Rivaroxaban was approved and launched in Japan in April 2012 as the second target-specific oral anticoagulant indicated for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). Although target-specific oral anticoagulants including rivaroxaban do not need regular monitoring, measuring their activity might be helpful in some clinical situations, including before urgent surgery, in the acute phase of a thromboembolic or bleeding event, or with suspected overdose.

Despite several limitations, prothrombin time (PT) may be a suitable parameter for assessing anti-Xa activity under rivaroxaban treatment, although its distribution in Japanese NVAF patients is still unclear. It is already known that PT is prolonged with an increase in rivaroxaban plasma concentration, so this study aimed to clarify the PT distribution, patients’ characteristics and clinical outcome in this cohort.

### Methods

**Data Collection**

Rivaroxaban was prescribed in 115 NVAF patients between May 21, 2012 and July 12, 2013. We recorded their status, including background details, criteria for the initiation or discontinuation of rivaroxaban, incidence of side effects, and the distribution of PT (reagent: HemosIL RecombiPlasTin 2G [Instrumentation Laboratory Company, USA]; analyzer: Coagtron-180 [Kyowa Hakko Kirin Co, Japan]; normal range, 9.7–12.9 s). PT values at 3 different time points were sampled: (1) anytime at the outpatient clinic (maximum value was used), (2) peak and (3) trough (3 h after drug intake and just before drug intake during steady hospitalization, respectively). Cre-atinine clearance (CCr) was calculated using the Cockcroft-Gault equation: CCr[ml/min] = (140−age[years]) × body weight[kg] / (72×serum creatine[mg/dl]) ×0.85, if female) × creatine. Side effects included major or minor bleeding and gastrointestinal symptoms. Major bleeding was defined as a bleeding event requiring hospitalization. The data collection was part of the Shinken Database, a prospective, hospital-based cohort of cardio-vascular diseases in an urban area of Japan, for which the Ethics Committee at the Cardiovascular Institute granted ethi- cal permission. All patients gave written informed consent.

**Statistical Analysis**

Categorical and consecutive data are presented as number (%) and mean±standard deviation, respectively. The chi-square test and the unpaired t-test were used for group comparisons (Table). The time-dependent PT distribution is presented using a scatter gram (Figure). Statistical analyses were performed using SPSS for Windows version 19.0 software (Chicago, IL, USA). Statistical significance was set at a 2-sided P-value <0.05.

### Background:

Prothrombin time (PT) distribution in Japanese nonvalvular atrial fibrillation (NVAF) patients under rivaroxaban therapy remains to be clarified.

### Methods and Results:

Between May 2012 and July 2013, 115 NVAF patients received rivaroxaban (PT was measured in 94; reagent: recombiplastin). In these patients, (1) PT values were distributed widely from patient to patient and from peak to trough, (2) the time-dependence was obscure with sampling at any time in the outpatient clinic, and (3) the incidence of adverse events was too low for analyzing the relation with PT.

### Conclusions:

We report the distribution of PT for Japanese NVAF patients under rivaroxaban therapy in real-world clinical practice. (Circ J 2014; 78: 763–766)

### Key Words:

Anticoagulation; Atrial fibrillation; Rivaroxaban

**R**ivaroxaban was approved and launched in Japan in April 2012 as the second target-specific oral anticoagulant indicated for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). Although target-specific oral anticoagulants including rivaroxaban do not need regular monitoring, measuring their activity might be helpful in some clinical situations, including before urgent surgery, in the acute phase of a thromboembolic or bleeding event, or with suspected overdose.

