ISSN 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

Pharmacogenomic of warfarin and its implication on international normalized ratio and dosing: A narrative review

Agil Wahyu Wicaksono[1,2]*, Selma Mutiara Hani[2],

[1]Molecular and Cell Biology Department, Faculty of Medicine, Universitas IPB, Bogor, [2]Master's Programme in Biomedical Science, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta

https://doi.org/10.22146/ijpther.4712

Submitted: 01-06-2022
Accepted : 20-12-2024

Keywords:
pharmacogenetics; pharmacogenomics; warfarin; international normalized ratio; polymorphism

ABSTRACT

Genotype is an important factor in warfarin dosing requirements and affects the risk of excess anticoagulant use due to its narrow treatment window, high drug interactions, and frequent bleeding. The CYP2C9 and VKORC1 genotypes have a strong and consistent association with warfarin dose requirements, and the algorithms of dosing incorporating genetic and clinical information are stable warfarin dose predictions. The review article aimed to investigate the association between the genotype of CYP2C9 and VKORC1 and the current relevant dosing recommendations for warfarin in various patients. The secondary purpose was to correlate genotype with the international normalized ratio (INR). It was a narrative review of the most recent reference (observational, trial study, and RCT) on the clinical application of pharmacogenomic testing for warfarin pharmacokinetics and pharmacodynamics and its impact on INR over the last 5 yr from the PubMed and SAGEPub databases. Six studies were included in this review and showed how the genetic polymorphisms and dosage responses of different groups differed. Pharmacogenetic algorithms meet non-inferior and superior criteria for reducing dose titration compared to traditional dosing approaches, and predict actual maintenance doses well. Bleeding mostly occurred in the first mo of treatment, with no significant difference in the frequency of total bleeding between groups. Genotype-based dosing of warfarin increased the proportion of time in the therapeutic INR range (% TTR) and reduced the time to reach a therapeutic INR. Administration of CYP2C9 and VKORC1 genotypes based on warfarin may be beneficial in patients with atrial fibrillation, mechanical valve replacement, and bleeding prophylaxis for hip or knee arthroplasty. Stable warfarin doses were achieved in statistically more patients in the genotype-targeted group (47%) than in the traditional group (22%).

ABSTRAK

Genotipe merupakan faktor penting dalam mempertimbangkan kebutuhan dosis warfarin dan dapat mempengaruhi risiko efek samping antikoagulan karena jendela terapi yang sempit, interaksi obat yang tinggi, dan sering mengakibatkan perdarahan. Genotipe CYP2C9 dan VKORC1 memiliki hubungan yang kuat dan konsisten dengan kebutuhan dosis warfarin tersebut. Algoritma pemberian dosis yang menggabungkan informasi genetik dan faktor klinis dapat memprediksi dosis warfarin yang stabil. Namun berbagai penelitian terkait farmakogenomik pada warfarin masih terus berkembang dan menunjukkan hasil yang beragam. Tujuan kajian pustaka ini adalah untuk mengkaji hubungan antara genotipe CYP2C9 dan VKORC1 dan rekomendasi dosis warfarin yang relevan saat ini pada pasien dengan berbagai kasus. Tujuan kedua adalah untuk mengkorelasikan genotipe dengan nilai *international normalised ratio* (INR). Artikel ini merupakan tinjauan naratif dari referensi terbaru 8 tahun terakhir (penelitian observasi, penelitian percobaan, dan RCT) pada aplikasi klinis pengujian farmakogenomik untuk farmakokinetik dan farmakodinamik warfarin, serta dampaknya terhadap INR dari *database* PubMed dan SAGEPub. Enam penelitian telah dimasukkan dalam tinjauan ini dan menunjukkan bagaimana polimorfisme genetik kelompok yang berbeda akan menyebabkan respons dosis yang berbeda pula. Algoritme farmakogenetik memenuhi kriteria non-inferior dan superior dalam mengurangi titrasi dosis dibandingkan dengan pendekatan dosis tradisional dan mampu

*corresponding author: agilwahyuwicaksono1692@mail.ugm.ac.id

memprediksi dosis pemeliharaan aktual dengan baik. Kejadian perdarahan paling banyak terjadi pada bulan pertama pengobatan dengan tidak ditemukan perbedaan yang signifikan pada frekuensi perdarahan total antarkelompok. Dosis warfarin berbasis genotipe meningkatkan proporsi waktu dalam kisaran INR terapeutik (% TTR) dan mengurangi waktu untuk mencapai INR terapeutik. Pemberian warfarin berbasis genotipe CYP2C9 dan VKORC1 bermanfaat bagi pasien dengan fibrilasi atrium, penggantian katup mekanis, dan profilaksis perdarahan pada artroplasti pinggul atau lutut. Dosis warfarin yang stabil dicapai pada pasien yang secara statistik lebih banyak pada kelompok berdasarkan genotipe (47%) dibandingkan pada kelompok dosis tradisional (22%).

