CHAPTER VI

CONCLUSION

This observational study was performed in 107 Thais outpatients who were taking stable dose of warfarin for at least 2 months at The King Chulalongkorn Memorial Hospital. Sixty one patients (57%) were female, mean age was 48.2 ± 13.1 years old; INR was 2.1 ± 0.6 and warfarin dose range from 4.5 to 70 mg/wk. There were no CYP2C9*2 in Thais. Allelic frequency of CYP2C9*3 was 2.0% (95%CI 1.0%-5.0%) which was comparable to Asians except Indian. VKORC1 haplotype group A (75%) was the major group in Thai population. However, allelic frequency of VKORC1 haplotype of Thais was significantly different from Chinese, Japanese, Malaysian and Indian. Most of Thai population had VKORC1 AA/CYP2C9*1/*1 which required warfarin about 21 mg/week.

Mean weekly warfarin dose and clearance was significantly different between CYP2C9*1 and CYP2C9*3 genotypes. CYP2C9*3 was associated with lower warfarin maintenance dose due to lower clearance of warfarin (PK effect) while it was not associated with pharmacodynamic parameters. Furthermore, the mean weekly warfarin dose and total plasma warfarin concentration were significantly different among VKORC1 BB, AB and AA genotypes, $p<0.0001$. VKORC1 AA haplotypes were associated with lower warfarin dose requirement, decreasing in Factor II activity, and increasing in INR:Cp (PD effect) while it was not associated with clearance. Moreover, VKORC1 AA haplotypes was related to risk of bruises and minor bleeding.

In conclusion, this study exhibits a stepwise multiple linear regression model for estimation of warfarin maintenance dose for Thai patients. Using simplified factors containing age, weight, INR:Cp, CYP2C9*3 and VKORC1 genotypes could explained about 59.5% of the variance in warfarin maintenance dose.

Genetic factors including CYP2C9*3 and VKORC1 genotypes played the important role on the interindividual variation in warfarin maintenance dose in Thai population.

The limitations of this study include the following:

1. This study has analyzed plasma total warfarin concentration, not s-warfarin or its metabolites which are the more active forms.
2. The estimation equation did not include the effect of drug interaction of Amiodarone, therefore, the equation is not recommended for patient taking Amiodarone which is a strong enzyme inhibitor (significance level 1).

Consideration for further study:

1. Future research with prospective randomized controlled clinical studies are required to determine the cost-benefit outcome from genetic based dosing regimen.

2. Effect of other genetic factors such as gamma-Glutamyl Carboxylase gene (*GGCX*) and Apolipoprotein E gene (*APOE*) on warfarin dose are required.