CHAPTER I

INTRODUCTION

1.1 Rationale and Background

Warfarin, the most widely prescribed oral anticoagulant, has been used over 50 years to prevent and to treat venous thromboembolism, to prevent acute myocardial infarction and to prevent embolism in patients with prosthetic heart valves or atrial fibrillation. Warfarin is a racemic mixture of S-isomer and R-isomer. S form is 2 to 5 times more potent than R form.[1] Warfarin is metabolized to inactive form by cytochrome P450 enzyme system in the liver while S-isomer is oxidized by CYP2C9, CYP2C19 and CYP2C18 and R-isomer is oxidized by CYP1A1, CYP1A2 and CYP3A4.[2] It exerts anticoagulant effect by inhibiting the vitamin K epoxide reductase (VKOR), the product of *VKORC1* gene in the vitamin K cycle. Thus, interrupt the conversion of vitamin K epoxide to vitamin KH_2 which is a cofactor in the gamma-carboxylation process of activation the vitamin K-dependent proteins (coagulation factor II, VII, IX, X and protein C and S).[3-5]

Warfarin has narrow therapeutic index, it may cause bleeding if dosed too high and blood clotting if dosed too low. The most important complication is bleeding occurring about 7.6 per 100 patient-years (major and fatal bleeding were 1.1 and 0.25 per 100 patient-years respectively).[6] Thus, warfarin dose is usually in sub-therapeutic range because physicians are afraid of their side effects including minor, major and fatal bleeding. In clinically practice, dosing regimen is usually based on age, INR level and indication. Moreover, maintenance dose is varied, ranging from 4 mg to 80 mg per week. It has been shown that there are high intraindividual, interindividual and interethnic variability of warfarin doses. There are many factors interfering pharmacokinetics and pharmacodynamics of warfarin such as drug interactions (drug-drug, drug-food and drug-herb

interactions), patient compliance, other diseases and genetic factors. Therefore, it is difficult to adjust or predict the appropriate dose for individual patient.

CYP2C9 accounts for about 20% of the cytochrome P450 enzymes in human.[7] CYP2C9 polymorphism is associated with the decrease in the metabolism of S-warfarin. CYP2C9*2 and CYP2C9*3 alleles reduces enzymatic activity about 30% and 80%, respectively. Thus, the variant forms of the enzyme has impact on warfarin treatment by decreasing the hepatic clearance, increasing anticoagulant effect and risk of bleeding.[6] Recently, at least 30 alleles of CYP2C9 genotypes have been identified.[8] Only 2 coding variants, termed CYP2C9*2 and CYP2C9*3, are common. In addition, the frequencies of CYP2C9 variants are different among various ethnic groups. CYP2C9*2 is found in 8-20% in Caucasians but not found in Asians (Japanese, Chinese and Korean). The frequencies of CYP2C9*3 are higher in Caucasians (5-16%) than in Asians (1-5%).[9] Many studies have shown that CYP2C9 polymorphisms are associated with lower dose requirement of warfarin during induction and maintenance phase with an increase risk of bleeding. [10-15]

Vitamin K epoxide reductase complex subunit 1 gene (*VKORC1*) has been identified.[16,17] As Rieder et al. [18] has concluded, VKORC1 haplotype group A which is associated with a lower warfarin dose and usually found in the Asian-American population. Haplotype group B which is associated with a higher dose of warfarin and commonly found in the African-American.

Many studies have investigated association of warfarin doses and pharmacokinetic and pharmacodynamic factors involving CYP2C9 and VKORC1 genotypes in differences population such as Caucasian, African and Asian.[19-23] However, the best-fit equation to predict warfarin dose requirement for Thai population has not yet been proposed. Therefore, the purpose of this study was to investigate the prevalence and effect of CYP2C9 and VKORC1 genotypes and

to establish the equation for prediction the maintenance dose of warfarin by using genetic and non-genetic factors among Thai population.

1.2 Hypothesis

Warfarin dose requirement are different in each group of VKORC1 and CYP2C9 polymorphisms.

1.3 Objectives

1.3.1 To determine the association of CYP2C9, VKORC1 polymorphisms and coagulation factors on warfarin maintenance dose.

1.3.2 To determine prevalence of CYP2C9, VKORC1 polymorphisms in Prosthetic Heart valve patients.

1.3.3 To establish equation for prediction of warfarin maintenance dose.

1.4 Expected Outcomes

1.4.1 The influence of CYP2C9 polymorphisms, VKORC1 and other factors on warfarin maintenance dose which are the preliminary data to adjust dose of warfarin in different genotypes.

1.4.2 The equation for predicting warfarin maintenance dose may be useful in the clinical practice.