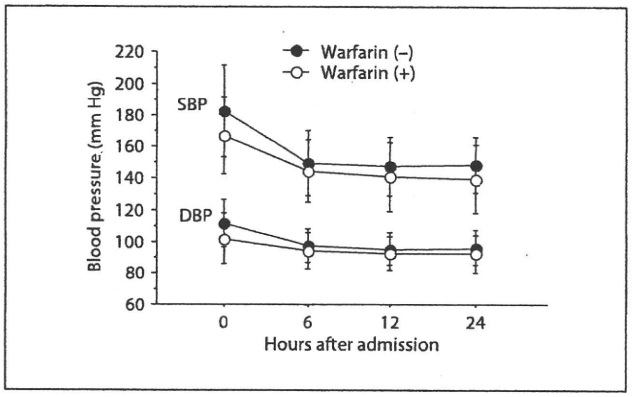

Fig. 1. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) every 6 h after hospitalization in patients on (open circle) and not on warfarin. The error bars show standard deviation. There were differences between the warfarin group and the control group in the SBP ($p = 0.004$) and the DBP ($p < 0.001$) at admission. No significant differences were found at the other measurement points.

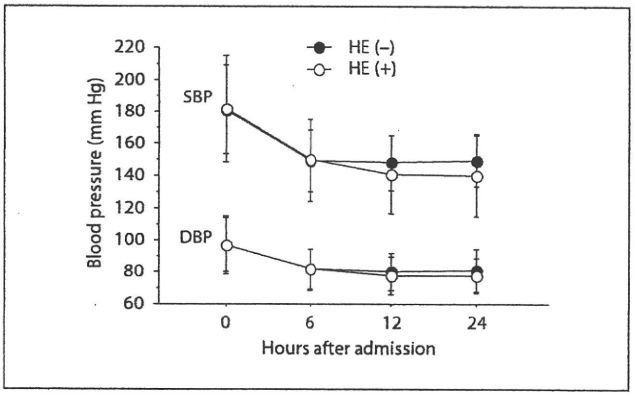

Fig. 2. Changes in the systolic blood pressure (SBP) and diastolic blood pressure (DBP) every 6 h after hospitalization in the HE group (open circle) and in the non-HE group. The error bars show standard deviation. Differences were observed between the HE group and the non-HE group in the SBP 12 h ($p = 0.002$) and 24 h ($p = 0.001$) after hospitalization. No significant differences were found at the other measurement points.

Table 2. Clinical characteristics of the warfarin and control groups restricted to patients with follow-up CT scans

	Warfarin group (n = 38)	Control group (n = 308)	p value
Age, years	69.7 ± 12.4	65.7 ± 12.7	0.071
Male gender	27 (71)	169 (55)	0.058
SBP at admission, mm Hg	169 ± 23	183 ± 29	0.004
DBP at admission, mm Hg	87 ± 18	98 ± 17	<0.001
Time interval to the follow-up CT, h	12.0 (6.0–24.0)	19.0 (7.5–24.0)	0.163
Characteristics of hematoma			
Admission HV, cm^3	28.2 ± 51.4	18.1 ± 22.4	0.031
Final HV, cm^3	43.6 ± 79.6	21.4 ± 28.2	0.001
HE	15 (39)	48 (16)	<0.001

Values are presented as numbers (percentage), mean ± SD, or median (interquartile range). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

control group. Finally, HE occurred more frequently in the warfarin group than in the control group ($p < 0.001$; table 2).

Although admission systolic ($p = 0.004$) and diastolic ($p < 0.001$) blood pressures were lower in the warfarin group than in the control group, there were no significant differences between the two groups in systolic and diastolic blood pressures 6, 12 and 24 h after hospitalization among the 346 patients (fig. 1).

In total, 63 patients (18%) fulfilled the criteria for HE (HE group); the remaining 283 patients (82%) constituted the non-HE group. Significantly more patients in the HE group were treated with warfarin than in the non-HE group ($p < 0.001$). Patients in the HE group more frequently had liver disease ($p = 0.002$). On admission, more patients in the HE group had an INR ≥2.0 than in the non-HE group ($p = 0.001$), and the HE group patients had a higher blood glucose level ($p = 0.012$) and a higher

Table 3. Clinical characteristics of the HE and non-HE groups

	HE group (n = 63)	Non-HE group (n = 283)	p value
Age, years	65.2 ± 13.4	66.4 ± 12.6	0.510
Male gender	37 (59)	159 (56)	0.712
Warfarin treatment	15 (24)	23 (8)	<0.001
Antiplatelet treatment	2 (3)	3 (1)	0.203
Smoking	26 (41)	122 (43)	0.790
Drinking	27 (43)	118 (42)	0.866
Hypertension	55 (87)	259 (92)	0.296
Diabetes mellitus	15 (24)	72 (25)	0.787
Hypercholesterolemia	13 (21)	103 (36)	0.017
Hypocholesterolemia	3 (5)	9 (3)	0.535
Heart disease	16 (25)	47 (17)	0.102
Liver disease	14 (22)	25 (9)	0.002
Previous ischemic stroke	13 (21)	38 (13)	0.144
SBP at admission, mm Hg	182 ± 32	181 ± 28	0.799
DBP at admission, mm Hg	96 ± 19	97 ± 17	0.816
INR ≥2.0	11 (17)	15 (5)	0.001
Blood glucose, mmol/l	9.0 ± 4.6	7.8 ± 2.9	0.012
NIHSS score at admission	18 (12–31)	12 (7–17)	<0.001
Time interval to the first CT, h	1.5 (0.9–2.1)	2.0 (1.0–3.7)	0.018
Time interval to the follow-up CT, h	16.0 (6.0–24.0)	20.0 (7.0–24.0)	0.295
Characteristics of hematoma			
Admission HV, cm^3	26.4 ± 42.7	17.6 ± 22.2	0.020
Final HV, cm^3	50.5 ± 68.6	17.9 ± 23.0	<0.001
Multiple hematomas	15 (24)	35 (12)	0.020
Irregularly shaped hematoma	31 (49)	68 (24)	<0.001
Intraventricular bleeding	41 (65)	105 (37)	<0.001
Putaminal hemorrhage	25 (40)	111 (39)	0.946
Thalamic hemorrhage	20 (32)	109 (39)	0.315
Lobar hemorrhage	11 (17)	33 (12)	0.211
Pontine hemorrhage	14 (22)	19 (7)	<0.001
Cerebellar hemorrhage	1 (2)	9 (3)	0.495
mRS at 30 days or at discharge			
Length of hospital stay, days	25 (19–34)	25 (20–31)	0.124
mRS score ≥3	55 (87)	194 (69)	0.003
In-hospital mortality (mRS score = 6), %	29	2	<0.001

Values are presented as numbers (percentage), mean ± SD, or median (interquartile range). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

NIHSS score ($p < 0.001$) than the control group patients. The time interval from ICH onset to the first CT scan ($p = 0.018$) was significantly shorter in the HE group than in the non-HE group (table 3).

Significant differences were observed between the HE group and the non-HE group in systolic blood pressure 12 ($p = 0.002$) and 24 h ($p = 0.001$) after hospitalization (fig. 2).

Both the HV on admission ($p = 0.020$) and the final HV ($p < 0.001$) were larger in the HE group than in the non-HE group. Furthermore, there were significantly more multiple hematomas ($p = 0.020$), irregularly shaped hematomas ($p < 0.001$), intraventricular bleeds ($p < 0.001$), and pontine hemorrhages ($p < 0.001$) in the HE group than in the non-HE group (table 3).

The number of patients with an mRS score ≥3 at 30 days or at discharge was higher in the HE group than in the non-HE group ($p = 0.003$); moreover, in-hospital mortality (mRS score of 6) was higher in the HE group than in the non-HE group ($p < 0.001$; table 3).

Table 4. Multivariate regression analysis for HE

Multivariate analysis	Odds ratio (95% CI)	p value[1]
Warfarin treatment	5.75 (2.41–13.8)	<0.001
Liver disease	2.59 (1.12–5.99)	0.026
NIHSS score, per 1-score increase	1.10 (1.04–1.15)	<0.001

CI = Confidence interval.

[1] In addition to age and gender, the following confounders that showed an association ($p < 0.1$) with each feature of clinical characteristics on univariate analysis were used for multivariate logistic regression analysis: hypercholesterolemia, blood glucose, time interval to the first CT, admission HV, multiple hematomas, irregularly shaped hematoma, intraventricular bleeding, pontine hemorrhage. Although INR ≥2.0 was significantly associated with HE on univariate analysis, it was not used in the multivariate analysis because warfarin treatment was a more significant confounder.

A multivariate logistic regression analysis using the confounders ($p < 0.1$) as independent variables with adjustments for age and gender showed that warfarin treatment (OR = 5.75, 95% CI = 2.41–13.8, $p < 0.001$), liver disease (OR = 2.59, 95% CI = 1.12–5.99, $p = 0.026$) and NIHSS score (OR = 1.10, 95% CI = 1.04–1.15, $p < 0.001$, per 1-score increase) on admission were found to be independently related to HE (table 4).

Discussion

In this study, we focused on the relationship between hematoma size and long-term anticoagulant therapy. The present study's major finding was that prior medication with warfarin was predictive of HE in patients with acute ICH.

The frequency of HE in patients on warfarin therapy was reported to be 27–54% [5, 17–19]. In a retrospective study of 1,006 patients with ICH, patients on warfarin had a 4.8-fold higher risk of HE in comparison to the patients not on warfarin [20]. Flibotte et al. [5] reported that warfarin therapy was the sole predictor of HE. Yasaka et al. [18] showed that an INR value ≥2.0 within 24 h of ICH was an important predisposing factor for HE. In the present study, not only were the admission HV and final HV larger but also HE occurred more frequently in patients on warfarin than in those not on warfarin. The potential mechanisms include the unmasking of preexisting subclinical intracerebral bleeding by the use of warfarin [21] so that the bleeding is more protracted and hematomas are larger in patients on warfarin than in patients not on warfarin.

The mortality of ICH in patients on warfarin at 3 weeks to 3 months is 16–54% [4, 20, 22]. Flibotte et al. [5] noted that warfarin increased the risk of in-hospital hematoma expansion, and that this hematoma expansion appeared to be in part responsible for warfarin's effect on ICH mortality. In the present study, of the 10 deaths in the warfarin group, 8 patients (80%) had HE. Therefore, HE during the acute stage of ICH appears to increase the mortality rate. Previous studies reported that early HE was a major cause of mortality [14, 23].

A relationship between HE and poor clinical outcome was previously reported and explained by brain herniation and edema introduced by HE [23–25]. Davis et al. [26] reported that hematoma growth is an independent determinant of both mortality and functional outcome after ICH. For each 1-ml increase in the absolute ICH volume, patients are 7% more likely to deteriorate from independence to assisted independence, or from assisted independence to poor outcome [26]. It is thought that the mass effect related to HE eventually progresses and results in a poor prognosis.

