Intracranial Hemorrhage During Dabigatran Treatment
– Case Series of Eight Patients –
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Background: The incidence of intracranial bleeding during dabigatran treatment is lower than that during warfarin treatment. The characteristics of intracranial hemorrhage during dabigatran therapy, however, remain unclear. Methods and Results: The clinical data and treatment summaries of 9 intracranial bleeds that developed during dabigatran treatment in 8 patients with non-valvular atrial fibrillation were retrospectively reviewed. Five patients had small–moderate subdural hematomas, 2 had intracerebral hemorrhage and 1 had traumatic subarachnoid and parenchymal hemorrhage associated with cerebral contusion. Activated partial thromboplastin time upon admission ranged from 31.6 to 72.4 s. After admission, systolic blood pressure in the 2 patients with intracerebral hemorrhage was maintained below 140 mmHg, and the subdural hematomas in 4 patients were surgically treated. None of the hematomas became enlarged and outcome was good in most cases. Conclusions: Hematomas that arise due to acute intracranial bleeding during dabigatran treatment seem to remain small to moderate, hard to expand, and manageable. (Circ J 2014; 78: 1335–1341)

Key Words: Blood pressure; Dabigatran; Intracranial hemorrhage; Novel oral anticoagulant

The RELY phase III trial of dabigatran found a significantly lower incidence of intracranial bleeding in patients treated with dabigatran (150 and 110 mg b.i.d.) than with warfarin.1 The incidence of intracranial bleeding during dabigatran treatment is lower not only in patients younger, but also in those older than 75 years of age.2,3 Patients treated with warfarin sometimes develop intracranial hemorrhage and the outcome of such patients is poor due to the development of large hematomas and their subsequent expansion.4,5 The characteristics of intracranial hemorrhage during dabigatran therapy, however, remain unclear. Therefore, we analyzed data from 9 intracranial hemorrhages that developed in 8 patients treated with dabigatran.
plex concentrate, head computed tomography (CT) findings, hematoma size, hematoma expansion, surgical treatment, blood pressure control, diabetes mellitus, smoking habit and modified Rankin Scale (mRS) score before onset and at discharge. We also studied data regarding hypertension, renal dysfunction, liver disease, past history of stroke, major bleeding history, predisposition to bleeding, concomitant therapy such as antiplatelet and non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol (consuming ≥8 alcoholic drinks per week) according to HAS-BLED score criteria for evaluating risk of major bleeding.7 Chronic subdural hematoma (CSDH) was defined as follows: thickness <10 mm, small; 10–19 mm, medium; and >20 mm, large. We defined other intracranial hematomas according to diameters <15, 15–29 and >30 mm as small, medium and large, respectively.

### Case Reports

**Case 1** A 79-year-old man with NVAF treated with dabigatran (110 mg b.i.d.) underwent brain magnetic resonance imaging (MRI) to evaluate an unruptured intracranial aneurysm at the left anterior communicating artery. The size and shape of the aneurysm had remained constant and the patient had an asymptomatic 9-mm thick CSDH at the left frontal area (Table). Three days later, APTT was 31.4 s and follow-up brain CT indicated no change in the size of the hematoma. Dabigatran was switched to warfarin and the hematoma disappeared after 3 months without any symptoms.

**Case 2** Brain CT confirmed CSDH at the left frontal and temporal areas of an 87-year-old woman with atrial fibrillation treated with dabigatran (110 mg b.i.d.) who presented with headache and gait disturbance (Figure 1; Table). The physician in charge continued the dabigatran to avoid brain infarction, but the symptoms did not improve over the next 6 days.

