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Research Article

Current Practice of Warfarin Anticoagulation Therapy in China

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Abstract

The vitamin K antagonist warfarin has been used as a common oral anticoagulant to treat and prevent thromboembolic conditions in deep vein thrombosis, pulmonary embolism, atrial fibrillation, and heart valve replacement. Although Novel Oral Anticoagulants (NOACs), such as dabigatran, rivaroxaban, edoxaban, and apixaban, have been gaining acceptance and popularity in recent years, warfarin will likely remain as an important option due to its affordability and decades long experience of clinical use. In patients with moderate-to-severe mitral stenosis or those who underwent mechanical heart valve replacement, warfarin is the recommended anticoagulant as per clinical guidelines. The top indications for warfarin treatment in China are Atrial Fibrillation (AF) and Heart Valve Replacement (HVR), accounting for more than 60% of all patients. This is followed by deep vein thrombosis/pulmonary embolism (DVT/PE) (up to 30%) among other indications. Among AF patients with high stroke risk (CHADS2≧2 and CHA2DS2-VASc≧2) in Chinese hospitals, a large proportion of patients were taking antiplatelets instead of anticoagulants. Many physicians may be reluctant to prescribe oral anticoagulants in elderly AF patients due to fear of bleeding events and may underestimate the benefits of oral anticoagulants to reduce stroke risk. Also, despite demonstrated advantage of pharmacogenetic dosing approach in helping patients achieve and maintain within therapeutic INR window, an empirical approach to warfarin dosing is used in vast majority of cases. Clearly more education and promotion on warfarin anticoagulation is needed among healthcare professionals and patients in China to maximize its benefits and reduce adverse complications.

Keywords: Anticoagulation, Clinical practice, Warfarin, China healthcare

Introduction

With the aging population in China, the incidences of cardiovascular diseases have risen over the years. According to an epidemiological study published in 2021, the prevalence of Atrial Fibrillation (AF) was 1.8%, which equates to about 7.9 million people aged 45 or more in China [1]. The AF prevalence was higher in the ≥75 age group, which are 5.4% and 4.9% among men and women respectively. According to an epidemiological update published in 2018, Venous Thromboembolism (VTE) was more common in elderly individuals, with the overall annual incidence of Deep Vein Thrombosis (DVT) alone, Pulmonary Embolism (PE) alone, and PE with DVT reported as 30.0, 8.7, and 3.0 per 100,000 population in China, respectively [2]. This is an increase in incidence compared with findings reported 10 years ago. AF and VTE could lead to detrimental cardiovascular complications, thereby significantly reducing the quality of life in patients. There is an up to 5-fold increase in the risk of ischemic stroke in patients with AF, which accounts for 20-30% of all ischemic stroke cases, while VTE is one of the leading causes of cardiovascular death, along with Myocardial Infarction (MI) and ischemic stroke [3-6]. Furthermore, a Taiwanese study reported a

3-fold increase in the risk of VTE in patients with AF [7]. For this reason, the safety and effectiveness of oral anticoagulants to treat and prevent thromboembolism in cardiovascular diseases has received increased attention in recent years.

As a type of vitamin K antagonist, warfarin has been used as a common oral anticoagulant to treat and prevent thromboembolic conditions in DVT, PE, AF, and Heart Valve Replacement (HVR) [8-10]. Due to large interindividual variability and narrow therapeutic window, warfarin therapy requires routine monitoring of International Normalized Ratio (INR) to prevent thromboembolism (under-coagulation) or bleeding (over-coagulation) especially during initial phase of dosing. In recent years, Novel Oral Anticoagulants (NOACs), such as dabigatran, rivaroxaban, edoxaban, and apixaban have been developed with superior efficacy than warfarin in the prevention of stroke, while having lower incidence rates of thromboembolism and bleeding [11-13]. Also, NOACs do not require monitoring and are able to achieve anticoagulant effects quickly due to short half-lives [14]. While NOACs have been gaining acceptance and popularity in anticoagulant treatment, warfarin will likely remain as an important oral anticoagulant option since the costs of NOACs might be prohibitive to socio-economically disadvantaged patients and assays to measure the plasma levels or activity of NOACs are not widely available to inform timing for emergency surgeries [15-17]. This review discusses current practice of oral anticoagulant therapy in China and showcases how patients receiving warfarin are educated and followed-up for adequate anticoagulant control in typical tertiary (top-tier) hospitals in China.