Liver disease, blood glucose level, time interval from onset, admission HV and presence of an irregularly shaped hematoma were reported to be factors predisposing to HE by Fujii et al. [23, 27] and Kazui et al. [28]. Liver dysfunction can also affect the progression of ICH [27–29]. Fujii et al. [27] demonstrated that the incidence of HE increases significantly with the severity of liver dysfunction. Decreased levels of coagulant factors caused by both warfarin and liver disease may increase the risk of ICH enlargement.

The relationship between HV on admission and HE has been disputed [24, 27, 28, 30]. Early CT scanning appears to increase the rate of detection of enlarging hematomas [14, 23, 27]. Therefore, early admission after onset seems to be related to continuous active bleeding after the initial CT scan.

Previous studies have shown that elevated blood pressure increased the risk of HE [28, 30]. In the present study, because blood pressure control during the acute stage was better in the warfarin group than in the control group, blood pressure did not appear to affect the high frequency of HE in the warfarin group.

The present study had several limitations. Since it was a nonrandomized and uncontrolled study, there may have been some selection bias. Furthermore, although the

blood pressure 12 h after admission was lower in the HE group than in the control group, it was not possible to address blood pressure management and HE prevention because the patients received a variety of antihypertensive therapies, and the data regarding blood pressure values after the initial 24 h were not fully available. Evaluation of the appropriate management of the blood pressure in patients with acute ICH on warfarin treatment will require prospective trials involving a large number of patients on warfarin. The relationship between prior antiplatelet therapy and HE or poor outcome in ICH patients is not proven clearly [4, 5, 20, 31]. Moreover, in the present study, we included 5 patients on warfarin and antiplatelet into the warfarin group and analyzed those cases as patients who received warfarin. We thought the antithrombotic effects of the warfarin were more remarkable than those of the antiplatelet drugs. Although there was no significant difference between antiplatelet therapy and HE on univariate analysis in the present study, it was reported that dual antithrombotic therapy with warfarin and antiplatelet drugs had a more significant influence on HE than single antithrombotic therapy with warfarin or antiplatelets in a recent study [20]. Thus, we had better examine the effect of the combination therapy of warfarin and antiplatelets in a large number of patients.

In conclusion, long-term warfarin therapy appears to be an independent factor for HE.

Acknowledgements

This study was supported by Research Grants for Cardiovascular Diseases (15C-1, 18C-2, and 21A-4) from the Ministry of Health, Labour and Welfare, and Grants in Aid for Clinical Research from the National Hospital Organization, Japan.

References

1 Wintzen AR, de Jonge H, Loeliger EA, Bots GT: The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. Ann Neurol 1984;16:553–558.

2 Kase CS, Robinson RK, Stein RW, DeWitt LD, Hier DB, Harp DL, Williams JP, Caplan LR, Mohr JP: Anticoagulant-related intracerebral hemorrhage. Neurology 1985;35:943–948.

3 Franke CL, de Jonge J, van Swieten JC, Op de Coul AA, van Gijn J: Intracerebral hematomas during anticoagulant treatment. Stroke 1990;21:726–730.

4 Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM: The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med 2004;164:880–884.

5 Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J: Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology 2004;63:1059–1064.

6 Yamaguchi T: Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Stroke 2000;31:817–821.

7 Toyoda K, Okada Y, Ibayashi S, Inoue T, Yasumori K, Fukui D, Uwatoko T, Makihara N, Minematsu K: Antithrombotic therapy and predilection for cerebellar hemorrhage. Cerebrovasc Dis 2007;23:109–116.

8 Hosomi N, Naya T, Ohkita H, Mukai M, Nakamura T, Ueno M, Dobashi H, Murao K, Masugata H, Miki T, Kohno M, Kobayashi S, Koziol JA, Japan Standard Stroke Registry Study Group: Predictors of intracerebral hemorrhage severity and its outcome in Japanese stroke patients. Cerebrovasc Dis 2009; 27:67–74.

9 Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, Khatri P, Stettler B, Adeoye O, Moomaw CJ, Broderick JP, Woo D: Warfarin use leads to larger intracerebral hematomas. Neurology 2008;71:1084–1089.

10 Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J: The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996;27:1304–1305.

11 Huttner HB, Steiner T, Hartmann M, Köhrmann M, Juettler E, Mueller S, Wikner J, Meyding-Lamade U, Schramm P, Schwab S, Schellinger PD: Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke 2006;37:404–408.

12 Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke 1993;24:987–993.

13 Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. N Engl J Med 2001; 344:1450–1460.

14 Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T: Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 1996;27:1783–1787.

15 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for assessment of handicap in stroke patients. Stroke 1988;19:604–607.

16 Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC: Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. Neurology 1994;44:133–139.

17 Steiner T, Rosand J, Diringer M: Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. Stroke 2006;37:256–262.

18 Yasaka M, Minematsu K, Naritomi H, Sakata T, Yamaguchi T: Predisposing factors for enlargement of intracerebral hemorrhage in patients treated with warfarin. Thromb Haemost 2003;89:278–283.

19 Huttner HB, Schellinger PD, Hartmann M, Kohrmann M, Juettler E, Wikner J, Mueller S, Meyding-Lamade U, Strobl R, Mansmann U, Schwab S, Steiner T: Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. Stroke 2006;37:1465–1470.

20 Toyoda K, Yasaka M, Nagata K, Nagao T, Gotoh J, Sakamoto T, Uchiyama S, Minematsu K: Antithrombotic therapy influences location, enlargement, and mortality from intracerebral hemorrhage. The bleeding with antithrombotic therapy (BAT) retrospective study. Cerebrovasc Dis 2009;27:151–159.

21 Rosand J, Hylek EM, O'Donnell HC, Greenberg SM: Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. Neurology 2000;55: 947–951.
22 Sjöblom L, Hårdemark HG, Lindgren A, Norrving B, Fahlén M, Samuelsson M, Stigendal L, Stockelberg D, Taghavi A, Wallrup L, Wallvik J: Management and prognostic features of intracerebral hemorrhage during anticoagulant therapy: a Swedish multicenter study. Stroke 2001;32:2567–2574.
23 Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R: Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. Stroke 1998;29: 1160–1166.
24 Toyoda K, Okada Y, Minematsu K, Kamouchi M, Fujimoto S, Ibayashi S, Inoue T: Antiplatelet therapy contributes to acute deterioration of intracerebral hemorrhage. Neurology 2005;65:1000–1004.
25 Zazulia AR, Diringer MN, Derdeyn CP, Powers WJ: Progression of mass effect after intracerebral hemorrhage. Stroke 1999;30: 1167–1173.
26 Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T, Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators: Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 2006;66:1175–1181.
27 Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O: Hematoma enlargement in spontaneous intracerebral hemorrhage. J Neurosurg 1994;80:51–57.
28 Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T: Predisposing factors to enlargement of spontaneous intracerebral hematoma. Stroke 1997;28:2370–2375.
29 Niizuma H, Shimizu Y, Nakasato N, Jokura H, Suzuki J: Influence of liver dysfunction on volume of putaminal hemorrhage. Stroke 1988;19:987–990.
30 Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A: Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke 2004;35:1364–1367.
31 Caso V, Paciaroni M, Venti M, Alberti A, Palmerini F, Milia P, Billeci AM, Silvestrelli G, Biagini S, Agnelli G: Effect of on-admission antiplatelet treatment on patients with cerebral hemorrhage. Cerebrovasc Dis 2007; 24:215–218.

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2011;31:170–176
DOI: 10.1159/000321766

Received: May 6, 2010
Accepted: September 27, 2010
Published online: December 3, 2010

Effect of Prothrombin Complex Concentrate on Hematoma Enlargement and Clinical Outcome in Patients with Anticoagulant-Associated Intracerebral Hemorrhage

Takahiro Kuwashiro[a] Masahiro Yasaka[a, b] Ryo Itabashi[a] Hideaki Nakagaki[a]
Fumio Miyashita[a] Hiroaki Naritomi[a] Kazuo Minematsu[a]

[a]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, and
[b]Department of Cerebrovascular Disease, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan

Key Words
Intracerebral hemorrhage · Hematoma enlargement · Warfarin · Prothrombin complex concentrate

Abstract
Background: The present study was carried out to determine the effect of prothrombin complex concentrate (PCC) on hematoma enlargement (HE) and the early clinical outcome of intracerebral hemorrhage (ICH) patients on long-term warfarin treatment. ***Methods:*** The medical records and computed tomography (CT) images of 50 consecutive ICH patients on long-term warfarin treatment (35 men, 15 women; 69 ± 12 years old) were reviewed. International normalized ratio (INR) values, frequency of HE and clinical outcome were compared between patients treated with and without PCC. ***Results:*** INR values on admission were above 2.0 in 37 patients, of whom 19 were given PCC (PCC group) and 18 were not given PCC (control group). In these 37 patients, the frequency of HE ($p = 0.017$), the number of patients with a poor clinical outcome (modified Rankin Scale score ≥3 at 30 days or at discharge; $p = 0.045$) and in-hospital mortality ($p = 0.042$) were significantly higher in the control than in the PCC group. On multivariate logistic regression analysis with adjustment, PCC administration was independently associated (odds ratio 0.03, 95% confidence interval 0.00–0.63; $p = 0.023$) with a reduction in poor clinical outcome in ICH patients whose INR values were >2.0 on admission. ***Conclusions:*** Immediate INR reversal with PCC may prevent HE and subsequent poor outcome.

Introduction

Intracerebral hemorrhage (ICH) is a life-threatening complication of oral anticoagulation therapy. The relative risk of ICH during warfarin treatment is more than 10-fold in patients over 50 years of age [1]. Warfarin use increases not only the risk of ICH frequency but also the risk of hematoma enlargement (HE), thus worsening the severity of ICH and resulting in a poor outcome [2–8].

When serious ICH occurs in patients on warfarin treatment, immediate and complete reversal of coagulopathy is important. In order to reverse the effect of warfarin, vitamin K, fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) is given in addition to reduction or discontinuation of warfarin, depending on the international normalized ratio (INR) value. It has been reported that PCC administration reverses the INR value

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/11/0312–0170$38.00/0

Accessible online at:
www.karger.com/ced

Takahiro Kuwashiro, MD, Department of Medicine and Clinical Science
Graduate School of Medical Sciences, Kyushu University
3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 (Japan)
Tel. +81 92 642 5256, Fax +81 92 642 5271
E-Mail tkuwashi@intmed2.med.kyushu-u.ac.jp

faster than FFP or vitamin K [4, 9–13]. However, the effects of PCC administration on preventing HE and on clinical outcome have not yet been clearly demonstrated.

The aim of the present study was to examine the efficacy of PCC for ICH in patients on warfarin treatment with respect to HE.