INTRODUCTION

Warfarin is the most prescribed anticoagulant which is administered orally worldwide.[1] It is often used as a prophylactic in patients who have a high-risk condition for thromboembolic events such as atrial fibrillation, artificial heart valve, or transient ischemic attack.[2-4] Warfarin's properties are a narrow treatment window, high drug interactions, and frequent bleeding.[5]

Between 1996 and 2011, treatment with warfarin in patients with newly developed atrial fibrillation tripled and it was associated with a positive effect on the prevention of thromboembolic events. The largest decrease in thromboembolic events was observed in patients treated with a CHA2DS2VASc score above 1, in both treated and non-warfarin-treated patients. The increasing use of warfarin causes an increase in bleeding incidence (3.29% in 1996 to 3.90% in 2011).[6]

Treatment with warfarin is further complicated by significant interpersonal variations in the dose required for optimal therapeutic effect. For most indications, it is defined as a 2.0 – 3.0 international normalized ratio (INR). Genotype is an important factor in warfarin dosing requirements and also affects the risk of excess anticoagulant and bleeding, especially in the first months of warfarin use.[7] The cytochrome P450 (CYP) 2C9 and vitamin K epoxide reductase complex 1 (VKORC1) genotypes have a strong association with warfarin dose requirements and the warfarin dosing algorithms.[8]

Although many studies have examined the pharmacogenomics of warfarin, the incidence of warfarin is still quite high. In the US, warfarin is a major cause of accounting for 33% of hospitalizations for side effects in the elderly population.[9] A retrospective cohort study in Thailand of 1604 patients taking warfarin found an incidence rate of 3.13 events per 100 person-years.[10] Another more recent study found an even higher incidence rate of warfarin therapy complications, at 4.91 events per 100 person-years.[11]

This article reviewed the association between CYP2C9 and VKORC1 genotypes and the current relevant dosing recommendations for warfarin in various patients. In addition, the correlation of the genotype of warfarin with INR value was discussed.

MATERIAL AND METHODS

This article has reviewed the most recent literature (observational, experimental, and RCTs) on the clinical application of pharmacogenomic testing of warfarin metabolism and its impact on INR in the past 8 yr. Readers are recommended to recent extensive reviews for a general overview of this issue. Owing to space constraints, primary research on this topic has to be the focus of our work. PubMED and SAGE Pub were used to search the medical literature. The following keywords were used in the literature search: "warfarin", "warfarin pharmacogenomics", and "warfarin pharmacogenetics".

RESULTS

A total of 135 articles (104 from PubMed database and 31 from SAGE Pub database) were collected. However, only six article that meet the inclusion and exclusion criteria (FIGURE 1).

Metabolism of warfarin

As an anticoagulant, warfarin (3-a-acetonylbenzyl-4-hydroxycoumarin, also known as coumarin, is available as a racemic combination, with the S form having 3–5 times more active than the R form. CYP2C9 is the major mixed-function oxidase responsible for the hydroxylation of S-warfarin, whereas the R-isoform is metabolized by CYP1A2, CYP3A4, and CYP2C19.[12] The efficacy of warfarin is principally due to its powerful, stereospecific inhibitory impact on an enzyme involved in clot formation. Hydroquinone (a reduced form of vitamin K) is required for the activation of c-glutamyl carboxylase-catalyzed clotting factors. Vitamin K is converted to 2,3 epoxides during this reaction, which must be rapidly recycled in a reduced form.[13] The enzyme vitamin K epoxide reductase complex 1 (VKORC1) catalyses this reaction, and warfarin competes it specifically. The result is depletion of the reduced form of vitamin K and inhibition of the clotting components, which finally leads to inhibition of clot formation. Warfarin was approved as an anticoagulant as early as the 1950s. However, the experimental evidence of the impact of CYP2C9 genetic polymorphism on the warfarin maintenance dose required in patients receiving anticoagulation therapy was first published in the 1990s.[14]