Warfarin vs. NOACs

Since 2009, NOACs, such as rivaroxaban, dabigatran, apixaban, and edoxaban, have been approved for market authorization in China. Results from large, randomized Phase 3 trials showed that NOACs achieved non-inferior efficacy to warfarin in preventing stroke or systemic embolism, with lower or similar rates of bleeding. In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism) trial in patients with nonvalvular atrial fibrillation (NVAF), rivaroxaban was noninferior to warfarin for the primary endpoint of preventing stroke or systemic embolism, with less frequent occurrences of intracranial and fatal bleeding [12]. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, compared to AF patients receiving warfarin, those receiving 150 mg dabigatran had lower rates of stroke and systemic embolism with similar rates of major hemorrhage, while those receiving the lower dose of 110 mg had similar rates of stroke and systemic embolism but with lower rates of major hemorrhage [13]. In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, apixaban demonstrated superior efficacy to warfarin in preventing stroke or systemic embolism, with lower rates of bleeding and mortality [11]. In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial, edoxaban treatment was also noninferior to warfarin in preventing stroke or systemic embolism with lower rates of bleeding and cardiovascular-related mortality [18]. Despite having at least non-inferior efficacy at preventing thromboembolic events, it is considered that the risk of gastrointestinal bleeding might be higher in those receiving NOACs, especially for older patients. Since 2018, the cost of NOACs have decreased significantly since China implemented a national centralized drug purchase policy, which includes dabigatran, rivaroxaban, edoxaban, and apixaban [19]. Studies have shown that, over the long-term, NOACs could be cost-effective options in the healthcare system of China [19-21]. A study on the health insurance claims data indicates that oral anticoagulant use among AF patients in Shanghai had risen from 19.46% to 56.75% between 2015 and 2020, mainly due to prescription increases for NOACs [22]. In 2015, warfarin was the most predominant oral anticoagulant prescribed. In 2019, however, the number NOAC prescriptions became the same as warfarin, whereas in 2020 it even exceeded the number of warfarin prescriptions. Clearly, the use of anticoagulants, and especially NOACs, in AF patients has received more emphasis in recent years. Warfarin is still cheaper than NOACs even after insurance reimbursement and is therefore more easily accepted by the general public in China. On the other hand, patients taking warfarin need to undergo routine INR monitoring and dose adjustments if necessary. Nevertheless, guidelines from AHA/ACC/HRS (American College of Cardiology/American Heart Association/Heart Rhythm Society) and ESC (European Society of Cardiology) recommend warfarin over NOACs in patients with moderate-to-severe mitral stenosis or a mechanical heart valve [9,23].

Clinical Use of Warfarin in China

Despite the large interindividual variability in warfarin dose/response and the delay in reaching pharmacologic steady-state, warfarin remains the anticoagulant of choice for many patients, especially in economically disadvantaged populations. Through literature review, it can be observed that AF and valve replacement were the top indications for receiving warfarin treatment in China, accounting for more than 60% of all patients (Figure 1). This is followed by DVT/PE (up to 30%) among other indications.

Atrial Fibrillation

AF is one of the most common types of arrhythmias seen in the clinic. Patients with AF have significantly increased risk for thromboembolic events, congestive heart failure, and mortality, with the most serious complication being ischemic stroke, especially in the elderly and other patients with high-risk factors [24, 25]. It is estimated that there are at least 10 million AF patients in China, with at least 65% of those having nonvalvular AF [26, 27]. The risk of having ischemic stroke is at least 5 to 6 times greater in patients with nonvalvular AF compared to the healthy population [28]. The $CHADS_2$ classification scheme has been widely used for evaluating stroke risk in AF patients (Table 1A). Due to the limitation of $CHADS_2$ in categorizing a large proportion of patients as "intermediate risk" recommended for using either aspirin or warfarin, the 2010 ESC guidelines introduced a new score, the $CHA2DS_2$-VASc, in which two other criteria, the presence of vascular disease and female sex were included for evaluation (Table 1B). Traditionally, anticoagu-

lation therapy is recommended for patients with a $CHADS_2$ score of 2 or more, while the 2016 ESC guidelines for management of AF recommend anticoagulation therapy for patients with CHA2DS2-VASc score of 1 or more for men, and 2 or more for women [29]. Figure 2 shows the percentage of antithrombotic medication use, including oral anticoagulants and antiplatelets, among AF patients with CHADS2 ≧2 and CHA2DS2-VASc ≧2 in Chinese hospitals, for whom current guidelines recommend anticoagulation for stroke prevention. It can be seen that for most hospitals, other than the one reported by *Guo, et al. and Li, et al*. [30,31], the percentages of AF patients taking either warfarin or NOACs are between 5 to 40%, whereas those taking antiplatelet therapy, such as aspirin or clopidogrel, are between 50 to 90%. *Guo et al*. [30] reported the highest percentage of patients taking NOACs; that plus the those taking warfarin makes the percentage of patients on oral anticoagulants above 75%. *Li, et al*. [31] also reported 57.2% of AF patients were taking warfarin. This may reflect thorough implementation of anticoagulation guidance recommendation in AF patients in those two healthcare facilities. Previous studies have suggested that older age, multi-morbidities, and polypharmacy were major reasons for prescribing antiplatelets instead of oral anticoagulants [32-34].

