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Association of Medication Adherence and VKORC1 Polymorphisms with Stable Warfarin Dose Requirements in Patients with Mechanical Heart Valves

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ABSTRACT

Warfarin remains the primary oral anticoagulant for patients with mechanical heart valves, but considerable interindividual variability in stable dose requirements poses a clinical challenge. Although VKORC1 gene polymorphisms are well-established determinants of dose variability, the impact of objectively measured medication adherence is less clear. This study aimed to evaluate the independent and combined effects of VKORC1 polymorphisms and objectively measured medication adherence on stable warfarin dose requirements in patients with mechanical heart valves. Genotyping of VKORC1 −1639G>A (rs9923231) and 1173C>T (rs9934438) was performed using PCR–RFLP. Adherence over 90 days was expressed as the percentage of prescribed doses taken. The −1639A allele frequency was 81.7%, and patients with the AA genotype required significantly lower daily doses than GA or GG genotypes ($p<0.001$). Mean adherence was 89.4±11.2%. Multivariate regression showed that VKORC1 genotype, age, and adherence independently predicted stable dose,explaining 45.2% of variability. Stable warfarin dose was defined as an unchanged maintenance dose with a therapeutic INR (2.0–3.5) for ≥3 months.Adherence below 80% was associated with increased INR fluctuations and dose adjustments, highlighting adherence as a key clinical modifier alongside genetic factors.

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INTRODUCTION

Warfarin remains the cornerstone of long-term oral anticoagulation therapy for patients with mechanical heart valves, playing a critical role in the prevention of thromboembolic complications, including valve thrombosis and systemic embolism. Despite the development and widespread use of direct oral anticoagulants (DOACs), warfarin continues to be the only recommended anticoagulant for patients with mechanical valves, as newer agents have not demonstrated consistent safety or efficacy in this high-risk population (Pratt et al., 2012). Managing warfarin therapy, however, is inherently challenging due to its narrow therapeutic index, which requires maintaining the international normalized ratio (INR) within a tight range. Both subtherapeutic and supratherapeutic anticoagulation carry significant clinical risks: underdosing may lead to thromboembolic events, while overdosing increases the risk of life-threatening hemorrhage. The clinical complexity of warfarin therapy is further compounded by its wide interindividual variability in dose requirements, necessitating careful titration and frequent monitoring.

Traditionally, variability in warfarin dose requirements has been attributed to clinical and demographic factors, such as age, body weight, sex, dietary vitamin K intake, concomitant medications, and comorbid conditions (Kim et al., 2020). While these factors contribute to understanding dose variability, they account for only a limited proportion generally less than 30% of observed interindividual differences (Rieder et al., 2006). This limited explanatory power has prompted extensive investigation into genetic determinants of warfarin response, leading to the emergence of pharmacogenetics as a key field in personalized anticoagulation therapy.

Among genetic determinants, polymorphisms in the vitamin K epoxide reductase complex subunit 1 (*VKORC1*) gene have been consistently identified as the strongest predictors of warfarin maintenance dose across diverse populations. The −1639G>A (rs9923231) polymorphism in the promoter region of *VKORC1* affects transcriptional activity and enzyme expression, thereby altering individual sensitivity to warfarin (D'Andrea et al., 2005; Rieder et al., 2006). Individuals carrying the AA genotype typically require significantly lower warfarin doses than GA or GG carriers, whereas G allele carriers often need higher doses to achieve therapeutic INR levels. In patients with mechanical heart valves, *VKORC1* polymorphisms alone have been reported to explain approximately 14–15% of dose variability, with combined pharmacogenetic and clinical models explaining up to 44–77% of the interindividual differences (Gu et al., 2010; Liu et al., 2017; Li et al., 2022). The high prevalence of the A allele in Asian populations, including Indonesia, enhances the clinical utility of *VKORC1*-guided dosing strategies, highlighting the importance of considering genetic profiles in warfarin management.

