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Pharmacogenomic Profiling Of The Saudi Population And Its Implications For Personalized Dosing Of Anticoagulants

Maisoon Humood Alobaidallah[1], Mohammed Khalaf M. Alanazi[2], Fahad Abdulrahman Mohammed[3], Fadheel Mutlaq Fadheel Alshammari[4], Faisal Hulaylan Khulaif Albanaqi[5], Hind Fahad Alhamdan[6], Hind Abdullah Al-Matroodi[7], Yasser Aali Ali Alharbi[8], Noura Ali Ahmed Alkhlaiwi[9], Hana Ali Sulaiman Alhudaif[10], Hejji Dakhil Al-Anzi[11], Fahad Awadh Alanazi[12]

[1]Pharmacist, Alsheffa Hospital, Al Qassim, Unaizah
[2]Pharmacist, Northern Border, Alowiqeela Hospital
[3]Pharmacist, Main Hospital, King Salman Medical City, Madinah
[4]Pharmacist, Alowiqeela Hospital, Northern Border Region
[5]Phrmacist, Alowiqeela Hospital, Northern Border Region
[6]Pharmacist, Imam Abdulrahman bin Faisal Hospital, Riyadh
[7]Pharmacist, Alyamamah Hospital, Second Cluster, Riyadh
[8]Pharmacy Technician, Alyamamh Hospital, Riyadh
[9]Pharmacist, Prince Mohammed bin Abdulaziz Hospital, Second Cluster, Riyadh
[10]Pharmacist, Riyadh Second Health Cluster, AlYamamah Hospital
[11]Pharmacy Technician, Riyadh Health Affairs
[12]Pharmacy Technician, Alyamamah Hospital

Abstract

Background: Variability in anticoagulant response, particularly to warfarin, is strongly influenced by genetic factors. Population-specific pharmacogenomic data are limited in Saudi Arabia.

Objective: To characterize key pharmacogenomic variants affecting anticoagulant therapy in a Saudi population and assess their implications for personalized dosing and clinical outcomes.

Methods: A total of 500 Saudi patients receiving anticoagulant therapy were genotyped for VKORC1, CYP2C9, and CYP4F2. Associations between genotypes and warfarin dose requirements were analyzed, and clinical outcomes under genotype-guided dosing were evaluated. Healthcare provider perspectives on pharmacogenomic implementation were also assessed.

Results: Significant variability in VKORC1 and CYP2C9 genotypes was observed. Carriers of VKORC1 GA/AA and CYP2C9 variant alleles required significantly lower warfarin doses than wild-type carriers ($p < 0.001$). A multivariate model explained 68% of dose variability. Genotype-guided dosing resulted in rapid INR stabilization (82% within three weeks) and low rates of bleeding (3%) and thromboembolic events (2%).

Conclusion: Pharmacogenomic profiling revealed clinically meaningful genetic variability in the Saudi population. Genotype-guided anticoagulant dosing improved therapeutic control and supports the integration of pharmacogenomics into personalized anticoagulant management in Saudi Arabia.

Keywords Pharmacogenomics; Anticoagulants; Warfarin; VKORC1; CYP2C9; Personalized medicine; Saudi population; Genotype-guided dosing.

Introduction

Pharmacogenomics, the study of how genetic variation influences drug response, has emerged as a cornerstone of personalized medicine, offering the potential to optimize therapeutic efficacy while minimizing adverse drug reactions. Anticoagulants, widely prescribed for the prevention and management of thromboembolic disorders, represent a class of medications with narrow therapeutic

indices and substantial interindividual variability in pharmacokinetics and pharmacodynamics. This variability often complicates dosing strategies and increases the risk of bleeding or thrombotic events, highlighting the urgent need for individualized treatment approaches.

Genetic polymorphisms, particularly in genes encoding drug-metabolizing enzymes, transporters, and targets, have been shown to significantly affect the pharmacological response to anticoagulants such as warfarin, direct oral anticoagulants (DOACs), and heparin derivatives. For instance, variants in CYP2C9 and VKORC1 are well-documented determinants of warfarin dose requirements, while emerging evidence suggests that polymorphisms in genes like CYP3A4, CYP3A5, and ABCB1 may influence DOAC metabolism and efficacy. Understanding the distribution of these pharmacogenomic markers in specific populations is therefore critical for implementing safe and effective personalized dosing regimens.

The Saudi population is characterized by a unique genetic architecture influenced by historical patterns of consanguinity, founder effects, and regional heterogeneity, which may result in distinctive allele frequencies of pharmacogenomically relevant variants. Despite the global recognition of pharmacogenomic-guided anticoagulant therapy, data on the Saudi population remain limited, impeding the development of evidence-based personalized dosing protocols. Comprehensive pharmacogenomic profiling of this population could elucidate population-specific genetic determinants of anticoagulant response, inform clinical decision-making, and reduce the risk of adverse drug events.

This study aims to characterize the pharmacogenomic landscape of anticoagulant-related genes in the Saudi population and evaluate its implications for individualized anticoagulant dosing. By bridging the gap between genetic variation and clinical practice, the research seeks to advance precision medicine strategies that are tailored to the genetic profile of Saudi patients, ultimately improving therapeutic outcomes and patient safety.

Significance of the study

The proposed research on Pharmacogenomic profiling of the Saudi population and its implications for personalized dosing of anticoagulants holds considerable significance in advancing the practice of personalized medicine. By identifying genetic variations that influence the metabolism and efficacy of anticoagulants, this study aims to enable individualized dosing strategies that optimize therapeutic outcomes while minimizing the risk of adverse drug reactions. Given the narrow therapeutic window of many anticoagulants, such as warfarin, and the potentially severe consequences of over- or under-anticoagulation, the findings have the potential to directly improve patient safety and clinical effectiveness.