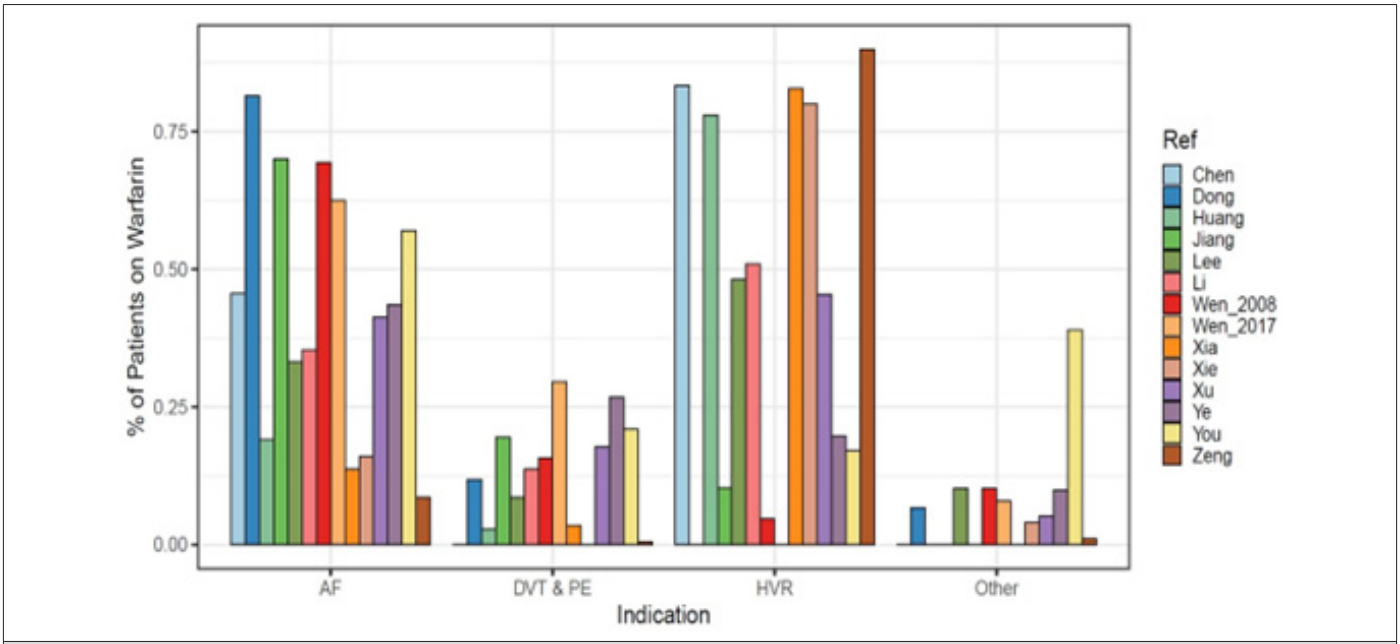

Figure 1: Percent of patients with AF (atrial fibrillation), DVT & PE (deep vein thrombosis and pulmonary embolism), HVR (heart valve replacement), and other indications receiving warfarin in China [51,58,60,79-89]. The results were based on literature search in PubMed, CNKI (China National Knowledge Infrastructure), and Wanfang Data with the following keywords: warfarin, dose, dosage, dosing, Chinese. The search period was from inception of the database to Dec 2022. This yielded a total of 76 records in PubMed, 47 records in CNKI, and 165 records in Wanfang Data, from which 14 references were selected with applicable data.

Table 1: Evaluation criteria for the $CHADS_2$ and $CHA2DS_2$-VASc Scores.

Table 1A:

CHADS2 Score	
Condition	**Points**
Congestive heart failure	1
Hypertension (HTN)	1
Age ≥75	1
Diabetes mellitus	1
Prior stroke or Transient Ischemic Attack (TIA)	2
Maximum Score	6

Table 1B:

CHA2DS2-VASc Score	
Condition	**Points**
Congestive heart failure	1
HTN	1
Age 65-74	1
Age ≥75	2
Diabetes mellitus	1
Prior stroke or TIA	2
Vascular disease (previous myocardial infarction, arterial disease, or aortic plaque)	1
Sex category-female sex	1
Maximum Score	9

Heart Valve Replacement

Valvular heart disease is a condition where any valve in the heart was damaged or diseased. By adversely affecting blood circulation, valvular heart disease has a negative impact on patients' quality of life and can even lead to death. Heart valve replacement surgery is the main treatment option for severe valvular heart disease. There are two choices for valve replacement, mechanical or bioprosthetic valves. In China, the incidence of valvular heat disease is estimated to be 2.34‰~2.72‰ [35]. About 80,000 heart valve replacement surgeries are performed in China each year, with 70% of those being mechanical heart valve replacement [36,37].

Mechanical heart valves are usually more durable than bioprosthetic valves. However, after implantation, mechanical heart valves may cause the formation of thrombus, and patients who underwent mechanical heart valve replacement are required to receive lifetime anticoagulation therapy for the prevention of thromboembolism, whereas only 3 months of anticoagulation therapy is required for those receiving bioprosthetic valve replacement [38,39]. In many settings, including bioprosthetic valve replacement, NOACs have become the anticoagulant of choice due to their favorable safety and efficacy profiles. However, clinical guidelines recommend patients who underwent mechanical heart valve replacement to receive warfarin instead of NOACs based on results of the phase II study comparing dabigatran and warfarin (RE-ALIGN, Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement), which was stopped prematurely due to excess stroke and bleeding with the dabigatran doses tested [40]. In patients receiving mechanical heart valve replacement, it is best to start anticoagulation therapy within the next day of surgery in order to prevent thromboembolic complications. Due to warfarin's mechanism of action, its full antithrombotic effects will only be reached after about 5 days into therapy. Therefore, clinical guidelines recommend heparin or low-molecular weight heparin be used for anticoagulation bridging until INR reaches therapeutic level for two consecutive days [41]. In China, patients undergoing heart valve replacement are usually hospitalized for 1 to 2 weeks after surgery. Before patients are discharged, nursing staff will educate patients on the proper use of warfarin using pamphlet handout similar to Table 2. Patients' understanding about warfarin use will be evaluated using a questionnaire similar to Table 3, and areas with insufficient understanding will be trained specifically by the nursing staff. After discharge, patients return for outpatient follow-up once a week for INR check and dose adjustment if necessary. Frequency for follow-up visits gradually decrease to once every 2 weeks and then once a month eventually.

