The prevalence of atrial fibrillation (AF) has been increasing, and it is now the most commonly encountered form of arrhythmia in clinical practice. An epidemiological survey reported that the prevalence of AF in Japan was about 0.8 million in 2010 and is projected to exceed 1 million in 2030.

AF is not a lethal arrhythmia, but if left untreated, ischemic stroke occurs in approximately 5% of patients with non-valvular AF each year, thereby increasing its mortality rate. A meta-analysis of randomized trials showed that anticoagulation treatment significantly reduces the incidences of stroke and vascular events compared with aspirin; however, a recent randomized study reported that if adequate anticoagulation control was not achieved, no superiority of anticoagulant therapy over antiplatelet therapy was observed.

D-dimer is a fibrin degradation product that forms as a result of thrombogenesis and fibrinolysis. Increasing D-dimer levels may reflect atrial thrombus formation and higher embolic risks in patients with AF, and anticoagulant therapy may decrease D-dimer levels.

The relationship between anticoagulation control quality and D-dimer levels in patients with AF has not been thoroughly evaluated, so we prospectively examined it in the present study.

**Background:** Anticoagulation control quality affects the incidence of thromboembolic events in atrial fibrillation (AF) patients. However, the effects of anticoagulation control quality on the prothrombotic state of AF patients are unclear.

**Methods and Results:** Ninety-five AF patients who had been treated with warfarin were prospectively followed-up for 449±92 days. We analyzed whether time in the therapeutic range (TTR) of the international normalized ratio (INR) of prothrombin time, percentage of INR values in the range (%INR), and coefficient of variation of INR values (CV-INR) were related to D-dimer levels. The mean values of TTR, %INR, and CV-INR were 62%, 59%, and 0.19, respectively, and their median values were 67%, 63%, and 0.19, respectively. TTR was significantly correlated with %INR (R²=0.917, P<0.01), but not with CV-INR (R²=0.050, P=0.26). The mean and median D-dimer levels were 0.79 and 0.60 μg/ml, respectively. Low TTR, low %INR, and high CV-INR were found to contribute to high D-dimer levels (P=0.02, 0.03, and 0.02, respectively).

**Conclusions:** In AF patients treated with warfarin, not only the duration outside the target INR range, but also the fluctuation in INR level may influence the prothrombotic state. (Circ J 2012; 76: 317–321)

**Key Words:** %INR; Thromboembolic risk; TTR; Warfarin

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The dimer level was measured at the end of the follow-up period (August to October 2010). Patients were excluded from the analysis if the duration of their anticoagulant therapy was less than 6 months.

**Anticoagulation Control Measures**

The time in the therapeutic range (TTR) of the INR is the proportion of the estimated period in which the INR is within the target range to the total follow-up period. TTR was calculated using the method described by Rosendaal et al., which assumes that changes between consecutive INR measurements are linear over time. The percentage of INR values in the range (%INR) was calculated by taking the number of INR results within the target range and dividing it by the total number of INR tests performed during the follow-up period. CV-INR was defined as the coefficient of variation of the INR values for each patient. The target INR range was defined according to the Japanese guidelines for AF pharmacotherapy.

**Statistical Analysis**

Continuous variables are presented as the mean ± standard deviation together with 95% confidence intervals, and categorical variables are presented as the number of patients and/or percentage values. The patients were divided into 2 groups based on the median TTR value, and then the clinical characteristics of the 2 groups were compared. D-dimer levels were compared between the 2 groups divided according to the median values of TTR, %INR, CV-INR and percentage of the period below the target INR range. The significance of any differences was tested with Fisher’s exact probability test or the chi-square test for categorical variables and with the Student’s t-test for continuous variables. A P value <0.05 was accepted as statistically significant. The correlation between anticoagulation control measures was tested with Pearson’s correlation coefficient. The correlation between D-dimer levels and INR values measured at the same time was also tested with Pearson’s correlation coefficient. Data analysis was performed...
Anticoagulation Control Quality and D-Dimer in AF

Results

Baseline Patient Characteristics
The mean age of the patients was 69±10 years. Approximately half of the patients were ≥70 years old, and 79% were men (Table 1). The target INR range was 1.6–2.6 for all but 4 patients aged 70 years or more in whom the target INR range was defined as 2.0–3.0 because they had valvular AF. Permanent AF accounted for approximately half of the patients.

INR Tests and Anticoagulation Control Measures
The mean follow-up period was 449±92 days, and the mean interval between INR tests was 36±9 days (Table 2). INR was within the target range for 62% of the follow-up period. INR values lower than the target range accounted for 31% of the follow-up period, and those higher than the target range accounted for 7% of the follow-up period.

More than 80% of patients had at least 1 risk factor for stroke (eg, age ≥75 years, hypertension, diabetes mellitus, heart failure, or a history of stroke or transient ischemic attack). The mean CHADS2 score was 2.5±1.2.

with Statview version 5.0 for Windows (Abacus concepts, Piscataway, NJ, USA).

Figure 1. Relation between anticoagulation control measures. (A) Scatter plots of time in the therapeutic range (TTR) versus percentage of INR values in range (%INR). (B) Scatter plots of TTR versus the coefficient of variation of INR values (CV-INR). INR, international normalized ratio.

Figure 2. D-dimer levels and anticoagulation control measures. The patients were divided into 2 groups based on the median values of TTR (A), %INR (B), and CV-INR (C). D-dimer levels were significantly higher in the low TTR (TTR <67%), low %INR (%INR <63%), and high CV-INR (CV-INR ≥0.19) groups. The error bar indicates the mean±standard deviation. Abbreviations as in Figure 1.
The mean TTR, %INR, and CV-INR values were 62%, 59%, and 0.19, respectively, and their median values were 67%, 63%, and 0.19, respectively (Table 2). TTR significantly correlated with %INR (R²=0.917, P<0.01), but not with CV-INR (R²=0.050, P=0.26) (Figure 1).