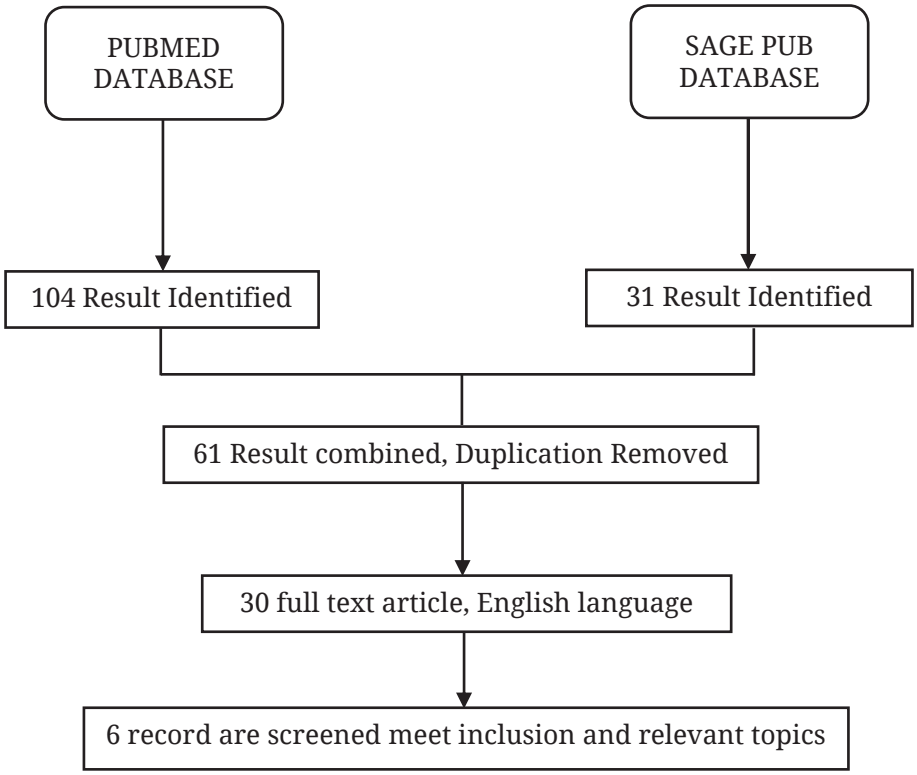

FIGURE 1. Flowchart showing the study selection procedure and results.

Polymorphism of CYP2C9 and VKORC1

A series of retrospective and prospective studies have shown the considerable effect of polymorphisms in CYP2C9 and VKORC1 on the metabolism and anticoagulant action of warfarin. Individuals homozygous for the CYP2C9*1 allele [as opposed to CYP2C9*2 (R144C) and CYP2C9*3 (I359L) homozygotes] have a higher maintenance dose requirement. Individuals with heterozygous CYP2C9 gene alleles *1, *2, or *3 frequently have an intermediate phenotype.[15]

Initial study on the VKORC1 gene revealed a link between numerous different genetic variants and phenotypic variations in warfarin metabolism. However, larger cohort studies have allowed researchers to identify two haplotypes, each of which includes at least six variants in the complete non-coding regions of the VKORC1 gene. Individuals with homozygous haplotype A have a resistant phenotype, whereas those with homozygous haplotype B have a sensitive phenotype. On the other hand, individuals with heterozygous alleles have an intermediate response.[16]

Clinical Pharmacogenomics

Several studies have examined how the genetic polymorphisms and dosage responses of different groups differ (TABLE 1). More than 15 yr ago, a clear link between interindividual variability in warfarin response and the most common gene polymorphisms in its mechanism of action and metabolism was discovered.[17] Nonetheless, the usefulness of genotyping before prescribing warfarin is still debated.[18] The biggest roadblock to bringing pharmacogenetics dosage into the clinical application is the lack of conclusive proof that genotyping improves the efficacy or safety of the therapy. However, large-scale experiments are required to obtain this evidence. Only a trend toward a decreased risk of clinically meaningful hemorrhagic or thromboembolism events was reported in the two latest largest RCTs, which involved 1597 and 2264 patients, respectively.[4,5] As a result, the majority of trials relied heavily on laboratory predictions.

