Table 4
Incidence rates and adjusted hazard ratios for coronary heart disease and ischemic strokes by serum 1,5-anhydro-D-glucitol levels in men and women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			p for trend
	≥23.1	14.1–23.0	≤14.0	
Number of subjects	854	865	376	
Person-years	9606	9814	3878	
Coronary heart diseases				
Cases, *n*	22	25	17	
Incidence rates/1000 person-years	2.3	2.5	4.4	
Model 1[a]	1	1.36 (0.76–2.44)	2.17 (1.14–4.13)	0.02
Model 2[a]	1	1.41 (0.78–2.52)	2 10 (1.10–4.02)	0.03
Model 3[a]	1	1.37 (0.76–2.46)	1.76 (0.85–3.63)	0.12
Ischemic strokes				
Cases, *n*	19	22	12	
Incidence rates/1000 person-years	2.0	2.2	3.1	
Model 1[a]	1	1.25 (0.67–2.31)	1.58 (0.76–3.27)	0.22
Model 2[a]	1	1.24 (0.67–2.31)	1.56 (0.75–3.24)	0.23
Model 3[a]	1	1.21 (0.65–2.25)	1.23 (0.54–2.82)	0.56

Parentheses indicate 95% confidence intervals.

[a] Model 1: adjusted for age, sex, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

lence of diabetes or anti-diabetic medication was clearly lower than those with 14.0 μg/mL or less, also had significantly elevated risks. This suggested the possibility that many subjects without overt diabetes who had postprandial hyperglycemia with excretion of glucose in the urine were included in this middle category. Measurement of serum 1,5-AG levels can be useful to detect individuals at greater risk for CVD even among those without overt diabetes. In fact, the sensitivity analyses in non-diabetic subjects with almost normal plasma glucose levels also showed similar results, which reinforced these findings.

In men, the relationship between serum 1,5-AG levels and stroke was much clearer than that with CHD. The prevalence of hypertension increased with decrease in serum 1,5-AG levels, but the prevalence of hypercholesterolemia did not change, irrespective of serum 1,5-AG levels. Such discrepancies in the relationships between serum 1,5-AG levels and risk factors for CVD may account for the difference observed between risk of stroke and that of CHD.

In women, no significant relationship was observed between serum 1,5-AG levels and the risk for all CVD or each CVD subtype, although a similar increase in the risk for CHD was found. Previous meta-analyses have shown either that women with diabetes have a higher risk for CHD than men with diabetes [18,19], or that there was no sex difference [20]. The DECODE study also showed that the HR of death from CVD in individuals with 2-h glucose levels of 11.1 mmol/L or greater tended to be higher among women than among men [5]. The present results show an opposite sex difference, and the reason is not clear. However, the prevalence of diabetes at baseline was much lower in women than in men, and the incidence rate of all CVD and each CVD subtype was also relatively lower in women. Such discrepancies in basic characteristics

Table 5
Sensitivity analyses of incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in non-diabetic men with fasting or postprandial plasma glucose levels of less than 6.1 mmol/L, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			p for trend
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	388	349	77	
Person-years	4326	3636	703	
All cardiovascular diseases				
Cases, *n*	22	40	8	
Incidence rates/1000 person-years	5.1	11.0	11.4	
Model 1[a]	1	1.75 (1.04–2.96)	1.65 (0.73–3.72)	0.07
Model 2[a]	1	1.76 (1.04–2.98)	2.00 (0.88–4.55)	0.03
Coronary heart diseases				
Cases, *n*	14	17	2	
Incidence rates/1000 person-years	3.2	4.7	2.8	
Model 1[a]	1	1.26 (0.62–2.57)	0.71 (0.16–3.15)	0.96
Model 2[a]	1	1.18 (0.57–2.43)	0. 86 (0.19–3.86)	0.89
All strokes				
Cases, *n*	8	23	6	
Incidence rates/1000 person-years	1.8	6.3	8.5	
Model 1[a]	1	2.58 (1.15–5.79)	3.11 (1.07–9.00)	0.01
Model 2[a]	1	2.51 (1.11–5.66)	3.68 (1.26–10.75)	0.01
Ischemic strokes				
Cases, *n*	7	15	5	
Incidence rates/1000 person-years	1.6	4.1	7.1	
Model 1[a]	1	1.97 (0.80–4.85)	3.05 (0.96–9.69)	0.045
Model 2[a]	1	1.92 (0.77–4.75)	3.45 (1.08–11.05)	0.03

Parentheses indicate 95% confidence intervals.

[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

between men and women might result in the sex difference. In addition, the involvement of selection bias cannot be completely eliminated in women. Further studies with sufficient samples and CVD events in women are necessary to clarify this problem.

Measurement of serum 1,5-AG levels could detect not only those with persistent hyperglycemia but also those with transient postprandial hyperglycemia who are likely to be at higher risk for development of diabetes in the near future. Accordingly, decrease in serum 1,5-AG levels might be related with the elevated risk of CVD. The previous epidemiological studies also reported the association of postprandial hyperglycemia with risk of CVD [4–6], and the present results are not inconsistent with them. However, the mechanism remains still inconclusive, and two hypotheses could be considered. First, hyperglycemia itself is a risk for atherosclerotic diseases. Second, hyperglycemia is just a reflection of insulin resistance which is closely related to risk factors for atherosclerotic diseases. In the present study, adjustments for insulin resistance-related factors, waist circumferences or triglycerides, hardly changed the results. This indirectly suggests that serum 1,5-AG levels are independently related with a risk for CVD from insulin resistance, and we infer that hyperglycemia itself might be a risk.

OGTT cannot be conducted easily in the routine clinical setting or during health check-ups because it requires overnight fasting in blood sampling, longer time and extra costs. Conversely, measurement of serum 1,5-AG can be performed easily with a single non-fasting blood sample and is relatively low cost. Serum 1,5-AG levels do not fluctuate very much within an individual if glucose is not excreted into urine; however, it varies widely among individuals [1–3,13,21,22]. Accordingly, periodic measurement of serum 1,5-AG might be important for the early detection of a decrease from the normal level in each individual.

It is also well known that hemoglobin A_{1c} (HbA_{1c}) is useful for the diagnosis of diabetes or as a marker of glycemic control, and elevated HbA_{1c} is associated with increased risk for macro- and micro-complications [15–17,23]. HbA_{1c} can also be measured in a single non-fasting blood sample. However, red cell turnover and hemoglobinopathies influence HbA_{1c} levels, and this has been often identified as a problem [23,24]. In contrast, serum 1,5-AG levels are not affected by red cell turnover and hemoglobinopathies. In terms of screening higher risk individuals among the general population, a combination of HbA_{1c} and serum 1,5-AG measurements might be better choice.

The present analysis had several limitations. First, some aspects of medical history were unknown, including gastric resection, hyperthyroidism and renal glycosuria, which can lower 1,5-AG levels. Second, the present dataset did not include measurement of HbA_{1c} levels or OGTT; therefore, comparison of HbA_{1c} or OGTT with serum 1,5-AG was not possible. Third, a single serum 1,5-AG measurement at baseline may have lead to an underestimation of the association between serum 1,5-AG levels and CVD due to regression dilution bias [25].

In conclusion, the present analyses suggest that in men measurement of serum 1,5-AG was useful to detect individuals at increased risk for CVD, regardless of the presence or absence of diabetes. Measurement of serum 1,5-AG levels might be a useful tool for screening in the clinical setting or during health check-ups. However, this is the first report with a limited population of Japanese, and these findings should be further investigated by studies with sufficient samples and CVD events among various populations, races and geographical areas.

Conflict of interest

None to be declared.

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bjh research paper

Prospective multicentre cohort study of heparin-induced thrombocytopenia in acute ischaemic stroke patients

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Summary

Acute ischaemic stroke patients sometimes receive heparin for treatment and/or prophylaxis of thromboembolic complications. This study was designed to elucidate the incidence and clinical features of heparin-induced thrombocytopenia (HIT) in acute stroke patients treated with heparin. We conducted a prospective multicentre cohort study of 267 patients who were admitted to three stroke centres within 7 d after stroke onset. We examined clinical data until discharge and collected blood samples on days 1 and 14 of hospitalization to test anti-platelet factor 4/heparin antibodies (anti-PF4/H Abs) using an enzyme-linked immunosorbent assay (ELISA); platelet-activating antibodies were identified by serotonin-release assay (SRA). Patients with a 4Ts score ≥4 points, positive-ELISA, and positive-SRA were diagnosed as definite HIT. Heparin was administered to 172 patients (64·4%: heparin group). Anti-PF4/H Abs were detected by ELISA in 22 cases (12·8%) in the heparin group. Seven patients had 4Ts ≥ 4 points. Among them, three patients (1·7% overall) were also positive by both ELISA and SRA. National Institutes of Health Stroke Scale score on admission was high (range, 16–23) and in-hospital mortality was very high (66·7%) in definite HIT patients. In this study, the incidence of definite HIT in acute ischaemic stroke patients treated with heparin was 1·7% (95% confidence interval: 0·4–5·0). The clinical severity and outcome of definite HIT were unfavourable.

