



## Long-Term Experience of Anticoagulant Therapy in Chinese Patients with Mechanical Valves

Yi-Ting Tsai, Chih-Hsien Lee, Gou-Jieng Hong, Chih-Yuan Lin,  
Chung-Yi Lee, and Chien-Sung Tsai\*

*Division of Cardiovascular Surgery, Department of Surgery,  
Tri-Service General Hospital, National Defense Medical Center,  
Taipei, Taiwan, Republic of China*

**Background:** Many targets of the currently therapeutic range of the international normalized ratio anticoagulant therapy for patients with mechanical heart valves were recommended on the base of Caucasian patient groups. To the best of our knowledge it is not clear whether this therapeutic range is optimal for corresponding Chinese individuals. **Methods:** Between January 1996 and January 2005 inclusively, 229 patients undergoing heart-valve replacement with a mechanical device at the Tri-Service General Hospital, Taipei, were enrolled into this study. Mean patient age was  $58.8 \pm 14.5$  years. Various collected data pertaining to these 229 patients following aortic-valve replacement ( $n=87$ ), mitral valve replacement ( $n=109$ ) and double-valve replacement ( $n=33$ ) with the CarboMedics prosthetic heart valve were analysed herein, and all associated complications were investigated retrospectively. **Results:** During the course of treatment for these 229 enrolled patients, the mean warfarin sodium dose administered was  $2.81 \pm 0.75$  mg per day and the mean international normalized ratio value was  $2.04 \pm 0.73$ . Perioperative mortality occurred for seven patients (3.06%), whilst major bleeding events occurred for 16 patients (1.17% per patient-year), and thromboembolism events for 14 patients (1.02% per patient-year). **Conclusion:** From our study, to keep international normalized ratio anticoagulant therapy above 1.5 is enough to prevent mechanical-valve associated thrombosis on Chinese patient groups.

Key words: international normalized ratio, mechanical heart valve, anticoagulants, heart-valve replacement, thrombosis

### INTRODUCTION

Despite more than a decade of continual technological and performance improvements in the field of mechanical and biological heart valves, the ideal prosthetic heart valve would still appear to not have been developed. Current biological implants require no long-term anticoagulation therapy, but to the best of our knowledge, they would not yet appear to be sufficiently durable. Mechanical prosthetic heart valves still appear to face the dual risks of thromboembolism and bleeding complications. For all such mechanical implants, treatment with oral anticoagulants must be carried out under the specifications of the International Normalized Ratio (INR) at some stage or

other. There were many recommends about the therapeutic range for the INR value for patients having received mechanical heart valves<sup>1-4</sup>, but they almost based on Caucasian patient groups.

It would appear that Chinese patients, in general, seem to be less vulnerable to thrombotic disease than is the case for Caucasians, and the former would also appear to require a lower-intensity level of anticoagulation therapy, when needed, than is the case for their Caucasian counterparts<sup>5-7</sup>. Guidelines for the optimal anticoagulant therapeutic range for Chinese patients having been fitted with mechanical heart valves would also appear to still be somewhat elusive, however. The purpose of this study was to examine the correlation between the relative intensity of anticoagulation therapy administered to prosthetic heart-valve recipients, and the occurrence of procedure-associated adverse events, and to determine the optimal range of INR value for Chinese mechanical heart-valve-recipients.

### MATERIALS AND METHODS

#### Patient Population

A total of 229 patients undergoing first-time mechani-

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\*Corresponding author: Chien-Sung Tsai, Division of Cardiovascular Surgery, Department of Surgery, Tri-Service General Hospital, 325, Sec. 2 Cheng-Gong Road, Taipei 114, Taiwan, Republic of China. Tel:+886-2-8792-7212; Fax: +886-2-8792-7376; E-mail: sung1500@mail.ndmctsgh.edu.tw

Table 1 Clinical characteristics and treatment of patients receiving mechanical heart valve replacement

|                                      | Total (n=222) |
|--------------------------------------|---------------|
| Age at surgery (years)               | 58.8 ± 14.5   |
| Male gender                          | 62%           |
| Mitral/aortic/mitral + aortic valves | 105/85/32     |
| Warfarin sodium dose (mg per day)    | 2.81 ± 0.75   |
| International normalized ratio       | 2.04 ± 0.73   |

cal heart-valve replacement between January 1996 and January 2005 inclusively at the Tri-Service General Hospital, Taipei, were enrolled into this study retrospectively. Patients who died within the perioperative period (defined as during surgery or within the 30-day period immediately following surgery; n=7) were excluded from our analysis. A total of 222 subjects were registered onto the study during 10 years. All of them were followed up for more than 1 year (6 for 1 year, 15 for 2 years, 12 for 3 years, 26 for 4 years, 20 for 5 years, 26 for 6 years, 43 for 7 years, 33 for 8 years, and 41 for 9 years). The average length of follow up is 6.15 years.

