Chapter

Knowledge, Adherence, and Quality of Life among Warfarin Therapy Users

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Abstract

Patient knowledge and understanding of the therapy are an important factor in treatment success. Multiple factors were identified to cause a treatment failure such as side effects of the medications, rejection of the diagnosis by patients, lack of patient understanding about their medication, noncompliance, and the cost of medication. In addition, improvements in patient medication counseling and education may help in prevention of many adverse drug interactions, drug-drug or food-drug interactions, in turn enhancing medication adherence which depends basically on a patient's acceptance of the information about the health threat itself. For these reasons, an evaluation of patients' knowledge of medicine and its use may help screen for problems in therapy and improve therapeutic outcomes. The results of this evaluation may also be used to educate providers about areas of potential problems in which they may be able to influence change.

Keywords: warfarin, knowledge, adherence, quality of life

1. Anticoagulation therapy

Coumarins have been used clinically since the 1950s and are likely the most widely studied medicines currently in clinical use [1, 2]. Anticoagulation therapy with warfarin has been a standard clinical practice to prevent ischemic stroke in patients associated with atrial fibrillation (AF) [3–6]. A meta-analysis demonstrates that adjusted-dose warfarin reduces stroke risk by 64% when compared to placebo, which is corresponding to an absolute annual risk reduction in all strokes of 2.7%, while antiplatelet agents reduce stroke risk by 22% [7]. In the ACTIVE W trial, anticoagulation therapy had a relative risk reduction of all strokes by 40% when compared to the combination of clopidogrel and aspirin, with no difference in bleeding events between both treatments [8]. Furthermore, anticoagulants may reduce the risk of death rate in AF patients by 38% [9], so about 70–80% patients with AF are suitable for the long-term use of warfarin [10, 11].

However, it increases the risk for major bleeding. Clinical studies revealed that the risk of intracranial hemorrhage, the most common type of bleeding, is as great as that of thromboembolic events warfarin is used to prevent [12, 13].

Therefore, the optimal use of warfarin for atrial fibrillation requires precise assessment of established risk factors of bleeding, such as advanced age, hypertension, stroke, alcoholism, and malignancy [14]. In addition, rigorous reporting of

warfarin-associated bleeding is warranted, as patients who bleed often discontinue treatment, which put them at a higher risk of thromboembolism [15, 16].

1.1 Warfarin pharmacodynamics

Warfarin is a drug derived from 4-hydroxycoumarin group and acts by inhibiting vitamin K epoxide reductase, an enzyme which recycles vitamin K into its reduced form (**Figure 1**). Reduced vitamin K is responsible for carboxylation of the specific blood clotting factors II (prothrombin), VII, IX, and X as well as anticoagulant factor protein C and protein S [18–20]. Thus warfarin is not a direct antagonist of vitamin K but rather acts by depletion of reduced vitamin K in tissues.

As shown in **Figure 2**, inhibition of the reduction of vitamin K results in a reduction in the conversion of fibrinogen to fibrin which in turn reduces clot formation.

1.2 Warfarin pharmacokinetics

Warfarin is a racemic mixture of two optically active isomers, the R and S enantiomers [18]. Warfarin is highly water soluble and rapidly absorbed from the gastrointestinal tract and has high bioavailability [22, 23]. The bioavailability of warfarin is more than 95% [24, 25], and some reports had applied 100% bioavailability when developing models [26, 27].

Warfarin reaches maximal blood concentrations about 1.5 hours after oral administration [22, 28]. The plasma half-life of racemic warfarin mixture is 36–42 hours [29], and this means that it takes 5–7 days to reach steady state since warfarin is started or when the dosage is adjusted.

The antithrombotic effect of vitamin K anticoagulants has conventionally been attributed to their anticoagulant effect, which in turn is mediated by the reduction of the four vitamin K-dependent coagulation factors (II, VII, IX, and X). The vitamin K-dependent clotting factors have varying half-lives: 6 hours for factor VII, 24 hours for factor IX, 36 hours for factor X, and 60–72 hours for factor II (prothrombin). Thus, the anticoagulant effect (reduce coagulation of blood, prolonging the clotting time) develops in 2 days, whereas an antithrombotic effect (reduce formation of blood clots (thrombi)) of warfarin requires 6 days of treatment [30].

Numerous environmental factors such as drugs, diet, and various disease states were identified to affect warfarin by altering its kinetics and dynamics [31]. Drugs such as cholestyramine can reduce the absorption of warfarin, thus reducing its anticoagulant effect. R-warfarin is metabolized primarily by CYP1A2 and CYP3A4, while S-warfarin is metabolized primarily by CYP2C9 [32]. Potential warfarin drug interactions could occur with a concomitant administration of medicines that are metabolized by these P450s, and as a consequence, a number of metabolic medicine interactions have been reported for warfarin. For example, drugs such as cimetidine, amiodarone, and omeprazole potentiate the anticoagulant effect of warfarin by inhibiting its metabolism, whereas some drugs like barbiturates, rifampin, azathioprine, and carbamazepine inhibit the anticoagulant effect by enhancing its clearance [33]. In addition, long-term alcohol consumption has a similar potential to increase the clearance of warfarin [34].

Aspirin [35] and nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of warfarin-associated bleeding by inhibiting platelet function [36].

