Predictors of International Normalized Ratio Variability in Patients With Atrial Fibrillation Under Warfarin Therapy

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Background: Variability in the international normalized ratio (INR) of prothrombin time has been suggested to be related to outcome in patients with atrial fibrillation (AF) under warfarin therapy, but its determinants remain unclear.

Methods and Results: The study population consisted of 626 AF patients under warfarin therapy in the Shinken Database (n=22,230). INR variability was calculated by Fihn's method. Determinants of high log INR variability (defined as over mean-standard deviation) were determined by logistic regression analyses. Symptomatic heart failure (odds ratio [OR] 3.974, 95% confidence interval [CI] 2.510–6.292), older age (≥75 years old; OR 2.984, 95% CI 1.844–4.826) and severe renal dysfunction (eGFR <30 mL/min/1.73 m²; OR 3.918, 95% CI 1.742–8.813) were identified as independent predictors of high INR variability on multivariate logistic regression analysis.

Conclusions: The determinants of INR variability in AF patients under warfarin therapy could assist Japanese clinicians in identifying patients likely to show unstable warfarin control irrespective of the definition of the target INR range.

Key Words: Anticoagulation; Atrial fibrillation; International normalized ratio variability; Warfarin

Atrial fibrillation (AF) is associated with increased risks of ischemic stroke and death, both of which are reduced by anticoagulation therapy.1 Despite increased usage of direct oral anticoagulants (DOACs) in real-world practice,2,3 warfarin is still frequently used in patients with AF, presumably because of limited indications or the high medical cost of DOACs.

The anticoagulation intensity of warfarin therapy is monitored by the prothrombin time-international normalized ratio (INR). As poor INR control is closely associated with the incidence of adverse outcomes, including thromboembolism and bleeding,4-9 it is important to predict patients expected to have poor INR control. The time in the therapeutic range (TTR), which reflects the proportion of days within a target INR range, has been widely used for evaluating the quality of warfarin control10-12 and predictors of low TTR have been identified.13-15

Apart from the TTR, the concept of INR variability, reflecting stability of the INR under warfarin therapy, has been developed.16 Although INR variability has not been as clinically relevant as TTR, several reports have identified that it can predict adverse events, including bleeding and thromboembolism, under warfarin therapy, independently of TTR.8,9,17 The independency of INR variability and TTR is reasonable because the 2 measurements evaluate different aspects of INR control: INR variability measures the degree of instability of INR control,16 while TTR calculates the time period in which the INR is controlled within the therapeutic range.10 Accordingly, the predictors of poor control of INR based on INR variability may be different from those based on TTR. However, there have been few reports on the predictors of INR variability to date,18 and to our knowledge there have been no such studies in patients with AF.

In the present study, we identified independent predictors of INR variability in patients with AF under warfarin therapy in a single hospital-based cohort from the Shinken Database.19,21

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Methods

Study Population
The Shinken Database, which was established in June 2004, contains data on all new patients attending the Cardiovascular Institute Hospital, Tokyo, Japan (abbreviated in Japanese as ‘Shinken’), excluding foreign travellers and patients with active cancer. A total of 22,230 new patients were registered in the database up to March 2014.

We identified 1,154 patients with AF on warfarin therapy in this database. Among these, we screened for patients who received their first warfarin prescription within 90 days after the first visit and continued treatment for more than 12 months in the hospital. Accordingly, 626 patients fulfilling these eligibility criteria were included in the study (Figure 1).

