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Polymorphisms in Genes Encoding Metalloproteinase 9 and Lymphotoxin-Alpha can Influence Warfarin Treatment

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Abstract

Objectives: Warfarin treatment is influenced by environmental and genetic factors. The influence of polymorphisms in genes encoding metalloproteinase 9 (MMP9), lymphotoxin-alpha (LTA) andTNFSF14 (LIGHT), related to the inflammatory process of coronary artery disease, on warfarin dose and time to reach target was investigated in this study.

Methods: Outpatients on warfarin treatment (n=227), 20 to 92 years, were enrolled at the Institute Dante Pazzanese of Cardiology (IDPC). Genomic DNA was obtained from peripheral whole blood to evaluate *MMP9* rs17576 (Gln279Arg, A>G), *LTA* rs1041981 (Thr60Asn, C>A) and rs909253 (c.252T>C) and *TNFSF14*rs2291668 (c.147C>T) and rs344560 (Lys214Glu, G>A) polymorphisms by pyrosequencing in Q24PyroMark.

Results: The patients carrying *MMP9* rs17576GG genotype were more likely to require a lower warfarin weekly dose (OR: 2.73, 95% CI: 1.01-7.41, p=0.048). Also, *LTA* rs909253 variant was associated with a longer time to reach the target international normalized ratio (INR) (OR: 1.98, 95% CI: 1.02-3.86, p=0.043). Age was inversely correlated with the target INR (r=-0.387, p<0.001), and dose was directly correlated with time to reach target INR (r=0.244, p<0.001).

Conclusion: *MMP9* rs17576 variant may have an important influence on warfarin weekly dose, and that *LTA* rs909253 polymorphism may also influence the time to reach the target INR.

Keywords: Gene polymorphism; INR; *LTA; MMP9; TNFSF14;* Warfarin.

Introduction

Anticoagulant therapy has been increasingly used due to its efficiency and applicability in various pathologies [1]. The most commonly indicated anticoagulant is warfarin, an oral drug that acts inhibiting the synthesis of vitamin K dependent clotting factor [2].

Indications include prevention and treatment of inflammation triggering diseases such as deep vein thrombosis, extensive anterior myocardial infarction, valve prostheses and bioprosthetic (first three months), atrial fibrillation, intracardiac thrombus, among other cardiovascular diseases, which lately are the leading cause of morbidity and mortality worldwide [3].

It is known that coumarin-type drugs cause many adverse effects, especially risk of bleeding, justifying the need of very strict therapeutic control [4]. In order to decrease the chance of side effects, warfarin treatment has to be continuously monitored by international normalized ratio (INR).

Maintaining the patients within a narrow target range of INR does not always guarantee therapy safety and effectiveness [2]. Interestingly, age, concomitant drugs, comorbidities, vitamin K intake and other environmental factors alongside genetic predispositions are responsible for almost half of warfarin dose variability [5].

Polymorphisms in genes encoding warfarin target (*VKORC1*) and metabolism (*CYP2C9*) have been shown to influence dose and time to reach target INR in patients treated with warfarin [6-8]. Different ethnic groups are also observed to have variations in polymorphisms frequencies [9].

Other candidate SNPs have been studied in relation to warfarin dosage, like in gamma-glutamyl carboxylase (GGCX), calumenin (CALU), CYP2C19, epoxide hydrolase I (EPHX1) and CYP4F2 [10-13]. However, scarce studies include genes related to inflammation, a process deeply connected to main warfarin indications in cardiovascular diseases.

The inflammatory response caused by these diseases can induce the activation of coagulation. Inflammation and coagulation have reciprocal amplifying effects, potentially constituting an environment that is highly proinflammatory and procoagulant in severe disease states. Elucidating these mechanisms increases our understanding of the pathological and pathophysiological events of severe clinical diseases, and may yield new therapeutic targets in the near future [14].

The aim of this study was to verify associations between variability of warfarin response and polymorphisms in inflammation related genes: tumor necrosis factor superfamily member 14 also known as LIGHT (TNFSF14) (rs2291668 and rs344560), lymphotoxin-alpha (LTA) (rs1041981 and rs909253) and metalloproteinase 9 (MMP9) (rs17576).