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**Table. Case Series**

| Case No. | Age (years) | Gender | Time from onset to first CT | Type of intracranial bleeding | Recent head injury | Dose of dabigatran | Period since dabigatran commenced | APTT (s) at admission | Prothrombin complex concentrate | Size of hematoma | Expansion of hematoma | Surgical treatment | mRS before and after | Hypertension history | Anti-hypertensive medicine | BP at admission | BP before admission | BP control after admission | Diabetes mellitus | Creatin clearance (ml/min) | Renal dysfunction, creatinin ≥2.26 mg/dl | Liver disease | Stroke history | Prior major bleeding or predisposing to bleeding | Elderly ≥65 years old | Antiplatelet | NSAIDS | Alcohol | Smoking |
|----------|-------------|--------|-----------------------------|-------------------------------|--------------------|-------------------|---------------------|-------------------------------|------------------------|---------------------------|-----------------|---------------------|------------------|---------------------|----------------|---------------------|---------------------|----------------|---------------------|------------------|----------------|------------------|-----------------|--------|--------|--------|--------|
| 1        | 79          | M      | Asymptomatic                | CSDH                          | No                  | 110 b.i.d.        | 1 month             | 31.6                          | No                     | 1,500 IU                  | Small, 9 mm thick | No                  | None              | 0, 0 after 7 days | Yes                | No                   | 100/75             | 126/70         | Yes                | No               | No                  | Yes              | No                  | No                  |
| 2        | 87          | F      | 1 month                     | CSDH                          | Yes                 | 110 b.i.d.        | 6 months            | 47.2                          | No                     | No                       | Medium, 15 mm thick | No                  | Burr-hole evacuation | 0, 0 after 3 months | No                | No                   | 120/60             | 104/60         | No                 | No               | No                  | No               | No                  | No                  |
| 3        | 80          | F      | 19 days                     | CSDH                          | Yes                 | 110 b.i.d.        | 3 months            | 46.9                          | No                     | No                       | Medium, 14 mm thick | No                  | Burr-hole evacuation | 0, 0 after 2 weeks | No                | No                   | 156/89             | 112/81         | No                 | No               | No                  | No               | No                  | No                  |
| 4        | 86          | M      | On the day of symptom       | CSDH                          | Yes                 | 110 b.i.d.        | 1 month             | 37.5                          | No                     | No                       | Medium, 8 mm thick; right, 11 mm thick | No                  | Burr-hole evacuation | 0, 0 after 21 days | No                | No                   | 123/69             | 129/72         | No                 | No               | No                  | No               | No                  | No                  |
| 5        | 74          | M      | 4 days                      | CSDH                          | Yes                 | 110 b.i.d.        | 8 days              | 38.2                          | No                     | No                       | Medium, 19 mm thick | No                  | Burr-hole evacuation | 0, 0 after 28 days | No                | No                   | 130/79             | 124/82         | No                 | No               | No                  | No               | No                  | No                  |

(Table continued the next page.)
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### Case 4
An 86-year-old man given dabigatran (110 mg b.i.d.) for prevention of stroke associated with paroxysmal atrial fibrillation developed walking difficulties and started to fall easily (Table). Head CT showed bilateral CSDH, and APTT on admission was 37.5 s. Dabigatran was stopped and the hematoma was treated by burr-hole evacuation from which the patient fully recovered. Anticoagulant therapy was not restarted due to the patient and family's concern about the risk of recurrent hemorrhage.

### Case 5
A 74-year-old man treated with dabigatran (110 mg b.i.d.) fell and hit his head after consuming alcohol. He presented at a hospital 6 weeks later with gait disturbance, right hemiparesis and incontinence. Head MRI showed CSDH on the left side (Table), and APTT was 38.2 s. Burr-hole evacuation was done and he recovered uneventfully. Anticoagulation with dabigatran 110 mg b.i.d. was resumed.

### Case 6
An 87-year-old woman on dabigatran (110 mg b.i.d.) was referred to National Hospital Organization Kyushu Medical Center. Upon admission, APTT was 47.2 s and CT confirmed that the hematoma had not expanded. Dabigatran was stopped for 24 h, the hematoma was evacuated through a burr-hole and then dabigatran was started again 48 h later. The patient fully recovered.

| Case No. | Age (years) | Gender | Time from onset to first CT | Type of intracranial bleeding | Recent head injury | Dose of dabigatran | Period since dabigatran commenced | APTT (s) at admission | Prothrombin complex concentrate | Size of hematoma | Expansion of hematoma | Surgical treatment | mRS before and after | Hypertension history | Anti-hypertensive medicine | BP at admission | BP before admission | BP control after admission | Diabetes mellitus | creatin clearance (ml/min) | Renal dysfunction, creatinin >2.26 mg/dl | Liver disease | Stroke history | Prior major bleeding or predisposing to bleeding | Elderly ≥65 years old | Antithrombotic | NSAIDS | Alcohol | Smoking |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 86 | F | 1 h | Traumatic subarachnoid hemorrhage | No | 110 b.i.d. | 10 months | 45.8 | No | Small, diameter <15 mm | No | None | 0, 0 after 14 days | No | Normal | 149/84 | 128/61 | No | No | Normal | 35 | No | Normal | No | Yes | No | Ex smoker |
| 5 | 74 | M | 9 months | Hemorrhage in the contusion lesion | No | 110 b.i.d. | 9 months | – | – | Medium, diameter <30 mm | No | None | 0, 2 after 14 days | No | Normal | – | – | No | No | Normal | 38 | No | Normal | No | Yes | No | No |
| 6 | 87 | M | 3 months | Thalamic hemorrhage | No | 110 b.i.d. | 3 months | 44.7 | – | Medium, diameter <30 mm | No | None | 1 h and 20 min | No | Normal | 164/85 | – | NA | No | No | Normal | 55 | – | Normal | No | Yes, aspirin | No | No |
| 3 | 80 | F | 5 h and 30 min | Putaminal hemorrhage | No | 110 b.i.d. | 10 months | 72.4 | 500 IU | Medium, 5 ml, diameter <30 mm | No | None | 1 and 20 min | Yes | Normal | 154/90 | – | Yes <140 mmHg | No | Normal | Yes, aspirin | No | Normal | No | No |