Data Collection at the Initial Visit
After obtaining an ECG and chest X-ray, the cardiovascular status of each patient was evaluated by echocardiography, exercise test, 24-h Holter recordings and blood laboratory data when necessary. In addition to sex, age, height and weight, we collected data on cardiovascular diseases, including heart failure (HF: New York Heart Association class ≥2), valvular heart disease (moderate or severe stenosis or regurgitation on echocardiography), coronary artery disease, hypertrophic and dilated cardiomyopathy, and history of disabling cerebral infarction or transient ischemic attack. The presence of cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg on admission), diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin ≥6.5%), dyslipidemia (use of statins or drugs for lowering triglycerides, low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL or triglyceride ≥150 mg/dL), chronic kidney disease (estimated glomerular filtration rate [GFR] <60 mL/min/m²), chronic obstructive pulmonary disease and use of anticoagulant or antiplatelet medications. Body mass index was calculated as weight in kilograms divided by height in meters squared. The GFR was estimated using the new Japanese coefficient for the modified isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease study equation (GFR = 194 × Scr −1.094 × Age −0.287 × 0.739 [if female]).

Definition of AF
AF at the initial visit was diagnosed on 12-lead surface ECG and 24-h Holter recordings. It was also diagnosed based on any medical history of AF from referring physicians.

Measurement of Prothrombin Time
Prothrombin time was measured routinely (with intervals of 1–3 months) for dose adjustment of warfarin (reagent: HemosIL RecombiPlasTin 2G, Instrumentation Laboratory, Bedford, MA, USA; analyzer: Coagtron-180, Kyowa Hakko Kirin, Tokyo, Japan; normal range, 9.7–12.9 s). For calculation of INR variability, INR measured at the outpatient clinic between 3 and 12 months after initiation of warfarin therapy was used. The average frequency of INR measurement between 3 and 12 months was 7.4 ± 2.7 times (Figure 2). We excluded the in-hospital data points so we could exclude measurements performed under temporal discontinuation of warfarin because of surgery or bleeding.

INR Variability
INR variability was calculated by Fihn’s method with the following equation, which calculates the time-weighted INR variance:

\[
\sigma = \sqrt{\frac{1}{n-1} \sum_{i=2}^{n} \frac{(INR_i - INR_{i-1})^2}{\tau_i}}, \quad \tau = t_i - t_{i-1},
\]

The difference in 2 INR measurements was squared and divided by the time interval in days, and the values at each time interval were averaged. The INR variability was defined as its square root. We log-transformed INR
Patients’ Characteristics

The characteristics of the patients in the present study are shown in Table 1. Patients in the high-INR variability group were older, were more likely to be female and had lower body weight than those in the non-high-INR variability group. Moreover, the patients in the high-INR variability group had higher prevalence of ischemic heart disease, valvular heart disease, cardiomyopathy and symptomatic HF. Hypoalbuminemia, anemia and renal dysfunction were more prevalent, and renin-angiotensin inhibitors and class III/IV antiarrhythmic drugs were more often prescribed for patients in the high-INR variability group.

Predictors for High INR Variability

The results of univariate models of logistic regression analysis for high INR variability are shown in Table 2A. Using the factors significantly associated with high INR variability, the multivariate logistic regression analysis was performed (Table 2B). In the multivariate model, symptomatic HF (odds ratio [OR]: 3.974, 95% confidence interval [CI]: 2.510–6.292), older age (≥75 years old) (OR: 2.984, 95% CI: 1.844–4.826) and severe renal dysfunction (eGFR <30mL/min/1.73m²; OR: 3.918, 95% CI: 1.742–8.813) were identified as independent predictors of high INR variability.

Given that INR variability, by definition, is affected by the intervals of INR measurement, we additively performed a multivariate logistic regression analysis in subjects with relatively frequent INR measurement (INR measurement ≥6 times; excluding the lowest tertile of frequency of INR measurement). Accordingly, we obtained mostly consistent results as compared with those in the total patient cohort: the ORs of symptomatic HF, older age (≥75 years old) and severe renal dysfunction (eGFR <30mL/min/1.73m²) were 3.635 (95% CI: 2.151–6.144), 2.270 (95% CI: 1.296–3.974) and 3.398 (95% CI: 1.267–9.116), respectively.
Predictors of High INR Variability

Although the association between symptomatic HF and poor INR control has been reported previously, proper explanations have not been proposed. One possible mechanism may be unstable drug metabolism via liver dysfunction caused by congestive liver and/or renal dysfunction from the use of diuretics by patients with symptomatic HF, although it is not assumed there are so many outpatients in such an unstable state. Similarly, polypharmacy is often seen in patients with HF, especially those with a greater number of comorbidities, which would substantially modify the pharmacokinetics. Indeed, polypharmacy increases...