Keywords: acute stroke care, anticoagulation, heparin, platelet, thrombocytopenia.

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Immune-mediated heparin-induced thrombocytopenia (HIT), which is caused by platelet-activating IgG antibodies that recognize platelet factor 4 bound to heparin (anti-PF4/heparin Abs), is a relatively common side effect of heparin therapy and presents a strong risk factor for thromboembolic events associated with high mortality and morbidity (Warkentin, 2007a). Prospective studies in Western countries have shown that the prevalence of HIT is 0·3–5% of patients treated with unfractionated heparin (UFH), which varies depending on the clinical settings (Warkentin *et al*, 1995, 2000; Kappers-Klunne

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et al, 1997). Thrombotic complications occur in approximately one-third to one-half of HIT patients (Warkentin, 2007a). On the other hand, some studies of UFH therapy for acute stroke reported no cases of HIT (Toth & Voll, 2002; Camerlingo *et al*, 2005). To elucidate the prevalence of HIT in acute ischaemic stroke patients who were treated with heparin, we organized a prospective multicentre cohort study that included systematic collection of blood for detection of the antibodies that cause HIT.

Some clinical guidelines do not recommend prescribing heparin in acute ischaemic stroke, and others recommend it mainly for the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) (Albers *et al*, 2004; Cardiovascular Disease Educational and Research Trust, 2006; Adams *et al*, 2007). At the participating stroke centres in our study, in addition to the prevention of DVT and PE, UFH is given during the acute phase of ischaemic stroke to the following: patients with emboligenic heart disease or superimposed thrombi on the carotid plaque to prevent embolic complications; patients with particular stroke aetiologies, including cerebral arterial dissection and vasculitis; and patients with embolic stroke of unknown origin until the presence of heart disease is excluded by the results of prolonged electrocardiography and transesophageal echocardiography (Caplan, 2003).

In a previous study of 137 stroke patients who were treated with UFH, 21 patients (15·3%) developed thrombocytopenia (≥40% fall in platelet counts) during or after heparin therapy, and five of these 21 patients had an additional ischaemic stroke (Ramirez-Lassepas *et al*, 1984). A recent study of 200 neurological patients treated with UFH for at least 5 d, including 102 patients with cerebrovascular disorders, demonstrated that 41 patients (20·5%) had anti-PF4/heparin Abs and 5 (2·5%) developed HIT, when the serological diagnosis was made from the presence of antibodies detected by an enzyme-linked immunosorbent assay (ELISA) (Harbrecht *et al*, 2004).

Only a few studies have investigated the prevalence of HIT in acute stroke patients receiving UFH, especially in the Asian population (Kawano *et al*, 2008). In our previous retrospective report of acute ischaemic stroke patients who were treated with UFH, 0·5% of the patients developed HIT diagnosed by both the clinical scoring systems and the serological assays, including ^{14}C-serotonin release assay (SRA) (Kawano *et al*, 2008). However, our retrospective study assessing the prevalence of HIT was limited by the fact that was that antibodies were not assayed in all patients. This limitation may cause an under diagnosis of HIT.

Thus, we performed this prospective multicentre cohort study in 267 patients to determine a more accurate incidence of HIT in patients with acute ischaemic stroke and to elucidate the clinical features of HIT.

Methods

Study design

A prospective multicentre cohort study.

Subjects and settings

This study was conducted in three Japanese stroke centres at the then National Cardiovascular Centre (currently the National Cerebral and Cardiovascular Centre, Osaka), Research Institute for Brain and Blood Vessels Akita (Akita), and Kumamoto University (Kumamoto). Between October 2006 and May 2007, all consecutive patients who met the following criteria were enrolled. Eligible patients were 20 years of age or older and admitted within 7 d after the onset of acute ischaemic stroke, including cerebral infarction and transient ischaemic attack. Patients were excluded for any of the following: (i) active infectious endocarditis, (ii) urgent neurosurgery or cardiovascular surgery would be required, (iii) chronic thrombocytopenia (defined as a platelet count $<100 \times 10^9$/l for more than 30 d), (iv) haematopoietic malignancy and (v) an ongoing need for an anticancer-drug treatment. The study was approved by the research ethics committee of each centre. Heparin therapy was provided to a number of patients depending on the physician's decision (mainly considering the type of stroke and/or the patient's clinical status as described in the Introduction.)

Evaluation

The following patient characteristics were obtained: age, sex, height, body weight, body-mass index, modified Rankin Scale (mRS) score (van Swieten *et al*, 1988) before stroke onset, vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, current and past smoking habits, drinking habit, including occasional drinking), past history (autoimmune disease, haemodialysis, renal dysfunction, angina, myocardial infarction, cerebral infarction, transient ischaemic attack, pulmonary thromboembolism, extremity gangrene, amputation of an extremity, angiography, heparin exposure, surgical procedure and HIT), platelet counts, antiplatelet/anticoagulant drug use and blood transfusions. The timing and period of heparin administration (including heparin flushes), changes in platelet count, and alternative anticoagulant therapy for HIT (if given) were also examined. Other risk factors for stroke, such as emboligenic heart diseases including atrial fibrillation, were assessed based on the criteria from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study (Adams *et al*, 1993). Based on the neurological, radiological, cardiological and haematological profiles, the stroke subtype was determined according to the TOAST subtype classification system by a consensus of stroke neurologists. The neurological severity of each patient was assessed by an experienced stroke neurologist according to the National Institutes of Health Stroke Scale (NIHSS) score (Lyden *et al*, 1994) on admission and discharge, and at 3 months after onset. Patient global outcome was also assessed with mRS (van Swieten *et al*, 1988).

Clinical evaluation. The clinical probability of HIT was assessed using the 4Ts scoring system (Warkentin & Heddle, 2003), which is composed of four clinical features that are

given scores of 0, 1, or 2; magnitude of thrombocytopenia; timing of platelet count fall (in relation to heparin therapy); thrombosis or other sequelae; and presence of other explanations for thrombocytopenia. The case reports of the patients, filled out by their physicians, were assessed independently in a blinded fashion by the external Data Assessment Committee, which consisted of two stroke neurologists, according to the 4Ts scoring system after the patient follow-up was completed. If the judgment was not concordant between the two stroke neurologists, they discussed the cases to reach a final consensus and decision. Based on the 4Ts score, the estimated pretest probabilities of HIT were categorized into three groups: low (0–3), intermediate (4–5) and high (6–8) scores. We diagnosed the patients with an intermediate or a high score as 'potential HIT' and those with a low score as 'clinical non-HIT'. These objective assessments for the clinical probability of HIT were done after the patient follow-up was completed as described above, so that no results influenced clinical management. Therefore, some patients were ultimately diagnosed as HIT even though the physicians in charge did not suspect HIT as described in details in the Results section.

Serological evaluation. Blood samples were collected from all patients on the first (to the third) and 14th (±4) hospital days to be tested for anti-PF4/heparin Abs using ELISA (Asserachrom HPIA; Diagnostica Stago, Asnieres, France). The assays were performed in a blinded fashion after patient follow-up was completed. ELISA was performed according to the manufacturer's instructions. The titres of the samples were expressed as values of optical density (OD). The result was considered positive when the titre was greater than the cut-off value, which was determined using the reference control for each kit. To confirm the diagnosis of HIT, SRA was measured for all patients with a positive ELISA and/or ≥4 points in the 4Ts scoring system (n = 29). In addition, samples from 39 patients selected randomly from among all the patients were tested by SRA as a control. Samples were measured as described elsewhere at the Platelet Immunology Laboratory, McMaster University (Hamilton, ON, Canada) blinded to all clinical, platelet count and serological data (Warkentin *et al*, 1992). Any sample that produced ≥10% mean serotonin release with <10% release in the presence of high heparin (at a final concentration of 100 u/ml) and the anti-FcγRIIa monoclonal antibody (IV.3) was considered SRA-positive.

Diagnosis

Based on the results of both the 4Ts clinical score and the serological assays, patients were categorized into four groups as follows: (i) definite HIT (4Ts score ≥4 points with positive results in both ELISA and SRA), (ii) possible HIT (4Ts score ≥4 points with positive result in either ELISA or SRA) and (iii) clinically suspected HIT (4Ts score ≥4 points with negative results in both ELISA and SRA), seropositive status (4Ts score <4 points with positive in both ELISA and SRA). The remaining patients were categorized as HIT unlikely.