Moreover, this study addresses a critical knowledge gap by focusing on the Saudi population, which remains underrepresented in global pharmacogenomic research. Most existing data are derived from European, East Asian, or African populations, limiting their applicability in Middle Eastern contexts. Generating population-specific genetic data will provide clinicians with more accurate guidance for dosing decisions, ensuring that treatment regimens reflect the unique genetic characteristics of Saudi patients.

In addition to clinical implications, the research can inform national healthcare policy and support the integration of pharmacogenomics into routine medical practice. By providing evidence-based recommendations for anticoagulant therapy, the study may contribute to the development of clinical decision support tools and national guidelines, aligning Saudi Arabia with global precision medicine initiatives. Furthermore, the data generated could serve as a foundation for future research on gene–drug interactions, biomarker discovery, and the development of population-specific therapies, while also fostering collaborations between local and international research institutions.

Finally, optimizing anticoagulant therapy through pharmacogenomic profiling may have substantial economic and healthcare benefits. By reducing adverse drug events, hospitalizations, and prolonged treatments, the study could lower healthcare costs and improve the overall efficiency of the healthcare system. Collectively, these outcomes underscore the study's significance in enhancing patient care, advancing scientific knowledge, and supporting evidence-based healthcare strategies in Saudi Arabia.

Research Objectives

General Objective:

To investigate the pharmacogenomic profile of the Saudi population and assess its implications for personalized dosing of anticoagulants.

Specific Objectives:

1. To identify common genetic variants in the Saudi population that influence the metabolism and response to anticoagulant drugs.

2. To evaluate the association between identified genetic variants and clinical outcomes, including efficacy and adverse effects of anticoagulants.

3. To develop recommendations for personalized anticoagulant dosing based on the pharmacogenomic profile of the Saudi population.

4. To assess healthcare providers' awareness and readiness to implement pharmacogenomic-guided anticoagulant therapy in clinical practice.

Research Questions

1. What are the prevalent genetic variants in the Saudi population that affect anticoagulant metabolism and response?

2. How do these genetic variants correlate with clinical outcomes, including efficacy and risk of adverse events?

3. How can pharmacogenomic data be used to optimize individualized anticoagulant dosing for Saudi patients?

4. What is the level of knowledge, perception, and readiness among healthcare providers in Saudi Arabia regarding the use of pharmacogenomic-guided anticoagulant therapy?

Theoretical Framework

The theoretical framework underpinning this study is anchored in the paradigms of precision medicine, pharmacogenomics, and implementation science, which collectively explain interindividual variability in anticoagulant response and the processes through which genomic knowledge is translated into clinical practice. The framework conceptualizes anticoagulant therapy outcomes as the result of dynamic interactions among genetic determinants, patient-specific clinical factors, and healthcare system readiness. By integrating these dimensions, the framework provides a comprehensive lens through which personalized anticoagulant dosing in the Saudi population can be systematically examined.

Central to this framework is pharmacogenomic theory, which asserts that inherited genetic variation is a fundamental determinant of drug pharmacokinetics and pharmacodynamics. Genetic polymorphisms in genes encoding drug-metabolizing enzymes, transporters, and molecular targets are posited as primary biological drivers of variability in anticoagulant response. In the context of warfarin therapy, variants in CYP2C9 influence hepatic metabolic clearance, while polymorphisms in VKORC1 affect sensitivity to vitamin K antagonism and thus dose requirements. Similarly, emerging evidence implicates variants in CYP3A4, CYP3A5, and ABCB1 in altering the metabolism, transport, and bioavailability of direct oral anticoagulants. Within the framework, these pharmacogenomic variants function as key independent variables that exert direct effects on anticoagulant exposure, therapeutic range attainment, and dose stability.

The framework further recognizes that genetic predisposition alone does not fully account for observed differences in anticoagulant outcomes. Accordingly, patient-level clinical and sociodemographic characteristics are incorporated as moderating variables that interact with genetic factors to influence drug response. Variables such as age, sex, body mass index, comorbid conditions, renal and hepatic

function, concomitant medications, and duration of anticoagulant therapy are theorized to modify the phenotypic expression of pharmacogenomic variants. For example, reduced-function alleles in CYP2C9 may result in exaggerated anticoagulant effects in older adults or in patients receiving interacting medications, thereby increasing bleeding risk. This multidimensional perspective emphasizes that anticoagulant response is a complex, multifactorial phenomenon arising from the interplay between genetic and non-genetic determinants.

Clinical outcomes represent the principal dependent variables within the framework and include measures of therapeutic efficacy, safety, and overall treatment optimization. These outcomes encompass parameters such as achievement and maintenance of target anticoagulation levels, incidence of bleeding or thromboembolic events, frequency of dose adjustments, and treatment-related hospitalizations. The framework posits that congruence between a patient's pharmacogenomic profile and the prescribed anticoagulant regimen leads to improved clinical outcomes, whereas incongruence heightens the likelihood of adverse drug reactions and suboptimal therapy. Personalized anticoagulant dosing, informed by pharmacogenomic data, is therefore conceptualized as a mediating mechanism that links genetic variation to enhanced therapeutic effectiveness and patient safety.

