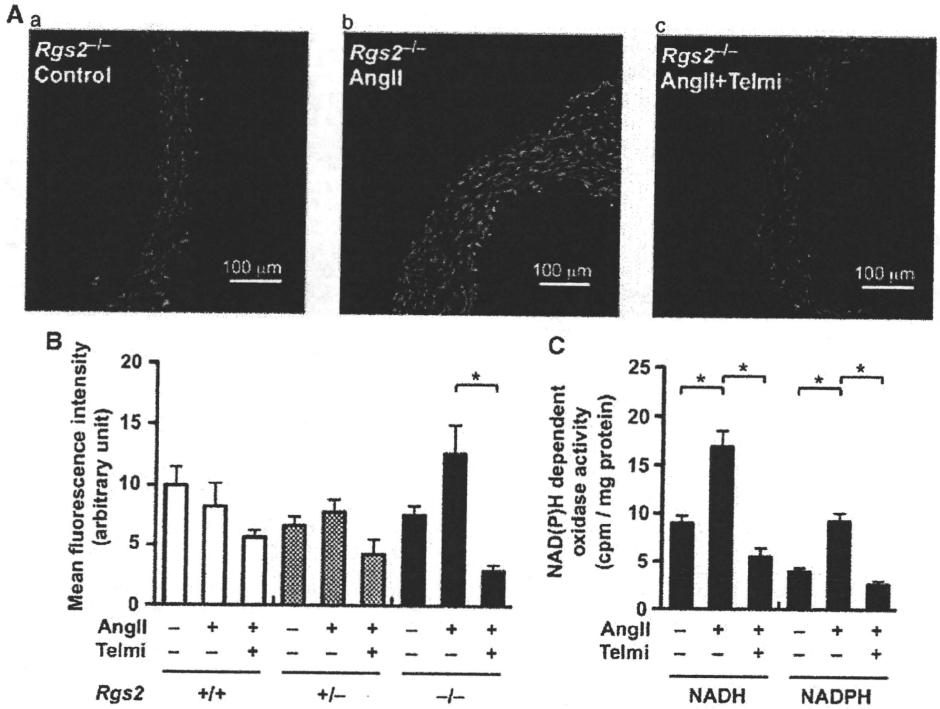

Figure 5 Comparison of oxidative stress in the aortic wall in mice treated with AngII or AngII plus telmisartan. (**A**), Representative photographs of *in situ* superoxide production in the aortic wall using dihydroethidium staining in $Rgs2^{-/-}$ mice of the Control group (a), the AngII group (b) and the AngII+Telmi group (c). (**B**), Quantitative analysis of superoxide production in the aortic wall. For quantification of ethidium fluorescence at the aortic wall, the fluorescence intensity was calculated using the ImageJ software and is expressed in arbitrary units. (**C**), Effect of telmisartan on NAD(P)H dependent oxidase activity of aorta homogenates using lucigenin-enhanced chemiluminescence in $Rgs2^{-/-}$mice. NAD(P)H oxidase activity was measured as described in Methods section. As a control, NADPH oxidase inhibitor, diphenyleneiodium, reduced NADH and NADPH oxidase activities below measurable limits. Results are expressed as mean ± s.e.m. in the control group ($Rgs2^{+/+}$: n=5, $Rgs2^{+/-}$: n=5, $Rgs2^{-/-}$: n=5), the AngII group ($Rgs2^{+/+}$: n=11, $Rgs2^{+/-}$: n=21, $Rgs2^{-/-}$: n=12) and the AngII+Telmi group ($Rgs2^{+/+}$: n=14, $Rgs2^{+/-}$: n=15, $Rgs2^{-/-}$: n=15). *$P<0.001$.

exacerbation of vascular phenotypes in all genotypes under our experimental condition. Thus, we examined the impact of Rgs2 deficiency on the therapeutic effect of low-dose telmisartan in AngII-infused mice.

