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【 ORIGINAL ARTICLE 】

A Simple Formula for Predicting the Maintenance Dose of Warfarin with Reference to the Initial Response to Low Dosing at an Outpatient Clinic

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Abstract:

Objective The pharmacodynamic effect of warfarin varies among individuals, and its maintenance dose is widely distributed. Although many formulae for predicting the maintenance dose of warfarin have been developed, most of them are complex and not in practical use.

Methods and Materials Among 12,738 new patients visiting the Cardiovascular Institute between 2004 and 2009, we identified 127 patients (66.6±8.8 years, 89 men) with atrial fibrillation for whom warfarin was newly started with an initial dose of 2 mg/day and the international normalized ratio (INR) at 1 year after warfarin was started was within the therapeutic range. The prediction models for the maintenance dose were developed by an exponential equation and a first-order equation.

Results The initial response of the INR to the dose of 2 mg/day (initial INR) ranged from 1.00-3.24 (mean 1.43), while the maintenance dose of warfarin ranged from 0.5-14 mg (mean 3.8 mg). The maintenance dose showed an exponential correlation to the initial INR: (predicted maintenance dose) $=5.522\times$ (initial INR)$^{-1.556}$ ($R^2=0.795$, $p<0.001$). Excluding the patients with a poor response to the initial dose (initial INR <1.1, n=32) permitted a simple correlation with a first-order approximation: (predicted maintenance dose) $=-2.009\times$ (initial INR) $+6.172$ ($R^2=0.706$, $p<0.001$).

Conclusion We developed a simple formula for predicting the maintenance dose of warfarin using the initial response of the INR to low-dose warfarin.

Key words: atrial fibrillation, anticoagulants, warfarin

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Introduction

Although novel oral anticoagulants (NOACs) have become widely used (1, 2), the improvement of warfarin usage remains a topic of concern in reference to atrial fibrillation (3, 4) and mechanical valves (5). The merits of warfarin include its strong and continuous anticoagulative effect, although this effect unfortunately has significant inter- and intra-individual differences (6, 7). Therefore, the continuous measurement of the intensity and adjustment of dosing of warfarin is necessary. To this end, the intensity of the effect of warfarin is measured by the prothrombin time with the international normalized ratio (INR) (8).

When warfarin is newly started, the optimal dose for the therapeutic range is explored through trial and error. At this time, fluctuation of the INR is frequently observed, especially in the early phase after the initiation of warfarin (4). Naturally, such fluctuations increase the risk of thromboembolism or bleeding (9).

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Table 1. Characteristics of Study Subjects.

	n=127
Male / Female, n	89 / 38
Age, years	66.6±8.8
Body height, cm	162.7±9.2
Body weight, kg	61.5±11.3
Maintenance dose of warfarin, mg	3.76±1.84
Primary reason for anticoagulation, n (%)	
Atrial fibrillation, n (%)	127 (100)
Statin use, n (%)	13 (10.2)
Amiodarone use, n (%)	1 (0.8)

Empirically, the dose of warfarin is known to converge to a certain degree with an individual's pharmacokinetic characteristics, called a maintenance dose (10). Numerous studies have searched for predictors of an individual's maintenance dose of warfarin, including evaluations of the influence of environmental clinical factors, demographic variables, and variations in the CYP2C9 and VKORC1 genes (6, 11-14). In addition, algorithms for predicting the maintenance dose using these predictors have been developed (13-22). However, such algorithms have not been used in daily clinical practice because most of them are complex and require genetic testing. A simpler method for predicting the maintenance dose would therefore be helpful.

In line with this point of view, the initial response to warfarin should be focused on because it involves various individual characteristics related to the pharmacokinetics of warfarin (15, 18). Therefore we intended to develop a simple formula predicting the maintenance dose of warfarin through the initial response of the INR to a 2 mg dose.

Materials and Methods

Study population

Among 12,738 new patients visiting the Cardiovascular Institute between 2004 and 2009, we identified 434 patients for whom warfarin had been newly started (initial doses of 1 mg, 2 mg, 3 mg, and 4 mg for 20, 173, 227, and 14 patients, respectively). Among the 173 patients with an initial warfarin dose of 2 mg/day, we selected 127 with atrial fibrillation whose INR was controlled within the therapeutic range (1.6-2.6, regardless of age) (23-25) at 1 year after warfarin was started.