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Patients and Methods

Study subjects

Two-hundred-twenty-seven individuals (20 to 92 years) under warfarin treatment were selected at the outpatient Oral Anticoagulation Sector of Institute Dante Pazzanese of Cardiology (IDPC), Sao Paulo, Brazil. The subjects signed an informed consent form and agreed to have their blood drawn for genotype analysis. Biodemographic and pharmacotherapy information were obtained from patients' medical files and the outpatient anticoagulation data base. Ethnicity was self-declared.

For each patient, the first day with at least three consecutive measures within target INR range was considered the date of reaching a stable target INR. This date was used to collect medical record and warfarin treatment data.

This study was approved by the Ethical Committee of IDPC and the School of Pharmaceutical Sciences at the University of Sao Paulo (SPS-USP), Sao Paulo, Brazil.

Genotyping analysis

Genomic DNA was extracted from EDTA-treated whole blood using QIAamp DNA Blood kit (Qiagen Inc, Alameda, USA). Quantification of DNA obtained were determined using the Nanodrop ND-1000 spectrophotometer (NanoDrop Technologies Inc, Wilmington, USA) and its integrity was evaluated by 0.8% agarose gel electrophoresis after staining with Gel Red® (Biotium Inc, Hayward, USA).

The *MMP9*rs17576 (Gln279Arg, A>G), *LTA* rs1041981 (Thr60Asn, C>A) and rs909253 (c.252T>C) and *TNFSF14*rs2291668 (c.147C>T) and rs344560 (Lys214Glu, G>A) polymorphisms were determined by pyrosequencing. Initially DNA samples were amplified using a PCR with PyroMark PCR kit (Qiagen GmbH, Hilden, Germany), which has biotinylated and a non biotinylated primers (Invitrogen, Carlsbad, USA) specific for each polymorphism. PCR was carried out with an initial denaturation at 95°C for 15 min; 45 cycles of template denaturation 94°C for 30 s, hybridization 60°C for 30 s and extension 72°C for 30 s; and final extension of 72°C for 10 min. The amplicons were purified by hybridization procedure using vacuum system (WELSH, Niles, USA) PCR to isolate biotinylated single DNA strands, which were sequenced using the PyroMark Q24 (QIAGEN GmbH, Hilden, Germany). Genotype assignment was performed in the PyroMark Q24 software (QIAGEN GmbH, Hilden, Germany) and 10 % of the samples were randomly reanalyzed for quality control procedure.

Statistical analysis

The minimum sample size of 213 patients was calculated using the precision value of 5 mg and the standard deviation of 15 mg of warfarin weekly dose, 5.0 % of significance level (α) and a statistical power of 95.0%. Chi-square analysis was used to test polymorphisms for Hardy-Weinberg equilibrium (HWE) expectations.

Since weekly warfarin dose did not have a normal distribution, the nonparametric Kruskall-Wallis test was used to compare warfarin dose variation across genotypes. Patients were grouped in quartiles of the weekly dose of warfarin and analyzed the first quartile against the last three, and last quartile against the first three. The influence of clinical variables and genotypes on warfarin response was evaluated by univariate and multivariate logistic regression analyses. Spearman rank correlation coefficient (r) was used to verify if the polymorphisms correlated with increased warfarin dose to reach the target INR.

The statistical analyses were performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, USA), and a p value <0.05 was considered as significant.

Results

Study population characteristics

Our study included 227 warfarin treated patients with a mean age of 67.5 ± 13.4 years, ranging from 20 to 92 years, including 118 females (51.8%) and 109 males (48%), 189 Caucasians (83.3%). Arterial hypertension (70.9%) and atrial fibrillation (67.8%) were the most common comorbidities. Considering concomitant medications, most of the patients underwent treatment with medications that can increase INR (72.2%), although they also took medications that have no known effect on INR values (94.2%).

As shown in (Table 1), the target INR ranged from 2.0 to 3.0 for 78% of the patients. The mean target INR reached was 2.51 ± 0.34, and the mean weekly warfarin dose within target INR range was 25.4 ± 12.8 mg.

Interestingly, Spearman correlation analysis showed a weak inverse correlation between age and dose (r=-0.387, p<0.001), age and time to reach the target INR (r=-0.297, p<0.001) and a weak direct correlation between dose and time to reach the target INR (r=0.244, p<0.001).