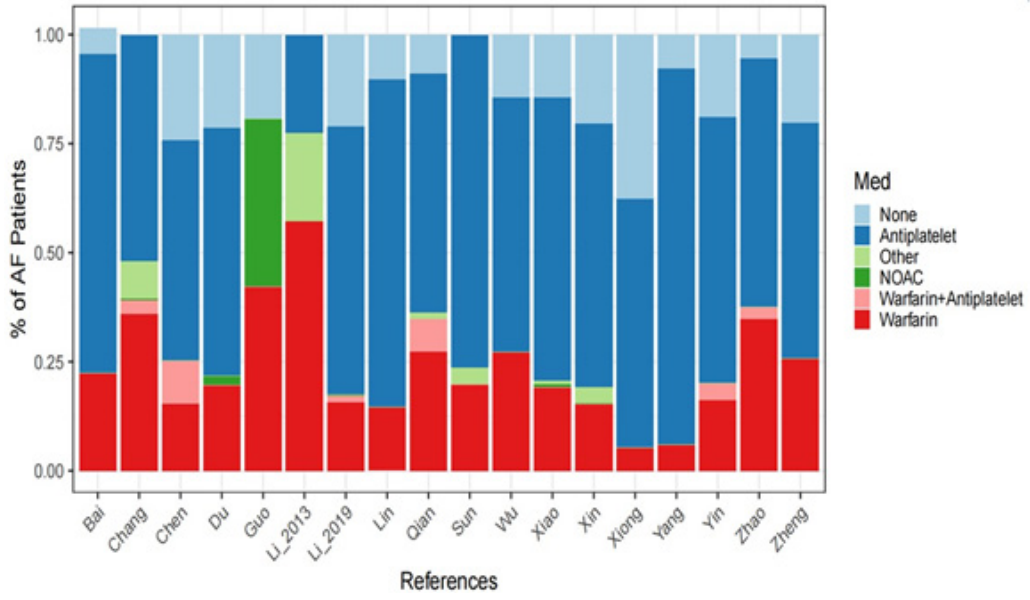

Figure 2: Antithrombotic medication use among AF patients with $CHADS_2 \geqq 2$ and CHA_2DS_2-VASc $\geqq 2$ in Chinese hospitals [30,31,90-105]. The results were based on literature search in PubMed, CNKI (China National Knowledge Infrastructure), and Wanfang Data with the following keywords: atrial fibrillation, anticoagulation, anti-thrombosis, medication, Chinese. The search period was from inception of the database to Dec 2022. This yielded a total of 5 records in PubMed, 121 records in CNKI, and 96 records in Wanfang Data, from which 18 references were selected with applicable data.

Table 2: Education pamphlet handout for new patients taking warfarin in typical tertiary (top-tier) hospitals in China.

1. What is warfarin?
Warfarin is an oral anticoagulant that is widely used to prevent and treat thromboembolism in patients with atrial fibrillation, patients with heart valve replacement, or patients who have suffered a heart attack.
2. Why should you receive anticoagulation therapy with warfarin?
Warfarin is an anticoagulant that can prevent the formation of thrombus. A thrombus can be formed in veins, arteries, heart ventricles, or heart valves and can cause obstruction of blood vessels. For example, a thrombus formed in veins can pass through the heart and migrate to lungs, causing pulmonary embolism, or migrate to the brain, causing stroke.
3. How should you take warfarin?
Warfarin should be taken once a day, preferably at the same time in the evening, either before or after dinner. The dosage of warfarin should be recorded for monitoring purposes. If you forgot taking your medication within 4 hours of your medication time, you should take your medication right away. If you forgot taking your medication for longer than 4 hours, you should skip your medication for the day and take medication as usual the next day; do not double your dose the next day.
4. Why should you undergo laboratory blood testing?

