Anticoagulation is one of the most significant tasks for preventing stroke in atrial fibrillation (AF) patients.\(^1,2\) Dabigatran was approved and launched in Japan in late March 2011, and 6 months later more than 70,000 units had been sold. However, a considerable number of patients have had severe bleeding because of prescription of dabigatran to patients with contraindications (mostly severe renal dysfunction). Thus, an awareness of the need to screen candidates at risk for dabigatran therapy has developed.

**Methods**

**Data Collection**

Dabigatran was prescribed for the first time at the Cardiovascular Institute, Tokyo, on March 25, 2011 and subsequently, clinical data from 196 consecutive NVAF patients under dabigatran therapy had been collected by November 15, 2011. We recorded the status of these patients, including their backgrounds, the criteria for initiation or discontinuation of dabigatran, incidence of side effects, and the distribution of APTT (normal range, 25–35 s). Side effects included epigastric symptoms, diarrhea, and major and minor bleeding. Major bleeding was defined as bleeding events requiring hospital admission. Other bleeding was defined as minor. The Ethical Committee at the Cardiovascular Institute granted permission for this study, and all patients gave written informed consent. The study was performed in accordance with the Declaration of Helsinki.

**Statistical Analysis**

The categorical and consecutive data are presented as number (%) and mean±standard deviation, respectively. In addition, the percentages of adverse events (thromboembolic events, side effects, and discontinuation) are presented as ratios of the number of events and patients. The chi-square test and the unpaired t-test were used for group comparisons (Table). The peak (at 3 h after drug intake) and trough values (just before drug intake) of APTT obtained during hospitalization are presented using a boxplot (Figure A). The APTT values in the morning and afternoon at outpatient clinics are also presented using a boxplot (Figure B). Statistical analyses were performed using SPSS for Windows version 19.0 software. Statistical significance was set at a 2-sided P-value <0.05.

**Results**

**Characteristics of the Patients (Table)**

Our study included 140 (71.4%) men (mean age, 66.8 years).
The CHADS2 score was \( \geq 2 \) in 30.1% of patients. Approximately 40% of patients had been previously prescribed with warfarin. A low dose of dabigatran (220 mg/day) was administered to 119 (64%) patients. The following criteria were used for dose reduction: age (\( \geq 70 \) years; 69.0%), creatinine clearance (<50 ml/min; 9.5%), and use of verapamil and amiodarone (21.1% and 3.2%, respectively). No thromboembolic events occurred during the observation period (109.9 ± 75.2 days).

### Side Effects and Discontinuation (Table)
Side effects were observed in 35 (18.8%) patients. Epigastric symptoms was the most frequent (14.5%) side effect followed by minor bleeding (3.2%) and diarrhea (2.6%). Minor bleeding (n=6) included hematuria in 3 patients and bloody stool, hemorrhoidal bleeding, and subcutaneous bleeding in 1 patient each. No patient had major bleeding. The side effects were more prevalent in patients receiving a reduced dose than in those receiving the customary dose (P=0.011). Dabigatran was discontinued in approximately 28.1% of the patients because of side effects (7.1%) or a scheduled temporal use (12.2%).

### Distribution of APTT (Figure)
Among the hospitalized patients, APTT values with the customary dose (n=12) ranged from 36.3 to 52.6 s (mean, 44.9) and from 33.4 to 46.0 s (mean, 38.0) at the peak and trough, respectively, but those with a reduced dose (n=15) ranged more widely: 39.0–63.2 s (mean, 48.0) and 30.9–53.7 s (mean, 39.8) at the peak and trough, respectively (Figure A).

Among outpatients, APTT values with the customary dose ranged from 36.0 to 63.0 s (mean, 46.6, n=22) and from 37.0 to 65.0 s (mean 46.8, n=20) in the morning and afternoon, respectively, while those with a reduced dose ranged from 29.0 to 69.0 s (mean, 48.4, n=39) and from 28.0 to 65.0 s (mean, 44.2, n=31), respectively. In both groups, APTT sometimes showed a high value (Figure B).

### Discussion
We show here a wide variation in APTT among Japanese NVAF patients under dabigatran therapy, especially in those with a reduced dose. In the present study, although the APTT values in the hospitalized patients with the customary dose were distributed in
a relatively narrow range, they ranged more widely in those with a reduced dose and in those at the outpatient clinic, where some of them exceeded 60 s, twice the normal value. One possible explanation for the variation could be the low bioavailability of dabigatran etexilate, which is only 6%, and therefore, a slight change in absorption could affect the drug’s concentration.\(^3\) In addition, any variation would be easily augmented by renal dysfunction. Actually, in the present study, most of the patients with a reduced dose and showing a wide variation in APTT were older than 70 years, which could be linked to variable absorption and also renal dysfunction.

**Study Limitations**

First, our database consisted of a cohort at a single cardiovascular hospital. Therefore, the results should be carefully interpreted because the patients’ backgrounds, the criteria for usage, and the patient management might differ from other institutes. Second, although we sometimes found APTT >60 s in the present study, we could not analyze whether the high APTT values were directly linked to bleeding risk because of the small cohort and short observation period. This remains a matter for future investigations.

**Conclusions**

We showed a wide distribution of APTT values in Japanese NVAF patients under dabigatran therapy, which should aid in the screening of patients at a bleeding risk under dabigatran. Further studies are required to evaluate whether high APTT values obtained in daily clinical practice are associated with bleeding risk.

**Disclosure**

None declared.

**References**