The prosthetic valves used throughout were Carbo-Medics prosthetic heart valves. The first time a patient's INR value was checked on the fifth day subsequent to launching the patient's warfarin sodium drug regimen in the hospital, and the procedure was repeated as many times as proved necessary until the INR value lay within the deemed optimal therapeutic range (INR=1.5-3.0). All patients were required to visit our hospital as outpatients for a cardiological and INR check-up once a week for a period of 1 month, following which, such check-ups were set for once a month. For all patients experiencing a bleeding or thromboembolism event, the patient's INR value at the time of the event would be checked and recorded. Data pertaining to estimated INR value and prescribed dose of warfarin sodium were retrieved from chart review. Late valve-related events were categorized in accordance with the guidelines for reporting morbidity and mortality devised by the American Association of Thoracic Surgery, and the Society of Thoracic Surgeons' *ad-hoc* committee.

RESULTS

The total observation time for all study-included patients was 1,366 patient years. The demographic characteristics of patients are shown in Table 1. A total of 222 patients (138 males) were enrolled into this study. Mean patient age at time of surgery was 58.8±14.5 years. Of the 222 patients participating in this study, 85 underwent a

Table 2 Follow-up events in patients receiving mechanical heart valve replacement

|                                                         | Patients (n=222) |
|---------------------------------------------------------|------------------|
| Patients (n=222) Total follow-up period (patient-years) | 1366             |
| Valve explant (patient-years)                           | 5/1366 (0.37%)   |
| Total thromboembolic events (patient-years)             | 14/1366 (1.02%)  |
| Ischemic stroke                                         | 11               |
| Limb embolization                                       | 2                |
| Valve thrombosis                                        | 1                |
| Total bleeding events (patients-years)                  | 16/1366 (1.17%)  |
| Hemorrhage stroke                                       | 7                |
| Upper gastrointestinal bleeding                         | 7                |
| Hemothorax                                              | 1                |
| Retroperitoneal hematoma                                | 1                |

single aortic-valve replacement, 105 patients underwent single mitral-valve replacement, and 32 patients underwent simultaneous aortic and mitral-valve replacement. The mean warfarin sodium dose was 2.81 ± 0.75mg/day and the INR value was 2.04 ± 0.73. Perioperative mortality occurred for 7 patients (3.06%). Major bleeding events arose for 16 patients (1.17% per patient-year), this including 7 patients experiencing hemorrhagic cerebral stroke, 7 featuring upper gastrointestinal bleeding, 1 suffering hemothorax, and 1 revealing a retroperitoneal hematoma. Seven patients, who have suffered hemorrhagic cerebral stroke, got permanent neurological defect and needed rehabilitation programs. The others could recovery completely from the bleeding events after adequate management. During the 16 patients with bleeding episodes, 1 belongs to the subgroup of aortic valve replacement (1/85), 10 belong to mitral valve replacement (10/105), and 5 belong to double valve replacement (5/32). Thromboembolism (TE) events occurred for 14 patients (1.02% per patient-year) including 11 patients experiencing ischemic cerebral stroke, 2 featuring limb embolization, and 1 suffering valve thrombosis. Eleven patients, who have suffered ischemic cerebral stroke, got permanent neurological defect and needed rehabilitation programs. The other three patients, who have suffered limb embolization and mechanical valve thrombosis, needed another surgical procedure to resolve the thromboembolic problems. During the 14 patients, 9 belong to the subgroup of arotic valve replacement (9/85), and 5 belong to mitral valve replacement (5/105). There is no any one happening thromboembolic episodes in the subgroup of double valve replacement. Five patients experienced valve explant due to infection or thrombosis accounting for a rate of 0.37% per patient-year (Table 2).

## DISCUSSION

The usual recommendation regarding INR for patients with mechanical valve replacement is 2.0 to 3.5. However, the targets of the currently therapeutic range of the international normalized ratio anticoagulant therapy were nearly recommended on the base of Caucasian patient groups. Although Chinese groups consists a large portion of the world population, we can not find properly recommendations regarding INR range for Chinese patients with mechanical valve replacement. As we survey the adverse episodes associated with INR in our patients, we found some difference regarding proper INR range adopted in our country for patients with mechanical valve replacement. It is apparent that a lower INR than the usual recommendation has been traditionally adopted in Taiwan for a long period. In this article we want to find whether different racial people need different proper therapeutic INR range, or we are running a wrong traditional program for patients with mechanical valves.