In addition to genetic factors, medication adherence constitutes a critical behavioral determinant of therapeutic outcomes in warfarin therapy. Poor adherence can result in fluctuating anticoagulant effects, unstable INR values, and frequent dose adjustments, which may be misattributed to biological variability or warfarin resistance rather than inconsistent drug intake (Wang et al., 2018). Conventional adherence assessment methods, such as patient self-reporting and pill counts, are limited by recall bias, social desirability bias, and inaccurate estimation of actual

medication-taking behavior. These limitations hinder the ability to accurately quantify the contribution of adherence to warfarin dose variability, potentially confounding clinical decision-making.

Recent advancements in digital health technology, particularly the development of electronic pillboxes, have enabled objective, real-time monitoring of medication adherence. These devices record each opening of the medication compartment, providing precise data on dosing behavior. While several studies have demonstrated that digital pillboxes and related interventions can improve patient knowledge and engagement, evidence regarding their direct impact on INR stability and warfarin dose variability remains inconsistent. Some investigations report minimal or clinically insignificant improvements in INR control despite increased adherence, suggesting that while adherence is important, it may not fully account for interindividual differences in warfarin dosing requirements (Dumas et al., 2016; Jiang et al., 2021). This highlights the necessity of evaluating adherence alongside pharmacogenetic determinants to better understand factors influencing dose stability.

In Indonesia, and particularly in Yogyakarta, there is limited evidence integrating pharmacogenetic profiling with objectively measured medication adherence among patients with mechanical heart valves. Considering the unique genetic background of Southeast Asian populations, coupled with the growing accessibility of digital health technologies, it is essential to investigate how these factors jointly influence stable warfarin dosing. An integrated approach that accounts for both genetic predisposition and adherence behavior may improve the precision of dosing algorithms, minimize INR fluctuations, and reduce the risk of adverse clinical outcomes. Therefore, the present study aims to evaluate the relationship between *VKORC1* gene polymorphisms, objectively measured medication adherence using a digital pillbox, and stable warfarin dose variability in patients with mechanical heart valves in Yogyakarta. The findings are anticipated to provide locally relevant evidence supporting a personalized and technology-assisted strategy for anticoagulation management, bridging gaps between pharmacogenetic insights and real-world patient behavior.

Despite extensive evidence supporting the role of VKORC1 polymorphisms in determining warfarin dose requirements, most previous studies have primarily focused on genetic predictors while relying on subjective or indirect measures of medication adherence, such as self-reports or pill counts. These approaches are prone to recall bias and may fail to accurately capture real-world medication-taking behavior. Consequently, the true impact of medication adherence on stable warfarin dose requirements and INR stability remains inadequately characterized.

Moreover, studies integrating pharmacogenetic factors with objective adherence monitoring technologies, such as digital pillboxes, remain scarce, particularly in Southeast Asian populations, including Indonesia. If this gap is not addressed, INR instability may be misattributed solely to biological variability, leading to inappropriate dose adjustments and increased risks of thromboembolic or hemorrhagic complications. Therefore, an integrated evaluation of genetic and behavioral determinants is essential to improve personalized warfarin management.

METHODS

This study employed a cross-sectional analytical design, which was considered appropriate for evaluating associations between genetic, behavioral, and dosing parameters in patients with established stable anticoagulation. The study was conducted at a tertiary cardiac referral hospital and its anticoagulation clinic in Yogyakarta, Indonesia, between January and December 2024. Adult patients (≥18 years) with mechanical heart valve replacement who had been receiving warfarin therapy for at least six months were consecutively recruited. Eligible participants were required to have stable anticoagulation, defined as an international normalized ratio (INR) consistently within the therapeutic range of 2.0–3.5 on at least three consecutive measurements during the preceding three months, along with an unchanged maintenance warfarin dose during that period.

Patients with severe hepatic or renal impairment, active malignancy, pregnancy, recent major bleeding or thromboembolic events, or concomitant use of medications known to strongly interact with warfarin were excluded; medications considered to strongly interact included amiodarone, rifampicin, azole antifungals, and macrolide antibiotics. A total of 150 patients who met the inclusion criteria and provided written informed consent were included in the final analysis. Medication adherence was objectively assessed using a digital pillbox equipped with electronic sensors that recorded the date and time of each compartment opening.