Methods

We studied 50 patients on warfarin treatment who were admitted to our stroke care unit within 3 days after ICH onset from January 1999 to December 2003. Patients with ICH due to aneurysmal rupture, vascular malformations, hemorrhagic transformation after brain infarction or brain tumor, as well as those who hemorrhaged primarily into the ventricles, were excluded. There were 35 men and 15 women, and their median age was 72 years (range 16–89 years). Twenty-two patients were given PCC (PCC group) and the remaining 28 were not (control group).

Written informed consent was obtained from the patients or their family before PCC was given. We used a commercially available PCC (PPSB-HT Nichiyaku; Nihon Pharmaceutical, Tokyo, Japan) which contains 500 IU of factors II, VI, IX and X, as well as 380 U of protein C, in 25 ml. For each patient, the decision to administer PCC, as well as the decision regarding how much to administer, was made by the physicians in charge based on our previous studies [14–16]. The INR values of all patients were examined on admission, within 2 h after PCC administration and 24 h after.

The presence, location and volume of ICH were verified on CT scan immediately following admission. The second CT examination was routinely performed within 24 h after admission. Additional CT scans were performed if a patient deteriorated clinically. All CT scans were reviewed and evaluated by neuroradiologists and neurologists who were blinded to the patients' clinical status. The locations of the hematomas were classified as putaminal, thalamic, lobar, pontine, cerebellar or other locations.

To calculate the ICH volume, the 3 diameters were multiplied and then divided by 2 ($A \times B \times C/2$) [17–20], where the longest diameter (A) and the largest diameter (B) perpendicular to A were measured using the centimeter scale on CT films of the slices showing the largest ICH area. The height of the hematoma (C) was calculated by multiplying the number of slices involved by the slice thickness. Hemorrhage volume within the ventricular system was not assessed. Parenchymal hemorrhage was considered to have enlarged when the volume on the follow-up CT was 1.4 times greater than the volume on the admission CT [21].

Hematoma volume (HV) on admission, final HV, frequency of HE and other baseline characteristics, such as age, gender, smoking status (previous and current), alcohol consumption (≥2 drinks per day), hypertension, diabetes mellitus, hypercholesterolemia, heart disease (including arrhythmia), liver disease (cirrhosis, active hepatitis, alcoholic liver damage, fatty liver and others), previous symptomatic ischemic stroke and previous symptomatic ICH, were compared between the 2 groups. Vascular risk factors were identified as follows: a history of antihypertensive medication, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on admission for hypertension; fasting blood glucose ≥126 mg/dl, positive 75-gram oral glucose tolerance test result or a history of antidiabetic medication and insulin for diabetes mellitus, and serum total cholesterol ≥220 mg/dl or a history of antihypercholesterolemic medication for hypercholesterolemia.

Systolic blood pressure, diastolic blood pressure and blood glucose were also assessed. In the acute stage, all patients had their systolic and diastolic blood pressures measured every 6 h after admission.

The patients' neurological state was evaluated by neurologists. Neurological deficits on admission were evaluated using the National Institutes of Health Stroke Scale (NIHSS) score. The clinical outcome was assessed using the modified Rankin Scale (mRS) score (from 0 to 5) at 30 days or at discharge, whichever occurred sooner [22]. Death was assigned an mRS score of 6 [23]. Good and poor outcomes were defined as an mRS score of 0–2 and 3–6, respectively.

Continuous values are expressed as means ± SD or medians and range. The clinical characteristics of ICH patients given PCC were compared to those of the ICH patients not given PCC using the χ^2 test, the unpaired Student's t test and the Mann-Whitney U test, as appropriate. In patients with an INR >2.0, similar comparisons were made, as an INR >2.0 was found to be one of the predisposing factors for enlargement of ICH in patients treated with warfarin [14]. A p value less than 0.05 was considered significant. Then, the background characteristics of patients with a good outcome and those with a poor outcome were compared. To identify the independent predictors for poor outcome, a multivariate logistic regression analysis with adjustments for age and gender was conducted using the clinical characteristics that showed a significant ($p < 0.05$) or marginally significant ($0.05 \leq p < 0.1$) correlation with each indicator as independent variables on univariate analyses.

Results

The primary underlying diseases that required anticoagulation were nonvalvular atrial fibrillation in 27 patients, mitral or aortic valve replacement in 8, deep vein thrombosis in 4, dilated cardiomyopathy in 3, old myocardial infarction in 3, coronary artery bypass graft for ischemic heart disease in 2, complicated atheromatous lesions in the aortic arch in 2 and peripheral arterial disease in 1. Thirty-five patients had a past history of brain infarction.

PCC was given to reverse the INR in 22 of the 50 ICH patients a median of 7.0 h (range 1.0–71.5 h) after the onset of ICH. The PCC doses were 1,500 IU in 3 patients, 1,000 IU in 2 and 500 IU in 17. INR values on admission were not significantly different between the PCC and control groups ($p = 0.215$). No significant differences were found between the groups for most of the baseline characteristics, including the frequency of vitamin K or FFP administration and systolic and diastolic blood

pressures on admission and 6, 12 and 24 h after hospitalization (table 1).

HE tended to be more frequent in the control group than in the PCC group (43 vs. 18%; p = 0.076), although admission HV, final HV and other hematoma characteristics were not different between the groups (table 1). The frequency of poor outcome (71 vs. 45%; p = 0.063) and in-hospital mortality (25 vs. 5%; p = 0.064) tended to be higher in the control group than in the PCC group (table 1).

The admission INR value was >2.0 in 37 of the 50 ICH patients on warfarin treatment. Of these 37, 19 were given PCC, while the other 18 patients were not. Two patients were given 1,500 IU of PCC, 2 were given 1,000 IU and 15 were given 500 IU. INR values on admission, administration frequency of vitamin K and FFP, baseline clinical characteristics and hematoma characteristics were not significantly different between the 19 patients in the PCC group and the 18 in the control group with an admission INR >2.0 (table 2).

Though the difference in HE was not significant between the 2 groups when all 50 ICH patients on warfarin were included, HE was more common in the control group than in the PCC group (56 vs. 16%; p = 0.017) for subjects with an admission INR >2.0 (table 2; fig. 1).

The number of patients with a poor outcome (78 vs. 42%; p = 0.045) and the in-hospital mortality (33 vs. 5%, p = 0.042) were significantly higher in the control group than in the PCC group among the patients with an admission INR >2.0 (table 2).

INR values 2 h [median 1.17 (range 0.89–1.72) vs. 1.85 (1.27–4.00); p < 0.001] and 24 h [median 1.14 (range 0.89–1.48) vs. 1.52 (1.17–3.00); p < 0.001] after PCC administration were significantly lower in the PCC group than in the control group. Furthermore, similar results [2 h after: median 1.21 (range 0.89–1.72) vs. 2.09 (1.85–4.00), p < 0.001; 24 h after: median 1.14 (range 0.89–1.48) vs. 1.70 (1.17–3.00), p = 0.003] were seen among patients whose admission INR was >2.0 (table 3).

Of the 37 patients with an admission INR >2.0, 22 had a poor outcome at 30 days or at discharge, while 15 had a good outcome. With respect to the clinical characteristics of these 37 patients, diastolic blood pressure (89 ± 20 vs. 77 ± 17 mm Hg; p = 0.054) and NIHSS score [median 14 (range 1–42) vs. 7 (1–30); p = 0.085] on admission tended to be higher in patients with a poor outcome than in those with a good outcome (table 4).

With respect to hematoma characteristics, the final HV was larger in the 22 patients with a poor outcome than in the 15 with a good outcome (60.7 ± 92.3 vs. 11.2 ± 12.8 cm^3; p = 0.047; table 4). Admission HV tended to be larger (39.2 ± 65.3 vs. 9.5 ± 10.5 cm^3; p = 0.091) and thalamic hemorrhage tended to be more frequent (64 vs. 33%; p = 0.099) in patients with a poor outcome than in those with a good outcome (table 4).

PCC was given more frequently to patients with a good outcome than to patients with a poor outcome (73 vs. 36%; p = 0.045), though there was no significant difference in the administration frequencies of vitamin K (60

Table 1. Clinical characteristics of the PCC and control groups

	PCC group (n = 22)	Control group (n = 28)	p value
Baseline characteristics			
Age, years	69.7 ± 8.2	68.7 ± 13.9	0.773
Males	15 (68%)	20 (71%)	0.804
Smoking	11 (50%)	18 (64%)	0.310
Drinking	9 (41%)	10 (36%)	0.707
Hypertension	19 (86%)	23 (82%)	0.999
Diabetes mellitus	4 (18%)	6 (21%)	0.999
Hypercholesterolemia	10 (45%)	7 (25%)	0.130
Heart disease	15 (68%)	20 (71%)	0.804
Liver disease	1 (5%)	3 (11%)	0.621
Previous ischemic stroke	15 (68%)	20 (71%)	0.804
Previous ICH	5 (23%)	2 (7%)	0.217
SBP on admission, mm Hg	165 ± 27	166 ± 25	0.881
DBP on admission, mm Hg	82 ± 20	86 ± 17	0.466
INR on admission	2.29 (1.14–3.96)	2.24 (1.11–4.23)	0.215
INR >2.0 on admission	19 (86%)	18 (64%)	0.108
Blood glucose, mg/dl	136 ± 56	137 ± 57	0.957
NIHSS score on admission	11 (2–34)	7 (1–42)	0.293
Vitamin K administration	15 (68%)	14 (50%)	0.196
FFP administration	1 (5%)	5 (18%)	0.211
Characteristics of hematoma			
Admission HV, cm^3	15.6 ± 16.3	29.2 ± 59.1	0.301
Final HV, cm^3	20.3 ± 23.6	44.4 ± 84.3	0.200
HE	4 (18%)	12 (43%)	0.076
Putaminal hemorrhage	3 (14%)	8 (29%)	0.306
Thalamic hemorrhage	11 (50%)	15 (54%)	0.802
Lobar hemorrhage	4 (18%)	7 (25%)	0.734
Pontine hemorrhage	2 (9%)	1 (4%)	0.576
Cerebellar hemorrhage	2 (9%)	1 (4%)	0.576
mRS at 30 days or at discharge			
mRS ≥3	10 (45%)	20 (71%)	0.063
In-hospital mortality (mRS = 6)	1 (5%)	7 (25%)	0.064

Values are presented as numbers of patients (percentage), means ± SD or medians (range). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

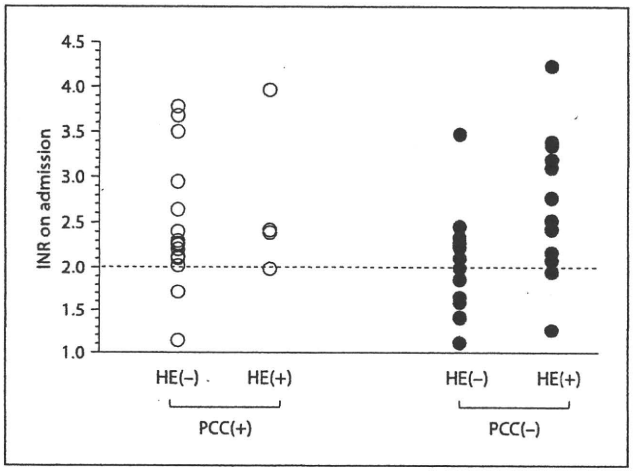

Fig. 1. HE according to INR value on admission shown on a scatter diagram. Though there was no significant difference in the frequency of HE between the PCC and the non-PCC groups for the whole group of 50 ICH patients on warfarin treatment, HE was more common in the non-PCC than in the PCC group (56 vs. 16%; p = 0.017) for subjects with an admission INR >2.0.

