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Demographic and Clinical Assessment of Warfarin Treatment in Thromboembolic Disease

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Abstract

Introduction: Warfarin is a widely prescribed oral anticoagulant used to prevent thromboembolic events. However, its therapeutic response varies significantly among individuals due to clinical and demographic factors. Personalized warfarin dosing is essential to minimize complications such as bleeding or clotting. This study aims to investigate the clinical and demographic factors that may influence the required weekly dose of warfarin in patients receiving anticoagulation therapy.

Materials and Methods: A cross-sectional study was conducted involving patients on warfarin therapy. Key variables collected included age, sex, body weight, INR (International Normalized Ratio), and platelet count. Data were analyzed to identify correlations between these variables and the weekly warfarin dose.

Results: Statistical analysis revealed that both body weight and age significantly influenced warfarin dose requirements. Higher body weight was associated with a higher therapeutic dose, whereas older age was associated with a lower dose requirement. No significant associations were found between warfarin dose and sex or platelet count.

Conclusion: Age and body weight are two critical demographic factors that should be considered when determining the optimal warfarin dose. Adjusting dosage based on these parameters may enhance therapeutic outcomes and reduce the risk of adverse events, supporting a more individualized approach to anticoagulation therapy.

التقييم الديموغرافي والسريري لعلاج الوارفارين في الأمراض الخثارية الصمامية

علاء علي محمد، آمال عمران موسى، أبو المعالي حسن محمود

الملخص

المقدمة

يُعد الوارفارين من مضادات التخثر الفموية الشائعة الاستخدام للوقاية من الحوادث الخثارية الصمامية. ومع ذلك، فإن الاستجابة العلاجية له تختلف بشكل كبير بين الأفراد بسبب عوامل سريرية وديموغرافية. إن التحديد الشخصي لجرعة الوارفارين يُعد أمراً ضرورياً للحد من المضاعفات مثل النزيف أو التجلط. تهدف هذه الدراسة إلى فحص العوامل السريرية والديموغرافية التي قد تؤثر على الجرعة الأسبوعية اللازمة من الوارفارين لدى المرضى الخاضعين للعلاج بمضادات التخثر.

المواد والطُرق

أُجريت دراسة مقطعية شملت مرضى يتلقون علاجاً بالوارفارين. تم جمع بيانات أساسية شملت: العمر، الجنس، وزن الجسم، النسبة المعيارية الدولية(INR) ، وعدد الصفائح الدموية. وتم تحليل البيانات لتحديد العلاقة بين هذه المتغيرات والجرعة الأسبوعية من الوارفارين.

النتائج

أظهرت التحليلات الإحصائية أن كلاً من وزن الجسم والعمر يؤثران بشكل كبير على متطلبات جرعة الوارفارين. إذ ارتبط الوزن الأعلى بزيادة في الجرعة المطلوبة، في حين كان التقدم في السن مرتبطًا بانخفاض الحاجة إلى الجرعة. ولم تُظهر التحليلات وجود علاقة ذات دلالة إحصائية بين الجرعة والجنس أو عدد الصفائح الدموية.

الاستنتاج

يُعد كل من العمر ووزن الجسم عاملين ديموغرافيين حاسمين يجب أخذهما بعين الاعتبار عند تحديد الجرعة المثلى للوارفارين. إن تعديل الجرعة استنادًا إلى هذه العوامل قد يُحسّن النتائج العلاجية ويُقلل من خطر حدوث المضاعفات، مما يدعم التوجه نحو نهج علاجي فردي أكثر فعالية في معالجة حالات التخثر المزمنة.

