Original Articles/นิพนธ์ต้นฉบับ

Genetic Determinants of Response to Warfarin in Thai Patients.

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Abstract

Background: Genetic variants of the enzyme that metabolizes warfarin, cytochrome P-450 2C9 *(CYP2C9),* and of a key pharmacologic target of warfarin, vitamin K epoxide reductase *(VKORC1),* contribute to differences in patients' responses to various warfarin doses, but the role of these variants in Thai patients has not been reported.

Objectives: To determine the influence of *VKORC1* and *CYP2C9* genetic variants on the maintenance therapeutic doses of warfarin that keep the international normalize ratios (INRs) between 2.0-3.0 and to assess the probability of over-anticoagulation (INR ≥4) by these genetic variants.

Methods: We studied 80 Thai warfarin-requiring patients who were treated at Ramathibodi Hospital. After informed consent, blood sampling was obtained from patients who had therapeutic INR and had stable maintenance warfarin dose. DNA was extracted from the white blood cells of the peripheral blood sample by conventional methods. *CYP2C9* and *VKORC1* genotypes were determined by the polymerase chain reaction (PCR) method. Warfarin dosage and clinical information were collected from the medical records .

Results: The frequencies of AA, GA, GG (wild type) polymorphisms at -1639 of *VKORC1* were 63.8, 28.7, and 7.5%, respectively. Regarding the *CYP2C9* polymorphisms, 92.5% of all alleles were *CYP2C9*1* (wild type) and 7.5% were *CYP2C9*1/CYP2C9*3.* The mean warfarin maintenance dose differed significantly among the three *VKORC1* genotypes, at 3.3 mg/day for AA, 5.4 mg/day for AG, and 6.0 mg/day for GG ($p<0.001$). Patients with *CYP2C9* variants, compared to those without, had a statistically significant higher odds ratio (OR) of having an INR ≥4 in the first month of therapy (OR: 7.39, $p=0.045$).

Conclusion: Genetic variation in *VKORC1* and *CYP2C9* appears to have a different influence on maintenance dose and anticoagulation related outcome such as the probability of over-anticoagulation.

Keywords: warfarin, *VKORC1, CYP2C9,* Thai

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Introduction

Warfarin, an oral anticoagulation with the vitamin K antagonist, reduces the rate of thromboembolic events for patients in a variety of clinical settings[1]. Warfarin therapy is challenging because there is wide variation among patients in response and therefore in dose requirement. However, warfarin therapy can lead to serious bleeding events. Safe and effective oral anticoagulation with warfarin requires frequent monitoring and dosage adjustment. Factors influencing warfarin dose include age, race, weight, concomitant medications, co-morbidities, and dietary vitamin K intake, as well as genetic variation in the genes that code for cytochrome P450 2C9 *(CYP2C9)* and vitamin K epoxide reductase *(VKORC1).*

Common genetic variants of *CYP2C9,* the enzyme that is primarily responsible for the metabolism of S-warfarin, decrease enzymatic activity compared to wild type enzyme. The *CYP2C9*2, CYP2C9*3* variants are associated with lower warfarin dose requirements[2-5] and a higher risk of serious bleeding events[2,4,6]. The evidence of the association between *CYP2C9* genotype and warfarin dosing requirements is robust. Patients with variant genotypes showed an increased risk of over-anticoagulation, bleeding and lower dosing requirements[7-9].

Anticoagulation activity of warfarin results from inhibition of hepatic vitamin K epoxide reductase *(VKOR)* that affects the synthesis of various coagulation factors. Recently, variants of the genetic variants of hepatic vitamin K epoxide reductase complex subunit 1 gene *(VKORC1)* have been described to have potentially functional consequences. Several studies have found a significant association between warfarin maintenance dose and *VKORC1* variants[9-14]. There is evidence that *VKORC1* status may be associated with over-anticoagulation. Homozygotes for the *VKORC1* low-dose genotype (AA) were found to be a significant factor associated with an INR >5 [9]. Wadelius et al. found that homozygosity for *CYP2C9* and *VKORC1* variant alleles increased the risk of over-anticoagulation during initiation of therapy with the hazard ratios of 21.84 (95% CI: 9.46, 50.42) and 4.56 (95% CI: 2.85, 7.30), respectively[15].