The most interesting aspect of our study was the observed therapeutic efficacy of telmisartan. Low-dose telmisartan significantly improved survival, inhibited vascular remodeling such as aneurysmal formation and enlargement of aortic diameter, and decreased aortic oxidative stress in $Rgs2^{-/-}$ mice. These effects, mostly observed in the aorta, were independent of blood pressure reduction and were not observed in $Rgs2^{+/+}$ mice (Figures 2–5). In $Rgs2^{+/-}$ mice, low-dose telmisartan exhibited partial therapeutic effects such as improvement of survival, inhibition of aneurysm formation and reduction of enlarged aortic diameter, although there were no significant differences (Figures 2–4). These Rgs2 deficiency-dependent vascular protective effects of low-dose telmisartan could be explained by the following mechanisms. Some reports have shown that telmisartan and another ARB, valsartan, prevent vascular remodeling through inhibition of oxidative stress, inflammation and degradation of the extracellular matrix independent of their antihypertensive effects.[20,24–26] Heximer *et al.*[9] have reported that responsiveness to another ARB, candesartan, is more sensitive in $Rgs2^{-/-}$ mice than $Rgs2^{+/+}$ mice with regard to its antihypertensive and organ protection effects. Thus, vascular protective effects through inhibition of oxidative stress by low-dose ARB may be exaggerated in $Rgs2^{-/-}$ mice as a result of its antagonism for excessive AT_1R signaling. Moreover, some reports have characterized new functions of telmisartan as a partial agonist for peroxisome proliferator-activated receptors (PPARs).[22,23,27] Activation of PPARα by agonists or telmisartan induces an anti-inflammatory response through the repression of nuclear factor-κB signaling in umbilical vein endothelial cells and aortic smooth muscle cells *in vitro*[27,28] and inhibits macrophage infiltration and reduces aortic dilatation in a mouse model of aortic aneurysm.[29] PPARα and PPARγ improve lipid and glucose metabolism, respectively.[30] Low-dose telmisartan in $Rgs2^{-/-}$ mice improved lipid metabolism but did not affect glucose metabolism, as shown in the Table 1. Therefore, these protective effects of telmisartan in $Rgs2^{-/-}$ mice might be dependent on the anti-inflammatory response via PPARα activation, and Rgs2 deficiency might affect enhancement of the anti-inflammatory effect of telmisartan. Taken together, these results show that the therapeutic effect of low-dose telmisartan might be higher in the aorta of $Rgs2^{-/-}$ mice than in that of $Rgs2^{+/+}$ mice through both AT_1R blockade and PPARα activation.

Hypertension is a major risk factor of cardiovascular disease. Human *RGS2* genetic polymorphism is associated with the pathogenesis of hypertension in different races[11–14] that may result from Gαq-signal acceleration by RGS2 dysfunction. Our mouse study did not indicate a relationship between Rgs2 deficiency and the development of atherosclerosis and aneurysm *in vivo*. Instead, we found that low-dose telmisartan would be beneficial in AngII-induced vascular remodeling, dependent on Rgs2 deficiency and dysfunction. This

study suggests that ARB might be more useful for protection from cardiovascular events in hypertensive subjects with risk alleles in the *RGS2* gene than other antihypertensive drugs. This concept might be applicable for personalized medicine on the basis genetic information.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Enlargement of Acute Intracerebral Hematomas in Patients on Long-Term Warfarin Treatment

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Key Words
Intracerebral hemorrhage · Hematoma enlargement · Warfarin · Mortality

