

Efficient dosage regimen for introduction of warfarin treatment after cardiovascular surgery in Japanese patients: comparisons between coronary artery bypass grafting and surgery for valvular heart disease

Junichi Kawana,^{1,2} Toshiya Koyanagi,³ Tetsuya Sumiyoshi⁴
Kazuhiko Hanada,¹ Tetsuo Ohno,² Hiroyasu Ogata¹

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 coronary artery bypass grafting (CABG), was the most efficient and safe method for determining the optimal dose within 10 days of a procedure. In the present investigation, we extended this regimen to patients who had undergone cardiovascular surgery, including heart valve surgery. The percentage of patients achieving the optimal warfarin dose on the 9th day was 83.3% after CABG, but was as low as 47.4% after heart valve surgery. In the patients who had undergone heart valve surgery, we changed the regimen, such that the loading dose of warfarin was set at 5 mg/day on the first and second day. As a result, the percentage of patients achieving the optimal warfarin dose on the 9th day was 75% after CABG and 78.6% after heart valve surgery. In this regimen, the serious adverse events, such as major bleeding and thromboembolism, did not occur. We have demonstrated that the regimens were the most efficient and safe methods for determining the optimal dose within 10 days of a procedure, both in patients who had undergone CABG or heart valve surgery, by applying different methods for scheduled administration of warfarin.

KEY WORDS: warfarin, anticoagulant therapy, coronary artery bypass, heart valve replacement

I. Introduction

Since thromboembolism, including cerebral infarction, after cardiovascular surgery is a serious complication, the anticoagulant warfarin has been extensively used for its prophylaxis. In our hospital, the dose of warfarin has traditionally been adjusted based on each physician's experience of daily measured thrombotest (TT) values following initiation of treatment. However, it has been difficult to obtain stable TT values due to the fluctuations in the daily dose of warfarin; it has also been difficult to control and maintain the TT value in the target therapeutic range between 10 and 20% (corresponding to prothrombin time-

international normalized ratio (PT-INR) of 1.8-2.8) for up to 10 days after coronary artery bypass grafting (CABG) in most patients. In advance of this investigation, for the purpose of shortening the time needed to determine the individual optimal dose of warfarin, we had studied a method for initiating warfarin treatment based on theories of pharmacokinetics and pharmacodynamics in patients who had undergone CABG.¹⁾ From this study we had proposed a "CABG-Warfarin-Regimen (CWR)," namely a regimen for initiating warfarin treatment after CABG, 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 post procedure. Subsequently the dose of warfarin is adjusted on the 7th day or later based on the TT value; this allows determination of the individual optimal dose within 10 days of the procedure in 70% of patients. In this study, we applied the proposed "CWR" method to patients who had undergone cardiovascular surgery other than CABG for whom warfarin treatment was an absolute requirement. The objective was to shorten the time needed to determine the individual optimal dose of warfarin after cardiovascular surgery.

¹Department of Biopharmaceutics & Clinical Pharmacokinetics, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan, ²Department of Pharmacy, ³Department of Cardiology, Sakakibara Heart Institute, Japan Research Promotion Society for Cardiovascular Diseases, ⁴Department of Cardiovascular Surgery, Japanese Red Cross Kumamoto Hospital. A part of this article was presented at The 13th Annual Meeting of the Japanese Society of Pharmaceutical Health Care and Sciences, September 2003, Kobe.

Received July 22, 2008; Accepted October 9, 2008

II. Methods

Patients who had undergone CABG and those who had undergone surgery for valvular heart disease (mitral valve replacement, aortic valve replacement, double valve replacement, and mitral valvuloplasty) were candidates for study inclusion. Methods for the introduction of warfarin treatment were examined in a stepwise manner as Study I and Study II. The target TT value was set to between 10 and 20% (corresponding to PT-INR of 1.8–2.8). Heparin was available for administration if required. Patient characteristics examined were sex, age, weight, surgical procedure, status of warfarin administration and 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. Cumulative warfarin doses in every 5-day-interval, and the TT values (on the 5th and 10th day, and the day of discharge) were also evaluated.

1. Study (Fig. 1; CWR)

Warfarin was administered according to the “CWR” method¹⁾ to both patient groups (who had undergone CABG or heart valve surgery). The details of the “CWR” method were as follows.

