which abolished the description of contraindication for ICH on the official label of nicardipine in June 2011.

The optimal target SBP for hyperacute ICH patients remains uncertain. As stated above, the Japanese guidelines suggested a target SBP of less than 180 mmHg and the recent ASA/AHA guidelines referred to the probable safety

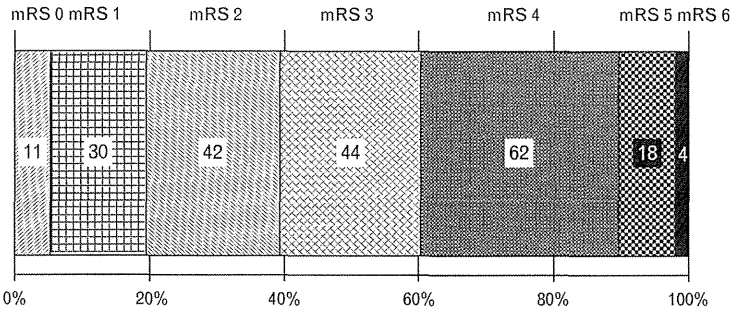

FIGURE 3 The modified Rankin scale at 3 months. Number in the bar indicates patients' number. mRS, modified Rankin scale.

of the target SBP to be less than 140 mmHg without thoroughly describing the efficacy of lowering to this level [13,16]. The European Stroke Initiative advocates the target BP of 160/100 mmHg [29]. The present target of SBP 160 mmHg or less was in the middle of these guideline-based goals. The median SBP levels at 90 min and later were below 140 mmHg, suggesting more than half of our patients were indicative of the intensive treatment arm (SBP lowering to less than 140 mmHg) in the INTERACT 2 and ATACH II [14,15]. Seventeen Japanese institutes, including nine of the present participating ones, began to register patients for the ATACH II in 2012 to clarify and better justify the target SBP goal.

There are some limitations that need to be addressed. First, this was not a randomized trial but an observational study with a comparison to previous studies. The ongoing ATACH II, in which we are involved, will overcome this limitation. Second, hematoma volume in our cohort was relatively small because of the inclusion criterion (<60 ml) and might have caused better outcomes than the predicted ones from historical control studies. At least, the median initial NIHSS score (13) was high compared with those of the INTERACT (9) and the BAT Retrospective Study (12) [10,24].

It is of critical importance and immediate urgency to improve the proportion of favorable outcomes after ICH. As the present study has a similar study design as the ATACH II [15] and some of the authors are also participating in this trial, the present study has the value as a pilot study to ascertain that the ATACH II is feasible in Japan. This study provides some new information and may be used to plan how to proceed to maximize the success of the ongoing ATACH II.

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Conflicts of Interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

Few treatment strategies have been demonstrated to be beneficial for acute intracerebral haemorrhage. In the present prospective study, the authors demonstrated safety and feasibility of nicardipine-based BP lowering treatment with target SBP levels of 120–160 mmHg among Japanese patients with acute intracerebral haemorrhage. This study has provided important information on BP lowering treatment as potentially effective treatment. The strength is its prospective design and well standardized intervention protocol. Although this study does not involve control patients, definite evidence of this treatment strategy will be established by ongoing large-scale randomized controlled trials.

Reviewer 2

The strength of the paper is in being the first demonstration that nicardipine infusion to reduce blood pressure after intracerebral haemorrhage is safe well below 160 mmHg, thereby extending guideline suggestions. Its weakness is in the lack of a control group and in the limitation to small intracerebral haemorrhage with mild disease.

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Nationwide survey of neuro-specialists' opinions on anticoagulant therapy after intracerebral hemorrhage in patients with atrial fibrillation

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ABSTRACT

Purpose: A nationwide survey was conducted regarding anticoagulant therapy in patients with acute intracerebral hemorrhage (ICH) on warfarin with nonvalvular atrial fibrillation (NVAF).
Methods: A questionnaire on standard therapeutic strategy for warfarin-related ICH in patients with NVAF was mailed to 416 institutes.
Results: A total of 329 physicians (79%) responded with a completed questionnaire. On admission, all respondents stopped warfarin medication and 94% normalized the international normalized ratio (INR) mainly by Vitamin K (63%), followed by fresh frozen plasma (20%), and prothrombin complex concentrate (10%). Afterwards, 91% of the respondents restarted anticoagulation and 3% used antiplatelet for prevention of thromboembolism, but the remaining 6% disagreed with restarting antithrombotic therapy. As contraindications for resuming anticoagulation, recurrent ICH (59%) and poor functional condition (59%) were often chosen. Of those who restarted anticoagulation, the timing was within 4 days in 7%, 5 to 7 days in 21%, 8 to 14 days in 25%, 15 to 28 days in 28% and 29 days or later in 18%. The major key finding on follow-up CT to restart anticoagulation was the absorption tendency of hematomas (47%). When restarting anticoagulation, 76% of the respondents used warfarin alone and 20% used either unfractionated heparin plus warfarin or heparin alone.
Conclusion: A large majority of respondents responsible for ICH management stopped oral warfarin medication and normalized INR on admission, and restarted anticoagulation after acute ICH in patients with NVAF. However, the strategies to normalize INR and to restart anticoagulant therapy varied greatly and depended on each individual physician's decision.

