INFLUENCE OF GENETIC POLYMORPHISM IN WARFARIN DOSE REQUIREMENT IN SOUTH INDIAN POPULATION

PROJECT REPORT

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DM Trainee

DEPARTMENT OF CARDIOLOGY

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TITLE

“INFLUENCE OF GENETIC POLYMORPHISM IN WARFARIN DOSE REQUIREMENT IN SOUTH INDIAN POPULATION”

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DECLARATION

I, Dr Ramasubramanian N.S, hereby declare that the project in this book, titled “Influence of genetic polymorphism in warfarin dose requirement in South Indian population” was undertaken by me under the supervision of the Faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram

Dr Ramasubramanian N.S

Date: DM Cardiology Trainee

Forwarded

The candidate, Dr Ramasubramanian N.S, has carried out the minimum required project.

Thiruvananthapuram

Prof. Dr Ajit Kumar V.K, Head of Department of Cardiology

SCTIMST
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Dr. Ramasubramanian N.S
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INTRODUCTION
**Introduction:**

Current treatment of prevention of stroke, peripheral embolism and thrombus in mechanical valves require oral anticoagulation, which has flip sides of benefit against risk of development of bleeding including life threatening intracranial bleeds. Though newer drugs are emerging apart from Coumarin derivatives to counteract the risks, none has been found risk free and cost effective in our setting, hence left with options of oral anticoagulants, which has a thin line separating benefits vs. risks. Developments in pharmacogenetics research, has made our understanding of how anticoagulants exert their beneficial role and influences the dose requirement. Various approaches and algorithms were formulated in order to reduce bleeding and improve treatment efficacy and sustainability. In recent researches, it was found that pharmacogenetic based warfarin dosing improves patients’ time in achieving therapeutic INR and reduced bleeding complications.

“The risk of bleeding is another one but of course as we are weighing the risk of stroke over bleeding, most of the time the risks outweigh the benefits in that respect” - Ontario.

Among various genotypes, VKORC1(1) has been found to have maximum effect in determining warfarin dose which accounts for 25 ± 8% of the variance in warfarin dose while CYP2C9 explains approximately 6–10%(2)(3). In view of unique ethnic variations in our country, hence we undertook this study to evaluate the prevalence of VKORC1 and their role in warfarin dosing in our south Indian population.
AIMS & OBJECTIVES
Summary of Proposal:

This is an observational study of patients receiving oral anti-coagulants after heart valve replacement, to assess \textit{VKORC1} gene polymorphism (-1639G>A) as a predictor of Warfarin dose required to maintain the target international normalised ratio (INR).

Hypothesis:

We hypothesize that patients carrying both mutated alleles in the \textit{VKORC1} gene (AA homozygous genotype) requires lower dose of Warfarin to maintain the target INR compared to patients harbouring a single mutant allele (GA heterozygous genotype) or both wild-type alleles (GG homozygous genotype).

Aim of the study:

This study aims to use the \textit{VKORC1} (-1639G>A) genotypes to predict the optimal initial dose of warfarin required to maintain target INR in patients.

Objectives:

i) To determine the frequency of \textit{VKORC1} promoter gene polymorphism (-1639G>A, rs9923231), in South Indian patients.

ii) To correlate \textit{VKORC1} genotypes with the dose of warfarin required to maintain the target INR.
REVIEW OF LITERATURE
**Review of literature:**

Early traces of warfarin was noted in the 1920s, when cattle in the Northern USA and Canada were afflicted by an outbreak of an unusual disease, characterised by fatal bleeding, either spontaneously or from minor injuries. Mouldy silage made from sweet clover (*Melilotus alba* and *M. officinalis*) was implicated, and L M Roderick in North Dakota showed that it contained a haemorrhagic factor that reduced the activity of prothrombin. However, it was not until 1940 that Karl Link and his student Harold Campbell in Wisconsin discovered that the anticoagulant in sweet clover was 3,3′-methylenebis(4-hydroxy coumarin). Further work by Link led in 1948 to the synthesis of warfarin, which was initially approved as a rodenticide in the USA in 1952, and then for human use in 1954. The name warfarin is derived from *WARF* (Wisconsin Alumni Research Foundation) and – *arin* from coumarin
**Mechanism of action:**

Orally administered coumarin-based anticoagulants work by inhibiting vitamin K epoxide reduction by VKORC1 and, thus, block the recycling of vitamin K epoxide and reduced vitamin K (quinone) to the fully reduced quinol form, which is required, along with CO2 and O2, by the vitamin K-dependent (VKD) hepatic γ-glutamyl carboxylase (GGCX) for the biosynthesis of doubly anionic carboxyglutamate (gla) residues on various VKD coagulation factors in the liver. These coagulation factors, including factors II, VII, IX and X, protein C and protein S become activated only through the enzymatic transformation of numerous glutamic acid side chains to gla residues which, in turn, can bind calcium ions to complex with and anchor to anionic phospholipids on platelet surfaces where clotting can proceed. (Figure 1)
Figure 1: WARFARIN AND MODE OF ACTION

Warfarin pharmacokinetic and pharmacodynamics pathway. Warfarin is administered as a racemic admixture of R and S enantiomers. The more potent S enantiomer is metabolized principally by Cytochrome P4502C9 (CYP2C9). The pharmacological effect of warfarin is mediated by the inhibition of Vitamin K epoxide reductase complex 1 (VKORC1). This results in the decreased concentrations of activated clotting factors (II, VII, IX and X) producing therapeutic anticoagulation.
**PHARMACODYNAMIC AND PHARMACOKINETICS OF WARFARIN:**

Warfarin, lipid-soluble coumarin derivative is well absorbed with a bioavailability of over 95%, and a high percentage is bound to plasma albumin for transport through the circulatory system and distribution to internal tissues. Because of non-stereo selective synthesis, coumarins have generally been administered as a racemic mixture of R- and S-enantiomers. Anticoagulant efficacy of the S-enantiomer of coumarin derivatives is about three- to five-fold greater compared to that of the R-enantiomer, but clearance of the S-enantiomers is more rapid(4). Most coumarins such as warfarin or acenocoumarol are eliminated in the liver. Warfarin has a measured circulating half-life of 24–33 hours (h) and 35–58 h for its S- and R-enantiomers, respectively(5). The S-enantiomers are metabolised by CYP2C9 and the R-enantiomers by various other cytochrome P450 isoenzymes.

