

## Efficient dosage regimen for introduction of warfarin treatment after coronary artery bypass grafting in Japanese patients

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We investigated a regimen for introduction of warfarin treatment in patients who had undergone coronary artery bypass grafting (CABG) with the objective of shortening the time needed to determine the individual optimal dose of warfarin. We initiated warfarin treatment with five different regimens and compared the percentage of patients whose thrombotest (TT) values ranged between 10 and 20% (corresponding to a PT-INR of 1.8–2.8) on the 9th day, after starting warfarin administration. Using a regimen in which warfarin was administered at 5 mg/day on the 1st day as the loading dose, at 3 mg/day from the 2nd day as the maintenance dose, and in which the dose was adjusted on the 7th day or later based on the TT value, the percentage of patients achieving the optimal warfarin dose on the 9th day was 73.1%. This regimen has reached the optimal dose of warfarin more efficiently compared with other four methods. In this regimen, the serious adverse events, such as major bleeding and thromboembolism, did not occur. This method was considered to be most efficient and safe regimen for introduction of warfarin treatment after CABG for determination of the individual optimal dose within 10 days of a procedure.

KEY WORDS: warfarin, anticoagulant therapy, coronary artery bypass

### I. Introduction

Warfarin has been the most extensively used oral anti-coagulant worldwide. The drug has been demonstrated to be effective for the prevention and treatment of thromboembolism in patients with acute myocardial infarction or atrial fibrillation and patients subjected to valve replacement.<sup>1)</sup> It is possible to determine the optimal dose of warfarin based on the thrombotest (TT) value or prothrombin time-international normalized ratio (PT-INR). However, it is not easy for clinicians to estimate the optimal initial dosage of warfarin to attain such a narrow therapeutic range of PT-INR for each patient, because there is wide variation in the anticoagulant response to warfarin between and even within patients. It is known that pharmacokinetic (PK) and pharmacodynamic (PD) factors contribute to the large individual variation in its anti-coagulant effect.<sup>2,3)</sup> A number of studies have been pub-

lished on nomogram seeking to determine the optimal dose of warfarin,<sup>4,5)</sup> but an efficient and safe method is not established. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy recommended a method for initiating warfarin treatment in which the drug was administered at doses between 5 and 10 mg for the first 1 or 2 days, and the dose was then adjusted based on PT-INR.<sup>1)</sup>

In our hospital, the dose of warfarin has traditionally been adjusted based on each physician's experience of daily measured TT values following initiation of treatment. However, using this approach, the optimal dose of warfarin could not necessarily be established by 10 days after surgery or the day of discharge. In this study, we sought to establish a regimen for initiating warfarin treatment in patients who had undergone coronary artery bypass grafting (CABG) based on PK/PD theories, for the purpose of shortening the time needed to determine the individual optimal dose.

### II. Methods

Patients who had undergone CABG were candidates for study inclusion. Five administration regimens with different initial doses, maintenance doses and/or timing of adjustment of the warfarin dose were compared as regimens for the initiation of warfarin treatment (Table 1). Warfarin

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**Table 1** Summary of regimens for the initiation of warfarin treatment after CABG

Study	Therapeutic target thrombotest value	Initial dose	Maintenance dose	The day which adjusts warfarin dose
Study A	free hand*	free hand*	free hand*	free hand*
Study B	10–20%	3 mg	free hand*	free hand*
Study C	10–20%	3 mg	3 mg	5th day
Study D	10–20%	3 mg	3 mg	7th day
Study E	10–20%	5 mg	3 mg	7th day

\*: According to physician’s decision

was administered once a day after the evening meal. Heparin was available for administration if required, between four days after CABG. Patient characteristics examined were sex, age, weight, status of warfarin administration, laboratory test value of coagulation activity (TT value), and presence of hemorrhagic and thromboembolic events. The primary end point was the percentage of patients whose TT values reached their therapeutic target value on the 9th day after starting warfarin administration; this was defined as the percentage of patients achieving the optimal warfarin dose.

Written informed consent was obtained from all subjects following clear explanation of the study objectives. This research program was approved by the Ethics Committee of Sakakibara Heart Institute Hospital.

**1. Study A (Retrospective survey)**

Data on doses of warfarin and TT values were retrospectively collected from clinical records of patients who received warfarin by conventional regimens for initiating warfarin treatment based on the physician’s experience.