1.3 Dietary vitamin K

As the action of warfarin is modified by vitamin K, a variable dietary intake of vitamin K may alter the extent of the anticoagulation effect. An increased intake of

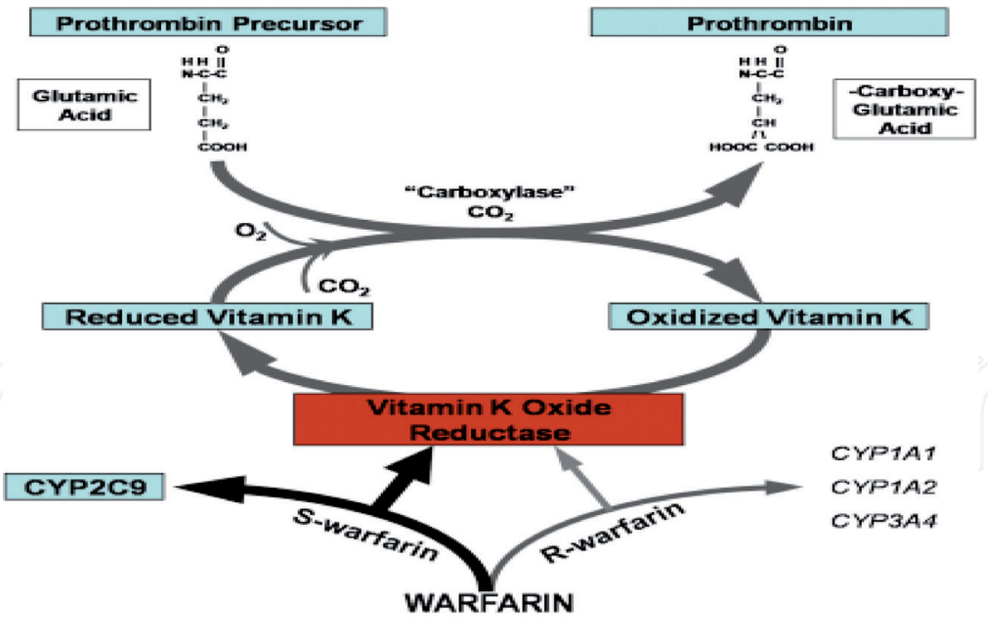

Figure 1.
Mechanism of action of warfarin [17].

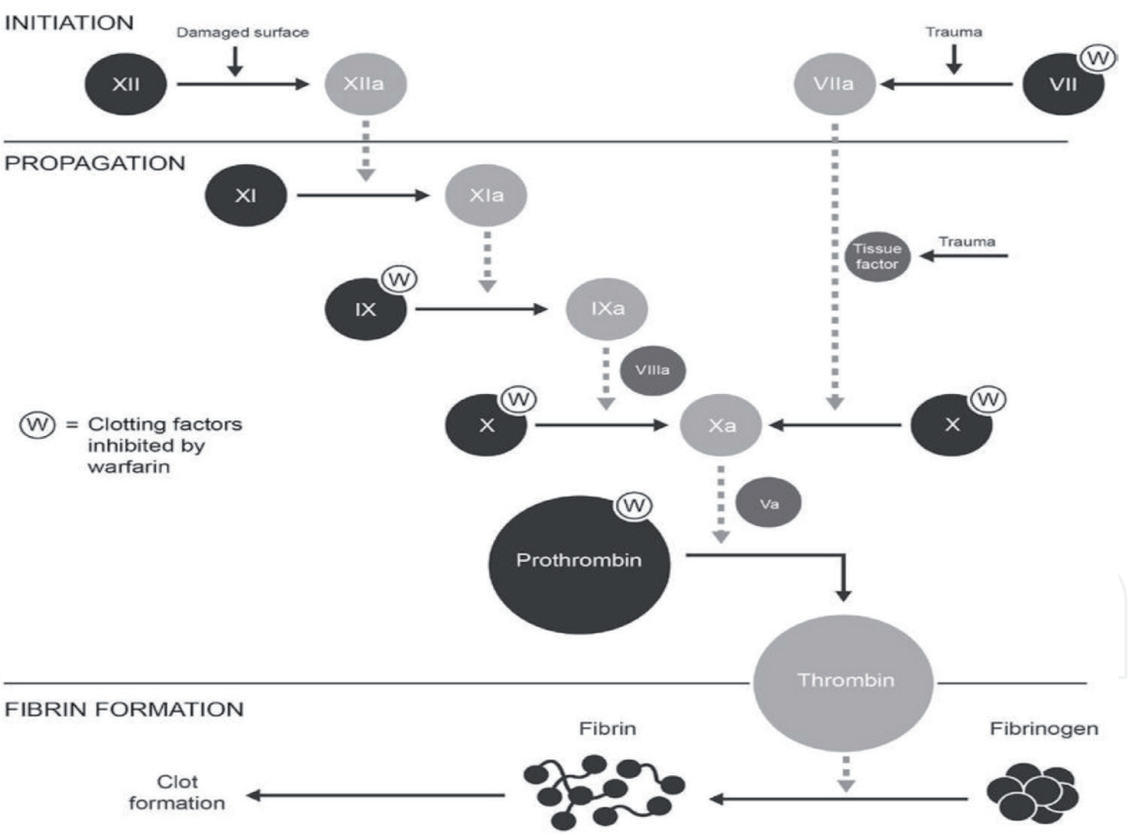

Figure 2.
Warfarin's effects on the clotting cascade [21].

dietary vitamin K (foods high in vitamin K include leafy green vegetables (cooked and raw), broccoli, brussels sprouts, cabbage, pickled cucumber, asparagus, kiwifruit, okra, green beans, and salad greens like lettuce) or vitamin K-containing supplements will increase the production of functional coagulation factors depending on vitamin K which is sufficient to reduce the anticoagulant response to warfarin [37]. Furthermore, patients with poor dietary intake of vitamin K often have a less stable control of anticoagulation [38]. It has been suggested to provide these

unstable anticoagulated patients (with poor vitamin K intake) with oral vitamin K supplementation. However, unrecognized intake of such can lead to warfarin resistance [37].

The drug-grapefruit juice interaction enhances plasma concentration (C_{max}) of orally concomitantly administered drugs. This interaction has been reported with 40 pharmaceutical products, including the vitamin K antagonist [39]. Grapefruit can affect the metabolism of a variety of medications through the cytochrome P450 enzyme system located in the small intestine and liver. The enzymes that are affected are 3A4, 1A2, and 2A6. The (R) enantiomer of warfarin is metabolized by CYP1A2 and CYP3A4, which could contribute to this theoretical interaction of warfarin with grapefruit [40].