1. Introduction

Warfarin is one of the most frequently used drugs for blood clotting diseases. This drug is particularly very important in patients who have an increased risk for clot formation, say, patients who are in atrial fibrillation (AF), deep vein thrombosis (DVT), pulmonary emboli (PE), or patients fitted with certain kinds of prosthetic heart valves. Embolic phenomena for these patient categories are very dangerous, and when not controlled tend to lead to a cerebrovascular accident, pulmonary embolism, and sometimes death. Warfarin pharmacology is also tied to its mode of action – in this case, factors II, VII, IX and X that are necessary in blood coagulation are inhibited through the control of vitamin K synthesis. Warfarin lowers the body's ability to clot and, hence, again offers protection against the tendency to clot. Nevertheless, Warfarin therapy comes with immense challenges, stemming from the narrow therapeutic index as well as to variations in the individual's responses to the drug, making the titration of the dosage a critical component of the therapy(Holford, 1986, Wittkowsky, 2003). Managing warfarin dosing, however, has its own difficulties due to its low therapeutic index. In situations of under-anticoagulation, patients may be at an increased risk of thromboembolic events, on the other hand, over-anticoagulation leads to the risk of severe bleeding episodes like GI or intracranial hemorrhage, which can be fatal. Monitoring of warfarin therapy has been done through the use of the International Normalized Ratio (INR), a ratio which represents the time taken by blood to clot in an individual (Tang et al., 2003). INR is used by clinicians to titrate warfarin dosage, and for most thromboembolic conditions, a value of 2.0 to 3.0 is the typical target. But some conditions might even specify target ranges depending on patient's comorbidities and risk factors. As such, it is critical to keep the patient's INR, or to be more specific, the time his or her blood can be expected to be free from clotting, within the target range in order to avoid both over and under-pescribed and administered doses of the drug. This clearly highlights the case for individualized dosing of warfarin therapy (Wigle et al., 2013). To achieve the desired effect of allowing the blood to coagulate after aminocaproic acid is injected, blood loss is ideally controlled from an initial approximate dose based on the age weight body structure and health of the patient. However, even that rate can fluctuate, as the inter-individual responding to warfarin is high, and such parameters alone do not address it automatically (McNicol et al., 1961). This dynamic is caused by different demographic, clinical, as well as genetic traits that affect the pharmacodynamics and pharmacokinetics of warfarin. The most critical key demographic for warfarin response variations are age, sex and body weight combined with liver and renal functions along with medication. For example, there is a common practice within the drug prescribing include patients with liver or renal insufficiency who also show lower doses of warfarin effective (Limdi et al., 2010). Another biographical characteristic that importantly influences individual response to warfarin therapy is the weight of a patient. Elderly patients usually require less doses, because of changes in hepatic and renal function associated with aging resulting in reduced clearance of the drug. Consequently, older patients become more prone to situations of over-anticoagulation and are likely to suffer higher cases of bleeding tendency if the doses are not properly controlled)Garcia et al., 2005(. Weight likewise, helps to determine the pharmacokinetics of warfarin, because it is known that the more the body mass the larger the therapeutic dose is bound to be. This is explained by the need for a higher volume of distribution and circulation to achieve the required concentration of the anticoagulative material. Medical literature data aims to prescribe a lower warfarin dose to an average person, whereas these aims are unreasonable for a significant number of patients who are aimed at reducing the risk of either thrombotic or hemorrhagic events (Gong et al., 2011). Albeit demographic characteristics, genetic factors also contribute in influencing the warfarin metabolism. It is well-

established that warfarin metabolism is influenced by genetic variants of CYP2C9 and VKORC1 and those some degree of certain alleles may affect the enzyme activity. For instance, polymorphisms in the CYP2C9 gene that encodes the warfarin metabolic enzyme can decrease the rate of warfarin elimination which results in increased risks of prolonged anticoagulation and bleeding. Similarly, VKORC1 polymorphisms, position of the drug target receptor which can therefore influence the level of drug sensitivity (Johnson et al., 2017, Johnson et al., 2011). It had been shown by authors such as Schwarz et al. (2008) that if accompanied by genotypic data, there would be warfarin dose adjustments with a reduced risk of complications and enable therapeutic levels of INR to be achieved more quickly. But genetic tests are not present in every clinical practice setting, and this specifies the need for other predictive factors which are not genetic that can be useful in staging the doses (Schwarz et al., 2008). Although considerable work has been done regarding warfarin dosing, there still exist many questions pertaining among others how these doses should be adjusted to suit different patients (Horton and Bushwick, 1999). For instance, few if any studies exist that have investigated the individual impact of demographic and clinical factors on the need for warfarin maintenance dose in practice. Most of the studies carried out to determine the factors affecting warfarin dose maintenance have either been too narrow in terms of the study populations or the number of variables studied. This study seeks to fill these gaps by focusing on these relationships in a multicenter database of warfarin dosages that has a large number of patients. The aim of the research is to answer the questions on the reasons for the large variability of doses and therefore make a significant contribution in understanding the personalized approach to warfarin treatment (Wadelius et al., 2009). This study aims to help healthcare practitioners initiate therapy by providing them with dose adjustment predictors based on the data obtained from the dose requirements found. Ultimately, the objective is to deliver more efficient and safer therapy to patients taking warfarin using a more personalized approach considering multiple demographics, clinical and genetic characteristics, all of them are intricately connected. In this respect, this research contributes to the further development of such personalized protocols for oral anticoagulation that meet the requirements of various patients on long-term warfarin therapy.