TABLE 1. Summary of recent studies about the pharmacogenomics of warfarin

Author	Patients	Methods	Result	Remarks
Xu *et al.* [19]	Clinical starting treatment for patients with artificial heart valves	A randomized, double-blind controlled trial was performed to evaluate the genotype-guided dose algorithm (CYP2C9, VKORC1, and CYP4F2) using the clinical-guided algorithm.	It took less time for the study group to reach a stable dose than the control group (mean: 42.09 23,655 d vs 33.52 20.044 d, p = 0.009). TTRs in the control and study groups were 47.257 and 47.461%, respectively (p = 0.941). The INR variation of patients with the CYP2C9*1/*3 genotype was higher than that of those with the CYP2C9*1/*1 genotype (p=0.024). Highly sensitive respondents had a higher probability of INR than 4.0 or higher than normal and sensitive respondents (p< 0.05).	Genotypic-guided warfarin dosing is safe and effective in achieving stable dosing. Patients with the CYP2C9*1/*3 genotype and highly sensitive responders, who are part of a high-risk patient population with mechanical heart valves, would benefit from pharmacological testing.
Gage *et al.*[20]	Patients at six U.S. medical facilities aged 65 years and older started taking warfarin for elective knee or hip replacement surgery.	The genetic informatics randomized clinical trial of warfarin for the prevention of deep vein thrombosis was conducted when enrollment began in April 2011 and ended in October 2016.	In the genotype-guided group, 87 patients (10.8%) achieved at least one of the endpoints compared with 116 patients (14.7%) in the clinically-guided warfarin group (absolute difference 3.9% [95% CI: 0.7% 7.2%)], p = 0.02; relative rate [RR], 0.73 [95% CI, 0.560.95]). Individual events were 2 vs 8 for heavy bleeding (RR, 0.24; 95% CI: 0.051.15), 56 vs 77 for INR 4 or higher (RR: 0.71; 95%CI: 0.510.99), 33 vs 38 for VTE (RR: 0.85; 95% CI: 0.541.34), and there were no deaths in the genotype-guided group compared with the clinically guided group.	Genotype-directed warfarin dosing, compared with clinically-guided doses, reduces the combined risk of major bleeding, an INR of 4 or greater, venous thrombosis, or death in patients undergoing hip orthopedic surgery or knee and was treated with warfarin around surgery. The cost-effectiveness of individualized warfarin doses will require further study.

TABLE 1. Cont.

Author	Patients	Methods	Result	Remarks
Guo *et al.*[21]	Eighteen-year-old patient with atrial fibrillation or deep vein thrombosis who has never taken warfarin or has never bled.	From September 2014 to April 2017, 15 hospitals in China participated in a multicenter, randomized, single-blind, parallel-controlled experiment. 9 follow-up visits were made during the 12-wk. Percentage of time within the treatment range of the internationally normalized ratio within the first 12 wk of starting warfarin dosing was the primary endpoint.	660 subjects were enrolled and randomly assigned to either genotype-based or regular dosing. The genotype-targeted dose group spent more time in the therapeutic range than the control group (58.8% vs. 53.2% [95% CI:1,110,2]; p = 0.01). The genotype-based dosing group reached the internationally normalized ratio target earlier than the control group. The warfarin normal susceptibility group had a higher percentage of time within the treatment range in the first 12 wk (60.8 vs. 48.9%; 95% CI:1,124,4). Both groups had a low incidence of adverse events.	Genotype-guided warfarin dosing produced better results than clinical standard dosing.
Hao *et al.*[22]	Patients who had heart valve replacement surgery at Asia Heart Hospital of Wuhan	Patients were randomly assigned to genotype-dependent warfarin doses or the clinically controlled warfarin doses. The TaqMan genotyping assay was used to genotype CYP2C9 and VKORC1 (1639 GA). The algorithm of the International Warfarin Pharmacogenetics Consortium was used to predict the dose of warfarin. Patients in the control group (n = 1130) were clinically managed. The main result was to compare the incidence of adverse events during a 90-d follow-up. The secondary objective was to explain the effects of pharmacogenetic interventions on achieving initial treatment goals, stable maintenance doses, and length of hospital stay.	The analysis included a total of 2245 patients. During the follow-up period, 49 incidents occurred. Compared to the clinical dosing group, genotype-based dosing strategies include major bleeding (0.26 vs. 0.63%; hazard ratio 0.44; 95%CI: 0.131.53; p= 0.20) or thrombotic events (0.89 vs. 0.63%). Did not affect (1.61%; hazard ratio 0.56; 95%CI: 0.271.17; p = 0.12). Patients in the genotype-induced group reached the international treatment sensitivity ratio in a shorter time (3.8 ± 2.0 vs. 4.4 ± 2.0 d, p=0.001) than patients in the standard-dose group. The length of hospital stay did not change (p = 0.28).	In Chinese valve replacement patients, warfarin drug genetic testing according to the methodology of the International Warfarin Pharmacology and Genetics Consortium does not improve anticoagulant results.
Mak *et al.*[23]	The author recruited patients using two anticoagulant clinics in the Los Angeles area.	After informed consent, blood samples were collected and genotyped for vitamin K epoxide reductase (VKORC1), CYP2C9 * 2, CYP2C9 * 3, and CYP4F2. Data on demographics, clinical care, and warfarin doses were collected from the charts.	291 patients (120 Caucasians, 127 Hispanics, and 44 Asians). The highest warfarin was reported in Caucasians, lower in Hispanics, and lowest in Asians with wildtype genotypes for VKORC1, CYP2C9*2, CYP2C9*3, and CYP4F2. In Caucasians, Hispanics, and Asians, homozygous VKORC1 variant carriers were found in 15, 15, and 79%. In Caucasians and Hispanics, each VKORC1 mutation was related to progressively lower ADW dosages, whereas in wildtype/ heterozygote Asians were ambiguous. CYP2C9 variations were linked to lower ADW doses; CYP2C9*2 and CYP2C9*3 mutations were more common in Caucasians than Hispanics, but rare to nonexistent in Asians.	There were differences in the effects of ADW dose requirements and clinical factors among the ethnic groups. A single whole-race model may not be the best predictor of warfarin dose needs.
Pachenko *et al.*[24]	Outpatients and inpatients were recruited at 8 canters in Ural, and Siberia. The study included untreated warfarin patients aged >18 y.o. who had been on anticoagulant therapy for at least 6 mo.	It was randomized and open-label. The pharmacogenetic group, warfarin load, and therapeutic dose were calculated by a gauge algorithm which takes into account the polymorphisms of CYP2C9 and VKORC1. After receiving the INR results, the warfarin dose was adjusted. In the standard group, warfarin was prescribed at a starting dose of 5 mg/d and it was titrated from day 3. The standard-dose group, CYP2C9 and VKORC1 polymorphisms were analyzed after the follow-up period was completed.	Pharmacogenomic administration compared to prescribing a starting dose of 5 mg reduced major bleeding (0 vs 6; p = 0.031) and time to target INR (11 [9-14] vs 17). [15-24] d; p = 0.046) and the frequency of INR fluctuations was 4.0 or higher (11 vs. 30.9%; p = 0.002).	The benefits of pharmacogenetic dosing were achieved primarily in patients with high warfarin sensitivity.