The genetic polymorphisms did not show a deviation from Hardy-Weinberg equilibrium (P>0.05). Therefore we can assume that genotype frequencies in our population remained constant throughout generations in the absence of other evolutionary influences, such as

Variables	Data	N[d]
Biodemographic Data		
Age, years	67.5 ± 13.4	227/227
Women	52.0%	118/227
Ethnics: Caucasian	83.3 %	189/227
Non Caucasian	16.7 %	38/227
Diseases		
Arterial Hypertension[a]	70.9%	158/223
Atrial Fibrillation[c]	69.1%	154/223
Cardiac Failure[a]	39.5%	88/223
Dyslipidemia[b]	35.9%	80/223
Obesity[c]	13.5%	30/223
Acute myocardial infarction[c]	11.2%	25/223
Hypothyroidism[b]	11.2%	25/223
Stroke[a]	7.6%	17/223
Chronic Renal Failure[a]	4.0%	09/223
Nephrotic Syndrome[b]	0.5%	01/223
Other Diseases non related with INR[c]	98.6%	220/223
Concomitant medications[d]		
INR increase	72.2%	161/223
INR decrease	28.7%	64/223
Increase and/or decrease INR	3.1%	07/223
Without influence on INR	94.2%	210/223
Average of number of medications used	4.4 ± 2.6	223
Target INR Range (2.0-3.0)[e]	78.0%	177/227
Weekly dose warfarin, mg	25.4 ±12.8	227

[a]Comorbidities that increase INR. [b]Comorbidities that decrease INR. [c]Comorbidities without clinical influence. [d]Data from 4 patients are missing. [e]Target INR range for mechanical valves and recurring systemic embolism is 2.5-3.5 and for other indications is 2.0-3.0 (29). INR: International Normalization Ratio; N: Number of Patients.

Table 1: Biodemographic and clinical data of the studied population

non-random mating, mutation, selection, genetic drift, gene flow and meiotic drive [15]. We also have noticed that ethnics, gender, target INR and use of medications that interfere with warfarin treatment, did not have different distribution among the genotypes of all polymorphisms studied (data not shown).

Effects of polymorphisms on warfarin dose and time to reach the target INR

MMP9 rs17576 (Gln279Arg, A>G) polymorphism was associated with variability in warfarin dose to reach the target INR (p=0.01). The median dose of warfarin in patients carrying GG genotype was lower than the carriers of the *A* allele and (AA+AG genotypes) (p<0.05) using Bonferroni correction for multiple comparison tests (Table 2). When compared homozygous ancestral and the mutated the difference remains significant. On the other hand, warfarin weekly dose was not influenced by the *LTA* and *TNFSF14* variants.

In order to evaluate the relationship of the genetic polymorphisms with the response to warfarin, the study population was grouped into quartiles of the weekly warfarin dose (Figure 1). Patients who had reached a stable INR with a warfarin weekly dose within the first quartile (≤ 17.50 mg/week) were considered as using low dose. The median of age of each quartile is shown in (Figure 2), this distribution is significant (p<0.05) like in correlate test.

The univariate logistic regression analysis showed that *MMP9* rs17576 GG genotype was associated with low dose of warfarin per week (OR: 3.05, 95% CI: 1.20-7.80, p=0.02) (Figure 3). Moreover, variables such as age, gender, ethnicity (Caucasian *versus* non Caucasian), target INR, atrial fibrillation (AF) and cardiac failure influence the warfarin response (p<0.05) (data not shown)

The multivariate logistic regression analysis was carried out using age, gender, ethnics, target INR, AF and cardiac failure as covariates. As shown in (Figure 4), *MMP9* rs17576 GG genotype remained significantly associated with low dose of warfarin (OR: 2.73, 95% CI: 1.01-7.41, p=0.048).

The variability of the time to reach dose stabilization within target INR was evaluated in 184 patients, showing a median of 21 (Interquartile range: 7-70) days. The patients were also grouped into quartiles according to the time to reach the target INR, as shown in (Figure 1B). The median age of each quartile is shown in (Figure 2B), this distribution is significant (p<0.05).

The univariate logistic analysis revealed that *LTA* rs1041981 *A* allele (CA+AA genotypes) and rs909253 *C* allele (CT+CC genotypes) were related (p=0.04) to increased time to reach target INR (4th quartile: >70 days) (Figure 3B). In the multivariate logistic analysis adjusted by covariates the patients carrying the *LTA* rs909253 *C* allele are more likely to need longer time to reach the target INR (OR: 1.98, 95%CI: 1.02-3.85; p=0.043) (Figure 4B).