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

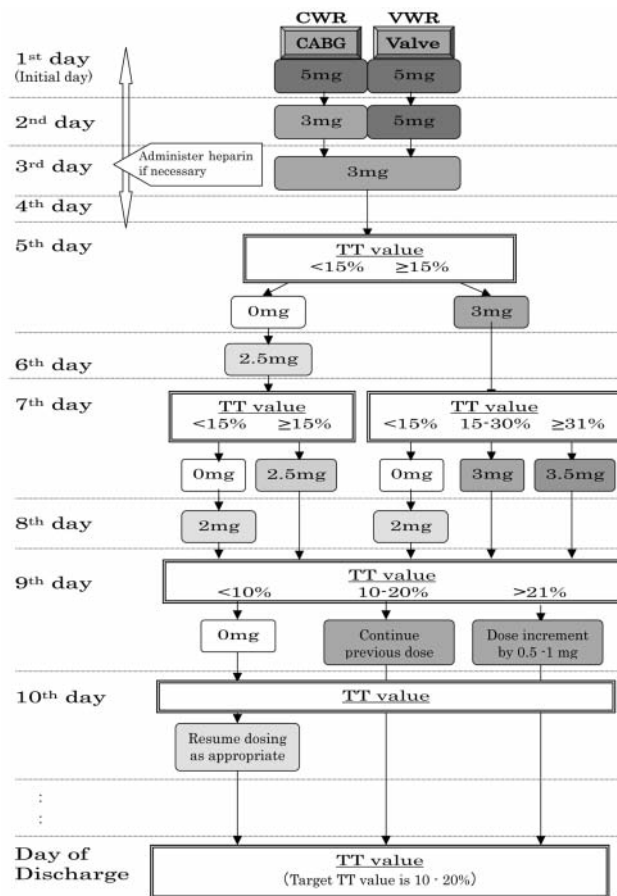


Fig. 1 Dosage regimen for introduction of warfarin treatment after cardiovascular surgery.

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 the patients on the day of discharge.

2. Study II (Fig. 1; CWR and VWR)

Warfarin was administered to patients who had undergone CABG according to the “CWR” method. In the case of patients who had undergone heart valve surgery, we modified the “CWR” method, such that the loading dose of warfarin was set at 5 mg/day on the first and second day. Warfarin was administered according to the “Valve surgery-Warfarin-Regimen (VWR)” method. The details of the “VWR” method were as follows.

Warfarin was administered at 5 mg/day on the first and second day as the loading dose, and at 3 mg/day from the 3rd day as the maintenance dose. After the 4th day, warfarin was administered according to the same method as “CWR.”

Table 1 Patient background

	Study I		Study II	
	CABG	Heart valve surgery	CABG	Heart valve surgery
N (male/female)	18 (16/2)	19 (10/9)	20 (18/2)	28 (16/12)
Age (yr-old)	63.6±10.6	60.0±15.0	67.2±7.7	62.1±14.1
Body weight (kg)	61.3±10.5	55.9±11.7	61.5±8.4	56.2±9.3
Surgical time (min)	241±76	238±66	213±61	195±50
Cardiopulmonary bypass time (min)	143±69	134±37	114±37	99±29
TT (%)	67.2±25.6	66.1±30.2	64.8±27.9	61.4±29.7
Platelet (10 ⁴ /mm ³)	7.6±2.2	7.9±2.4	7.7±2.6	8.1±2.9

Mean±SD

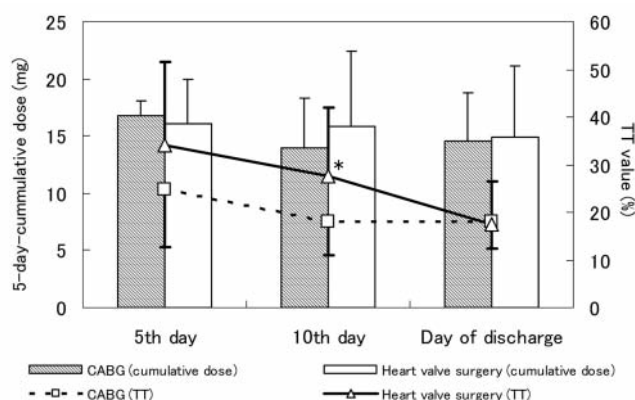


Fig. 2 Comparison of time course change of thrombotest (TT) value and cumulative dose of warfarin over 5 days in patients who had undergone CABG or heart valve surgery (Study I). Mean±SD, *p<0.05 vs CABG (TT)

Data were statistically analyzed by paired t-test and χ^2 test using SPSS statistical software (version 11.0; SPSS Inc., Chicago, Ill), and differences were considered to be statistically significant when p<0.05.

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.