**2. Study B**

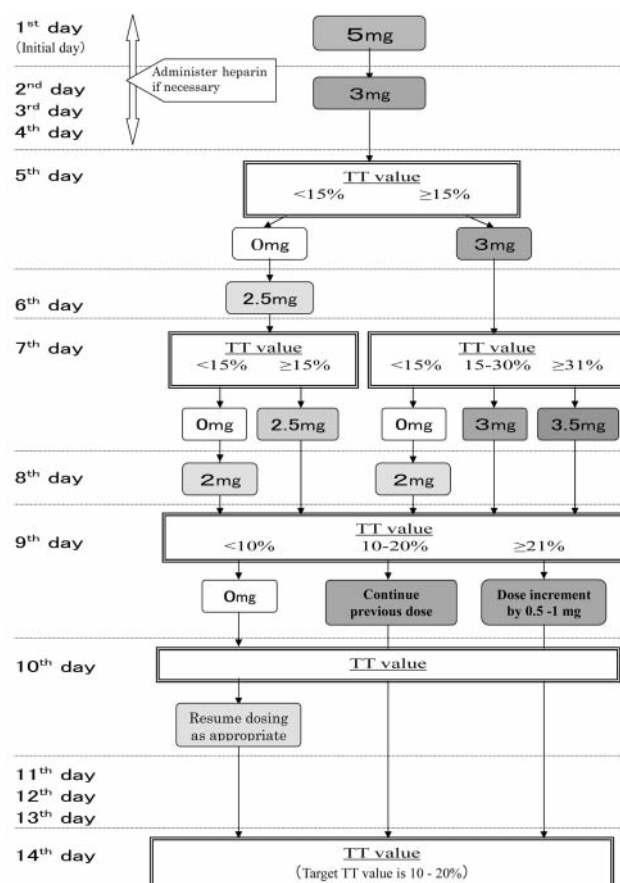
The initial dose of warfarin and the therapeutic target TT value were set at 3 mg/day and a range of 10 to 20% (corresponding to a PT-INR of 1.8–2.8), respectively. Timing and amount of dose adjustment were left to the discretion of the physician.

**3. Study C**

The initial dose of warfarin and the therapeutic target TT value were same as Study B. The maintenance dose from the 2nd day was set at 3 mg/day, the TT values were measured on the 3rd day, the 5th day, the 7th day and the 9th day. The dose of warfarin was adjusted on the 5th day or later based on the TT value. In addition, TT values were measured in all patients on the 14th day and/or on the day of discharge.

**4. Study D**

The initial dose and the maintenance dose of warfarin



**Fig. 1** Dosage regimen for introduction of warfarin treatment after CABG (Study E).

and the therapeutic target TT value were same as Study C. The TT value was measured on the 5th day, the 7th day and the 9th day. The dose of warfarin was adjusted on the 7th day or later based on the TT value. TT values were measured in all patients on the 14th day and/or on the day of discharge, same as Study C.

**5. Study E**

The initial dose of warfarin was set at 5 mg/day. The maintenance dose from the 2nd day and the therapeutic

target TT value were same as Study D. The details of the regimen of Study E were as follows (Fig. 1).

Warfarin at 5 mg/day was administered on the first day as the loading dose and at 3 mg/day from the 2nd day as the maintenance dose. TT values were measured on the 5th day, at which time administration was stopped and 2.5 mg of warfarin was administered on the 6th day if the TT value was less than 15% (corresponding to PT-INR of 2.2). TT values were again measured on the 7th day, at which time administration was stopped and 2 mg of warfarin was given on the 8th day if the TT value was still less than 15%. Administration of warfarin at 2.5 mg/day was continued when the TT value was 15% or higher.

On the other hand, when the TT value on the 5th day was 15% or higher, the dose was continued at 3 mg/day and the TT value was measured on the 7th day; at this point administration was stopped and 2 mg of warfarin was given on the 8th day when the TT value was less than 15%. Administration was continued at 3 mg/day when the TT value was between 15 and 30%; the dose was increased to 3.5 mg when the TT value was 31% or higher.

TT values were measured in all patients on the 9th day; the administration of warfarin was suspended and resumed with monitoring of TT values after an interval of one day when the TT value was less than 10%; administration was continued at the previous doses when the TT value was between 10 and 20% (corresponding to PT-INR of 1.8–2.8); the dose of warfarin was increased by 0.5–1 mg when the TT value was 21% or higher. TT values were measured in all patients on the 14th day and/or on the day of discharge.

