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.
the clinical features of HIT. Of HIT in patients with acute ischaemic stroke and to elucidate study in 267 patients to determine a more accurate incidence patients. This limitation may cause an under diagnosis of HIT. limited by the fact that was that antibodies were not assayed in all ever, our retrospective study assessing the prevalence of HIT was developed HIT, when the serological diagnosis was made from patients with cerebrovascular disorders, demonstrated that 41 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 14C-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 × 109/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 embolicigenic 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 antplatelet 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
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 (2.271 OD value) 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 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/m²)           | 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 (≥22 cups) (%) | 49 (28.5)                | 21 (22.1)                   | 0.249   |
| Previous IHD (%)      | 33 (19.2)                 | 5 (5.3)                     | 0.002   |
| Previous CVD (%)      | 61 (35.5)                 | 28 (29.5)                   | 1.000   |
| Previous PTE (%)      | 0                         | 0                            |         |
| 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, haemodialysis; 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 (<10^9/l) | Duration of UFH up to the day of platelet nadir (days) | Duration of UFH (day) | Thrombotic complication | NIHSS on admission | mRS on discharge |
|----|-------------|--------|--------------|----------------|------------|------------|----------------------|-------------------------|---------------------------------|----------------------|-----------------------|------------------|------------------|
| 1  | 62          | Male   | CI, HTN      | Other          | 4          | +(2.271) + (63.9) | 331                  | 107                     | 11                               | 7                    | None                  | None             | 23               |
| 2  | 64          | Female | CI, HTN, AF  | CE             | 5          | +(1.725) + (51.6) | 436                  | 286                     | 18                               | 10                   | None                  | None             | 16               |
| 3  | 88          | Female | AF           | CE             | 5          | +(2.086) + (11.0) | 156                  | 99                      | 7                                | 15                   | None                  | None             | 4                |
| 4  | 67          | Male   | HTN, DM, AF  | CR             | 4          | −(0.138) − (<1)  | 281                  | 210                     | 14                               | 7                    | DVT                   | None             | 4                |
| 5  | 82          | Male   | CI, HTN, AF  | CR             | 4          | −(0.052) − (<1)  | 137                  | 27                      | 1                                | 4                    | None                  | None             | 4                |
| 6  | 66          | Male   | MI, HTN      | CE             | 4          | −(0.102) − (<1)  | 583                  | 225                     | 13                               | 17                   | None                  | None             | 1                |
| 7  | 69          | Female | HTN, AF      | CE             | 5          | −(0.091) − (<1)  | 297                  | 120                     | 23                               | 6                    | RI                    | None             | 7                |
| 8  | 70          | Female | HTN, AF      | CE             | 0          | +(1.666)* + (53.2) | 141                  | 123                     | 4                                | NA†                  | None                  | None             | 2                |
| 9  | 59          | Female | HTN, AF, AID | CE             | 0          | +(1.505) + (76.8) | 163                  | 158                     | 18                               | NA†                  | None                  | None             | 15               |
| 10 | 87          | Male   | IHD, HTN, AF | CE             | 0          | +(0.977) + (13.3) | 200                  | 150                     | 13                               | NA†                  | None                  | None             | 8                |
| 11 | 90          | Female | HTN, AF      | CE             | 2          | +(2.378) + (28.8) | 235                  | 210                     | 9                                | NA†                  | IHD                   | None             | 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.
thromboembolic events.

thrombin inhibitors, nor did the patients develop additional
HIT received treatment with alternative anticoagulants, such as
or delayed onset HIT. None of the patients classified as definite

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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, 41% of the acute stroke patients treated
with heparin were suspected clinically of having HIT with
24 points in the 4Ts scoring system. Among them, 17% (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-Lasepas 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 (≥15 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

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.

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.

Our results were similar to those reported in other studies of
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Having definite HIT were unfavourable. Outcome of acute stroke patients who were diagnosed as considered for HIT diagnosis. The clinical severity and HIT and the results of serological tests should be carefully syndrome in which both the clinical profile consistent with ischaemic stroke patients treated with UFH was 1Æ2010). 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: 0Æ4–5.0). 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-Al 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.

Source of funding
Grant from the Bayer Scholarship for Cardiovascular Research, Japan Cardiovascular Research Foundation. Health and Labour Sciences Research Grant from the Japanese Ministry of Health, Labour and Welfare (Research on Clinical Trials’ Infrastructure Development). Grant-in-Aid from the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation of Japan (06-51).

