Anticoagulation Stability Depends on CHADS₂ Score and Hepatorenal Function in Warfarin-treated Patients, Including Those with Atrial Fibrillation

Keita Odashiro¹, Taku Yokoyama¹, Mitsuhiro Fukata¹, Takeshi Arita¹, Toru Maruyama² and Koichi Akashi¹

¹Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan
²Faculty of Arts and Science, Kyushu University, Fukuoka, Japan

Aim: Although warfarin remains important despite the widespread use of nonvitamin K antagonist oral anticoagulants (NOACs), to date, the reality of warfarin use in the “NOACs era” is unclear. This multicenter observational study aimed to clarify the key factors contributing to warfarin treatment stability.

Methods: The practical use of warfarin, stability of warfarin therapy, and factors contributing to this stability were investigated in community-based hospitals through a real-world study. Clinical data were retrospectively extracted from the medical records of warfarin-treated Japanese patients (age, 71.3 ± 5.5 years) with atrial fibrillation (AF), prosthetic heart valve, or other concerns requiring anticoagulation. Treatment stability was considered as time in therapeutic range of international normalized ratio of prothrombin time (TTR: %). The factors contributing to TTR were investigated, including CHADS₂ score components.

Results: Mean CHADS₂ score was highest (1.38 ± 0.88, \(p < 0.001\)), and most CHADS₂ score components in addition to hepatorenal dysfunction were factors contributing to the low TTR in patients with AF (\(n = 176\)). The similarity was found in overall patients who were prescribed warfarin (\(n = 518\)). TTR decreased according to the CHADS₂ score component accumulation. Gender, dose and prescription interval of warfarin, and co-administration of antiplatelet agents did not correlate with the low TTR.

Conclusions: This retrospective study demonstrated that the CHADS₂ score component accumulation and hepatorenal dysfunction are factors significantly contributing to the low TTR, which is indicative of poor warfarin treatment stability, in patients such as those with AF.

Key words: Anticoagulation, Atrial fibrillation, CHADS₂ score, Hepatorenal function, Warfarin

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Introduction

In this decade, a marked change has occurred with respect to anticoagulation as a result of the worldwide use of nonvitamin K antagonist oral anticoagulants (NOACs). Anticoagulation is essential in patients with atrial fibrillation (AF), prosthetic heart valve, and deep vein thrombosis leading to pulmonary embolism. NOAC is globally characterized based on its noninferior or superior efficacy and safety relative to those of well-controlled warfarin in the worldwide clinical megatrials [1,4]. However, conventional warfarin cannot be completely converted to NOAC in anticoagulated patients, and warfarin has its specific value as a dose-controllable oral anticoagulant for the safety monitoring of patients requiring anticoagulation in whom NOAC is contraindicated. Because of this concern, there are limited data with respect to the real-world warfarin use and quality of warfarin care in this “NOACs era.” Therefore, this study aimed to clarify the reality of warfarin use, stability of this treatment, and factors affecting this stability in the registered outpatient clinics of the Japanese community-based hospitals.
Material and Methods

Study Population
Clinical data were collected for 518 patients (199 females and 319 males, mean age of 71.3 ± 5.5 years) who had been prescribed warfarin, a conventional vitamin K antagonist oral anticoagulant capable of strict dose adjustment under drug monitoring. All these patients were outpatients who had been followed up regularly at least for more than 6 months at one of the 11 community-based hospitals affiliated to the Kyushu University Hospital, Fukuoka, Japan. Patients who had been prescribed warfarin at a regular interval of longer than 56 days were included. Treating physicians were cardiologists who were familiar with the updated Guidelines of Japanese Circulation Society (JCS) concerning the indication of anticoagulation associated with warfarin or NOAC, reviewed the adherence of warfarin and advised outpatients to avoid foods rich in vitamin K when prescribed warfarin. Informed consent was obtained from all participants prior to the enrollment in the study. The study was approved by the individual institutional review board concerning ethics of clinical research and was conducted according to the updated Declaration of Helsinki (2008). The Department of Medicine and Biosystemic Science at the Kyushu University Hospital (Fukuoka, Japan) was responsible for the study design and data management.