Statistical analysis

The variables between the groups of patients treated with and without heparin were compared using Fisher's exact test and the Wilcoxon test. For NIHSS, the change, NIHSS score at discharge minus that at admission, was also determined. Statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

A total of 267 patients (mean age 71·7 years; 66·2% men), who were admitted to three stroke centres within 7 d after stroke onset during a 6-month period, were enrolled. Intravenous UFH was administered to 172 patients (64·4%: heparin group) (Fig 1). Male gender, atrial fibrillation, previous ischaemic heart disease, history of surgery using UFH, and history of intra-arterial catheter procedures were significantly more common in patients treated with than without UFH (Table IA). In regard to stroke subtype, large artery atherosclerosis and cardioembolism were more frequent in patients treated with UFH, and small vessel occlusion was more frequent in those without UFH treatment. There was no significant difference in the history of antiplatelet drug use before admission between the patients treated with (66 cases, 38·4%) and without UFH (32 cases, 33·7%) (P = 0·508) (Table IA). Both the NIHSS score at discharge (median, 2 vs. 1, P = 0·020) and mRS at 3 months after stroke onset (median, 2 vs. 1, P < 0·001) were higher in patients treated with UFH (Table IB).

The incidence of HIT

Anti-PF4/heparin Abs were detected at any time point in 22 patients (12·8%) in the heparin group and in 3 (3·2%) of 95 patients who did not receive intravenous UFH respectively (Fig 1), and the difference was significant (P = 0·008). Seven patients (4·1%) were diagnosed as having potential HIT according to the 4Ts score (≥4 points). All seven patients had intermediate scores. Among them, three showed positive results in both ELISA and SRA, to give an incidence of definite HIT of 1·7% [95% confidence interval (CI): 0·4–5·0]. Possible HIT, clinically suspected HIT, and seropositive status were 0%, 2·3% (n = 4), and 2·3% (n = 4), respectively (Fig 1). Of the 95 patients with a positive ELISA who did not receive heparin within 3 months before admission and/or during hospitalization, three were SRA-negative. The OD values of anti-PF4/heparin Abs detected by ELISA seemed a little higher in definite HIT patients than the seropositive status group, although statistical analysis was not performed because of the

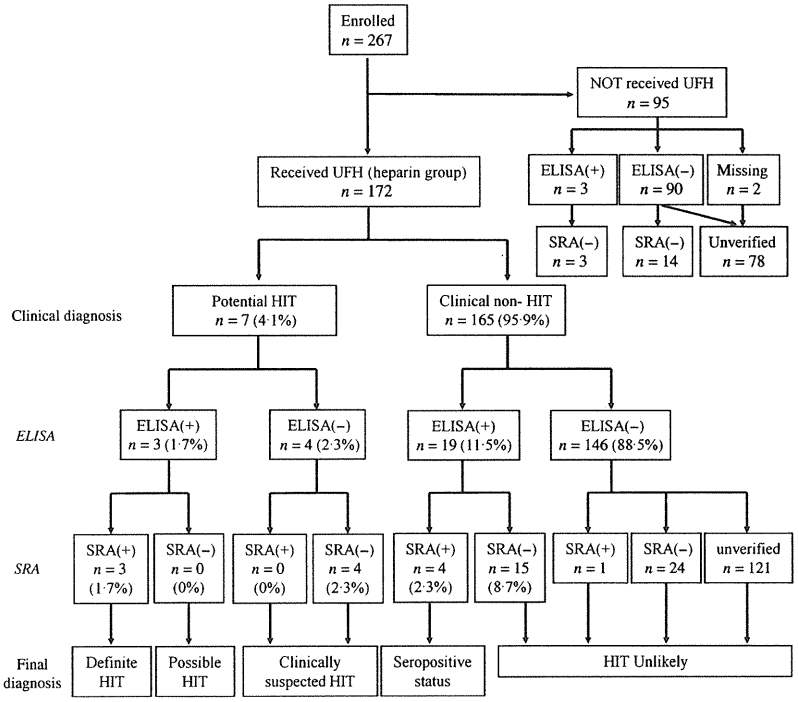

Fig 1. Flow chart for diagnosis of heparin-induced thrombocytopenia. HIT, heparin-induced thrombocytopenia; UFH, unfractionated heparin; ELISA, enzyme-linked immunosorbent assay; SRA, serotonin-release assay.

small sample size (Table II). OD values in ELISA did not correlate with the mean percentage release in SRA (Fig 2). However, the proportion of samples with positive-SRA to those with negative-SRA was greater in the samples with ≥1·5 OD value in ELISA as compared to those with <1·5 OD value. The prevalence of positive-ELISA was not significantly different between patients who received UFH for five or more days (15·9%) and for <5 d (11·4%).

Clinical course and the treatment of definite HIT patients

Only one (Case 3) of three definite HIT patients was suspected of having HIT by the treating physician. This patient had atrial fibrillation and an infarct in the right anterior and middle cerebral arteries. The admission NIHSS score was 17 (Table II). The patient's platelet count decreased from 156 to 99×10^9/l (approximately a 37% fall) in the typical HIT window (5–10 d) and recovered to 227×10^9/l soon after stopping heparin administration on day 7 due to the suspicion of HIT. The patient had a further fall in platelet count, from 227 to 99×10^9/l (approximately a 56% fall), after day 10 with a high OD value (2·086) in ELISA and a weak positive SRA (11% release) (Table II). The patient died due to deterioration from an underlying stroke. The very weak SRA, which was performed during the second platelet count fall, argues somewhat against this patient having HIT. However, HIT antibodies sometimes become weaker very quickly (Warkentin & Kelton, 2001; Greinacher *et al*, 2009), and so it is possible that the SRA would have been stronger during the first platelet count fall.

The other two patients (Cases 1 and 2) that ultimately met the criteria for definite HIT in this study were not suspected of having HIT by their physicians. One patient (Case 1) experienced a stroke of other determined aetiology due to arterial dissection in the intracranial left vertebral artery. The admission NIHSS score was 23 (Table II). The patient had bilateral cerebellar and brain stem infarcts. UFH was administrated for 7 d, and UFH flushes for intravascular catheter were continued for an additional 4 d. The patient showed a 52·0% decrease in platelet count, from 331 to 107×10^9/l, that began on day 5 of heparin with relatively high values in SRA (63·9% release) and ELISA (2·271 OD value) (Table II). Death occurred from stroke on day 11. The other patient (Case 2) with a previous history of recent transient ischaemic attacks had a cardioembolic stroke due to atrial fibrillation 9 d after urgent hemiarch replacement due to aortic dissection. The admission NIHSS score was 16. The patient's platelet count declined from 436 to 286×10^9/l (a drop of approximately 34%) during the typical HIT window of days 5–10 with relatively high values in SRA (51·6% release) and ELISA (1·725 OD value); although the platelet count evolution may be explained by a platelet count profile of post-cardiovascular surgery with cardiopulmonary bypass overshooting around postoperative day 14 and returning gradually to the baseline (Table II). The patient was dependent at discharge and at 3-month follow-up.

Table I. (A) Demographic data of patients treated or not with unfractionated heparin (UFH) and (B) clinical data of patients treated or not with UFH.

	With UFH (n = 172; 64·4%)	Without UFH (n = 95; 35·6%)	*P*-value
(A)			
Age (years), median (range)	71 (23–98)	73 (42–93)	0·515
Male gender (%)	122 (70·9)	53 (55·8)	0·015
Weight (kg)	60·1 ± 12·2	59·4 ± 11·6	0·673
BMI (kg/m^2)	23·3 ± 3·8	23·4 ± 3·7	0·936
HTN (%)	133 (77·3)	74 (77·9)	1·000
DM (%)	55 (32·0)	30 (31·6)	1·000
CRF (%)	17 (9·9)	5 (5·3)	0·247
HD (%)	3 (1·7)	0 (0)	0·555
Atrial fibrillation (%)	59 (34·3)	11 (11·6)	<0·001
Smoking (%)	78 (45·3)	37 (38·9)	0·303
Drinking (≥2 cups) (%)	49 (28·5)	21 (22·1)	0·249
Previous IHD (%)	33 (19·2)	5 (5·3)	0·002
Previous CVD (%)	51 (29·7)	28 (29·5)	1·000
Previous PTE (%)	0	0	–
Previous DVT (%)	4 (2·3)	1 (1·1)	0·658
History of heparin use within 3 months (%)	6 (3·5)	0 (0)	0·180
History of surgery using heparin	33 (19·2)	3 (3·2)	<0·001
History of intra-arterial catheter procedure (%)	43 (25·0)	8 (8·4)	<0·001
History of warfarin use (%)	18 (10·5)	5 (5·3)	0·176
History of antiplatelet agency use (%)	66 (38·4)	32 (33·7)	0·508
Stroke subtype			
TIA (%)	9 (5·2)	20 (21·1)	<0·001
Stroke (%)	163 (94·8)	75 (78·9)	
LAA (%)	38 (23·3)	5 (6·7)	
CE (%)	64 (39·3)	5 (6·7)	<0·001
SV (%)	26 (16·0)	48 (64·0)	
OT + UD (%)	35 (21·5)	17 (22·7)	
Platelet count (×10^9/l)	222 (103–583)	230 (119–483)	0·670
NIHSS score on admission, median (range)	5 (0–32)	3 (0–20)	<0·001
(B)			
Treatment during the hospital stay			
Warfarin use (%)	70 (40·7)	9 (9·5)	<0·001
Antiplatelet agency use (%)	105 (61·0)	84 (88·4)	<0·001
Cessation of heparin (%)	142 (82·6)	0	<0·001
Alternative anticoagulation (%)	67 (39·0)	37 (38·9)	1·000
Intra-arterial catheter procedure during the hospital stay (%)	70 (40·7)	0 (0)	<0·001
Surgery with heparin use during the hospital stay	7 (4·1)	0 (0)	0·053
Thromboembolic vents or death	25 (14·5)	4 (4·2)	0·012
Recurrence of ischaemic stroke	12 (7·0)	2 (2·1)	
Thromboembolic events during catheter	4 (2·3)	0	
Other thromboembolism	7 (4·1)	2 (2·1)	
React of heparin infusion	1 (0·6)	0	
Death	5 (2·9)	0	
NIHSS score at discharge, median (range)	2 (0–42)	1 (0–20)	–
NIHSS change, discharge-admission (range)	−2 (−21 to 19)	−1 (−8 to 9)	0·020
mRS at discharge, mean (median)	2 (0–6)	1 (0–5)	0·002
mRS at 3 months, median (range)	2 (0–6)	1 (0–5)	<0·001

