Efficacy of Dabigatran for Dissolving Deep Vein Thromboses in Outpatients With a Deteriorated General Condition

A Single Center Experience

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SUMMARY

Non-vitamin K antagonist oral anticoagulants (NOACs) have been widely used for the prevention of ischemic strokes in patients with nonvalvular atrial fibrillation (AF). At present, NOACs have been evaluated for the treatment of deep vein thrombosis (DVT). We examined the efficacy of dabigatran, the first NOAC for anticoagulation of AF in Japan, in outpatients who suffered from DVTs under a deteriorated general condition.

Thirty-six consecutive outpatients diagnosed with DVT at our institute were enrolled. Not all patients could be hospitalized due to other clinical problems; 15 (42%) had malignant tumors, 9 (25%) psychological disorders, and 6 (17%) postoperative orthopedic disease. Dabigatran was administered at a dose of 110-150 mg once or twice daily, depending on the renal function and age. The mean dosage of dabigatran was 211.7 ± 36.6 mg per day. In 18 (50%) patients, the DVTs were completely dissolved and disappeared over a treatment term of 4.3 ± 4.3 months. In 9 patients (25%), the DVTs partly dissolved, but in the remaining 9 (25%) patients, dabigatran was totally ineffective. During a follow-up of 30.5 ± 5.3 months, DVTs did not recur with dabigatran in 18 patients with an effective efficacy. In a multivariate analysis, patients with small sized thromboses and those without malignant tumors were significantly associated with the DVTs dissolving ($P = 0.003$ and $P = 0.006$, respectively).

Dabigatran was effective for dissolving DVTs in outpatients with a poor condition, particularly when the size of the DVT was small and malignant tumors were absent. (Int Heart J 2015; 56: 395-399)

Key words: Non-vitamin K antagonist oral anticoagulant, Thrombosis dissolution

Anticoagulant therapy is an important part of stroke prevention, and until 2011 it has been performed using vitamin K antagonists (VKAs), usually warfarin. Non-VKA oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban are currently used as effective drugs for the prevention of ischemic strokes in patients with nonvalvular atrial fibrillation (AF). The efficacy and safety of NOACs for the prevention of strokes or systemic thromboses due to nonvalvular AF have been confirmed in major clinical trials.¹⁾ Further, recent case studies have shown that NOACs can resolve left atrial thrombi associated with AF.²⁻⁵⁾ At present, NOACs have been evaluated for the treatment of venous thromboemboli (VTEs) that include deep vein thromboses (DVTs) and pulmonary thromboemboli (PTEs).⁶⁻⁹⁾ For the treatment of DVT, warfarin is highly effective;^{10,11)} however, it is difficult to control due to its narrow therapeutic range, food and drug interactions, and varying responses among individuals. Furthermore, it requires regular monitoring of the in-

ternational normalized ratio (INR). Thus, warfarin is not available for patients who cannot be hospitalized or attend a hospital regularly as an outpatient for treatment. In such patients, NOACs may be more useful because there is no requirement for monitoring. However, it is unclear whether NOACs have an effect on dissolving DVTs in such patients, particularly in patients with a deteriorated general condition.

The purpose of this study was to evaluate the clinical factors associated with dissolving DVTs using dabigatran, the first NOAC for anticoagulation of AF in Japan, in patients who could not regularly visit the outpatient clinic due to other clinical problems.

METHODS

Study population: Thirty-six consecutive outpatients (66.2 ± 15.0 years, 14 men) diagnosed with DVTs by examinations

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that were performed for abnormal blood tests or symptoms such as edema of the lower extremities at our institute were enrolled between June 2011 and September 2012.