Data Extraction
Baseline characteristics, laboratory findings, and medications were extracted from medical records in the outpatient clinic from April 2011 to December 2014. Routine examinations were performed regularly at the discretion of the treating physicians at the outpatient clinics. Hypertension was defined as a casual blood pressure of ≥140/90 mmHg and/or ongoing antihypertensive treatment. Diabetes was defined as a fasting serum glucose level of ≥126 mg/dl, casual serum glucose level of ≥200 mg/dl, HbA1c level of ≥6.5% based on the National Glycohemoglobin Standardization Program (NGSP), and/or ongoing antidiabetic medications. Dyslipidemia was also defined as a serum LDL cholesterol level of ≥140 mg/dl and/or serum HDL cholesterol level of <40 mg/dl or the prescription of lipid-lowering agents. AF recording was attempted based on the standard or ambulatory ECG performed at regular visits. Definitions of valvular, nonvalvular, paroxysmal, persistent or permanent AF were based on the updated Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS2013). Brain computed tomography (CT) or magnetic resonance imaging was performed for as many as possible enrolled patients. CHADS2 score is widely used to stratify the stroke risk in patients with AF and was calculated based on symptoms, physical findings, and medical records (1 point was assigned for the presence of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, whereas 2 points were assigned for an episode of stroke or transient ischemic attack). With respect to hepatorenal dysfunction, creatinine clearance (CCr: ml/min) was estimated using the Cockcroft–Gault’s equation and liver dysfunction was considered as an AST level of ≥40 IU/L and/or ALT level of ≥40 IU/L.

Anticoagulation
The anticoagulant efficacy of oral warfarin administration was evaluated based on the international normalized ratio of prothrombin time (INR), and the stability of this efficacy was estimated based on the time in therapeutic range (TTR: %), which shows the proportion of time spent in the optimal range of INR. Follow-up INR data were collected by reviewing outpatients’ medical records. In the Guidelines issued by JCS, the target range of INR varies depending on the indications of warfarin and patients’ age. In brief, the recommended INR for chronic thromboembolic pulmonary hypertension (CTEPH) is 1.5–2.5 and that for AF is 1.6–2.6 for aged patients (≥75 years) and 2.0–3.0 for the other patients with AF. Concerning mechanical heart valve prosthesis, there are no guidelines for optimal INR in the Guidelines issued by JCS. Therefore, optimal INR was set in the range from 2.0 to 3.0 according to the prospective domestic multicenter study in Tokyo district. These optimal INR ranges are set under the recognition that Japanese are less vulnerable to thromboembolic diseases and more vulnerable to intracranial hemorrhage than Caucasians. The enrolled patients were divided into three groups depending on the indication of warfarin: (1) patients with AF, (2) those undergoing heart valve replacement (HVR) with prosthetic valve, and (3) those with other concerns requiring anticoagulation. Hence, TTR was calculated according to the individually recommended range of INR. Actual calculation was performed using conventional Rosendaal method of linear interpolation between consecutive INR values in each patient. TTR does not reflect the short-term anticoagulating status of warfarin exposure. For the reliability of TTR, the cases with a calculation window of less than 56 days were excluded. One TTR value was obtained per patient with a calculation window of the latest 2–6 months.

Statistical Analysis
Continuous data were expressed as means ± SD,
Table 1. Baseline characteristics of the patients prescribed with oral warfarin