We collected the following patient information: (1) demographic characteristics [including the creatinine clearance (CCr); Cockcroft-Gault equation], (2) the primary indication for warfarin treatment, (3) dose of warfarin at 1 year after the initiation (the maintenance dose), (4) the initial response of the INR to the dose of 2 mg/day obtained at 2 to 4 weeks (initial response of the INR), (5) the INR under the maintenance dose, and (6) the use of concomitant drugs known to have clinically significant interactions with warfarin, including carbamazepine, phenytoin, rifampin, rifampicin, antibiotics, statins, and amiodarone. All subjects were Japanese.

Statistical analyses

First, we demonstrated the distribution of study patients according to the initial response of the INR and the maintenance dose of warfarin. We then displayed the relationship between the initial response of the INR and the maintenance dose using a scattergram, where we acquired a prediction formula that approximates the maintenance dose. Finally, we evaluated the correlation between the predicted maintenance dose and the actual dose using the coefficient of determination (R^2).

Statistical analyses were performed using the SPSS software program for Windows, version 19.0 (IBM, Armonk, USA). Statistical significance was set at a two-sided p value of <0.05.

Results

Patient characteristics in the present study (n=127) are summarized in Table 1. The mean age was 66.6±8.8 years, and men accounted for 70.1% of the population (n=89). No patients were taking carbamazepine, phenytoin, rifampin, rifampicin, or antibiotics. Statins and amiodarone were prescribed for 13 patients (10.2%) and 1 patient (0.8%), respectively.

The initial response of the INR ranged from 1.00-3.24 (mean 1.43) (Fig. 1). A total of 95 patients (74.8%) were below the therapeutic range (<1.6), and 32 (25.2%) showed a low response (<1.1).

At 1 year after the initiation of warfarin, the maintenance dose ranged from 0.5-14 mg/day (mean 3.8 mg/day) (Fig. 2). The INR under the maintenance dose ranged from 1.61-2.58 (mean 1.94).

The relationship between the initial response of the INR and the maintenance dose of warfarin is shown in Fig. 3, where the scattergram did not show a linear relationship but an exponential one. Therefore, we first fitted an exponential curve with the following approximation formula (Fig. 3A): (predicted maintenance dose) =5.522× (initial response of the INR)$^{-1.556}$ (prediction formula 1). The coefficient of determination (R^2) between the predicted dose and the actual dose was 0.795 [95% confidence interval (CI): 0.726-0.851, p<0.001].

When we excluded patients with a poor response to 2 mg/day (initial response of the INR <1.1, n=32), we found a linear relationship between the initial response of the INR and the maintenance dose and were able to fit it to a first-order approximation (n=95, Fig. 3B): (predicted maintenance dose) =−2.009× (initial response of the INR) + 6.172 (prediction formula 2). The coefficient of determination (R^2) was 0.706 (95% CI: 0.588 - 0.793, p<0.001). After excluding patients with a low initial response of the INR (n=95), we analyzed the relationship between various clinical variables and the maintenance dose of warfarin. The results of

