

# Optimal PT-INR after Prosthetic Valve Replacement: Queen Sirikit Heart Center's Experience\*

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## Abstract

**Background:** Anticoagulant therapy after valve replacement using mechanical valve is indispensable for prevention of thromboembolism. On the other hand, hemorrhagic complications due to overdosed anticoagulations also deteriorate the patients.

**Objectives:** The purpose of this study was to investigate the PT-INR value of the patients who underwent mechanical valve replacement with anticoagulant-related complications compared with those who had no complications. In addition, we aimed to identify the optimal PT-INR value not leading to either hemorrhagic or thromboembolic complications.

**Materials and Methods:** From September 2007 to April 2008, a total of 432 patients who underwent mechanical valve replacement with 962 postoperative follow-up visits were investigated for the PT-INR values and anticoagulant-related complications. The patients were divided into 3 groups: Group I had no complication, Group II had bleeding complications either minor (i.e. gingival bleeding, small subcutaneous ecchymosis or minimal hematuria) or major (i.e. cerebral hemorrhage and large hematoma requiring surgical drainage), and Group III had thromboembolic complications. In addition, Group II was redistributed into 3 subgroups: Group IIa had the PT-INR < 2.50, Group IIb had the PT-INR between 2.50-3.50 and Group IIc had the PT-INR > 3.50. Continuous variables were expressed as a mean + standard deviation. The P values < 0.05 were considered as statistically significant.

**Results:** There were 209 males and 223 females with age ranged from 16 to 80 years (mean 48.87 ± 11.35). The visit times ranged from 1 to 9 visits (mean 2.22 ± 1.27). Mean PT-INR values in Groups I, II and III were 2.57 ± 1.15 (n = 846), 4.09 ± 2.32 (n = 113) and 2.19 ± 1.73 (n = 3) respectively. The PT-INR in Group III showed no difference from the other groups. However, the mean PT-INR in Group II was significantly higher than those of Group I (p < 0.05). Among the hemorrhagic complication cases (n = 113), the mean PT-INR values in Groups IIa, b and c were 1.72±0.50, 3.13±0.26 and 5.17±2.35, respectively. The PT-INR values in Groups IIb and IIc were significantly higher than Group IIa (p < 0.05).

**Conclusions:** 1) The anticoagulant-related bleeding complications usually occurred when the PT-INR values were high especially when > 3.50. 2) The thromboembolic complication could occur even when the PT-INR values were in the therapeutic range. 3) The optimal PT-INR value should not be higher than 3.50.

**Key words:** anticoagulant, prosthetic valve replacement, PT-INR, warfarin

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**INTRODUCTION**

It is generally known that anticoagulant therapy after valve replacement using a mechanical valve is indispensable for prevention of thromboembolism<sup>1</sup>. However, overdosing of anticoagulations can deteriorate the patients<sup>2,3</sup>. Measuring the prothrombin time-international normalized ratio (PT-INR) as recommended by the American Heart Association (AHA) is an alternative way to ensure that patients after heart valve replacement will reach an optimal therapeutic range of anticoagulant therapy<sup>4</sup>. Since bleeding is a serious adverse event after anticoagulant treatment, some physicians suggest slightly lower PT-INR values (2.0-3.0) than values recommended by the AHA (2.5-3.5) in patients at high risk of bleeding<sup>5</sup>. Only a few studies in Asian population were published and they usually recommended that lower dose was appropriate<sup>6,7</sup>. Using the therapeutic range of PT-INR as suggested by Europeans and Americans has also been questioned whether it is too high for Thai people. This preliminary study was designed to verify whether the optimal range recommended by AHA is suitable for Thais and also to determine new optimal range that might minimize the occurrence of thromboembolism and bleeding.

**MATERIALS AND METHODS**

Between September 2007 to April 2008, 432 patients underwent mechanical heart valve replacement with 962 post-operative follow-up visits at Queen Sirikit Heart Center of The Northeast Thailand. All medical records were reviewed for the PT-INR values and the anticoagulant-related complications. The patients were divided into 3 groups: Group I were patients who had no anticoagulant complications whereas the other 2 Groups consisted of patients with complications. If they had bleeding either minor (such as gingival bleeding, small subcutaneous ecchymosis or minimal hematuria) or major (such as cerebral hemorrhage, gross hematuria or large hematoma requiring surgical drainage), they were classified as Group II. In Group III, all patients had thromboembolic complications. The hemorrhagic complication cases in Group II were subdivided into 3 groups according to the basis of the optimal range of PT-INR (2.5-3.5) proposed by AHA's guideline. They were Groups IIa, IIb and IIc which patients had PT-INR

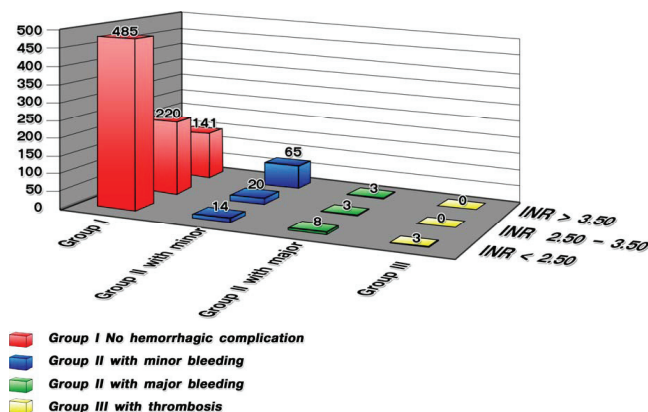
values as <2.5, 2.5-3.5 and >3.5 respectively. Continuous variables are expressed as a mean ± standard deviation. Differences among group were analyzed by using one-way ANOVA. P values < 0.05 were considered as statistical significance.