Warfarin dosage should be adjusted based on International Normalized Ratio (INR) to achieve safe anticoagulation level. In general, INR should be between 2 and 3 to prevent bleeding and thromboembolism. Specifically, the following therapeutic INR ranges apply for patients undergoing mechanical heart valve replacement: 1) aortic valve replacement: 1.8-2.5; 2) mitral valve replacement, or aortic and mitral valve replacement: 2.0-2.5; 3) tricuspid valve replacement: 2.5-3.0. For patients undergoing bioprosthetic valve replacement or mitral/tricuspid annuloplasty, warfarin should be taken within 6 months after surgery, and INR should be maintained between 1.8 and 2.2. For patients with atrial fibrillation undergoing bioprosthetic valve replacement, long-term warfarin treatment should be initiated, and INR should be maintained between 1.8 and 2.5. INR should be checked regularly during hospitalization. After discharge, INR should be checked once a week, then once every 2 weeks when stable, then once a month. Monitoring frequency should be gradually decreased, but preferably no less then once every 3 months.
5. While taking warfarin, what factors could influence the drug effect?
Many factors, such as genetics, concomitant medication, food, environment, health status, other illnesses, could affect the anticoagulation effect of warfarin. Patients taking warfarin should quit smoking and curb heavy drinking, since smoking and drinking alcoholic beverages could increase warfarin metabolism. Food that can affect anticoagulation effect of warfarin may include the following: ● Decrease: spinach, cabbage, carrot, tomato, broccoli, egg yolk, green tea, etc. ● Increase: mango, garlic, walnut, fish oil, grapefruit, etc. Medication that can affect anticoagulation effect of warfarin may include the following: ● Decrease: 1) barbiturates: phenobarbital; 2) sedatives: diazepam ● Increase: 1) antibiotics: roxithromycin, clarithromycin, moxifloxacin; 2) antacid: cimetidine; 3) oral hypoglycemic drugs: tolbutamide; 4) nonsterodal anti-inflammatory drugs: indomethacin; 5) antiarrhythmic drugs: amiodarone.
6. What are some side effects while taking warfarin?
Common side effects of warfarin include bleeding and thrombosis, due to overdosing and underdosing, respectively. Therefore, it is important to properly adjust doses to prevent side effects. ● Symptoms of bleeding may include gum bleed while brushing teeth, nosebleed, excessive bleeding from minor cuts, longer bleed during menstruation, blood in urine and feces, serious headache and stomachache. ● Symptoms of thrombosis may include numb or tingling sensation of extremities, changes in vision or loss of vision, slur in speech or loss of speech, headache or difficulty in breathing due to unknown reasons.
7. Important notices
● You should strictly take warfarin according to doctor's prescription and should not take aspirin or medication containing salicylic acid without doctor's permission. If you'd like to start or stop a medication, please let us know. ● Oral anticoagulation therapy should not affect your normal lifestyle. You may enjoy exercise in moderation, such walking or swimming; however, you should not over-exert yourselves and try to avoid incurring wound or injury. ● You may travel but should avoid sitting for long periods of time. You should bring enough medication and take them at the same time during the day. You should try to maintain a balanced diet while traveling. Please remember to check your INR after your travels. ● If you are pregnant or may become pregnant, please contact your doctor. ● If you'd like to have a tooth extraction or undergo gastroscopy, you should let your doctor know.

Table 3: Evaluation for patient's understanding about warfarin.

1. What is warfarin?
A. An oral anticoagulant B. An oral coagulant C. An antiplatelet D. Don't know
2. What is the reason for you to take warfarin?
A. Atrial fibrillation B. Pulmonary embolism C. Venous thrombosis D. Valve replacement
3. What is the benefit for you to take warfarin?
A. To prevent thrombus B. To prevent bleeding C. To improve heart function D. Don't know
4. How long do you need to take warfarin?
A. 2-3 months B. 1 year C. long term D. Don't know
5. At what time do you take warfarin during the day?
A. Morning B. Noon C. Evening D. Don't know
6. While taking warfarin, which lab result do you need to monitor regularly?
A. INR (International Normalized Ratio) B. Platelet C. Hemoglobin D. Don't know
7. While taking warfarin, how often do you need to monitor the anticoagulation lab result?
A. Once a week after hospital discharge, then once every 2 weeks, then once a month when stable B. Once a month after hospital discharge, then once every 3 months, then forgo monitoring when stable C. No need to monitor anticoagulation lab result after hospital discharge D. Don't know

8. What do you think is the main adverse effect while taking warfarin?
A. Thrombosis and bleeding B. Skin necrosis C. Hair loss D. Don't know
9. Which of the following factors could affect anticoagulation? (Choose all that apply)
A. Illnesses B. New concomitant medication C. Changes in dietary or lifestyle habits D. Don't know
10. If you forgot taking your medication yesterday and only remembered this morning, what should you do?
A. Do not take my medication right away but take the same dose at my usual time today.
B. Take my medication right away, then also take another dose at my usual time today.
C. Take my medication at my usual time today but double the dose.
D. Don't know
Evaluation Results:
□ Very Good (more than 9 questions correct) □ Good (more than 8 questions correct)
□ Average (more than 6 questions correct □ Below Average (less than 6 questions correct)

Venous Thromboembolism and Pulmonary Embolism

Venous Thromboembolism (VTE) is a disease that includes DVT and PE. DVT occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body due to the abnormal coagulation of blood in the venous cavity, occurring more frequently in the lower rather than upper extremity [42]. This may be caused by the slow blood flow in the veins or injuries to blood vessel walls, leading to high coagulation state in the blood. Pulmonary embolism is a related condition and usually happens when a blood clot in the lower extremity travels to the lungs and blocks a blood vessel. A frequent, sometimes disabling complication of DVT is Post-Thrombotic Syndrome (PTS), which occurs in 20-50% of patients within 2 years [43,44]. This condition can cause chronic pain, swelling, and other symptoms in the legs of patients who have had DVT. There have been no reports on the incidence of DVT in the Chinese population based on large sample analysis. However, based on a preliminary cross-sectional study, the incidence of DVT of lower extremity was 10.2% in 372 high-risk hospitalized patients in Zhongshan hospital in Shanghai, including bedridden stroke patients, post-surgery bedridden patients, and patients in surgical intensive care unit [45]. In the clinic, treatment of DVT includes the following aspects:

1) prevent the growth and spread of a clot, alleviate the swelling and pain of lower extremity, and prevent the development of PE;

2) clear the blood clot as soon as possible to resume blood flow in veins, preserve heart valve function as much as possible, and prevent DVT relapse and minimize development of PTS with long-term anticoagulation.