Table 2. Clinical characteristics of the PCC and control groups with INR >2.0 on admission

	PCC group (n = 19)	Control group (n = 18)	p value
Baseline characteristics			
Age, years	68.9 ± 8.5	66.7 ± 14.9	0.577
Males	12 (63%)	15 (83%)	0.269
INR on admission	2.39 (2.02–3.96)	2.44 (2.07–4.23)	0.867
NIHSS score on admission	10 (2–34)	6 (1–42)	0.209
Vitamin K administration	13 (68%)	10 (56%)	0.420
FFP administration	1 (5%)	3 (17%)	0.340
Characteristics of hematoma			
Admission HV, cm^3	16.1 ± 17.4	38.8 ± 72.3	0.193
Final HV, cm^3	21.6 ± 25.2	60.8 ± 102.1	0.114
HE	3 (16%)	10 (56%)	0.017
mRS at 30 days or at discharge			
mRS ≥3	8 (42%)	14 (78%)	0.045
In-hospital mortality (mRS = 6)	1 (5%)	6 (33%)	0.042

Values are presented as numbers of patients (percentage), means ± SD or medians (range).

vs. 63%; p = 0.823) and FFP (0 vs. 18%; p = 0.131) between the groups (table 4).

On multivariate logistic regression analysis using the significant ($p < 0.05$) and marginally significant ($0.05 \leq p < 0.1$) characteristics as independent variables with adjustments for age and gender, NIHSS score on admission (odds ratio 1.30, 95% confidence interval 1.01–1.69; p = 0.045 per 1-score increase) was independently related to poor outcome, and PCC administration (odds ratio 0.03, 95% confidence interval 0.00–0.63; p = 0.023) was independently associated with a reduction in poor outcome in the ICH patients with an admission INR >2.0 (table 5).

Table 3. Correction of INR value with PCC

	PCC group	Control group	p value
All patients			
INR on admission	2.29 (1.14–3.96)	2.24 (1.11–4.23)	0.215
INR after 2 h	1.17 (0.89–1.72)	1.85 (1.27–4.00)	<0.001
INR after 24 h	1.14 (0.89–1.48)	1.52 (1.17–3.00)	<0.001
Patients with INR >2.0			
INR on admission	2.39 (2.02–3.96)	2.44 (2.07–4.23)	0.867
INR after 2 h	1.21 (0.89–1.72)	2.09 (1.85–4.00)	<0.001
INR after 24 h	1.14 (0.89–1.48)	1.70 (1.17–3.00)	0.003

Values are presented as medians (range).

Discussion

In the present study investigating ICH in patients on warfarin treatment, the frequencies of HE, poor outcome and in-hospital mortality were significantly higher in the non-PCC (control) group than in the PCC group among patients with an admission INR >2.0. Moreover, PCC administration was one of the independent factors associated with a good clinical outcome in ICH patients on warfarin treatment.

Although there are no standard guidelines for reversing the anticoagulant effect in patients with ICH on warfarin, PCC appears to be a logical treatment for immediate reversal of the anticoagulant effect in such patients. The present study clearly demonstrated that HE occurred more frequently in ICH patients not treated with PCC than in those treated with PCC when the admission INR was >2.0. Flaherty et al. [24] reported that there was a trend toward a difference in HV according to INR levels in 51 ICH patients taking warfarin. Our previous report

Table 4. Characteristics of patients with mRS ≥3 or ≤2 (INR >2.0) at 30 days or at discharge

	mRS ≥3 (n = 22)	mRS ≤2 (n = 15)	p value
Baseline characteristics			
Age, years	67.1 ± 13.9	69.0 ± 8.6	0.639
Males	17 (77%)	10 (67%)	0.708
Smoking	14 (63%)	8 (53%)	0.531
Drinking	7 (32%)	8 (53%)	0.191
Hypertension	19 (86%)	11 (73%)	0.408
Diabetes mellitus	5 (23%)	3 (20%)	0.999
Hypercholesterolemia	8 (36%)	4 (27%)	0.724
Hypocholesterolemia	2 (9%)	1 (7%)	0.999
Heart disease	15 (68%)	12 (80%)	0.481
Liver disease	2 (9%)	2 (13%)	0.999
Previous ischemic stroke	17 (77%)	10 (67%)	0.708
Previous ICH	2 (9%)	4 (27%)	0.198
SBP on admission, mm Hg	171 ± 30	156 ± 22	0.111
DBP on admission, mm Hg	89 ± 20	77 ± 17	0.054
INR on admission	2.38 (2.07–4.23)	2.40 (2.02–3.78)	0.914
Blood glucose, mg/dl	154 ± 66	127 ± 53	0.212
NIHSS score on admission	14 (1–42)	7 (1–30)	0.085
Characteristics of hematoma			
Admission HV, cm^3	39.2 ± 65.3	9.5 ± 10.5	0.091
Final HV, cm^3	60.7 ± 92.3	11.2 ± 12.8	0.047
HE	10 (45%)	3 (20%)	0.166
Putaminal hemorrhage	7 (32%)	3 (20%)	0.481
Thalamic hemorrhage	14 (64%)	5 (33%)	0.099
Lobar hemorrhage	4 (18%)	3 (20%)	0.999
Pontine hemorrhage	1 (5%)	1 (7%)	0.999
Cerebellar hemorrhage	2 (9%)	1 (7%)	0.999
Reversal of anticoagulation			
Vitamin K administration	14 (63%)	9 (60%)	0.823
FFP administration	4 (18%)	0	0.131
PCC administration	8 (36%)	11 (73%)	0.045

Values are presented as numbers of patients (percentage), means ± SD or medians (range). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

Table 5. Multivariate regression analysis for mRS ≥3 (INR >2.0)

Multivariate analysis	Odds ratio (95% CI)	p value
Age (per 1-year increase)	0.91 (0.80–1.03)	0.136
Gender (male)	4.12 (0.25–67.4)	0.321
DBP at admission (per 1-mm Hg increase)	1.01 (0.95–1.07)	0.687
NIHSS score on admission (per 1-point increase)	1.30 (1.01–1.69)	0.045
Final HV (per 1-cm^3 increase)	0.98 (0.94–1.03)	0.479
Thalamic hemorrhage	6.63 (0.69–64.2)	0.102
PCC administration	0.03 (0.00–0.63)	0.023

Multivariate logistic regression analysis was performed using the clinical characteristics that showed a significant ($p < 0.05$) or marginally significant ($0.05 \leq p < 0.1$) correlation with each indicator as independent variables on univariate analyses with adjustments for age and gender. CI = Confidence interval; DBP = diastolic blood pressure.

indicated that an INR value <2.0 on admission or for 24 h after immediate INR reversal with PCC prevented HE [14]. Therefore, it seems that immediate INR reversal is required to prevent HE in acute ICH patients with an INR >2.0.

Reversal of the effects of warfarin with PCC and vitamin K in patients with life-threatening neurological emergencies has been reported to be more rapid and effective than with FFP and vitamin K [9–12]. Siddiq et al. [13] reported that PCC in combination with FFP and vitamin K required less time for correction of warfarin-associated coagulopathy in neurosurgical emergencies than FFP and vitamin K alone.

Though PCC normalizes the INR more rapidly than FFP or vitamin K infusion, its effect on clinical outcomes has not yet been demonstrated. According to Boulis et al. [9], although the rate of correction was greater and the time to correction was shorter for PCC than for FFP, no difference in neurological outcomes was detected between patients treated with PCC and those treated with FFP. Although the present study did not include many data on FFP, it showed the effect of PCC administration not only on INR reversal but also on the subsequent outcome in patients whose INR value on admission was >2.0. Results such as the above were shown in the present study, but it may be necessary to perform randomized controlled trials with larger numbers of patients to more precisely evaluate the effect of PCC on outcome.

Kazui et al. [25] reported that HE was seen in 20% of intracranial hemorrhage patients not treated with antithrombotic agents, and enlargement of hematoma had stopped within 6 h after onset in 83% and within 24 h in 100%. Kawamata et al. [26] resumed anticoagulation in 12 patients with intracranial hemorrhage related to warfarin within 3 days and found no HE or rebleeding. Therefore, in order to avoid worsening hemorrhagic complications, an interval of 3 days wherein the INR is fully corrected with PCC may be required before resumption of anticoagulation.

Previous studies have shown that elevated blood pressure increases the risk of HE [25, 27]. Blood pressure control in the acute phase of hemorrhage in patients treated with warfarin appears to be as important as in those not treated with warfarin. In the present study, there was no significant difference with regard to 24-hour blood pressure control between the PCC group and the non-PCC group nor between the good outcome group (mRS score ≤ 2) and the poor outcome group (mRS score ≥ 3). Therefore, it seems that the effect of PCC found in the present study was not associated with blood pressure.

The present study has several limitations. Since the study was a nonrandomized, uncontrolled design, there might have been some selection bias. Furthermore, the patients received a variety of combination therapies. Administration criteria for PCC, vitamin K and FFP were not well defined, and the doses were not uniform. Prospective trials involving large populations of patients on warfarin are needed to overcome these limitations and clarify the remaining unresolved issues.

In conclusion, immediate INR reversal with PCC may prevent HE and subsequent poor outcome for ICH patients on warfarin treatment.

Acknowledgments

This study was supported by Comprehensive Research on Cardiovascular and Life-Style Related Diseases Grants-in-Aid and by a Research Grant for Cardiovascular Diseases (21A-4) from the Ministry of Health, Labor and Welfare, Japan.

Disclosure Statement

No conflicts of interest exists.

References

1 Wintzen AR, de Jonge H, Loeliger EA, Bots GT: The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. Ann Neurol 1984;16:553–558.

2 Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM: The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med 2004;164:880–884.

3 Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J: Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology 2004;63:1059–1064.

4 Huttner HB, Schellinger PD, Hartmann M, Köhrmann M, Juettler E, Wikner J, Mueller S, Meyding-Lamade U, Strobl R, Mansmann U, Schwab S, Steiner T: Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. Stroke 2006;37:1465–1470.