1.4 Warfarin monitoring

The relation between blood clotting and coumarin derivatives was established by Dam and Doisy who shared the Nobel Prize in 1943 for their work [41, 42]. Warfarin has a narrow therapeutic index in which effectiveness and safety are a tight balance between stroke risk and bleeding risk; hence, careful dose titration and monitoring are required.

The prothrombin time (PT) test is the most common test used to monitor vitamin K anticoagulant therapy [43]. The normal prothrombin time is 12–14 seconds [44]. As PT monitoring of warfarin treatment is not standardized when expressed in seconds, a calibration model which was adopted in 1982 is now used to standardize reporting by converting the PT ratio measured with the local thromboplastin into an international normalized ratio (INR) [45]. INR is calculated by raising the prothrombin time ratio (PT; the patient's prothrombin time divided by a reference normal prothrombin time to the power of international sensitivity index (ISI)) as follows (Eq. (1)):

$$INR = \left(\frac{\text{Patient PT}}{\text{Mean normal PT}}\right)^{ISI} \quad (1)$$

where ISI relates the sensitivity of a given thromboplastin (a tissue factor used as a reagent in PT test) to the sensitivity of the World Health Organization's first primary international reference preparation of thromboplastin, which was assigned an ISI of 1.0 [46]. Each manufacturer assigns an ISI value for any tissue factor they manufacture which is usually between 1.0 and 2.0.

Instead of a specific value of the INR target, a therapeutic window is utilized as the recommended target range for specific diagnosis, e.g., in atrial fibrillation the clinical benefits of warfarin are highly dependent on maintaining the INR within the therapeutic range of between 2 and 3, while mechanical heart valve replacement often requires a slightly higher target range of INR (2.5–4.0) [47–50]. As shown in **Figure 3**, INRs below this range increase the risk of stroke, while INR values above 3 or 4 are associated with increased bleeding rate [51].

Further quality assessment of the treatment involves calculation of time spent in the therapeutic range (TTR). In Rosendaal method, the difference between two consecutive INR readings, which was within the target range, was divided by the total difference between them [52].

1.5 Warfarin-related adverse drug events

The most common side effect from over-anticoagulation is bleeding from any anatomical site. There are many risk factors that increase the risk of hemorrhage

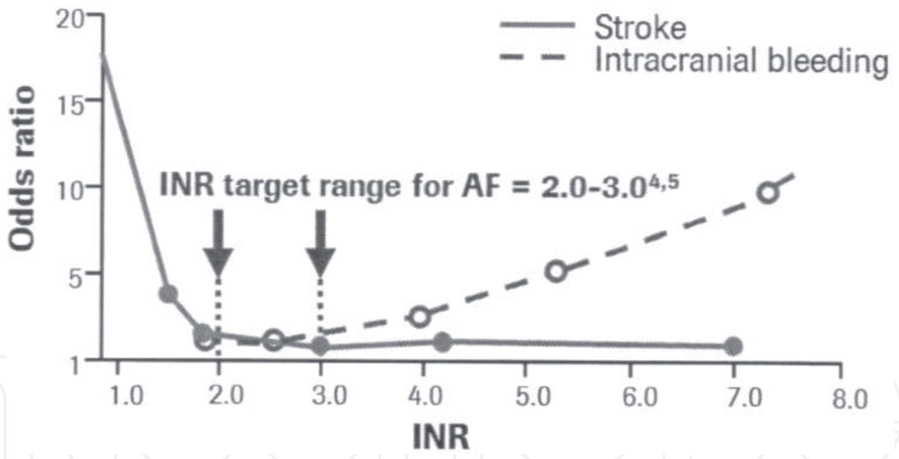

Figure 3.
Maintaining INR in the therapeutic range is crucial to prevent strokes and avoid bleeding [51].

in patients on oral anticoagulant therapy, such as increasing age (≥60); previous stroke; comorbidities, i.e., diabetes mellitus; recent myocardial infarction; anemia (defined as hematocrit <30%); the presence of malignancy; concomitant; antiplatelet usage; uncontrolled hypertension; liver/renal failure; and previous gastrointestinal bleed [53].

The most feared hemorrhagic complication of anticoagulants is the intracranial hemorrhage (ICH) which accounts for approximately 90% of deaths from warfarin-associated hemorrhage and for the majority of disability among survivors [54]. Nonetheless, ICH rates in clinical trials conducted in AF patients on oral anticoagulant therapy are small, reported to be between 0.3 and 0.6% per year [55], and the absolute increase in major extracranial hemorrhages is even smaller, at ≤0.3% per year [56]. The risk of ICH associated with warfarin use was twice that of aspirin, but the absolute risk was small at 0.2% per year [7].

Other than hemorrhage, other important side effects of warfarin are acute thrombotic complications, such as skin necrosis and limb gangrene [57, 58].

2. Patients' knowledge about warfarin therapy

2.1 Factors impacting patient's knowledge about warfarin therapy

Evidence from the literatures suggests that patients' knowledge about their warfarin therapy is generally poor with many demographic and clinical factors influencing their level of knowledge [2, 59–74].

IN the USA, a 52-item questionnaire related to the knowledge of warfarin was administered to 100 patients with atrial fibrillation in a face-to-face interview with a dietitian [69]. The survey questions were compiled based on five categories: general warfarin knowledge, compliance, drug interactions, herbal or vitamin interactions, and diet. For the total population, the average percentage of correct responses was 36%. The average score by category was 64% (general knowledge), 71% (compliance), 17% (drug interactions), 7% (herbal or vitamin interactions), and 23% (diet). Results from the former study suggested that in general, patients on warfarin, especially those at highest risk of stroke, had a poor understanding of their medication.

In Germany, in a study aimed to investigate the patients' knowledge on anticoagulants and the patient characteristics associated with low knowledge, an 8-item multiple-choice test was developed and distributed to 59 anticoagulated medical

inpatients of a German university hospital [66]. The scoring range was 0–8 points (each correct answer giving 1 point). The average knowledge was 55% with the most often wrong answers about questions regarding drug-drug and drug-food interactions. The former study revealed no significant correlation between the total test score and any of the patient characteristics.