Table 1. Characteristics of AF Patients in a Study of INR Variability Under Warfarin Treatment

| Demographics | Total (n=626) | Non-high-INR var (n=519) | High-INR var (n=107) | P value |
|--------------|--------------|--------------------------|----------------------|---------|
| Age, years   | 65.8±11.5    | 65.2±10.9                | 68.7±13.6            | 0.004   |
| ≥75 years    | 147 (23.5)   | 102 (19.7)               | 45 (42.1)            | <0.001  |
| Male sex     | 457 (73.0)   | 383 (73.8)               | 74 (69.2)            | 0.340   |
| Body weight, kg | 64.4±13.8   | 65.0±13.9                | 61.5±13.0            | 0.020   |

Comorbidities and risk factors

Current smoker 67 (10.7) 56 (10.8) 11 (10.3) 1.000
Hypertension 329 (52.6) 258 (49.7) 71 (66.4) 0.002
Dyslipidemia (treated) 190 (30.4) 137 (26.4) 53 (49.5) <0.001
Diabetes 123 (19.6) 95 (18.3) 28 (26.2) 0.081
Chronic kidney disease 451 (72.0) 366 (70.5) 85 (79.4) 0.075
Ischemic heart disease 74 (11.8) 54 (10.4) 20 (18.7) 0.021
Valvular heart disease 105 (16.8) 71 (13.7) 34 (31.8) <0.001
Cardiomyopathy 54 (8.6) 39 (7.5) 15 (14.0) 0.037
Congenital heart disease 5 (0.8) 3 (0.6) 2 (1.9) 0.204
Symptomatic HF (NYHA ≥2) 181 (28.9) 123 (23.7) 58 (54.2) <0.001
Previous stroke or TIA 41 (6.5) 29 (5.6) 12 (11.2) 0.050
Previous hemorrhage 9 (1.4) 9 (1.7) 0 (0) 0.370
COPD 5 (0.8) 3 (0.6) 2 (1.9) 0.204
Paroxysmal AF 290 (46.3) 240 (46.2) 50 (46.7) 1.000
Persistent AF 336 (53.7) 279 (53.8) 57 (53.3) 1.000

Medications

β-blockers 74 (11.8) 64 (12.3) 10 (9.3) 0.510
RAS inhibitors 288 (46.0) 224 (43.2) 64 (59.8) 0.002
Class I antiarrhythmic agents 167 (26.7) 146 (28.1) 21 (19.6) 0.073
Class III antiarrhythmic agents 48 (7.7) 38 (7.3) 10 (9.3) 0.432
Class IV antiarrhythmic agents 127 (20.3) 101 (19.5) 26 (24.3) 0.291
Digoxin 144 (23.0) 120 (23.1) 24 (22.4) 1.000

Laboratory data

Albumin, g/dL 4.1±0.5 4.1±0.4 3.9±0.6 0.001
<3.5g/dL 46 (7.3) 29 (5.6) 17 (15.9) <0.001
eGFR, mL/min/1.73m² ≥60mL/min/1.73m² 50.5±15.4 51.6±14.5 45.4±18.1 <0.001
<60mL/min/1.73m² 141 (22.5) 120 (23.1) 21 (19.6) <0.001
30<eGFR<60mL/min/1.73m² 409 (65.3) 344 (66.3) 65 (60.7) <0.001
<30mL/min/1.73m² 42 (6.7) 22 (4.2) 20 (18.9) <0.001
Unknown 34 (5.4) 33 (6.4) 1 (0.9) <0.001
Hemoglobin, mg/dL 13.9±1.7 14.0±1.6 13.5±2.2 0.005
<11mg/dL 31 (5.0) 19 (3.7) 12 (11.2) 0.003
BNP, pg/mL 342.8±44.8 302.9±385.2 482.0±602.4 <0.001
Time in therapeutic range, % 62.5±27.2 63.7±27.6 56.6±24.6 0.015