1. Introduction

Anticoagulant therapy using warfarin is recommended for prevention of ischemic stroke associated with atrial fibrillation (AF). However, this therapy is also associated with increased risk of intracerebral hemorrhage (ICH) and may worsen patients' outcomes [1–3]. Among patients with ICH, the proportion of patients receiving anticoagulant therapy before ICH onset has recently been increasing [4,5]. According to a multicenter observational study between 1999 and 2003 in Japan, 8.7% of registered patients with acute ICH were prior users of warfarin [5].

Warfarin use is known to be a predictor of hematoma enlargement, especially when the international normalized ratio (INR) value is high [6,7]. Previous studies have shown that early hematoma enlargement is a major cause of clinical deterioration and mortality

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[8–10]. Thus, continuation of warfarin at ICH onset may lead to an increased incidence of hematoma enlargement and higher mortality. Conversely, withholding warfarin may cause development of thromboembolic complications, especially in patients with AF or mechanical prosthetic valves. There is a considerable dilemma concerning when to restart anticoagulant therapy following ICH. Furthermore, deep vein thromboses and pulmonary embolisms are relatively common preventable causes of morbidity and mortality in patients with acute ICH [11–13]. In such cases, it is advisable to consider early initiation of anticoagulant therapy.

To date, there is no established guideline for appropriate antithrombotic therapy after acute ICH in patients with AF who are on warfarin. The aim of this study was to reveal the current physicians' opinions regarding anticoagulant therapy after acute ICH in patients with nonvalvular AF (NVAF) using a nationwide survey in Japan.

2. Patients and methods

A nationwide web survey of antihypertensive treatment for acute ICH was previously conducted in 1424 certified training institutes recommended by the Japan Stroke Society, the Japan Neurosurgical Society or the Societas Neurologica Japonica in 2008 [14]. Of 600 respondents to this survey, 416 respondents (345 neurosurgeons, 56 neurologists, and 15 others) agreed to answer additional surveys for ICH management. The present questionnaire was mailed to these 416 respondents in October 2009. The deadline for response was set at the end of December 2009.

The questionnaire consisted of 4 questions on the institutional conditions for acute ICH management and 7 questions on the therapeutic strategy for acute warfarin-related ICH (Table 1). All answers were multiple choice, and multiple selection was allowed only on question 8 (Q8). Replies to the following 7 questions were requested from respondents who treat one or more warfarin-related ICH patients per year.

3. Results

Of a total of 416 surveys sent out, 329 respondents (79%). Of the 329 respondents, 266 were neurosurgeons (80.9%) (Q1; Table 2). Overall, the respondents had spent a median of 23 years in clinical medicine (Q2). The median number of ICH patients annually treated ranged between 41 and 60 (Q3). In more than half of the institutes (54.2%), 1 to 5 patients were treated with warfarin due to NVAF before ICH (Q4). A total of 10 respondents did not usually treat patients with acute ICH on warfarin, and 4 left this question blank (Q4). The remaining 315 responses were used in the analysis for Q5 to Q7.

Table 1
The questionnaire.

Institutional conditions for acute intracerebral hemorrhage (ICH) management
Q1. What is your specialty?
Q2. How long is your career in clinical medicine?
Q3. How many acute ICH patients (hospitalized within 7 days of onset) are treated in your hospital per year?
Q4. How many acute warfarin-related ICH patients with nonvalvular atrial fibrillation (hospitalized within 7 days of onset) are treated in your hospital per year?
Therapeutic strategy for acute warfarin-related ICH
Q5. Do you agree to stop anticoagulant therapy on admission?
Q6. Do you agree to normalize INR on admission? How do you primarily normalize it?
Q7. Do you agree to restart anticoagulation?
Q8. Which condition do you think is a contraindication to restart anticoagulation?
Q9. When do you restart anticoagulation?
Q10. Which CT finding is available to determine the timing of restarting anticoagulation?
Q11. Which drug do you choose to restart anticoagulation?

ICH: intracerebral hemorrhage, INR: international normalized ratio, CT: computed tomography.

All 315 respondents agreed to stop oral warfarin on admission (Q5). Of these, 295 (93.7%) agreed to normalize INR on admission mainly by Vitamin K (199 respondents, 63.2%), followed by FFP (64 respondents, 20.3%) and PCC (31 respondents, 9.8%) (Q6).

To prevent thromboembolism, 286 respondents (90.8%) resumed anticoagulant therapy, 10 (3.2%) started antiplatelet therapy instead of anticoagulation, and 19 (6.0%) disagreed with any antithrombotic therapies (Q7). In Q8 to Q11, responses from the 286 respondents who agreed with resumption of anticoagulation were used. Recurrent ICH and poor functional status corresponding to the modified Rankin Scale score of 4 or 5 were two major contraindications against restarting anticoagulation (170 respondents, 59.4% for each), followed by dementia or frequent falls (139, 48.6%), suspected cerebral amyloid angiopathy (107, 37.4%), multiple brain microbleeds on T2*-weighted magnetic resonance imaging (MRI) (85, 29.7%), advanced age (≥80 years, 71, 24.8%), and so on (Q8).