Discussion

AF is one of the most frequent indications of warfarin that leads to an inflammatory process. Many cytokines have been associated with the occurrence of AF and maintenance of the sinusoidal rhythm after the pharmacological and surgical intervention of AF [16]. This direct inflammatory response is seen not only in AF, but also in most of the indications of warfarin. The exacerbation of the inflammatory process is linked to pro-coagulants and also inhibitors of natural mechanisms of anticoagulation [17]. However, there are no described interactions between the studied cytokines and complement system activation pathways according to the Complement Map Database [18].

The inflammation/coagulation interface probably participates in a variety of disease processes. This is most clear in severe sepsis, but emerging data also suggests an important role in inflammatory bowel disease [19]. Patients with rheumatoid arthritis exhibit an increased risk of myocardial infarction [20], potentially providing another mechanism in which inflammation contributes to thrombosis-specifically athero-thrombosis. Futhermore, the general concept of inflammation-mediated downregulation of natural anticoagulants can be seen in common disease, such as atherosclerosis and diabetes, [21].

Polymorphism	Genotype	Frequency	N	Warfarin weekly dose		*P value*[a]
		(%)		Median	25th-75th	
MMP9 rs17576 (Gln279Arg, A>G)	AA[b]	41.9	95	25.00	16.25-33.75	*0.01*
	AG	48.0	109	26.25	17.50-35.00	
	GG	10.1	23	16.25	8.75-26.25	
	G allele	34.2				
TNFSF14 rs2291668 (c.147C>T)	CC[b]	71.4	162	23.75	17.50-35.00	*0.98*
	CT	25.5	58	26.25	13.75-34.06	
	TT	3.1	07	23.75	26.25-35.00	
	T allele	15.9				
TNFSF14 rs344560 (Lys214Glu, G>A)	GG[b]	86.4	196	24.38	17.50-35.00	*0.75*
	GA	12.7	29	25.00	15.00-30.63	
	AA	0.9	02	29.38	Ø	
	A allele	7.3				
LTA rs1041981 (Thr60Asn, C>A)	CC[b]	40.8	92	25.00	15.00-34.69	*0.22*
	CA	48.2	110	23.75	16.25-32.81	
	AA	11.0	25	28.75	20.00-36.88	
	A allele	35.2	160			
LTA rs909253 (c.252T>C)	TT[b]	40.8	93	25.00	15.00-34.38	*0.19*
	CT	48.7	110	23.75	26.25-32.81	
	CC	10.5	24	28.75	20.00-37.81	
	C allele	34.8				

[a]Kruskall-Wallis test and Bonferroni correction for multiple comparison test (GG was different from AA+AG genotypes (p<0.05). [b]Ancestral allele (www.ncbi.nlm.nih.gov).

Table 2: *MMP9, LTA* and *TNFSF14* polymorphisms frequencies and warfarin weekly dose