Among the 3 coumarin derivatives, warfarin and acitrom (acenocoumarol) are the ones commonly used in our setting. The coumarin derivatives mainly differ in their half-life. Acenocoumarol has the shortest half-life of 11 h, followed by warfarin with 36–42 h and the longest half-life is seen in phenprocoumon with approximately 140 h [4–7]. Clearance of the coumarins is not similar, with acenocoumarol and warfarin completely dependent on hydroxylation by cytochrome p450 (CYP), while phenprocoumon can be eliminated as hydroxylated metabolites and as parent compound and hence less dependent on hydroxylation by CYP. Dindivan is a indane dione derivative, with 88% protein binding, and half life of 5-10 hrs and predominantly metabolised by liver.
Figure 2: Warfarin pharmacokinetics and pharmacodynamics

Although the VKORC1-inhibitory effect of R-warfarin is considerably less than that of S-warfarin, when co-administered as a racemic mixture, effect a relatively steady combined anticoagulant effect until they are metabolically cleared. The pharmacokinetic profile is shaped by a combination of S-warfarin reaching its peak concentration faster, followed by a longer steady state, by less potent, R-warfarin plasma level(6)

Warfarin is characterized by narrow therapeutic index, high inter-individual or intra-individual variability in response to treatment(7) and risk of bleeding, which demands consistent monitoring and watchfulness clinically. Major and fatal bleeding

events occur at a rate of 7.2 and 1.3 /100 patient years, respectively, according to a meta-analysis of 33 studies(8).

Other Vitamin K antagonists also depend on similar metabolism. Other used Vit K antagonists were acenocoumarol and phenprocoumon. These coumarins differ in their half life with acenocoumarol having shortest half life of 11 hrs and warfarin having half life of 36-42 hrs, while phenprocoumon found to have the longest half life of 140 hrs. Similar to half life, acenocoumarol differs in clearance by being entirely dependent on CYP p450 hydroxylation process, while warfarin also depends on reduction process as well as hydroxylation process(9).

<table>
<thead>
<tr>
<th>Direction of switch</th>
<th>Transition 95% CI factor</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin to phenprocoumon</td>
<td>0.41</td>
<td>0.39–0.43</td>
</tr>
<tr>
<td>Phenprocoumon to warfarin</td>
<td>2.36</td>
<td>2.24–2.48</td>
</tr>
<tr>
<td>Acenocoumarol to phenprocoumon</td>
<td>0.84</td>
<td>0.79–0.89</td>
</tr>
<tr>
<td>Phenprocoumon to acenocoumarol</td>
<td>1.15</td>
<td>1.08–1.22</td>
</tr>
<tr>
<td>Acenocoumarol to warfarin</td>
<td>1.85</td>
<td>1.78–1.92</td>
</tr>
<tr>
<td>Warfarin to acenocoumarol</td>
<td>0.53</td>
<td>0.51–0.55</td>
</tr>
</tbody>
</table>

**Dosing:**

Warfarin is usually dosed empirically with initial dose prescribed, typically followed by at least weekly measurement of the INR and subsequent dose adjustment. The initial dose based on population averages is usually 4-5 mg/day, but in some settings, it is common to use loading doses during the first few days of anticoagulation.
Irrespective of the method used to initiate warfarin, stable doses to achieve an INR of 2-3 range from 1 to 20 mg/day. The process to define the appropriate dose can take weeks to months and during this period, patients are at increased risk of over- or under-anticoagulation, and thus risk of bleeding or thromboembolism.

**Interaction with other factors:**

Warfarin effects depend on various environmental factors such as intake of Vitamin K, illness, gender, age, concurrent medications and body surface area and by genetic variation(10). Progresses in pharmacogenetics have identified various genes around 30 genes, which have effect in mechanism of action of warfarin and interindividual variability in dose.

Genetic polymorphisms, SNPs (Single Nucleotide Polymorphism) being the most common, are minimal changes in genetic information, present in more than 1% of the population, usually considered to be normal variants, but nevertheless, in certain circumstances, they may have a phenotypic impact. Single nucleotide polymorphisms may fall within coding sequences of genes, non-coding regions of genes, or in the intergenic regions between genes. SNPs within a coding sequence will not necessarily change the amino acid sequence of the protein that is produced, due to degeneracy of the genetic code. SNPs that are not in protein coding regions may still have consequences for gene splicing, transcription factor binding, or the sequence of non-coding RNA. These genetic polymorphisms make an important contribution to the great inter-individual and inter-ethnic variability in drug response.
Genetic literature:

The genes with the strongest literature support, and strong influence in warfarin dosing, are CYP2C9, VKORC1 and CYP4F2. Additionally, genome-wide association studies have identified an independently significant single nucleotide polymorphism (SNP) in the CYP2C cluster.

**CYP2C9 and warfarin**

CYP2C9 is a hepatic drug-metabolizing enzyme in the cytochrome P450 (CYP450) superfamily, and is the primary metabolizing enzyme of S-warfarin. CYP2C9 has over 60 known variant alleles. Individuals homozygous for the reference CYP2C9 allele (CYP2C9*1) have the “normal metabolizer” phenotype. Each named CYP2C9 star (*) allele is defined by one or more specific SNPs and to date, and 18 alleles have been associated with decreased enzyme activity.

The two most common decreased function alleles among individuals of European ancestry are CYP2C9*2 (c.430C>T; p.Arg144Cys; rs1799853) and CYP2C9*3 (c.1075A>C; p.Ile359Leu; rs1057910). CYP2C9 allele frequencies differ between racial/ethnic groups(11). In vitro and in vivo studies suggest CYP2C9*2 and *3 impair metabolism of S-warfarin by ~30-40% and ~80-90%, respectively, compared to patients homozygous for CYP2C9*1. Individuals with these genotypes were predisposed to increased risk of bleeding due to poor warfarin metabolism, hence may require low dosage of warfarin. Additional CYP2C9 alleles (CYP2C9*5, *6, *8, and *11) are associated with decreased function of the CYP2C9 enzyme and contribute to dose variability. These alleles are found with the highest frequency among those of African ancestry.
**VKORC1 and warfarin**

*VKORC1* encodes the vitamin K epoxide reductase protein, the target enzyme of warfarin. VKORC1 catalyzes the conversion of vitamin K-epoxide to vitamin K, which is the rate-limiting step in vitamin K recycling(12).