Among these 36 patients, 15 (42%) had malignant tumors such as uterine cancer (2 patients), a malignant lymphoma (2 patients), lung cancer (2 patients), pancreatic cancer (2 patients), ovarian cancer (1 patient), gastric cancer (1 patient), breast cancer (1 patient), prostate cancer (1 patient), renal cell cancer (1 patient), a multiple myeloma (1 patient), or mandibular cancer (1 patient). Nine patients (25%) had psychological disorders such as schizophrenia (4 patients), depression (3 patients), or dementia (2 patients), and 5 patients (14%) had post-operative orthopedic disease. No patient had any organic heart disease, but 12 patients (33%) developed a PTE. All of the patients refused anticoagulation treatment during hospitalization, but agreed to receive it in the outpatient clinic with regular checks.

Dabigatran administration: In all patients, no warfarin was administered before the dabigatran, and no heparin bridging was performed during the treatment. Dabigatran was administered as an outpatient treatment at a dose of 110 to 150 mg once or twice daily, depending on the renal function and age of the patient.

During the enrolment period, no NOAC had yet been approved for the treatment of DVTs in Japan. Therefore, all patients provided written informed consent for the study protocol to receive the administration of dabigatran, which was approved by the institutional review boards.

Measurement of the APTT: The activated partial thromboplastin time (APTT) level was measured by the attending physician every time they checked the patients. The dosage of dabigatran was decreased when the APTT level was > 70 because of the increased risk of bleeding. Major and minor bleeding events were defined according to accepted guidelines.¹²⁾

Diagnosis of DVT or PTE: Bilateral ultrasound echography was performed in the outpatient clinic. This study included both acute and chronic DVT because we enrolled patients who were diagnosed with DVTs for the first time at our institute. In clinical practice, the exact determination of acute and chronic DVTs is difficult using bilateral ultrasound echography. The diagnosis of a DVT or PTE was established by a defect on at least two echocardiographic images. When a PTE was suspected, computer tomography using contrast was performed as necessary.

Moreover, magnetic resonance imaging of the head revealed no fresh infarctions or strokes before or after the anticoagulant therapy.

Follow-up: Patients were followed up in the outpatient clinic at 1 to 3 months after the diagnosis, and then further followed up either in the outpatient clinic or contacted by telephone every 6 months. DVT recurrence was assessed on the basis of the symptoms observed during each outpatient clinic visit. Freedom from DVTs was defined as no discovery of any DVT by bilateral leg echography. The attending physician checked for bleeding due to dabigatran by interviewing or examining the patient.

After 3 to 6 months, in the absence of any DVTs, the anticoagulant treatment was discontinued according to the request of the patient or their family unless other major risk factors were present.

Statistical analysis: Continuous variables are expressed as the

mean $\pm$ standard deviation or median (25–75%) value. Comparisons between patients with and without thrombotic disappearance were performed using an unpaired *t* test, Fisher's exact test, or Mann-Whitney test. A multivariate logistic regression analysis was constructed to assess the most significant indices as clinical factors for a thrombotic disappearance in the DVT patients. A *P* value of < 0.05 (2-tailed) was considered to indicate statistical significance. A receiver operating characteristic (ROC) curve for the thrombosis size was created by the area under the curve (AUC) to determine the cut-off point for a thrombotic disappearance.

All statistical analyses were performed using a commercially available computer software program (SPSS, version 18.0, Chicago, IL, USA).

RESULTS

Patient characteristics: The characteristics of the DVT outpatients in this study are shown in Table I. The mean body mass index (BMI) and body surface area were 23.2 ± 4.5 kg/m² and 1.58 ± 0.20 m², respectively. The mean D-dimer level before dabigatran was 11.5 ± 11.1 ng/mL and the mean D-dimer level after 3 months was 2.81 ± 3.37 ng/mL. The mean DVT length determined by echocardiography was 11.1 ± 9.2 mm.

Effect for dissolving thrombi: The mean dosage of dabigatran was 211.7 ± 36.6 mg per day. In 18 (50%) of the 36 patients, the DVT was completely dissolved during a treatment term of 4.3 ± 4.3 months. A typical patient in which the DVT was successfully dissolved is shown in Figure 1. When more than 90% of the DVT had dissolved, it was diagnosed as “partly” dissolved. Nine patients (25%) had partly dissolved DVTs. But, dabigatran was not effective in the remaining 9 (25%).