McCabe and colleagues [68] described the self-management knowledge and behaviors of patients with recently detected AF. One hundred subjects were interviewed by telephone to assess knowledge after 2-week hospitalization. They found a knowledge deficit related to the purpose of medication and complications of warfarin. The knowledge deficits were greater in older subjects and in subjects with less formal education. The patients aged between 65 and 74 years had knowledge scores of 26.6 (out of a possible 50), as compared to 19.1 for those aged between 75 and 94 years ($P = 0.001$); this may be due to cognition disorders. Despite knowledge deficits among the patients, they were high adherent to taking medication and anticoagulation monitoring.

In England, a pilot study to examine patient's knowledge and perceptions of AF and their anticoagulant treatment before and after a brief educational intervention was conducted [67]. Thirty-three patients completed the baseline interview; by then, they were given an information booklet which explained about AF, treatment options and their benefits/risks, and what the INR is and what factors may affect it. They were reassessed to their knowledge and perceptions of AF in a follow-up assessment session. Out of 33 (35.5%) patients that completed the follow-up assessment, 52% were aware about anticoagulants preventing blood clots, which increased to 70% post-intervention. However, few patients were aware of the benefit of stroke prevention associated with anticoagulants. The intervention significantly improved patient's knowledge of the target INR range and factors that may affect INR levels ($P = 0.001$ and $P = 0.014$, respectively); however, it had little effect on increasing awareness of the bleeding risks associated with anticoagulants.

To measure patient's knowledge about warfarin and to identify factors related to higher level of knowledge, Hu et al. [64] conducted a telephone survey among 100 patients with mitral valve replacement (MVR) using a validated 20-item questionnaire. They found that about 61% of participants had insufficient knowledge of warfarin therapy (score ≤ 80%). Among all variables studied, age was negatively related to warfarin knowledge scores, while family incomes greater than US$25,000, education greater than grade 8, and being employed significantly related to higher warfarin knowledge scores ($P < 0.05$). However, gender and ethnicity were not related to warfarin knowledge scores.

Besides all literatures mentioned above, the knowledge of warfarin therapy was tested in a sample of 122 patients attending at the warfarin clinic using 9 questions with a maximum score of 1.0 [71]. They found the level of knowledge was generally poor with more obvious knowledge deficient about the possible consequences of under- or over-anticoagulation, drugs that might interact with warfarin, and management of a missed dose. In their study, they found that increasing age negatively impacts upon knowledge about warfarin therapy. The mean warfarin knowledge scores declined with advancing age; <65-year-olds scored 0.47; 65–74-year-olds scored 0.44; and >75-year-olds scored 0.39. Other sociodemographic factors such as lower family income, limited health literacy, unemployment status, and lower education levels appeared to negatively influence patients' knowledge. However, they did find a weak but positive correlation between patients' knowledge of warfarin therapy and the number of INR values that were within the target range (Correlation coefficient r 0.20, $P = 0.024$).

Roche-Nagle et al. [2] evaluated the patient perception of anticoagulation risks, tablet recognition skills, and complications of warfarin therapy in 150 patients

attending the anticoagulation clinic. Majority of the patients (n = 125, 83%) were able to identify the 1 mg tablet correctly, 105 (70%) identified the 3 mg tablet, and 98 (65%) identified the 5 mg tablet correctly. In addition, about 60% were aware about the potential complications from over- and underdosage with warfarin; however, only 33 (22%) were unaware that restrictions on alcohol use are required when taking warfarin. This study suggested that patient knowledge regarding anticoagulation therapy is not optimal, and consequently, a significant group may be at risk from serious complications because of this inadequate knowledge.

To investigate whether the knowledge and perceptions of antithrombotic therapy differ between ethnic groups in the UK, Nadar et al. [75] conducted a cross-sectional questionnaire survey among 180 patients attending anticoagulation clinic (135 white European, 29 Indo-Asian, and 16 Afro-Caribbean). The average knowledge score among all participants was 5.5 out of 9, with no significant differences between all ethnic groups. However, this study highlighted the gaps in the knowledge of patients from ethnic minorities and suggested that these groups should receive a special attention in the provision of information. Moreover, they have identified age as a negative factor of warfarin knowledge with the lowest score among patients older than 61 years.

In a historical cohort with questionnaires to 242 patients discharged from hospital, identified from hospital pharmacy records as being prescribed warfarin frequency of testing and levels of INR within 6 months of discharge, the level of INR aimed at by GP, complication rates, and patient knowledge about anticoagulation were measured [72]. Only 27% of all patients answered more than 8 out of 10 questions correctly. In this study, higher education level was identified as a predictor of high knowledge, but there was no relationship between the knowledge level and the INR control.

In Qatar, a cross-sectional survey using a 20-question questionnaire was delivered to 140 patients who were taking warfarin for at least 2 months [76]. Out of 12 questions about warfarin knowledge, 10 questions were derived from the Oral Anticoagulation Knowledge (OAK) test that was developed by Zeolla et al. [77]. The OAK questions covered the topics on warfarin drug interaction; interpretation of INR value, food, and vitamin K; effect of missing a dose; and when to seek a medical attention. In this study, the satisfactory level was considered answering 10 out of 12 questions (≥75%). They found that 79 patients (56%) had a satisfactory level of knowledge. The lowest score was in the knowledge of management of missing a dose and drug-drug interaction.

Another study using the OAK test was conducted in Jordan among 117 patients using warfarin, who were selected randomly [78]. They found that the majority (64%) of respondents can distinguish between different strengths of warfarin tablets by color. However, a deficit in knowledge was obvious in the areas of vitamin K and drug interactions with warfarin, skipping dose management, and PT/INR test. It was suggested that including clinical pharmacist services in the anticoagulation clinics may result in the improvement of patients' knowledge toward warfarin use and PT/INR test.