Abstract
Background: The relationship between warfarin administration and the frequent development of enlarged hematomas in patients with acute intracerebral hemorrhage (ICH) is controversial. The present study was carried out to examine this issue. ***Methods:*** This study reviewed 41 patients with nontraumatic ICH within 24 h after stroke onset from 1999 to 2003 who received long-term warfarin treatment (29 men and 12 women, 70 ± 12 years old) and 323 patients who had not been on warfarin (177 men and 146 women, 66 ± 13 years old). The hematoma volume (HV) on admission, final HV, frequency of hematoma enlargement (HE) and other background characteristics were investigated. ***Results:*** Both the HV on admission ($p = 0.031$) and final HV ($p = 0.001$) were larger in patients on warfarin than in those not receiving warfarin. HE occurred more frequently ($p < 0.001$), and mortality at 30 days or at discharge was higher ($p = 0.003$) in the warfarin group than in the control group. A multivariate adjusted logistic regression analysis 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 the National Institutes of Health Stroke Scale score (OR = 1.10, 95% CI = 1.04–1.15, $p < 0.001$, per 1-score increase) on admission were independently related to HE. ***Conclusions:*** Acute ICH in patients on long-term warfarin treatment appears to be associated with HE.

Introduction

A spontaneous intracerebral hemorrhage (ICH) is one of the most serious hemorrhagic complications associated with warfarin treatment. Oral anticoagulant therapy with warfarin not only increases the risk of ICH, but also worsens ICH outcomes [1–8]. It is unclear whether hematoma enlargement (HE) occurs more frequently or the final hematoma volume (HV) is greater in patients with acute brain hemorrhage who are on long-term warfarin treatment. Wintzen et al. [1] found no differences in the rate of progression, mortality or degree of recovery between patients with anticoagulant-associated hemorrhage and those with spontaneous intracranial hemorrhage. However, Franke et al. [3] demonstrated that the volume of the supratentorial hematoma was significantly greater in patients on anticoagulant treatment than in those not on anticoagulant therapy. Flibotte et al. [5]

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showed that hematoma expansion occurred more frequently in patients on warfarin than in those not on warfarin, and that hematoma expansion was associated with a trend toward increased 3-month mortality. Flaherty et al. [9] reported that warfarin use was associated with larger initial ICH volume when international normalized ratio (INR) values were >3.0; the results concerning HE were uncertain. The differences in these studies' results may be due to differences in the site and cause of bleeding, as well as the intensity of warfarin treatment.

To elucidate the relationship between hematoma size and long-term anticoagulant therapy, the HV and background characteristics of patients treated with warfarin were compared with those of patients not on warfarin. In addition, the clinical course of ICH patients on long-term warfarin therapy during the acute stage was compared to that of patients not on warfarin.

Methods

In this study, 424 consecutive patients with nontraumatic ICH who were admitted to the cerebrovascular division within 24 h after stroke onset from January 1999 to December 2003 were assessed. Patients were selected from the prospectively recorded database that included all inpatients admitted to the stroke care unit. Any patients with ICH due to an aneurysmal rupture, vascular malformations, hemorrhagic transformation after brain infarction and brain tumor, as well as those who experienced a hemorrhage primarily into the ventricles were excluded. Of the 424 patients, 60 were ineligible because they had been on antiplatelet therapy but not on anticoagulant therapy, and were thought not to be appropriate for the control group. The remaining 364 patients (206 men and 158 women, aged 66 ± 13 years) were therefore enrolled in the present study.

The medical records and computed tomography (CT) scans of the 41 patients who had been on long-term warfarin treatment (warfarin group) and the 323 patients who had not been on warfarin (control group) were reviewed. The first CT examination was performed exactly on admission, the second CT scan was performed routinely within 24 h after admission, and the third CT scan was performed within a few days after the second CT scan. Additional CT scans were performed if a patient deteriorated clinically. We reviewed the time interval from ICH onset to the first CT scan and the time interval from onset to the follow-up CT scan used for the determination of HE. The location, number, shape and volume of the hematomas as well as the presence of ventricular bleeding were noted. The locations of the hematomas were classified as putaminal, thalamic, combined, lobar, pontine, cerebellar, or other locations. All CT scans were reviewed and evaluated by neuroradiologists and neurologists who were blinded to the patients' clinical status. The time of ICH onset was defined as the time when the subject or a companion reported the acute onset of a neurological deficit. When the time of onset could not be clearly specified, the time that the subject was last known to be normal was taken as the time of onset.