The timing to restart anticoagulation was within 4 days after stroke onset in 21 respondents (7.3%), 5 to 7 days in 60 (21.0%), 8 to 14 days in 71 (24.8%), 15 to 28 days in 80 (28.0%) and 29 days or later in 50 (17.5%) (Q9). As an appropriate finding to restart anticoagulation on follow-up computed tomography (CT), the largest number of respondents used the finding of absorption tendency of hematoma (135 respondents, 47.2%) (Q10). To restart anticoagulation, warfarin alone was used by 216 respondents (76%), unfractionated heparin alone or combined with warfarin by 57 (19.9%), and anticoagulation following antiplatelets by 7 (2.4%) (Q11).

4. Discussion

The present study revealed the current opinions of Japanese neurospecialists on stopping, reversing, and restarting anticoagulant therapy in NVAF patients who developed warfarin-related ICH. The first major finding was that all respondents answered that they discontinue warfarin and 94% of the respondents agreed with normalization of INR at the time of admission for ICH patients; vitamin K was the first choice agent for more than half of respondents and PCC and FFP were relatively uncommon choices. The second major finding was that 91% of the respondents agreed with resumption of anticoagulant therapy for ICH patients, though the timing for restarting anticoagulation varied greatly.

Emergent discontinuation of anticoagulant therapy and normalization of INR on admission were consistent with several recommendations and guidelines [15–17]. However, the first choice methods for normalization were different among guidelines. In the European Stroke Initiative (EUSI) recommendation of 2006, administration of PCC or FFP with additional use of vitamin K was primarily recommended [15]. The American Heart Association (AHA)/American Stroke Association (ASA) guidelines of 2010 describe that patients should receive intravenous vitamin K as Class I, and add that vitamin K should remain an adjunct to a more rapidly acting initial therapy for life-threatening warfarin-associated hemorrhage. As such an initial therapy, PCC is regarded to have fewer complications compared to FFP (Class IIa) [16]. The Japanese Guidelines for Management of Stroke 2009, published after the deadline for the present survey, lists vitamin K, FFP, and PCC as methods for normalization, and recommends PCC more strongly than FFP [17]. PCC contains high levels of vitamin K-dependent coagulant proteins (factors II, VII, IX, and X) and requires smaller volumes of infusion than FFP. Thus, treatment with PCC reversed anticoagulation more rapidly than FFP [18,19]. However, PCC without vitamin K was reported to result in a re-increase of INR and clinical deterioration [20]. Thus, the combination of PCC and vitamin K seems to be the best treatment for the normalization of INR. However, in the present survey, only 10% of respondents chose PCC. Relatively uncommon use of PCC may be due to its off-label use for ICH patients in Japan. Use of FFP for ICH is also off-label medication in Japan. In addition, formulation of the

Table 2
Answers to the questionnaire.

Question	Multiple choice answers	Respondents	%
Q1. Specialty (n = 329)	Neurosurgery	266	80.9
	Neurology, vascular neurology	55	16.7
	Other	7	2.1
	No answer	1	0.3
Q2. Length of career (n = 329)		Median 23 (IQR 18–27) years	
Q3. Number of ICH patients (n = 329)	20	44	13.4
	21–40	85	25.8
	41–60	58	17.6
	61–80	43	13.1
	81–100	42	12.8
	101	57	17.3
Q4. Number of warfarin-related ICH patients (n = 329)	None	10	3.0
	1–5	176	53.5
	6–10	97	29.5
	11–20	33	10.0
	21	9	2.7
	No answer	4	1.2
Q5. Interruption of anticoagulation on admission (n = 315)	Agree	315	100.0
	Disagree	0	0
Q6. Normalization of INR and first choice method (n = 315)	Agree, by vitamin K	199	63.2
	Agree, by fresh frozen plasma	64	20.3
	Agree, by prothrombin complex concentrates	31	9.8
	Agree, by another method	1	0.3
	Disagree	19	6.0
	No answer	1	0.3
Q7. Restart anticoagulation (n = 315)	Agree	286	90.8
	Disagree with anticoagulation, agree with start antiplatelet therapy instead	10	3.2
	Disagree with any antithrombotic therapy	19	6.0
Q8. Contraindication for restarting anticoagulation (multiple selection allowed) (n = 286)	Recurrent ICH	170	59.4
	Poor functional status (mRS 4–5)	170	59.4
	Dementia or frequent falls	139	48.6
	Suspected cerebral amyloid angiopathy	107	37.4
	Multiple microbleeds on MRI	85	29.7
	Advanced age (80 years old)	71	24.8
	History of gastrointestinal bleeding	44	15.4
	Atrial fibrillation is not chronic but paroxysmal	28	9.8
	Other	21	7.3
	No contraindication	20	7.0
Q9. Timing to restart anticoagulation (n = 286)	Day following ICH onset	1	0.3
	2–4 days following ICH onset	20	7.0
	5–7 days following ICH onset	60	21.0
	8–14 days following ICH onset	71	24.8
	15–28 days following ICH onset	80	28.0
	29 days following ICH onset	50	17.5
	Others	3	1.0
	No answer	1	0.3
Q10. Supportive CT findings for restarting anticoagulation (n = 286)	Discontinuation of hematoma growth	80	28.0
	Absorption tendency of hematoma	135	47.2
	Complete absorption of hematoma	49	17.1
	Other findings than hematoma	20	7.0
	No answer	2	0.7
Q11. Drug chosen for restarting anticoagulation (n = 286)	Oral warfarin alone	216	75.5
	Heparin (alone or concomitant use with oral warfarin)	57	19.9
	Antiplatelet drug, followed by warfarin	7	2.4
	Other	5	1.7
	No answer	1	0.3