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CRF, chronic renal failure; HD, haemodyalysis; IHD, ischaemic heart disease; CVD, cerebrovascular disease; PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; TIA, transient ischaemic attack; LAA, large artery atherosclerosis; CE, cardioembolism; SV, small vessel occlusion; OT, stroke with alternative aetiology; UD, stroke of undetermined aetiology; UFH, unfractionated heparin; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale.

Table II. Clinical features of HIT patients.

Pt	Age (years)	Gender	Past history	Stroke subtype	4Ts score	ELISA (OD)	SRA (mean % release)	Platelet count ($\times 10^9$/l) Baseline	Nadir	Duration of UFH (day)	Duration of UFH up to the day of platelet nadir, days	Thrombotic complication	NIHSS on admission	mRS on discharge
Definite HIT														
1	62	Male	CI, HTN	Other	4	+(2·271)	+(63·9)	331	107	11	7	None	23	Dead
2	64	Female	CI, HTN, AF	CE	5	+(1·725)	+(51·6)	436	286	18	10	None	16	4
3	88	Female	AF	CE	5	+(2·086)	+(11·0)	156	99	7	15	None	17	Dead
Clinically suspected HIT														
4	67	Male	HTN, DM, AF, CRF	CE	4	−(0·138)	−(<1)	281	210	14	7	DVT	7	4
5	82	Male	CI, HTN, AF	CR	4	−(0·052)	−(<1)	137	27	1	4	None	10	4
6	66	Male	MI, HTN	CE	4	−(0·102)	−(<1)	583	225	13	17	None	12	1
7	69	Female	HTN, AF	CE	5	−(0·091)	−(<1)	297	120	23	6	RI	7	4
Seropositive status														
8	70	Female	HTN, AF	CE	0	+(1·666)*	+(53·2)	141	123	4	NA†	None	13	2
9	59	Female	HTN, AF, AID	CE	0	+(1·505)	+(76·8)	163	158	18	NA†	None	15	4
10	87	Male	IHD, HTN, AF	CE	0	+(0·977)	+(13·3)	200	150	13	NA†	None	8	5
11	90	Female	HTN, AF	CE	2	+(2·378)	+(28·8)	235	210	9	NA†	IHD	29	5

ELISA, enzyme-linked immunosorbent assay; SRA, serotonin-release assay; OD, optical density; CI, cerebral infarction; IHD, ischaemic heart disease; HTN, hypertension; DM, diabetes mellitus; AF, atrial fibrillation; CRF, chronic renal failure; MI, myocardial infarction within 4 weeks; AID, autoimmune disease; RI, renal infarction; DVT, deep vein thrombosis; other, stroke of other determined aetiology; CE, cardioembolism; NA, not applicable.

*ELISA was negative (OD: 0·079) in the sample drawn 7 d after admission, when SRA was positive. ELISA was positive (OD: 1·666) in the sample obtained 1 week later.

†Patient did not demonstrate thrombocytopenia.

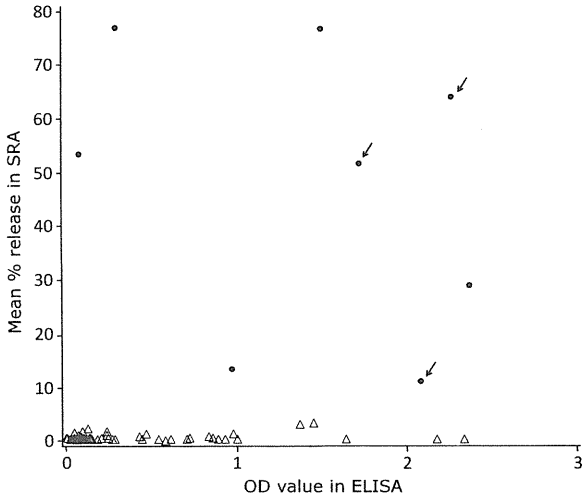

Fig 2. The correlation of optical density (OD) values for anti-platelet factor 4/heparin antibodies detected by enzyme-linked immunosorbent assay (ELISA) and mean percentage release by serotonin-release assay (SRA). These values showed poor correlation. Arrows indicate the data points of the three patients who met the criteria for definite HIT. •, SRA-positive cases, including one patient classed as 'HIT unlikely': OD = 0·298, and mean percentage release = 76·74; △, SRA-negative cases.

None of the patients in this study met the diagnosis of rapid or delayed onset HIT. None of the patients classified as definite HIT received treatment with alternative anticoagulants, such as thrombin inhibitors, nor did the patients develop additional thromboembolic events.

Discussion

HIT should be recognized as a clinicopathological syndrome because none of the currently available HIT diagnostic tools have sufficient sensitivity and specificity to be used as the primary or only tool to diagnose HIT. Thus, both clinical and serological diagnoses are crucial. In this prospective study, clinical probability was assessed using the 4Ts scoring system, which is a popular method, by two independent stroke neurologists who were blinded from the results of serological assays. As a result, 4·1% of the acute stroke patients treated with heparin were suspected clinically of having HIT with ≥4 points in the 4Ts scoring system. Among them, 1·7% (95% CI: 0·4–5·0) had platelet activating antibodies against the complexes of PF4 and heparin detected by ELISA and SRA, supporting the diagnosis of definite HIT. All of these definite HIT patients had intermediate scores in the 4Ts as well as four clinically suspected HIT cases, as shown in Table II. Thus, it was very difficult to distinguish HIT patients from non-HIT patients through clinical information alone. This may possible explain why only one among three definite HIT cases was suspected of having HIT by the treating physicians.

Our results were similar to those reported in other studies of patients with ischaemic stroke (Ramirez-Lassepas *et al*, 1984; Harbrecht *et al*, 2004) and the frequency of definite HIT was less than in surgical patients (Kappers-Klunne *et al*, 1997; Warkentin, 2007b). For two of the three definite HIT patients reported here, one had a possible alternative aetiology that could explain her platelet count fall (Case 2) and the other had a weak positive-SRA (Case 1) as described in detail in the Result section. Thus, we cannot exclude the possibility that these two patients might not have had HIT. If we exclude these patients, the incidence of HIT could be as low as 0·6%. However, this result was compatible with our previous retrospective study of the same patient population (the incident of HIT was 0·5%) (Kawano *et al*, 2008). Therefore, we can conclude that the incidence of HIT in acute stroke patients treated with UFH seems to be approximately 0·5–1·7%. These results emphasize that HIT diagnosis should be considered in the management of acute ischaemic stroke.

Another major finding was that the clinical severity and outcome of acute stroke patients who were diagnosed as having definite HIT were unfavourable. In particular, the in-hospital mortality of definite HIT was very high (66·7%). Previous reports also indicated that mortality was high in HIT patients (Warkentin *et al*, 1995, 2000; Kappers-Klunne *et al*, 1997). The present study is unique in that initial neurological severity and clinical outcomes of stroke patients with HIT were determined. The NIHSS score on admission (median, 17) in definite HIT was quite high, and the outcome at 90 d was poor. However, the poor outcome of those patients appeared to be mainly due to the severity of the initial stroke rather than HIT. Although clinical severity and outcome of patients treated with UFH were unfavourable compared to those without UFH, the patients with UFH intrinsically might be at high risk of thromboembolic complications because those patients more frequently had systemic atherosclerotic changes or embolic sources. In fact, stroke subtypes were distributed differently between patients with and without UFH in our study. Hoh *et al* (2005) reported significantly less favourable outcomes, including new thromboembolic episodes and deaths in patients with subarachnoid haemorrhage who developed HIT compared to those without HIT. They found that more patients with HIT showed a poorer Fisher Grade than those without HIT, although the diagnosis of HIT was based on clinical criteria, and serological examinations were not mandatory in the study (Hoh *et al*, 2005). It should be considered that serious neurological conditions might be vulnerable to HIT.