Relationships Among Clinical Characteristics and TTR
The patients were assigned to the low TTR group (TTR <67%) or the high TTR group (TTR ≥67%) based on the median TTR value (Table 1). The proportions of elderly patients (≥70 years old) and patients with a target INR range of 1.6–2.6 were smaller in the low TTR group than in the high TTR group (P<0.01 for each). Among the comorbid conditions, only diabetes mellitus showed a significant difference in prevalence between the 2 groups (P<0.01).

Relationship Between Anticoagulation Control Measures and D-Dimer Levels
D-dimer level was measured in 86 (91%) of 95 patients (Table 2). The mean and median D-dimer levels were 0.79 and 0.60 μg/ml, respectively. D-dimer level was higher in the low TTR group than in the high TTR group (0.94±0.97 vs. 0.55±0.38 μg/ml, P=0.02) (Figure 2A). This was also true for %INR (0.92±0.97 for %INR <63% vs. 0.57±0.38 μg/ml for %INR ≥63%, P=0.03) (Figure 2B). D-dimer level was higher in the high CV-INR group (CV-INR ≥0.19) than in the low CV-INR group (CV-INR <0.19) (0.94±0.91 vs. 0.57±0.53 μg/ml, P=0.02) (Figure 2C).

D-dimer level was higher in patients with the period below the target range (≥20%) than in those with the period <20% (0.92±0.93 vs. 0.55±0.43 μg/ml, P=0.02) (Figure 3). D-dimer levels negatively correlated with INR values measured at the same time (R²=0.324, P<0.01) (Figure 4).

Discussion

Major Findings
The major findings of the present study are as follows. First, the mean and median TTR values were similar to those of %INR, and there was a significant correlation between TTR and %INR. Second, poor control of anticoagulation was associated with elevated D-dimer levels.

Correlation Between TTR and %INR
TTR and %INR are indicators of anticoagulation control quality. However, both indices have advantages and disadvantages. In the calculation of TTR, changes between consecutive INR tests are evaluated using linear interpolation. A previous study demonstrated the high validity and reproducibility of TTR, however, the process used to calculate TTR is too complex to allow it to be widely used in the clinical setting. In contrast, %INR is simple to calculate, but does not assess the actual number of days in which INR is within the target range.

In the present study, the mean and median TTR values were similar to those of %INR, and a significant correlation was detected between the 2 indices. In contrast, a previous study reported that the mean TTR value was lower than that of %INR. The difference in the interval between INR tests might have contributed to the difference between the present study (36 days) and the previous study (2 months or more). Because extreme out-of-range INR values could lower the TTR, these effects become stronger in proportion to the interval between INR tests. The present study results suggest that %INR approximates TTR and can be therefore used as a substitute for TTR.

Anticoagulation Control Quality and D-Dimer Levels
D-dimer levels are increased in patients with non-valvular AF and remain high compared with those of individuals displaying sinus rhythm even after warfarin treatment. Some previous studies have demonstrated a relationship between D-dimer levels and subsequent adverse events in AF patients receiving anticoagulant therapy. For example, Nozawa et al. reported that patients with higher D-dimer levels displayed greater incidences of cerebral infarction, transient ischemic attack, and peripheral artery embolism.
The correlation between anticoagulation control quality and D-dimer levels is still controversial. Some previous studies\(^{20,21}\) found no significant correlation between INR levels and D-dimer levels in patients with AF. However, anticoagulation control quality might not have been evaluated appropriately in those studies;\(^{20,21}\) a single determination of INR was used in the analysis. In the present study, TTR and %INR were adopted for the analysis, and low TTR and low %INR values were associated with high D-dimer levels. This result suggests that anticoagulation control quality influences the prothrombotic state of AF patients receiving anticoagulant therapy.

In the present study, D-dimer levels negatively correlated with INR values measured at the same time. Hence, thrombus formation could occur when the anticoagulation intensity is lower than the target INR range, and patients with a longer period below the target range had higher D-dimer levels. The majority of patients with low TTR or low %INR values controlled below the target range may have high D-dimer levels.\(^{22,23}\)

In the present study, a high CV-INR was also a determinant of high D-dimer levels. Nozawa et al reported that ischemic stroke occurred more frequently in patients in whom the anticoagulation control intensity fluctuated widely.\(^{24}\) It is unclear why fluctuations in the INR level contribute to thrombogenesis, but thrombus formation might be facilitated by the alteration in the balance between coagulation and fibrinolysis.

Study Limitations
First, although the patients were followed-up prospectively, their treatment was not selected in a randomized fashion. Second, the population of the present study was too small to draw a definite conclusion. Third, D-dimer level was only determined at the end of the follow-up period. Therefore, the results could have differed if D-dimer levels had been measured repeatedly. Fourth, because D-dimer levels vary widely from patient to patient, we compared D-dimer level between the groups of patients with equal to or higher than and those with lower than the median value of TTR, %INR or CV-INR, instead of using a collinear approximation of relation between these values. Finally, because of the strong correlation between TTR and %INR (R=0.917), it seemed less likely that differences could be evaluated correctly by multivariate analysis including these 2 parameters. Therefore, multivariate analysis was not performed.

Conclusions
Although our study is limited for the above reasons, it confirmed that %INR can substitute for TTR and that anticoagulation control quality influences the prothrombotic state of AF patients.

Disclosures
Financial support: none for any authors. Conflicts of interest: none for any authors.

References