The 14 respondents who answered "None" or "No answer" in Q4 were exempted from replies to Q5 to Q11. The 29 respondents who did not agree with restart of anticoagulation in Q7 were exempted from replies to Q8 to Q11.
IQR: interquartile range, ICH: intracerebral hemorrhage, INR: international normalized ratio, MRI: magnetic resonance imaging, CT: computed tomography.

questions with just one choice was a possible cause of the lesser use of FFP or PCC.

In the EUSI recommendation, it is described that restarting anticoagulation therapy would not benefit patients with lobar ICH [15]. The AHA/ASA guidelines recommend avoidance of long-term anticoagulation as treatment for nonvalvular AF after spontaneous lobar ICH because of the relatively high risk of recurrence [16]. In contrast, the Japanese guidelines do not mention whether restarting anticoagulation should be abstained in some patients [17]. A majority of the present respondents agreed with resumption of anticoagulant therapy for patients with warfarin-related ICH in general: recurrent ICH, poor functional status, and dementia or frequent falls were three major conditions for which restarting anticoagulation is not chosen. Microbleeds on MRI have been reported to be independently related to the incidence of warfarin-related ICH [21]. Since paroxysmal AF was reported to have a similar stroke risk and a similar benefit from anticoagulant therapy to those with sustained AF [22], this condition does not seem to be a good reason not to restart anticoagulation.

The timing to restart anticoagulation is described as 10 to 14 days after ICH onset in the EUSI Recommendation [15]. The AHA/ASA guidelines do not state the timing of restarting anticoagulation clearly [16]. The Japanese guidelines recommend use of heparin after

normalization of INR in patients with an elevated risk for embolism, but do not mention the timing of heparinization [17]. Among the present respondents, the timing to restart anticoagulation varied greatly and was relatively late compared to that proposed in the EUSI Recommendation. Early resumption of warfarin within 3 days after intracranial hemorrhage onset was reported not to cause any re-bleeding in 12 patients [23]. In contrast, some studies have stressed a low incidence of embolism following discontinuation of anticoagulant therapy during acute ICH [24,25]. Thus, this timing is an important and undetermined matter. One fifth of the present respondents chose heparin (alone or with concomitant use of oral warfarin) as an agent for resumption. Use of warfarin alone limits the carboxylation of protein C, and concomitant heparin use may prevent such a hypercoagulant condition.

The present study was designed to investigate standard therapeutic opinions at each institute for patients with warfarin-related ICH. However, real strategies in clinical practice for normalization and resumption of anticoagulant therapy may depend on individual conditions in each patient. To overcome this limitation, a multicenter prospective observational study on this theme is currently underway.

Conflict of interest

Koga receives research support from Japan Cardiovascular Research Foundation (The Bayer Scholarship for Cardiovascular Research). Okada receives an honorarium from Mitsubishi Tanabe Pharma and a consulting fee from Lundbeck. Minematsu receives research support from the Ministry of Health, Labor and Welfare, Japan, Research Grants for Cardiovascular Diseases, Grant-in-Aid, the Foundation for Biomedical Research and Innovation, Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin Pharma, Inc., and Hitachi Medical Corporation. Toyoda receives research support from Grants-in-Aid from the Ministry of Health, Labor and Welfare, Japan.

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Effect of Serum Lipid Levels on Stroke Outcome after rt-PA Therapy: SAMURAI rt-PA Registry

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Key Words

Acute stroke · Brain infarction · Dyslipidemia · High-density lipoprotein cholesterol · Statins · Thrombolysis

Abstract

Background: The effects of lipid levels on clinical outcomes after ischemic stroke are controversial. Whether admission lipid levels and prior statin use are associated with early intracerebral hemorrhage (ICH) and long-term functional outcome after recombinant tissue plasminogen activator (rt-PA) therapy for stroke patients was investigated. ***Methods:*** Ischemic stroke patients who received intravenous rt-PA from a multicenter registry were studied. Lipid levels on admission, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglyceride levels, as well as prior statin use, were assessed. The primary outcome was favorable outcome at 3 months corresponding to a modified Rankin Scale score ≤1. The secondary outcome was any or symptomatic ICH within the initial 36 h. ***Results:*** Of 489 enrolled patients (171 women, 70.8 ± 11.6 years old), 60 used statins prior to stroke, 93 developed ICH (19.0%), and 188 (38.4%) had a favorable 3-month outcome. Of the lipid levels, only the HDL-C level was an independent predictor of favorable outcome after multivariate adjustment for baseline characteristics (OR 1.95, 95% CI 1.10–3.47 per 1 mmol/l; p = 0.023) and after further adjustment for pretreatment radiological findings (OR 2.03, 95% CI 1.07–3.84; p = 0.029). For the 187 stroke patients without cardioembolism, the HDL-C level was more strongly associated with favorable outcome (OR 4.94, 95% CI 1.91–12.76 per 1 mmol/l; p = 0.001). There were no significant associations between ICH and any lipid levels. Prior statin use was not associated with outcomes. ***Conclusions:*** The admission HDL-C level was associated with favorable outcome 3 months after intravenous rt-PA therapy in stroke patients without cardioembolism.