In the present study, four of 165 clinical non-HIT patients were positive by both ELISA and SRA. None of these patients demonstrated thrombocytopenia, nor did they die. A thromboembolic event occurred in one patient who developed an ischaemic heart event. Previous reports suggested that high OD values in ELISA and/or strong-positive SRA results were associated with a high degree of diagnostic accuracy for HIT (Warkentin *et al*, 1995, 2008; Lo *et al*, 2007). However, despite high OD values (≥1·5 units) in ELISA (Cases 8, 9, 11) or strong-positive (≥50% serotonin release) SRA results (Cases 8, 9), these patients did not develop HIT (Table II). One of the clinical non-HIT patients was ELISA-negative but SRA-positive and did not

develop any thrombocytopenia, thromboembolic event, or death. Furthermore, three of 95 patients without UFH were positive only by ELISA. In the present study, we blindly evaluated anti-PF4/heparin Abs in all clinical HIT and clinical non-HIT patients. Even if the results of anti-PF4/heparin Abs were positive, all patients with positive results would not always demonstrate HIT, and some of the positive results might not be pathological findings. Therefore, we should be aware of false negative and false positive results in both serological tests, and that diagnosis by the detection of anti-PF4/heparin Abs alone (even with a high OD value in ELISA and/or a strong-positive SRA result) can result in an overdiagnosis of HIT.

This study had some limitations. First, none of the patients underwent venous ultrasound; therefore, subclinical DVT, which is the typical thrombotic complication associated with HIT, may have been underdiagnosed. Second, the dose of UFH could be a determinant for the occurrence of HIT, as stoichiometrically optimal ratios of PF4:heparin influence immunization (Greinacher *et al*, 2008; Warkentin *et al*, 2010). However, in the present study, the dose and blood levels of UFH were not investigated.

In conclusion, the incidence of definite HIT in acute ischaemic stroke patients treated with UFH was 1·7% (95% CI: 0·4–5·0). HIT should be recognized as a clinicopathological syndrome in which both the clinical profile consistent with HIT and the results of serological tests should be carefully considered for HIT diagnosis. The clinical severity and outcome of acute stroke patients who were diagnosed as having definite HIT were unfavourable.

Author contribution

The study concept and design by H. Kawano, H. Yamamoto, S. Miyata, M. Izumi, and T. Hirano; writing by H. Kawano, H. Yamamoto, and S. Miyata; data collection by H. Kawano, H. Yamamoto, N. Toratani, M. Izumi, and T. Hirano; blinded independent assessments of the 4Ts score by S. Sato and S. Okamoto; ELISA assay by S. Miyata and I. Kakutani; SRA assay by Jo-AI. Sheppard and TE. Warkentin; analysis and interpretation of data by H. Kawano, H. Yamamoto, S. Miyata, and A. Kada; drafting of the manuscript by H. Kawano, H. Yamamoto, and S. Miyata; critical revision of the manuscript for important intellectual content by K. Toyoda, K. Nagatsuka, H. Naritomi, TE. Warkentin, and K. Minematsu; study supervision by M. Uchino and K. Minematsu.

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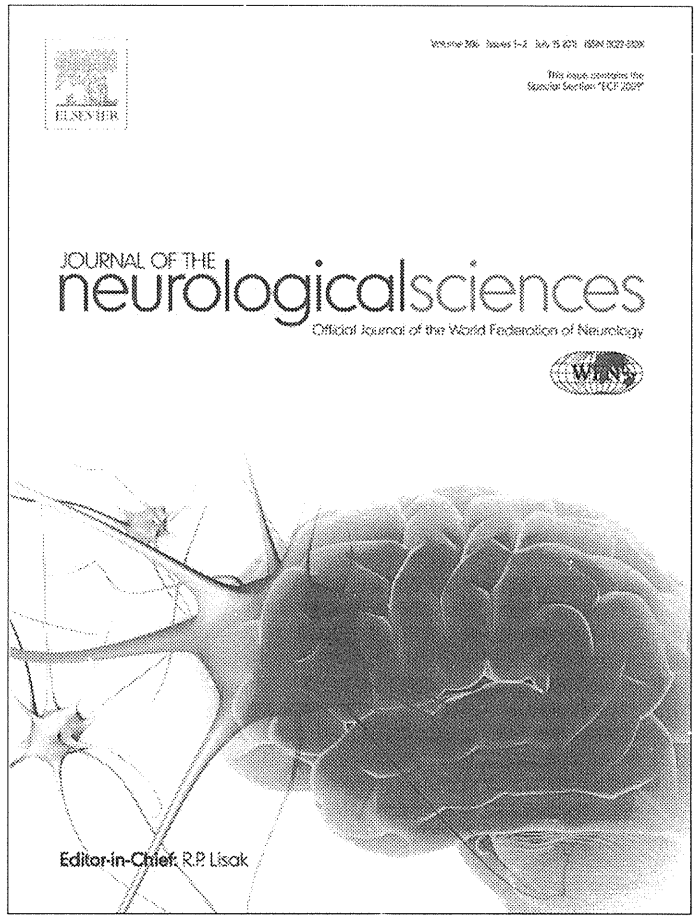

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$CHADS_2$ score is associated with 3-month clinical outcomes after intravenous rt-PA therapy in stroke patients with atrial fibrillation: SAMURAI rt-PA Registry

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ABSTRACT

Purpose: The aim of this study was to examine whether $CHADS_2$ score is associated with clinical outcomes following recombinant tissue type plasminogen activator (rt-PA) therapy in stroke patients with atrial fibrillation (AF).

Methods: We studied 218 consecutive stroke patients with AF [126 men, mean age 74.2 (SD 9.6) years] who received intravenous rt-PA therapy. $CHADS_2$ score was calculated as follows: 2 points for prior ischemic stroke and 1 point for each of the following: age ≥ 75 years, hypertension, diabetes, and congestive heart failure.

Results: Congestive heart failure was documented in 23 patients, hypertension in 138, age ≥ 75 years in 116, diabetes in 35, and prior stroke in 35. The distribution of each $CHADS_2$ score was: score of 0, 16.1% of patients; 1, 30.3%; 2, 29.4%; and 3 to 5, 24.3%. The median initial NIHSS score for each $CHADS_2$ category was 12 (IQR 8–17), 16 (10–20), 14.5 (10–20.75), and 16 (11–21), respectively ($p = 0.168$). Symptomatic ICH within the initial 36 h was found in 2.9%, 4.6%, 6.3%, and 0% of patients with each $CHADS_2$ category, respectively. Cardiovascular events within 3 months occurred in 0%, 0%, 7.8% and 5.7%, respectively. Percentage of patients with chronic independence at 3 months corresponding to modified Rankin Scale ≤ 2 was 57.1%, 45.5%, 31.3%, and 28.3%, respectively. Adjusted $CHADS_2$ score was inversely associated with chronic independence (OR 0.72, 95% CI 0.55–0.93).

Conclusion: Lower $CHADS_2$ score was associated with chronic independence at 3 months after intravenous rt-PA therapy in stroke patients with AF.

1. Introduction

Atrial fibrillation (AF) is a major cause of ischemic stroke and systemic thromboembolism. Several risk stratification schemes have been developed to quantify the risk of stroke in patients with AF. The $CHADS_2$ score is an easy-to-use classification scheme that estimates the risk of ischemic stroke in patients with AF. It is well-validated and derived from pooled individual data from a large number of multicenter trial participants who had nonvalvular AF and were prescribed aspirin. [1,2] High-risk patients with $CHADS_2$ scores ≥ 3 are reported to benefit from warfarin therapy. [2] Physicians can use the $CHADS_2$ score to make decisions about antithrombotic therapy based on patient-specific risk of stroke, and the score is also applied to predict hemorrhagic events in high-risk patients for stroke treated with anticoagulation. [3–5] Regarding stroke outcomes, one study reported a positive association between $CHADS_2$ score and all-cause mortality after stroke. [6] However, the association between the score and functional outcomes after stroke has not yet been elucidated.

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Table 1
Baseline characteristics of patients according to $CHADS_2$ score.

	Total	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ 2	$CHADS_2$ 3–5	p
Patients, n (%)	218	35 (16.1)	66 (30.3)	64 (29.4)	53 (24.3)	NA
Men, n (%)	126 (57.8)	22 (62.9)	43 (65.2)	36 (56.3)	25 (47.2)	0.226
Age, mean ± SD	74.2 ± 9.6	67.2 ± 5.1	71.0 ± 8.5	76.9 ± 11.1	79.3 ± 6.9	<0.001
Congestive heart failure, n (%)	23 (10.6)	0 (0)	2 (3.0)	3 (4.7)	18 (34.0)	<0.001
Hypertension, n (%)	138 (63.3)	0 (0)	39 (59.1)	53 (82.8)	46 (86.8)	<0.001
Age ≥ 75 years, n (%)	116 (53.2)	0 (0)	22 (33.3)	50 (78.1)	44 (83.0)	<0.001
Diabetes, n (%)	35 (16.1)	0 (0)	3 (4.6)	14 (21.9)	18 (34.0)	<0.001
Prior stroke, n (%)	35 (16.1)	0 (0)	0 (0)	4 (6.3)	31 (58.5)	<0.001
ASPECTS on initial CT (n = 215), median (IQR)	9 (7–10)	9 (8–10)	8 (7–10)	9 (8–10)	9 (8–10)	0.319
Internal carotid artery occlusion (n = 217), n (%)	41 (18.9)	7 (20.0)	9 (13.9)	14 (21.9)	11 (20.8)	0.660
Initial NIHSS, median (IQR)	15 (9.75–20)	12 (8–17)	16 (10–20)	14.5 (10–20.75)	16 (11–21)	0.168

NA: not applicable.