5 Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators: Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 2006;66:1175–1181.

6 Kuwashiro T, Yasaka M, Itabashi R, Nakagaki H, Miyashita F, Naritomi H, Minematsu K: Enlargement of acute intracerebral hematomas in patients on long-term warfarin treatment. Cerebrovasc Dis 2010;29:446–453.

7 Toyoda K, Yasaka M, Nagata K, Nagao T, Gotoh J, Sakamoto T, Uchiyama S, Minematsu K; Bleeding with Antithrombotic Therapy Study Group: Antithrombotic therapy influences location, enlargement, and mortality from intracerebral hemorrhage. The Bleeding with Antithrombotic Therapy (BAT) Retrospective Study. Cerebrovasc Dis 2009;27:151–159.

8 Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, Kyne L, Duggan J, Moroney J, McCormack PM, Daly L, Fitz-Simon N, Harris D, Horgan G, Williams EB, Furie KL, Kelly PJ: Stroke associated with atrial fibrillation – incidence and early outcomes in the north Dublin Population Stroke Study. Cerebrovasc Dis 2010;29:43–49.

9 Boulis NM, Bobek MP, Schmaier A, Hoff JT: Use of factor IX complex in warfarin-related intracranial hemorrhage. Neurosurgery 1999;45:1113–1119.

10 Cartmill M, Dolan G, Byrne JL, Byrne PO: Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergency. Br J Neurosurg 2000;14:458–461.

11 Fredriksson K, Norrving B, Sttomblad LG: Emergency reversal of anticoagulation after intracerebral hemorrhage. Stroke 1992;23:972–977.

12 Makris M, Graves M, Phillips WS, Kitchen S, Rosendaal FR: Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. Thromb Haemost 1997;77:477–480.

13 Siddiq F, Jalil A, McDaniel C, Brock DG, Pineda CC, Bell RD, Lee K: Effectiveness of factor IX complex concentrate in reversing warfarin associated coagulopathy for intracerebral hemorrhage. Neurocrit Care 2008;8:36–41.

14 Yasaka M, Minematsu K, Naritomi H, Sakata T, Yamaguchi T: Predisposing factors for enlargement of intracerebral hemorrhage in patients treated with warfarin. Thromb Haemost 2003;89:278–283.

15 Yasaka M, Sakata T, Minematsu K, Naritomi H: Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication. Thromb Res 2003;108:25–30.

16 Yasaka M, Sakata T, Naritomi H, Minematsu K: Optimal dose of prothrombin complex concentrate for acute reversal of oral anticoagulation. Thromb Res 2005;115:455–459.

17 Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J: The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996;27:1304–1305.

18 Huttner HB, Steiner T, Hartmann M, Köhrmann M, Juettler E, Mueller S, Wikner J, Meyding-Lamade U, Schramm P, Schwab S, Schellinger PD: Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke 2006;37:404–408.
19 Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke 1993;24:987–993.
20 Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. N Engl J Med 2001; 344:1450–1460.
21 Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T: Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 1996;27:1783–1787.
22 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for assessment of handicap in stroke patients. Stroke 1988;19:604–607.
23 Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC: Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. Neurology 1994;44:133–139.
24 Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, Khatri P, Stettler B, Adeoye O, Moomaw CJ, Broderick JP, Woo D: Warfarin use leads to larger intracerebral hematomas. Neurology 2008;71:1084–1089.
25 Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T: Predisposing factors to enlargement of spontaneous intracerebral hematoma. Stroke 1997;28:2370–2375.
26 Kawamata T, Takeshita M, Kubo O, Izawa M, Kagawa M, Takakura K: Management of intracranial hemorrhage associated with anticoagulant therapy. Surg Neurol 1995;44: 438–443.
27 Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A: Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke 2004;35:1364–1367.

Blood Pressure Levels and Bleeding Events During Antithrombotic Therapy

The Bleeding With Antithrombotic Therapy (BAT) Study

Kazunori Toyoda, MD; Masahiro Yasaka, MD; Shinichiro Uchiyama, MD; Takehiko Nagao, MD; Jun Gotoh, MD; Ken Nagata, MD; Yukihiro Koretsune, MD; Tomohiro Sakamoto, MD; Kazunori Iwade, MD; Masahiro Yamamoto, MD; Jun C. Takahashi, MD; Kazuo Minematsu, MD; on behalf of The Bleeding With Antithrombotic Therapy (BAT) Study Group

Background and Purpose—A prospective, multicenter, observational cohort study was conducted to clarify the association between major bleeding events and blood pressure (BP) levels during follow-up before development of bleeding events in antithrombotic users.

Methods—A total of 4009 patients taking oral antithrombotic agents for cardiovascular or cerebrovascular diseases (2728 men, 69±10 years old) were followed. Changes in systolic and diastolic BPs between entry and the last clinic visit before intracranial hemorrhage (ICH) or extracranial hemorrhage were assessed.

Results—Over a median follow-up of 19 months, ICH developed in 31 patients and extracranial hemorrhage developed in 77. Entry BP levels were similar among patients with ICH, those with extracranial hemorrhage, and those without hemorrhagic events. Both systolic BP and diastolic BP were relatively high during follow-up as compared with the levels at entry in patients with ICH, whereas they showed plateaus in patients with extracranial hemorrhage and patients without hemorrhagic events. Average systolic BP levels between 1 and 6 months (hazard ratio, 1.45; 95% CI, 1.08 to 1.92 per 10-mm Hg increase) and between 7 and 12 months (hazard ratio, 1.47; 95% CI, 1.05 to 2.01) as well as average diastolic BP levels between 7 and 12 months (hazard ratio, 2.05; 95% CI, 1.15 to 3.62) were independently associated with development of ICH after adjustment for established ICH predictors. The optimal cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg using receiver operating characteristic curve analysis.

Conclusions—An increase in BP levels during antithrombotic medication was positively associated with development of ICH, suggesting the importance of adequate BP control for avoiding ICH. BP levels did not appear to be associated with extracranial hemorrhage. (***Stroke*. 2010;41:1440-1444.)**

Key Words: anticoagulation ■ antiplatelet therapy ■ hypertension ■ intracerebral hemorrhage ■ stroke

Antithrombotic therapy is regarded as an essential primary and secondary preventive strategy for cardiovascular diseases and stroke.[1,2] However, bleeding events are inevitable complications of this therapy; in particular, intracranial hemorrhage (ICH) is a typical life-threatening event.[3] Carefully regulated warfarin therapy to international normalized ratios between 2 and 3 doubles the risk of ICH, and aspirin increases the risk by approximately 40%.[4]

Hypertension is a firmly established risk factor for ICH in the general population[5] as well as in warfarin users.[4] In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), in which 72% of enrolled patients with stroke were receiving antiplatelets and 10% were receiving anticoagulants, ICH was reduced by half after mean blood pressure (BP) -lowering by 9/4 mm Hg.[6] Thus, adequate antihypertensive therapy seems to prevent ICH during antithrombotic therapy. This raises an essential issue: whether antithrombotic users who finally developed ICH and other bleeding events had high BP levels throughout follow-up as well as how such patients' BP levels changed during follow-up.

Received January 28, 2010; final revision received February 18, 2010; accepted March 12, 2010.

From the Departments of Cerebrovascular Medicine (K.T., K.M.) and Neurosurgery (J.C.T.), National Cerebral and Cardiovascular Center, Suita, Japan; the Department of Cerebrovascular Disease (M.Y.), National Hospital Organization Kyushu Medical Center, Fukuoka, Japan; the Department of Neurology (S.U.), Tokyo Women's Medical University School of Medicine, Tokyo, Japan; the Department of Neurology (T.N.), Tokyo Metropolitan HMTC Ebara Hospital, Tokyo, Japan; the Department of Neurology (J.G.), National Hospital Organization Saitama Hospital, Saitama, Japan; the Department of Neurology (K.N.), Research Institute for Brain and Blood Vessels, Akita, Japan; the Clinical Research Institute (Y.K.), National Hospital Organization Osaka National Hospital, Osaka, Japan; the Department of Cardiovascular Medicine (T.S.), Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; the Department of Cardiology (K.I.), National Hospital Organization Yokohama Medical Center, Yokohama, Japan; and the Department of Neurology (M.Y.), Yokohama City Brain and Stroke Center, Yokohama, Japan.

Correspondence to Kazunori Toyoda, MD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan. E-mail toyoda@ hsp.ncvc.go.jp

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.580506**

To determine the incidence and severity of bleeding complications in patients with cardiovascular diseases and stroke treated with oral antithrombotic therapy in Japan, a prospective, multicenter, observational study (the Bleeding with Antithrombotic Therapy [BAT] Study) was conducted. In its initial report of the overall results, adding antiplatelets to warfarin or single antiplatelet therapy doubled the risk of life-threatening or major bleeding events.[7] Here, the association between these patients' BP levels during follow-up and development of bleeding events was determined.

Patients and Methods

The BAT Study was a prospective, multicenter, observational cohort study on the incidence and severity of bleeding complications in antithrombotic users. A total of 4009 patients (2728 men, 69±10 years [mean±SD]) who were taking oral antiplatelet agents or warfarin for cardiovascular or cerebrovascular diseases were consecutively enrolled from 19 stroke and cardiovascular centers that were balanced regionally in Japan and observed for 2 to 30 months between October 2003 and March 2006. The study protocol, inclusion/exclusion criteria, and general results were published previously.[7] The medical ethics review boards of the participating institutes approved the study protocol, and all patients provided written informed consent.

Based on bleeding events during follow-up, the patients were divided into 3 groups: an "ICH group" for the patients developing any symptomatic ICH; an "extracranial hemorrhage (ECH) group" for those developing a life-threatening or major bleeding event other than ICH; and a "non-H group" for those without any life-threatening or major bleeding event. Bleeding events were classified according to the definition by the Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke study (MATCH).[8] Briefly, life-threatening bleeding was defined as: any fatal bleeding event; a drop in hemoglobin of ≥50 g/L; hemorrhagic shock; symptomatic ICH; or transfusion of ≥4 U of red blood cells. Major bleeding was defined as significantly disabling, severe intraocular bleeding, or transfusion of ≤3 U of red blood cells. Secondary hemorrhagic transformation of an ischemic stroke was not regarded as a bleeding event. When the patients developed a life-threatening or major bleeding event, observation was discontinued.

Comorbidities (ischemic and hemorrhagic stroke, heart disease, neoplasms, and liver cirrhosis) and cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, hypocholesterolemia [serum total cholesterol <130 mg/dL on enrollment], current or previous smoking habit, and alcohol consumption ≥2 drinks per day) listed in this study were the same as those in the previous study.[7] Follow-up evaluations were normally performed every month; each time, BP was measured using a mercury sphygmomanometer.