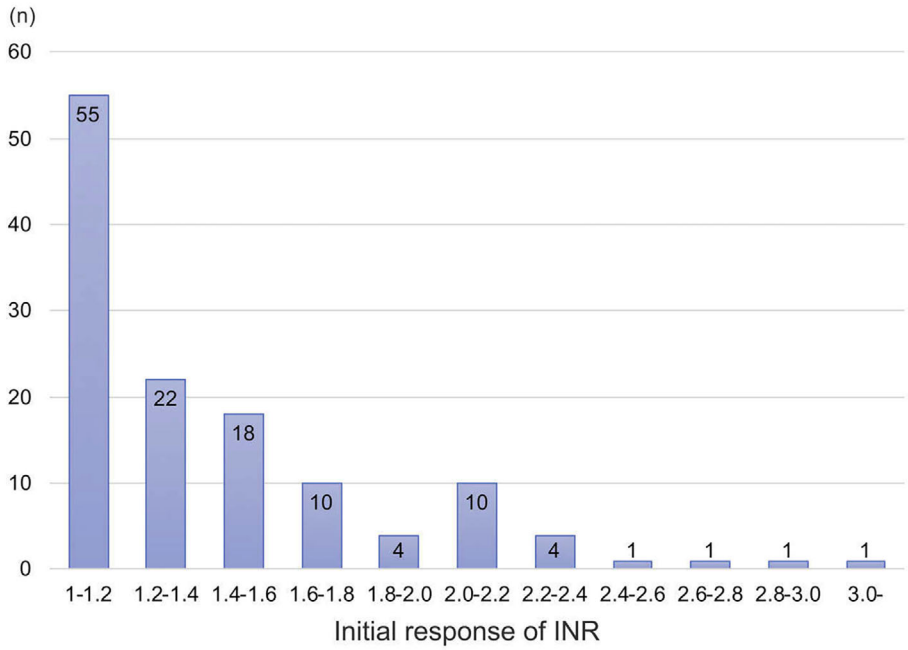

Figure 1. **The distribution of the study patients according to the initial response of the INR.**

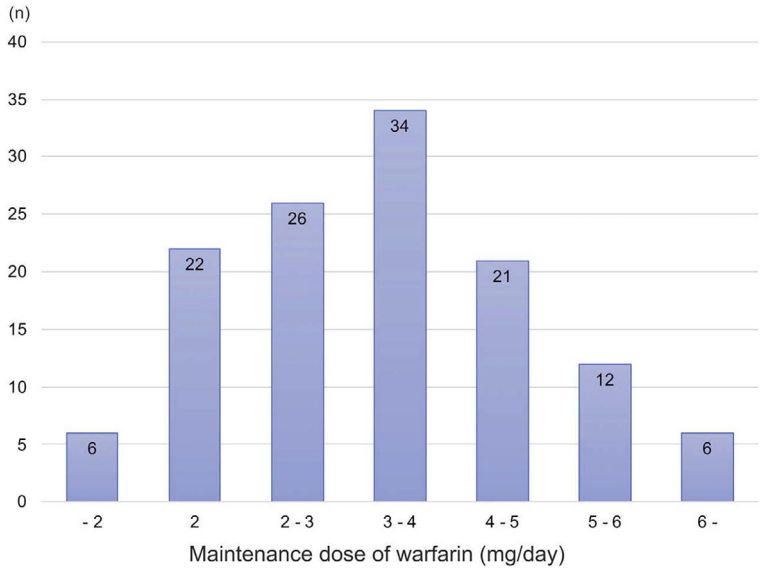

Figure 2. **The distribution of the study patients according to the maintenance dose of warfarin at 1 year.**

simple and multiple linear regression analyses for the maintenance dose are shown in Table 2. In simple linear regression models, the initial response of the INR, age, body weight, congestive heart failure, and CCr and statin use were significantly associated with the maintenance dose. In the multiple regression model, only the initial response of the INR was independently associated with the maintenance dose of warfarin.

The differences in the characteristics between the patients with a low initial response of the INR (<1.1) and others (≥ 1.1) are displayed in Table 3. Patients with a low initial response of the INR tended to be younger and have a higher body weight, higher creatinine clearance, and lower prevalence of congestive heart failure than others.

Discussion

Major findings

In the present study, we developed a simple exponential formula that was able to predict the maintenance dose through the initial INR under 2 mg/day dosing of warfarin. When patients with a poor response to the initial dose (initial INR <1.1) were excluded, a first-order approximation formula could be developed. In the multivariate analysis, the initial INR was the only independent predictor of the main-