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) therapy is a standard treatment for acute stroke. Several clinical characteristics including higher National Institutes of Health Stroke Scale (NIHSS) score, advanced age, large infarct volume, high blood pressure, and interna! carotid artery occlusion were reported to be associated with poor clinical outcome following IV rt-PA therapy for acute stroke. [7–10] However, there is no risk stratification scheme to detect early cardiovascular events and clinical outcomes after IV rt-PA therapy. This study aimed to investigate the ability of $CHADS_2$ score to predict clinical outcomes at 3 months after IV rt-PA therapy using our multicenter registry. [10,11]

2. Subjects and methods

Patients were derived from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. [10] The details of this study have been described previously. [10] In brief, this study involved 600 consecutive stroke patients treated with IV rt-PA from October 2005 (when the therapy was approved in Japan) through July 2008 in 10 stroke centers in Japan. Patient eligibility for alteplase (rt-PA) therapy was determined based on the Japanese guideline for IV rt-PA therapy, [12] which followed the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study and the Japan Alteplase Clinical Trial (J-ACT). [13,14] Patients on warfarin therapy were included only when the pretreatment prothrombin time international normalized ratio (PT-INR) was <1.7. 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 (the recommended dose in Japanese guidelines and the approved labeling) intravenously, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 hour. Safety and efficacy of 0.6 mg/kg alteplase therapy was confirmed by a post-marketing multicenter study (the Japan Alteplase Clinical Trial 2: J-ACT 2) [15] and a post-marketing nationwide survey (the Japan post-Marketing Alteplase Registration Study: J-MARS). [16] We collected baseline data including sex, age, comorbidities (clinical congestive heart failure, hypertension, diabetes mellitus, and atrial fibrillation), oral warfarin intake,and initial neurologic deficits using the National Institutes of Health Stroke Scale (NIHSS), extension of early ischemic change on pretreatment CT as assessed by the Alberta Stroke Program Early CT Score (ASPECTS), and internal carotid artery occlusion on MRA or carotid ultrasound.

$CHADS_2$ score was derived from the individual stroke risk factors: congestive heart failure (C), hypertension (H), age ≥ 75 years (A), diabetes mellitus (D), and prior stroke (S). Two points were given for prior stroke, and 1 point was assigned for each of the other factors. [1,2]

The clinical outcomes were as follows: any and symptomatic intracerebral hemorrhage (ICH) within the initial 36 h; cardiovascular events within 3 months; and independence and unfavorable outcome at 3 months. ICH was defined as CT evidence of new hemorrhage, and symptomatic ICH was defined as that associated with neurological deterioration corresponding to an increase of ≥4 points from the baseline NIHSS score. A cardiovascular event was defined as any ischemic or hemorrhagic stroke, acute coronary syndrome, aortic dissection, peripheral arterial embolism, or deterioration of congestive heart failure. Independence corresponded to a modified Rankin Scale (mRS) score of 0–2, and unfavorable outcome to an mRS of 5 or 6.

Statistical analysis was performed using JMP 7.0 statistical software (SAS Institute Inc., Cary, NC, USA). Results are expressed as mean ± standard deviation other than when specified. Baseline characteristics were compared between patients with each $CHADS_2$ score component using χ^2 tests, unpaired *t*-tests, and the Mann–Whitney *U* test, as appropriate. The prevalence of each clinical outcome in patients with each

Table 2
Clinical outcomes of patients according to $CHADS_2$ score.

	$CHADS_2$ category				Model 1			Model 2		
	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ 2	$CHADS_2$ 3–5	Odds ratio[a]	95% CI	p	Odds ratio[a]	95% CI	p
Intracerebral hemorrhage (ICH), n (%)	7 (20.0)	18 (27.3)	25 (39.1)	14 (26.4)	1.06	0.84–1.34	0.617	1.07	0.84–1.35	0.601
Symptomatic ICH, n (%)	1 (2.9)	3 (4.6)	4 (6.3)	0 (0)	0.74	0.37–1.34	0.340	0.73	0.36–1.35	0.370
Cardiovascular event, n (%)	0 (0)	0 (0)	5 (7.8)	3 (5.7)	1.59	0.92–2.75	0.092	1.60	0.91–2.86	0.101
Recurrent ischemic stroke, n (%)	0 (0)	0 (0)	3 (4.7)	1 (1.9)	1.40	0.65–2.89	0.358	1.61	0.63–4.06	0.290
mRS ≤ 2 at 3 months, n (%)	20 (57.1)	30 (45.5)	20 (31.3)	15 (28.3)	0.74	0.57–0.94	0.015	0.72	0.55–0.93	0.015
mRS ≥ 5 at 3 months, n (%)	3 (8.6)	17 (25.8)	21 (32.8)	25 (47.2)	1.53	1.19–1.99	0.001	1.58	1.21–2.11	0.001

Model 1: adjusted by sex and initial NIHSS score.
Model 2: adjusted by sex, initial NIHSS score, ASPECTS, and presence of internal carotid artery occlusion.
[a] Per 1 point increase of $CHADS_2$ score.

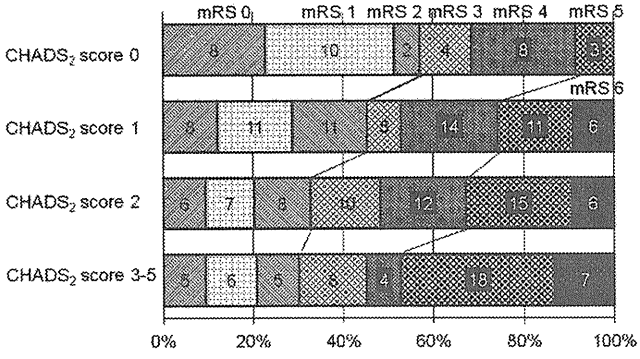

Fig. 1. $CHADS_2$ score and modified Rankin Scale at 3 months after stroke onset. The percentage of patients with mRS ≤ 2 gradually decreased as $CHADS_2$ score increased. In contrast, that of patients with mRS ≥ 5 gradually increased as $CHADS_2$ score increased.

$CHADS_2$ score group was calculated. Multivariate adjustment with sex and initial NIHSS (model 1) and that with sex, initial NIHSS, ASPECTS, and presence of internal carotid occlusion (model 2) were performed for clinical outcomes. All statistical tests were 2 sided, and probability values <0.05 were considered significant.

3. Results

Of a total 600 consecutive patients in the SAMURAI rt-PA Registry, 258 [146 men, mean age 75.1 (SD 10.0) years] had atrial fibrillation. Of these, 14 patients for whom no information on congestive heart failure, hypertension, diabetes, or prior stroke was available and 26 patients with prior disability corresponding to an mRS ≥ 3 were ineligible for the study. Thus, 218 patients [126 men, mean age 74.2 (SD 9.6) years] were studied.

Of these 218 patients, 29 (13.3%) took warfarin orally and PT-INR was less than 1.7 in all these patients on admission. Congestive heart failure was documented in 23 patients (10.6%), hypertension in 138 (63.3%), age ≥ 75 years in 116 (53.2%), diabetes in 35 (16.1%), and prior stroke in 35 (16.1%). The median $CHADS_2$ score was 2, the lower quartile was 1, and the higher quartile was 2. The distributions of each $CHADS_2$ score were: 35 patients with a $CHADS_2$ score of 0, 66 with 1, 64 with 2, 29 with 3, 19 with 4, 5 with 5, and none with 6. Because of the small number of patients with $CHADS_2$ score ≥ 3, patients were categorized into 4 groups as follows: $CHADS_2$ 0, $CHADS_2$ 1, $CHADS_2$ 2 and $CHADS_2$ 3 to 5. Patients with $CHADS_2$ score ≥ 3 are regarded as having high risk for stroke in the original study. [2]

Table 1 shows baseline characteristics in the 4 groups. ASPECTS, initial NIHSS score, and frequency of internal carotid artery occlusion did not differ among the 4 groups. Clinical outcomes in each group are shown in Table 2. There were no significant associations between any or symptomatic ICH and $CHADS_2$ groups. More than 5% of patients with $CHADS_2$ scores of 2 to 5, but none of those with $CHADS_2$ scores of 0 and 1, had cardiovascular events within 3 months after stroke onset. After adjustment for sex and initial NIHSS score, $CHADS_2$ score tended to be positively related to cardiovascular events within 3 months ($p = 0.092$). Of a total 8 patients with cardiovascular events, 4 had recurrent ischemic stroke. Three of them had a $CHADS_2$ score of 2 and one had a score of 3. Two of them developed stroke before recommencing anticoagulation (2.8% of 71 patients without recommencement), and two developed stroke after recommencing anticoagulation (1.4% of 147 patients with recommencement).