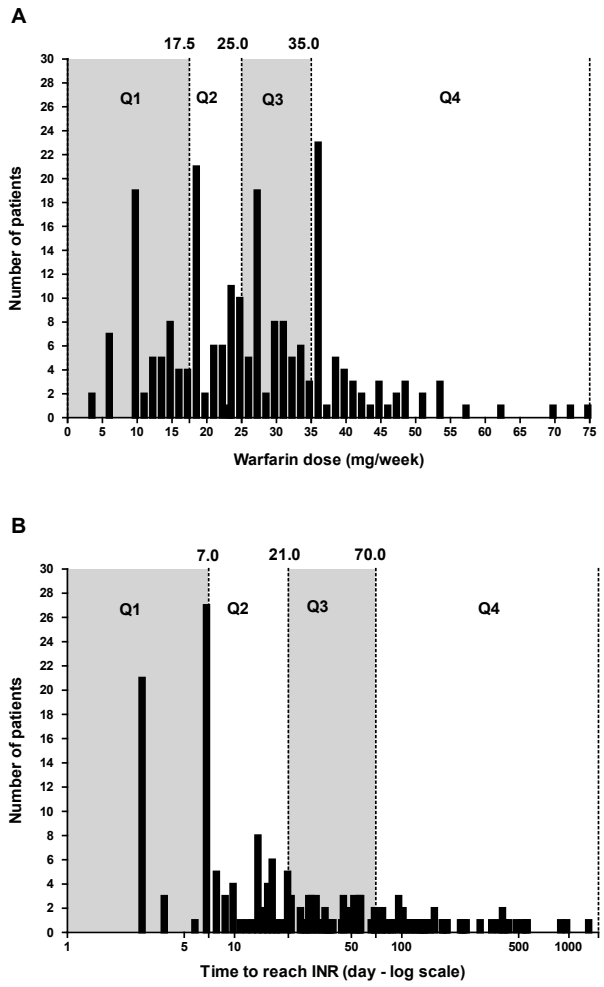

Figure 1: Distribution of the patients in relation to warfarin dose (A) and time to reach the target INR (B) grouped into quartiles. Q1: Quartile 1; Q2: Quartile 2; Q3: Quartile 3; Q4: Quartile 4; INR: International Normalized Ratio.

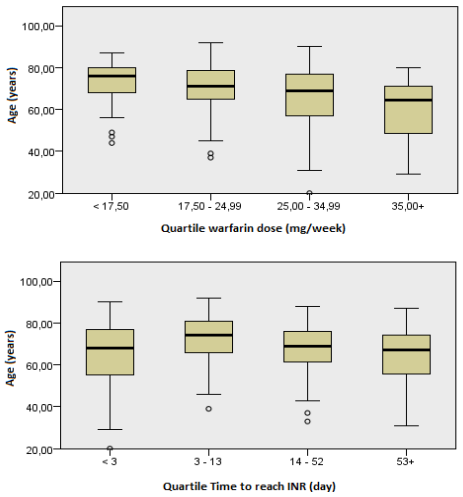

Figure 2: Median age of each quartile to warfarin dose (A) and time to reach the target INR (B) grouped into quartiles. INR: International Normalized Ratio.

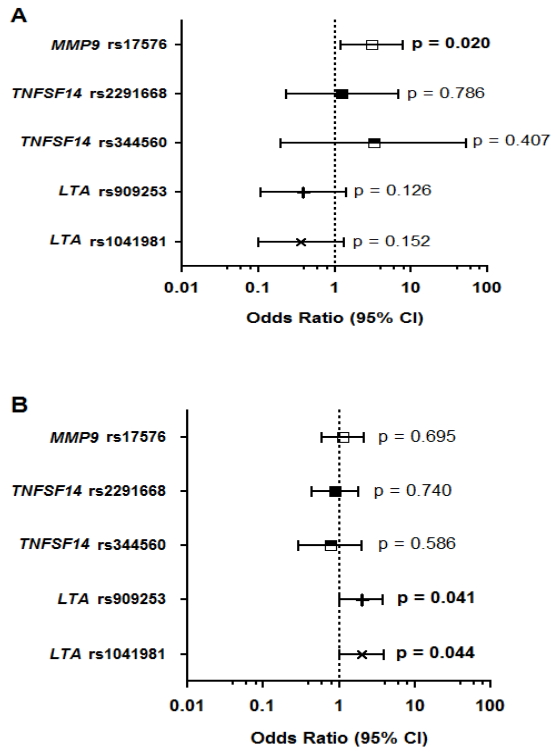

Figure 3: Univariate Logistic regression analysis. Risk for low weekly dose (quartile 1) of polymorphisms homozigotics patients (A) and risk for longer time to reach target INR (quartile 4) in mutated allele carriers (B).

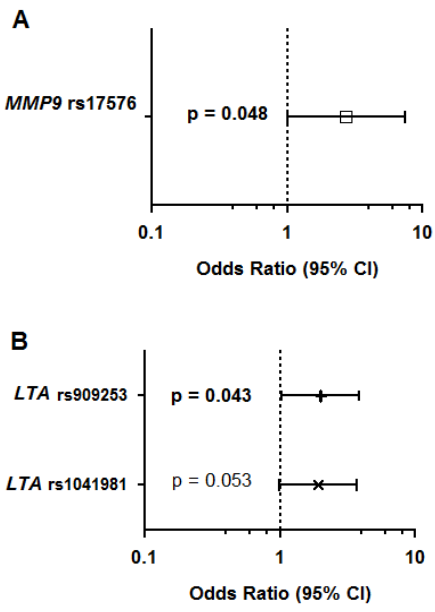

Figure 4: Multivariate logistic regression analysis. Risk for low weekly dose (quartile 1) in mg of polymorphisms homozygote's patients (A) and risk for longer time to reach target INR (quartile 4) in days of mutated allele carriers (B), after adjustment with covariates age, gender, ethnics, target INR, atrial fibrillation and cardiac failure.