In a study sought to determine the level of knowledge and to what extent patients adhere to OAC therapy, Van Damme et al. [79] developed a questionnaire comprising 10 multiple-choice questions, including 2 questions about each of the 5 knowledge domains: (1) general information about the functioning of the medication, (2) possible side effects, (3) interactions with food, (4) drug interactions, and (5) lifestyle. For each question, four possible answers were given, one of which was correct. In this cross-sectional study which included 57 patients, the median total score on the knowledge questionnaire was 7 on a scale of 0–10 with only 9 patients (15.7%) answering more than 8 questions correctly. They found that the

participants had moderate to poor knowledge regarding the kinds of medication that can be taken in case of headaches, the sports to be avoided, what to do when a dose of medication is missed, symptoms related to uncontrolled level of medication in the blood, the effect of alcohol in blood-thinning, and the influence of certain vitamins on the medications.

Finally, another study aimed to collect information on six items of anticoagulation counseling (mode of action of warfarin, adverse effects of over or under anticoagulation, drugs to avoid, action if bleeding or bruising occurs, and alcohol consumption) from 70 consecutive patients on anticoagulant therapy [74]. They found that most patients reported are being clearly advised on five of the six items, but their knowledge about anticoagulation was generally poor. Few patients were able to correctly identify adverse conditions associated with poor control of anticoagulation: bleeding was identified by only 30 (60%), and bruising by 23 (56%), and only 7 (14%) could identify 3 or more self-prescribed agents which may interfere with warfarin.

2.2 Relation of patients' warfarin knowledge to their therapeutic outcomes

To date, there are important published literatures that highlight the level of patients' knowledge about warfarin and its relation to the therapeutic outcome, as well as education strategies and their impact on therapy outcomes. In these literatures, there is a general consensus that improved patient knowledge about warfarin therapy improving therapeutic outcomes [59, 66, 71, 80–82].

Kagansky et al. [80] have measured patient's knowledge about warfarin by a warfarin knowledge-testing questionnaire. The questionnaire was submitted to elderly patients (n = 323) to assess their knowledge and impression on the quality of the relevant education that they received from the medical system on the following: risk of thromboembolic complications, prevention of thromboembolic complications by oral anticoagulation (OAC) therapy, the significance of OAC monitoring, and risk of bleeding. Among all participants, only 21.3% of the patients are satisfied about the education on OAC therapy that they received from the medical staff. In their study, patients with insufficient education on OAC therapy were more likely to increase major bleeding events (5.2 per 1000 patient-months) compared with no education (1.1 per 1000 patient-months). This study also showed that older patients with better knowledge about their warfarin therapy had 45% of their INR values within the therapeutic range than patients with poorer knowledge (35%); $P < 0.001$.

These findings were supported by another study [81] which reported that older patients (n = 125) who possessed a better understanding of warfarin therapy spent about 70% of the time within the therapeutic INR range than those with a poorer understanding (63%). The results of this latter study, however, were not statistically significant, reflecting the large amount of variability within each group and also possibly due to the limited number of patients included.

In Italy, Barcellona and colleagues [82] developed a questionnaire concentrated mainly on the patients' understanding of why they were taking oral anticoagulants, the mechanism of the therapy through its regular assumption, dietary behavior (vegetable intake), current diseases that did not require hospitalization, interactions with other drugs, and assumption of other drugs. It was administered to a group of 219 consecutive anticoagulated patients attending the thrombosis center. The percentage time spent in the therapeutic range was calculated using the INR Day Program by Rosendaal et al. [52]. The difference in time spent in the range between patients who knew why they were taking the oral anticoagulant and those who did not was statistically significant only in the older group (89% vs. 76%, $P = 0.04$).

In another study of Barcellona et al. [59], the time spent within the therapeutic range by patients taking oral anticoagulants was improved by two different, consecutive educational approaches on the crucial aspects of oral anticoagulant therapy. In this study, 240 patients were randomly allocated into three groups; a course that focused on the questions in the interview was given to the first group (n = 80); a brochure containing the correct answers to questions was given to the second (n = 81); nothing was provided for the third (n = 79). A significant difference was found in the TTR between the quarters preceding and following the interview with 13% increase in the mean TTR among all groups.

Not all studies have found a positive correlation between patient knowledge and outcomes of warfarin therapy. In a sample of 52 patients, knowledge of warfarin therapy was assessed with an 18-question multiple-choice test and associated with anticoagulation control [62]. The anticoagulation control was defined as the number of blood tests in the appropriate therapeutic range divided by the number of blood tests performed during the 60-day period. This study showed no significant association between knowledge or education and the proportion of INRs within the therapeutic range. Moreover, insufficient education on OAC as perceived by the patient or caregiver was one of the significant predictive factors for bleeding complications (OR 8.83).

In Fang et al.'s [83] study, health literacy was measured using the bilingual short-form Test of Functional Health Literacy in Adults (s-TOFHLA), dichotomized as "limited" (score 0–22) and "adequate" (score 23–36) among 179 anticoagulated English- or Spanish-speaking patients. INR control was assessed by calculating the time in therapeutic range for each patient using an adapted linear interpolation method [52], defined as the proportion of person-time within the target therapeutic range over the total person-time of follow-up. It was found that patients with limited health literacy were more likely to have incorrect answers to most questions addressing warfarin-related knowledge and numeracy with incorrect answers to questions about warfarin's mechanism of action, side effects, medication interactions, and frequency of monitoring, after adjusting for age, sex, ethnicity, education, cognitive impairment, and years on warfarin. However, limited health literacy was not significantly associated with TTR over the previous 12 months.

In the USA, another study aimed to explore the association between literacy and numeracy skills among patients on warfarin, and their anticoagulation control was conducted among 143 patients older than 50 years attending 2 anticoagulation clinics [84]. They found that The INR variability was higher among patients with lower literacy ($P = 0.009$) and lower numeracy skills ($P = 0.004$). The time in the range was similar among patients at different literacy levels ($P = 0.9$); however, patients with lower numeracy level spent more time above their therapeutic range ($P = 0.04$) and had a trend of less time spent in range ($P = 0.10$).