Thus, the purpose of this study was to evaluate the relative effects of *CYP2C9* and *VKORC1* genotypes on patients' outcomes including maintenance therapeutic dose of warfarin, frequency of over-anticoagulation, and bleeding events in Thai patients.

Materials and Methods

Inclusion criteria

All Thai patients whose ages were more than 15 years and received warfarin treatment between September 2003 and Febuary 2007 in the Department of Medicine, Ramathibodi Hospital were included. All had a confirmed initial warfarin exposure date. International normalized ratio (INR) measurements were collected at every visit.

Exclusion criteria

Patients were excluded if they were of Caucasian or African race, unable to provide verbal and written consent, unable to provide a blood sample for genotyping, had liver or renal failure, used drugs that affect warfarin's metabolism or had incomplete data.

Genotype definition

CYP2C9 and *VKORC1* status were determined as described by Busakornruangrat et al[16] and Klamchuen et al[17], respectively. When comparing the differences in outcomes between patients with different *VKORC1* status, all comparisons were made between AA ('low dose'), GA, and GG ('high dose') genotype groups, with GG as the reference group. We chose GG as the reference group because GG is a wild type. *VKORC1* status was modeled as a dummy variable to allow the effects of AA and GA to vary freely. *CYP2C9* was modeled as a binary variable, with the *1/*1 (wild type) genotype defined as the

reference group and *1/*3 genotypes defined as the variant group.

Outcomes and statistical analysis

The characteristics of the patients were compared in the *CYP2C9* genotype groups and the *VKORC1* genotype groups with the use of Fisher's exact test.

Maintenance dose

Stable maintenance warfarin dose that kept the INRs between 2.0-3.0 was defined as a dose that did not vary by more than 10% in the previous 4 weeks and INRs varied less than 15%. Average maintenance dose of warfarin was compared among genotypes with the use of one way ANOVA and Bonferroni tests. Data were presented as mean (SD).

Above-range INRs

The association of *CYP2C9* and *VKORC1* status and the probability of having at least one above-range INRs were assessed using logistic regression models, with and without adjustment for potential confounders. Above range INR was defined as an INR ≥4. We assessed the probability of one above range INR during the first month, three months, and six months after warfarin therapy.

Definition of bleeding events

The association of *CYP2C9* and *VKORC1* status and bleeding that included minor and major bleedings was assessed according to Fihn et al[18].

Table 1. Patients' baseline characteristics.

Variable	VKORC1 AA (N=51)		VKORC1 GA (N=23)		VKORC1 GG (N=6)		P- value
	No. of patients	Percent	No. of patients	Percent	No. of patients	Percent	
Sex							
Male	18	35.3	10	43.5	4	66.7	0.31
Female	33	64.7	13	56.5	2	33.3	
Age (years)	48.1*	16.0**	47.3*	15.3**	38.5*	19.1**	0.39
CYP2C9							
Wild type *1/*1	48	94.1	22	95.7	4	66.7	0.08
Variant *1/*3	3	5.9	1	4.4	2	33.3	
Indication							
Venous thrombo-embolism	42	82.4	22	95.7	5	83.3	0.58
Atrial fibrillation	3	3.8	0	0	0	0	
Antiphospholipid syndrome	2	2.5	0	0	0	0	
Retinal vein occlusion	2	3.9	1	4.4	0	0	
Others	2	3.9	0	0	1	16.7	

(* = mean, ** = SD)