|                        | total (n=518) | AF (n=176) | HVR (n=161) | others (n=181) | p value |
|------------------------|--------------|------------|-------------|----------------|---------|
| gender (female/male)   | 199/319      | 71/105     | 60/101      | 68/113         | 0.810   |
| age (y.o.)             | 71.3±5.5     | 70.8±5.9   | 70.5±5.9    | 72.5±4.6       | 0.002   |
| albumin (g/dl)         | 3.3±0.3      | 3.3±0.3    | 3.4±0.3     | 3.4±0.3        | 0.144   |
| CCr (ml/min)           | 64.3±7.7     | 65.2±8.2   | 63.9±6.8    | 63.7±7.9       | 0.109   |
| congestive heart failure (%) | 19/518 (3.7) | 11/176 (6.3) | 3/161 (1.9) | 5/181 (2.8) | 0.073   |
| hypertension (%)       | 321/518 (62.0) | 138/176 (78.4) | 83/161 (51.6) | 100/181 (55.2) | <0.001 |
| diabetes mellitus (%)  | 67/518 (12.9) | 34/176 (19.3) | 10/161 (6.2) | 23/181 (12.7) | 0.002   |
| stroke (%)             | 11/518 (2.1) | 5/176 (2.8) | 3/161 (1.9) | 3/181 (1.7)    | 0.713   |
| CHADS2 score           | 1.15±0.86    | 1.38±0.88  | 0.91±0.88   | 1.15±0.77      | <0.001  |
| liver dysfunction (%)  | 20/518 (3.9) | 10/176 (5.7) | 2/161 (1.2) | 8/181 (4.4)    | 0.095   |
| warfarin dosage (mg)   | 1.5±0.7      | 1.5±0.8    | 1.5±0.7     | 1.4±0.7        | 0.675   |
| prescription interval (days) | 32±6       | 32±5      | 32±5        | 30±6           | 0.010   |
| TTR (%)                | 68.3±10.8    | 67.5±10.7  | 70.9±9.8    | 66.7±11.3      | 0.001   |
| antiplatelet therapy (%) | 73/518 (14.1) | 43/176 (24.4) | 14/161 (8.7) | 16/181 (8.8)  | <0.001  |

αCreatinine clearance (CCr) was calculated using Cockcroft-Gault’s equation. βTime in therapeutic range (TTR) was calculated by Rosendaal’s method.

Patients undergoing heart valve replacement (HVR) with prosthetic valve and showing atrial fibrillation (AF) were included to HVR group. All the continuous variables were not distributed normally, and intergroup comparison was performed by nonparametric method.

and discrete variables were shown as counts and percentage. Normality of continuous data distribution was examined using the Kolmogorov–Smirnov test. If data were not normally distributed, intergroup differences were compared by nonparametric analyses using the Mann–Whitney or Kruskal–Wallis test. Discrete variables were analyzed using the Fisher’s exact or Pearson’s χ² test. Univariate and multivariate analyses were performed to identify the factors affecting TTR for determining the treatment stability of oral warfarin administration. Multiple correlation analysis was used to evaluate the relationships between TTR and clinical indices. Thereafter, multiple regression analysis was performed to determine factors that significantly affect TTR. Regression coefficients (β) indicating difference in TTR per unit change in corresponding variables were obtained. None of the variables with missing data qualified. The criteria for entering into the regression model were data showing significant correlation coefficient or clinically meaningful data. When CHADS² score was incorporated, age was not incorporated into the regression model to avoid multicollinearity. Practical computation was performed using Predictive Analytics of Software 18.0 version for Windows package (SPSS, Inc., IBM, Chicago, IL, USA). A difference with a two-sided p value of <0.050 was considered to indicate statistical significance.

Results

Patients’ Baseline Characteristics

Baseline characteristics of enrolled patients have been detailed in Table 1. Patients’ age ranged from 46 to 87 years with median age of 71 years. Distribution of CCr was 22–85 ml/min with a median CCr of 65 ml/min. Albumin distribution was 2.5–4.5 g/dl with a median value of 3.3 g/dl. With respect to the warfarin treatment, median dose and interval of prescription were 1 mg (1–5 mg) and 28 days (14–42 days), respectively. TTR ranged from 30% to 91% with a median of 70%. Mean TTR, dose, and interval of warfarin prescription did not differ depending on the heart valve (n=161), those undergoing HVR with prosthetic valve and showing atrial fibrillation (AF) were included to HVR group. All the continuous variables were not distributed normally, and intergroup comparison was performed by nonparametric method.