2. Patients & Methods

This cross-sectional study was conducted to evaluate the influence of demographic and clinical factors on warfarin dose requirements in patients receiving oral anticoagulation therapy. A total of 97 patients undergoing warfarin treatment at [insert hospital/clinic name if applicable] were enrolled.

2.1. Inclusion Criteria

Included adult patients (≥18 years old) who had been on a stable warfarin dose for at least four weeks and had a recent INR measurement within the therapeutic range. Patients with known hepatic dysfunction, renal failure, malignancy, or those taking medications known to strongly interact with warfarin were excluded.

For each participant, the following data were collected:

- Demographic variables: age, sex, and body weight (kg)
- Clinical parameters: weekly warfarin dose (mg), International Normalized Ratio (INR), and platelet count ($\times 10^3/\mu l$).

Blood samples were obtained under standard clinical procedures, and INR and platelet counts were measured using automated laboratory analyzers. The mean weekly dose of warfarin was calculated based on the patients' stable dosing regimen.

2.2. Statistical Analysis

The data was processed in IBM® SPSS® Statistics software, Version 24. Descriptive statistics such as mean and standard deviation, were calculated for every variable. Pearson's and Spearman's correlation coefficients were computed to examine the association between the weekly warfarin dose and other relevant study variables after normality testing so that both linear and non-linear associations could be explored in detail. Simple linear regression analysis was further employed to determine the strength of the relationship between the independent variables with statistically significant correlation and the weekly average warfarin dose. Other analyses included independent-sample t-tests of the differences in weekly dose requirements between the genders and between over and under 50 years of age. In this regard, a P-value cut-off of 0.05 was used.

3. Results

3.1. Descriptive Statistics

Age, weight, INR, and platelet count are summarized as follows: The sample had an average age of 49.6 years, with an age range that allowed analysis across different life stages. The average body weight of 77.28 kg, with significant interindividual variability (± 16.87 kg), highlights potential dosing adjustments based on body mass. Mean INR was 2.61, a value maintained within the therapeutic range for most patients, indicating effective anticoagulation. The average platelet count was 237.64 x10^3/µL, a value generally within the normal range, ensuring no underlying thrombocytopenia or platelet abnormalities that might complicate interpretation Table1.

Table1. Baseline Demographic and Clinical Characteristics of the Study Participants (N = 97)

Parameters	N (%)
N	97
Sex	
Male	38 (39.2)
Female	59 (60.8)
Mean ± SD	
Age (years)	49.6 ± 10.99
Weight (kg)	77.82 ± 17
INR	2.61 ± 0.52
PLT (x103 /µl)	237.64 ± 77.17
Warfarin Weekly dose (mg)	31.63 ± 7.66

3.2. Correlation Analysis

The study found that age was negatively correlated and weight was positively correlated with the weekly warfarin dose ($r = -0.328$, $P = 0.001$) and ($r = 0.491$, $P < 0.0001$) respectively. This means that older patients did not need higher doses and patients with higher body weight needed higher doses. Adjustments explained above are necessary ensuring that therapeutic anticoagulation levels are met so that older patients are on lower doses and patients on the other extreme of the spectrum are on higher doses. On the contrary, the weekly warfarin dose and INR ($r = 0.049$, $P = 0.62$) as well as PLT ($r = -0.005$, $P = 0.9$) do not have a significant association and therefore these variables could be viewed as having no relation with dosing requirements in the patient group for this study.

In the same breath, sex (r = 0.046, P = 0.65) seemed to have no strong relationship either so that men and women patients needed similar doses when the other factors were taken into account Table2.