## 6. Statistical analysis

Differences between two groups in each case were analyzed by an unpaired t-test. Population statistical data between groups were statistically analyzed by ANOVA. Statistical analysis was performed using SPSS software (version 11.0; SPSS Inc., Chicago, Ill). Differences where  $p < 0.05$  in a two-tailed test were considered to be significant. All data were expressed as mean $\pm$ SD. The ratio of patients achieving the optimal warfarin dose was calculated by the Kaplan-Meier method, and statistical significance was evaluated by a log-rank test.

## III. Results

The present study was conducted with 113 Japanese patients who had undergone CABG with cardiopulmonary bypass. Table 2 shows the background of patients enrolled in Studies A–E. No differences were found among groups in age, body weight, TT value (%) and total protein concentration (mg/dl) at the beginning of warfarin treatment. In these studies, the serious adverse events, such as major bleeding and thromboembolism, did not occur.

### 1. Study A (Retrospective survey)

The initial doses ranged between 3 and 5 mg/day, and the mean dose was  $4.4 \pm 0.9$  mg/day. The percentage of patients achieving the optimal warfarin dose on the 9th day and 14th day after starting the administration were only 14.3% and 28.6%, respectively (Table 3). Most patients were discharged from hospital without achieving the optimal TT value. The numbers of dose adjustments in the patients whose TT value reached the target range was  $6.0 \pm 2.7$  times.

**Table 2** Background of the patients participated

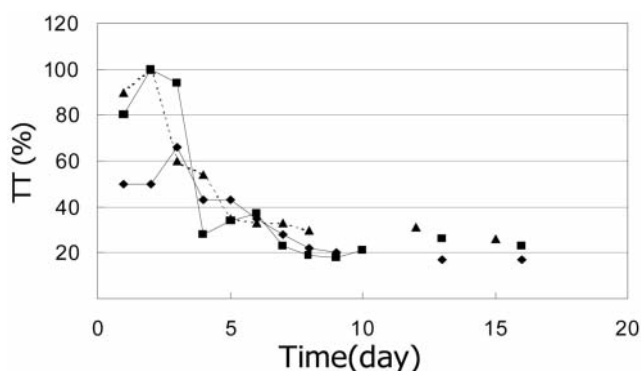
Study	Number of patients	Age (year)	Weight (kg)	Thrombotest (%)	Total protein (mg/dl)
Study A	21	65.9 $\pm$ 10.1 (51–82)	62.1 $\pm$ 11.0 (41.7–73.4)	73.5 $\pm$ 19.9 (45–100)	5.41 $\pm$ 0.53 (4.6–6.7)
Study B	12	67.0 $\pm$ 8.3 (46–77)	63.4 $\pm$ 9.4 (52–86)	62.2 $\pm$ 30.3 (19–100)	5.69 $\pm$ 0.57 (4.4–6.5)
Study C	21	63.1 $\pm$ 9.6 (35–76)	66.1 $\pm$ 12.3 (39–97)	64.3 $\pm$ 8.4 (38–100)	5.32 $\pm$ 0.42 (4.4–5.9)
Study D	26	65.2 $\pm$ 7.7 (52–78)	64.7 $\pm$ 20.3 (48–78)	73.1 $\pm$ 17.9 (43–100)	5.39 $\pm$ 0.44 (4.6–6.5)
Study E	33	68.0 $\pm$ 6.8 (53–82)	63.6 $\pm$ 8.7 (49–83.1)	71.9 $\pm$ 21.3 (41–100)	5.35 $\pm$ 0.50 (4.0–6.4)

mean $\pm$ SD (range)

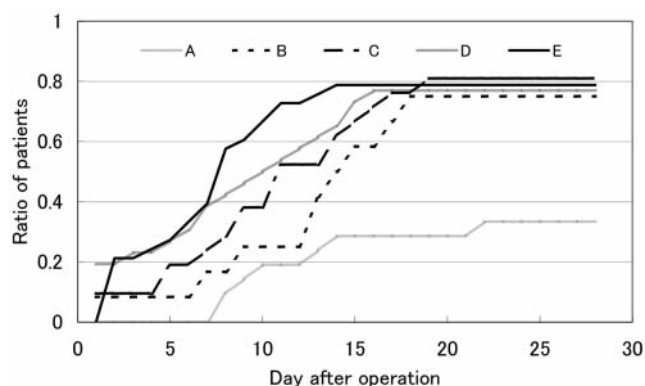
**Table 3** Percentages of patients achieving the optimal warfarin dose