Mutations in VKORC1 have been observed in two specific regions of the protein primary sequence. The first region comprising the C-terminal transmembrane alpha helix includes two functional domains: the CIVC redox motif (aa 132 – 135) and, adjacent by just one turn further along the helix, the TYA warfarin binding motif (aa 138 – 140)(13). Mutations targeting this region are thought to impair warfarin binding and therefore result in a reduced coumarin effect. The second region, where mutations in *VKORC1* are observed to cluster, is the large (50 to 70 amino acid residues long depending on precise topological assignment) extra-membranous loop that joins the first two N-terminal transmembrane α-helices. In this loop, three highly conserved amino acid residues (Cys43, Cys51, Ser67) were shown by Rost et al. to be essential for VKORC1 activity(14), suggesting the loop is involved in VKOR catalysis and that its overall structure and function are very sensitive to local mutational perturbations. Jin et al. found Cys43 and Cys 51 do not have a large impact on VKOR activity in their experimental system(15). Mutations in this loop region, although distant by linear primary sequence from the warfarin binding site, also lead to coumarin resistance.

*VKORC1* intronic polymorphism influencing median warfarin dose in human patients was identified by D'Andrea et al. in 2005(16). This polymorphism was shown to be part of the complex haplotype *VKORC1*#2. In this haplotype, a single promoter SNP (*VKORC1* c.-1639 G>A, rs9923231) alters a transcription factor binding site, leading to reduced mRNA expression and subsequently total VKOR enzyme activity of haplotype *VKORC1*#2 is reduced to approximately 30–50%(17). Similarly linear dose response was
demonstrated, reflected by a dose reduction of 25% and 50% when comparing homozygous VKORC1 to heterozygous VKORC1*2, and homozygous VKORC1*2 genotypes, respectively. VKORC1 polymorphism and its role in dose requirement of warfarin and their role in largest part of interindividual coumarin dose variation was also well demonstrated(18).

VKORC1 -1639 G>A has emerged as the primary SNP in pharmacogenetic dose requirements for coumarinic oral-anticoagulants. In persons with heterozygous GA genotype, the VKOR enzyme shows intermediate activity and therefore higher maintenance mean daily drug dose requirement. The highest requirement of oral anticoagulant has been observed with wild type GG genotype where the enzyme is not defective at all and is fully functional.

Other common VKORC1 SNPs or haplotypes do not further improve warfarin dose prediction(19). The c.-1639G>A allele frequency varies among different ancestral populations, and largely explains the differences in average dose requirements between whites, blacks and Asians(17).
**CYP4F2 and warfarin**

CYP4F2 is a primary liver vitamin K oxidase which catalyzes the metabolism of vitamin K to hydroxy-vitamin K1 and removes vitamin K from the vitamin K cycle (20). It acts as an counterpart to VKORC1 in limiting excessive accumulation of vitamin K. Furthermore, including this CYP4F2 variant in warfarin dosing models that included CYP2C9, VKORC1 and clinical factors improved the accuracy of dose prediction (21). This correlation has been confirmed in subsequent studies with those of European and Asian ancestry, though not those of African ancestry (22). Two large meta-analyses (from Chinese literature) suggested statistically significant but modest impacts of 8-11% higher warfarin doses in A allele carriers (23).

**Trials and Meta-analysis correlating VKORC1 with warfarin dose:**

Sconce et al (24) investigated the contribution of age, CYP2C9 and VKORC1 genotype, and body size to warfarin-dose requirements. It found that the mean warfarin daily dose requirement was highest in CYP2C9 homozygous wild-type patients, compared with those with the variant *2 and *3 alleles (P < .001) and highest in patients with the VKORC1 (position -1639) GG genotype compared with those with the GA genotype and the AA genotype (P < .001).

Carlquist et al (25) did a large prospective study of warfarin genetic dose-determinants – found that carriage of a single or double CYP2C9 variant, reduced warfarin dose 18-72%, and of a VKORC1 variant by 65%. Genotype-based modeling explained almost one-half of dose-variance. A quantitative dosing algorithm incorporating genotypes for 2C9 and VKORC1 could substantially improve initial warfarin dose-selection and reduce related complications.
Reitsma et al (26) studied on C1173T polymorphism in intron 1 of the VKORC1 gene which has been claimed to determine the interindividual variability in the response to vitamin K antagonist therapy (VKA), and found that those with T allele polymorphism were predisposed to high risk of bleeding than C allele polymorphism.

Randomised trials – Genetic testing and dose requirement:

D'Andrea et al. (16) whose discovery of polymorphism in VKORC1 gene, prone to influence the mean daily maintenance dose- found that the dose required is significantly lower in 1173TT patients (3.5 mg; p<0.001) than in 1173CT patients (4.8 mg; p=0.002) and 1173CC patients (6.2 mg). Militaru et al. have demonstrated the influence of the c.-1639G>A polymorphism on the time to therapeutic INR(27).

Rieder et al (17). studied the VKORC1 gene in 186 Caucasian subjects and identified two A and B haplotypes. A/ A subjects required a significantly lower warfarin maintenance dose (2.7 mg) than A/ B subjects (4.9 mg) and B/ B subjects (6.2 mg).

Montes et al. also showed A allele of the c.-1639G>A polymorphism in the VKORC1 gene was associated with lower dose requirement of acenocoumarol in patients on anticoagulant therapy (28).

One metaanalysis (29)(30)(31) from British Columbia – suggested that time in therapeutic INR showed difference of 6.67% in favour of genetic based warfarin dosing. 7 studies reported 2211 patients with reports of haemorrhagic and thromboembolic events - RR was significant, RR = 0.57 (95% CI 0.33, 0.99), in favour of genotype based dosing, with moderate heterogeneity, I² = 60%

CoumaGen study (32) - a randomized study of PG-guided warfarin initiation versus standard care (5mg/day after a load), masked to patients (n=200) and investigators. It is a first randomised trial to incorporate both CYP2C9 and VKORC1 genotyping, as well as age and weight, into the PG-algorithm, and it analyzed results by
intention to treat. PG-guided dosing predicted stable maintenance dose significantly better. The primary endpoint of percent of out-of-range INRs and the secondary endpoint of time-in-therapeutic range were not met. However, 2 pre-specified genetic subgroups of interest (i.e., those with either multiple variants or with no variants), experienced an absolute 10% reduction in out-of-range INRs with PG-guidance (p=0.03).