The mechanisms are described for the various actions such as the induction of tissue factor on the surface of leukocytes, especially monocytes, increased fibrinogen concentration, increased C-reactive protein, exposure of procoagulant lipids, activation the complement system and action of pro-inflammatory cytokines that cause the activation of the coagulation system while inhibiting fibrinolysis and the natural anticoagulation [14,17].

The inflammatory cytokineTNFSF14, also known as LIGHT, is involved in cell survival and proliferation in the regulation of innate and adaptive immune response [22-24]. In this study, no association was found between polymorphisms in *TNFSF14* and variability in weekly dose of warfarin. However, carriers of *TNFSF14* rs344560 AA genotype showed decrease in LIGHT binding avidity for its receptor DcR3 predisposing patients to unwarranted inflammation [25], possibility leading to dysregulation of warfarin response, due to exacerbation of coagulation.

Dysregulated expression of LIGHT leads to profound inflammation and loss of T cell tolerance, which may induce expression of matrix metalloproteinases (MMPs) and pro-inflammatory factors in endothelial cells leading to progression of the atherogenesis [26].

MMPs degrade collagens of the extracellular matrix and have an important role in vascular remodeling besides clinical and subclinical atherosclerosis. They are involved in leukocyte infiltration, intimal thickening, increase atherosclerotic lesion, thus promoting atherosclerotic plaque instability and rupture [27,28]. It has been shown an association of the *MMP9* rs17576 *G* allele with high plasma concentrations of MMP9 and increased risk for cardiovascular mortality [29]. Moreover other authors showed that high levels of *MMP9* expression in atherosclerotic plaque is involved in the atherosclerosis remodeling process [30].

We have found an association between *MMP9* rs17576 polymorphism and lower dose of warfarin to reach target INR. However, there are no studies investigating *MMP9* polymorphism in warfarin treated patients. Nevertheless, high MMP9 concentrations can lead to intravascular coagulation by cleaving the tissue factor pathway inhibitor (TFPI) that is a multivalent proteinase inhibitor of tissue factor-induced coagulation [31].

Even though MMP9 plasma concentration was not determined in our study, we believe that the MMP9 rs17576 polymorphism could have been decreased, because this polymorphism does not always predict its plasmatic concentration, as it shown in a study with obese patients [32].

Another cytokine involved in atherosclerosis is LTA, which is expressed in activated T and B lymphocytes, macrophages and smooth muscle cells (SMC) [33]. LTA induces the production of adhesion molecules and cytokines, suggesting its contribution to the pathogenesis of atherosclerosis, coronary artery disease and inflammatory process [34,35]. Furthermore, *LTA* polymorphism was associated with increased risk for other inflammatory diseases development such as rheumatoid arthritis, acute myocardial infarction and other cardiovascular diseases [36-38].

Our study showed an association between *LTA* rs909253 (T>C) and a longer time to reach the target INR. This may be explained by an increase in *LTA* production and consequent elevation of overall inflammatory state, thus a systemic inflammatory in balance could make warfarin dose adjustment more difficulty to stabilize in target INR.

The weak inverse correlation between age and dose could be because elderly patients have a reduced hepatic metabolism [39]. Moreover, the indirect correlation between age and time can be associated with the hospital's anticoagulation standard protocol. It begins with a daily standard dose of 5 mg and after 3 days patients are re-evaluated, to gradually increase or reduce the dosage. This enables patients with low dose requirements to have their dose stabilized faster, as supported by the direct correlation between the dose and time.

Conclusion

In conclusion, the findings from this study showed that *MMP9* rs17576 and *LTA* rs909253 polymorphism also influenced the warfarin dose and time to reach the target INR in our study population.

Besides the common variants involved in the pharmacokinetics and pharmacodynamics of warfarin, polymorphisms in inflammation-related genes may also play an important role in warfarin therapy monitoring.

This information can help maintain therapeutic dose and reduce the risk of developing complications caused by changes in INR. For warfarin therapy, a prior knowledge of the patient's genotype can be used to decide the warfarin dose required by each individual.

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