Distribution was found to be approximately equal in the three groups of enrolled patients: patients with AF (n=176), those undergoing HVR with prosthetic heart valve (n=161), and those with other diseases requiring warfarin (n=181). In the AF group, patients with nonvalvular AF (NVAF) formed the majority (n=161), whereas patients with permanent NVAF (n=48) and those with paroxysmal NVAF (n=53) were equally distributed. Patients with mechanical bi-leaflet valve and showing permanent AF were categorized as showing valvular AF and included in the
Table 2. Multivariate analysis of the contribution of clinical indices to TTR in AF patients (n=176)

| Variables                        | model 1 |          |         | model 2 |          |         |
|----------------------------------|---------|----------|---------|---------|----------|---------|
|                                  | $\beta$ | 95% CI   | $p$ value | $\beta$ | 95% CI   | $p$ value |
| Continuous                       |         |          |         |         |          |         |
| CCr (ml/min)                     | 0.43 (0.33) | 0.25–0.61 | <0.001  | 0.40 (0.31) | 0.21–0.58 | <0.001  |
| Discrete                         |         |          |         |         |          |         |
| liver dysfunction                | −9.54 (−0.21) | −15.44–−3.64 | 0.002  | −9.35 (−0.20) | −15.17–−3.53 | 0.002  |
| CHADS2 score                     | −3.83 (−0.32) | −5.40–−2.25 | <0.001  | −15.54 (−0.24) | −23.43–−7.65 | <0.001  |
| stroke                           |         |          |         |         |          |         |
| congestive heart failure         |         |          |         |         |          |         |
| hypertension                     | −7.40 (−0.17) | −13.46–−1.35 | 0.017  | −7.10 (−0.08) | −12.26–−2.00 | 0.024  |
| diabetes mellitus                | −3.93 (−0.15) | −7.29–−0.57 | 0.022  | −3.93 (−0.15) | −7.29–−0.57 | 0.022  |
| aging (≥75 years)                | −0.20 (−0.01) | −3.37–2.98 | 0.902  | −0.20 (−0.01) | −3.37–2.98 | 0.902  |

Regression coefficients ($\beta$), standardized $\beta$ (parenthesis) and 95% confidence interval (95% CI) of $\beta$ in individual variable are indicated. Coefficient of determination ($R^2$), global $\chi^2 (F)$ value and variance inflation factor (VIF) in model 1 were 0.40, 13.90 ($p<0.001$) and $\leq 1.36$, whereas those in model 2 were 0.43, 10.39 ($p<0.001$) and $\leq 1.48$, respectively.

HVR group. Patients with diseases other than AF or HVR included those with deep vein thrombosis (n=83) with or without CTEPH, markedly impaired left ventricular function (n=74) because of organic heart diseases such as old myocardial infarction or dilated cardiomyopathy, and inherent thrombogenic tendency (n=16). Hypertension ($p<0.001$) and diabetes ($p=0.002$) were significantly prevalent in the AF group compared with the other two groups. Consequently, CHADS2 score in AF group was greater compared with that in the other groups ($p<0.001$). Antiplatelet agents were more prescribed to patients with AF than to those in the other two groups ($p<0.001$). TTR in patients undergoing HVR was greater than that in those in the remaining groups ($p=0.001$).

Analysis in Patients with AF

Factors contributing to TTR were explored in patients with AF (n=176). Two multiple regression models were set to handle CHADS2 score as a single contributor (model 1) or individual CHADS2 component as a possible independent contributor (model 2). Table 2 shows the results of the two settings. CCr ($p<0.001$) and liver dysfunction ($p=0.002$) were factors significantly contributing to TTR in these two models, whereas CHADS2 score was a factor that significantly contributed to TTR both as a single component ($p<0.001$) and as an individual component ($p=0.001–0.022$) except for hypertension ($p=0.248$) and senescence ($p=0.902$). In both models, gender ($p=0.845–0.909$), dose ($p=0.297–0.307$) and prescription interval ($p=0.255–0.385$) of warfarin, and concomitant antiplatelet therapy ($p=0.596–0.612$) showed no contributions, whereas serum albumin showed marginal positive contribution to TTR ($p=0.039–0.052$). Concerning the overall multivariate model fitting, the coefficient of determination ($R^2$) was 0.40 and global $\chi^2 (F)$ value and variance inflation factor (VIF) in model 1 were 0.40, 13.90 ($p<0.001$) in model 1, whereas $R^2$ and $F$ values in model 2 were 0.43 and 10.39 ($p<0.001$), respectively. Variance inflation factor (VIF), indicative of multicollinearity, was $\leq 1.36$ in model 1 and $\leq 1.48$ in model 2.