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Introduction

Dyslipidemia is a known risk factor for ischemic stroke. High total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels and a low high-density lipoprotein cholesterol (HDL-C) level increase the risk of ischemic stroke [1–4], though low TC and LDL-C levels may increase the risk of intracerebral hemorrhage (ICH) [2, 5–7]. Lipid levels may affect stroke outcome in an opposite manner. High TC and LDL-C levels have been reported to be associated with better functional and vital outcomes after stroke [8–12]. Also, some studies showed a positive relationship between a high HDL-C level and good outcome after stroke [8, 13]. In contrast, a low LDL-C level increased the risk of early symptomatic ICH [14], and TC levels were associated with worse functional outcome in ischemic stroke patients after receiving thrombolysis or endovascular embolectomy [15]. Thus, the real contribution of lipid levels to stroke outcome, particularly after thrombolysis, is still controversial. In addition, prior use of a hydroxymethylglutaryl-CoA reductase inhibitor (statin) modifies lipid levels and makes interpretation of the contributions of lipid levels unclear.

We attempted to identify underlying risk factors that predict stroke outcomes after intravenous (i.v.) recombinant tissue plasminogen activator (rt-PA) from a multicenter observational study [Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry] [16–19]. We hypothesized that lipid levels on emergency admission were useful prognostic predictors after rt-PA. In this study, whether admission lipid levels, as well as prior statin use, were associated with early ICH and functional outcomes 3 months after rt-PA therapy in acute ischemic stroke patients was investigated.

Methods

A total of 600 consecutive patients with acute ischemic stroke who received i.v. rt-PA therapy from October 2005 to July 2008 at 10 Japanese stroke centers were enrolled in the SAMURAI rt-PA Registry. The methods and overall general results of this multicenter study have been reported previously [16]. Patients' eligibility for alteplase therapy was determined based on the Japanese guideline for i.v. rt-PA therapy [20]. Each local ethics committee approved the retrospective collection of clinical data from the database and submission of the data to our central office. Each patient received a single alteplase dose of 0.6 mg/kg (not exceeding 60 mg) i.v., with 10% given as a bolus within 3 h of stroke onset followed by a continuous i.v. infusion of the remainder over 1 h. The endovascular thrombectomy devices had not been approved in Japan during this observation period, and they were not used.

Demographic factors, risk factors, cardiovascular comorbidities, medications prior to stroke onset including statins, vital signs and blood tests on emergency admission (including TC, HDL-C, LDL-C, and triglyceride levels), onset-to-treatment time, baseline National Institutes of Health Stroke Scale (NIHSS) score, and i.v. antihypertensives just before rt-PA infusion as listed in table 1 were assessed. Japanese physicians determined statin use principally based on Japan Atherosclerosis Society Guidelines [21]. Blood samples were principally taken at first assessment in the emergency room. No information about fasting or nonfasting status at the time of emergency admission was obtained. Lipid profiles were analyzed at the laboratory of each institution that was mostly checked by the Lipid Standardization Program administered by one specific laboratory (Osaka Medical Center for Health Science and Promotion). The laboratory is a member of the Cholesterol Reference Method Laboratory Network. Prior to i.v. rt-PA, all patients underwent brain computed tomography (CT) or magnetic resonance (MR) imaging. For MR examinees, early ischemic change was quantified using the Alberta Stroke Program Early CT Score (ASPECTS) on diffusion-weighted imaging (DWI), and the arterial occlusion site was identified on MR angiography as previously described [17, 22, 23]. Stroke subtype was defined according to the criteria of the Trial of Org 10172 in Acute Stroke Therapy [24], and the patients were divided into two groups: those with cardioembolism and those without.

The primary outcome was a favorable functional outcome at 3 months, corresponding to a modified Rankin Scale (mRS) score of 0 or 1. The secondary outcome was any or symptomatic ICH within the initial 36 h. Any ICH was defined as CT evidence of new ICH. Symptomatic ICH was defined according to the NINDS/Cochrane protocol as any ICH associated with neurological deterioration corresponding to an increase of ≥ 1 point from the baseline NIHSS score [14, 16], and according to the SITS-MOST [25] protocol as parenchymal hemorrhage type II combined with an increase of ≥ 4 points from the baseline NIHSS score. The examiners at the 3-month clinics were familiar with patients' stroke features in some hospitals and not in others.