Study	Percentages of patients achieving the optimal warfarin dose (%)	
	9th day	14th day
Study A (Retrospective survey)	14.3	28.6
Study B	25.0	50.0
Study C	38.1	71.4
Study D	50.0	73.1
Study E	73.1	78.8

mean±SD



**Fig. 2** Time course of changes in TT values in 3 patients who successfully achieved a satisfactory effect of warfarin by continuation of administration at 3 mg after CABG.



**Fig. 3** Kaplan-Meier analysis of the ratio of patients who attended an optimal dose (D vs E,  $P=0.04$ ; compared using a log-rank test).

## 2. Study B

The percentages of patients achieving the optimal warfarin dose on the 9th day and 14th day after starting the administration were 25.0% and 50%, respectively (Table 3). The numbers of dose adjustments in the patients whose TT value reached the target range was  $2.5 \pm 1.4$  times.

## 3. Study C

The percentages of patients achieving the optimal warfarin dose on the 9th and 14th day after starting the administration were 38.1% and 71.4%, respectively (Table 3). Figure 2 shows the time course of changes in TT values in 3 patients who successfully achieved a satisfactory effect of warfarin by continuation of administration at 3 mg after CABG. It is evident from the figure that the TT value did not reach a steady state by the 5th day. This in turn led to prolongation of the time required to achieve the optimal dose.

## 4. Study D

The percentages of patients achieving the optimal warfarin dose on the 9th and 14th days after starting the administration were 50.0% and 73.1%, respectively (Table 3).

## 5. Study E

The percentages of patients achieving the optimal warfarin dose on the 9th and 14th days after starting the administration were 73.1% and 78.8%, respectively (Table 3). The numbers of dose adjustments in the patients whose TT value reached the target range was  $1.5 \pm 1.3$  times.

## 6. Kaplan-Meier analysis of the patients achieving the optimal warfarin dose

The ratio of patients achieving the optimal warfarin dose was calculated by Kaplan-Meier analysis (Fig. 3). Patients who were discharged without achieving the optimal dose were also included in the analysis. Among regimens examined for the initiation of warfarin treatment, the regimen used in Study E gave the highest percentage of patients whose TT value reached a range between 10 and 20% on the 9th day. A statistically significant difference in the percentage was found between Study D and Study E by the log rank test ( $p=0.04$ ).

## IV. Discussion

Warfarin exerts anticoagulant and antithrombotic effects by suppressing biosynthesis of vitamin K-dependent

coagulation factors (prothrombin, and factors VII, IX and X) and increasing proteins induced by vitamin K absence or antagonist. Vessel ES et al reported that the elimination half life of warfarin from the blood was 36.3 hr after a single administration at 0.75 mg/kg in healthy adult males. The anticoagulant effect appeared 12 to 24 hr after administration and lasted for 48 to 72 hr.<sup>6)</sup> Although warfarin suppresses biosynthesis of vitamin K-dependent coagulation factors, it does not affect their decomposition. Thus, its pharmacological effect appears after a lag time, due to the breakdown of preexisting coagulation factors in the blood. Regarding the relationship between the blood concentration and effect of warfarin, Sheiner LB first proposed a linear model.<sup>7)</sup> Later, Holford NH proposed a PK/PD model based on combination of a one-compartment model for blood concentration of warfarin and a maximum effect model for prothrombin complex activity.<sup>8)</sup> Using this model he reported that the effect of warfarin reached a steady state 4 or 5 days following administration of initial and maintenance doses of 15 mg and 7.5 mg, respectively.<sup>8)</sup>

On the other hand, Fennerty A et al investigated 50 patients with venous thromboembolic disease using a method for predicting the maintenance dose based on a three-day-warfarin-induction regimen and dose adjustment on the basis of PT on the 4th day.<sup>9)</sup> Warfarin was given for 3 days by a flexible induction dose regimen. The maintenance dose was determined based on the PT on the 4th day. From the view point of PK/PD of warfarin, however, laboratory test value of coagulation activity on the 4th day are not considered to reach the steady state following the regimen reported by Fennerty A et al. This is because the dose of warfarin can be changed as required immediately after the early stage in these regimens.