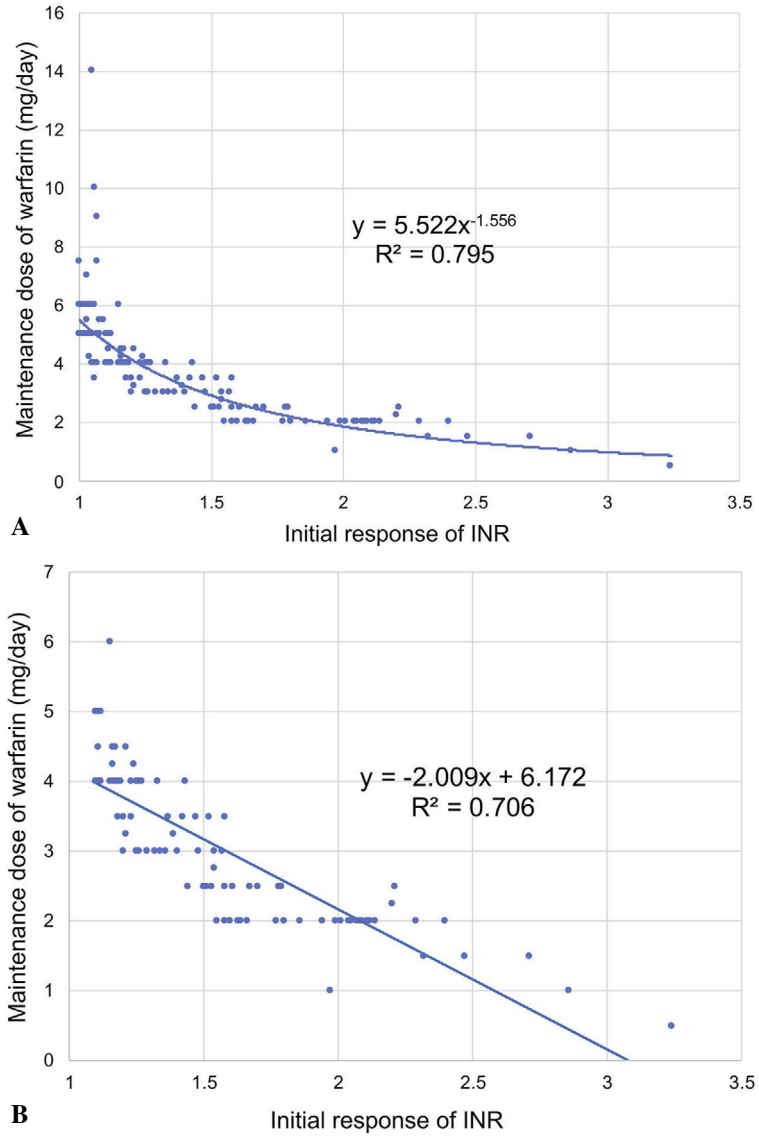

Figure 3. **The relationship between the initial response of the INR and the maintenance dose of warfarin. (A) Total patients (n=127), where the prediction formula was expressed as an exponential approximation. (B) After excluding patients with a low initial response of the INR (<1.1) (n=95), where the prediction formula was expressed as a first-order approximation.**

tenance dose of warfarin.

Distribution of the INR and maintenance dose of warfarin

The initial response of the INR with 2 mg/day dosing of warfarin did not reach the therapeutic range in 74.8% of subjects in the present study. This rate was similar to that in a previous report at a European outpatient clinic (62.2%) (26). The patients with a low initial response of the INR (<1.1) tended to be younger with a higher body weight, better kidney function, and lower prevalence of congestive heart failure than others, which would have been responsible for the high clearance and consequent low plasma concentration of warfarin. Furthermore, the low response of the INR may also have been affected by a low adherence, interaction of food or drugs, and genetic variants of the CYP2C9 and VKORC1 genes. Of note, the low initial response of the INR likely involves all factors that affect the plasma concentration of warfarin and its effect on the activity of vitamin K.

In a nationwide registry in Japan (J-RHYTHM Registry), the maintenance dose of warfarin was reported to be 2.9±1.2 mg (mean INR 1.9) (23). Two other reports in a single-hospital database also showed similar maintenance dosages of 2.68±0.95 mg (range, 1.0-6.0 mg) (27) and 3.05±1.20 mg (range, 0.5-7.0 mg) (21). The maintenance dose in our study (3.76±1.83 mg/day) was a little bit higher than those in the previous studies, presumably due to the younger age of the present study population.

The comparison with previous prediction formulas

The first report predicting future warfarin dose requirements based on early INR values was published over 40 years ago (28). Since then, several reports have shown a re-

lationship between the initial response to warfarin and the required maintenance dose (29-33). Lazo-Langner et al. (31) constructed a three-staged formula that predicts the maintenance warfarin dose in an exponential formula using the INR at days 3, 5, and 8 with an initial dose of 10 mg. In addition, Le Gal et al. (32) reported a rather simple linear predicting formula that included the INR at days 5 and 8 with an initial dose of 10 mg. The predictive accuracy in the study of Lazo-Langner et al. (R^2=0.417) (31) was lower than in that of Le Gal et al. (R^2=0.643 and 0.774 for days 5 and 8, respectively) (32). Although these multiple-staged formulas may be methodologically appropriate, they cannot be simply applied to daily clinical practice because of racial differences in the drug response (34) or differences in the medical circumstances. Therefore, in the present study, we developed a single-staged predicting formula that showed an acceptable predicting accuracy (R^2=0.706).