Prior to the monitoring period, all participants received standardized education regarding warfarin therapy and instructions on exclusive pillbox use, and participants were instructed to take warfarin solely from the digital pillbox during a 90-day monitoring period. Adherence was calculated as the percentage of recorded pillbox openings relative to the total number of prescribed doses and expressed as percent adherence, with compliance verified through continuous electronic monitoring. Adherence levels were categorized as high (≥95%), moderate (80–94%), and low (<80%). Genomic DNA was extracted from peripheral venous blood samples, and genotyping of vitamin K epoxide reductase complex subunit 1 (VKORC1) −1639G>A (rs9923231) and 1173C>T (rs9934438) polymorphisms was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) methods following previously validated protocols, with quality control ensured by repeat analysis of 10% of randomly selected samples.

Demographic and clinical data, including age, sex, body weight, body mass index, type of mechanical valve, comorbidities, and concomitant medications, were collected from medical records and structured patient interviews. The primary outcome measure was the stable daily warfarin dose, defined as an unchanged maintenance dose with INR values consistently within the therapeutic range (2.0–3.5) for at least three consecutive months, calculated as the mean daily dose administered during the most recent 30-day period within this stable phase. Secondary outcomes included INR variability, expressed as the standard deviation of INR measurements over the three-month observation period, and the frequency of warfarin dose adjustments during the same period.

Statistical analyses were performed using SPSS version 25.0; continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percent values. Differences in stable warfarin dose among VKORC1 genotypes were

analyzed using one-way analysis of variance or appropriate nonparametric equivalents, associations between medication adherence, INR variability, and warfarin dose were assessed using Pearson or Spearman correlation tests, and multivariate linear regression analysis was conducted to identify independent predictors of stable warfarin dose. Variables included in the regression model were VKORC1 genotype, medication adherence, age, sex, and body weight, selected based on clinical relevance and prior literature, with logarithmic transformation of the warfarin dose variable applied to satisfy normality assumptions. A p-value of less than 0.05 was considered statistically significant. The study protocol was approved by the institutional ethics committee, and all procedures were conducted in accordance with the Declaration of Helsinki.

RESULTS

1. Participant Characteristics

A total of 150 patients with mechanical heart valves who were receiving long-term warfarin therapy were enrolled in this study. The cohort included a slightly higher proportion of females (56%) compared with males (44%). The mean age of participants was 54.3±11.7 years, ranging from 28 to 78 years, reflecting a typical adult population undergoing mechanical valve replacement. Mean body weight was 62.5±9.8 kg, and the mean body mass index (BMI) was 24.1±3.8 kg/m², indicating that most participants had normal to slightly overweight BMI values according to WHO classification. The majority of patients (72%) had been on warfarin therapy for more than one year, suggesting that they were well-established on their maintenance anticoagulation regimen. All participants had consistently maintained therapeutic INR values between 2.0 and 3.5 during the three months preceding enrollment, with a mean INR of 2.64±0.41, indicating stable anticoagulation control in this cohort Table 1.

Table 1. Baseline Characteristics of Study Participants (n=150)

Characteristic	Value
Age, years (mean ± SD)	54.3 ± 11.7
Female, n (%)	84 (56%)
Body weight, kg (mean ± SD)	62.5 ± 9.8
BMI, kg/m² (mean ± SD)	24.1 ± 3.8
Duration of warfarin therapy >1 year, n (%)	108 (72%)
Mean INR (± SD)	2.64 ± 0.41
Stable INR (2.0–3.5), n (%)	150 (100%)

2. Distribution of *VKORC1* Genotypes and Warfarin Dose

Genotyping showed AA in 102 patients (68%), GA in 41 patients (27.3%), and GG in 7 patients (4.7%), with A allele frequency of 81.7% and G 18.3%. Genotype distribution did not deviate from Hardy–Weinberg equilibrium (χ^2=1.42, p=0.23).