Analysis in Overall Patients

Factors significantly affecting TTR were analyzed in all patients enrolled (n=518). Because all continuous data distributions were not normal ($p<0.001$), Spearman’s crude multiple correlation analysis was performed, and positive correlations among TTR vs. CCr, TTR vs. albumin, and CCr vs. albumin were highly significant. The same was true when age was set as a control variable (Table 3). Multiple linear regression analysis demonstrated that CCr ($p<0.001$) and albumin ($p=0.001–0.002$) positively contributed to TTR, whereas age negatively contributed to TTR ($p<0.001$). Liver dysfunction was a significant negative contributor to TTR ($p<0.001$). CHADS2 also affects TTR as a total score ($p<0.001$) and as individual components ($p=0.001–0.032$) as shown in Table 4. In contrast, gender ($p=0.480–0.567$), co-administration of antiplatelet agents ($p=0.515–0.999$), and dose ($p<0.184–0.309$) and prescription interval ($p=0.151–0.168$) of warfarin were not factors significantly contributing to the low TTR. $R^2$ was 0.34, global $F$ value was 13.90 ($p<0.001$), and VIF remained $\leq 1.13$ in model 1, and those in model 2 were 0.32, 10.39 ($p<0.001$), and $\leq 1.27$, respectively. Clinical variables of liver dysfunction and serum albu-
components (Fig. 1B). Gender, dose and prescription interval of warfarin, and co-administration of antiplatelet agents showed no significance in overall analysis or AF-limited analysis. Age distribution, average TTR, and CHADS2 score in this AF group are similar to those in a domestic registry of patients with AF anticoagulated with warfarin at the Fushimi district of Kyoto, Japan (TTR of 65.9% in elderly and mean CHADS2 score of 2.1 ± 1.3)\(^1\sub{14}\), implying that patients with AF enrolled in our study are similar to those enrolled in a standard community-based Japanese survey attempting primary prevention of ischemic stroke associated with NVAF as a cardiogeriatric rhythm disorder.

**Discussion**

**Main Findings**

The main findings of this retrospective multicenter observational study are as follows: (1) almost all CHADS2 components in addition to hepatorenal dysfunction are risk factors lowering TTR in the overall as well as patients with AF prescribed warfarin (Tables 2 and 4), (2) serum albumin reflecting nutritional status was also a factor positively contributing to TTR (Table 4), and (3) TTR and CCr showed evident decline according to the accumulation of CHADS2 components (Fig. 1B). Gender, dose and prescription interval of warfarin, and co-administration of antiplatelet agents showed no significance in overall analysis or AF-limited analysis. Age distribution, average TTR, and CHADS2 score in this AF group are similar to those in a domestic registry of patients with AF anticoagulated with warfarin at the Fushimi district of Kyoto, Japan (TTR of 65.9% in elderly and mean CHADS2 score of 2.1 ± 1.3)\(^1\sub{14}\), implying that patients with AF enrolled in our study are similar to those enrolled in a standard community-based Japanese survey attempting primary prevention of ischemic stroke associated with NVAF as a cardiogeriatric rhythm disorder.

**TTR in Warfarin Therapy**

To date, the use of warfarin is challenging because of narrow therapeutic range and highly variable patient responses; hence, frequent drug monitoring and appropriate dose regulation are required in patients. Warfarin is a racemic mixture of \(R\) and \(S\) enantiomers and is metabolized by the hepatic cytochrome P450s but not excreted by the kidneys. However, the importance of renal function on the clearance of drugs metabolized by the liver is reported. Abdelhafiz et al.\(^1\sub{15}\) demon-

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**Table 3.** Crude and age-adjusted correlation between the continuous variables (\(n=518\))

| Correlation       | \(r\)  | \(p\) value | \(r^*\) | \(p\) value* |
|-------------------|--------|-------------|---------|-------------|
| TTR vs. CCr       | 0.298  | <0.001      | 0.363   | <0.001      |
| TTR vs. albumin   | 0.239  | <0.001      | 0.305   | <0.001      |
| CCr vs. albumin   | 0.197  | <0.001      | 0.289   | <0.001      |

*Age-adjusted correlation with age as a control variable. \(r\), correlation coefficients.