Alcohol usage history, ≥8 drinks/week; CSDH, chronic subdural hematoma (thickness: <10 mm, small; 10–19 mm, medium; ≥20 mm, large); hypertension history, uncontrolled, systolic blood pressure >160 mmHg; liver disease, cirrhosis, bilirubin >2x normal, AST/ALT/ALP >3x normal; other intracranial hematoma: diameter <15 mm, small; 15–29 mm, medium; ≥30 mm, large; renal dysfunction, creatinin >2.26 mg/dl; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; mRS, modified Rankin Scale; NSAID, non-steroidal anti-inflammatory drug.
b.i.d.) to prevent recurrent cardioembolic stroke associated with NVAF fell and hit her head. She developed headache and presented at hospital, where head CT confirmed traumatic subarachnoid hemorrhage (Figure 2; Table). APTT was 45.8 s. Dabigatran was stopped for 4 days and resumed. One week later, she fell and hit her head again. Head CT showed a contusion on the right frontal lobe. Dabigatran was stopped for 7 days and the hematoma in the area of contusion was monitored. The hematoma did not expand and she recovered. Dabigatran (110 mg b.i.d.) was started once again.

**Case 7** A 92-year woman given dabigatran 110 mg b.i.d. with mRS 4 due to a previous stroke suddenly became unconscious and developed right hemiparesis. She was transferred to hospital 1 h 20 min later. Head CT showed a left thalamic

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**Figure 1.** Head computed tomography of an 87-year-old woman (case 2) on days 1, 6, 7 and 3 months thereafter. The arrows show that subdural hematoma on day 1 has not expanded by day 6. The patient fully recovered at 3 months after burr-hole evacuation on day 7.

**Figure 2.** Head computed tomography of an 87-year-old woman (case 6): (Upper) traumatic subarachnoid hemorrhage on days 1 (arrow) and 5; (Lower) head contusion on days 1 (arrow), 3 and 7.
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period and resulted in good outcome, is remarkable. Seven of the 9 episodes resulted in mRS scores of 0 or 1. The acute hematoma at the putamen was particularly small and did not expand, with good outcome of mRS 1 at discharge irrespective of advanced APTT of 72.4 s on admission. This phenomenon might have been due to not only strict blood pressure control in the 2 patients with intracerebral hemorrhage but also the characteristics of novel oral anticoagulants including dabigatran, which do not affect plasma concentration of factor VII or of complexes of tissue factor and factor VIIa that are essential for the first reaction in the coagulation cascade. Warfarin suppresses factor VII production even within the therapeutic range of prothrombin time, which is a reason why the incidence of intracranial hemorrhage and major bleeding are higher on warfarin than novel oral anticoagulants including dabigatran, and why acute intracranial hematoma developing during warfarin therapy easily expands.1,4,5,8–13

Another explanation might be that dabigatran interacts selectively and reversibly with the active site of the thrombin molecule but does not inhibit thrombin activatable fibrinolysis inhibitor generation, leading to downregulation of fibrinolysis and has a short half-life of 12–17 h, leading to early excretion from the body.1,14,15 It seems that recent findings of experimental studies are consistent with the present case series analy-

Discussion

That all 9 of the hematomas associated with CSDH as well as traumatic subarachnoid and intracerebral hemorrhages were small to moderate, remained unchanged during the observation period and resulted in good outcome, is remarkable. Seven of the 9 episodes resulted in mRS scores of 0 or 1. The acute hematoma at the putamen was particularly small and did not expand, with good outcome of mRS 1 at discharge irrespective of advanced APTT of 72.4 s on admission. This phenomenon might have been due to not only strict blood pressure control in the 2 patients with intracerebral hemorrhage but also the characteristics of novel oral anticoagulants including dabigatran, which do not affect plasma concentration of factor VII or of complexes of tissue factor and factor VIIa that are essential for the first reaction in the coagulation cascade. Warfarin suppresses factor VII production even within the therapeutic range of prothrombin time, which is a reason why the incidence of intracranial hemorrhage and major bleeding are higher on warfarin than novel oral anticoagulants including dabigatran, and why acute intracranial hematoma developing during warfarin therapy easily expands.1,4,5,8–13

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Because dabigatran treatment does not rule out hematoma expansion,
20 guidelines on how to reverse dabigatran activity in major hemorrhage need to be established. Reviews and experiments suggest that this can be rapidly achieved using 4-factor prothrombin complex concentrate, activated prothrombin complex concentrate and antibodies.

Hematomas that arise due to acute intracranial bleeding during dabigatran treatment seem to remain small to moderate, are unlikely to expand, and are manageable.

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