Statistical Methods

All analyses were performed using JMP 7 statistical software (SAS Institute Inc, Cary, NC). Average levels of systolic and diastolic BPs (SBP and DBP, respectively) between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry were assessed for the Cox proportional hazards regression analysis. BP levels at the last clinic visit of the observation period (the last visit before bleeding events for the ICH and ECH groups) and the average BP levels of all the follow-up measurements except for the levels at entry and at the last visit were assessed for the annual incidence and 95% CIs of ICH and the receiver operating characteristic (ROC) curves analysis. To compare baseline clinical characteristics and BP levels among the ICH, ECH, and Non-H groups, 1-way factorial analysis of variance with post hoc comparison by Dunnett test (with Non-H patients as control subjects) was used for continuous variables, and the χ^2 test was used for categorical variables. To examine the associations of BP levels and their changes with the development of ICH, a Cox proportional hazards regression analysis was performed using a forced entry method of established ICH predictors, including sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin. Goodness of fit of the statistical model was tested using the likelihood ratio in the Whole Model Test and Akaike information criterion. Finally, the optimal cutoff BP levels to predict impending development of ICH (in other words, to predict the last clinic visit before ICH) were determined using ROC curves based on all the BP measurements during follow-up. A probability value <0.05 was considered statistically significant.

Results

Of 4009 enrolled patients, 1891 (47.2%) were taking single antiplatelet agents, 349 (8.7%) were taking dual antiplatelet agents, 1298 (32.4%) were taking warfarin, and 471 (11.7%) were taking warfarin plus antiplatelet agents. The main antiplatelet agents used in the enrolled patients were described previously.[7] Briefly, aspirin monotherapy, ticlopidine monotherapy, and aspirin plus ticlopidine were the major choice for both antiplatelet users (1340, 394, and 220 patients, respectively) and warfarin plus antiplatelets users (336, 69, and 49 patients, respectively). At entry, the median international normalized ratio was 1.97 (interquartile range, 1.69 to 2.33) in warfarin users (taking warfarin alone or warfarin plus antiplatelets).

During the median observation period of 19 months (interquartile range, 13 to 23 months), 108 life-threatening or major bleeding events, including 31 ICH and 77 ECH, occurred. In warfarin users, the median international normalized ratio at entry was 2.06 (interquartile range, 1.95 to 2.30) in the ICH group, 2.06 (1.65 to 2.46) in the ECH group, and 1.96 (1.69 to 2.33) in the Non-H group (P=0.149); and the median international normalized ratio at the last visit before bleeding events or on the day of the event was 2.28 (1.74 to 2.68) in the ICH group and 2.24 (1.75 to 3.06) in the ECH group (P=0.993). Among the 3 groups, observation period (P<0.001), age (P=0.003), use of warfarin (P=0.002), and neoplasm (P=0.013) were significantly different (Table 1).

Figure 1 shows the time courses of the BP levels. Both SBP and DBP levels at entry were similar among the 3 groups (Table 1). During follow-up, both SBP and DBP were relatively high as compared with the levels at entry in the ICH group, and they plateaued in the ECH and Non-H groups. BP levels were not significantly different among the 3 groups in any BP measurements.

The association of BP with the development of ICH was determined after adjustment for sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin (Table 2). Average SBP levels between 1 and 6 months (hazard ratio [HR], 1.45; 95% CI, 1.08 to 1.92 per 10-mm Hg increase) and between 7 and 12 months (HR, 1.47; 95% CI, 1.05 to 2.01) as well as average DBP levels between 7 and 12 months (HR, 2.05; 95% CI, 1.15 to 3.62) were independently associated with ICH. The probability value of likelihood ratio in the Whole Model Test after multivariate adjustment was 0.055 for SBP at entry, 0.007 for average SBP between 1 and 6 months, 0.014 for average SBP between 7 and 12 months, 0.114 for average SBP after 13 months, 0.066 for DBP at entry, 0.046 for average DBP between 1 and 6 months, 0.010

Table 1. Patients' Baseline Clinical Characteristics

	ICH	ECH	Non-H	P
Patient no.	31	77	3901	
Observation period, months	11 (5–14)	11 (6–14)	19 (14–23)	<0.001
Age, years	73±7	71±10	69±10	0.003
Male	81%	75%	69%	0.173
Use of warfarin*	61%	61%	44%	0.002
Comorbidities				
Ischemic stroke	68%	44%	55%	0.060
Hemorrhagic stroke	6%	1%	2%	0.122
Heart disease, arrhythmia	77%	74%	67%	0.217
Neoplasm	19%	12%	7%	0.013
Liver cirrhosis	6%	4%	2%	0.197
Risk factors				
Hypertension	65%	57%	61%	0.746
Diabetes mellitus	26%	34%	26%	0.296
Hypercholesterolemia	36%	32%	42%	0.173
Hypocholesterolemia	3%	1%	1%	0.152
Smoking habit, current	19%	10%	14%	0.269
Smoking habit, previous	29%	47%	36%	
Alcohol consumption	10%	6%	5%	0.413
SBP at entry, mm Hg	134.6±13.2	130.8±18.5	132.5±17.9	0.597
DBP at entry, mm Hg	74.8±12.3	74.5±10.4	75.6±11.0	0.672

Data are medians (interquartile range) for the observation period, means±SD for age and BP, and percent of patients for others.
*Taking warfarin alone or warfarin plus antiplatelets.

for average DBP between 7 and 12 months, and 0.117 for average DBP after 13 months. Thus, SBP between 1 and 6 months, SBP between 7 and 12 months, and DBP between 7 and 12 months showed relatively good fitness. Akaike information criterion was 446.4, 438.1, 326.4, and 204.4 for each SBP measurement and 447.0, 443.3, 325.6, and 204.5 for each DBP measurement, respectively. Based on Akaike information criterion, SBP and DBP after 13 months were better than other BP measurements in regard to goodness of fit.

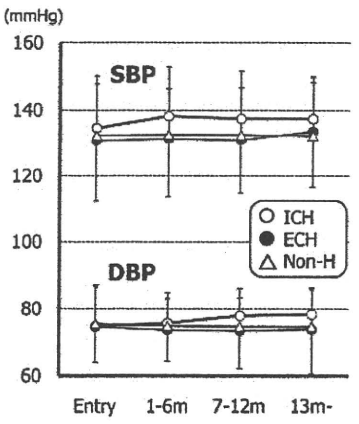

Figure 1. Time courses of BP. Average levels of SBP and DBP between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry are plotted. ICH indicates patients developing any symptomatic ICH; ECH, patients developing a life-threatening or major bleeding event other than ICH; Non-H, patients without any life-threatening or major bleeding event. All patients are included at entry and during 1 and 6 months; 21 patients with ICH, 53 patients with ECH, and 3293 Non-H patients are included during 7 and 12 months; and 13 patients with ICH, 30 patients with ECH, and 2936 Non-H patients are included after 13 months.

Table 2. Multivariate-Adjusted HR and 95% CI of BP Parameters for Development of ICH*

	HR	95% CI	P
SBP			
Level at entry	1.09	0.88–1.34	0.435
Mean level between 1 and 6 months	1.45	1.08–1.92	0.013
Mean level between 7 and 12 months	1.47	1.05–2.01	0.026
Mean level after 13 months	1.29	0.93–1.76	0.120
DBP			
Level at entry	0.97	0.68–1.39	0.880
Mean level between 1 and 6 months	1.28	0.78–2.13	0.337
Mean level between 7 and 12 months	2.05	1.15–3.62	0.016
Mean level after 13 months	1.50	0.89–2.53	0.126

*Per 10-mm Hg increase. Adjusted for sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin.

Because the observation was discontinued within 6 months or within 12 months for many patients, especially for those with ICH and ECH, the following analyses were performed using BP levels at the last clinic visit and the average BP levels of all the follow-up measurements except for the levels at entry and at the last visit. At the last visit, both SBP and DBP were higher in the ICH group than in the Non-H group (141.7±13.6/81.3±10.3 mm Hg versus 132.4±17.8/74.7±10.9 mm Hg, $P=0.011$ for SBP and $P=0.003$ for DBP). Figure 2 shows annual incidence of ICH according to BP levels. ICH risk increased linearly as both SBP and DBP levels at the last clinic visit increased; the risk did not increase linearly as BP levels at entry or those during follow-up increased.

To predict the impending development of ICH, the optimal cutoff SBP level determined using ROC curves was ≥130 mm Hg with a sensitivity of 89.3%, specificity of

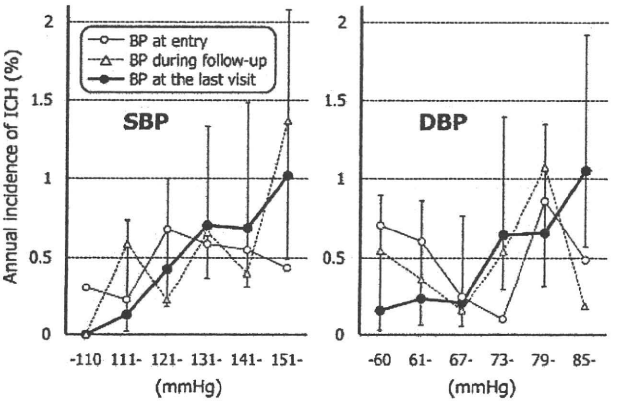

Figure 2. Annual incidence of ICH according to SBP and DBP levels. Bars indicate 95% CI for BP at the last clinic visit. "BP during follow-up" means average BP levels of all the follow-up measurements except for the levels at entry and at the last visit.

41.8%, and an area under the ROC curve of 0.659; the optimal cutoff DBP level was ≥81 mm Hg with a sensitivity of 53.6%, specificity of 74.2%, and an area under the ROC curve of 0.676. Both SBP3 ≥130 mm Hg (OR, 6.23; 95% CI, 2.16 to 26.35; $P<0.001$) and DBP3 ≥81 mm Hg (OR, 3.49; 95% CI, 1.64 to 7.52; $P=0.001$) were independently associated with ICH after adjustment for the 8 established ICH predictors.

Discussion

A major new finding of the present observational study was that BP levels during the follow-up, but not the level at entry, were independently associated with the development of ICH. In particular, ICH risk increased linearly as BP levels at the last clinic visit increased. The estimated cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg. BP levels did not appear to be associated with major systemic (excluding intracranial) bleeding events.

Hypertension is an established modifiable risk factor for ICH during warfarin therapy along with intensity of anticoagulation, concomitant use of antiplatelets, and smoking and heavy drinking habits.[4] However, major trials involving anticoagulant users failed to show entry BP level as a predictor for major bleeding events.[9–11] To resolve the contradiction, we designed the present study, which assessed BP levels during follow-up. The present antithrombotic users developing ICH had approximately 2 to 4 mm Hg higher entry SBP than those without bleeding events, which was not statistically significant. However, their SBP and DBP increased by an average of approximately 4 mm Hg at the follow-up as compared with at entry, and this increase may trigger ICH. Such an increase might result from careless BP management or resistance to antihypertensive therapy. Regardless of the cause, avoidance of a BP increase would lessen the risk for ICH.

