## References


- 1. Wu AH. Pharmacogenomic-guided dosing for warfarin: too little too late? Pers Med. 2018;15(2):71-73. doi:10.2217/pme-2017-0080
- 2. Giraldo-Ocampo S, Diaz-Ordoñez L, Silva-Cuero YK, et al. Frequency of polymorphisms in the CYP2C9, VKORC1, and CYP4F2 genes related to the metabolism of Warfarin in healthy donors from Cali, Colombia. Medicine (Baltimore). 2023;102(30):e34204. doi:10.1097/MD.0000000000034204
- 3. Ivashchenko D, Rusin I, Sychev D, Grachev A. The frequency of CYP2C9, VKORC1, and CYP4F2 polymorphisms in Russian patients with high thrombotic risk. Med Kaunas Lith. 2013;49(12):517-521.
- 4. Quiñones LA, Miranda C, Roco A. Cardiovascular pharmacogenomics: clinical applications in Latin America. Published online 2017.
- 5. Hunt BJ, Levi M. Urgent reversal of vitamin K antagonists. BMJ. Published online January 4, 2018:j5424. doi:10.1136/bmj.j5424
- 6. Anzabi Zadeh S, Street WN, Thomas BW. Optimizing warfarin dosing using deep reinforcement learning. J Biomed Inform. 2023;137:104267. doi:10.1016/j.jbi.2022.104267
- 7. Kimmel SE. Warfarin pharmacogenomics: current best evidence. J Thromb Haemost. 2015;13:S266-S271. doi:10.1111/jth.12978
- 8. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005;352(22):2285-2293. doi:10.1056/NEJMoa044503
- 9. Dean L. Warfarin therapy and VKORC1 and CYP genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, eds. Medical Genetics Summaries. National Center for Biotechnology Information (US); 2012. http://www.ncbi.nlm.nih.gov/books/NBK84174/
- 10. Eljilany I, Elarref M, Shallik N, et al. Genetic and non-genetic factors impact on INR normalization in preprocedural warfarin management. Pharmacogenomics Pers Med. 2021;14:1069-1080. doi:10.2147/PGPM.S322743


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February 20, 2024 / Version 1.0


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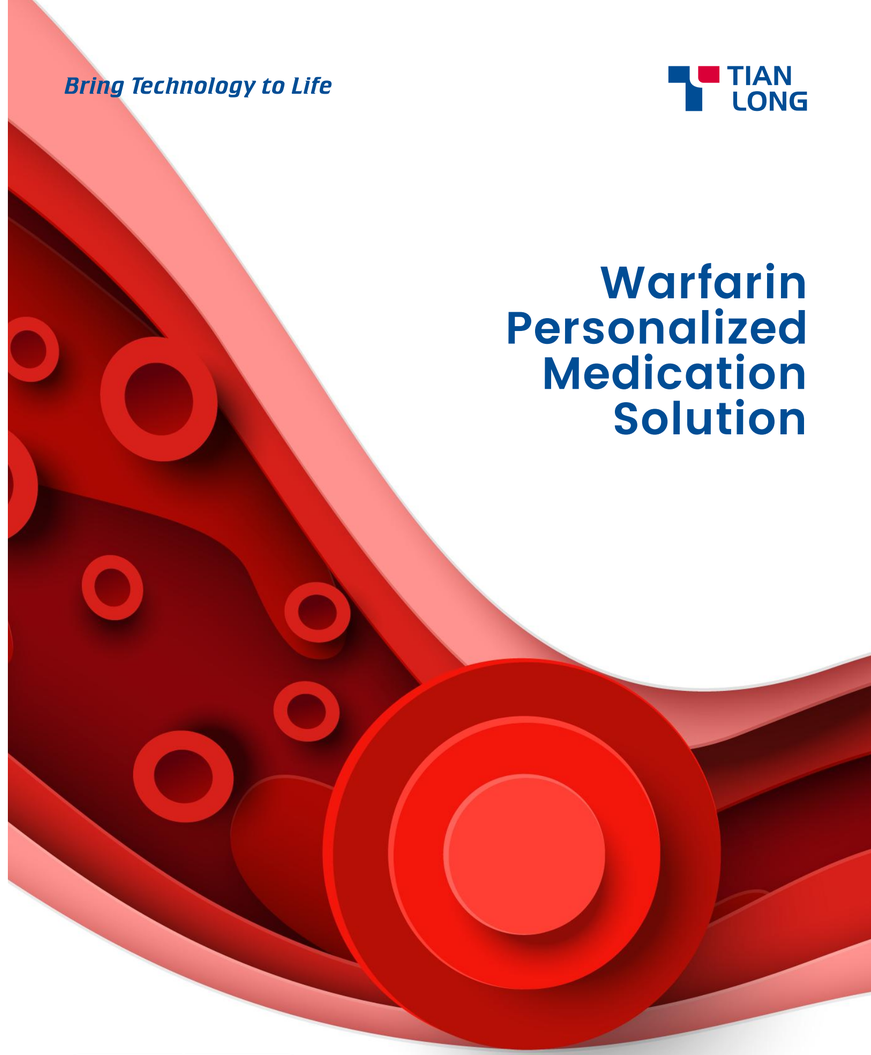
TIAN LONG