There is considerable individual variation in the maintenance dose of warfarin. Factors affecting the variation of the maintenance dose of warfarin have also been explored. Garcia D et al studied the influence of age and gender in 12,202 patients with atrial fibrillation, and demonstrated that the maintenance dose decreased with age, and that was lower in females than in males.<sup>10)</sup> Since it has been reported that the maintenance dose of warfarin is affected by a number of factors including age, gender, body weight, laboratory test values of hepatic function, concomitant use of drugs, genetic polymorphism of *CYP2C9* and *VKORC1*,<sup>11)</sup> it is possible to incorporate these factors into the regimen. However, it has been pointed out that these genetic factors and clinical characteristics can ex-

plain only 56% of variation of the maintenance dose.<sup>12)</sup> In addition, the percentage contribution of age, gender, body weight, *CYP2C9* and *VKORC1* polymorphisms was reported to be 33.7% in Japanese patients,<sup>13)</sup> and was lower than that reported in Westerners. As the present study was conducted with Japanese patients who had undergone CABG, individual differences in age, body weight and genetic polymorphism considered to be small. Therefore, without considering these factors, we investigated dosage regimen for introduction of warfarin treatment after CABG.

As there was a report that thromboembolism could be induced under these conditions when the TT value was 25% or higher, the target TT value in the patients subjected to CABG was set at a range of 10 to 20%.<sup>14)</sup>

Study A, the retrospective survey of patients treated, where the dose of warfarin had been empirically changed at an early stage by the physician, demonstrated that most patients were discharged without reaching the target TT value.

The steady state doses of warfarin in 69 out-patients whose TT value was maintained between 10 and 20 (mean±SD; 16.1±3.0) % were surveyed, retrospectively. Daily doses of warfarin in these patients varied between 0.5 and 6.0 mg, and the mean daily dose was 2.8±1.1 mg. Based on the result of the mean daily dose, the initial dose and therapeutic target TT value were set at 3 mg/day in Study B. A similar result as Study A was obtained in Study B where the initial dose and TT value were set in advance of starting the treatment.

From pharmacokinetic and pharmacodynamic studies, the effect of warfarin was found to reach a steady state 5 days after starting treatment. In Study C, TT values were evaluated on the 5th day. As a result, the percentage of patients whose TT value reached the target range exceeded 70%, though the time required to achieve the optimal dose was not reduced. The prolongation of the time required to achieve the optimal dose may be explained by a transient enhancement of coagulation activity due to surgical invasion. It is known that the blood coagulation system is generally activated during the perioperative period by invasive surgery and contact of blood with an extracorporeal circuit. Furthermore, patients are in a transient hypercoagulable state for a few days after the procedure,<sup>15, 16)</sup> suggesting possible prolongation of the time required for the TT value to reach a steady state. It can also be speculated that increasing the dose on the 5th day, at a time when warfarin did not exert its full effect, resulted in a delay in achieving an optimal effect and to an



excessive anticoagulant effect.

Based on these considerations, TT values were evaluated on the 7th day in Study D. Furthermore, to shorten the time required to achieve the optimal dose, the loading dose of warfarin on the first day was increased to 5 mg in Study E. The Study E regimen enabled us to achieve the optimal dose within 10 days.

For the patients who had undergone CABG, the antiplatelet therapy only by aspirin is a first choice, and combined use of warfarin is restrictive at the real world. As the study subjects in the present investigation were patients with ischemic heart disease who had undergone CABG, individual differences in age and body weight were considered to be small. It is necessary to examine whether the regimen for introduction of warfarin treatment after CABG is applicable to super-elderly people or the patient of low weight. And, it is unclear whether the duration of the hypercoagulable state is similarly increased in patients subjected to different surgical procedures. In the future, we would like to investigate a regimen for initiating warfarin treatment in patients subjected to surgery for valvular heart diseases, including mechanical valve replacement, which inevitably requires anticoagulant treatment.

## V. Conclusion

We have demonstrated that the regimen in which warfarin was administered at 5 mg/day on the first day as the loading dose, at 3 mg/day from the 2nd day, and adjusted on the 7th day post procedure (Regimen of Study E; Fig. 1), was the most efficient and safe method for determining the optimal dose within 10 days of a procedure. This would therefore be recommended as the regimen for introduction of warfarin treatment after CABG.

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