Discussion

In the present study, we determined the predictors of high INR variability in AF patients under warfarin therapy using a single-center cohort in a cardiovascular hospital. The independent predictors of high INR variability in the present study were symptomatic HF, older age (≥75 years old) and severe renal function (estimated GFR <30mL/min/1.73m²). The results were mostly consistent when we excluded the patients with infrequent INR measurements.
INR Variability With Warfarin in NVAF

8 TTR reflects the achievement of appropriate anticoagulation intensity, and not necessarily stability, of the treatment regimen.

9 In contrast, INR variability measures the stability, but not intensity of anticoagulation. Therefore, the predictive capabilities of INR variability and TTR for thromboembolism and/or bleeding can be independent, and in some cases INR variability may be superior to TTR, as reported in a cohort of hospitalized AF patients.

5 In patients with non-adherence to the therapeutic regimen, TTR and INR variability would be closely associated with each other, which may partially explain why some of the factors associated with high INR variability were the same as those reported for low TTR.

Clinical Implications

The situation for estimating INR control is complex in Japan, because the Japanese guidelines recommend different target ranges of INR control according to age (i.e., 2.0–3.0 and 1.6–2.6 for patients <70 and ≥70 years, respectively). Moreover, several reports have suggested that a target INR of 1.6–2.6 for younger NVAF patients may be

| Table 2. Univariate and Multivariate Logistic Regression Analysis Showing the Factors Significantly Associated With High INR Variability |
|---------------------------------------------------------------|
| **A. Univariate models**                                      |
| Variables | OR (95% CI) | P value |
| **Female** | 1.256 (0.797–1.979) | 0.326 |
| Age ≥75 years | 2.967 (1.910–4.610) | <0.001 |
| Body weight <50kg | 1.687 (0.969–2.936) | 0.065 |
| Hypertension | 1.995 (1.290–3.087) | 0.002 |
| Dyslipidemia | 2.737 (1.787–4.191) | <0.001 |
| Ischemic heart disease | 1.980 (1.129–3.472) | 0.017 |
| Valvular heart disease | 2.939 (1.823–4.739) | <0.001 |
| Cardiomyopathy | 2.007 (1.062–3.790) | 0.032 |
| Symptomatic HF (NYHA ≥2) | 3.811 (2.477–5.863) | <0.001 |
| 2 or more comorbidities* | 3.454 (2.250–5.301) | <0.001 |
| Albumin <3.5 mg/dL | 3.192 (1.684–6.050) | <0.001 |
| eGFR ≥60 mL/min/1.73 m² | Ref. |  |
| 30≤eGFR<60 mL/min/1.73 m² | 1.080 (0.623–1.842) | 0.778 |
| eGFR <30 mL/min/1.73 m² | 5.195 (2.423–11.137) | <0.001 |
| eGFR unknown | 0.173 (0.022–1.335) | 0.092 |
| Hemoglobin <13 mg/dL | 2.158 (1.388–3.355) | 0.001 |

| **B. Multivariate model**                                      |
| Symptomatic HF (NYHA ≥2) | 3.974 (2.510–6.292) | <0.001 |
| Age ≥75 years | 2.984 (1.844–4.826) | <0.001 |
| eGFR ≥60 mL/min/1.73 m² | Ref. |  |
| 30≤eGFR<60 mL/min/1.73 m² | 1.012 (0.578–1.773) | 0.966 |
| eGFR <30 mL/min/1.73 m² | 3.918 (1.742–8.813) | 0.001 |
| eGFR unknown | 0.297 (0.038–2.344) | 0.249 |