European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) and Clarification of Optimal Anticoagulation through Genetics (COAG)(33)(34) trials examined the efficacy of genotype-guided warfarin dosing in randomized controlled trials.

In a homogenous European population, the EU-PACT trial showed shorter time to stable dose, improved percent time in therapeutic range, and reduced number of episodes with an INR>4 using a pharmacogenetic dosing algorithm compared to standard dosing(34).

The COAG trial was conducted in an ethnically diverse cohort with 27% of participants of African ancestry(33). Overall, COAG did not show a difference in time to stable dose, percent time in therapeutic range, reduction in number of episodes with INR >4 or <2, or bleeding risk with a pharmacogenetic dosing algorithm compared to a clinical algorithm. In non-blacks, the pharmacogenetic dosing algorithm arm had more patients whose stable dose was within 1 mg per day of the algorithm-predicted dose (57 vs 39%, respectively). In contrast, the pharmacogenetic dosing algorithm was less accurate at predicting within 1 mg/day of the stable dose than the clinical algorithm in blacks (38 vs 48% respectively). Blacks were more likely to have an INR above range with pharmacogenetic dosing, which could be due to the genotyping panel in the COAG trial being limited to CYP2C9*2, *3 and VKORC1 c.-1639G>A. Other variants that influence warfarin dose and are more common in blacks (i.e., CYP2C9*5, *6, *8, and *11 and rs12777823) were not
genotyped in the COAG trial and their absence likely led to significant overdosing in patients with these alleles. Recent updated CPIC guideline 2017 recommends against pharmacogenetic dosing of warfarin in blacks when only \(CYP2C9^*2\) and \(^*3\) genotype results are available.

The Genetics-InFormatics Trial (GIFT) was a randomized controlled trial examining the effectiveness and safety of genotype-guided dosing versus clinical algorithm dosing in orthopedic patients with a composite outcome that included symptomatic and asymptomatic venous thromboembolism, major hemorrhage, INR \(\geq 4\), and death. It is the first warfarin pharmacogenetics trial powered for clinical outcomes. GIFT included genotyping for \(CYP2C9^*2\) and \(^*3\), \(CYP4F2^*3\), and \(VKORC1-1639\), but did not include the African-specific \(CYP2C9\) alleles or rs12777823. The results of GIFT presented recently in early 2017 revealed a 27% reduction in the composite outcome with genotype-guided versus clinical algorithm dosing, documenting the clinical benefits of a genotype-guided approach to warfarin dosing.

Due to the difficult management of VKA and the risk of bleeding and thromboembolic events, multiple attempts had been taken to develop algorithms in order to establish the therapeutic dose that would protect the patient from these risks. The algorithms developed to estimate the stable therapeutic doses of warfarin, acenocoumarol or phenprocoumon are based both on clinical and pharmacological characteristics of the patients (age, gender, body mass index, concomitant therapy with amiodarone, statins, antifungals, antibiotics, ACE inhibitors, liver failure, kidney failure) and on mutations that directly or indirectly influence the therapy with VKA (polymorphisms in the VKORC1, CYP2C9, CYP4F2, and GGCX genes). Although the algorithms establishing the stable dose of VKA...
antagonists have shown good results in reducing the frequency of adverse reactions, studies did not indicate a good cost-efficiency ratio.

The Gage and IWPC algorithms or minor adjustments to them have been the algorithms used in both randomized controlled trials and most of the prospective dosing studies.

**Genotype and drug dose variability:**

Common variants in *CYP2C9, VKORC1*, and *CYP4F2* account for up to 18%, 30%, and 11% respectively, of the variance in stable warfarin dose among patients of European ancestry(36), but because of differing allele frequencies across populations, these variants explain less of the dose variability in patients of other ancestries.
In particular, *CYP2C9*2 is virtually absent in Asians, and additional *CYP2C9* alleles (e.g. *5, *6, *8, and *11 alleles) occur almost exclusively in persons of African ancestry and contribute to dose variability in this population.

Veclser et al(37) studied the influence of combined genotypes on interindividual variability in warfarin dose-response. Study on the effects of polymorphisms in: *CYP2C9*, *VKORC1*, calumenin (CALU), gamma-glutamyl carboxylase (GGCX) and microsomal epoxide hydrolase (EPHX1) on warfarin dose requirements showed that warfarin daily dose was predominantly determined by *VKORC1* and *CYP2C9* genotypes (partial \( r^2 \) = 0.21; 0.20, respectively). Together with age and body weight, these two genotypes explained 63% of the dose variance.

Consistently, all studies found *VKORC1* genotype as the main predictor of coumarin dosage, whereas *CYP2C9* genotype influence was found to be of minor impact(38)(39)(40). As combinations of polymorphisms in *VKORC1* and *CYP2C9* have been shown to lead to an elevated risk for bleeding events, Genotype-dependant dosage selection would be a tailored, personalized adaptation, which might lead to a significant reduction of initiation phase related complications.

Polymorphisms(41) in the *VKORC1* gene are associated with warfarin maintenance dose requirements among both African Americans and Caucasians. However, these polymorphisms may not be as useful in predicting over-anticoagulation among African Americans. With empirical warfarin dosing, individuals with *VKORC1*-1639G>A are likely to require shorter time to achieve first INR in therapeutic range, but have no difference in time to stable dose.

Randomised trial(31) on warfarin dosing based on pharmacogenetic based warfarin dosing vs standard of care found that genetic based warfarin dosing has shown >10% improvement in time in maintaining stable therapeutic INR,
decreased time to reach therapeutic INR with less change in drug dosage, more patients achieve therapeutic INR range within 25 days, and decrease suprathereapeutic INR.

Recently, polymorphisms of other proteins which influence vitamin K transport and metabolism including apolipoprotein E (APOE), calumenin (CALU), \(\gamma\)-glutamyl carboxylase (GGXC) and microsomal epoxide hydrolase (EPHX1) were shown to affect coumarin dose only marginally. Thus, the effects from these interactions on dosage are small compared to the effects of VKORC1 and CYP2C9 polymorphisms which, together with age and body mass, account for nearly 63% of variance in coumarin dosage(37).