III. Results

The present study was conducted with 85 Japanese patients who had undergone cardiovascular surgery including CABG or surgery for valvular heart disease. Table I shows the background of patients enrolled in Study I and II. No differences were found between groups in age, body weight, surgical time, cardiopulmonary bypass time, thrombotest and platelet at the beginning of warfarin treatment. In these studies, the serious adverse events, such as major bleeding and thromboembolism, did not occur.

1. Study I

In Study I, both the 18 patients who had undergone CABG and the 19 patients who had undergone heart valve surgery received warfarin in accordance with the “CWR” method. As a result, the percentage achieving the optimal warfarin dose on the 9th day (the primary end point) was 83.3% in the patients who had undergone CABG, but was 47.4% in the patients who had undergone heart valve surgery. Furthermore, this difference was statistically significant.

Figure 2 shows a comparison of the time course of changes in TT values between patients who had undergone CABG and heart valve surgery. TT values were 24.7±12.0%, 18.1±7.2% and 18.0±5.7% in the 5th day, 10th day and the day of discharge, respectively, in patients who had undergone CABG. On the other hand, TT values markedly changed from 34.2±17.4% on the 5th day to 27.6±14.4% on the 10th day and 17.5±8.9% on the day of discharge in the patients who had undergone heart valve

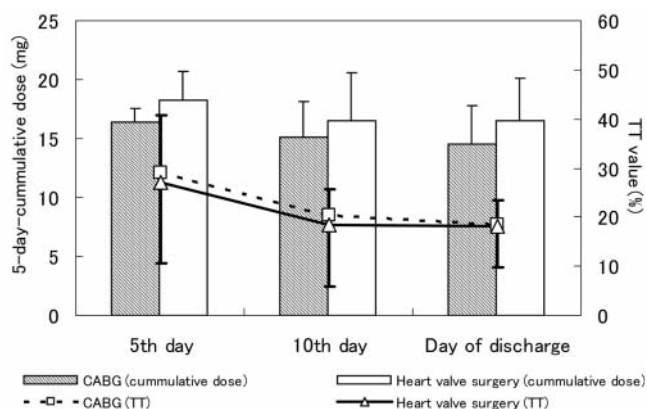


Fig. 3 Comparison of time course change of thrombotest (TT) value and cumulative dose of warfarin over 5 days in patients who had undergone CABG or heart valve surgery (Study II). Mean \pm SD

surgery. However, there were no statistical differences in cumulative doses of warfarin in each 5-day-interval between patients who had undergone CABG and heart valve surgery.

2. Study II

In Study II, warfarin was administered according to the “CWR” method to 20 patients who had undergone CABG, and according to the “VWR” method to 28 patients who had undergone heart valve surgery. The percentage of patients achieving the optimal warfarin dose on the 9th day (the primary end point) was 75% in those who were given warfarin by the “CWR” method after CABG. The corresponding value was 78.6% in patients who received warfarin by the “VWR” method after heart valve surgery.

Figure 3 shows a comparison of the time course of changes in TT values between patients who had undergone CABG and those who had undergone the surgery of valvular heart diseases. In patients who had undergone CABG, TT values changed from $29.1\pm 18.4\%$ on the 5th day to $20.5\pm 14.6\%$ on the 10th day and $18.5\pm 8.9\%$ on the day of discharge. On the other hand, TT values changed from $26.9\pm 13.9\%$ on the 5th day to $18.5\pm 8.9\%$ on the 10th day and $18.2\pm 5.4\%$ on the day of discharge in patients who had undergone heart valve surgery.

IV. Discussion

Post-operative anticoagulant therapy is crucial for prophylaxis of thromboembolic complications, such as cerebral infarction, in patients undergoing cardiovascular surgery. However, up to now it has taken considerable time to determine the maintenance dose of warfarin, due to large individual variations in its anticoagulant effect. Therefore, there has been a pressing need to establish a

method for efficient initiation of warfarin treatment.

Previously, we first investigated a method for scheduled initiation of warfarin treatment in patients who had undergone CABG, and established the “CWR” method which enabled us to initiate warfarin treatment efficiently in those patients.¹⁾ We then attempted to establish a method for scheduled initiation of warfarin treatment in patients who had undergone heart valve surgery, including mechanical valve replacement that inevitably requires anticoagulant treatment.