# Warfarin Personalized Medication Solution



**Precision Medicine**

## BACKGROUND

Warfarin, a derivative of dicoumarol, is the first clinical oral anticoagulant approved by the US FDA[1]. It has been commonly applied in the treatment and prevention of thromboembolic events, such as deep vein thrombosis, pulmonary embolism, atrial fibrillation, myocardial infarction and stroke, with typical annual prescriptions of 0.5% - 1.5% worldwide[2,3].

## Mechanism of Action

Warfarin competitively inhibits the enzymatic activity of the vitamin K epoxide reductase complex 1 (VKORC1), whose catalytic property is essential for maintaining the dynamic equilibrium of vitamin K between the reduced and oxidized states (Figure 1)[4,5]. Through this mechanism, warfarin can deplete functional vitamin K reserves, and thereby reduce the synthesis of active vitamin-K-dependent clotting factors II, VII, IX and X, as well as the regulatory factors protein C, protein S and protein Z, leading to reduced formation of blood clots[4].

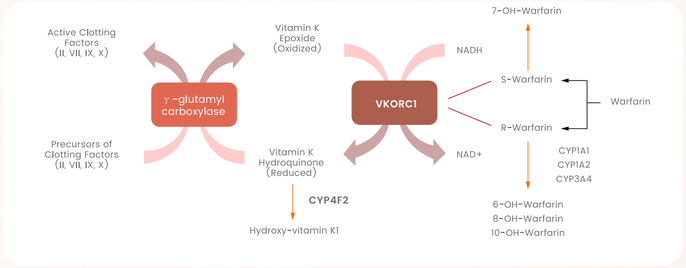



Figure 1. Mechanism of action and metabolism of warfarin (Adapted of Quiñones et al. 2017[4] & Hunt and Levi 2018[5]).

## Adverse Effects of Irrational Warfarin Dosing

As a narrow therapeutic index drug, warfarin therapy requires a persistent monitoring on drug intensity, which is usually indicated by the prothrombin international normalized ratio (INR)[3]. In patients with supratherapeutic INR (INR > 4), risks of bleeding and hemorrhage, as well as complications of warfarin necrosis, osteoporosis, purple toe syndrome and calcification, may increase. It has been reported that 16% of major bleeding incidents and 2.9% of fatal incidents are associated with irrational warfarin use[6]. In contrast, for people lacking adequate dose maintenance, i.e., INR < 2, the anticoagulant therapy normally inefficacious and the risk of thromboembolic events increases[6].

## Gene Polymorphism and Drug Efficacy

Accumulated evidence has demonstrated a consistent and strong relationship between polymorphisms in certain genes (in particular, genes coding for the cytochrome P450 family 2 subfamily C polypeptide 9 enzyme (CYP2C9), VKORC1, and cytochrome P450 4F2 (CYP4F2)) and warfarin maintenance dose[7]. Among the three genes, *VKORC1* haplotype, the encoded enzyme of which directly targeted by warfarin, contributes to approximately 25% of the variance in warfarin dose requirements . Carriers of the AA genotype in the VKORC1 promoter region (c.-1639) have been detected associating with significantly increased sensitivity and lower dose requirements [8] of warfarin (Figure 2)[6,9].