Result

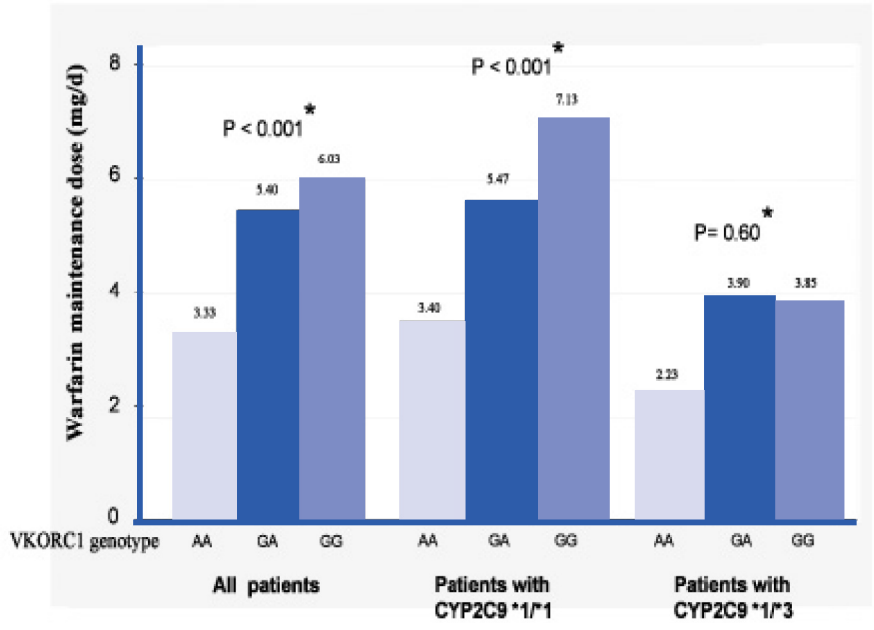
A total of 80 subjects were included in the analyses. The frequencies of AA, GA, GG (wild type) polymorphisms at -1639 of *VKORC1* were 63.8, 28.7, and 7.5%, respectively. Regarding the *CYP2C9* polymorphisms, 92.5% of all alleles were *CYP2C9*1* (wild type) and 7.5% were *CYP2C9*1/CYP2C9*3*. Table 1 described the clinical, genetic, and demographic characteristics of the cohort stratified by *VCORC1* polymorphisms. There was no significant difference among patients with the various *CYP2C9* genotypes and *VKORC1* genotypes with respect to age, sex, and underlying diagnosis.

Maintenance dose

The effect of VKORC1 genotype on warfarin maintenance dose stratified by *VKORC1* genotype and *CYP2C9* status was shown in figure 1. The mean (±SD) maintenance doses of warfarin per day differed significantly based on *VKORC1* genotype: 3.3 (±1.3) mg/day for genotype AA, 5.4 (±1.7) mg/day for genotype GA, and 6.0 (±2.7) mg/day for genotype GG (P < 0.001). Post hoc analysis showed that there was significant difference of maintenance warfarin dose between genotype AA and GA and between AA and GG but not between genotype AG and GG. There was a trend for higher dose requirement of warfarin in *CYP2C9* wild type although it was not statistically significant (Figure 2).

Above-range INRs

During the first month of warfarin therapy, 14% of all patients had at least one INR that was ≥4. At three months and six months of therapy, the percentage of patients who at some points had an INR ≥4 increased to 25 and 29%, respectively. The odds ratio (OR) of having an INR ≥4 was significantly higher for *CYP2C9*1/*3* compared to *CYP2C9*1*1* during the first month but not for three months or six months of warfarin therapy (Table 2). During the first month, three months, and six months of warfarin therapy, patients with *VKORC1* AA and GA genotype did not have an effect on over- anticoagulation. The interaction between *VKORC1* and *CYP2C9* was not statistically



(* one-way ANOVA)

Fig.1 *Effect of VKORC1 genotype on warfarin maintenance dose stratified by VKORC1 genotype and CYP2C9 status.*