**RESULTS**

During 8 months of this study, all patients with valve replacement had mean age of 44.87 ± 11.35 years, ranging from 16-80 years. They had average visits of 2.22 ± 1.27 times (Table 1). The mean PT-INR+SD value of three groups were 2.57 ± 1.15, 4.09 ± 2.32 and 2.19 ± 1.73, respectively. When compared among three groups, significant differences of mean PT-INR valve were observed (Table 2 and Figure 2). According to three PT-INR values in Group II in which hemorrhagic complications occurred, most patients were in Group IIc. These results indicated that an increased risk of hemorrhagic complication correlated with an increased PT-INR values (Table 3). In addition, there was an association between the number of patients in group IIa with minor bleeding and the increasing PT-INR values, however, there was no correlation in either group IIB with major bleeding or group III with thromboembolic complications (Figure 1). Among different PT-INR values, the development of

**Table 1** Patients' characteristics

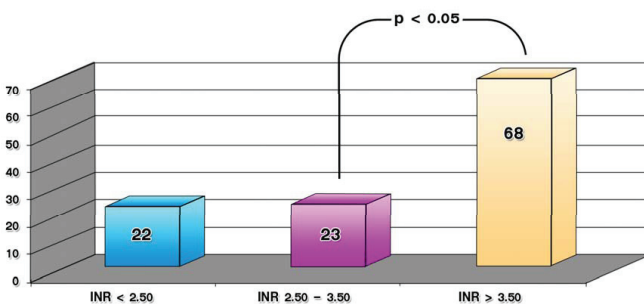
Sex	(n) = 432	Age (yrs.)	Visit (times)
Male	209	16-80	1-9
Female	223	(Mean 48.87 ± 11.35)	(Mean 2.22 ± 1.27)



**Figure 1** Distributions of PT-INR value and various groups

**Table 2** Mean PT-INR values in 962 post-operative follow up visits and the difference of mean PT-INR values among groups.

Group	(n) = 962	Mean PT-INR ( $\pm$ SD)	Sig p < 0.05
Group I (No Complication)	846	2.57 $\pm$ 1.15	S
Group II (Minor & Major Bleeding)	113	4.09 $\pm$ 2.32	S
Group III (Thromboembolism)	3	2.19 $\pm$ 1.73	S



**Figure 2** On the PT-INR distribution in the cases of hemorrhagic complications

**Table 3** Mean PT-INR values in the hemorrhagic complication cases (n = 113) and the difference of mean PT-INR values among groups.

Group	(n) = 113	Mean PT-INR ( $\pm$ SD)	Sig p < 0.05
Group A (INR < 2.50)	22	1.72 $\pm$ 0.50	S
Group B (INR 2.51 - 3.50)	23	3.13 $\pm$ 0.26	S
Group C (INR > 3.50)	68	5.17 $\pm$ 2.35	S

hemorrhagic complications occurred significantly when PT-INR value is 3.50 or over (Figure 2).

## DISCUSSION

Mechanical heart valve prosthesis can induce thrombogenic events and needs anticoagulant treatment to reduce this risk<sup>8,9</sup>. However, there is a risk of hemorrhagic events with anticoagulants. The optimal PT-INR is under debate and different ranges of PT-INR have been proposed. In 1990 the British Society of Haematology recommended the PT-INR values of 3 and 4.5<sup>10</sup>. In the United states, the AHA guideline recommended an PT-INR between 2.5-3.5

whereas study in the Netherlands suggested the optimal INR was between 3.0 and 4.0<sup>11</sup>. However, studies from various Asian countries suggested lower range of PT-INR from 1.4 to 2.5<sup>6,7,12-17</sup>. In this our preliminary study, we collected the 8-month data from 432 patients with 962 visits and followed the AHA's Guideline to control the PT-INR values between 2.5 to 3.5. After anticoagulant treatment, there was significant difference of mean PT-INR values among 3 groups (Table 2). The group with bleeding complications had the mean PT-INR of 4.09  $\pm$  2.32 that higher than the AHA guideline. The group with no complications had the mean PT-INR of 2.57  $\pm$  1.15 that within the range recommended by the AHA guideline. However, the patients with valve thrombosis had the mean PT-INR of 2.19  $\pm$  1.73 that lower than the recommendation (<2.5). In comparison to the bleeding complication group (Table 3), we found that there were significant differences among the mean PT INR of < 2.5, 2.5-3.5 and > 3.5 (Groups IIa, b and c). This result can be concluded that the patients with PT-INR higher than 3.5 has high opportunity to have bleeding complication. However, the mean PT-INR that lower than 2.5 (Group IIa) had the overlapping value with the thrombotic group (Group III, Table 2). Therefore, in our study, PT-INR lower than 2.5 probably cannot be a baseline to protect the thrombotic event. Although various Asian studies suggested the different PT-INR values, the present result was based on AHA recommendation and had the most effective. Nevertheless, long term follow-up data are needed to confirm finally.

In conclusion, we found a clear relation between range of PT-INR value and bleeding complication in patients with mechanical valve prostheses and PT-INR value 2.5-3.5 recommended by the AHA guideline are suitable for Thais.

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