Based on differences in average BP levels at the last visit between the ICH group and the other 2 groups, we hypothesized that the cutoff SBP level to predict impending development of ICH was roughly between 132 and 142 mm Hg, and the cutoff DBP level was roughly between 75 and 81 mm Hg. After ROC curve analyses, 130/81 mm Hg appears to be the cutoff level. Although the statistical power judged from the area under the ROC curve is not strong, this cutoff level seems to be reasonable, because recent guidelines from the European Society of Hypertension and the European Society of Cardiology and those from the Japanese Society of Hypertension advocated <130/80 mm Hg as the target BP level in diabetics and in high- or very-high-risk patients.[12,13] Real target BP levels during antithrombotic therapy should be determined by systematic comparative trials.

Combination therapy with antithrombotics and antihypertensives appears to be preventive for ICH. In the interim report of the Secondary Prevention of Small Subcortical Strokes (www.sps3.org/), in which SBP was lowered to <149 mm Hg or <130 mm Hg, risk of ICH was less than expected in patients with stroke taking aspirin alone or aspirin plus clopidogrel (personal communication). Success in reducing ICH in PROGRESS, in which 82% of enrolled patients were receiving antithrombotics, was reviewed.[6] On the other hand, an angiotensin receptor blocker, telmisartan, did not reduce the risk of ICH for antiplatelet users who recently had ischemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study (HR, 0.81; 95% CI, 0.63 to 1.05)[14]; the relatively small number of patients developing ICH may be a reason for this failure to show an effect.

Major systemic (not intracranial) bleeding events developed under identical BP levels as those in our patients without major bleeding events. This indicates that hypertensive damage to gastrointestinal, dermal, and other systemic circulations is milder than the damage to cerebral circulation. Preventive strategies other than antihypertensives, including proton pump inhibitors and H2 receptor antagonists, appear to be promising for reducing gastrointestinal bleeding.[15,16]

The limitations of the present study include the relatively short duration of the observation period and the small numbers of bleeding events as a result, which may affect the statistical results and made it difficult to perform subanalyses for patients with different clinical backgrounds and different antithrombotic regimens. Second, information on patients' antihypertensive therapy was not given. Third, clopidogrel, a universal antiplatelet agent, was not used in our patients because the agent was approved for use in Japan in 2006, after the study was finished. Finally, data of many patients were not included in the analysis of the follow-up BP measurements during 7 and 12 months and after 13 months partly because of early discontinuance of the observation due to bleeding events. To overcome this limitation and to introduce a message that BP levels at the last clinic visit are important for ICH risk, we used the BP levels at the last visit for some analyses, including the ROC. However, it is not originally appropriate to use the last available measurement as a predictor of a bleeding event in a prospective study.

Because ischemic events are much more common than bleeding events, the use of antithrombotic agents has been increasing. The present study suggests that one should be careful to avoid BP elevations in antithrombotic users, and it is important to lower their BP adequately to avoid ICH.

Appendix

Chief Investigator: K. Minematsu, National Cerebral and Cardiovascular Center.

Central Trial Office: K. Toyoda, A. Tokunaga, and A. Takebayashi, National Cerebral and Cardiovascular Center; M. Yasaka, National Hospital Organization Kyushu Medical Center.

Investigators and Institutions: S. Uchiyama, Tokyo Women's Medical University School of Medicine; M. Yamamoto, Yokohama City Brain and Stroke Center; T. Nagao, Tokyo Metropolitan HMTC Ebara Hospital; T. Sakamoto, Kumamoto University; M. Yasaka, National Hospital Organization Kyushu Medical Center; K. Iwade, National Hospital Organization Yokohama Medical Center; K. Nagata, Research Institute for Brain and Blood Vessels Akita; J. Gotoh, National Hospital Organization Saitama Hospital; Y. Koretsune, National Hospital Organization Osaka Medical Center; K. Minematsu and J. Takahashi, National Cardiovascular Center; T. Ochi, National Hospital Organization Kokura Hospital; T. Umemoto, National Hospital Organization Shizuoka Medical Center; T. Nakazato, National Hospital Organization Chiba-East Hospital; M.

Shimizu, National Hospital Organization Kobe Medical Center; M. Okamoto, National Hospital Organization Osaka Minami Medical Center; H. Shinohara, National Hospital Organization Zentsuji National Hospital; T. Takemura, National Hospital Organization Nagano Hospital; and M. Jougasaki and H. Matsuoka, National Hospital Organization Kagoshima Medical Center.

Sources of Funding

This study was supported in part by a Research Grant for Cardiovascular Diseases (15C-1) and a Grant-in-Aid (H20-Junkanki-Ippan-019) from the Ministry of Health, Labour and Welfare of Japan and a Grant-in-Aid for Scientific Research (C, #20591039) from the Japan Society for the Promotion of Science.

Disclosures

None.

References

1. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154: 1449–1457.
2. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71–86.
3. Toyoda K. Pharmacotherapy for the secondary prevention of stroke. *Drugs.* 2009;69:633–647.
4. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. *Stroke.* 2005;36:1588–1593.
5. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke.* 2003; 34:2060–2065.
6. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, Davis S, Donnan G, MacMahon S, Neal B, Warlow C, Woodward M. Writing Committee for the PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke.* 2004;35:116–121.
7. Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, Uchiyama S, Gotoh J, Nagao T, Yamamoto M, Takahashi J, Minematsu K. The Bleeding with Antithrombotic Therapy (BAT) Study Group: dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective multicenter observational study. *Stroke.* 2008;39:1740–1745.
8. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364: 331–337.
9. Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in atrial fibrillation. *Arch Intern Med.* 1996;156: 409–416.
10. Gorter JW. for the Stroke Prevention In Reversible Ischemia Trial (SPIRIT), and European Atrial Fibrillation Trial (EAFT) Study Groups. Major bleeding during anticoagulation after cerebral ischemia. Patterns and risk factors. *Neurology.* 1999;53:1319–1327.
11. Lip GY, Frison L, Grind M. SPORTIF Investigators. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J.* 2007;28:752–759.
12. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. Management of arterial hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2007;25:1105–1187.
13. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. Japanese Society of Hypertension Committee. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). *Hypertens Res.* 2009;32:3–107.
14. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW. PRoFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med.* 2008;359: 1225–1237.
15. Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD, Johnson DA, Mahaffey KW, Quigley EM, Harrington RA, Bates ER, Bridges CR, Eisenberg MJ, Ferrari VA, Hlatky MA, Kaul S, Lindner JR, Moliterno DJ, Mukherjee D, Schofield RS, Rosenson RS, Stein JH, Weitz HH, Wesley DJ. American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2008;52:1502–1517.
16. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet.* 2009;374:119–125.

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Sex-Related Differences in the Risk Factor Profile and Medications of Patients With Atrial Fibrillation Recruited in J-TRACE

Hiroshi Inoue, MD[1]; Takashi Nozawa, MD[1]; Tadakazu Hirai, MD[1]; Shinya Goto, MD[2]; Hideki Origasa, PhD[3]; Kazuyuki Shimada, MD[4]; Shinichiro Uchiyama, MD[5]; Takayuki Hirabayashi, MD[6]; Yukihiro Koretsune, MD[7]; Shiro Ono, MD[8]; Tooru Hasegawa, MD[9]; Yasuo Sasagawa, MD[10]; Yoshiaki Kaneko, MD[11]; Yasuo Ikeda, MD[12] for the J-TRACE Investigators

Background: Clinical characteristics, including risk factors for thromboembolism, and medications differ between men and women with atrial fibrillation (AF) in Western countries. Whether such a difference exists for Japanese patients with AF is unclear, so data from J-TRACE were used to investigate this issue.

Methods and Results: A total of 2,892 patients (2,028 men, 864 women; 70.3 years old) with AF were analyzed for the respective prevalences of risk factors and medications. CHADS2 score was calculated to determine thromboembolic risk level. Women were older (P<0.001), and more frequently had heart failure (P<0.001), and hypertension (P=0.051) than men. The proportion of subjects aged 75 years or older was higher among women than among men (P<0.001). CHADS2 score was therefore significantly higher in women than in men (2.05±1.29 vs 1.88±1.33, P<0.001). Sex-related differences were not observed for the prevalence of diabetes mellitus, myocardial infarction or ischemic stroke, nor did warfarin usage differ between men and women.

Conclusions: Sex-related differences were observed in the risk factor profile and medications of Japanese patients with AF. CHADS2 score was higher in women than in men. (*Circ J* 2010; **74:** 650–654)

Key Words: Atrial fibrillation; CHADS2 score; Clinical characteristics; Medications; Sex differences

Atrial fibrillation (AF) is a common cardiac arrhythmia seen in general practice as well as in the cardiology clinic. The prevalence of AF differs between men and women in Western countries,[1–3] and also in Japan.[4,5] Several studies have reported that there are sex-related differences in the clinical characteristics and medications of patients with AF.[6–10] A prospective, cohort study indicated that the effects of AF on the risk of stroke were greater in women than in men after adjustment for age and comorbidity.[9] Other studies also showed that AF is associated with an increase in cardiovascular events, including mortality and stroke, especially in women.[7,11,12] Some risk stratification schemes consider women to be at high risk for ischemic stroke,[13,14] while others do not.[15,16] However, because the sex-related differences in risk factors for cardiovascular diseases and medications of Japanese patients with AF have yet to be clarified, registry data for a large, nation-wide, multicenter, cooperative study, J-TRACE (The Japan Thrombosis Registry for Atrial Fibrillation, Coronary or Cerebrovascular Events),[17,18] were analyzed to address this issue in the present study.