| **C. Multivariate model (INR measurement ≥6)**                  |
| Symptomatic HF (NYHA ≥2) | 3.635 (2.151–6.144) | <0.001 |
| Age ≥75 years | 2.270 (1.296–3.974) | 0.004 |
| eGFR ≥60 mL/min/1.73 m² | Ref. |  |
| 30≤eGFR<60 mL/min/1.73 m² | 1.455 (0.738–2.867) | 0.279 |
| eGFR <30 mL/min/1.73 m² | 3.398 (1.267–9.116) | 0.015 |
| eGFR unknown** | – | – |

*Two or more of following comorbidities: hypertension, diabetes, dyslipidemia, ischemic heart disease, valvular heart disease, cardiomyopathy, previous stroke or TIA, previous hemorrhage, COPD, and chronic kidney disease. **OR for eGFR unknown was not determined for model C because of a lack of numbers. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

bleeding events in NVAF patients under anticoagulant therapy, which would be, in part, the result of INR instability.

Older age was associated with high INR variability in our study, suggesting that these patients were at high risk of poor INR control, consistent with previous reports that elderly patients were also associated with low TTR. These patients would have unstable pharmacokinetics because of low body weight, polypharmacy and/or liver and renal dysfunction.

Severe renal dysfunction was also associated with high INR variability in our study. It is rather difficult to explain the direct association between renal function and high INR variability because warfarin is almost entirely dependent on hepatic elimination. The possible explanation may be the linkage of higher age and estimated GFR, based on the equation itself, and accordingly concomitant medications and comorbidities, which are both characteristics of elderly patients and/or renal dysfunction.

It remains a matter of discussion whether INR variability and TTR measure different characteristics of anticoagulation control. TTR reflects the achievement of appropriate anticoagulation intensity, and not necessarily stability, of the treatment regimen. In contrast, INR variability measures the stability, but not intensity of anticoagulation. Therefore, the predictive capabilities of INR variability and TTR for thromboembolism and/or bleeding can be independent, and in some cases INR variability may be superior to TTR, as reported in a cohort of hospitalized AF patients. In patients with non-adherence to the therapeutic regimen, TTR and INR variability would be closely associated with each other, which may partially explain why some of the factors associated with high INR variability were the same as those reported for low TTR.
acceptable based on the results of risk-benefit analysis. In this regard, using TTR to evaluate the quality of INR control in NVAF patients is potentially confusing in current Japanese clinical practice. In contrast, it could be advantageous to discuss INR variability, which does not depend on the definition of target INR.

Our results will help physicians to identify patients likely to show unstable warfarin control irrespective of the definition of the TTR. If patients have risk factors for high INR variability, they may require frequent hospital visits to help achieve acceptable INR control.

Study Limitations
First, at present there is no agreed-upon method for calculating INR variability, they may require frequent hospital visits to help achieve acceptable INR control.

Study Limitations
First, at present there is no agreed-upon method for calculating INR variability, which would reflect the quality of INR control. This, in this analysis, INR variability was calculated by INR measurements between 3 and 12 months after commencement of warfarin administration, which would reflect the quality of INR control only in the early phase. Finally, our dataset did not include information on alcohol abuse or patients with severe liver/renal impairment, which potentially could affect the INR control.

Conclusions
The present study identified clinical factors related to high INR variability in AF patients under warfarin therapy. The determinants of INR variability in AF patients under warfarin therapy could assist Japanese clinicians in identifying patients likely to show unstable warfarin control irrespective of the definition of the target INR range.

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Conflict of Interest
S.S. received research funding and remuneration from Nippon Boehringer Ingelheim. T.Y. received research funding from Nippon Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Nippon Boehringer Ingelheim, Daiichi-Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Eisai and Ono Pharmaceutical.

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