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### Table. Clinical Characteristics and Information Regarding Rivaroxaban Therapy in Patients With Nonvalvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Total n=115</th>
<th>15 mg n=89</th>
<th>10 mg CCR &lt;50 ml/min n=9</th>
<th>10 mg CCR ≥50 ml/min n=17</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td>88 (76.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>68.6±11.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body weight, kg</strong></td>
<td>67.1±10.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Creatinine clearance, ml/min</strong></td>
<td>77.9±23.4</td>
<td>80.3±20.6</td>
<td>43.8±8.1</td>
<td>85.1±28.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prothrombin time before starting any anticoagulants, s</strong></td>
<td>10.4±0.6 (n=27)</td>
<td>10.4±0.6 (n=22)</td>
<td>10.5±0.6 (n=2)</td>
<td>10.4±0.4 (n=3)</td>
<td>0.958</td>
</tr>
<tr>
<td><strong>CHADS2 score</strong></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 points</td>
<td>47 (40.9)</td>
<td>32 (36.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 point</td>
<td>31 (27.0)</td>
<td>24 (27.0)</td>
<td>2 (22.2)</td>
<td>5 (29.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>0 point</td>
<td>37 (32.2)</td>
<td>33 (37.1)</td>
<td>1 (11.1)</td>
<td>3 (17.6)</td>
<td>0.220</td>
</tr>
<tr>
<td><strong>CHA2DS2-VASc score</strong></td>
<td>0.048</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 point</td>
<td>96 (83.5)</td>
<td>71 (79.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point</td>
<td>19 (16.5)</td>
<td>18 (20.2)</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>0.135</td>
</tr>
<tr>
<td><strong>Previous warfarin use</strong></td>
<td>36 (31.3)</td>
<td>24 (27.0)</td>
<td>5 (55.6)</td>
<td>7 (41.2)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Previous dabigatran use</strong></td>
<td>29 (25.2)</td>
<td>22 (24.7)</td>
<td>1 (11.1)</td>
<td>6 (35.3)</td>
<td>0.273</td>
</tr>
<tr>
<td><strong>Antiplatelet use</strong></td>
<td>17 (14.8)</td>
<td>13 (14.6)</td>
<td>0 (0.0)</td>
<td>4 (23.5)</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Catheter ablation scheduled</strong></td>
<td>25 (21.7)</td>
<td>23 (25.8)</td>
<td>2 (7.7)</td>
<td>6 (35.3)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Use with electrical cardioversion</strong></td>
<td>3 (2.6)</td>
<td>3 (3.4)</td>
<td>0 (0.0)</td>
<td>0.343</td>
<td></td>
</tr>
<tr>
<td><strong>Use with chemical cardioversion</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Temporal use for noncardiac operation</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>History of bleeding diseases</strong></td>
<td>2 (1.7)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>0.356</td>
</tr>
<tr>
<td><strong>Criteria for renal dose (10 mg)</strong></td>
<td>–</td>
<td>–</td>
<td>9 (100.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Reasons other than creatinine clearance</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5 (58.8)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Co-administration of clarithromycin</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1 (5.9)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Dual antiplatelet therapy</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1 (5.9)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Oldest old (≥85 years)</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2 (11.8)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Physician’s discretion</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10 (58.8)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Patient’s request</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3 (17.6)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Thromboembolic events</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3 (17.6)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Transient ischemic attack</strong></td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>Systemic thromboembolism</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3 (17.6)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>8 (7.0)</td>
<td>4 (4.5)</td>
<td>1 (11.1)</td>
<td>3 (17.6)</td>
<td>0.130</td>
</tr>
<tr>
<td><strong>Epiagastic symptoms</strong></td>
<td>3 (2.6)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>2 (11.8)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Intracranial bleeding</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Major bleeding (extracranial)</strong></td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>Minor bleeding</strong></td>
<td>5 (4.3)</td>
<td>3 (3.4)</td>
<td>1 (11.1)</td>
<td>1 (5.9)</td>
<td>0.525</td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td>14 (12.2)</td>
<td>8 (9.0)</td>
<td>3 (33.3)</td>
<td>3 (17.6)</td>
<td>0.078</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>5 (4.3)</td>
<td>3 (3.4)</td>
<td>0 (0.0)</td>
<td>2 (11.8)</td>
<td>0.239</td>
</tr>
<tr>
<td><strong>Coincidence of bleeding diseases</strong></td>
<td>3 (2.6)</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>2 (11.8)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Elevation of prothrombin time</strong></td>
<td>1 (0.9)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.863</td>
</tr>
<tr>
<td><strong>Elevation of soluble fibrin monomer complex or D-dimer</strong></td>
<td>1 (0.9)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.863</td>
</tr>
<tr>
<td><strong>Temporal use for catheter ablation</strong></td>
<td>4 (3.5)</td>
<td>3 (3.4)</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>0.733</td>
</tr>
<tr>
<td><strong>Temporal use for cardioversion</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
</tbody>
</table>