In Malaysia, two previous studies have been conducted to assess the patients' knowledge and relate their knowledge to INR control [85, 86]. Hasan et al. [85] assessed the anticoagulation knowledge and INR control among patients on warfarin. In this cross-sectional study, 156 randomly sampled patients were interviewed using a validated interviewer-administered questionnaire, and all patients' INR readings were recorded from 2008 to 2010. The authors found the average score of patients knowledge was 66.5% + 36.0% on how warfarin works, 42.9% + 44.9% for interaction between warfarin and alcohol, and 49.2% + 21.1% for adverse effects. Among all variable studied, they found a negative correlation between patients' knowledge and age ($P = 0.001$, $r = -0.293$) and a positive correlation between patients' knowledge and their education level ($P = 0.001$, $r = 0.365$). Furthermore, no significant correlation was found between patients' INR control and their

knowledge on the mechanism of action of warfarin, the interaction between warfarin and alcohol, and the side effects of warfarin.

Another cross-sectional survey was conducted at the Warfarin Clinic of Hospital Teluk Intan, Malaysia, and tended to determine the factors that correlated with the patient's knowledge of warfarin therapy, the level of medication adherence, and INR control [86]. A total of 52 patients were interviewed with a mean ± SD age of 58.73 ± 9.55 years. Only 44.2% of patients knew about their medications, but the medication adherence was fairly good at 76.1%. The study showed that age, income level, level of education, and literacy in various languages were significantly associated with the patient's knowledge on warfarin therapy ($P < 0.05$). The study did not find any association between anticoagulation and the level of knowledge of anticoagulation. However, the major limitation of the former two studies is the limited sample size used.

It is also important to highlight that some of the aforementioned studies, regardless of their results, are limited by the use of a non-validated warfarin knowledge-testing instruments or questionnaire to evaluate patient knowledge [2, 66–69, 73–75, 86]. Validation indicates that the questionnaire has been thoroughly tested for content validity, measures of question difficulty, readability, and item/person reliability. Only after a knowledge assessment instrument has been validated can sound scientific conclusions be drawn from its results [87]. The appropriate psychometric methodology must be followed to ensure that an assessment measure is valid and reliable for testing the specific objectives or constructs. In theory, this process demonstrates that an instrument's results are accurate, consistent, reproducible, and stable over time [87–89].

To date, only two questionnaires measuring patient knowledge of warfarin therapy have been validated: the Oral Anticoagulation Knowledge test, created and validated by Zeolla et al. [77], and the Anticoagulation Knowledge Assessment (AKA) questionnaire, designed and validated by Briggs et al. [90].

In Zeolla et al. [77], the Oral Anticoagulation Knowledge, a new instrument, was developed by four nationally recognized anticoagulation experts to ensure content validity. The test was administered to 72 subjects on warfarin and 27 from a group of age-matched subjects not on warfarin to assess construct validity. Subgroups of warfarin subjects were retested approximately 2–3 months after initial testing to assess test-retest reliability. The OAK test was administered to 74 subjects taking warfarin and 27 age-matched subjects not on warfarin. In this study, subjects taking warfarin scored significantly higher than those not on warfarin (72% vs. 52%, respectively; $P < 0.001$), supporting the construct validity of the instrument. Test-retest reliability was acceptable, with a Pearson's correlation coefficient of 0.81, and the internal consistency reliability was 0.76. However, the association between the level of knowledge and clinical outcomes was not tested.

Another validated tool is the Anticoagulation Knowledge Assessment test, which was developed by Briggs et al. [90]. It is a 29-multiple-choice instrument that measures patient knowledge in 9 content areas, each worth 3.45 points. The validity of the instrument was assessed among 60 patients managed in two anticoagulation clinics who had received warfarin therapy for a mean of 28 months. The majority (80%) of patients who participated in the study had 12 or more years of education. The instrument was designed to be self-administered at a sixth grade reading level. Content validity of the instrument verified that the AKA instrument contains a variety of questions of varying levels of cognitive difficulty. However, the authors did not report whether they performed key reliability assessments (e.g., internal reliability or test-retest reliability); furthermore, they did not examine the relationship between patient's knowledge and the anticoagulation control.

In literature, Baker et al. [91] used the validated AKA questionnaire. Correctly answering 21 questions (72.4%) or more was needed for the determination of adequate knowledge of anticoagulation therapy (passing score). Interestingly, this cross-sectional study showed that 74% (n = 185) of patients receiving long-term warfarin therapy had achieved a pass rate. Statistically, no significant correlation between warfarin knowledge and INR control was found. These results may have been inflated as the questionnaire is a self-completed questionnaire at home and there is a possibility of assistance from others.

On the other hand, the impact of educational program in reducing the clinical adverse event rates was tested by a randomized trial [92]. They reported a decrease in the adverse event rates by threefold less in the educated group compared to the control group. This supports the significant and independent impact of the educational program on the reduction in risk of events (OR 0.25, 95% CI 0.1–0.7).

Similarly, other studies showed that patient knowledge has a positive effect in the clinical outcomes with the highest rate of major bleeding events among patients who had poor knowledge about warfarin [80, 93]. In Beyth et al.'s [93] study, there was a reduction in hospitalizations among patients receiving structured warfarin education compared to those in a control group (3 vs. 9 hospitalizations, respectively, out of a total of 12 hospitalizations; $P = 0.08$). Moreover, the time spent within the therapeutic range was higher in the educated group than in the control normal care group (56% vs. 32%; $P < 0.001$).

In summary, evidence from previous studies, such as Davis et al. [62] (n = 52), Fang et al. [83] (n = 139), Estrada et al. [84] (n = 143), Group TNAS [72] (n = 242), and Baker et al. [91] (n = 260) suggested no association between patients' warfarin knowledge and anticoagulation control. Some of the results of these latter studies, however, cannot be generalized because of their use of small sample sizes [62], number of variables relating to patient knowledge measured [62], and use of non-standardized data collection techniques [91].