**FDA STATEMENT AND CPIC RECOMMENDATION:**

In 2007, the FDA modified the warfarin label, stating that CYP2C9 and VKORC1 genotypes may be useful in determining the optimal initial dose of warfarin. The label was further updated in 2010 describing recommendations for initial dosing ranges for patients with different combinations of CYP2C9 and VKORC1 genotypes.

**Table 1 Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on CYP2C9 and VKORC1 genotype using the warfarin product insert approved by the US Food and Drug Administration**

<table>
<thead>
<tr>
<th>VKORC1: −1639G&gt;A</th>
<th>CYP2C9*1/*1</th>
<th>CYP2C9*1/*2</th>
<th>CYP2C9*2/*2</th>
<th>CYP2C9*2/*3</th>
<th>CYP2C9*3/*3</th>
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<tbody>
<tr>
<td>GG</td>
<td>5–7</td>
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<tr>
<td>GA</td>
<td>5–7</td>
<td>3–4</td>
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<td>0.5–2</td>
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<td>AA</td>
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<td>3–4</td>
<td>0.5–2</td>
<td>0.5–2</td>
<td>0.5–2</td>
</tr>
</tbody>
</table>

Reproduced from updated warfarin (Coumadin) product label.

**CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (CPIC) RECOMMENDATION: 2017**

The influence of common genetic variation in VKORC1 on variability in warfarin dose was captured by a single polymorphism (either _1639G_A or 1173C_T) across all racial groups. Incorporation of additional VKORC1 SNPs or haplotypes...
did not improve dose prediction. Therefore, current evidence supports the use of \_1639G\_A (or 1173C\_T) to capture dose variability related to \textit{VKORC1}. Both \textit{VKORC1} and \textit{CYP2C9} influenced warfarin dose among individual patients.

**Therapeutic Recommendations: Adults**

*Recommendations for warfarin maintenance (chronic) dosage based on genetic information*

![Diagram of therapeutic recommendations for warfarin maintenance dosage](image)

1. For loading dose, a pharmacogenetics-based warfarin initiation dose algorithm could be considered.
2. Carriers of \textit{CYP2C9*5, *6, *8 or *11} variant alleles (e.g., "1/8, 1/11, 8/11"): Decrease calculated dose by 15-30%.
3. For loading dose, a pharmacogenetics-based warfarin initiation dose algorithm could be considered.
Recommendations for Pediatric Patients:

Genetic polymorphism in various population:

Reider et al(17) –found that VKORC1*2 is highly prevalent in patients of Asian origin (up to 95%), whereas in African populations, VKORC1*2 representing 15% of alleles. In European cohorts, VKORC1*2 shows a prevalence of about 40%. This population-specific distribution is reflected by low coumarin requirement in Asian, intermediate doses in European, and high doses in African populations as has been shown by several independent studies(1) (42).
In a Turkish study, Variant allele frequencies for polymorphisms in the VKORC1 40%, CYP2C9*2 13%, CYP2C9*3 were 15%, often for the same genotype and similar results form another Turkish population studies, respectively, were 50%, 10% and 13%. Results of the Turkish patients is different from Asian and African Americans, it is similar to the most Caucasian populations(43).

All Asian VKORC1 polymorphisms are seen in around 90-95%(6). African Americans are more sensitive to warfarin in the Caucasians and require higher doses than Asians. In summary, the black population has the highest dose requirements for warfarin, moderate in the white population, is the lowest in Asians(44).

Study done in Malaysian population in various migrants found that Indian migrants had higher prevalence of G allele (86% vs. 26% Malaysian vs. 18% Chinese), GG genotype (78% vs. 8% Malaysian vs. 4% Chinese).

There is difference in the distribution of VKORC1 -1639 G>A genotypes between different world populations. The AA genotype is more frequent in Chinese than that in the Caucasians. The frequency of VKORC1 -1639A allele was higher in...
Chinese (94.6%), Japanese (90.1%) and European (39.8%) populations. The VKORC1 -1639A allele frequency in the northern Indian population was 14.22%. The dose requirements of oral anticoagulants were also found to be in accordance with the trend shown by the genotypes.

**Prevalence studies in India:**

Kumar et al (45), studied VKORC1 polymorphism in South Indian population and found that VKORC1 variant A allele to be in 10% of population. This contrasts with other Asian population like China, Japan and Indonesia.

Kaur et al (46), evaluated VKORC1 polymorphism in North Indian population in state of Uttar Pradesh, and found wild ‘G’ variant at 92.8% and ‘A’ allele variant at 7.2%. Combination of Genotypes GG, GA, and AA were 88%, 9% and 2.7% respectively. Similar dose reduction was noted in GA and AA genotype compared to GG genotype.

Rathore et al (47), studied 50 patients in north India, where prevalence of A allele was found to be 22%. Overall AA contributed 2% of the studied population.

Kalpana et al (48) study in Bangalore, showed GG most common at 57%, GA genotypes were 36%, AA was found in 6% of population. Wild variant G allele constituted around 78.5%.

Shalia (49) et al study found that VKORC 1 and CYP2C9 polymorphism showed expected dose reduction in warfarin requirement in their population. There was significant correlation (r=0.51, P<0.001) observed between the dose estimated by pharmacogenetic algorithm of Sconce et al (2005) and actual stable therapeutic dose. INR
was high for mutant variants (3.8 to 4) after first dose suggesting that they require decreased mean daily dose of Warfarin.

De et al(50) in Bangalore, studied CYP2C9 polymorphisms, in 476 acenocoumarol-treated CVT patients. Genotype evaluation suggested higher percentage of wild variant types and requirement of low dose of acenocoumarol with presence of variant alleles. Simultaneous requirement of phenytoin reduced acenocoumarol dose to achieve therapeutic INR.
MATERIALS AND METHODS
Study population:

This is a prospective observational study involving in-depth interviews and case studies. The study subjects consists of patients who need anticoagulation with Warfarin after prosthetic mitral valve replacement for rheumatic heart disease (RHD). Two hundred and twenty two patients who satisfied the inclusion criteria from those attending the INR clinic of SCTIMST run by Cardiology Department were recruited into this study. This sample size was calculated based on the minor allele frequency of VKORC1 gene polymorphism (-1639 G>A) of 0.10 - 0.20, as previously reported in Indian populations, assuming 95% confidence interval. A sample size of 196 samples, (rounded off to 200) was estimated to have an adequate power of 80%.