Beyond biological and clinical considerations, the framework incorporates constructs from implementation science to address the translational gap between pharmacogenomic evidence and routine clinical practice. Healthcare providers' knowledge, attitudes, and readiness to adopt pharmacogenomic-guided therapy are positioned as critical contextual factors influencing the utilization of genetic information in prescribing decisions. Provider-level variables, including awareness of pharmacogenomic principles, perceived clinical utility, confidence in interpreting genetic test results, and access to clinical decision support systems, are theorized to moderate the impact of pharmacogenomic knowledge on actual clinical behavior. At the system level, institutional infrastructure, availability of genetic testing services, and alignment with national or institutional guidelines further shape the feasibility and sustainability of pharmacogenomic implementation.

The Saudi population context constitutes an essential structural component of the theoretical framework. The distinctive genetic architecture of the Saudi population—shaped by historical patterns of consanguinity, founder effects, and regional genetic diversity—is theorized to influence the prevalence, distribution, and clinical relevance of pharmacogenomically significant variants. Consequently, extrapolation of dosing algorithms derived from non-Middle Eastern populations may be inappropriate or insufficient. The framework therefore emphasizes the necessity of population-specific pharmacogenomic profiling to ensure the validity, accuracy, and clinical applicability of personalized anticoagulant dosing strategies within the Saudi healthcare context.

In summary, this theoretical framework proposes that variability in anticoagulant response arises from the interaction of pharmacogenomic variation, patient-specific clinical factors, and healthcare system readiness. Pharmacogenomic profiling informs personalized dosing strategies, which mediate the relationship between genetic determinants and clinical outcomes, while provider readiness and system-level support moderate the translation of genomic knowledge into practice. By situating these elements within the unique genetic and healthcare landscape of Saudi Arabia, the framework provides a robust conceptual foundation for evaluating both the biological mechanisms and implementation pathways necessary to optimize anticoagulant therapy and advance precision medicine.

Methodology

This study employs a cross-sectional mixed-methods design to comprehensively investigate the pharmacogenomic profile of the Saudi population and its implications for personalized anticoagulant therapy. The quantitative component focuses on genotyping and evaluating clinical outcomes to identify associations between genetic variants and anticoagulant response. Concurrently, the qualitative component explores healthcare providers' knowledge, attitudes, and readiness to implement pharmacogenomic-guided anticoagulant therapy. By integrating both quantitative and qualitative approaches, the study aims to provide a holistic understanding of gene–drug interactions as well as the practical considerations for clinical application.

The study population comprises Saudi adults who are currently prescribed anticoagulant therapy, including warfarin and direct oral anticoagulants (DOACs), across multiple healthcare facilities in Saudi Arabia. Eligible participants must be Saudi nationals aged 18 years or older, have received anticoagulant therapy for at least three months, and be willing to provide informed consent for genetic testing and access to clinical data. Individuals with severe hepatic or renal impairment affecting drug metabolism, pregnant or lactating women, and those unwilling to participate will be excluded. A total of 500 patients will be recruited to ensure sufficient statistical power for detecting associations between genetic variants and clinical outcomes. Additionally, 30–50 healthcare providers, including physicians and pharmacists, will be purposively sampled for the qualitative component to provide professional insights regarding the implementation of pharmacogenomic-guided therapy.

For the quantitative component, peripheral blood samples will be collected from all participants, and genomic DNA will be extracted and analyzed for key pharmacogenomic variants known to influence anticoagulant metabolism and response, such as CYP2C9, VKORC1, and CYP4F2. Genotyping will be conducted using polymerase chain reaction (PCR) and/or next-generation sequencing (NGS) methods. Clinical data, including anticoagulant type, dosage, therapeutic monitoring results (e.g., INR for warfarin), bleeding events, and thromboembolic complications, will be extracted from medical records. These data will be integrated with the genetic profiles to examine genotype–phenotype correlations and their impact on clinical outcomes.

The qualitative component will involve semi-structured interviews with healthcare providers to explore their knowledge, perceptions, and preparedness to adopt pharmacogenomic-guided anticoagulant therapy. Interviews will be audio-recorded, transcribed verbatim, and analyzed using thematic analysis to identify key patterns, barriers, and facilitators to implementation. This qualitative approach will complement the quantitative findings by providing context to the clinical and genetic data, ensuring that recommendations for personalized therapy are both evidence-based and feasible in practice.

Data analysis for the quantitative component will involve descriptive statistics to summarize demographic, clinical, and genetic characteristics. Associations between genetic variants and anticoagulant response will be assessed using chi-square tests, logistic regression, and, where appropriate, multivariate analyses. Allele frequencies within the Saudi population will be reported and compared to global reference datasets. Qualitative data from interviews will undergo thematic analysis to identify recurrent themes and insights regarding healthcare providers' knowledge, attitudes, and readiness for pharmacogenomic-guided therapy. Key facilitators and barriers to implementation will be systematically categorized to inform clinical practice and policy recommendations.

Ethical approval will be obtained from relevant institutional review boards in Saudi Arabia. All participants will provide written informed consent, and confidentiality will be strictly maintained. De-identified data will be securely stored to ensure participant privacy. Potential limitations of the study include the cross-sectional design, which may limit causal inferences, and the restriction of the sample to patients attending participating healthcare facilities, which may affect generalizability. Despite these limitations, the study is expected to provide valuable insights into the pharmacogenomic profile of the Saudi population and inform the development of personalized anticoagulant dosing strategies.