Statistics

All calculations were performed using SPSS Statistics 17.0 Statistics software (IBM SPSS Inc.). A p value <0.05 was considered significant. Baseline lipid profiles and other characteristics were compared using the χ^2 test, Fisher's exact test, the unpaired t test, and the Mann-Whitney U test, as appropriate. Multivariate analysis was performed with a logistic regression model to determine whether each lipid profile was predictive of the outcomes. Since it was likely that lipid levels were highly correlated with each other, each lipid profile was separately entered into the regression model with adjustment for sex, age by forced entry, and the other nonlipid characteristics listed in table 1 by a backward selection procedure using $p > 0.10$ on the likelihood ratio test for exclusion (model 1). The analysis was also done by further adjustment with ASPECTS on DWI and occlusion of the internal carotid artery for MR examinees with supratentorial stroke (model 2). The multivariate analyses were repeated separately for patients with cardioembolism and for those without cardioembolism.

Table 1. Patients' clinical characteristics

Characteristics	Total	Prior statin		p value
		users (n = 60)	nonusers (n = 429)	
Women	171 (35.0)	19 (31.7)	152 (35.4)	0.567
Age, years	70.8 ± 11.6	72.0 ± 9.5	70.7 ± 11.9	0.420
Hypertension	300 (61.3)	47 (78.3)	253 (59.0)	0.004
Diabetes mellitus	92 (18.8)	19 (31.7)	73 (17.0)	0.007
Dyslipidemia	105 (21.5)	41 (68.3)	64 (14.9)	<0.001
Atrial fibrillation	198 (40.5)	27 (45.0)	171 (39.9)	0.447
Coronary heart disease	62 (12.7)	21 (35.0)	41 (9.6)	<0.001
Previous ischemic stroke	73 (14.9)	14 (23.3)	59 (13.8)	0.051
Prior medications				
Antithrombotics	170 (34.8)	38 (63.3)	132 (30.8)	<0.001
Antihypertensives	215 (44.0)	44 (73.3)	171 (39.9)	<0.001
Physiological data on admission				
Systolic blood pressure, mm Hg	150.9 ± 20.0	149.4 ± 21.8	151.2 ± 19.7	0.514
Diastolic blood pressure, mm Hg	81.6 ± 15.3	79.9 ± 15.6	81.8 ± 15.3	0.351
Pulse rate, bpm	79.6 ± 19.7	76.0 ± 20.2	80.2 ± 19.6	0.124
Body temperature, °C	36.3 ± 0.6	36.2 ± 0.5	36.4 ± 0.6	0.110
Laboratory data on admission				
Total cholesterol, mmol/l	4.89 ± 1.04	4.71 ± 0.84	4.92 ± 1.07	0.156
HDL-C, mmol/l	1.35 ± 0.37	1.26 ± 0.28	1.36 ± 0.38	0.022
LDL-C, mmol/l	2.95 ± 0.87	2.80 ± 0.77	2.97 ± 0.89	0.166
Triglycerides, mmol/l	1.33 ± 0.89	1.51 ± 1.14	1.30 ± 0.85	0.089
Blood glucose, mmol/l	7.65 ± 2.64	7.43 ± 2.26	7.68 ± 2.69	0.492
Creatinine, μmol/l	79.0 ± 59.8	84.5 ± 47.7	78.2 ± 61.4	0.448
Onset-to-treatment time, min	145 (122–165)	135 (120–164)	146 (125–166)	0.240
Baseline NIH Stroke Scale Score	12 (7–18)	12 (7–18)	12 (7–19)	0.687
i.v. antihypertensives just before rt-PA	139 (28.4)	18 (30.0)	121 (28.2)	0.773
Radiological findings for 402 MR examinees with supratentorial stroke				
ASPECTS on DWI ≥7	309 (76.9)	37 (74.0)	272 (77.3)	0.608
Arterial occlusion site				0.449
Internal carotid artery	68 (16.9)	11 (22.0)	57 (16.2)	
Middle cerebral artery	204 (50.7)	26 (52.0)	178 (50.6)	
Other	130 (32.3)	13 (26.0)	117 (33.2)	

Data are number of patients (%), median (interquartile range) for discontinuous variables, and mean ± SD for continuous variables.

Results

Of the 600 patients in the SAMURAI rt-PA Registry, 65 patients with a premorbid mRS score ≥2, 5 who were lost to follow-up at 3 months, and 41 who lacked information for one or more lipid levels on admission were excluded. Thus, 489 patients (171 women, 70.8 ± 11.6 years old) were included in this study. As compared with the excluded patients, the included patients more commonly took antihypertensives prior to stroke (p = 0.004) and more commonly had ASPECTS on DWI ≥7 (p = 0.020). Table 1 summarizes the patients' characteristics. Sixty patients (12.3%) used statins prior to their stroke. In these statin users, HDL-C levels were lower (1.26 ± 0.28 vs. 1.36 ± 0.38 mmol/l, p = 0.022), triglyceride levels tended to be higher (1.51 ± 1.14 vs. 1.30 ± 0.85 mmol/l, p = 0.089), and TC and LDL-C levels did not differ as compared with the remaining 429 non-statin users. Fifty-seven patients did not undergo MR imaging prior to rt-PA mainly due to contraindications, clinical instability, or time limitation. Of the remaining 432 MR examinees, 30 were diagnosed as having infratentorial strokes based on DWI and MR angiography findings.