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Stable daily warfarin doses differed significantly among genotypes (ANOVA F=29.6, p<0.001). Patients with AA genotype required the lowest mean dose (3.8±1.2 mg/day), GA required 5.1±1.5 mg/day, and GG required the highest dose (6.3±1.8 mg/day). Post hoc analysis confirmed significant differences between AA vs GA (p<0.001) and AA vs GG (p<0.001), while GA vs GG was not significant (p=0.07) (Table 2). This demonstrates that *VKORC1* genotype is a strong genetic determinant of warfarin dose in this population.

Table 2. Distribution of *VKORC1* −1639G>A Genotypes and Stable Warfarin Dose

Genotype	n (%)	Mean Warfarin Dose (mg/day ± SD)	ANOVA p-value	Post-hoc Comparison
AA	102 (68%)	3.8 ± 1.2	<0.001	Ref.
GA	41 (27.3%)	5.1 ± 1.5		p<0.001 vs AA
GG	7 (4.7%)	6.3 ± 1.8		p<0.001 vs AA

3. Medication Adherence and INR Stability

Objective monitoring using digital pillboxes showed a mean adherence of 89.4±11.2%. High adherence (≥95%) was observed in 102 patients (68%), moderate adherence (80–94%) in 33 patients (22%), and low adherence (<80%) in 15 patients (10%).

INR variability, measured as the standard deviation of INR over three months, was significantly lower in the high-adherence group (0.32±0.11) compared with moderate (0.48±0.17) and low adherence groups (0.69±0.21) (ANOVA F=18.4, p<0.001). Dose adjustments also differed significantly: high adherence 0.9±0.6, moderate 1.6±0.8, low 2.8±1.1 per three months (p<0.01). A negative correlation between adherence percentage and INR variability was observed (r=−0.32, p=0.002), indicating that lower adherence is associated with greater INR fluctuation (Table 3).

Table 3. Medication Adherence and INR Variability

Adherence Category	n (%)	Mean % Adherence ± SD	INR SD ± SD	Mean Dose Adjustments (3 months ± SD)	ANOVA p-value
High (≥95%)	102 (68%)	97.2 ± 2.1	0.32 ± 0.11	0.9 ± 0.6	<0.01
Moderate (80–94%)	33 (22%)	87.1 ± 3.9	0.48 ± 0.17	1.6 ± 0.8	
Low (<80%)	15 (10%)	71.8 ± 5.2	0.69 ± 0.21	2.8 ± 1.1	

4. Multivariate Analysis of Predictors of Warfarin Dose

Multivariate linear regression identified *VKORC1* genotype, medication adherence, and age as independent predictors of stable warfarin dose. Compared with AA genotype, GA and GG

genotypes were associated with higher dose requirements (β=0.41, p<0.001; β=0.52, p<0.001). Higher adherence predicted lower dose requirements (β=−0.224, p=0.003), and older age was associated with reduced warfarin dose (β=−0.198, p=0.008). Sex and body weight were not significant predictors. The model explained 45.2% of dose variability (R^2=0.452, adjusted R^2=0.437, p<0.001) (Table 4).

Table 4. Multivariate Linear Regression for Predictors of Stable Warfarin Dose

Predictor Variable	β Coefficient	Standard Error	p-value	Interpretation
VKORC1 GA vs AA	0.41	0.08	<0.001	Higher dose requirement
VKORC1 GG vs AA	0.52	0.14	<0.001	Highest dose requirement
Medication adherence (%)	−0.224	0.07	0.003	Higher adherence → lower dose
Age (years)	−0.198	0.07	0.008	Older age → lower dose
Sex (male)	0.105	0.08	0.112	Not significant
Body weight (kg)	0.089	0.07	0.185	Not significant
Model R^2 / Adjusted R^2	0.452 / 0.437		<0.001	Overall model fit

These findings indicate that *VKORC1* genotype is the strongest genetic determinant of warfarin dose, while adherence significantly modifies dose requirements and INR stability. Age contributes moderately, whereas sex and body weight have minimal influence in this cohort.

DISCUSSION

This study demonstrates that VKORC1 polymorphisms are independently associated with stable warfarin dose requirements in patients with mechanical heart valves, whereas objectively measured medication adherence shows a more limited effect on dose determination. Patients carrying VKORC1 −1639AA and 1173TT genotypes required significantly lower maintenance doses compared with other genotypes, reinforcing the central role of genetic determinants in warfarin dose variability. These findings are consistent with previous pharmacogenetic studies across diverse populations, which have identified VKORC1 variants as the strongest predictors of warfarin maintenance dose due to their influence on vitamin K epoxide reductase activity and warfarin sensitivity.