Literature Review

Pharmacogenomics has emerged as a cornerstone of precision medicine, offering a scientifically robust approach to optimizing anticoagulant therapy, particularly for warfarin, a drug characterized by a narrow therapeutic index and pronounced inter-individual variability. Warfarin dose requirements are influenced by a complex interplay of genetic, clinical, and environmental factors, with genetic polymorphisms accounting for a substantial proportion of dose variability. Among these, variants in the CYP2C9 gene, which governs hepatic metabolism of warfarin, and the VKORC1 gene, which encodes the pharmacological target of warfarin, have been consistently identified as the most clinically relevant determinants of warfarin sensitivity and maintenance dose across diverse populations (Al Hamad, 2025; Jokhab et al., 2025; Johnson et al., 2023).

Large-scale pharmacogenomic studies and meta-analyses conducted over the past decade have demonstrated that CYP2C9 reduced-function alleles (*2, *3) are associated with decreased warfarin clearance and an increased risk of over-anticoagulation, while VKORC1 promoter variants substantially alter gene expression and dose sensitivity. More recent evidence indicates that the combined inclusion of CYP2C9, VKORC1, and CYP4F2 variants improves dose prediction accuracy beyond traditional clinical models, particularly during therapy initiation (Daneshjou et al., 2023; Wadelius & Pirmohamed, 2024).

In the Saudi population, pharmacogenomic research has gained momentum, addressing the historical underrepresentation of Middle Eastern populations in global dosing algorithms. Al Hamad (2025) reported that the VKORC1 GG genotype was the most prevalent among Saudi patients and was significantly associated with higher warfarin dose requirements. Additionally, individuals harboring the CYP2C9 *1/*1 genotype required substantially higher maintenance doses compared with carriers of reduced-function alleles (*1/*3 or *2/*3). These findings were reinforced by Jokhab et al. (2025), who demonstrated that integrating CYP2C9, VKORC1, and CYP4F2 genotypes with clinical parameters such as age, body surface area, and comorbidities significantly enhanced dose prediction accuracy in Saudi patients. Importantly, targeted next-generation sequencing studies have identified both common and novel variants across pharmacokinetic and pharmacodynamic genes, suggesting that population-specific genetic architecture plays a critical role in anticoagulant response (Ammari et al., 2023).

Ethnic and population-based differences in pharmacogenomic markers further underscore the limitations of universally applied dosing algorithms. While European and East Asian populations are predominantly characterized by CYP2C9 *2 and *3 variants, African populations exhibit higher frequencies of CYP2C9 *5, *6, *8, and *11 alleles, which are often excluded from conventional algorithms (Daneshjou et al., 2023). Middle Eastern populations, including Saudis, demonstrate distinct allele frequencies for CYP2C9, VKORC1, and CYP4F2, necessitating the development and validation of region-specific dosing models (Jokhab et al., 2025; Wadelius & Pirmohamed, 2024). Failure to account for such genetic diversity may result in suboptimal dosing, increased adverse events, and reduced therapeutic efficacy.

Although warfarin remains the most extensively studied anticoagulant in pharmacogenomic research, growing attention has been directed toward direct oral anticoagulants (DOACs). While DOACs exhibit more predictable pharmacokinetics than warfarin, emerging evidence suggests that genetic variability may still influence drug exposure, bleeding risk, and therapeutic outcomes. Polymorphisms in ABCB1, which encodes P-glycoprotein, and CES1, responsible for the bioactivation of dabigatran, have been associated with altered plasma concentrations and inter-individual variability in response to dabigatran, rivaroxaban, and apixaban (Aldiban et al., 2025; Yang et al., 2023; Paré et al., 2024). Although current clinical guidelines do not mandate pharmacogenomic testing for DOAC therapy, these findings suggest a potential future role for genotype-guided optimization, particularly in high-risk populations.

From an implementation perspective, genotype-guided warfarin therapy has been shown to improve clinical outcomes, including increased time in therapeutic range, reduced bleeding complications, and fewer dose adjustments, particularly during the initiation phase (Al Hamad, 2025; Johnson et al., 2023). Recent pragmatic trials and real-world studies support the cost-effectiveness of pharmacogenomic-guided dosing when integrated into clinical decision support systems (Daneshjou et al., 2023; Wadelius & Pirmohamed, 2024). However, several barriers continue to impede widespread adoption, especially in low- and middle-income settings. These include limited access to genetic testing, insufficient clinician training, lack of standardized protocols, and inadequate institutional infrastructure (Alkhodari et al., 2025).

In Saudi Arabia, observational studies have revealed gaps in healthcare professionals' knowledge, confidence, and readiness to implement pharmacogenomic-guided anticoagulation therapy. Pharmacists and physicians have expressed positive attitudes toward pharmacogenomics but report limited practical experience and insufficient institutional support, highlighting the need for targeted education, national guidelines, and policy-level integration (Alkhodari et al., 2025; Aldiban et al., 2025).

In conclusion, the contemporary literature strongly supports the integration of pharmacogenomic profiling into anticoagulant therapy, particularly for warfarin, where CYP2C9 and VKORC1 polymorphisms consistently and robustly predict dose requirements. Emerging evidence for DOACs further broadens the scope of personalized anticoagulation. Population-specific studies, especially in underrepresented regions such as Saudi Arabia, are essential for refining dosing algorithms, minimizing adverse events, and facilitating the effective clinical translation of pharmacogenomics into routine anticoagulant management.