The inclusion criteria were patients who need anticoagulation with warfarin after prosthetic mitral valve replacement with tilting disc valve for rheumatic heart disease and having normal prosthetic valve function. This included patients on stable warfarin dosing with more than 18 years of age. Stable maintenance dose was conservatively defined as the average daily dosage that consistency yielded a minimum of 2 consecutive INR results within therapeutic range of 2-3 over previous 3 visits, over at least a 3 month period. The exclusion criteria were patients with renal dysfunction, patients with hepatic dysfunction and patients who do not give consent for genetic analysis.

Data collection

Data were collected in a pre-specified data collection proforma during an interview with patients who came to the INR clinic after prosthetic valve
replacement for adjusting warfarin dosage. The data collected included information about age, sex, body weight, height, current dose of warfarin, any previous adverse events related to warfarin and other medications, which the patient was taking, known to affect the metabolism or the dose of warfarin. These participants were given information regarding the research study. After ensuring that the participant had understood the information, patient’s informed consent was obtained in writing. The key (preferable the hospital identification No.) was used to re-identify the participant from the data. After obtaining consent, a phlebotomist/ qualified nurse drew 5 ml of blood sample into appropriately coded EDTA(ethylene, diamine,tetra,acetic acid- used as anti-coagulant) containing blood collection tubes.

**Genotyping of VKORC1 gene polymorphism (-1639 G>A)**

The isolation of DNA followed by genetic screening for VKORC1 gene (-1639 G>A) mutation was done at Inter-University Centre for Genomics and Gene Technology (IU-CGGT), Kerala University, Kariavattom. Identification of VKORC1 -1639 G>A mutation was carried out by PCR amplification followed by restriction fragment length analysis (PCR-RFLP). Oligonucleotide primers were designed using Primer Premier V5.0software. Genotypes were scored by electrophoresis of digested fragments, on 2\% agarose gel and visualized by staining with ethidium bromide. Direct sequencing of PCR amplicons was used to validate the observed genotypes.

**Data analysis :**

Data were analysed using standard statistical techniques by the investigators with supervision from the Statistical Department of the SCTIMST. The outcome variable for each patient were the stable therapeutic warfarin dose (mg/week), defined as the dose of warfarin required to maintain an INR in a target range. Multivariate linear regression model were used
to detect significant effects of \textit{VKORC1} (-1639 G>A) genotypes that influence Warfarin
dosing, adjusted for age, height and weight. The patients was categorized as those requiring
low dose (≤21 mg per week), high dose (≥49 mg per week) and intermediate doses (>21 and
<49 mg per week). Ordered logistic regression was applied to observe the rank ordering of
\textit{VKORC1} (-1639 G>A) genotypes on the three dosage categories.
RESULTS
Results:

In our study, 222 patient genotypes, who had mechanical valve replacement and on warfarin were studied. Out of 222, 109 were males and 113 were females. GG genotypes were found in 185, GA genotype in 33, and AA genotype in only 4 patients. A allele constituted 9.23% in our study population. (Table 1)

FIGURE 3: BASELINE DATA

In our study population, there were bleeding manifestations in 18 patients, accounting for 8%. There was no mortality in our study population during our study period. No lost to follow up in the study population. INR assessment was done predominantly in our Institute, but for few cases, whose INR done at outside centre were collected on follow-up or telephonically.
Table 1 BASELINE DEMOGRAPHICS

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER</td>
<td>109</td>
<td>113</td>
</tr>
<tr>
<td>AGE (mean±S.D)</td>
<td>49.55 ± 14.4</td>
<td>48.37 ± 10.7</td>
</tr>
<tr>
<td>AF</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>H/o Bleeding</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>MEAN INR(mean±S.D)</td>
<td>2.87 ± 0.79</td>
<td>2.94 ± 0.89</td>
</tr>
<tr>
<td>GG</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>GA</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>AA</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean dose of warfarin requirement were studied in individual genotypes. It was found that requirement of warfarin dose was higher in GG genotype than GA and AA genotypes, which was statistically significant. (Table 3)

Table 2: BASELINE GENOTYPES

<table>
<thead>
<tr>
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<th>MEAN DAILY DOSE REQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>222</td>
<td></td>
</tr>
<tr>
<td>GG (185)</td>
<td>5.4 ± 2.1</td>
</tr>
<tr>
<td>GA(33)</td>
<td>4.19±1.44</td>
</tr>
<tr>
<td>AA(4)</td>
<td>4.04±1.72</td>
</tr>
</tbody>
</table>
### TABLE 3: MEAN DOSAGE REQUIREMENT IN VKORC1 GENOTYPES

<table>
<thead>
<tr>
<th>VKORC1 (−1639G&gt;A), rs9923231, n=222</th>
<th>Mean Daily Dosage</th>
<th><em>p</em>-value (GG vs GA+AA)</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes</td>
<td>Freq. (n %)</td>
<td>Allele</td>
<td>Freq. (n %)</td>
</tr>
<tr>
<td>GG</td>
<td>185 (83.33)</td>
<td>G</td>
<td>403 (90.77)</td>
</tr>
<tr>
<td>GA</td>
<td>33 (14.86)</td>
<td>A</td>
<td>41 (9.23)</td>
</tr>
<tr>
<td>AA</td>
<td>4 (1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>222</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HWE**

### TABLE 4: DOSAGE REQUIREMENT IN DOMINANT GENETIC MODEL VS. WILD GENOTYPE VARIANT

Warfarin dose estimates were categorized as high-dose (≥49 mg per week), intermediate dose (>21 and <49 mg per week), and low-dose (≤21 mg per week) groups, and coded as 1, 2, & 3 respectively (according to *N Engl J Med* 2009;360:753-64), and renamed as warcode variable for ologit model.

**Table 2. Relationship between the Warfarin dose categories; high-dose (≥49 mg per week), intermediate dose (>21 and <49 mg per week), and low-dose (≤21 mg per week) and genotypes of the VKORC1 (−1639G>A), rs9923231 polymorphism**

- p<0.05 is significant, indicated in bold
- Model 1: unadjusted for other dependent variable
- Model 2: adjusted for age, BMI & sex
- Model 3: adjusted for age, BMI, sex & amiodarone

Proportional odds ratios of the ordered logit model show the odds of a patient with a variant genotype, either GA or AA or grouped as GA+AA as in the dominant genetic model, being in the low warfarin dose category versus the intermediate/high warfarin dose categories, or low/intermediate warfarin dose categories versus high warfarin dose category.
Need for daily dose requirement and weekly dose requirement was low in GA/AA genotypes when compared to GG genotypes.