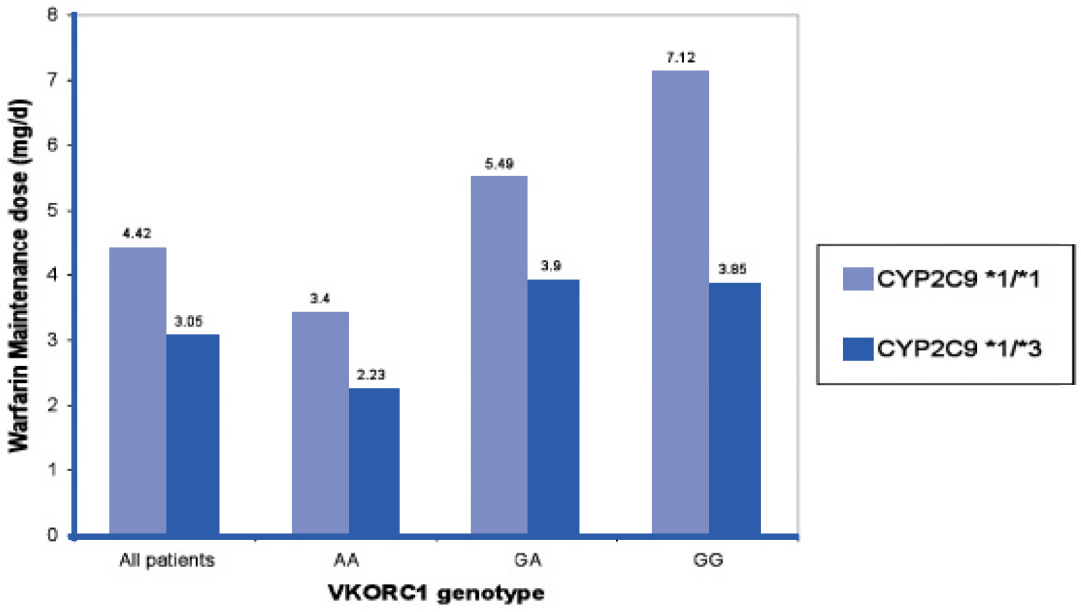


Fig.2 *Effect of CYP2C9 genotype on warfarin maintenance dose stratified by CYP2C9 status and VKORC1 genotype.*

Table 2. Risk of an INR ณ 4 during the first month, three months, and six months.

Exposure	Adjusted OR	(95% CI)	P Value
1 month			
CYP2C9 *1/*3	7.46	(1.06, 52.78)	0.044
VKORC1 AA	3.10	(0.22, 43.48)	0.401
VKORC1 GA	1.06	(0.06, 19.58)	0.969
3 months			
CYP2C9 *1/*3	5.79	(0.86, 39.19)	0.072
VKORC1 AA	0.99	(0.24, 15.22)	0.533
VKORC1 GA	1.93	(0.11, 9.05)	0.991
6 months			
CYP2C9 *1/*3	4.75	(0.70, 32.41)	0.111
VKORC1 AA	2.32	(0.30, 17.67)	0.416
VKORC1 GA	1.18	(0.14, 10.21)	0.883

CYP2C9 comparisons are between patients with wild-type (*1*1) and those with variant (*1*3).
VKORC1 comparisons are with patients with *VKORC1* genotype GG.

significant. Additionally, when the analyses were restricted to *CYP2C9* wild type or to *VKORC1* GG subjects, the results did not change appreciably, indicating that an interaction was unlikely.

Bleeding risk

Bleeding during warfarin treatment in this cohort occurred in three patients. None had major bleeding. The genotype of the first patient was *CYP2C9 1*1, VKORC1* GA and the other two were *CYP2C9 1*1, VKORC1* AA. INRs at bleeding events were 4.4, 5.8, and 6.0 respectively.

Discussion

This study aims to determine the relative influence of *CYP2C9* and *VKORC1* genotype on anticoagulation-related outcomes, i.e. bleeding event in addition to warfarin maintenance dose. Anticoagulant response to warfarin therapy is largely influenced by demographic, clinical, and genetic factors[19,20]. At least two genes are closely associated with warfarin dose requirements: the warfarin's target gene, *VKORC1,* and the gene of its main metabolizing enzyme, *CYP2C9* [3,12,13,21-23]. In 2007, the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research updated the label of warfarin to include information on genetic testing[19]. The FDA encourages personalized dosing in patients with *VKORC1* and *CYP2C9* variant alleles, and randomized clinical trials of pharmacogenetic dosing are now in progress in Europe and the United States.

Some researchers have reported an association between *VKORC1* genotype and over-anticoagulation. Schalekamp et al. reported an association between severe over-anticoagulation and a combination of the low-dose *CYP2C9* and *VKORC1* variants in acenocoumarol patients (OR = 3.83, 95% CI: 1.62, 9.05), but no relationship for either genotype by itself[8]. While these results are similar to ours, several important differences should be noted. The anticoagulants used in the study by Schalekamp et al, acenocoumarol and phenprocoumon, have a half-life of 11 and 140 hours, respectively, which is different from warfarin. Similarly, Meckley et al. also assessed over-anticoagulation among *CYP2C9* and *VKORC1* status[9]. The odds ratio of having an INR >5 was found to be significantly higher for *CYP2C9* variants compared to *CYP2C9* wild types during the first month, three months, and six months of warfarin therapy (OR=4.48, 95% CI: 1.18, 17.00; OR=4.47, 95% CI: 1.37, 14.62 and OR=3.08, 95% CI: 1.06, 8.98), respectively. Likewise, patients with VKORC1AA genotype were also more likely to be over-anticoagulated although it was not statistically significant.