The inverse relationship between the individual patient's level of knowledge about warfarin and the rate of adverse outcome events has been reported in other literatures [2, 68, 71, 80, 92].

3. Health-related quality of life of warfarin users

The term health-related quality of life (HRQoL) has been used when the concern of researchers is to investigate the influence of the disease and treatment on the quality of life of the individual [94]. This narrower concept has been used to avoid ambiguity between the definition of quality of life in the common sense and that used in clinical and medical trials.

Warfarin use is challenging [18], since it has a narrow therapeutic index; it interacts with other drugs, alcohol, and food [31, 95]; and the clinical response to it is affected by many factors such as patients' compliance and overall knowledge of therapy [74, 82]. Therefore, warfarin therapy requires a special care in order to control the desirable levels of blood coagulation and to prevent hemorrhagic and thromboembolic complications. Such care can lead to changes in the lifestyle of warfarin users since this involves changes in the dietary habits, the use of alcohol, and the performance of physical activity [96, 97], as well as the need to adhere strictly to the treatment regimen, the inconvenience of dosing adjustments, and the need for regular blood tests to monitor INR levels, together with the fear of complications such as the risk of minor or major bleeding and stroke [98]. All these changes caused by the use of anticoagulant treatment negatively affect the patient's

HRQoL. Perceived reduction in HRQoL is an important factor, which may influence the physician's prescription and patient's use of warfarin therapy.

To study the HRQoL of OAC users, authors have used different types of instruments. In a literature review regarding specific instruments available to evaluate the HRQoL of patients using OACs, the authors identified seven instruments [99]. In Brazil, a new specific instrument, the Duke Anticoagulation Satisfaction Scale (DASS), was developed by Samsa et al. [100] and recently validated by Pelegrino [101]. Some authors used a measurement of HRQoL obtained through the generic instrument such as the Medical Outcomes Survey 36-item Short Form (SF-36) [96, 100, 102, 103] and found that the more impaired HRQoL domains were physical aspects and vitality [96, 102], pain [100], physical functioning, and general health status [96].

In a cross-sectional study aimed to analyze the HRQoL and its relationship with gender, age, duration, and indication for the use of OAT, a total of 178 patients were interviewed, and the HRQoL was assessed through 8 domains of the SF-36 [104]. The means of the domains of the SF-36 ranged from 82 (social aspects) to 54.8 (physical aspects). In their study, the men had higher scores than the women in the majority of the domains of the SF-36, except for general health status. However, these differences were only significant in the domains, mental health, and pain. Elderly patients diagnosed with atrial fibrillation and with less than 1 year of medication use presented a worse HRQoL evaluation.

The HRQoL was also evaluated through a cross-sectional study with a sample composed of 72 patients with atrial fibrillation and mechanical heart valve at the anticoagulation outpatient unit of the Federal University of Bahia's University Hospital [105]. The patients were submitted to two quality of life evaluation questionnaires: SF-36 and DASS. The quality of life perception of the patients studied, based on both instruments, was positive regarding the treatment with OAC. The SF-36 presented an average score of 62.2 (±20.0). Among the SF-36 evaluated domains, the physical-emotional aspect was the most compromised one. The DASS presented an average score of 67.1 (±18.2), and the domain presenting a greater compromise was the one related to the treatment inconveniences. The authors identified many factors impacting patients' HRQoL; previous hemorrhagic event, comorbidities, drug interactions with medicines that increase the anticoagulant effect, lower education level in the SF-36, and younger age group influence a more negative perception of the QoL, whereas lower education level in the DASS and the duration of treatment for more than 1 year offer a more positive perception.

In a randomized, controlled trial including 333 atrial fibrillation patients using warfarin for stroke prevention, the impact of the long-term use of warfarin in their quality of life was assessed [97]. The results for their trial showed no significant differences between warfarin-treated and control patients on well-validated measures of functional status, well-being, and health perceptions. The mean score of health perceptions was 68.8 in the warfarin-treated group vs. 66.6 in the control group (scale of 0 to 100; 95% CI). In contrast, patients taking warfarin who had a bleeding episode had a significant decrease in health perceptions (−11.9; 95% CI). The authors concluded that warfarin therapy is not usually associated with a significant decrease in perceived health, unless a bleeding episode has occurred.

In an attempt to find the strategies to improve the HRQoL of patients undergoing anticoagulation therapy, a previous study found that patient self-management improves general treatment satisfaction and decreases patients' perception of treatment-related daily hassles, distress, and strain on their social network (Gadisseur et al., 2004). This is supported by other researchers who noted an improvement in many of treatment-related areas of QoL through patient self-management in comparison with routine anticoagulant care through family physicians [106, 107, 108].

4. Adherence toward warfarin

An assessment of warfarin adherence is important in improving patient's warfarin-taking behavior and INR control. Nonadherence includes not only a cessation of medication therapy but also taking the medication other than as prescribed (i.e., under-adherence, over-adherence, or not taking the dose at the prescribed time). Most studies reported medication adherence as a percentage of doses taken out of those prescribed over a specific period of time. While there is no general consensus on what constitutes adherence or nonadherence.

Nonadherence to OAC medication is generally problematic in practice. In a cohort study in the USA, 1005 patients with AF and taking warfarin are included, and there was a 32% reduction (from 65 to 44%) in the number of patients taking warfarin after 30 months [109].

Poor patient adherence to the prescribed drug regimen is often cited as an explanation for out-of-range INR measurements [110]. Despite this, there is little rigorous evidence of the level of adherence to warfarin, particularly among a broad spectrum of patients and anticoagulation practices. One reason for the lack of data on adherence to warfarin is the difficulty in measuring adherence [111].

In a prospective study of warfarin adherence, both under-adherence and over-adherence were measured among a sample of 145 patients at 3 anticoagulation clinics. The mean percentage of nonadherent days was 21.8% as measured by electronic medication event monitoring system (MEMS) [112].