INR Correlation with Genotype

The INR variation of patients with the CYP2C9*1/*3 genotype was higher than that of patients with the CYP2C9*1/*1 genotype (p=0.024), with an INR higher than 4.0, or higher than that of respondents without the genotype (p <0.05).[19] A study conducted by Guo *et al.* reported that the dose group based on genotype reached the target INR earlier than the control group.[21] In addition, patients in the genotype-induced group reached the international treatment sensitivity ratio in a shorter time (3.8 ± 2.0 vs. 4.4 ± 2.0 d; p=0.001) than patients in the standard-dose group.[22] A study conducted by Pachenko *et al.* showed that warfarin administration based on pharmacogenomics reduced the incidence of major bleeding compared to the initial dose of 5 mg (0 vs. 6; p = 0.031) and shortened the time to reach the target INR [11 (9-14) vs. 17 (15-24) d; p = 0.046]. In addition, the frequency of INR fluctuations was 4.0 or higher (11% vs. 30.9%; p = 0.002).[24]

DISCUSSION

The INR is a blood test that measures how long it takes for blood to clot. These tests are used to monitor and adjust the dosage of oral anticoagulant therapy, such as warfarin. The INR tests are also used to assess liver function. The INR is calculated by dividing a patient's prothrombin time (PT) test value by a laboratory's pooled normal plasma standard PT. The INR is then raised to an exponent based on the individual PT-initiating reagent. A normal INR is 1.0. Each increase of 0.1 means the blood is slightly thinner. A high INR usually means that the liver is not working as well as it could. An INR that is too low can mean that blood clots may not be prevented.[25] Pharmacogenomics plays a critical role in optimizing warfarin therapy by improving INR stability, reducing time to therapeutic INR, and minimizing adverse outcomes like bleeding.[26]

A study conducted by Mak *et al.*[23] with 291 enrolled patients (120 Caucasian, 127 Hispanic, and 44 Asian) had the most wild-type genotypes of VKORC1, CYP2C9*2, CYP2C9*3, and CYP4F2 among Caucasians. They found high warfarin requirements and were lower in Hispanics and lowest in Asians. Homozygous VKORC1 variant carriers were detected in 15, 15, and 79% of Caucasians, Hispanics, and Asians, respectively. Gradual reductions in the average daily warfarin (ADW) dose were associated with Caucasian and Hispanic VKORC1 mutants, however the wild-type/heterozygous Asian results were unclear. The CYP2C9 mutant was associated with lower ADW doses. The frequencies of CYP2C9*2 and CYP2C9*3 mutations were higher in Caucasians than in Hispanics but rarely in the absence of Asians. The frequency of CYP4F2 mutants was similar among ethnic groups, but the effect on the required warfarin dose was small.[23]

In Asian adults starting warfarin therapy, pharmacogenetic algorithms provide good criteria that are not inferior to traditional dosing approaches in reducing dose escalation and adequately predicting actual maintenance doses. Of the 322 randomized patients, the genotype-based group had a lower dose increase during the first 2 wk compared to the conventional dosing. The frequency of dose escalation was lower in the 1-, 2-, and 3-month genotype-induced groups but not in the frequency of INR measurements. The proportion of patients who experienced mild or severe bleeding, recurrent venous thromboembolism, or out-of-range INR values did not differ between the two groups. In predicting maintenance doses, the pharmacogenetic algorithm achieved an average percent error of R2 = 42.4% (P <0.001) and 7.4%.[27]