Recently, a pharmacogenetics-based approach has emerged (13-22, 26). Although genetic variants of the CYP2C9 and VKORC1 genes are associated with the maintenance dose of warfarin, the predictive value of such variants was shown to be relatively low (0.28-0.47) (18, 21). Regardless of the convenience of obtaining a response of the INR to the initial warfarin dosing, such evaluations should include differences in race, age, BMI, smoking, renal function, history of venous thrombosis, the use of drugs such as amiodarone, and any genetic variants.

Table 2. Factors Associated with Maintenance Dose.

Factors	n=95	
	β (per mg/day)	p value
Simple linear regression analysis		
Initial response of INR	-0.840	<0.001
Male	0.164	0.222
Age (years)	-0.197	0.056
Body weight (kg)	0.259	0.011
Congestive heart failure	-0.480	0.006
Creatinine clearance (mL/min)	0.263	0.021
AST (IU/L)	-0.147	0.204
ALT (IU/L)	-0.084	0.470
Statin use	-0.263	0.010
Amiodarone use	-0.102	0.327
Multivariate analysis		
Initial response of INR	-0.811	<0.001
Age (years)	-0.006	0.931
Body weight (kg)	0.021	0.767
Congestive heart failure	0.103	0.121
Creatinine clearance (mL/min)	0.017	0.840
Statin use	0.019	0.794

INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Clinical implications

The simple formula in the present study with Japanese patients showed a similar predictive accuracy to those in previous reports with Caucasian patients (29-33). The initial dose of 2 mg in the present study was much lower than those used in previous studies (4, 5, or 10 mg/day) (29-33), which may have helped prevent a rapid increase in the plasma concentration of warfarin. The appropriate timing for assessing the response to initial dosing in order to avoid thromboembolism should be further explored. Although the values of the maintenance dose calculated by our formula are presented to 4 decimal places, they should be rounded up to 0.5-mg values for easy calculation in order to be suited for practical use.

Limitations

Our study had several limitations. First, our formula cannot be easily adapted to patients with a low initial response of the INR (<1.1); such patients should be re-distributed based on the response to a higher dose of warfarin, which will require further investigations. Second, our formula cannot be used if the patient has an initial response of the INR >3.073 under 2 mg dosing, as 3.073 is an X-axis intercept with the formula in the present study (Fig. 3B). However, such an excessive response is rare presumably indicates that warfarin is not suited for the patient. In such cases, NOACs should be administered instead. Third, we retrospectively

Table 3. Difference of Patient Characteristics between Those with Low Initial Response of INR (<1.1) and Others (≥1.1).

	Initial response of INR<1.1 (n=32)	Initial response of INR ≥ 1.1 (n=95)	p value
Male, n (%)	25 (78.1)	64 (67.4)	0.241
Age (years)	63.0±8.1	68.5±8.6	0.002
Body weight (kg)	65.8±11.3	60.6±11.1	0.023
Congestive heart failure (%)	3.1	27.4	<0.001
Creatinine clearance (mL/min)	84.5±19.4	65.8±21.6	<0.001
AST (IU/L)	25.9±8.5	28.4±34.6	0.685
ALT (IU/L)	27.0±13.2	25.5±28.1	0.796
Statin use, n (%)	2 (6.25)	11 (11.6)	0.367
Amiodarone use, n (%)	0 (0.0)	1 (1.1)	0.445

INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

collected subjects who achieved a target INR of 1.6-2.6 at 1 year after the initiation of warfarin. Therefore, whether or not our formula can predict the maintenance dose of warfarin should be prospectively confirmed in the future.

Conclusion

We developed a simple formula for predicting the maintenance dose of warfarin using the initial response of the INR to 2 mg/day dosing of warfarin in Japanese patients. The predictive ability of this formula should be prospectively evaluated.

Author's disclosure of potential Conflicts of Interest (COI).
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