Table 2. Lipid profiles and outcomes at 3 months

	Favorable (n = 188)	Unfavorable (n = 301)	p value	Model 1			Model 2		
				OR	95% CI	p value	OR	95% CI	p value
Dyslipidemia	43 (22.9%)	62 (20.6%)	0.551	1.03	0.63–1.67	0.917	1.18	0.68–2.07	0.557
Prior statin use	23 (12.2%)	37 (12.3%)	0.985	0.95	0.52–1.74	0.863	1.27	0.61–2.64	0.528
TC, mmol/l	4.90 ± 0.97	4.89 ± 1.09	0.937	0.98[a]	0.79–1.21[a]	0.828	0.95[a]	0.74–1.22[a]	0.687
HDL-C, mmol/l	1.39 ± 0.39	1.32 ± 0.36	0.030	1.95[a]	1.10–3.47[a]	0.023	2.03[a]	1.07–3.84[a]	0.029
LDL-C, mmol/l	2.89 ± 0.86	2.98 ± 0.88	0.305	0.84[a]	0.66–1.07[a]	0.154	0.84[a]	0.64–1.10[a]	0.195
Triglycerides, mmol/l	1.39 ± 0.98	1.29 ± 0.83	0.249	1.03[a]	0.82–1.29[a]	0.827	1.03[a]	0.77–1.36[a]	0.858

TC = Total cholesterol. Model 1, adjusted for sex, age by forced entry, diabetes mellitus, onset-to-treatment time, baseline NIHSS score, and i.v. antihypertensives chosen by a backward selection procedure in nonlipid factors listed in table 1 (except for MR findings). Model 2, adjusted for sex, age by forced entry, blood glucose, baseline NIHSS score, i.v. antihypertensives, occlusion of the internal carotid artery chosen by a backward selection procedure in nonlipid factors listed in table 1, and MR findings (ASPECTS on DWI ≥7, occlusion of the internal carotid artery).

[a] Per 1-mmol/l increase.

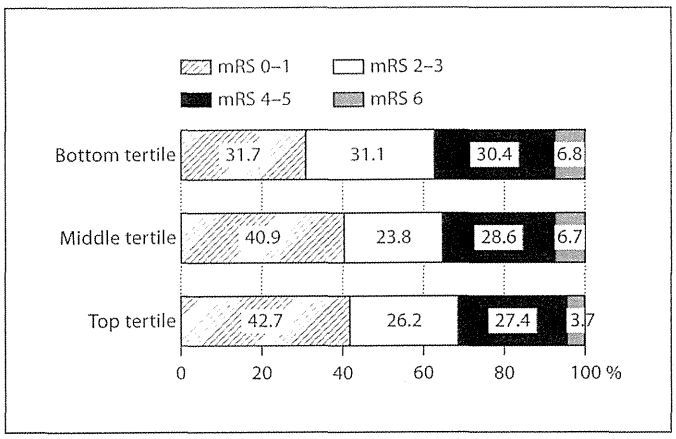

Fig. 1. mRS score at 3 months by each tertile of HDL-C level. Bottom tertile (<1.15 mmol/l): n = 161; middle tertile (1.15–1.46 mmol/l): n = 164; top tertile (≥1.46 mmol/l): n = 164.

Analyses of Overall Patients

Overall, 188 patients (38.4%) had a favorable outcome (mRS score ≤1) at 3 months. The HDL-C level was higher in patients with a favorable outcome than in those with an unfavorable outcome (1.39 ± 0.39 vs. 1.32 ± 0.36 mmol/l, p = 0.030), whereas other lipid profiles were not different between the two groups (table 2). In figure 1, the distribution of mRS scores in patients by each HDL-C level tertile is shown. The number of patients with a favorable outcome gradually increased as HDL-C levels increased. After multivariate analysis adjustment, the HDL-C level was the only lipid level that was independently related to favorable outcome (OR 1.95, 95% CI 1.10–3.47 per 1 mmol/l; p = 0.023). This relationship remained positive after further adjustment for MR findings using 402 patients who had a supratentorial stroke undergoing pretreatment MR examination (OR 2.03, 95% CI 1.07–3.84; p = 0.029).

ICH occurred in 93 patients (19.0%); 21 of these were symptomatic according to the NINDS/Cochrane definition and 4 were symptomatic according to the SITS-MOST definition. There were no significant associations between ICH and any lipid profiles on either univariate or multivariate analyses (table 3). Similarly, no lipid profiles were associated with symptomatic ICH per either definition.

Analyses of Patients with/without Cardioembolism

Stroke subtypes were cardioembolism in 302 patients (61.8%), large-artery atherosclerosis in 75 (15.3%), small-vessel occlusion in 26 (5.3%), and other types in 86 (17.6%). Of the 302 cardioembolic stroke patients, 110 (36.4%) had a favorable outcome at 3 months. On multivariate analysis, no lipid profiles were associated with a favorable outcome (e.g. OR 0.82, 95% CI 0.35–1.89 per 1 mmol/l of HDL-C).