An RCT study results from 660 adult Chinese patients showed that genotype-based dosing of warfarin increases the proportion of time in the therapeutic

INR range (% TTR) by 5.6% and reduces the time to reach a therapeutic INR. The INR increased rapidly in the first 2 wk, decreased slowly after 2 wk, and remained within the therapeutic range. The median time to reach a therapeutic INR was shorter in the genotyped gate group than that in the control group. Within 1–4 wk, the% TTR was higher in the genotyping group than in the control group. Within 18 wk, % TTR was higher in the genotyping group than in the control group. Within 112 wk, % TTR was higher in the genotype-based dosing group than in the control group.[21]

In contrast, studies from the Russian population showed that the interval required to reach the INR goal was significantly shorter in the pharmacogenetic group than in the standard-dose group [11 (914) vs. 17 (1524) d; p = 0.046]. In addition, the proportion of patients with an INR variation of 4.0 or greater from d 7 to d 30 was also significantly lower in the pharmacogenetics group than in the standard-dose group. However, these differences did not lead to a significant improvement in the TTR from 7 to 30 d after the start of warfarin therapy, nor did a 6-month follow-up lead to an overall significant improvement. However, between d 7 and 30 of treatment, the proportion of patients with a TTR of 70% or higher was twice as high in the pharmacogenetic group as in the standard-dose group.[24]

Adverse events have been reported by Guo *et al.*[21] It was recorded in 2020, and 652 participants were included in the measurement of safety results: 323 participants from the genotype lead group and 329 participants from the control group. There was no significant difference in the overall adverse events between the two groups. A total of 38 bleeding events (20 in the genotype lead group and 18 in the control group), 25 mild bleeding events (14 in the genotype lead group and 11 in the control group), 7 moderate bleeding events (3 in the genotype-induced and control groups), and 6 major bleeding events (2 in the genotype-induced group and 4 in the control group) were reported. The mortality rates for each group are shown. Only one thromboembolic event was included in the control group. There was no significant difference between the various safety parameters between the two groups.[21]

The results of a study by Panchenko *et al.*[24] showed that most bleeding events occurred in the first month of treatment in both (control and genotype induction groups). There was no significant difference in the frequency of total bleeding between groups. However, all 6 major bleedings were included in the standard-dose group. Specifically, 5 of the 6 major bleeding episodes occurred in at least one polymorphic carrier who increased warfarin sensitivity and was associated with elevated INR (3.4 and above).[24]

Genotype-induced warfarin administration was used in a study on mechanical valve patients to evaluate the efficacy and safety of genotype-induced warfarin administration in East Asians. Maintaining a stable dose is safe and probably more time-efficient. Pharmacological genomic testing helps to identify sensitive responders belonging to a high-risk subset of patients with the CYP2C9*1/*3 genotype and patients with artificial heart valves. The incidence of major bleeding and thromboembolic events in the study group was 97.0%. Compared to the control group, the study group required less time to reach a stable dose. The TTR were 47.257% and 47.461% in the control and study groups, respectively. Patients with the CYP2C9*1/*3 genotype had higher INR variability than patients with the CYP2C9*1/*1 genotype (p = 0.024). Very sensitive responders had an increased risk of INR above 4.0 (p <0.05) compared to normally sensitive responders. These results differ from those of Hao *et al.*[22] Genetic testing of warfarin drugs using the International Warfarin Pharmacology and Genetics

Consortium algorithm does not improve anticoagulant outcomes in Chinese valve replacement patients. There are several possible reasons for this finding. First, during the dose escalation process, only the patient's starting dose differed between the two groups. After the initial 35 d, the doctors adjusted the dose of warfarin based on the INRs of the two study groups. Second, few patients require a non-standard starting dose due to their genotype, and most patients taking conventional doses can achieve their target INR with a conventional clinical dosing increase. Finally, the CYP2C9 and VKORC1 genotypes can only explain approximately 50% of the individual differences. Warfarin doses and anticoagulant outcomes are also affected by other genotypes, lifestyles, diets, compliance, and drug interactions.[19,22]

Administration of warfarin based on CYP2C9 and VKORC1 genotypes may be beneficial for patients diagnosed with atrial fibrillation. In patients with atrial fibrillation, the percentage of time spent in the therapeutic INR range was higher in genotyped gates than in non-genotyped gates. However, there were no significant differences between the other two indications for warfarin treatment. Stable doses of warfarin were achieved in statistically more patients in the genotype-targeted group (47%) than in the genotype-targeted group (22%).[28]