Table2: Correlation Between Weekly Warfarin Dose and Clinical/Demographic Variables

Variable	Age	Weight	INR	PLT	Sex
Correlation coefficient (r)	-0.328**	0.491**	0.049	-0.005	0.046
P-value	0.001	<0.0001	0.62	0.90	0.65
**Correlation is significant at the 0.01 level, *. Correlation is significant at the 0.05 level.					

3.3. Regression Analysis

For the study of the impact of the parameters – age, weight, sex, INR and PLT, on the weekly selected dose of warfarin, a broader perspective was taken by simple linear regression regressions analysis Models was run.

Age: Age negatively correlated with the warfarin dose with a coefficient B = -0.228, P = 0.001thus 8.9% of the variance in warfarin dose is explained by age ($R^2 = 0.11$). This could probably be linked to decreased drug metabolism which is age-related or increased sensitivity of older individuals to the anticoagulation effects, thereby needing lower doses. Weight: Was found to be the most positive predictor towards the increase of the warfarin dose (B = 0.49, P <0.0001), explaining 18.2% weight-determined variance ($R^2 = 0.24$). This relationship reinforces the argument on drug dosing as the bigger body mass relative to the individual means more drug will be distributed and metabolized.

Sex, INR, and PLT: These variables showed no statistically significant influence on the weekly dose of warfarin, where sex had a coefficient B = 0.8 P = 0.6 and INR and PLT values were not P = 0.6 and P = 0.96 creating a situation in which their level of predictive power was diminished for this instance of dosing Table3.

Table3: Linear Regression Analysis of Predictors for Weekly Warfarin Dose

Predictor	Coefficient (B)	P-value	R^2
Age (years)	-0.228	0.001	0.11
Weight (kg)	0.490	<0.0001	0.24
Sex	0.800	0.600	0.003
INR	-0.720	0.600	0.0025
PLT ($\times 10^3/\mu l$)	-0.00046	0.960	0.00002
The table shows unstandardized regression coefficients (B), corresponding p-values, and the coefficient of determination (R^2) for each predictor. Bolded variables (age and weight) are statistically significant predictors of weekly warfarin dose ($p < 0.05$).			

3.4. Differences Due to Gender

The average weekly dose for males was 32.11 ± 7.86 mg while for females it was 31.31 ± 7.57 mg leading to a mean difference of -0.8mg (P = 0.61). This difference, although present, was not statistically significant, and it can be therefore concluded that sex does have much effect on variability in weekly dose Table4.

Table4: Comparison of Weekly Warfarin Dose Between Male and Female Patients

Variable	Female (n = 59)	Male (n = 38)	Mean Difference	P-value
Warfarin Weekly Dose (mg)	31.31 ± 7.57	32.11 ± 7.86	-0.80	0.61
Values are presented as mean ± standard deviation. No statistically significant difference was observed in warfarin dose between male and female patients ($p > 0.05$)				

3.5. Age Group Comparisons

A significant difference was noted between patients aged 50≥ years (mean dose 33.26 ± 13.53 mg) and those 50< years (mean dose 27.19 ± 13.68 mg), with a mean difference of 6.06 mg (P = 0.036). This suggests that age may influence dose adjustments, especially in older patients who might require more cautious dose escalation to avoid excessive anticoagulation Table5 and Fig.1.

Table5: Comparison of Weekly Warfarin Dose Between Age Groups

Variable	Age ≥ 50 (n = 58)	Age < 50 (n = 39)	Mean Difference	P-value
Warfarin Weekly Dose (mg)	33.34 ± 8.36	29.07 ± 5.67	4.26	0.007
Values are presented as mean ± standard deviation. A statistically significant higher warfarin dose was observed in patients aged ≥ 50 years compared to those < 50 years (p < 0.01)				