Application of the “CWR” method resulted in significantly lower percentages of patients achieving the optimal warfarin dose on the 9th day in the patient group who had undergone heart valve surgery. In addition, while TT values decreased to the therapeutic target range of between 10 and 20% (corresponding to PT-INR of 1.8–2.8) by the 10th day in patients who had undergone CABG, this did not happen in the patients who had undergone heart valve surgery. TT values, however, did fall into the therapeutic target range at the time of discharge in both groups and there was no difference in TT values between the groups at this point (Fig. 1). These results suggested that there was a difference in coagulant activity between the two groups only at the early post-operative stage. As an insufficient anticoagulant effect was obtained by the “CWR” method in patients who had undergone heart valve surgery at the early post-operative stage in Study I, warfarin (5 mg/day) was loaded for 2 days on the first and second day in these patients (“VWR” method) in Study II. As a result, in the patients who had undergone heart valve surgery, TT values reached their therapeutic target range earlier in Study II than in Study I. The percentage of patients achieving the individual optimal warfa-

rin dose on the 9th day in those who had undergone heart valve surgery was similar to that in patients who had undergone CABG (Fig. 3). We have therefore demonstrated that efficient dosage regimens for introduction of warfarin treatment could be achieved, both in patients who had undergone CABG or heart valve surgery, by applying different methods for scheduled administration of warfarin (Fig. 1).

It is known that the blood coagulation system is generally activated during the perioperative period around invasive surgery and contact of the blood with a cardiopulmonary bypass, and that patients are in a transient hypercoagulable state for a few days post-operatively.^{2, 3)} Such different states of the coagulation system in patients who had undergone different surgical procedures may be one of the reasons that different optimal methods for initiating warfarin treatment are required. It has been reported that platelet function is activated and the coagulation-fibrinolysis system is enhanced after CABG, regardless of the use of a cardiopulmonary bypass; furthermore, this effect lasted for four days or so after the procedure.⁴⁻⁶⁾ In addition, enhancement of fibrinolysis has been reported during the perioperative period in patients who had undergone prosthetic valve replacement.⁷⁾ However, there have been no reports on the direct comparison of activation of blood coagulation between the patients who had undergone CABG and those who had undergone heart valve surgery. Then, we compared background between the patients who had undergone CABG and those who had undergone heart valve surgery in order to compare the extent of surgical invasion; no statistical difference was found in background between the groups (Table 1). Thus, in the future it will be necessary to clarify reasons for the requirement of different optimal initial doses of warfarin between various surgical procedures from the viewpoints of platelet function, the coagulation-fibrinolysis system and the immune system.

V. Conclusion

We have demonstrated that the regimens were the most efficient and safe methods for determining the optimal dose within 10 days of a procedure, both in patients who had undergone CABG or heart valve surgery, by applying different methods for scheduled administration of warfarin. These methods would therefore be recommended as the regimen for introduction of warfarin treatment after cardiovascular surgery.

References

- 1) Kawana J, Koyanagi T, Sumiyoshi T, Hanada K, Ohno T, Ogata H: Efficient dosage regimen for introduction of warfarin treatment after coronary artery bypass grafting in Japanese patients. *J Jpn Coron Assoc* 2009; **15**: 98–103
- 2) Samama CM, Thiry D, Elalamy I, Diaby M, Guillosson JJ, Kieffer E, Coriat P: Perioperative activation of hemostasis in vascular surgery patients. *Anesthesiology* 2001; **94**: 74–78
- 3) Dixon B, Santamaria J, Campbell D: Coagulation activation and organ dysfunction following cardiac surgery. *Chest* 2005; **128**: 229–236
- 4) Lo B, Fijnheer R, Castigliego D, Borst C, Kalkman CJ, Nierich AP: Activation of hemostasis coronary artery bypass grafting with or without cardiopulmonary bypass. *Anesth Analg* 2004; **99**: 634–640
- 5) Yamauchi H, Ito M, Watanabe T, Satoh H, Matsui Y: Evaluation of hypercoagulable status after off-pump coronary artery bypass using platelet-derived microparticles. *Jpn J Cardiovasc Surg* 2007; **36**: 121–126 (in Japanese)
- 6) Casati V, Gerli C, Franco A, Della Valle P, Benussi S, Alfieri O, Torri G, D' Angelo A: Activation of coagulation and fibrinolysis during coronary surgery: on-pump versus off-pump techniques. *Anesthesiology* 2001; **95**: 1103–1109
- 7) Konagai N, Yano H, Maeda M, Kudo T, Ishimaru S: Optimal anticoagulant therapy after mechanical valve replacement reviewed in terms of activity of coagulation and fibrinolysis. *J Cardiovasc Surg* 2004; **33**: 9–12