The ICH volume was determined as follows [10–13]. The longest diameter (A) and the longest diameter (B) perpendicular to A were measured 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. To obtain the ICH volume, the 3 diameters were multiplied and then divided by 2 ($A \times B \times C/2$). Hemorrhage volume within the ventricular system was not assessed. The parenchymal hemorrhage was considered to have enlarged when the volume on the follow-up CT was 1.4-fold larger than the volume observed on the admission CT [14].

Admission HV, final HV, frequency of HE, and other baseline characteristics, such as age, gender, hypertension (a history of antihypertensive medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l, positive 75-gram oral glucose tolerance test, or a history of antidiabetic medication and insulin), hypercholesterolemia (serum total cholesterol ≥5.69 mmol/l or a history of antihypercholesterolemic medication), previous symptomatic ICH, previous symptomatic ischemic stroke, heart disease (including arrhythmia), liver disease (including cirrhosis, active hepatitis, alcoholic liver damage, and fatty liver), smoking habit (previous and current), and drinking habit (≥2 drinks per day) were compared between the two groups. In addition, the patients' systolic blood pressure, diastolic blood pressure, blood glucose, and INR for prothrombin time on admission were also assessed. In the acute stage, all patients had their systolic and diastolic blood pressures measured every 6 h after admission.

Each patient's neurological state was evaluated by a neurologist. The 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, grades 0–5) at 30 days or at discharge, whichever occurred sooner [15]. Death was assigned an mRS score of 6 [16].

Values are expressed as mean ± SD or median and interquartile range. The clinical characteristics of ICH patients on warfarin were compared to those of the ICH patients not on warfarin using the χ^2 test, unpaired Student's t test, and the Mann-Whitney U test as appropriate. A p value less than 0.05 was considered to be significant. The background characteristics of patients with and without HE were compared. To identify the independent predictors for HE, 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 a marginally significant ($0.05 \leq p < 0.1$) correlation with each indicator as independent variables based on univariate analyses.

Results

Thirty-six patients in the warfarin group were on warfarin only, and 5 were on both warfarin and antiplatelet therapy. The underlying diseases that required anticoagulation included: nonvalvular atrial fibrillation in 22 patients; mitral or aortic valve replacement in 7; deep vein thrombosis in 4; dilated cardiomyopathy in 3; coronary artery bypass graft for ischemic heart disease in 2; com-

Table 1. Clinical characteristics of the warfarin and control groups

	Warfarin group (n = 41)	Control group (n = 323)	p value
Age, years	69.9 ± 12.1	66.0 ± 12.9	0.067
Male gender	29 (71)	177 (55)	0.053
Smoking	24 (59)	133 (41)	0.035
Drinking	16 (39)	138 (43)	0.652
Hypertension	36 (88)	293 (91)	0.572
Diabetes mellitus	9 (22)	81 (25)	0.662
Hypercholesterolemia	15 (37)	103 (32)	0.545
Hypocholesterolemia	1 (2)	12 (4)	0.999
Heart disease	26 (63)	38 (12)	<0.001
Liver disease	4 (10)	41 (13)	0.802
Previous ischemic stroke	28 (68)	23 (7)	<0.001
Previous ICH	5 (12)	36 (11)	0.795
SBP at admission, mm Hg	173 ± 28	183 ± 30	0.036
DBP at admission, mm Hg	88 ± 18	98 ± 17	<0.001
INR ≥2.0	25 (63)	0 (0)	<0.001
Blood glucose, mmol/l	7.8 ± 3.2	8.2 ± 3.5	0.506
NIHSS score at admission	13 (6–27)	13 (8–19)	0.729
Time interval to the first CT, h	2.1 (1.0–5.6)	1.8 (1.0–3.2)	0.081
Characteristics of hematoma			
Admission HV, cm^3	33.5 ± 55.3	21.1 ± 28.3	0.022
Multiple hematomas	9 (22)	49 (15)	0.264
Intraventricular bleeding	21 (51)	140 (43)	0.339
Putaminal hemorrhage	11 (27)	132 (41)	0.083
Thalamic hemorrhage	23 (56)	113 (35)	0.009
Lobar hemorrhage	7 (17)	41 (13)	0.435
Pontine hemorrhage	2 (5)	35 (11)	0.234
Cerebellar hemorrhage	2 (5)	8 (3)	0.376
mRS at 30 days or at discharge			
Length of hospital stay, days	28 (18–32)	23 (19–31)	0.162
mRS score ≥3	27 (66)	240 (74)	0.249
In-hospital mortality (mRS score = 6), %	24	9	0.003