Methods

The details of J-TRACE have been reported elsewhere.[17,18] Briefly, J-TRACE has a steering committee of 5 members and 41 regional coordinators selected from 10 regions of Japan (Appendix 1). Recruitment of patients to investigate risk factor profiles and current status of medications for risk factors and for prevention of cardiovascular events in patients with

Received November 4, 2009; revised manuscript received December 18, 2009; accepted December 21, 2009; released online February 20, 2010 Time for primary review: 19 days

[1]Department of Internal Medicine, University of Toyama, Toyama, [2]Department of Internal Medicine, Tokai University, Isehara, [3]Department of Biostatistics, University of Toyama, Toyama, [4]Department of Cardiology, Jichi Medical University, Shimotsuke, [5]Department of Neurology, Tokyo Women's Medical University, Tokyo, [6]Department of Cardiology, Sunagawa City Medical Center, Sunagawa, [7]Institute for Clinical Research, Osaka National Hospital, Osaka, [8]Department of Cardiology, Saiseikai Yamaguchi Hospital, Yamaguchi, [9]Department of Cardiology, Hakodate Medical Association Hospital, Hakodate, [10]Sasagawa Clinic, Niigata, [11]Medical & Biological Science, Gunma University, Maebashi and [12]Department of Internal Medicine, Keio University, Tokyo, Japan
Mailing address: Hiroshi Inoue, MD, The Second Department of Internal Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: hiroshi@med.u-toyama.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-09-0802

Table 1. Clinical Characteristics of Japanese Patients With AF

	Men (n=2,028)	Women (n=864)	P value
Age (years)	69.4±9.4	72.6±8.5	<0.001
≥75 years (%)	32.0	44.5	<0.001
Chronic AF* (%)	68.8 (1,062/1,543)	66.1 (462/699)	0.199
BMI (kg/m²)	23.8±3.2	23.4±4.1	<0.001
CHF (%)	17.0	27.1	<0.001
Hypertension (%)	57.2	61.1	0.051
DM (%)	19.1	16.7	0.125
Ischemic stroke (%)	29.4	26.3	0.089
VHD (%)	10.1	21.1	<0.001
MI (%)	7.6	5.9	0.096
HC (%)	25.1	35.5	<0.001
Drinker (%)	46.3	5.2	<0.001
Smoker (%)	21.2	4.3	<0.001
CHADS2 score	1.88±1.33	2.05±1.29	<0.001

Data are mean±SD or % of patients.
*In the myocardial infarction and stroke categories; subtypes of AF were not specifically determined.
AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; MI, myocardial infarction; VHD, valvular heart diseases including valve replacement; HC, hypercholesterolemia.

prior stroke, myocardial infarction (MI) or AF began in January 2005 and ceased in December 2006.

Study Population

Patients aged 20–90 years were eligible for enrollment if they had at least 1 of the 3 cardiovascular diseases (stroke, MI or AF). The study protocol was approved by an Institutional Review Board at each participating site and all patients gave informed consent. Those in the AF category, and those in the stroke and MI categories who also had AF, comprised the study subjects for this subanalysis of J-TRACE. Those in the recovery phase of acute MI or acute stroke were not eligible for enrollment in J-TRACE.

Baseline Characteristics

All subtypes of AF were included. AF was diagnosed electrocardiographically using standard diagnostic criteria. Risk factors and comorbidities were collected from the medical record as baseline data. Among them were hypertension, diabetes mellitus, hypercholesterolemia, valvular diseases, MI, ischemic stroke, congestive heart failure, smoking, and drinking. Regular use of medications, including anticoagulants, antiplatelet agents, and drugs for hypercholesterolemia, hypertension, and diabetes mellitus, was also determined from the medical record. Each patient's CHADS2 score[15] was calculated to determine the level of cardioembolic risk: 1 point was given for advanced age (≥75 years), hypertension, congestive heart failure, or diabetes mellitus, and 2 points for prior stroke or transient ischemic attack.

Statistical Analysis

Continuous variables are shown as the mean±SD, and categorical variables as percentages. Continuous variables were compared by analysis of variance or Student's t-test, and categorical variables with the chi-square test, with $P<0.05$ considered significant.

Table 2. Distribution of CHADS2 Scores

CHADS2 score	Men	Women
0	15.9	11.1
1	28.4	25.0
2	23.5	29.6
3	19.2	20.6
4	10.5	10.0
5	2.2	3.4
6	0.3	0.3

Figures are % of patients.
P<0.001 between men and women.

Table 3. Age and CHADS2 Score

	Age			P value
	<65 years	65–74 years	≥75 years	
Men	1.24±1.12 (n=572)	1.63±1.22 (n=808)	2.74±1.17 (n=648)	<0.001
Women	1.38±1.16 (n=153)	1.57±1.14 (n=326)	2.72±1.12 (n=385)	<0.001

Data are mean±SD.

Results

Risk Factor Profile

A total of 2,892 patients (2,028 men, 864 women; mean age, 70.3 years) with AF comprised the study group. Numbers of patients and their mean age in the 3 categories were as follows: AF category, 1,543 men (68.9±9.6 years old) and 699 women (72.4±8.5); stroke category, 399 men (70.6±8.4) and 141 women (73.0±8.3); MI category, 86 men (71.7±8.1) and 24 women (75.3±8.0). Their clinical characteristics are summarized in **Table 1**. Some of the characteristics exhibited differences by sex. Women were older (P<0.001), and more frequently had congestive heart failure (P<0.001), hypertension (P=0.051), valvular diseases or valve replacement (P<0.001), and hypercholesterolemia (P<0.001) than the men, but drank (P<0.001) and smoked (P<0.001) less frequently than men. The proportion of subjects aged 75 years or older was higher and body mass index was slightly but significantly lower in women than in men (P<0.001, each case). The prevalences of chronic AF, diabetes mellitus, MI, and ischemic stroke did not differ between men and women.

The CHADS2 score was slightly but significantly higher in women than in men (**Table 1**, P<0.001) because of their higher prevalence of older age (≥75 years), hypertension, and congestive heart failure. The distribution of CHADS2 scores differed significantly between men and women (**Table 2**, P<0.001). It increased with age for both men and women, but did not differ between men and women in any age group (**Table 3**).

Medications

Medications are summarized in **Table 4**. Use of warfarin and antiplatelet agents did not differ between men and women. Reflecting the differences in prevalence of hypertension and hypercholesterolemia between men and women, drugs for the treatment of these diseases were used more frequently in women than in men (P<0.001, each case). In contrast, use of antidiabetic drugs was similar in men and women.

There were no apparent sex-related differences in the rate of use of warfarin or aspirin at any CHADS2 score (**Table 5**).

Table 4. Medications at Baseline

	Men	Women	P value
Warfarin	73.1	72.7	0.807
Antiplatelet agents	37.9	36.0	0.328
Aspirin	32.1	30.8	0.504
Ticlopidine	5.0	5.0	0.316
Cilostazol	2.0	1.3	0.191
Antihypertensives	71.8	78.8	<0.001
ACEI	17.4	14.8	0.087
ARB	28.4	32.2	0.039
β-blockers	21.4	21.3	0.927
Calcium antagonists	36.4	42.5	0.002
Diuretics	18.6	33.4	<0.001
Lipid-lowering drugs	16.7	26.4	<0.001
Statins	14.9	23.7	<0.001
Antidiabetic drugs	10.6	10.9	0.825
Oral	8.7	8.6	0.921
Insulin	1.4	2.2	0.111

Data are % of patients.
Only major drugs for treatment of comorbidities and prevention of thromboembolism are listed (see Uchiyama et al[18] for more detailed information on medications in J-TRACE).
ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Table 5. Use of Warfarin and Aspirin at Each CHADS2 Score

CHADS2 score	Warfarin use (%)		Aspirin use (%)	
	Men	Women	Men	Women
0	57.9	61.4	32.3	28.1
1	68.9	66.2	33.9	31.4
2	74.8	73.8	30.6	32.0
3	84.9	77.0	26.9	30.3
4	81.1	87.2	34.4	29.1
5	77.3	79.3	31.3	27.6
6	83.3	66.7	83.3	66.7
P value	<0.001	0.001	0.008	0.852

Warfarin usage differed significantly among CHADS2 scores in both men (P<0.001) and women (P=0.001). It increased gradually from approximately 60% to 80% as the score increased from 0 to 3 for both men and women; thereafter it reached a plateau, except in the case of women with a score of 6. Aspirin usage also differed significantly among CHADS2 scores in men (P=0.008), but not in women (P=0.852). It did not show any apparent score-dependent increase as observed in the case of warfarin usage.

Discussion

The major findings of the present study are as follows. First, there were sex-related differences in the risk factor profile and medications of patients with AF recruited in J-TRACE. Women were older and more frequently had hypertension, valvular diseases, congestive heart failure, and hypercholesterolemia than men. The prevalence of diabetes mellitus, ischemic stroke, and MI did not differ between men and women. Second, CHADS2 score was consequently slightly but significantly higher in women than in men with AF. This sex-related difference could be largely related to the higher proportion of women aged 75 years or older. Third, no sex-related differences in the use of warfarin or aspirin were observed at any CHADS2 score.

Risk Factor Profile of Patients With AF

Reports from Western countries[6–10] suggest that sex-related differences could exist in the risk factors for cardiovascular diseases of patients with AF. In the present study, mean age was higher and the prevalence of hypertension also tended to be higher in women than in men, consistent with the previous reports;[6–9] however, the prevalence of congestive heart failure was also higher in women than in men in the present study, a finding that is inconsistent with those reports from Western countries.[6–9] Notably, the prevalence of diabetes mellitus and of a prior history of ischemic stroke were not consistent.[6–9]

Cohort studies of the general population in Japan have indicated that the prevalences of hypertension and diabetes mellitus are higher in men than in women.[19–21] The prevalence of cardiac diseases was not higher in women than in men with AF,[4,5] so the higher prevalences of hypertension and congestive heart failure in women with AF found in the present study do not simply reflect the prevalence of these diseases in the general population of Japan. Valvular disease is a well-known risk factor for AF,[22] especially for Japanese women.[23] Drinking and smoking could promote the development of AF,[22–25] and were present more frequently in men than in women in the present study, as in the general population of Japan.[4,5,19–21] The electrophysiological properties of the atria differ between men and women,[26] so greater comorbidity and age might be required for AF to develop in women than in men.

Thromboembolic Risk

A sex difference in CHADS2 score was found in the present study, a finding consistent with the ATRIA study.[7] In the Euro Heart Survey the score might have been higher in women than in men, because mean age and the prevalences of hypertension, diabetes mellitus, and prior ischemic stroke were significantly higher in women than in men.[9] In some studies the levels of biomarkers of a prothrombotic state were higher in women with AF than in men with AF.[27,28] These findings could explain the inclusion of female sex as a risk factor in some schemes for predicting thromboembolic events in patients with AF.[13,14] In fact, among patients with acute stroke, embolic infarction is observed more frequently in women than in men.[29] It is difficult to determine the reasons for the sex-related difference in thromboembolic risk; however, some components of the CHADS2 score were observed more frequently in women in the ATRIA study,[7] Euro Heart Survey,[9] and in the present study.

Medications

Registry studies in Western countries have indicated that warfarin usage does not differ between men and women.[6,9] In the present study, the rate of warfarin usage did not differ between men and women as a whole nor did it differ between them at any CAHDS2 score (**Table 5**). Warfarin usage is at present not necessarily less frequent in women than in men, as reported in earlier registry[6] and community-based cohort[30] studies.

Use of aspirin and antidiabetic drugs was similar in men and women; however, drugs for hypertension and hypercholesterolemia were used more frequently by women than by men. The latter finding might reflect the sex-related differ-