**TABLE 5: INR AND THERAPEUTIC RANGES**

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>GG</th>
<th>GA</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIME IN THERAPEUTIC INR</strong></td>
<td>56 ± 21%</td>
<td>57 ±19 %</td>
<td>56± 19 %</td>
</tr>
<tr>
<td><strong>SUBTHERAPEUTIC INR</strong></td>
<td>23 ± 19%</td>
<td>22 ± 18 %</td>
<td>22 ± 18%</td>
</tr>
<tr>
<td><strong>SUPRATHERAPEUTIC INR</strong></td>
<td>20± 11%</td>
<td>20 ± 15 %</td>
<td>21 ± 15%</td>
</tr>
</tbody>
</table>
Figure 4: ALLELE FREQUENCY IN OUR POPULATION

**MUTANT ALLELE FREQUENCY**

- A: 9.2%
- G: 90.8%

FIGURE 5: VKORC1 GENOTYPE DISTRIBUTION

**Total**

- AA: 83%
- GA: 15%
- GG: 2%
Table 6: BLEEDING COMPLICATIONS

<table>
<thead>
<tr>
<th>Bleeding</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC bleed</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Major bleeding requiring blood transfusion</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>
**Figure 6: DeFinetti diagram**

De Finetti diagram with Hardy-Weinberg parabola

Controls

 SNP: SNP1

Controls:
Genotype 11: n = 185 (182.89) [observed(expected)], $\chi^2 = 0.024$
Genotype 12: n = 33 (37.21) [observed(expected)], $\chi^2 = 0.477$
Genotype 22: n = 4 (1.89) [observed(expected)], $\chi^2 = 2.345$

Allele frequency estimates and standard deviation:
Allele 1: 403/444 = 0.908 +/- 0.0145
Allele 2: 41/444 = 0.092 +/- 0.0145

Deviation from H-W equilibrium:
Inbreeding coefficient: $F = 0.11324$
Pearson's goodness-of-fit chi-square (df=1): $\chi^2 = 2.847$, p-value = 0.09157
Log likelihood ratio chi-square (df=1): $\chi^2 = 2.291$, p-value = 0.13009
**** Expected value lower than '5.01'. Chi-square tests may be invalid. ****
Exact Test (Elston & Forthofer, 1977): p-value = 0.09772
Deviation from Hardy Weinberg equilibrium was evaluated by De Finetti diagram. It revealed that there was no statistically significant deviation (p=0.097) from Hardy Weinberg Equilibrium, hence there was no human error in genotype sampling or biased sampling.

### TABLE 7: CHANCE OF SELECTING LOW WEEKLY DOSE WITH VKORC1 GENOTYPES

| warfcode  | Odds Ratio | Std. Err. | z   | P>|z|  | [95% Conf. Interval] |
|----------|------------|-----------|-----|-----|---------------------|
| 1.dominant | 2.768152  | 1.048162  | 2.69| 0.007| 1.317899            | 5.814304 |
| /cut1     | -1.380057  | .1804905  |     |     | -1.733811           | -1.026302 |
| /cut2     | 2.056092   | .2229537  |     |     | 1.619111            | 2.493073 |

**Interpretation:**
A person with GA/AA genotype has 2.79 times greater odds than person with GG genotype of being in the low warf code vs the combine middle and high warf code categories.

or low/medium warf code versus high warf code.
DISCUSSION
Discussion:

In our study of 222 patients, those who underwent valve replacements, genotypic assay revealed GG, GA and AA variants in proportion of 83%, 15% and 2% respectively. Allelic variants of “G” and “A” were found in 90.7% and 9.23% respectively. Prevalence of “A” allele in our study was comparable to other studies like Kumar et al, Kaur et al studies in Indian population (Table 8). Indian prevalence of “A” allele is different from other ethnic Asian population like Chinese, Malaysian and Japanese patients (Figure 7).

Table 8: INDIAN STUDIES IN VKORC1 POLYMORPHISM

<table>
<thead>
<tr>
<th>INDIAN STUDIES</th>
<th>POPULATION</th>
<th>‘G’ ALLELE PREVALENCE</th>
<th>‘A’ ALLELE PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al</td>
<td>Tamilnadu</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Kaur et al</td>
<td>North India (Uttar Pradesh)</td>
<td>92.8%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Rathore et al</td>
<td>North India (SGPGI)</td>
<td>78%</td>
<td>22%</td>
</tr>
<tr>
<td>Kalpana et al</td>
<td>Karnataka</td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>Index study</td>
<td>Kerala</td>
<td>91%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Our study also showed that mean daily dosage requirement of warfarin in individual genotypes GG, GA and AA were 5.46 ± 2.11, 4.20 ± 1.45, and 4.04 ± 1.73 respectively. Dosage requirement in patients with “A” allele were comparatively lower, which was statistically significant (p=0.0026). In view of relatively lower prevalence of “A” allele in our South Indian population, we are relatively resistant to warfarin dose, requiring higher dosage to achieve target INR.

In our study, males and females were in equal distribution (males: 49.5%, females: 50.5%). Mean age in both males and females in our population were 49.5±14.4 years and 48.9±10.73 years respectively. AF was seen in 41 patients accounting for 18.5%. Patients who maintained in therapeutic INR were 56.5%, and those who were in subtherapeutic INR and supratherepeutic INR were 22.5% and 20.5% respectively.

**Figure 7: VKORC1 POLYMORPHISM IN OTHER POPULATION**

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>‘A’ ALLELE PREVALENCE</th>
</tr>
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<tbody>
<tr>
<td>Chinese</td>
<td>92.4%</td>
</tr>
<tr>
<td>Japanese</td>
<td>91.8%</td>
</tr>
<tr>
<td>Indonesians</td>
<td>77%</td>
</tr>
<tr>
<td>Iran</td>
<td>55%</td>
</tr>
<tr>
<td>UK</td>
<td>43%</td>
</tr>
<tr>
<td>POPULATION</td>
<td>‘A’ ALLELE PREVALENCE</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Romania</td>
<td>42.2%</td>
</tr>
<tr>
<td>US</td>
<td>46.4%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>41%</td>
</tr>
<tr>
<td>African American</td>
<td>12.9%</td>
</tr>
<tr>
<td>North India</td>
<td>14%</td>
</tr>
</tbody>
</table>

Odds ratio of requirement of lower dose of warfarin in GA+AA genotypes combined in unadjusted, and after adjustment of age, sex and amiodarone were 2.7 and 2.59. Predictive value of requirement of low dose of warfarin in patients with GA and AA genotypes was more than 2 fold, which occurs irrespective of age, sex, BMI and usage of other drugs with interaction. AA genotype had more predictive accuracy than GA genotype to select low dose of warfarin (more than 4 fold predictive accuracy). Predictive accuracy of choosing low dose of warfarin was higher for AA>GA>GG. GG genotype required the highest dose of warfarin requirement to maintain therapeutic INR.