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**Table 4.** Multivariate analysis of the contribution of clinical indices to TTR (\(n=518\))

| Variables                  | model 1 | model 2 |
|---------------------------|---------|---------|
|                           | \(\beta\) | 95% CI  | \(p\) value | \(\beta\) | 95% CI  | \(p\) value |
| Continuous                |         |         |            |         |         |            |
| age (years)               | −       | −       | −          | −0.42   | −0.21 − 0.27 | <0.001 |
| CCr (ml/min)              | 0.21 (0.15) | 0.10−0.31 | <0.001 | 0.21 (0.15) | 0.09−0.32 | <0.001 |
| albumin (g/dl)            | 4.07 (0.12) | 1.51−6.64 | 0.002 | 4.61 (0.13) | 1.97−7.24 | 0.001 |
| Discrete                  |         |         |            |         |         |            |
| liver dysfunction         | −12.60 (−0.23) | −16.69−8.51 | <0.001 | −12.96 (−0.23) | −17.16−8.75 | <0.001 |
| CHADS2 score              | −5.28 (−0.42) | −6.22−4.34 | <0.001 |               |          |            |
| hypertension              |          |         |            | −3.06 (−0.14) | −4.78−1.34 | 0.001 |
| episode of stroke         |          |         |            | −12.59 (−0.17) | −18.13−7.05 | <0.001 |
| diabetes mellitus         |          |         |            | −4.87 (−0.15) | −7.26−2.48 | <0.001 |
| congestive heart failure  |          |         |            | −5.01 (−0.09) | −9.60−0.42 | 0.032 |

Regression coefficients (\(\beta\)), standardized \(\beta\) (parenthesis) and 95% confidence interval (95% CI) of \(\beta\) in individual variable are indicated. \(R^2\), \(F\) value and VIF in model 1 were 0.34, 13.90 (\(p<0.001\)) and ≤1.13, whereas those in model 2 were 0.32, 10.39 (\(p<0.001\)) and ≤1.27, respectively.

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min were incorporated into these multiple regression models because serum albumin was age dependent (\(r=−0.103, p=0.019\)) rather than reflecting liver function (\(r=0.582\)). Fig. 1A demonstrated the distribution of patients under the different CHADS2 scores ranging from 0 to 5. Patients showing CHADS2 score of 1 were most prevalent in AF group. The same was true in the other two groups. Fig. 1B indicated the TTR and CCr as a function of CHADS2 scores. Both TTR and CCr showed evident decline according to the accumulation of CHADS2 components.
ally correlated to warfarin dose \((p=0.053)\) in our study. TTR was also dependent on age \((p<0.001)\), liver function \((p<0.001)\), and all CHADS\(_2\) components (Table 4). Because warfarin binds highly to serum albumin, anticoagulation is intensified in patients with hypoalbuminemia, as observed in the elderly\(^{17}\). These findings indicate that TTR reflects not only the

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**Fig. 1.** (A) Distribution of patients prescribed with warfarin under different CHADS\(_2\) scores. Patients include those with atrial fibrillation (AF, \(n=176\)), those who underwent mechanical HVR surgery (\(n=161\)), and those with other diseases requiring warfarin (\(n=181\)). (B) Time in therapeutic range of prothrombin time (TTR) and creatinine clearance (CCr) as a function of CHADS\(_2\) scores in all the enrolled patients requiring warfarin (\(n=518\)). Data are means \(\pm SD\).
quality of warfarin care but also the total measure of nutrition and multiorgan functions in warfarin-treated elderly at risk of frailty.\(^\text{18}\)

In our study, TTR in the HVR group was better than that of the other groups (\(p=0.001\)). Considering TTR as a performance measure of anticoagulation, physicians treating patients with HVR may regulate warfarin diligently, and patients experienced HVR are adherent to anticoagulation, indicating that recognition of prosthetic valve may dominate over that of AF in both patients and physicians. Contrarily, French National Survey indicated that poor warfarin control is observed in patients with prosthetic heart valve.\(^{19}\)

Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) survey of the US National Registry also concluded that low TTR is associated with prior heart valve surgery and frailty.\(^{20}\)