In patients undergoing elective hip or knee arthroplasty and being treated perioperatively with warfarin, genotype-induced warfarin administration causes major bleeding, four or more INRs, venous thromboembolism, or combined death. The risk has decreased. Of the 1650 randomized patients [mean age 72.1 ± 5.4 yr; 63.6 men; 91.0 Caucasians), 1597 (96.8%) received at least one warfarin regimen in this study and completed the trial (n = 808 for genotype lead group vs. n = 789 for clinical lead group). A total of 87 patients (10.8%) in the genotype-induced warfarin group achieved at least one endpoint, and 116 patients (14.7%) in the clinically induced warfarin group achieved at least one endpoint. The number of individual events in the genotype-guided and clinical-guided groups ranged from 2 to 8 for major bleeding and 56 to 77 for INR 4 and above without death in venous thromboembolism.[20]

CONCLUSION

Pharmacogenomics has the potential role to improve the safety and efficacy of drugs in humans. As with many new drug therapies, early efforts are uncertain in many areas. To date, genetic variations in warfarin metabolism have been shown to be responsible for many drug dose fluctuations. Several research groups have integrated pharmacological genomics trials into the warfarin-dosing algorithm and found that fewer laboratory tests improved time within the treatment range. Investigating the "difficult" results of such tests requires extensive research, such as a reduction of significant bleeding or thrombosis. To date, cost-effectiveness studies have not proven that pharmacological genomic testing has significant advantages, but this only improves when simpler and cheaper tests/techniques have been developed. Will be done. Both anticoagulant clinics and community pharmacists are well-suited to assist patients and physicians in pharmacological genomics testing. Both academic institutions and businesses need to prioritize education in this area.

ACKNOWLEDGEMENTS

We would like to thank our colleagues who have supported during the preparation of this manuscript.

REFERENCES

1. Harikrishnan P, Palaniswamy C, Aronow WS. Update on pharmacologic therapy for pulmonary embolism. J Cardiovasc Pharmacol Ther 2014; 19(2):159-69.

https://doi.org/10.1177/1074248413506612
2. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2 SUPPL.):7S-47S. https://doi.org/10.1378/chest.1412S3
3. Voora D, Ginsburg GS. Clinical application of cardiovascular pharmacogenetics. J Am Coll Cardiol 2012; 60(1):9-20. https://doi.org/10.1016/j.jacc.2012.01.067
4. Held VE, Wolf ME, Hennerici MG. Antithrombotic therapy in transient ischemic attack patients. Front Neurol Neurosci 2014; 33:147-61. https://doi.org/10.1159/000351915
5. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, *et al*. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: A subgroup analysis of the RE-LY trial. Lancet Neurol 2010; 9(12):1157-63. https://doi.org/10.1016/S1474-4422(10)70274
6. Hansen PW, Sehested TSG, Fosbøl EL, Torp-Pedersen C, Køber L, Andersson C, et al. Trends in warfarin use and its associations with thromboembolic and bleeding rates in a population with atrial fibrillation between 1996 and 2011. PLoS One 2018; 13(3):1-14. https://doi.org/10.1371/journal.pone.0194295
7. Limdi NA, McGwin G, Goldstein JA, Beasley TM, Arnett DK, Adler BK, *et al*. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. Clin Pharmacol Ther 2008; 83(2):312-21. https://doi.org/10.1038/sj.clpt.6100290
8. Johnson JA, Cavallari LH. Warfarin pharmacogenetics. Trends Cardiovasc Med. 2015; 25(1):33-41. https://doi.org/10.1016/j.tcm.2014.09.001
9. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalization for adverse drug events in older Americans. Surv Anesthesiol 2012; 56(2):65-6. https://doi.org/10.1097/01.sa.0000412401.21757.36
10. Priksri W, Rattanavipanon W, Saejear W, Tanyasaensook K, Phrommintikul A, Chulavatnatol S, *et al*. Incidence, risk factors, and outcomes of warfarin-associated major bleeding in Thai population. Pharmacoepidemiol Drug Saf 2019; 28(7):942-50. https://doi.org/10.1002/pds.4781
11. Sombat B, Tongkaew S, Nilwaranon A, Mungthin M, Jongcherdchootrakul K, Lertwanichwattana T. Incidence and risk factors of warfarin therapy complications in community hospitals, central and eastern regions, Thailand: a retrospective, multicenter, cohort study. BMC Res Notes 2023; 16(1):4-11. https://doi.org/10.1186/s13104-023-06383-2
12. Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM, *et al*. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther 2008; 84(3):326-31. https://doi.org/10.1038/clpt.2008.10
13. Caldwell MD, Berg RL, Zhang KQ, Glurich I, Schmelzer JR, Yale SH, *et al*. Evaluation of genetic factors for warfarin dose prediction. Clin Med Res. 2007; 5(1):8-16. https://doi.org/10.3121/cmr.2007.724
14. Gulseth MP, Grice GR, Dager WE. Pharmacogenomics of warfarin: uncovering a piece of the warfarin mystery. Am J Heal Pharm AJHP Off J Am Soc Heal Pharm 2009; 66(2):123-33. https://doi.org/10.2146/ajhp080127
15. Wen MS, Lee M, Chen JJ, Chuang HP, Lu LS, Chen CH, et al. Prospective study of warfarin dosage requirements based on CYP2C9 and VKORC1 genotypes. Clin Pharmacol Ther 2008; 84(1):83-9. https://doi.org/10.1038/sj.clpt.6100453
16. Limdi NA, Wadelius M, Cavallari L, Eriksson N, Crawford DC, Lee MTM, *et al*. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. Blood 2010; 115(18):3827-34.