Of the 187 stroke patients without cardioembolism, 78 (41.7%) had a favorable outcome at 3 months. On multivariate analysis, the HDL-C level (OR 4.94, 95% CI 1.91–12.76 per 1 mmol/l; p = 0.001) was independently associated with a favorable outcome.

Table 3. Lipid profiles and ICH within the initial 36 h

	Present (n = 93)	Absent (n = 396)	p value	Model 1			Model 2		
				OR	95% CI	p value	OR	95% CI	p value
Dyslipidemia	20 (21.5%)	85 (21.5%)	0.993	0.99	0.54–1.82	0.983	1.01	0.52–1.96	0.968
Prior statin use	14 (15.1%)	46 (11.6%)	0.363	1.20	0.58–2.45	0.625	1.58	0.76–3.29	0.224
TC, mmol/l	4.89 ± 1.00	4.89 ± 1.06	0.988	1.07[a]	0.85–1.36[a]	0.568	0.97[a]	0.74–1.26[a]	0.791
HDL-C, mmol/l	1.34 ± 0.34	1.35 ± 0.38	0.824	0.87[a]	0.45–1.69[a]	0.675	0.75[a]	0.35–1.58[a]	0.449
LDL-C, mmol/l	2.87 ± 0.78	2.96 ± 0.89	0.380	0.95[a]	0.72–1.25[a]	0.708	0.87[a]	0.64–1.18[a]	0.371
Triglyceride, mmol/l	1.34 ± 1.18	1.32 ± 0.81	0.891	1.12[a]	0.85–1.47[a]	0.419	1.16[a]	0.87–1.53[a]	0.307

TC = Total cholesterol. Model 1, adjusted for sex, age by forced entry, diabetes mellitus, atrial fibrillation, prior antithrombotics, blood glucose, and i.v. antihypertensives chosen by a backward selection procedure in nonlipid factors listed in table 1 (except for MR findings). Model 2, adjusted for sex, age by forced entry, diabetes mellitus, atrial fibrillation, prior antithrombotics, blood glucose, onset-to-treatment time, i.v. antihypertensives, occlusion of the internal carotid artery chosen by a backward selection procedure in nonlipid factors listed in table 1, and MR findings (ASPECTS on DWI ≥7, occlusion of the internal carotid artery).

[a] Per 1-mmol/l increase.

Discussion

In this study, the effects of admission lipid levels and prior statin use on clinical outcomes in stroke patients receiving i.v. rt-PA were examined. The major finding of this study was that a higher HDL-C level was associated with completely independent activities of daily living at 3 months after multivariate adjustment for clinical and radiological characteristics. The association was clear in patients without cardioembolism, but was not confirmed in cardioembolic stroke patients. In the present cohort, no relationships between functional outcome and other lipid levels or prior statin use were identified. Besides, any lipid levels or prior statin use were not related to ICH.

Although HDL-C is a potent protective factor for cardiovascular diseases and stroke, it may be understudied as compared with LDL-C. HDL-C has not only a direct role against atherosclerosis to remove free cholesterol from macrophages in the arterial wall and return it to the liver, but it also inhibits prothrombotic and proinflammatory phenomena [26, 27]. In addition, HDL-C protects LDL from oxidation, promotes endothelial nitric oxide synthesis, and increases vasodilatation [26, 28]. These manifold effects, including antiatherosclerotic, vasoprotective, and neuroprotective effects, have been assumed to improve stroke outcome. Interestingly, the statistical significance of the contribution of HDL-C to favorable outcome was much higher in stroke patients without cardioembolism than overall patients, although the number of patients was much smaller. This result suggests that HDL-C has a larger protective effect for patients with atherothrombotic conditions. In contrast, LDL-C was not a predictor of a favorable outcome. Prior statin use in some patients might modify admission LDL-C levels and affect the results. Since the purpose of the present study was to assess the significance of lipid levels on emergency admission as a prognostic predictor, the fasting status of patients on admission was not considered relevant. Although the HDL-C level is little influenced by fasting or nonfasting, the LDL-C level appears to be influenced to some extent [29].

Statin use prior to stroke onset was reported to improve functional outcomes of general ischemic stroke patients [30–33]. For stroke patients treated with i.v. rt-PA, one study reported a positive association between statin use and favorable 3-month outcome [34], though another study found no such association [35]. The studies on thrombolysis including intra-arterial thrombolysis or endovascular intervention introduced a warning message that prior statin use and a low LDL-C level increased symptomatic ICH after treatment [14, 36]. In the present cohort, neither statin use nor any lipid levels were associated with ICH, which was also observed in previous studies only for patients treated with i.v. rt-PA [34, 35]. The discrepancies of results between the former studies and ours may be caused by the difference of not only treatment but baseline features. In our study, statin users had uncommonly hypertension compared with those in Meier et al. [36] (78.3 vs. 92.6%), and patients with LDL-C levels <85 mg/dl (2.20 mmol/l) were fewer than those in Bang et al. [14] (19.0 vs. 33%). Also, a lower dose of alteplase (0.6 mg/kg) than the standard Western dose may