One reason for this discrepancy is the differences of study population and surgical procedure between westerners and Japanese, that is, French National Survey enrolled very old hospitalized patients (87 ± 4 years), and the majority of the HVR in ORBIT-AF survey of the US National Registry seems to be the recent bioprosthetic aortic valve replacement with or without coronary artery bypass grafting. In contrast, our study enrolled less old (71 ± 6 years) Japanese outpatients, and over the half of them had undergone mechanical mitral valve replacement for valvular heart diseases in a distant past. Importance of permanent warfarin care in the mechanical HVR may penetrate into the patients’ and physicians’ consciousness.

**CHADS\(_2\) Score as Multiple Predictors**

In spite of emergence and widespread of NOAC, the inclusive use of NOAC in the elderly is limited owing to absence of established reversal agents and lack of evidence in the large-scale postmarketing survey. Renal function is generally age dependent as assessed in our study (CCr vs. age: \(r=-0.178\), \(p<0.001\)). This may preclude the long-term use of NOAC in the elderly who constitute the majority of warfarin population, and we speculate another reason for warfarin selection. It is a goal of future studies to explore the warfarin eligibility including onset AF,\(^{24}\) postablative AF recurrence,\(^{25, 26}\) left atrial enlargement,\(^{27}\) and drug efficacy of rhythm-control in patients with NVAF.\(^{28}\)

Reportedly, multiple comorbidities such as heart failure and diabetes are independent predictors of suboptimal TTR\(^{20, 29, 30}\). The present study demonstrated that quality of warfarin care is dependent on most CHADS\(_2\) components and CHADS\(_2\) total score per se in Japanese patients with AF (Table 2). Moreover, CHADS\(_2\) score was found to be a powerful predictor of warfarin treatment quality in overall anticoagulated patients (Table 4).

**Strengths and Limitations**

The present study has potential strengths with respect to warfarin prescription by specialists in the real-world outpatient clinics in Japan. The prescription was according strictly to the updated JCS Guidelines concerning anticoagulation.\(^{6, 7}\) Consequently, average TTR obtained by this study reached the approved level of domestic multicenter trial\(^{14}\). CHADS\(_2\) score was found to be expandable to the patients with not only AF but also other diseases requiring warfarin to predict TTR. Our retrospective study, however, permits a few limitations. First one relates to the study design and limited sample size. Prescription other than warfarin depended strongly on the discretion of the treating physicians. Adherence of warfarin among three groups had to be compared under the different optimal INR range although the width of INR range was set equally at 1.0 among the three groups (i.e., 1.5–2.5 for patients with CTEPH, 1.6–2.6 for aged patients with AF (≥75 years), and 2.0–3.0 for the other patients with AF or those with HVR). CHADS\(_2\) components except for hypertension and senescence were found to be factors affecting TTR in the AF group (Table 2), indicating bias of hypertensive elderly accumulated in this group although these findings imply that hypertensive patients are prone to develop AF.\(^{31}\)

Second, pharmacogenomics of warfarin metabolism such as VKORC1 and CYP2C9 polymorphisms were not considered. With respect to this concern, Tomita et al.\(^{32}\) reported that these polymorphisms affect dose but not stability of warfarin therapy in Japanese patients with NVAF. Third, the present study should have added more comprehensive baseline characteristics including socioeconomic as in the other studies.\(^{20, 33}\) There are still so many patients anticoagulated with warfarin in this “NOACs era.” One reason was supposed to be renal impairment in the elderly. However, 8.7% of our subjects showed CCr < 50 ml/min in this real-world study that cannot explain so many warfarin population, and we speculate another reason for warfarin selection is the occurrence of new
Conclusions

A traditional anticoagulant of warfarin does not lose its importance even in the “NOAC era.” This retrospective observational study demonstrated that CHADS2 score and hepatorenal dysfunction are factors significantly contributing to the low TTR in overall as well as patients with AF prescribed with warfarin. Considering that warfarin has its specific values in geriatric medicine, it is important to improve TTR in the elderly and to extract unknown factors affecting TTR that is a total appropriate measure of warfarin therapy.

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Conflicts of Interest/Disclosures

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Appendix

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