https://doi.org/10.1182/blood-2009-12-255992
17. D'Andrea G, D'Ambrosio RL, Di Perna P, Chetta M, Santacroce R, Brancaccio V, *et al*. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. Blood 2005; 105(2):645-9. https://doi.org/10.1182/blood-2004-06-2111
18. Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, *et al*. Clinical pharmacogenetics implementation consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther 2017; 102(3):397-404. https://doi.org/10.1002/cpt.668
19. Xu Z, Zhang SY, Huang M, Hu R, Li JL, Cen HJ, *et al*. Genotype-guided warfarin dosing in patients with mechanical valves: A randomized controlled trial. Ann Thorac Surg 2018; 106(6):1774-81. https://doi.org/10.1016/j.athoracsur.2018.07.026
20. Gage BF, Bass AR, Lin H, Woller SC, Stevens SM, Al-Hammadi N, *et al*. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: The GIFT randomized clinical trial. JAMA 2017; 318(12):1115-24. https://doi.org/10.1001/jama.2017.11469
21. Guo C, Kuang Y, Zhou H, Yuan H, Pei Q, Li J, *et al*. Genotype-guided dosing of warfarin in chinese adults: A multicenter randomized clinical trial. Circ Genomic Precis Med 2020; 13(4):e002602. https://doi.org/10.1161/CIRCGEN.119.002602
22. Hao Y, Yang J, Zheng X, Hu Y, Yan X, Zhang L. Chinese patients with heart valve replacement do not benefit from warfarin pharmacogenetic testing on anticoagulation outcomes. Ther Drug Monit 2019; 41(6):748-54. https://doi.org/10.1097/FTD.0000000000000664
23. Mak M, Lam C, Pineda SJ, Lou M, Xu LY, Meeks C, *et al*. Pharmacogenetics of warfarin in a diverse patient population. J Cardiovasc Pharmacol Ther 2019; 24(6):521-33. https://doi.org/10.1177/1074248419843530
24. Panchenko E, Kropacheva E, Dobrovolsky A, Titaeva E, Zemlyanskaya O, Trofimov D, *et al*. CYP2C9 and VKORC1 genotyping for the quality of long-standing warfarin treatment in Russian patients. Pharmacogenomics J 2020; 20(5):687-94. https://doi.org/10.1038/s41397-020-0157-2
25. Nelson FRT, Blauvelt CT. Laboratory evaluations. In: Nelson FRT, Blauvelt CTBTAM editors. A manual of orthopaedic terminology [Internet]. 8th ed. Philadelphia: W.B. Saunders; 2015. p. 163-76. https://doi.org/10.1016/B978-0-323-22158-0.00005-6
26. Vuorinen AL, Lehto M, Niemi M, Harno K, Pajula J, van Gils M, *et al*. Pharmacogenetics of anticoagulation and clinical events in warfarin-treated patients: A register-based cohort study with biobank data and national health registries in Finland. Clin Epidemiol 2021; 13:183-95. https://doi.org/10.2147/CLEP.S289031
27. Syn NL, Wong ALA, Lee SC, Teoh HL, Yip JWL, Seet RC, *et al*. Genotype-guided versus traditional clinical dosing of warfarin in patients of Asian ancestry: a randomized controlled trial. BMC Med 2018; 16(1):104. https://doi.org/10.1186/s12916-018-1093-8
28. Makar-Aušperger K, Krželj K, Lovrić Benčić M, Radačić Aumiler M, Erdeljić Turk V, Božina N. Warfarin dosing according to the genotype-guided algorithm is most beneficial in patients with atrial fibrillation: A randomized parallel group trial. Ther Drug Monit 2018; 40(3):362-8. https://doi.org/10.1097/FTD.0000000000000501