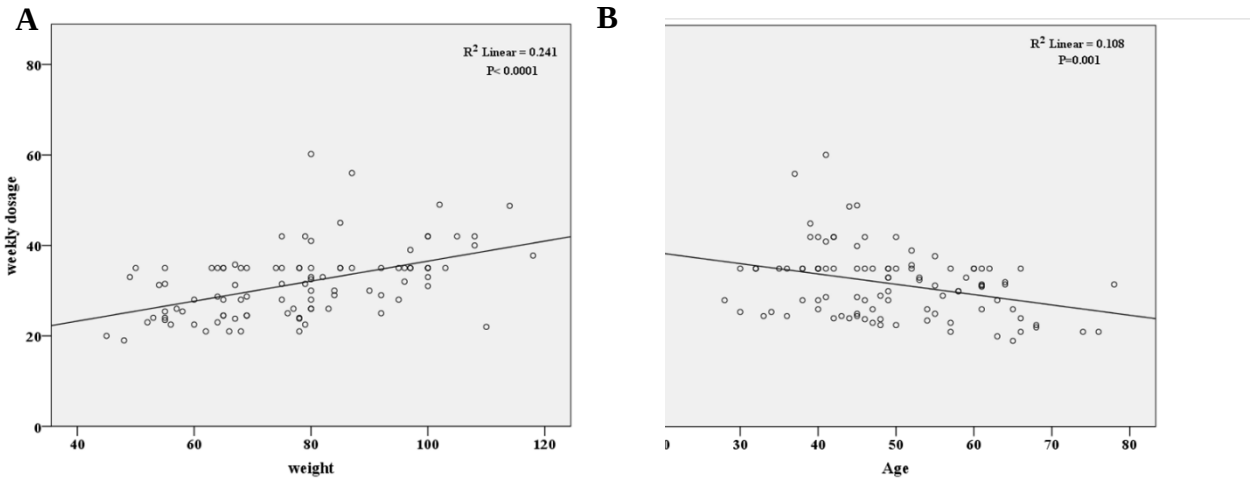

Figure1: Correlation Between Body Weight and Weekly Warfarin Dose

A) The scatter plot demonstrates a positive linear relationship between **body weight** and **weekly warfarin dose**. The regression line shows a moderate positive trend, with **R^2 = 0.241** and **p < 0.0001**, indicating a statistically significant correlation. Heavier patients tend to require higher weekly doses of warfarin. **B) Correlation Between Age and Weekly Warfarin Dose**. This scatter plot illustrates a negative linear correlation between **age** and **weekly warfarin dose**. The regression analysis yielded an **R^2 = 0.108** with a **p-value = 0.001**, suggesting a statistically significant inverse relationship. Older patients generally require lower warfarin doses.

4. Discussion

The results of this investigation bring to light the vicious underpinnings involved in the attainment in the warfarin dose that is deemed therapeutic, with demographic variables particularly body mass and age coming out as major factors. Among these, regarding the effective weight of the patient, the body weight was the underlying factor most correlating with the requirements for weekly doses of warfarin. This relationship can be explained by the fact that body weight has a bearing on the volume of distribution and metabolic clearance of warfarin, which implies that as a person's body mass increases, there is increased demand for the drug in order to achieve a therapeutic effect. This observation is in line with earlier studies that have most of the time emphasized the importance of weight adjusted dosing particularly in achieving and sustaining INR targets so as to prevent an increased risk of adverse effects like bleeding or thrombotic complications. For instance, a systematic review by Garcia et al. (2005) also expanded on the