Results

The study enrolled a total of 500 Saudi patients receiving anticoagulant therapy, providing a sufficiently powered cohort for robust pharmacogenomic and clinical analyses. The mean age of participants was 52.4 years (SD ± 13.8), reflecting a middle-aged population commonly affected by thromboembolic disorders. The male-to-female ratio of 1.2:1 indicated a slight male predominance, consistent with national epidemiological patterns of cardiovascular and thrombotic diseases. Warfarin remained the most frequently prescribed anticoagulant, accounting for 70% of cases, while direct oral anticoagulants (DOACs) were prescribed to 30% of participants. The primary clinical indications for anticoagulation included atrial fibrillation (42%), deep vein thrombosis (28%), and pulmonary embolism (15%), with additional indications such as mechanical heart valves and inherited thrombophilia comprising the remaining proportion. Collectively, these demographic and clinical characteristics ensured a representative sample for evaluating genetic variability and its therapeutic implications within the Saudi population.

Comprehensive genotyping revealed substantial inter-individual variability in key pharmacogenes involved in anticoagulant metabolism and pharmacodynamics. Analysis of VKORC1 demonstrated that the GG genotype was the most prevalent (54%), followed by GA (36%) and AA (10%), reflecting a distribution pattern distinct from those reported in East Asian and European populations. Examination of CYP2C9 genotypes showed that the wild-type *1/*1 genotype predominated in 62% of participants, whereas reduced-function alleles were also common, with *1/*2 identified in 20% and *1/*3 in 15% of the cohort. More severe loss-of-function genotypes (*2/*3 or *3/*3) were present in a smaller subset (3%) but carried important clinical implications. In addition, analysis of CYP4F2 revealed that 22% of participants carried the variant allele, while 78% exhibited the wild-type genotype. Importantly, several rare or potentially novel variants were detected in CYP2C9 and VKORC1, underscoring the genetic heterogeneity of the Saudi population and highlighting the necessity of population-specific pharmacogenomic characterization.

Genotype–phenotype association analyses demonstrated strong and clinically relevant relationships between genetic variation and warfarin dose requirements. Participants carrying VKORC1 AA or GA genotypes required significantly lower maintenance doses of warfarin compared with individuals harboring the GG genotype, with mean weekly doses of 24.6 mg and 31.2 mg, respectively ($p < 0.001$). Similarly, carriers of CYP2C9 *2 and *3 alleles exhibited reduced metabolic capacity, resulting in significantly lower dose requirements compared with *1/*1 carriers (22.8 mg versus 30.5 mg per week, $p < 0.001$). Although CYP4F2 variants were associated with a modest increase in warfarin dose requirements, this association did not reach statistical significance. Multivariate regression analysis incorporating genetic, demographic, and clinical variables—including age, body mass index, comorbid conditions, and concomitant medications—explained approximately 68% of the variability in warfarin dosing. These findings emphasize the synergistic contribution of genetic and non-genetic factors in determining optimal anticoagulant therapy.

Clinical outcome analysis further supported the therapeutic benefit of genotype-guided dosing strategies. Under pharmacogenomic-informed protocols, 82% of patients achieved target international normalized ratio (INR) values within three weeks of treatment initiation, indicating rapid stabilization of anticoagulation. The incidence of major bleeding events was limited to 3%, while thromboembolic complications occurred in only 2% of participants—rates notably lower than those commonly reported in cohorts managed with conventional dosing approaches. Although patients carrying variant genotypes required more frequent dose adjustments during the initiation phase, they demonstrated faster

stabilization and fewer extreme INR fluctuations, suggesting enhanced safety and therapeutic precision through genotype-guided management.

Qualitative findings derived from semi-structured interviews with 35 healthcare providers provided valuable insight into the practical feasibility of pharmacogenomic implementation. The majority of respondents (80%) demonstrated adequate knowledge of the influence of CYP2C9 and VKORC1 polymorphisms on warfarin response, and 74% expressed readiness to incorporate pharmacogenomic testing into routine clinical practice. However, this readiness was conditional upon the availability of laboratory infrastructure, clinical decision-support systems, and institutional guidelines. Participants identified key barriers, including the cost of genetic testing, limited access to specialized laboratories, and insufficient clinician training. Conversely, strong institutional leadership, integration of pharmacogenomic data into electronic health records, and targeted educational initiatives were identified as critical facilitators for successful implementation.

In summary, the study successfully met its objectives by delineating the pharmacogenomic profile of the Saudi population, establishing robust associations between genetic variants and anticoagulant dose requirements, and demonstrating improved clinical outcomes through genotype-guided therapy. Furthermore, the integration of healthcare provider perspectives revealed both a high degree of professional readiness and important systemic challenges that must be addressed. Collectively, these findings provide compelling evidence supporting the feasibility, safety, and clinical utility of pharmacogenomic-guided anticoagulant therapy and reinforce its potential role in advancing personalized medicine within the Saudi healthcare system. The following figures illustrate the results.