In Singapore, another cross-sectional survey aimed to validate a patient-reported medication adherence measure, the MMAS-8, within a convenience sample of 151 patients taking warfarin [113]. It was found that respondents with higher MMAS-8 scores are more likely to have a higher percentage of INRs within the therapeutic range ($P = 0.01$), higher adherence to diet recommendations ($P = 0.02$), and less perceived difficulty in taking all medications ($P < 0.001$); they were also more likely to take warfarin at the same time every day ($P < 0.001$). This study showed that the 8-item MMAS has good validity and moderate reliability in patients taking warfarin.

In the International Normalized Ratio Adherence and Genetics (IN-RANGE) study of 111 adults taking warfarin, factors impacting patient adherence toward warfarin were studied [114]. It was found that demographic factors like education and occupation and psychosocial factors (such as lower levels of mental health functioning and poor cognitive functioning) are associated with nonadherence. Specifically, nonadherence was greater among those with educational levels beyond high school and those currently employed (compared with those unemployed and retired).

In a literature review by Brown et al. [115], many factors associated with OAC adherence among patients with AF were summarized as disease- and drug-related; patient knowledge, beliefs, and abilities; health system-related; economics; patient-physician relationship; and patient demographic, psychosocial, and personality traits.

In another review article that identified many factors associated with nonadherence in older adults, Murray et al. [116] developed a conceptual model of general medication adherence to improve adherence, assist in adherence research, and facilitate the development of multidimensional adherence improvement interventions. They concluded from an extensive literature search that older adults are at special risk due to the burden of multiple chronic diseases and age-related factors, such as cognitive impairment and other environmental and social factors.

To assess barriers to OAC medication use among patients with AF, a new questionnaire was developed by Ingelgård et al. [65]. The authors identified 41 barriers to warfarin use and classified them into 4 groups: patient medical characteristics,

healthcare system factors, patient capability, and patient preference. On the other hand, Cohen et al. [117] summarized the factors that affect adherence to anticoagulation medication as factors related to disease (e.g., symptoms, long-term therapy, morbidities), drug (e.g., adverse events, duration, dose frequency and complexity, polypharmacy, cost), patient (e.g., lack of support, lack of disease knowledge, concerns, difficulty comprehending instructions, inability to adhere to restrictions), follow-up (e.g., shortage of time, costs associated with INR monitoring, patient unwilling to repeat testing, delay in laboratory reporting), and health system (e.g., patient-doctor relationship, reimbursement, lack of proper facilities or experience to manage therapy).

Added to the previous literature, Arnsten et al. [118] found significant relationships between various demographic characteristics and adherence. Noncompliance patients were more likely than warfarin-adherent patients to be younger (mean age 53.7 vs. 68.7 years), male, and nonwhite. Non-adherent patients were also more likely to report a lack of understanding or knowledge of the reason for taking warfarin and were also less likely to have a regular physician.

In Korea, a cross-sectional survey involving 204 patients aimed to identify factors affecting medication adherence and their relationships with anticoagulation control in Korean patients taking warfarin [119]. They found that 56 (27.5%) of 204 respondents were adherent. Their results showed that knowledge about warfarin exerts significant influence on medication adherence; however, medication adherence was not associated with good anticoagulation level as measured by INR.

The association between medication adherence and the clinical outcome of warfarin was also studied previously. In Davis et al. [62], adherence was found as one of the many factors that contribute to anticoagulation control. In this cross-sectional survey, the 4-item Morisky survey was used to assess self-reported adherence. The researchers found that adequate adherence was reported by 50% of patients and it was significantly associated with good anticoagulation control ($P = 0.01$) [120, 121].

In addition, this relationship between medication adherence and the clinical outcome of warfarin was also studied by Kimmel et al. [122]. In this prospective cohort study involving three coagulation clinics in Pennsylvania, 136 patients treated with warfarin for various indications (with a goal INR of 2–3), adherence to anticoagulation therapy was monitored using electronic MEMS medication bottle caps. The authors found patients who fail to adhere to warfarin therapy as prescribed are more likely to experience problems with anticoagulation control. Patients who missed >20% of bottle openings are two times more likely to have under-coagulation (adjusted OR 2.10). On the other hand, a significant effect on INR with over-adherence was also demonstrated; patients who had >10% extra pill bottle openings had a statistically significant increase in over-coagulation (adjusted OR 1.73). Furthermore, the authors estimated that poor patient adherence to medications is responsible for more than 53% of all hospital admissions.

In contrast, another cross-sectional study studied the relationship between adherence and other factors with the INR stability [123]. Among all patients, 90% (n = 156) had high and medium adherence, and 117 (75%) had INR stability up to 50% and 39 (25%) ≥ 75%. It was found that factors like adherence, age, level of education, socioeconomic level, interaction with other drugs, comorbidities, and vitamin K intake did not influence INR stability. However, longer anticoagulation time and drug cost were the factors related to the anticoagulation stability.

In studies among patients with diagnoses other than AF and on anticoagulation therapy, other psychosocial factors associated with poorer adherence were identified. These factors include depressive symptoms, pessimism, and a perceived lack of social support [111, 124, 125].

5. Factors impacting anticoagulation control

A retrospective cross-sectional study was conducted in community clinics in Israel aimed to assess the level of anticoagulation control achieved in patients with AF and to explore patient factors that influence the anticoagulation control [126]. The univariate and multivariate analyses were performed to explore the association of patient variables with anticoagulation control. They found that the mean TTR was 48.6% with about two-thirds of patients had poor anticoagulation control, as evidenced by TTR of <60%. Poor control was significantly associated with female sex, advancing age, and comorbid conditions. Heart failure was found to be an independent predictor of poor control (OR: 1.63).

A different cohort methodology was applied for assessing the likelihood of poor INR control among AF patients [127]. They used linear regression analysis to detect clinical factors associated with TTR and binary logistic regression to evaluate the predictive factors for different cut-off values of TTR. They explored various variables as independent predictors of poor TTR: female gender, age <50 years, ethnic minority status, smoking, more than two comorbidities, and being treated with a beta blocker, verapamil, or, inversely, amiodarone use.

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