It is known that the *CYP2C9*3* variant causes a major reduction in warfarin metabolism[24]. The largest prospective warfarin treated cohort study by Wadelius et al found that *CYP2C9*3* was strongly associated with supra-therapeutic anticoagulation (INR > 4) during the first five weeks of treatment ($P < 1.1110^{-16}$). Patients carrying *VKORC1* AA genotype had an increased risk of INR > 4 within five weeks (hazard ratio = 4.56, 95% CI: 2.85, 7.30; $P < 2.410^{-10}$). Similar to our study, *CYP2C9*3* variant significantly increased the risk of INR peaks > 4 during the first month of treatment but the *VKORC1* genotypes variant did not. We found that *CYP2C9* variant status seemed to be more strongly associated with over-anticoagulation than *VKORC1.* These findings may have important implications for clinical management of patients based on *VKORC1* and *CYP2C9* status. Additional studies are warranted.

Investigators at the University of Washington (Seattle) and Washington University (St. Louis) recently identified informative SNPs in *VKORC1* correlate with warfarin dose[12]. The 6853 SNP of the *VKORC1* gene correlated with greater gene expression of vitamin K epoxide reductase activity, suggesting that carriers of the G allele require greater warfarin doses because they have greater endogenous epoxide activity. The

mean therapeutic doses of warfarin per day differed significantly based on this SNP: 2.7 mg for genotype AA, 4.9 mg for genotype AG, and 6.2 mg for genotype GG ($P < 0.001$). Our study also showed that the mean maintenance dose of warfarin per day differed significantly based on *VKORC1* genotype. SNPs in *VKORC1* correlated with warfarin dose, but was statistically significant in only *CYP2C9*1* wild type because of the small number of patients' genotype variants. However, for the same *VKORC1* status, the warfarin maintenance dose based on *CYP2C9* status was not statistically significant although there was a trend that patients with wild type required higher dose of warfarin. While *VKORC1* status had a smaller influence on the majority of the clinical over-anticoagulant outcomes in this investigation, it was strongly associated with maintenance dosing requirements for warfarin treatment.

In some studies, *CYP2C9* variant alleles are associated with an increased risk of early bleeding[2,3]. The evidence for an association between *VKORC1* and bleeding is less clear. Reitsma et al reported that *VKORC1* genotype was associated with bleeding in phenprocoumon user (OR: 2.6, 95% CI: 1.2, 5.7) but not for acenocoumarol users (OR: 1.2, 95% CI: 0.6, 2.3); however, they did not control for *CYP2C9* variant status and it was a case-control study[25]. In comparison, in a recent large prospective study, Limdi et al did not find an association between *VKORC1* genotype and bleeding in warfarin treated patients for either major or minor hemorrhages[26]. The incidence of bleeding was rare in our study, bleeding during warfarin treatment occurred in only three patients (3.8%) and none had serious bleeding.

The present study has several limitations. First, because it is a retrospective cohort study, the sample may be biased towards patients who have been on warfarin for a longer period of time. Additionally, information about several potential confounders such as diet and concomitant medication use was unavailable. There are also sample size limitations as the study cohort contained only 6 patients of *VKORC1* GG and 6 patients of *CYP2C9* variants. Due to the paucity of these subjects, it is difficult to confidently assess the association between the *VKORC1* GG and *CYP2C9* variants group and many outcomes, which showed a trend towards a significant difference. We found that the effects of *VKORC1* variants on patient outcomes differed from those of *CYP2C9* variants. This may be a result of the effect of *CYP2C9* variants on warfarin half-life.

In conclusion, genetic variation in *VKORC1* and *CYP2C9* appears to have a different influence on maintenance dose and anticoagulation related outcome such as the probability of over-anticoagulation. Additional studies are needed to evaluate the potential incorporation of this effect into pharmacogenomic based warfarin dosing and management guidelines. Randomized control trial study of pharmacogenetics-based and clinically-based algolrithm are warranted.