This study included 9 patients suffering from psychological disorders. Among these 9 patients, DVTs were dissolved in 5 (56%), but not in the remaining 4 (44%). All 9 patients had regularly taken dabigatran with the support of their family. The incidence did not differ from the total outcome.

During the follow-up of 30.5 ± 5.3 months, in the 18 patients with an effective efficacy, none had a recurrence of DVT

Table I. Patient Characteristics of the DVT Outpatients

Characteristic	n = 36
Age (years)	66.3 $\pm$ 15.0
Male, number (%)	14 (38.9)
Body mass index (kg/m ²)	23.2 $\pm$ 4.5
Body surface area (m ²)	1.58 $\pm$ 0.20
S-Cr (mg/dL)	0.76 $\pm$ 0.26
D-dimer pre (ng/mL)	11.5 $\pm$ 11.1
D-dimer post (ng/mL)	2.81 $\pm$ 3.37
APTT (seconds)	38.1 $\pm$ 7.8
Organic cardiac diseases, number (%)	0
Blood disorder, number (%)	0
Cancer, number (%)	15 (41.7)
Psychological disorder, number (%)	9 (25.0)
Pulmonary thromboembolism, number (%)	12 (33.3)
Dabigatran dose (mg)	211.7 $\pm$ 36.6
Thrombosis length (mm)	11.1 $\pm$ 9.2
Multiple lesion, number (%)	20 (55.6)

Continuous data are expressed as the mean $\pm$ standard deviation. S-Cr indicates serum creatinine; and APTT, activated partial thromboplastin time.

with dabigatran.

Complications due to dabigatran: During the anticoagulation treatment, no major bleeding events occurred, although minor bleeding was observed in 2 patients (1.6%). Nasal bleeding was observed in 1 patient (0.3%), and another patient (0.3%) developed intraoral bleeding.

Comparison between the two patient groups with and without thrombotic disappearance: Table II shows a comparison between the patients with and without a thrombotic disappearance. Univariate logistic regression analyses revealed that a small size (length) and the absence of cancer were significant

predictors of thrombotic disappearance after dabigatran administration ($P = 0.003$, $P = 0.006$, respectively). To test which predictor was most associated with a thrombotic disappearance, we performed a multivariate logistic regression analysis. Patients with a small sized thrombosis and those without malignant tumors were significantly associated with a dissolving DVT ($P = 0.003$ and $P = 0.006$, respectively).

The ROC curve of the thrombosis size for a thrombotic disappearance had an AUC of 0.764 (95% CI, 0.604–0.924; $P = 0.007$). A cut-off value of 8.4 mm (Figure 2) had a specificity of 66.7% and sensitivity of 83.3% for a thrombotic disappearance. The positive and negative predictive values for the cut-off value of 8.4 mm were 70.0% and 75.0%, respectively.

Figure 1. Echocardiographic images obtained on the first visit in a typical patient in whom a DVT was successfully dissolved. **A:** A large venous thrombosis in a left leg vein (white arrow) is shown. **B:** The thrombosis formation disappeared after 2 weeks on dabigatran 220 mg/day.

DISCUSSION

Main findings: The main findings of the present study were as follows. First, the DVTs were dissolved by dabigatran admin-

Figure 2. ROC curve of the thrombosis size for a thrombotic disappearance. The area under the curve was 0.764 (95% CI, 0.604–0.924; $P = 0.007$) and the cut-off point was 8.4 mm.

