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WARFARIN DOSAGE ADJUSTMENT IN PATIENTS WITH GENETIC VARIABILITY

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ABSTRACT

Warfarin is a potent drug that when used judiciously and monitored closely, leads to substantial reductions in morbidity and mortality from thromboembolic events. However, even with careful monitoring, initiation of warfarin dosing is associated with highly variable responses between individuals and challenges achieving and maintaining levels within the narrow therapeutic range that can lead to adverse drug events. Genetic factors most correlated with warfarin dose requirements are variations in the genes encoding the enzymes cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKOR). Patients receiving warfarin who possess one or more genetic variations in CYP2C9 and VKORC1 are at increased risk of adverse drug events and require significant dose reductions to achieve a therapeutic international normalized ratio (INR). The results of this study suggests that the *CYP2C9*2* and *CYP2C9*3* polymorphisms associates an increased risk for over anticoagulation and bleeding events among patients using warfarin anticoagulant, although small numbers in some cases would suggest the need for caution in interpretation. To reduce the risk of adverse reactions in patients, screening for CYP2C9 variants helps the clinicians to develop the new required dosing protocols and surveillance techniques in patients using warfarin[14]. The theme of this review was explaining, of association of *CYP2C9*2* & *CYP2C9*3* variants are in over anticoagulation & bleeding events in warfarin therapy.

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INTRODUCTION

Warfarin, the most commonly prescribed anticoagulant, exhibits large interpatient variability in dose requirements. Management of warfarin therapy is a challenge because of variability in patient response due to a multiple factors including drug, diet, and disease-state interactions [14]. Patient-specific factors (eg, age, body size, race, concurrent diseases, and medications) explain some of the variability in warfarin dose, but genetic factors influencing warfarin response explain a significantly higher proportion of the variability in dose[1]. Warfarin is metabolized primarily via oxidation in the liver by CYP2C9, and exerts its anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (VKORC1). Three single nucleotide polymorphisms (SNPs), two in the *CYP2C9* gene and one in the *VKORC1* gene, have been found to play key roles in determining the effect of warfarin therapy on coagulation. A patient's *CYP2C9* and *VKORC1* genotype can be used to help determine the optimal starting dose of warfarin. The *CYP2C9* gene encodes one of the main enzymes involved in the metabolism of warfarin. Several variant *CYP2C9* alleles are associated with reduced enzyme activity and lower clearance rates of warfarin. Patients who carry at least one copy of such a variant allele (such as *CYP2C9*2* and *CYP2C9*3*) have reduced metabolism leading to higher warfarin concentrations. On average, they require a lower daily warfarin dose than patients who are homozygous for the wild-type *CYP2C9*1* allele. The dose of warfarin must be tailored for each patient according to the patient's INR response and the condition being treated.

Gene association Studies:

Candidate-gene association studies[2-5] have identified 2 genes responsible for the main proportion of the genetic effect: *CYP2C9*, which codes for the enzyme cytochrome P450 2C9 that metabolizes S-warfarin[4]and *VKORC1*, which codes for warfarin's target, vitamin K epoxide reductase.[5,6]The influence of *CYP2C9* and *VKORC1* has also been confirmed by genome-wide association studies among whites.[7-8]Among whites and Asians, *VKORC1* polymorphisms have shown a consistently significant influence on warfarin response, accounting for 11% to 32% of the variability in dose [9-10]Among North American blacks, *VKORC1* polymorphisms account for 4% to 10% of the variability in dose. [11-12]

Warfarin and dosing variability:

Warfarin dosing is highly variable between individuals. A number of factors affect warfarin dosing, including nongenetic factors (drug-drug interactions, environmental factors, including diet, alcohol consumption, and smoking) and genetic factors. There is ample evidence that genetic factors explain about 40% of warfarin dosing variability [13-14].

Table: 1 FDA-Approved Warfarin Dosing.[16]

	CYP2C9					
Allele	*1/*2 (Extensive Metabolizer)	*1/*2 (Intermediate Metabolizer)	***1/*3** (Slow Metabolizer)	*2/*2	*2/*3	*3/*3
VKORC1 GG (Normal)	5.7mg	5.7mg	3.4mg	3.4mg	3.4mg	0.5-2mg
VKORC1 AG (low Sensitivity)	5.7mg	3.4mg	3.4mg	3.4mg	0.5-2mg	0.5-2mg
VKORC1 **AA** Halo type (High Sensitivity)	3.4mg	3.4mg	**0.5-2mg**	0.5-2mg	0.5-2mg	0.5-2mg

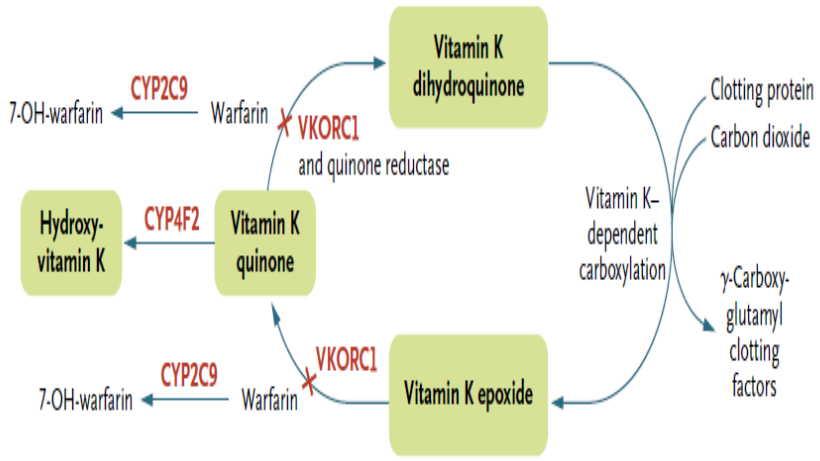

Figure: 1Mechanism of action of warfarin[15]:

- Warfarin works by inhibiting Vitamin K Epoxide Reductase (VKOR)
- VKOR helps recycle vitamin K which is important in proper functioning of clotting factors
- By inhibiting VKOR, warfarin alters the vitamin K cycle and results in the production of inactive clotting factors
- Polymorphisms exist in the gene for VKOR (VKORC1)

- VKORC1 (-1639 G/A) reduces vitamin K to make activated clotting factors
  - G allele: normal expression of VKOR
  - A allele: decreased expression of VKOR

- Lower dose requirements needed in -1639 G/A
- Lowest dose requirements needed in -1639 A/A

Table: 2 Percentage of VKORC1 genotypes.

VKORC1 (-1639 G/A)	AA	AG	GG
Caucasians	19%	56%	25%
Spanish	32%	40%	28%
Chinese	80%	18%	2%
African-Americans	0%	21%	79%

CONCLUSION

The role of VKORC1 and CYP 2C9 polymorphisms in warfarin therapy has been studied. The new and growing field of pharmacogenetics may one day enable clinicians to tailor a patient's warfarin regimen. However, because pharmacogenetics is still in its infancy, more clinical trials, especially prospective randomized studies, are needed to gain a full understanding of the true ramifications in terms of the efficacy and cost of such gene-guided drug therapy.The additional research question that should be addressed is that, whether genotypes require a different target INR, as there might be a substantial overlap in dose requirements with those patients not having the genetic variants. [14]

Conflict of interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

List of Abbreviations:

CYP2C9 -Cytochrome P 450 2 C 9
VKORCI - Vitamin K Epoxide Reductase Complex 1
SNP - Single Nucleotide Polymorphism
INR - International Normalized Ratio

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