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

plicated atheromatous lesions at the aortic arch in 2, and peripheral arterial disease in 1. Of the 41 patients, 28 had a history of brain infarction.

The following baseline characteristics were more common in the warfarin group than in the control group: smoking habit ($p = 0.035$); heart disease ($p < 0.001$); previous symptomatic ischemic stroke ($p < 0.001$), and admission INR ≥2.0 ($p < 0.001$). Admission systolic ($p = 0.036$) and diastolic ($p < 0.001$) blood pressures were lower in the warfarin group than in the control group (table 1).

HV on admission ($p = 0.022$) was larger in the warfarin group than in the control group. There were significantly more thalamic hemorrhages ($p = 0.009$) in the warfarin group than in the control group (table 1).

Although the frequency of a clinically poor outcome (mRS score ≥3) based on the mRS at 30 days or at discharge was not significantly different between the two groups, in-hospital mortality (mRS score of 6) was higher in the warfarin group than in the control group ($p = 0.003$; table 1).

Of the 364 patients, 3 had neurosurgery and 15 died before a second CT examination could be performed within 24 h. HE in the remaining 346 patients was examined. Both HV on admission ($p = 0.031$) and final HV ($p = 0.001$) were larger in the warfarin group than in the

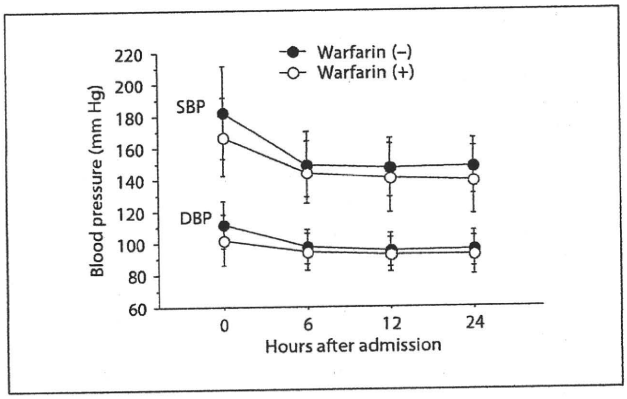

Fig. 1. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) every 6 h after hospitalization in patients on (open circle) and not on warfarin. The error bars show standard deviation. There were differences between the warfarin group and the control group in the SBP ($p = 0.004$) and the DBP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