Fig. 1 shows the association between $CHADS_2$ score and mRS at 3 months. $CHADS_2$ score was negatively related to chronic independence (mRS ≤ 2) and positively related to unfavorable outcome (mRS ≥ 5). Frequency of chronic independence decreased by 26% (95% CI 6–43%, $p = 0.015$) and that of unfavorable outcome increased by 53% (95% CI 19–99%, $p = 0.001$) for each 1-point increase in the $CHADS_2$ score after adjustment for sex and initial NIHSS score (model 1). Those associations were still significant after adding radiological profiles (ASPECTS and internal carotid artery occlusion) to the multivariate adjustment (model 2). After adjustment for sex and $CHADS_2$ score, initial NIHSS score was negatively associated with chronic independence (per 1 point increase, OR 0.86, 95% CI 0.81–0.90, $p < 0.0001$) and positively associated with unfavorable outcome (per 1 point increase, OR 1.16, 95% CI 1.07–1.19, $p < 0.0001$). After adjustment for $CHADS_2$ score and initial NIHSS score, female sex tended to be negatively related to chronic independence (OR 0.56, 95% CI 0.30–1.06, $p = 0.077$) and were not associated with unfavorable outcome (OR 1.28, 95% CI 0.67–2.44, $p = 0.456$).

Associations among each component of the $CHADS_2$ score are shown in Table 3. Advanced age was related to other $CHADS_2$ components apart from diabetes. Clinical outcomes of patients with and without each $CHADS_2$ component are shown in Table 4. Congestive heart failure, hypertension, and prior stroke were not related to any clinical outcomes. Advanced age was related to unfavorable outcome (mRS ≥ 5) at 3 months ($p = 0.002$), and diabetes was inversely related to chronic independence (mRS ≤ 2) at 3 months ($p = 0.029$).

4. Discussion

This study showed significant associations between $CHADS_2$ score and clinical outcomes following IV rt-PA therapy in acute stroke patients with AF. The major findings of this study were as follows. First, $CHADS_2$ score tended to be positively related to cardiovascular events within 3 months. The rate of cardiovascular events at 3 months after onset was more than 5% in patients with a $CHADS_2$ score of 2 or more. Second, the proportion of independent patients at 3 months decreased significantly as $CHADS_2$ score increased. $CHADS_2$ score was inversely related to independence (mRS ≤ 2) and positively related to unfavorable outcome (mRS ≥ 5) at 3 months.

Several established risk factors for stroke, including advanced age, high systolic blood pressure, hyperglycemia on admission, and diabetes

Table 3
Baseline characteristics of patients with and without each component of $CHADS_2$ score.

	Congestive heart failure		Hypertension		Age ≥ 75 years		Diabetes		Prior stroke	
	Y ($n = 23$)	N ($n = 195$)	Y ($n = 138$)	N ($n = 80$)	Y ($n = 116$)	N ($n = 102$)	Y ($n = 35$)	N ($n = 183$)	Y ($n = 35$)	N ($n = 183$)
Age	79.6 ± 9.7 *	74.4 ± 10.0	74.7 ± 10.3	73.2 ± 8.3	81.1 ± 4.7 §	66.3 ± 7.5	72.1 ± 13.1	74.6 ± 8.8	77.6 ± 7.8 ‡	73.5 ± 9.8
Male	12 (47.8)	114 (58.5)	80 (58.0)	46 (57.5)	52 (44.8) §	74 (72.6)	22 (62.9)	104 (56.8)	20 (57.1)	106 (57.9)
Congestive heart failure			16 (11.6)	7 (8.8)	19 (16.4) ‡	4 (3.9)	4 (11.4)	19 (10.4)	3 (8.6)	20 (10.9)
Hypertension	16 (69.6)	122 (62.6)			81 (69.8) *	57 (55.9)	26 (74.3)	112 (61.2)	25 (71.4)	113 (61.8)
Age ≥ 75 years	19 (82.6) ‡	97 (49.7)	81 (58.7) *	35 (43.8)			16 (45.7)	100 (54.6)	24 (68.6) *	92 (50.3)
Diabetes	4 (17.4)	31 (15.9)	26 (18.8)	9 (11.3)	16 (13.8)	19 (18.6)			7 (20.0)	28 (15.3)
Prior stroke	3 (13.0)	32 (16.4)	25 (18.1)	10 (12.5)	24 (20.7) *	11 (10.8)	7 (20.0)	28 (15.3)		
Initial NIHSS	20 (14–25) †	14 (9–19)	15 (10–20)	15 (9–20)	16 (11–21) *	14 (8–18.25)	10 (7–16) ‡	16 (11–20)	15 (11–21)	15 (9–20)

NIHSS: National Institutes of Health Stroke Scale.
* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.005$, § $p < 0.001$.

Table 4
Clinical outcomes of patients with and without each component of $CHADS_2$ score.

	Congestive heart failure		Hypertension		Age ≥ 75 years		Diabetes		Prior stroke	
	Y/N (n = 23/195)	OR* (95% CI)	Y/N (n = 138/80)	OR* (95% CI)	Y/N (n = 116/102)	OR* (95% CI)	Y/N (n = 35/183)	OR* (95% CI)	Y/N (n = 35/183)	OR* (95% CI)
Intracerebral hemorrhage (ICH)	6/58	0.69 (0.23–1.85)	46/18	1.70 (0.90–3.30)	36/28	1.30 (0.68–2.50)	12/52	1.35 (0.59–2.96)	8/56	0.59 (0.23–1.35)
Cardiovascular events within 3 months	3/5	4.18 (0.72–21.25)	7/1	3.59 (0.60–68.68)	6/2	2.28 (0.40–18.19)	2/6	1.98 (0.26–10.83)	1/7	0.65 (0.03–4.15)
mRS ≤ 2 at 3 months	3/82	0.30 (0.06–1.10)	47/38	0.58 (0.29–1.13)	36/49	0.75 (0.38–1.49)	11/74	0.37 (0.14–0.88)†	13/72	1.24 (0.52–2.30)
mRS ≥ 5 at 3 months	14/52	2.37 (0.86–6.67)	47/19	1.49 (0.74–3.09)	50/16	3.13 (1.53–6.65)†	11/55	1.84 (0.74–4.48)	12/54	1.02 (0.43–2.34)

mRS: modified Rankin Scale.
*Adjusted by sex, initial National Institutes of Health Stroke Scale (NIHSS) and other $CHADS_2$ components.
† $p<0.05$.
Symptomatic ICH was omitted from the analysis because of the small number of patients.

are also known to be predictive of neurological deterioration and poor vital and functional outcome in acute stroke. [17,18] Thus, a cumulative assessment of the risk factors could be a better predictor for stroke outcome than individual factors. Some components of the $CHADS_2$ score that were reported to be definite or potential outcome predictors following acute ischemic stroke [13,19–28] were not related to any outcomes after IV rt-PA therapy in the present patients, probably due to the small sample size. However, $CHADS_2$ score itself had a strong association with both favorable and unfavorable outcomes.

$CHADS_2$ score was originally associated with risk for embolic events, and tended to be related to cardiovascular events involving stroke recurrence within 3 months in the present patients. Thus, these cardiovascular complications appeared to have some effect on mRS at 3 months. The initial neurological severity was similar among patients with different $CHADS_2$ scores, and therefore does not seem to explain the poor outcome in patients with high $CHADS_2$ score. Since advanced age and diabetes are associated with pneumonia and other febrile diseases during acute stroke, [29,30] such complications in patients with high $CHADS_2$ score may affect outcomes at 3 months.

Frequency of major hemorrhage is high in AF patients on anticoagulation with $CHADS_2$ score of >1 or >2. [3,5] However, this study did not show significant increases in ICH associated with higher $CHADS_2$ scores after rt-PA therapy. Thus, early ICH after rt-PA also does not explain the poor outcome in patients with high $CHADS_2$ scores. Patients with PT-INR ≥ 1.7 were not included according to the guideline, [12] and this might explain the present lack of association between $CHADS_2$ score and ICH, which contrasts with findings from previous reports. In addition, exclusion of patients with an initial blood pressure of >185/110 mmHg and strict blood pressure management during the initial days according to the guidelines might also decrease ICH risk and mask the contribution of $CHADS_2$ score to ICH.