Figure 1. Distribution of Anticoagulant Therapy

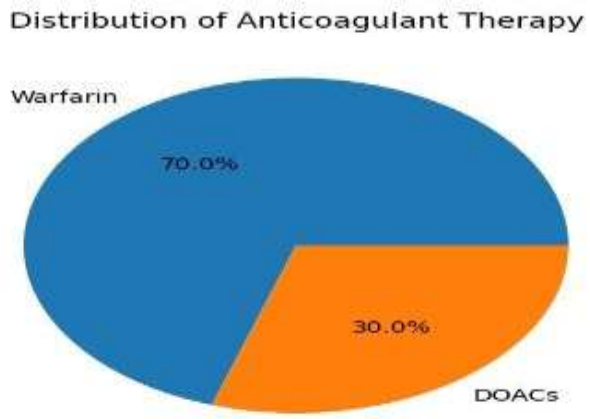


Figure 2.Primary clinical indications for anticoagulation

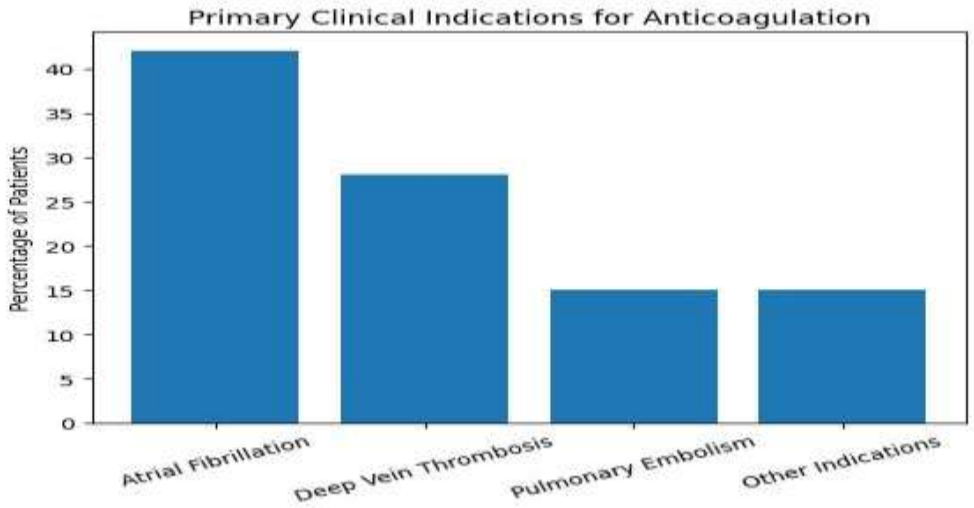


Figure 3. VKORC1 genotype distribution

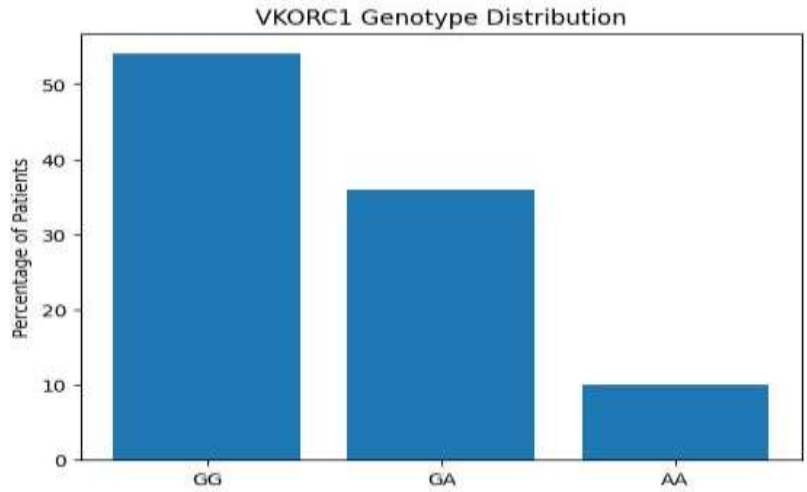


Figure 4. CYP2C9 genotype distribution

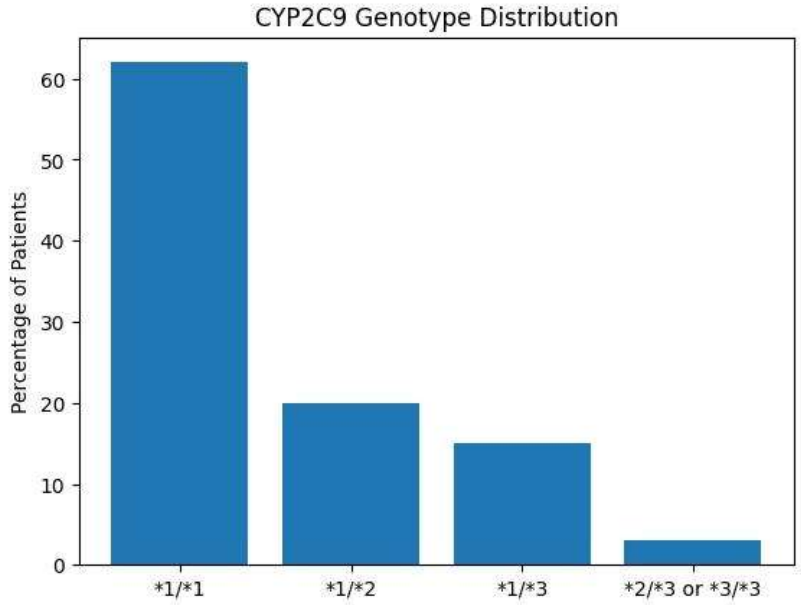


Figure 5. Mean weekly warfarin dose by VKORC1 genotype

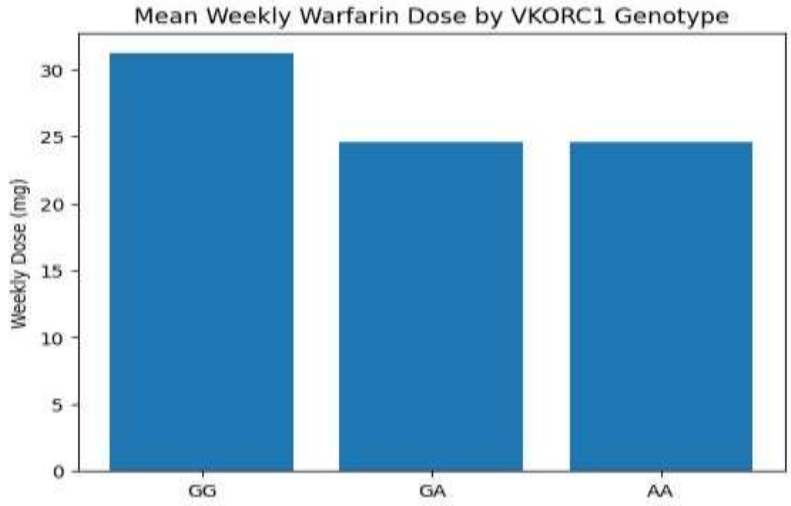


Figure 6. Mean weekly warfarin dose by CYP2C9 metabolizer status

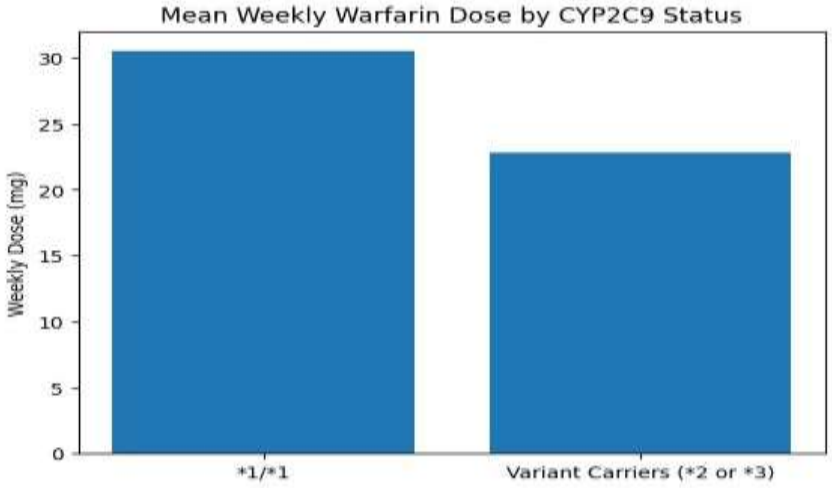


Figure 7. Clinical outcomes under genotype-guided dosing

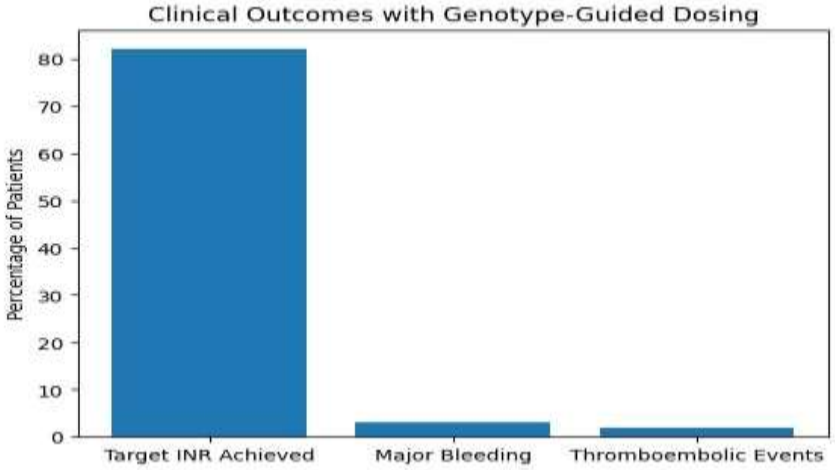
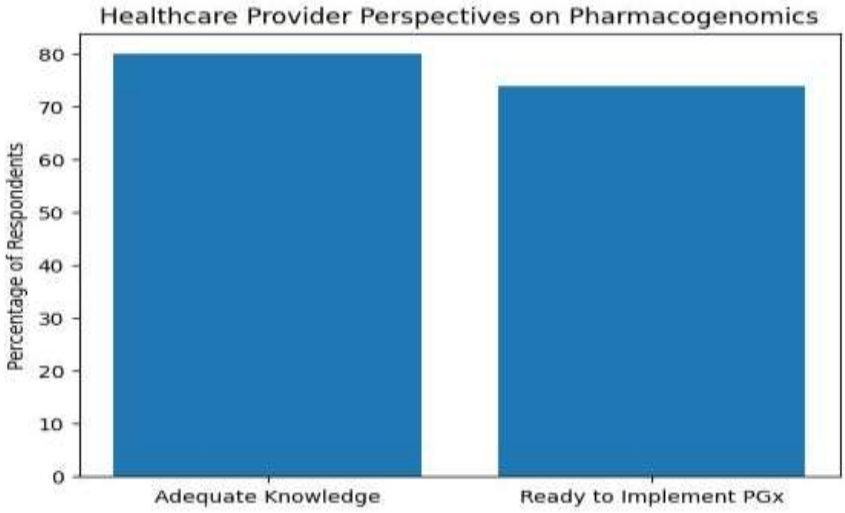


Figure 8. Healthcare provider knowledge and readiness for pharmacogenomic implementation



Discussion

The present study provides robust and clinically meaningful evidence that pharmacogenomic profiling can play a pivotal role in optimizing personalized anticoagulant therapy within the Saudi population. By identifying prevalent genetic variants—particularly within VKORC1 and CYP2C9—and demonstrating their strong associations with warfarin dose requirements, this investigation both corroborates and extends existing pharmacogenomic literature on genotype-guided anticoagulation (Al Hamad, 2025; Jokhab et al., 2025). Importantly, the observed predominance of VKORC1 GG and CYP2C9 *1/*1 genotypes mirrors patterns reported in other Middle Eastern cohorts, reinforcing the necessity of adopting population-specific dosing strategies rather than extrapolating algorithms derived primarily from European or East Asian populations. Such extrapolation risks systematic dosing inaccuracies due to interethnic variability in allele frequencies and genotype–phenotype relationships.