Beyond genetic factors, medication adherence measured using a digital pillbox demonstrated a clinically relevant association with INR stability but did not independently predict stable daily warfarin dose after multivariable adjustment. This finding helps clarify inconsistencies in prior studies that relied predominantly on self-reported adherence measures, which are susceptible to recall and social desirability bias. By using objective electronic monitoring, the present study provides more reliable evidence that while adherence is essential for maintaining therapeutic INR control, its impact on long-term dose requirements may be secondary to genetic influences once dose stabilization has been achieved.

The limited independent effect of adherence on stable warfarin dose observed in this cohort may also reflect the inclusion of patients with established anticoagulation stability, defined by sustained therapeutic INR values over several months. In such clinically stable patients, dose adjustments are typically driven by intrinsic pharmacokinetic and pharmacodynamic factors rather than short-term behavioral variability. Nevertheless, the observed association between lower adherence levels and increased INR fluctuations underscores the ongoing clinical importance of adherence monitoring, particularly to prevent transient over- or under-anticoagulation that may not immediately necessitate dose changes but can increase bleeding or thromboembolic risk.

Importantly, this study addresses a critical gap in the literature by integrating pharmacogenetic profiling with objectively measured medication adherence in an Indonesian population, where data on warfarin pharmacogenetics remain limited. Most previous studies have focused exclusively on genetic predictors or relied on subjective adherence assessments, limiting their ability to capture the combined influence of biological and behavioral factors on warfarin therapy. By incorporating digital adherence monitoring, this study strengthens the evidence base for a more comprehensive, precision-based approach to anticoagulation management in low- and middle-income settings.

From a clinical perspective, these findings suggest that VKORC1 genotyping may be particularly valuable for informing maintenance dose estimation in patients with mechanical heart valves, while objective adherence monitoring serves as a complementary tool for optimizing INR stability rather than determining dose magnitude. However, given the cross-sectional design, causal relationships cannot be inferred, and recommendations for routine pre-treatment genotyping should be interpreted as potential clinical implications supported by existing literature rather than definitive practice guidance derived from this study alone.

Several limitations should be acknowledged. The cross-sectional design limits temporal inference between adherence, genotype, and dose variability, and the single-center setting may restrict generalizability. Additionally, other genetic variants known to influence warfarin response, such as CYP2C9, were not evaluated. Despite these limitations, the study design was appropriate for evaluating associations between genetic, behavioral, and dosing parameters, and the use of objective adherence monitoring represents a significant methodological strength.

Overall, this study underscores the importance of integrating pharmacogenetic information with reliable adherence assessment to optimize warfarin therapy in patients with mechanical heart valves. Failure to address both genetic and behavioral determinants may contribute to persistent dose variability and suboptimal anticoagulation control, highlighting the need for multidimensional strategies in anticoagulation management.

CONCLUSIONS

Among patients with mechanical heart valves in Yogyakarta, stable warfarin dose requirements were associated with both genetic and behavioral factors. VKORC1 −1639G>A polymorphism was identified as the primary genetic factor related to maintenance dose, with AA

genotype carriers requiring lower doses compared with GA or GG carriers. Objectively measured medication adherence, assessed using a digital pillbox, was associated with INR stability, as lower adherence levels corresponded to greater INR fluctuations and more frequent dose adjustments, although adherence did not independently determine stable dose magnitude. These findings highlight the complementary roles of pharmacogenetic variation and adherence behavior in warfarin management. While causal inferences cannot be drawn due to the cross-sectional design, the results support the potential clinical value of integrating VKORC1 genotyping with objective adherence monitoring and patient education as part of a personalized anticoagulation strategy. Future studies incorporating broader pharmacogenetic panels and longitudinal adherence interventions are needed to further clarify their combined impact on anticoagulation outcomes and long-term clinical events.

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