The present study has some limitations which need to be discussed. First, this was a retrospective observational study with a relatively small population, which might affect the statistical findings. Second, the last component of $CHADS_2$ score was originally "prior stroke and transient ischemic attack"; however, our data on prior transient ischemic attack were incomplete, and accordingly $CHADS_2$ score in some patients might have been underestimated. Third, each component of $CHADS_2$ influenced the selection of eligible patients for rt-PA therapy; e.g., patients with advanced age and those with severe hypertension were not recognized as appropriate candidates for treatment. Thus, there were fewer patients with high $CHADS_2$ score than low $CHADS_2$ score. Although patients >80 years old and those with diabetes concomitant with prior stroke are not recommended to receive rt-PA in European countries, [31] they are eligible in the Japanese guideline. [12]

The present study indicates that risk stratification for AF patients using the $CHADS_2$ scheme is a useful predictor not only for risk of ischemic stroke but also for chronic independence following IV rt-PA therapy, regardless of anticoagulation status. Careful observation and preventive therapy for early clinical deterioration and complications may be required in such patients during the acute to subacute stage of stroke. However, the efficacy of acute intensive management of treatable $CHADS_2$ components, including acute blood pressure lowering and blood glucose normalization, for improvement of stroke outcome remains to be determined.

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Conflict of interest/disclosures

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Effects of hyperacute blood pressure and heart rate on stroke outcomes after intravenous tissue plasminogen activator

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Background and purpose **The present study clarifies associations between stroke outcomes after intravenous tissue plasminogen activator (tPA) and blood pressure (BP) as well as heart rate (HR) profiles.**

Methods **We assessed 125 patients with stroke who received tPA within 3 h of onset. We obtained baseline, mean, maximum, minimum, and coefficient of variation values for BP and HR during the initial 24 h. The primary outcome was independence at 3 months corresponding to a modified Rankin Scale score of 2 or less. The secondary outcomes were early neurological improvement at 24 h and intracerebral hemorrhage (ICH) within 36 h.**

Results **Among the patients, 64 (51%) achieved independence, 66 (53%) early improvement, and 26 (21%) developed ICH. The 24-h time courses of SBP ($P = 0.033$), pulse pressure (PP, $P = 0.007$), and HR ($P < 0.001$) were lower among patients who reached independence than among those who did not. After multivariate adjustment, 24-h mean levels of SBP (odds ratio 0.69, 95% confidence interval 0.48–0.97, per 10-mmHg increase), PP (0.63, 0.41–0.94), and HR (0.59, 0.42–0.80, per 10-bpm increase) were inversely associated with independence, as were their maximum and minimum values. In particular, mean SBP values were inversely associated with independence at 8–16 and 16–24 h (0.73, 0.54–0.97 and 0.66, 0.47–0.91, respectively), but not at 0–8 h (0.79, 0.57–1.07). Baseline and maximum SBP were inversely associated with early improvement. Maximum and coefficient of variation of SBP were associated with ICH.**

Conclusion **Lower SBP, PP, and HR values during the initial 24 h after tPA, especially at 8 h thereafter, were associated with independence at 3 months. *J Hypertens* 29:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: ADL, activities of daily living; BP, blood pressure; HR, heart rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator

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Introduction

Intravenous (i.v.) thrombolytic therapy using tissue plasminogen activator (tPA) is currently the only evidence-based pharmacotherapy for treating hyperacute ischemic stroke [1–3]. High baseline blood pressure (BP) prior to tPA reportedly results in poor outcomes for some patients after tPA partly because of an increased risk of intracerebral hemorrhage (ICH) [4–6] and favorable outcomes for others [7]. Thus, high baseline BP might not be an ideal outcome predictor. Other studies have revealed a close association between the course of high BP during the initial 24 or 72 h after stroke and poor long-term outcomes [7–9]. Generally, avoidance of an obviously elevated BP is recommended both before and soon after thrombolysis [10]. As BP often fluctuates on the day of stroke occurrence, generally reaching a peak upon hospital admission and falling thereafter [11,12], it is important to clarify which characteristics of acute BP profiles affect outcomes after tPA.

The results of the Japan Alteplase Clinical Trial (J-ACT) led to i.v. thrombolysis with alteplase (0.6 mg/kg) within 3 h of stroke onset being approved in Japan during 2005 [13]. The efficacy of this low-dose tPA strategy was determined by a postmarketing, multicenter, observational study [14]. According to the guidelines published by the Japan Stroke Society (JSS) [15], the vital signs of all of our patients were frequently measured during the initial 24 h after i.v. tPA thrombolysis. Thus, we obtained complete data for consecutive tPA-treated patients to analyze the initial 24-h course of BP. We also postulated that the 24-h course of heart rate (HR), which is another essential, easily measurable and understudied sign, could predict outcomes. We, therefore, clarified the influence of 24-h BP and HR profiles on

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early and long-term outcomes of stroke patients after receiving i.v. low-dose tPA.

Patients and methods

Patient population

We registered 130 consecutive Japanese patients with stroke who were treated with i.v. tPA within 3 h of symptom onset and admitted to our stroke care unit between October 2005 and August 2008. Patient eligibility for i.v. tPA therapy was determined based principally on the JSS guidelines [15], which follow the inclusion and exclusion criteria applied in the National Institute of Neurological Disorders and Stroke (NINDS) tPA study [1] and J-ACT [13]. All patients received i.v. alteplase at a dose of 0.6 mg/kg with 10% administered as a bolus, followed by continuous i.v. infusion of the remainder over a period of 1 h. Of these, two patients who did not receive the full dose of tPA because of changes in their condition including vomiting during i.v. infusion and three who did not have independent activities of daily living (ADL) corresponding to a modified Rankin Scale (mRS) score of at least 3 before stroke onset were excluded, leaving 125 eligible patients (93 men, 72.7 ± 9.0 years).

Assessment of blood pressure and heart rate

BP was measured in the supine position by trained nurses using a standard mercury sphygmomanometer; the average of two consecutive measurements spaced by 1–2 min, and additional measurements if the first two were quite different, was used for analysis [16]. Baseline BP and HR values of the patients were recorded immediately upon arrival at the emergency room. i.v. tPA therapy was initiated at the stroke care unit, and patients remained there for at least 2 days. After starting tPA infusion, BP and HR were measured every 15 min during the first 2 h, every 30 min from 2 to 6 h, and then hourly from 6 to 24 h. To characterize BP and HR profiles, we calculated the mean, maximum, minimum, and coefficient of variation (coefficient of variation = standard standard deviation/mean value × 100%) values during the initial 24 h after i.v. tPA, as well as the mean values between 0 and 8 h, 8 and 16 h, and 16 and 24 h. According to the guidelines, antihypertensive agents were administered when SBP was at least 185 mmHg or DBP at least 110 mmHg just before i.v. tPA, and SBP more than 180 mmHg or DBP more than 105 mmHg during the initial 24 h after i.v. tPA [10,15]. i.v. nicardipine was the first choice agent.

Baseline characteristics

We determined the following baseline characteristics from the prospective database: sex, age, hypertension (BP ≥140/90 mmHg before stroke onset or taking regular antihypertensive agents), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l, hemoglobin (Hb) A1c ≥6.5%, or taking antidiabetic agents), hyperlipidemia (total cholesterol ≥5.7 mmol/l, triglyceride ≥1.7 mmol/l, or taking antihyperlipidemic agents), atrial fibrillation (documented during hospitalization or a history of atrial fibrillation), previous symptomatic ischemic stroke, current smoking habit, and antihypertensive and antithrombotic use prior to onset. Stroke subtype was determined according to the TOAST subtype classification system [17].

On admission, blood tests included blood glucose and HbA1c. Kidney function was evaluated based on the estimated glomerular filtration rate (eGFR) using a revised equation for the Japanese population [18]; eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × 0.739 (for women). To calculate eGFR, the admission serum creatinine was used.

Before i.v. tPA, all patients underwent brain noncontrast CT, as well as intracranial magnetic resonance angiography (MRA, unless contraindicated). The Alberta Stroke Program Early CT score (ASPECTS) on CT, a 10-point quantitative topographic scoring method of early ischemic signs in the middle cerebral arterial (MCA) territory, as well as the arterial occlusion site ipsilateral to ischemia was assessed by at least two vascular neurologists [19]. AQ2

Outcomes

The primary outcome was independent ADL at 3 months corresponding to a mRS score of 2 or less. We researched the 3-month outcome by clinical examination at a hospital clinic (or by phone survey for patients whose neurological deficits were too severe to visit the clinic). The secondary outcomes consisted of early neurological improvement defined as a reduction of at least 4 points from the baseline National Institutes of Health Stroke Scale (NIHSS) score or a total NIHSS score of 0 or 1 at 24 h after i.v. tPA, and ICH defined as CT evidence of new ICH within 36 h after i.v. tPA regardless of additional symptoms.

Control of blood pressure and blood glucose

Control of BP and blood glucose after the initial 24 h was achieved principally according to the JSS guidelines 2004 [15]. During the initial weeks, the guidelines recommend to treat high BP only when BP exceeds 220/130 mmHg or patients have underlying severe cardiovascular diseases. However, we usually maintained BP levels in these weeks more strictly to less than 180/105 mmHg as we did during the initial 24 h. During the chronic stage, the guidelines recommend to lower BP to less than 170/95 mmHg as an example. The guidelines advocated that hyperglycemia should be corrected but did not specify absolute goals. We treated patients with antidiabetic agents principally when HbA1c exceeded 6.5%.

Statistical analysis

Data were statistically analyzed using JMP 7.0 software (SAS Institute Inc, Cary, North Carolina, USA). Statistical