Warfarin sodium is a coumarin-derivative anticoagulant which interferes with the cyclic interconversion of vitamin K and its 2, 3 epoxide. Vitamin K is a cofactor for the carboxylation of glutamate residues to  $\gamma$ -carboxyglutamates on the N-terminal regions of the vitamin K-dependent coagulation factors II, VII, IX, and X. Warfarin sodium is widely prescribed for the prevention of thromboembolism events for subjects undergoing/having undergone mechanical heart-valve replacement. Oral anticoagulation therapy is well established in many fields of medicine for the secondary prevention of cardiovascular thromboembolic accidents, thus it is important to control its therapeutic effect and to keep its possible risks at the lowest possible level. There exist a number of different thromboplastins that may elicit different values for prothrombin time subsequent to their administration to patients, thus, over time, the International Sensitivity index (ISI) and, thereafter, the INR have been developed as ways of measuring the level of oral anticoagulation and attempting to optimised it.

Oral anticoagulation therapy inherently bears the associated problem of bleeding disorders, and further, its progressively diminishing effect in a given clinical situation could lead to a thromboembolic episode<sup>8</sup>. To the best of our knowledge, it would appear that there exist a number of inconsistencies relating to the appropriate therapeutic INR range for Chinese patients having received mechanical heart valves. Nevertheless, it is our understanding at time of writing that most doctors in Taiwan set the ideal therapeutic range for patient INR value at from 1.5 to 3.0<sup>9</sup>, a range that would appear to be somewhat lower than the

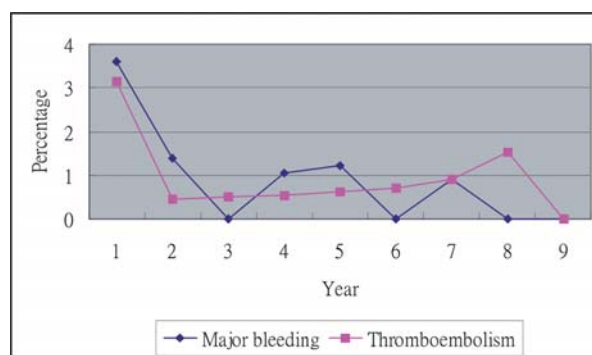


Fig. 1 Successive-year incidence of adverse events subsequent to heart valve-replacement surgery.

corresponding range employed in the U.S.A.<sup>3</sup> and a number of European countries<sup>2</sup>. It would appear that such clinical-practice differences relates to the conclusions of a number of studies pertaining to the purported lower thrombogenicity of the Chinese population compared to Caucasians<sup>7,10,11</sup>, although to the best of our knowledge, however, it would not appear to be entirely clear as to whether this therapeutic range for INR is necessarily optimal for individuals of Chinese descent. From the results of our study, we determined that the annual incidence of either thromboembolism events or major bleeding events following mechanical heart-valve replacement was less than two percent per year over the period from 1 year to 9 years post-surgery (Fig. 1), an incidence that would appear to be at least as good as corresponding figures reported from Western populations<sup>12,13</sup>.

Clearly thus, scheduling the anticoagulant dose in an optimal fashion could lead to a diminished rate of complications associated with heart-valve replacement, a subject that has been addressed in a number of international studies, several of which have heralded the introduction of INR self-management<sup>14,15</sup>. For a total of 53.8% (120/223) of patients participating in this study, clinicians were able to keep the patients' INR target value within the therapeutic range, for 12.6% (28/223) the INR value lay over 3.0 and for 33.6% (75/223) the figure was less than 1.5 for the first month subsequent to surgery. For the group of thromboembolism patients, however, only 36% of such individuals featured an INR value lying within our therapeutic range (1.5-3) at the time the patient experienced a thromboembolism event, and correspondingly, 57% revealed an INR value less than our lower limit of 1.5 (Fig. 2). Complementing such results, for the group of patients suffering a bleeding event, only 18% of such patients featured an INR value lying within our therapeutic range at time of event, with 63% of study participants exhibiting an INR value at

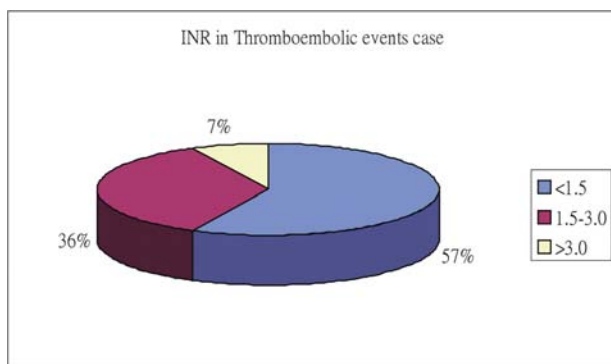


Fig. 2 INR at the time for patients experiencing a thromboembolism event.