The categorical and consecutive data are presented as n (%) and mean±standard deviation, respectively. The percentages of thromboembolic events, side effects, and discontinuation are presented as ratios of the number of events and patients. A transient ischemic attack occurred in a patient under a renal dose with CCR ≥50 ml/min (PT 18.3 s), and melena with colon diverticulitis also occurred in the same patient. Minor bleeding (n=5) included hematuria, nasal bleeding, subcutaneous bleeding, conjunctival bleeding, and oral bleeding in 1 patient each. Observation period was 85.2±80.5 days.
Figure. Time-dependent distribution of prothrombin time (PT) under rivaroxaban. Adverse events (AE) included any thromboembolism, and/or major/minor bleeding events. (A) Peak/trough PT values under rivaroxaban (3 h after/just before drug intake, respectively) during steady hospitalization (n=16). (B) Association between time-dependent PT and AE (n=94). (C) To identify differences in time-dependent changes of PT values in individual patients, all PT values obtained at the outpatient clinic were added to the trough/peak PT data in (A) with lines for each individual patient (n=16). Note that PT values in each patient were obtained on different days. CCr, creatinine clearance.
Results

Patients’ Characteristics and Outcomes
The patients’ characteristics are displayed in the Table. A renal dose of rivaroxaban (10mg/day) was administered to 26 patients, of whom only 9 had renal function determined (CCr <50ml/min). Other reasons for administering a reduced dose (n=17) were oldest old (≥85 years: 2), co-administration of clarithromycin and dual antiplatelet therapy (2), physician’s discretion (10), and patient’s request (3).

Distribution of PT (Figure)
For the hospitalized patients, PT values with the customary dose (15mg/day; n=16) at peak and trough ranged from 12.9 to 24.0 and from 10.1 to 12.3s (mean [95% confidence interval (CI)], 16.3 [14.7–17.8] and 11.1 [10.7–11.5]), respectively. Two sets of data were obtained for patients under a renal dose, in whom the peak/trough PT was 18.2/11.6s in the patient with CCr <50ml/min and 18.6/10.5s in the other with CCr ≥50ml/min (Figure A).

In the outpatients, PT values with the customary dose (n=75) ranged from 9.8 to 28.1s (mean [95% CI], 16.4 [15.5–17.3]), while for those under a renal dose with CCr <50 and ≥50ml/min (n=8/11), PT ranged from 14.2 to 24.0 and from 10.1 to 24.1s (mean [95% CI], 18.1 [15.5–20.8] and 16.6 [13.6–19.6]), respectively (Figure B).

To identify differences in the time-dependent changes of PT values in individual patients, all PT values obtained at outpatient clinic were added to the peak/trough values (Figure C).

Discussion
We report the distribution of PT values in real-world clinical practice in Japanese NVAF patients under rivaroxaban therapy in a cardiovascular hospital. In our patients, (1) PT values were distributed widely from patient to patient and from peak to trough, (2) the time-dependence was obscure with sampling at any time in the outpatient clinic, and (3) adverse events, including thromboembolism and/or major/minor bleeding, were too few for analyzing their relation with PT.

As is generally recognized, the serum concentration of rivaroxaban reaches a peak in 2–4h after intake and immediately decreases thereafter, which is supported by our peak/trough PT values. However, irrespective of such pharmacodynamics, our PT values for the outpatients consistently showed a wide distribution from morning to evening at any time during the daytime period at the outpatient clinic. The apparent discrepancy might be explained by wide variations among individuals in their response to and/or absorption of rivaroxaban. Therefore, careful interpretation of PT values should be made in consideration of the patient’s background, including age, renal function and timing of drug administration.

Our data are limited for several reasons, including the small population, selection bias of a single hospital-based cohort, and short follow-up period. More investigation will be necessary. Moreover, we should be aware that the different reagents used for PT are a concern. Our PT values, measured with recombinant tissue factor as the reagent, might underestimate the anti-Xa activity under rivaroxaban because it shows only a middle-range response to rivaroxaban compared with other reagents.

Conclusions
We report a sample distribution of PT values for Japanese NVAF patients under rivaroxaban therapy in real-world clinical practice, using data from a single hospital-based cohort. So far, the data are still limited, and much more future investigation is needed.

Disclosures
Dr Yamashita has received research grants from Boehringer-Ingelheim and Daiichi-Sankyo, and honoraria from Boehringer-Ingelheim, Bayer, Bristol-Meyers Squib, Pfizer and Daiichi-Sankyo.

References