Disclosures
Dr Izumi, Dr Toratani, MT. Kakutani, MPH. Kada, Dr Sato, and Dr Okamoto report no disclosure. Dr Kawano received honoraria from Mitsubishi Tanabe Pharma Co. Ltd., for scientific lecture. Dr Yamamoto served on a scientific advisory board on Behinger-Ingelheim, Data and Safety Monitoring Board of JASAP, scientific consultant for submission for drug of approval Mitsubishi Welpharma Co. Ltd, and received research grants as chief investigator from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan; H18-Riken-Wakate-005; and Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan; H19-Tokubetsu-Shitei-033, The Bayer Scholarship for Cardiovascular Research, Japan Cardiovascular Research Foundation, and Pfizer Health Research Foundation. Dr Miyata serves on the editorial advisory board for Japanese Journal of Transfusion and Cell Therapy, and Japanese Journal of Thrombosis and Hemostasis, received speaker’s honoraria from Mitsubishi Tanabe Pharma Co. Ltd., Daich Sankyo Co. Ltd., Sanofi Aventis, and GlaxoSmithKline, received research grants from Mitsubishi Tanabe Pharma Co. Ltd. and Daich Sankyo Co., Ltd, and research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan (15C-1, 17C-7, H21-Iyaku-Ippan-005), Grant-in-Aid from the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation of Japan (06-51). Dr Hirano served as a imaging reading panel of J-ACT II sponsored by Mitsubishi Tanabe Pharma Co. Ltd. and Kyowa Hakko Kirin corporation, and received a research grant from The Ministry of Education and Science of Japan Scientific Research grant-in-aid, 50346996 as principle investigator. BSc. Sheppard supported from Heart and Stroke Foundation of Ontario – HSFO, T6157, for Research Assistant. Dr Warkentin receive royalties from publishing of Book: Heparin-Induced Thrombocytopenia; Publisher: Informa Healthcare USA, 2007, served as a scientific consultant for Canyon Pharmaceuticals; GTI Inc.: GlaxoSmithKline; Faringenix, served as a speaker’s bureaus of GlaxoSmithKline; Pfizer Canada; Sanofi-Aventis, research supports form GlaxoSmithKline, GTI Inc, Heart and Stroke Foundation of Ontario; principal investigator; Grant Number T6157; and Heart and Stroke Foundation of Ontario grants NA6221 and T6763; co-investigator. Dr Nagatsuka received speaker’s honoraria from Tanabe Mitsubishi Co. Ltd, Otsuka Pharmaceutical Co. Ltd, Daiichi-Sankyo Pharmaceutical Co. Ltd, Pfizer Japan Co. Ltd, research supports from Lundbeck Inc., Mitsubishi Tanabe Pharma Co. Ltd, and Ministry of Health, Labour and Welfare, H22-Junkanki-Ippan-006, 2010. Dr Naritomi received speaker’s honoraria from Mitsubishi Tanabe Co. Ltd, Otsuka Pharmaceutical Co. Ltd, Kyorin Pharmaceutical Co. Ltd, and Kowa Co. Ltd. Dr Toyoda serves as an assistant editor of Stroke, received research grants from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan; 20-Junkanki-Ippan-019; Chief investigator. Dr Uchino received honoraria from Mitsubishi Tanabe Pharma.
Co Ltd, Sanofi-aventis, Daiichi-Sankyo Co Ltd., for scientific
lecture, and received a research grant from Japanese Ministry of
Education, Science, Sports and Culture/Grant-in aid for
Scientific Research, 20591003, and Gene therapy of Duchenne
muscular dystrophy. Dr Minematsu serves on the editorial
boards of Cerebrovascular Diseases, the International Journal of
Stroke, and the Journal of Stroke and Cerebrovascular Diseases
and receives research support from Astaras Pharma Inc.,
Takeda Pharmaceutical Co. Ltd., Sanofi-Aventis, Lundbeck
Inc., Mitsubishi Tanabe Pharma Co. Ltd., Kyowa Hakko Kirin
Pharma, Inc., Hitachi Medical Corporation, MHL, Japan,
Research Grants for Cardiovascular Diseases, Grant-in-Aid,
and the Foundation for Biomedical Research and Innovation,
and honoraria from Daiichi Sankyo Co Ltd.

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Heart Association; American Stroke Association
Stroke Council; Clinical Cardiology Council;
Cardiovascular Radiology and Intervention
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mum; International Union of Angiology; Union
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