Warfarin is composed of two active enantiomers (i.e. the S- and R-warfarin), where the former possesses 4-6 times higher anticoagulation potency than the latter [2,10] . Of these two enantiomers, S-warfarin is primarily metabolized by CYP2C9. Variants in the c.430 C>T and c.1075 A>C alleles of CYP2C9 reduced its enzymatic activity by 12-70% and almost 100%, respectively, resulting in significantly decreased maintenance doses and increased risks of serious and life-threatening adverse drug effects [8,10].

The CYP4F2 enzyme acts as an oxidase enzyme involving in vitamin K metabolism and blood clot formation. The genetic variant CYP4F2*3 (c.1297 G>A) has been found to be associated with a 8-11% of reduction in enzymatic activity and a 4-12% of increase in warfarin dose maintenance [10].

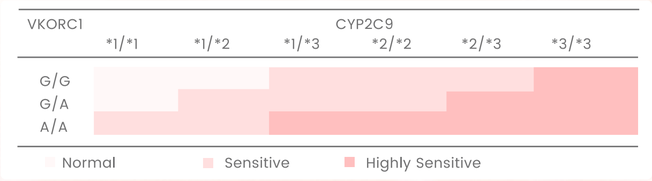



Figure 2. Patient sensitivity based on genotypes of VKORC1 and CYP2C9[6].

## WARFARIN PERSONALIZED MEDICATION SOLUTION

Considering the narrow therapeutic index, the large interindividual variability upon warfarin requirements and severe adverse effects of warfarin therapy, genetic polymorphism detection of key factors involving in warfarin metabolism seems to be vital to maintain the INR in the therapeutic range of 2.0 to 3.0 and to decrease risks of adverse drug effects. Tianlong Warfarin Personalized Medication Solution is designed to rapidly determine the presence of genetic single nucleotide variants or polymorphisms (SNP), including CYP2C9*2 (c.430 C>T), CYP2C9*3 (c.1075 A>C), VKORC1 (c.-1639 G>A) and CYP4F2*3 (c.1297 G>A) in specimen with its exclusive pharmacogenomic reagents and the Fascan 48E multi-channel fluorescence quantitative analyzer. The results can provide genetic clues to guide warfarin dosing in clinical practice.

Table 1. Protocol of genotype detection and warfarin dosing recommendation.

| Gene Locus | Genotype | Genotype |
|---|---|---|
| CYP2C9*2 (c.430 C>T) CYP2C9*3 (c.1075 A>C) | *2CC/*3AA | Regular |
| | *2CT/*3AA | Medium to Low |
| | *2CC/*3AC | Medium to Low |
| | *2TT/*3AA | Low |
| | *2CT/*3AC | Low |
| | *2CC/*3CC | Low |
| VKORC1 (c.-1639 G>A) | GG | Regular |
| | GA | Medium to Low |
| | AA | Low |
| CYP4F2*3 (c.1297 G>A) | GG | Regular |
| | GA | Slightly higher |
| | AA | High |

## Clinical Significance

Guide rational use of warfarin and lower the risk of adverse drug effects.

## Ordering Information

| Product Name | Specification | Specimen | Target Gene Location |
|---|---|---|---|
| LigSeq Reagent Kit (SNP-U2) | 20 T/Kit | 2 mL of EDTA anticoagulated whole blood | CYP2C9 (c.1075 A>C), CYP2C9 (c.430 C>T), CYP4F2 (c.1297 G>A), VKORC1 (c.-1639 G>A) |

## Features

**Reliable Detection**

Strong data analysis software; Internal control can monitor the whole detection process and ensure the accuracy of the detection results reach to over 99%.

**Easy Operation**

Free of sample extraction; Pre-filled reagents; No requirements for specialized equipment or techniques.

**High Efficiency**

Results are available in approximately 70 min after loading samples; Reports are easy to read.

**Integrated Solution**

Tianlong integrated solution from devices to reagents can ensure great compatibility and minimized systematic errors.

## Assay Workflow

1 Sample Collection — 2 Sample Detection — 3 Analysis and Report

*Detection directly after sample collection and report in about 70 min.