For acute anticoagulation of DVT, heparin and Low Molecular Weight Heparin (LMWH) can be used, usually for 7-10 days. Chronic anticoagulation with warfarin or NOACs should be maintained for at least 3 months, and some experts recommend continued treatment for 6-12 months after the first episode of idiopathic DVT and long-term treatment after DVT relapse [46]. To prevent the development of PE by limiting the movement of blood clots from lower extremity into lungs or heart, Inferior Vena Cava Filter (IVCF) can be used in patients with contraindication to anticoagulants. Furthermore, surgical procedures, such as thrombectomy or catheter-directed thrombolysis, can be used to remove or dissolve the clot in order to prevent DVT relapse and the development of PTS.

Warfarin Dosing in Chinese Population

Warfarin has a narrow therapeutic window and large interindividual variability in dosing due to both nongenetic and genetic factors. Nongenetic factors include patient's clinical characteristics such as age, height, weight, Body Surface Area (BSA), race, and use of interacting concomitant medications, and so forth. The most predominant genetic factors in warfarin dose/response include polymorphisms in cytochrome P450 (CYP) 2C9 and vitamin K epoxide reductase complex 1 (VKORC1). Together, genetic and nongenetic factors may account for about 50% of warfarin dose variability [47]. To improve warfarin dosing, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommended the use of pharmacogenetic dosing algorithms developed by the International Warfarin Pharmacogenetics Consortium (IWPC) and by *Gage, et al*. to inform dosing of warfarin using patients' genetic information [47-49]. Despite the benefits of pharmacogenetic dosing, in majority of cases in China, doctors would monitor patients' INR and adjust doses accordingly without having genotype information on hand. Figure 3 shows examples of dose adjustments according to INR monitoring in patients receiving warfarin after mechanical heart valve replacement at Huaihe Hospital of Henan University, with the goal of reaching and maintaining within the target INR window of 1.5-3. In all three cases, loading doses of 3.75 mg/day were prescribed for 2 to 4 days after surgery. After anticoagulation effect is realized within a week, doses would be increased, decreased or paused in response to the INR result on that day to maintain within therapeutic window before discharge from hospital.

To promote pharmacogenetic dosing, the Chinese Society of Cardiothoracic and Vascular Anesthesiology published expert advice on the use of genetic polymorphism and antithrombotic drugs in the clinic in 2017, recommending that patients undergo genetic testing when starting warfarin and that doses should be calculated based on CYP2C9*2, *3, and VKORC1-1639 G>A [50]. Furthermore, a number of pharmacogenetic algorithms based on local patients have been developed to achieve better predictive accuracy of stable warfarin doses in the Chinese population [51, 52]. Although pharmacogenetic dosing of warfarin has demonstrated superi-

or efficacy and safety in both Western and Chinese populations, there are ethnic differences in genotype distributions of VKORC1 and CYP2C9, resulting in different dosing requirements [53-56]. In contrast to the expected frequencies for VKORC1-1639 AA, AG, and GG in Whites (16.5%, 46.6%, and 36.9% respectively), at least 80% of the Chinese population have the AA genotype for VKORC1-1639 [57-60]. Also, the allele distribution for CYP2C9*1 in the Chinese population is at least 90%, as compared to a distribution of 70-80% in Whites for the wild type allele [49,58,61]. Furthermore, demographics characteristics, such as lower weight, height, and BSA, result in lower clearance rate and, thus lower dosing requirements, for warfarin in the Chinese population [52].