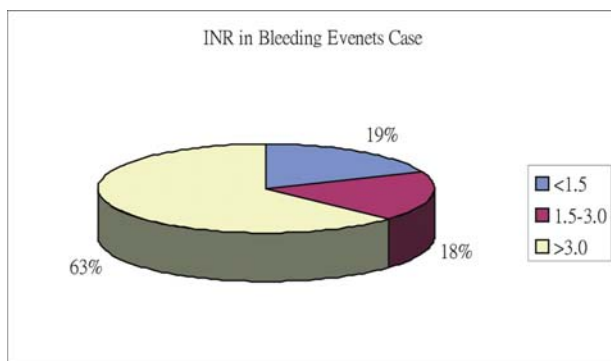


Fig. 3 INR at the time for patients experiencing a bleeding event.

time of event that exceeded the upper limit of our range (Fig. 3). Such data revealed that most of the observed thromboembolism events that arose for study participants occurred at an INR value of less than 1.5, and most of the observed bleeding events occurred at an INR value exceeding 3.0. Clearly thus, it remains important that clinicians should not only attempt to set an optimal INR range for patients having had mechanical heart valves inserted, but to also strive to increase the proportion of such patients that feature an INR value that lies within the recommended INR range. It would appear, thus, that the narrower the optimal target range for the desired therapeutic INR range that is set by clinicians, the lower is the likely incidence of adverse events such as bleeding or thromboembolism. Nevertheless, the relative likelihood for a clinician to be able to attain an INR value for a heart-valve recipient that lies within a narrow therapeutic INR range, and that clinician's ability to maintain the INR value within that narrow range for an extended period of time, should be pondered.

As has been reported often previously, there exists

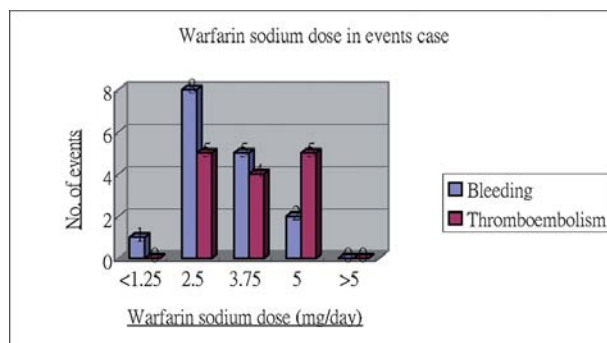


Fig. 4 Warfarin sodium dose at the time for patients experiencing a coagulation event.

significant variance between warfarin sodium dose and the elicited INR value. In this study, the mean warfarin sodium dose was 2.81 mg per day for the overall study population, 1 month subsequent to surgery, as it was considered that this period of time was the optimal period in our study. The mean warfarin sodium dose was 3.66 mg per day for patients who experienced thromboembolism events and 1.96 mg per day for patients who suffered bleeding events (Fig. 4). Clearly thus, some level of inconsistency exists between the warfarin sodium dose delivered and the development of adverse events. The dosage of warfarin sodium required to reach the recommended INR range may be influenced by many factors such as race, concomitant medication being administered and individual genotypes<sup>16,17</sup>. Another scenario that must be considered by attending clinicians is that those patients fitted with a mechanical heart valve need to follow, and precisely so, the prescribed anticoagulant therapy for their specific condition. Incorrect dosage, especially during the first 6-month period following surgery, carries a rather high risk of either severe bleeding or failure to prevent thromboembolism<sup>18</sup>. Subsequent to the first year of warfarin sodium anticoagulant treatment, such risks tend to decline and reach a fairly steady figure, at which level they may remain constant for years<sup>19</sup>, although the relative safety of oral warfarin sodium therapy needs to be closely monitored by serial determinations of blood prothrombin time and INR over a protracted period of time.

## CONCLUSION

Despite the observation that the optimal dose of warfarin sodium reveals significant race and individual-subject variability, anticoagulant therapy based upon the achieved PT-INR value would appear to be relatively constant. The data from our study, the PT-INR therapeutic

range between 1.5 and 3 for patients fitted with mechanical heart valves is enough to prevent mechanical-valve associated adverse events in Chinese patient groups.

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