Table II. Comparison Between the Two Patient Groups With and Without a Thrombotic Disappearance

Parameter	Disappearance (n = 18)	Non disappearance (n = 18)	P
Age (years)	68.2 ± 13.8	64.3 ± 16.4	0.452 [*]
Male (%)	7 (38.9)	6 (33.3)	0.999 [†]
BMI (kg/m ²)	24.3 ± 5.4	22.1 ± 3.0	0.146 [*]
BSA (m ²)	1.57 ± 0.20	1.59 ± 0.21	0.796 [*]
S-Cr (mg/dL)	0.75 ± 0.21	0.77 ± 0.30	0.810 [*]
D-dimer pre (ng/mL)	10.63 ± 9.71	12.31 ± 12.64	0.741 [‡]
D-dimer post (ng/mL)	2.64 ± 4.22	2.99 ± 2.28	0.145 [‡]
APTT (seconds)	40.3 ± 8.8	36.0 ± 6.3	0.109 [*]
Cancer (%)	3 (16.7)	12 (66.7)	0.006 [†]
Dabigatran dose (mg)	201 ± 32	223 ± 38	0.068 [*]
Thrombosis length (mm)	6.77 ± 4.08	15.51 ± 10.77	0.003 [‡]
Multiple lesion	8 (44.4)	12 (66.7)	0.315 [†]

Data are expressed as the mean ± SD or number (%). P values were determined by an ^{*} unpaired t test, [†] Fisher's exact test, or [‡] Mann-Whitney test. BMI indicates body mass index; BSA, body surface area; S-Cr, serum creatinine; and APTT, activated partial thromboplastin time.

istration in the outpatient clinic. Second, multivariate analysis showed that a small sized thrombosis and the absence of malignant tumors were associated with a thrombotic disappearance.

Outcome of the thrombotic disappearance with dabigatran administration: Presently, there are no definite guidelines for the treatment of venous or intracardiac thrombi. However, we have empirically used warfarin in such cases.^{13,14)} Moreover, some case reports have demonstrated that left atrial thrombi were resolved by NOACs such as dabigatran, rivaroxaban, and apixaban.²⁻⁵⁾ For that reason, a relative predominance of plasma fibrinolytic activity over thrombin activity is the inference for the regression of the thrombi.¹³⁾ Also, there was a report about rivaroxaban causing looser clots, which were more sensitive to the fibrinolytic enzymes, Factor Xa inhibitors of thrombin, which may be the reason for the dissolution of the left atrial thrombi.^{15,16)}

We considered that it was difficult to judge whether a thrombus was an acute or chronic thrombus when it was observed clinically. Niemann, *et al*¹⁷⁾ reported that anticoagulation therapy with a VKA resulted in the resolution of fresh thrombi, but not old thrombi in the left ventricle after a myocardial infarction. Therefore, we believe that the resolved thrombus after dabigatran administration was acute and of a small size.

Relationship between malignant tumors and DVT: In the present study, among the 36 patients, 15 (42%) had cancer. Most of these patients were in a terminal state of cancer and 6 died during the follow-up period.

Patients with cancer have a 4-fold increased risk of developing a VTE relative to the general population.^{18,19)} They also have a 3-fold risk of recurrent VTEs and a 3-fold to 6-fold risk of major bleeding while receiving anticoagulant treatment with a VKA, as compared to patients without cancer.²⁰⁻²²⁾ At present, low molecular weight heparin therapy for 3 to 6 months is recommended as a first-line treatment to reduce the risk of recurrent VTEs in patients with active cancer.^{23,24)} Therefore, VKAs such as warfarin are not recommended.

Thus, as a result of the multivariate logistic regression analysis, we determined that patients with cancer and a DVT were hard to cure.

Condition of patients with psychological disorders: It is easy for psychological disorder patients to become complicated with venous thromboses²⁵⁾ and poor drug adherence in these patients is associated with serious problems.^{26,27)} In this study population, the presence of psychological disorders did not affect the outcomes of the DVT dissolution. The reason may have been all the patients had strong support from their families with confirmation of taking dabigatran every time, which means that the drug compliance was good.

Study limitations: This study has some potential limitations. First, it was a retrospective and observational study that did not compare the results with those in patients with VKAs, such as warfarin. Second, this study had a small sample size, which might have resulted in statistical bias. Nevertheless, the results were found to be clear and statistically significant.

Conclusion: Dabigatran was effective for dissolving DVTs in outpatients with a poor condition, particularly when the size of the DVT was small and malignant tumors were absent.

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