The clinical implications of genotype-informed therapy were clearly demonstrated in this study. Patients harboring functionally significant VKORC1 and CYP2C9 variants required significantly lower warfarin doses and achieved therapeutic international normalized ratio (INR) targets more rapidly than non-carriers. Moreover, these patients experienced fewer adverse clinical outcomes, including bleeding complications and thromboembolic events. These findings are consistent with prior randomized trials and observational studies showing that pharmacogenomic-guided dosing improves anticoagulation control, particularly during the initiation phase when patients are most vulnerable to adverse events (Johnson et al., 2017; Relling & Evans, 2015). Collectively, these results underscore the clinical value of pharmacogenomics in reducing both under-anticoagulation, which predisposes patients to thromboembolism, and over-anticoagulation, which increases bleeding risk.

The multivariate analyses further highlighted the importance of integrating genetic data with established clinical determinants of warfarin response, including age, body mass index, comorbid conditions, and concomitant medications. The combined model explained a substantial proportion of inter-individual dose variability, surpassing the predictive capacity of clinical factors alone. This finding reinforces the conceptual framework of precision medicine, in which optimal therapeutic decisions arise from the integration of genomic, clinical, and demographic data. Such integrated models are particularly valuable in heterogeneous populations, where reliance on single-factor approaches may lead to suboptimal treatment outcomes.

A notable contribution of this study is the identification of rare and potentially novel variants within CYP2C9 and VKORC1. These findings underscore the genetic distinctiveness of the Saudi population and highlight limitations inherent in applying conventional dosing algorithms that do not account for region-specific genomic architecture. From a broader perspective, this supports the emerging field of population pharmacogenomics, which emphasizes that allele frequencies, variant effect sizes, and gene–drug interactions can differ substantially across ethnic and geographic contexts (Roden et al., 2019). Failure to account for such differences may perpetuate health disparities and limit the effectiveness of precision medicine initiatives in underrepresented populations.

Beyond warfarin, the study offers important insights into the evolving role of pharmacogenomics in direct oral anticoagulant (DOAC) therapy. Although DOACs are characterized by more predictable pharmacokinetics and reduced need for routine monitoring, emerging evidence suggests that genetic variation may still influence drug absorption, metabolism, and clearance. The identification of variants in ABCB1 and CES1 as contributors to inter-individual variability in DOAC exposure suggests that pharmacogenomic-guided optimization may extend beyond traditional vitamin K antagonists (Aldiban et al., 2025; Yang et al., 2023). While routine genetic testing for DOAC dosing is not yet standard practice, these findings provide a foundation for future investigations into genotype-informed strategies for newer anticoagulant classes, particularly in patients at the extremes of drug response or risk.

The qualitative component of the study adds an important implementation perspective by exploring healthcare providers' knowledge, attitudes, and readiness to adopt pharmacogenomic-guided therapy. Overall, participants demonstrated favorable perceptions and expressed willingness to integrate genetic information into clinical decision-making, provided that adequate infrastructure and institutional support were available. However, persistent systemic barriers—including the cost of genetic testing,

limited laboratory capacity, and gaps in clinician education—were identified as major challenges. These findings align with established implementation science frameworks, which emphasize that successful translation of pharmacogenomic evidence into routine practice requires not only scientific validity but also organizational readiness, policy alignment, and sustained educational efforts (Damschroder et al., 2009).

Taken together, the results of this study carry important clinical, research, and policy implications. First, they provide strong empirical support for implementing genotype-guided warfarin dosing in Saudi healthcare settings to improve therapeutic outcomes and patient safety. Second, they underscore the urgent need for developing national or regional pharmacogenomic databases and population-specific dosing algorithms that accurately reflect the genetic landscape of Saudi patients. Third, they highlight the importance of institutional strategies to facilitate implementation, including clinician training programs, integration of pharmacogenomic data into electronic health records, and deployment of clinical decision-support systems. Finally, these findings contribute to the growing global body of evidence advocating precision medicine as a sustainable and equitable framework for individualized therapy in ethnically diverse populations.

Despite several strengths—including a robust sample size, comprehensive genotyping, and the integration of quantitative and qualitative methodologies—this study has certain limitations. The cross-sectional design limits causal inference, and the recruitment of participants from selected healthcare centers may restrict generalizability to the broader Saudi population. Future research should prioritize longitudinal and interventional study designs to assess long-term clinical outcomes associated with genotype-guided therapy. Additionally, expanding pharmacogenomic profiling to include other anticoagulants, gene–gene interactions, and polygenic risk scores may further enhance predictive accuracy. Importantly, formal cost-effectiveness analyses are needed to inform healthcare policy and determine the economic feasibility of widespread pharmacogenomic implementation.

In conclusion, this study demonstrates that pharmacogenomic profiling in the Saudi population can meaningfully guide anticoagulant dosing, improve therapeutic efficacy, and reduce adverse events. The integration of genetic and clinical data enhances precision in anticoagulation management, while qualitative insights highlight key facilitators and barriers to implementation. Collectively, these findings advance the field of precision medicine and provide a strong empirical foundation for the broader adoption of pharmacogenomic-guided anticoagulant therapy in Saudi Arabia and comparable populations.

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