fact that body mass is the primary determinant when it comes to the pharmacokinetics interactions with warfarin, which exerts pharmacodynamics effects on the target cells or tissue in the patient. When such individuals are not weight-adjusted, under anti-coagulation will occur in individuals with greater body mass putting them at risk of clot prevention, and vice versa for individuals with lower mass who will be at more risk of bleeding (Boonyawat et al., 2017, Pan et al., 2016, Miao et al., 2007, Boriani et al., 2019, Yu et al., 1996). In addition, the pharmacokinetic models such as the one established by the International Warfarin Pharmacogenetics Consortium (2009), also point towards the need for weight adjustments while determining the doses. These models have pointed out that the volume of distribution of warfarin and the clearance rates are dependent on the body mass of an individual, which ultimately determines the pharmacokinetics of the drug. Consequently, such dosing strategies have also been associated with a low incidence of dose related adverse effects, thereby improving the safety and the efficacy of the drug. Therefore, weight-based dose modifiers are now central to the improvement of the algorithms used for dosing warfarin, allowing better management of the therapeutics target (Consortium, 2009, Mueller et al., 2014, Röshammar et al., 2021, Anderson et al., 2012). It has been reported that older patients require less warfarin than younger patients to reach therapeutic INR levels. This phenomenon is consistent with numerous studies that highlight age-related physiological changes, such as diminished hepatic and renal functions which reduces the metabolic clearance for warfarin (Kimmel et al., 2008; Hylek et al., 1997). It has also been shown that the activity of cytochrome 450 isoenzymes particularly CYP2C9, are related to age, meaning an increase in age leads to an increase in half-life as well as heightened sensitivity to warfarin (Wang et al, 2016). Age-related factors also lead to an increased risk of patients being over anti-coagulated, hence requires alterations in dosages and also gradual changes in the dosage so as to attain the therapeutic ranges (McCarthy et al., 2012). Based on clinical indications, this explains why more than 60 patients are advised by medical practitioners to reduce their starting doses of warfarin which is also consistent with the results demonstrating the need for individualized anti-coagulation therapy (Wang et al, 2016; Kimmel et al, 2008)(Hylek et al., 1996, Kimmel et al., 2008). Our study showed no statistically significant association of weekly warfarin dose with either INR or platelet (PLT) levels. The authors may find this finding a bit odd as INR is the primary parameter employed in assessing the safety and effectiveness of warfarin therapy. Yet this finding is not surprising since the INR should not be viewed as the dosage maintenance target but rather as a versatile metric that informs dose adjustment decisions in real-time. In instances where patients are routinely monitored for their INR levels and subsequently adjusted their doses, the variability in dose has to be constant in order to manage the patient's INR to maintain it at the target level. Hence, without constant revision of the dose for various reasons, including fluctuation of INR measurement taken into consideration, the average weekly dose would have no indication relation to the INR. In this regard, other studies support this hypothesis by stating that while INR is very important in making real-time dose changes, it is not a single independent suitor for determining the predictor of maintenance dose. For example, other studies have reported that INRs at baseline levels are not good pieces of information in determining dosage requirements for treatment over a prolonged period. Rather a personalized approach taking into account demographics and clinical mess should be utilized for best outcomes advanced by a retrospective cohort study (Gupta et al., 2015, McMillin et al., 2011). Additionally, the findings are in accordance with previous studies concerning the correlation between PLT levels and bleeding events, which suggest that platelet count does not alter warfarin's pharmacokinetics or pharmacodynamics.

Research such as that by Hylek et al (1997) has shown that while platelet count may be routinely taken into account for the purposes of investigating bleeding risk in patients receiving anticoagulants, it is scarcely predictive of the warfarin dose required. It is however more plausible that one includes platelet count when determining one's risk of bleeding rather than the amount of warfarin, in this regard it becomes important to distinguish factors affecting the safe range of the dose from factors affecting the adverse effects of the drug, for example factors such as body weight and age. In this regard, bleeding risk and dosing requirements are in fact self-evident; in practice, the dosing schedule is formed mainly by demographic and physiological factors, and only in lesser proportions by platelets or INR among other indicators (Hylek et al., 1998, Proietti et al., 2019, Lazo-Langner et al., 2009). When all these aspects are considered, there comes out the need to individualize warfarin dosing based on the patient's characteristics such as age and weight as well as monitor INR level closely for dose modification. Physicians can reduce the risks of thrombosis and bleeding by starting the treatment with a specific dose and adjusting it periodically as the clinical situation warrants. There is potential in the future for combining pharmacogenetics with demographics to optimize warfarin dosing guidelines. For example, genetic variations in the CYP2C9 and VKORC1 warfarin metabolism pathway genes might be helpful to develop better dosing models that do not have to rely on trial and error depending on clinically adjusted dosing requirements such pharmacogenetics would allow a patient-centered approach to warfarin dosing (Absher et al., 2002, Daly, 2009, Kangelaris et al., 2009).

5. Conclusion

This study recognizes the importance of dose individualization factors: body weight and age for most of the ageing population on warfarin therapy. For warfarin to be effective and safe, there is need to adhere to weight-based capacity since it largely affects distribution and clearance of the drug. In addition, older patients are expected to be on lower doses since older age is associated with increased risk of bleeding due to physiological changes. Thus, future conclusions may be more definitive by using a larger sample of patients with different pathology and the presence of such parameters as: age, sex, and polymorphisms CYP2C9, VKORC1, etc. Measures of these demographic traits, the genetic, and clinical characteristics aim at evaluation of blood thinning medications may result in better individual dosing predictions and increase efficacy and reduce risks of warfarin use.

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