Acknowledgement

This study was supported by Thailand Senior Researcher Fund.

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Original Articles/นิพนธ์ต้นฉบับ

ยีนที่มีผลต่อการตอบสนองของยา warfarin ในผู้ป่วยไทย

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บทคัดย่อ

ที่มา: การใช้ยา warfarin เพื่อป้องกันและรักษาภาวะหลอดเลือดอุดตันพบว่ามีภาวะแทรกซ้อนเลือดออกง่ายได้บ่อยซึ่งเกิดจากปัจจัยหลายอย่าง ปัจจัยหนึ่งที่สำคัญคือปัจจัยทางพันธุกรรม เช่น การที่มี polymorphism ของยีนที่ควบคุม cytochrome P-450 2C9 *(CYP2C9)* ซึ่งมีผลต่อขบวนการแปรรูปอณูของยา warfarin และ ยีน vitamin K epoxide reductase complex subunit-1 *(VKORC1)* ที่ควบคุมการสร้าง vitamin K epoxide reductase ทำให้มีการตอบสนองของยา warfarin ที่แตกต่างกันในผู้ป่วยแต่ละคน ซึ่งยังไม่มีรายงานการศึกษาในผู้ป่วยไทย

วัตถุประสงค์: เพื่อศึกษาถึงผลของ polymorphism ของยีน *VKORC1* และ *CYP2C9* ต่อขนาดของยา warfarin ที่ทำให้คงค่า INR (International Normalized Ratio) ให้อยู่ในช่วง 2.0 - 3.0 และดูผลของยีนนี้ต่อการเกิดภาวะต้านการแข็งตัวของเลือดที่มากผิดปกติ (ค่า INR ≥ 4)

วิธีการ: ศึกษากลุ่มผู้ป่วยคนไทย 80 คนที่ได้รับการรักษาด้วยยา warfarin ที่โรงพยาบาลรามาธิบดีและยินยอมเข้าร่วมการศึกษา ทำการสกัด DNA จากเม็ดเลือดขาวของผู้ป่วยและแยกชนิดของยีน *CYP2C9* และ *VKORC1* โดยกระบวนการ polymerase chain reaction (PCR) และทำการศึกษาย้อนหลังดูความสัมพันธ์กับขนาดของยาที่ผู้ป่วยได้รับและข้อมูลทางคลินิกจากเวชระเบียนผู้ป่วย

ผลการศึกษา: ความถี่ของ polymorphism ที่ตำแหน่ง -1639 ของยีน *VKORC1* ชนิด AA, GA, GG (wild type) พบร้อยละ 63.8, 28.7 และ 7.5 ตามลำดับ ในส่วนของ *CYP2C9* polymorphism ชนิดที่พบมากที่สุดคือ *CYP2C9*1/CYP2C9*1* (wild type) โดยพบร้อยละ 92.5 อีกร้อยละ 7.5 เป็น *CYP2C9*1/CYP2C9*3* ค่าเฉลี่ยของขนาดของยา warfarin ที่ทำให้คงค่า INR ให้อยู่ในช่วง 2.0 - 3.0 มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติสำหรับยีน *VKORC1* คือ 3.3 มก./วัน ในกลุ่ม AA, 5.4 มก./วัน ในกลุ่ม AG และ 6.0 มก./วัน ในกลุ่ม GG (P<0.001) ผู้ป่วยกลุ่มที่มี *CYP2C9* variants จะมีโอกาสเกิดค่า INR ≥ 4 มากกว่ากลุ่ม wild type โดยเฉพาะในช่วงหนึ่งเดือนแรกของการรักษา (OR: 7.39 , P=0.045)

สรุป: ความแตกต่างของ polymorphism ของยีน *VKORC1* และ *CYP2C9* มีผลต่อการตอบสนองต่อยา warfarin ทั้งในแง่ของขนาดของยาที่ใช้เพื่อคงค่า INR ให้อยู่ในระดับ 2.0-3.0 และต่อการเกิดภาวะต้านการแข็งตัวของเลือดที่มากผิดปกติ ซึ่งทำให้เสี่ยงต่อการเกิดภาวะเลือดออกง่าย

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