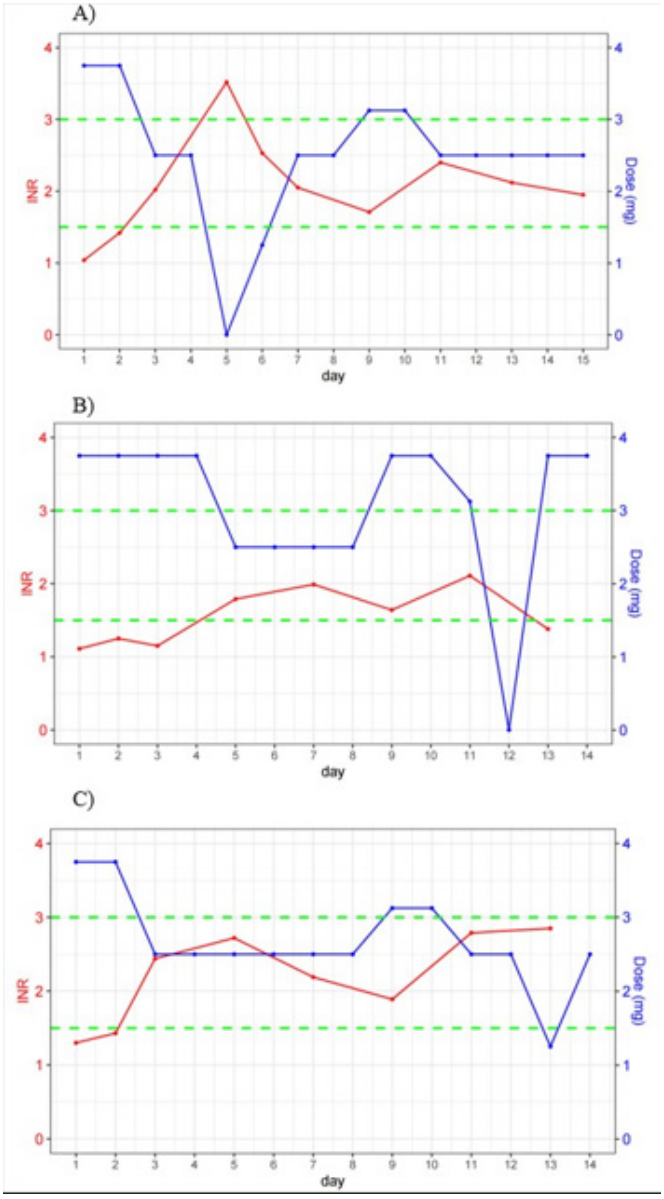

Figure 3: Dose adjustments and INR response in patients initiating warfarin after mechanical heart valve replacement at Huaihe Hospital of Henan University. The target INR range (1.5-3) was indicated by the green dashed lines. This data was collected as part of a study to improve warfarin dosing in Chinese patients. The study was carried out in accordance with the Declaration of Helsinki Principles. All subjects provided written informed consent to participate in the study, which was reviewed and approved by the Ethics Committee of Henan University.

Discussions

Warfarin was initially discovered and marketed as a rat poison in 1948. After learning that its overdose could be treated with vitamin K, warfarin was later transitioned into clinical use as a therapeutic anticoagulant [62]. Today, warfarin remains one of the most commonly prescribed drugs to treat and prevent thromboembolic conditions in AF, DVT, PE, and HVR. Due to differences in clinical and genetic factors, warfarin has a large interindividual variability among patients, which requires routine INR monitoring and dose adjustments to achieve and maintain within therapeutic window. In recent years, NOACs, such as dabigatran, rivaroxaban, edoxaban, and apixaban, have been approved and accepted as alternatives to warfarin in many indications. NOACs have several advantages

compared to warfarin. Firstly, NOACs have a rapid onset and offset action due to fast absorption and short elimination half-lives, thus erasing the need for heparin bridging in patients undergoing surgery [63]. Secondly, patients taking NOACs do not need to undergo routine INR monitoring to make dose adjustment, since NOACs have fixed daily doses except in special cases, such as impaired renal function [64]. Thirdly, the therapeutic effects of NOACs are not affected by food intake, and therefore patients do not have any dietary restrictions [65]. In China, medical insurance could reimburse NOACs for inpatients, and up to 70% of the cost for outpatient. Many outpatients, such as those with non-valvular AF, need to pay the remaining 30% at their own expense, which remain too high ($1740/year) for those in socioeconomically disadvantaged rural areas [66]. Additionally, clinical guidelines recommend patients with mechanical heart valves or moderate-to-severe mitral stenosis to receive long-term anticoagulation with warfarin [9,23]. According to a study on oral anticoagulant prescription trends covering 189,006 prescriptions of 67 hospitals in 5 major regions of China (Beijing, Shanghai, Hangzhou, Guangzhou, and Chengdu), warfarin prescription accounts for as much as 72% of patients in 2017 [67]. Clearly, warfarin remains an important anticoagulant option in the era of NOACs.

According to our literature review, AF and HVR account for more than 60% of all patients, with DVT/PE accounting for up to 30% among other indications in China (Figure 1). With one of the fastest growing aging populations in the world, China has seen significant increase in the incidence and prevalence of AF over the past 20 years [68]. It is estimated there are at least 10 million AF patients in China, and 62% of the AF cases affected people aged 65 and above [27]. AF is associated with significantly higher risk of major systemic thromboembolism and ischemic stroke compared to healthy population. Therefore, treatment with oral anticoagulant is essential to prevent and treat thromboembolic complications. The 2010 ESC guidelines recommend that patients with $CHADS_2 \geqq 2$ should receive oral anticoagulant, while for the new score CHA_2DS_2-VASc, the 2016 ESC guidelines recommend that men with a score of 1 and women with a score of 2 be preferably treated with oral anticoagulant [29,69]. Our literature review suggests that among AF patients with high stroke risk in Chinese hospitals ($CHADS_2 \geqq 2$ and $CHA2DS_2$-VASc $\geqq 2$), a large proportion of patients were taking antiplatelets instead of anticoagulants. Our findings are consistent with results from previous studies suggesting of significant underuse of warfarin in Chinese patients with AF [70-72]. This underuse of oral anticoagulants is in contrary to clinical guideline recommendations and may have many reasons. Many physicians in China may be reluctant to prescribe oral anticoagulants in elderly AF patients due to the fear of bleeding events and underestimation of the benefit of oral anticoagulant to reduce the stroke risk. Furthermore, the cost and inconvenience of frequent INR monitoring may be a concern for patients, which may lead to noncompliance and discontinuation of therapy. Antiplatelet treatment is indicated for secondary prevention of coronary events but only modestly reduced stroke in AF patients not receiving anticoagulation [73]. Results from a population-based cohort study using electronic health records from 52,178 high-risk patients with AF (CHA_2DS_2-VASc $\geqq 2$) in Hong Kong suggest that warfarin and NOACs were associated with lower risk of ischemic stroke and all-cause mortality than antiplatelets [34]. Clearly, more education emphasizing on the importance of anticoagulation to prevent stroke is needed among health professionals in China to reverse the current trend.