Italian study(51) in 2013 found that only 58% of patients started on OAC for atrial fibrillation achieved therapeutic INR at hospital discharge. Different studies in European countries showed that therapeutic INR achievement in France, Germany, Italy and United Kingdom were 48%, 44%, 46% and 65% respectively(52). In US ORBIT-AF(53) registry, it was found that mean and median TTR of 65% ± 20% and 68%(interquartile range [IQR] 53%-79%).59% of overall 5290 patients achieved INR of 2-3.
Among patients who had bleeding, males were 8 and females were 10. Among the bleeding manifestations, 5 had a major bleeding including 2 had intracranial bleed, 3 had major bleeding requiring blood transfusion, 13 had minor bleeding which resolved with conservative management. Most of them happened in form of skin ecchymosis. All such episodes occurred during supratherapeutic INR >4.0.
LIMITATIONS
Limitation:

Current study has some limitations in form of low sample size, to be representative of the whole population. India with its unique diversity has wide range of genomic variations with regional differences. Our study was an observational study of prevalence of VKORC1 genetic polymorphism, and no controls used. Evaluation of bleeding complications was done over a period of 1 year, with retrospective information in most patients, hence predisposing to recall bias. In acitrom using patients, who constituted 30% in our population, Warfarin dose was calculated based on warfarin equivalent dose of acitrom, thereby can cause minor variations in exact warfarin doses.
CONCLUSION
Conclusion:

Genetic prevalence of VKORC1 polymorphism in 1638 allele G>A (A allele) in Kerala population is 9.23%. It is comparable to other Indian population as per studies done previously. Dose requirement of warfarin is comparatively lesser in patients with “A” allele compared to those having “G” allele. Heterozygote’s and homozygote’s for “A” allele require statistically significant dose reduction of warfarin dose. Achievement of therapeutic INR (TTR) in our study population is 57%.
BIBLIOGRAPHY


ANNEXURE
PROFORMA
**Data Collection Proforma**

**Study Title:** Influence of Genetic Polymorphisms in Warfarin Requirement in a South Indian Population.

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Name:</td>
</tr>
<tr>
<td>2.</td>
<td>Hosp. No:</td>
</tr>
<tr>
<td>3.</td>
<td>Age:</td>
</tr>
<tr>
<td>4.</td>
<td>Sex:</td>
</tr>
<tr>
<td>5.</td>
<td>Height:</td>
</tr>
<tr>
<td>6.</td>
<td>Weight:</td>
</tr>
<tr>
<td>7.</td>
<td>BMI:</td>
</tr>
<tr>
<td>8.</td>
<td>Date of performing MVR:</td>
</tr>
<tr>
<td>9.</td>
<td>Rhythm: Sinus rhythm / Atrial fibrillation</td>
</tr>
<tr>
<td>10.</td>
<td>Warfarin initiated on (date):</td>
</tr>
<tr>
<td>11.</td>
<td>Initial dose:</td>
</tr>
<tr>
<td>12.</td>
<td>Maintenance dose (in last 3 months):</td>
</tr>
<tr>
<td>13.</td>
<td>Time to reach maintenance dose (Days):</td>
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<td>14.</td>
<td>Aspirin therapy: Yes / No If yes – Dose:</td>
</tr>
<tr>
<td>15.</td>
<td>Number of INR Clinic /Hospital visits till maintenance dose reached:</td>
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<tr>
<td>16.</td>
<td>Other medications patient is currently taking (for past 3 months):</td>
</tr>
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<td>17.</td>
<td>History of any adverse events:</td>
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<tr>
<td></td>
<td>a. Major bleeds (requiring blood transfusion/interruption of warfarin therapy, Intracranial bleeding)</td>
</tr>
<tr>
<td></td>
<td>(i) Dose of Warfarin at that point:</td>
</tr>
<tr>
<td></td>
<td>(ii) Patient taking that dose for how many days:</td>
</tr>
<tr>
<td></td>
<td>(iii) INR at that point:</td>
</tr>
<tr>
<td></td>
<td>b. Thromboembolic events:</td>
</tr>
<tr>
<td></td>
<td>(i) Dose of Warfarin at that point:</td>
</tr>
<tr>
<td></td>
<td>(ii) Patient taking that dose for how many days:</td>
</tr>
<tr>
<td></td>
<td>(iii) INR at that point:</td>
</tr>
<tr>
<td>18.</td>
<td>LA size:</td>
</tr>
<tr>
<td>19.</td>
<td>LV function (Ejection fraction):</td>
</tr>
<tr>
<td>20.</td>
<td>Prosthetic valve function:</td>
</tr>
<tr>
<td>21.</td>
<td>VKORC1(-1639G&gt;A) Genotype: AA / AG / GG</td>
</tr>
</tbody>
</table>
IEC
Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

Dr. Harkrishnan S
Additional Professor
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Harkrishnan,

Thank you for submitting documents related to your proposal titled "INFLUENCE OF GENETIC POLYMORPHISM IN WARFARIN REQUIREMENT IN SOUTH INDIAN POPULATION" (IEC/374) to the IEC for review.

List of Documents
1. Covering letter addressed to the Chairman, IEC, SCTIMST
2. Copy of the IEC Approval Letter dated 20.05.2015.

IEC Recommendations

The request was approved.

Sincerely,

Mala Ramanathan
Member Secretary, IEC
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- [0] www.nytimes.com/2006/11/01/health/01stroke.html
  - 1 matches

3 pages, 633 words

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- Sensitivity: Medium
- Bibliography: Consider text
- Citation detection: Reduce Plag Level
- Whitelist: --
MASTER CHART