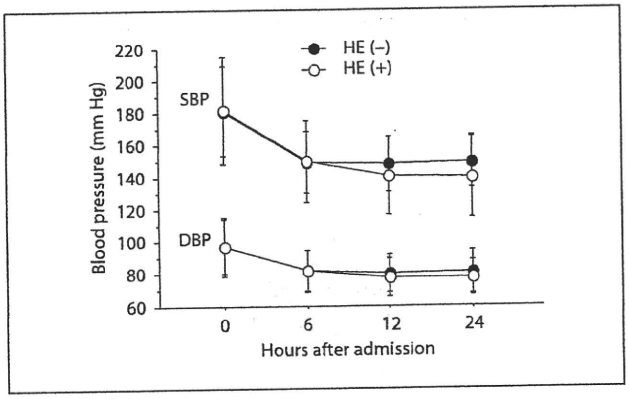

Fig. 2. Changes in the systolic blood pressure (SBP) and diastolic blood pressure (DBP) every 6 h after hospitalization in the HE group (open circle) and in the non-HE group. The error bars show standard deviation. Differences were observed between the HE group and the non-HE group in the SBP 12 h ($p = 0.002$) 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.

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

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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

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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.

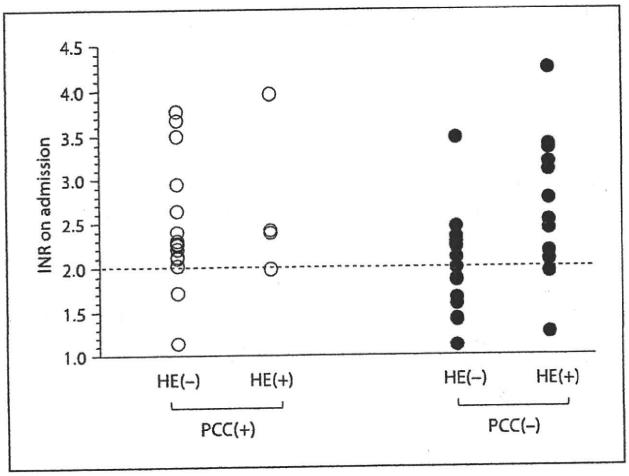

Fig. 1. HE according to INR value on admission shown on a scatter diagram. Though there was no significant difference in the frequency of HE between the PCC and the non-PCC groups for the whole group of 50 ICH patients on warfarin treatment, HE was more common in the non-PCC than in the PCC group (56 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

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Disclosure Statement

No conflicts of interest exists.

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Blood Pressure Levels and Bleeding Events During Antithrombotic Therapy

The Bleeding With Antithrombotic Therapy (BAT) Study

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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.

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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.

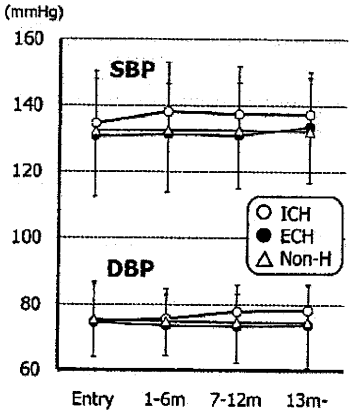

Figure 1. Time courses of BP. Average levels of SBP and DBP between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry are plotted. ICH indicates patients developing any symptomatic ICH; ECH, patients developing a life-threatening or major bleeding event other 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

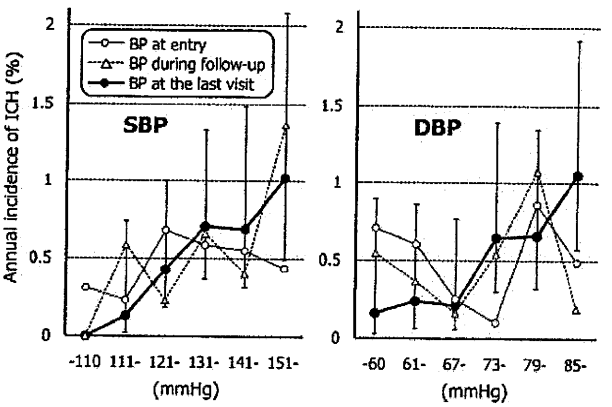

Figure 2. Annual incidence of ICH according to SBP and DBP levels. Bars indicate 95% CI for BP at the last clinic visit. "BP during follow-up" means average BP levels of all the follow-up measurements except for the levels at entry and at the last visit.