Apart from AF, the other big indication for warfarin use in China is HVR. Nowadays NOACs have gained more acceptance and are becoming the anticoagulants of choice to treat and prevent thromboembolism in many indications, but guidelines published by the AHA/ACC/HRS and ESC specifically recommend treatment with warfarin instead of NOACs in those with moderate-to-severe mitral stenosis or those who underwent mechanical heart valve replacement [9,23]. This recommendation was based on results of the REALIGN trial comparing dabigatran and warfarin in patients after heart valve replacement, which was stopped prematurely due to an excess of both stroke and bleeding with the dabigatran doses tested [40]. Furthermore, results from the INVICTUS (The Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies) trial indicated that among patients with rheumatic heart disease-associated atrial fibrillation, vitamin K antagonist therapy, such as warfarin, led to a lower composite rate of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding [74]. The current practice in China is for patients undergoing mechanical heart valve replacement is to take warfarin for the long-term, whereas for patients undergoing bioprosthetic valve replacement, warfarin should be taken within 6 months after surgery. Also, warfarin should be taken long-term in patients with atrial fibrillation undergoing bioprosthetic valve replacement. Patients undergoing heart valve replacement are usually hospitalized for 1 to 2 weeks after surgery. Before patients are discharged, nursing staff will educate patients on the proper use of warfarin using a pamphlet handout similar to Table 2, and then patients' knowledge will be evaluated using a questionnaire similar to Table 3. Any areas lacking in sufficient understanding will be reinforced by the nursing staff.

Warfarin has large inter individual variability in dosing among patients due to genetic (VKORC1, CYP2C9, CYP4F2*3, APOE ε2, ε3, ε4 etc.) and clinical factors (age, concomitant medication, weight, height, BSA, etc.) [75]. To promote pharmacogenetic dosing, the Chinese society of Cardiothoracic and Vascular Anesthesiology has published expert advice on the use of genetic polymorphism and antithrombotic drugs in 2017 and recommended patients to undergo genetic testing of CYP2C9*2, *3, and VKORC1-1639 G>A to inform the dosing of warfarin [50]. With regard to warfarin dosing in the Chinese population, one has to keep in mind that there are ethnic differences in VKORC1 and CYP2C9 genotype distributions between Chinese and Western populations. At least 80% of the Chinese population has the VKORC1-1639 AA genotype, and at least 90% has the CYP2C9*1 allele. Furthermore, differences in body weight and BSA may explain clearance and dosing differences between Chinese and Western populations [52]. Also, it has been reported that Chinese patients, and Asian patients in general, are more sensitive to warfarin anticoagulation, with a higher incidence

of major bleeding and intracranial hemorrhages than in Western countries [76,77]. According to the expert consensus published by the Chinese Society of Cardiology and Committee of Cardio-cerebral-Vascular of Gerontological Society of China, most patients who stopped receiving warfarin have INR below 1.5 for the long-term, and those who receive warfarin and have INR above 3.0 should undergo dose reduction or interruption to reduce bleeding risk [78]. Therefore, many physicians consider INR between 1.5 and 3.0 to be a "relative safe window". Since dosing algorithms based on Western patients may be unsuitable for the Chinese population, algorithms based on local patient populations have been developed to better inform dosing in Chinese patients. *Huang, et al*. [79] developed a pharmacogenetics-based dosing model using retrospective data from 266 Chinese patients. They then prospectively validated this model in 156 patients needing HVR and found that the pharmacogenetic-based dosing model was able to improve the time to reach stable dosing of warfarin [79]. Despite obvious advantages, in many hospitals in China, an empirical approach to warfarin dosing is used in patients after heart valve replacement surgery, where loading doses would be prescribed for the first few days after initiation, followed by adjustments in response to lab monitoring to help maintain INR within therapeutic window before patient discharge similar to Figure 3. Clearly, more education and promotion of pharmacogenetic dosing is needed among healthcare professionals and patients in China to fully realize its benefits.

Conclusions

Even in the age of NOACs, warfarin remains a commonly prescribed anticoagulant in China due to its affordability and decades long experience of clinical use. In patients with moderate-to-severe mitral stenosis or those who underwent mechanical heart valve replacement, warfarin is the recommended option as per clinical guidelines. In our literature review, we found that contrary to clinical guideline recommendations a large proportion of AF patients with high stroke risk were taking antiplatelets instead of anticoagulants in China. Furthermore, given the large interindividual variability in dose/response, pharmacogenetic dosing approach is helpful to guide dosing in patients initiating warfarin. Nevertheless, an empirical approach consisting of loading doses at the beginning followed by dose adjustments based on INR result of the day is still being used in the majority of Chinese hospitals. To further improve warfarin clinical practice, more education and training is needed among healthcare professionals and patients in China.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data Availability Statement

The data used to support findings of this study are included within the article.

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