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Anticoagulation with warfarin in Patients from Eastern Colombia: A Prospective Longitudinal Observational Study

Anticoagulación con warfarina en pacientes del oriente colombiano: estudio observacional analítico longitudinal con seguimiento prospectivo

Anticoagulação com varfarina em pacientes do leste colombiano: estudo observacional analítico longitudinal com acompanhamento prospectivo

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ABSTRACT

Introduction. Warfarin, an oral anticoagulant with a narrow therapeutic margin, exposes patients to risks associated with its therapy, underscoring the need for constant monitoring. In this context, this study evaluated the therapeutic follow-up of warfarin in anticoagulated patients at an ambulatory healthcare institution in eastern Colombia. **Methodology.** An observational analytical longitudinal study with prospective follow-up was conducted, including 244 patients, in which sociodemographic and clinical variables obtained from medical records were analyzed over a one-year period. **Results.** Within the participant cohort, 53.7% were female, and the prevailing diagnosis was atrial fibrillation and atrial flutter (46.3%). Generic warfarin was administered to 60.7% of participants, while 52.9% were concurrently prescribed an average of 5 medications. Alterations in weekly therapeutic dose showed significant correlation with time within therapeutic range ($p = 0.000$) and occurrence of adverse drug events ($p = 0.001$). Drug non-adherence (13.1%) emerged as the most frequent event. Assessment of 3,032 International Normalized Ratio results revealed a mean time in therapeutic range of 149 days, with an average of 6 tests falling within this range. **Discussion.** Suboptimal anticoagulation control was primarily associated with dose adjustments and patient non-adherence rather than manufacturer changes or comorbidities. These findings underscore the critical role of patient education in warfarin therapy

management, particularly among elderly populations with polypharmacy. **Conclusion.** Anticoagulation programs should implement rigorous monitoring of weekly therapeutic dose administration, complemented by continuous education regarding timing of intake, posology, and factors influencing the International Normalized Ratio. This recommendation has particular significance given the advanced age of most patients.

Keywords: Anticoagulants; Warfarin; International Normalized Ratio; Medication Therapy Management; Drug Monitoring; Therapeutic Index; Iron, Dietary; Plants.

RESUMEN

Introducción. La warfarina, un anticoagulante oral con estrecho margen terapéutico, expone a los pacientes a riesgos asociados a su terapia, subrayando la necesidad de una monitorización constante. En este contexto, el presente estudio evaluó el seguimiento terapéutico de la warfarina en pacientes anticoagulados atendidos en una institución ambulatoria de salud en el oriente de Colombia. **Metodología.** Se desarrolló un estudio observacional analítico de tipo longitudinal con seguimiento prospectivo, que incluyó 244 pacientes, en el cual se analizaron variables sociodemográficas y clínicas obtenidas de las historias clínicas durante un período de un año. **Resultados.** De los participantes, el 53.7% eran mujeres, y el diagnóstico más frecuente fue fibrilación y aleteo auricular (46.3%). El 60.7% recibió warfarina genérica, el 52.9% eran polimedicados con un promedio de 5 medicamentos. Se observó que el cambio de dosis terapéutica semanal se asoció significativamente con el cumplimiento del tiempo en rango terapéutico ($p = 0.000$) y con el desarrollo de eventos adversos a medicamentos ($p = 0.001$), siendo la no adherencia farmacológica (13.1%) el evento más frecuente. Se evaluaron 3,032 resultados de Razón Normalizada Internacional, con un tiempo medio en rango terapéutico de 149 días y una media de 6 pruebas en rango terapéutico. **Discusión.** El control anticoagulante subóptimo

estuvo asociado principalmente con ajustes de dosis y falta de adherencia del paciente, más que con cambios de fabricante o comorbilidades. Estos hallazgos subrayan el papel crítico de la educación del paciente en el manejo de la terapia con warfarina, particularmente en poblaciones de edad avanzada con polifarmacia. **Conclusión.** Se recomienda que los programas de anticoagulación implementen un seguimiento riguroso del consumo correcto de la dosis terapéutica semanal, acompañado de educación continua sobre la hora de la toma, posología y factores que afectan la Razón Normalizada Internacional. Esto es especialmente relevante considerando la edad avanzada de la mayoría de los pacientes.

Palabras clave: Anticoagulantes; Warfarina; Relación Normalizada Internacional; Administración del Tratamiento Farmacológico; Monitoreo de Drogas; Índice Terapéutico; Hierro de la Dieta; Plantas.

RESUMO

Introdução. A varfarina, um anticoagulante oral com estreita margem terapêutica, expõe os pacientes a riscos associados à sua terapia, sublinhando a necessidade de monitoramento constante. Nesse contexto, este estudo avaliou o acompanhamento terapêutico da varfarina em pacientes anticoagulados atendidos em uma instituição ambulatorial de saúde no leste da Colômbia. **Metodologia.** Foi desenvolvido um estudo observacional analítico de tipo longitudinal com acompanhamento prospectivo, que incluiu 244 pacientes, no qual foram analisadas variáveis sociodemográficas e clínicas obtidas dos prontuários médicos durante um período de um ano. **Resultados.** Dos participantes, 53.7% eram mulheres, e o diagnóstico mais frequente foi fibrilação e flutter atrial (46.3%). 60.7% receberam varfarina genérica, 52.9% eram polimedicados com uma média de 5 medicamentos. Observou-se que a mudança da dose terapêutica semanal se associou significativamente com o cumprimento do tempo em faixa terapêutica (p = 0.000) e com o desenvolvimento de eventos adversos a

medicamentos (p = 0.001), sendo a não adesão farmacológica (13.1%) o evento mais frequente. Foram avaliados 3,032 resultados de Razão Normalizada Internacional, com um tempo médio em faixa terapêutica de 149 dias e uma média de 6 testes em faixa terapêutica. **Discussão.** O controle anticoagulante subótimo esteve associado principalmente com ajustes de dose e falta de adesão do paciente, mais do que com mudanças de fabricante ou comorbidades. Estes achados sublinham o papel crítico da educação do paciente no manejo da terapia com varfarina, particularmente em populações de idade avançada com polifarmácia. **Conclusão.** Recomenda-se que os programas de anticoagulação implementem um acompanhamento rigoroso do consumo correto da dose terapêutica semanal, acompanhado de educação contínua sobre o horário da tomada, posologia e fatores que afetam a Razão Normalizada Internacional. Isto é especialmente relevante considerando a idade avançada da maioria dos pacientes.

Palavras-chave: Anticoagulantes; Varfarina; Coeficiente Internacional Normatizado; Conduta do Tratamento Medicamentoso; Monitoramento de Medicamentos, Índice Terapêutico, Ferro da Dieta; Plantas**.**

Introduction

Cardiovascular diseases are among the principal contributors to disability-adjusted life years (DALYs) and hospital admissions within the spectrum of non-communicable diseases, particularly in low-and middle-income countries (1). Thrombotic processes play a central role in the development of major clinical events, including ischemic heart disease, ischemic stroke, and venous thromboembolism (VTE) (1). Evidence from the Global Burden of Disease Study 2021 indicates that these conditions account for a substantial proportion of the DALY burden, with a marked impact observed in adults aged 50 to 74 years (2).

In the primary and secondary prevention of these pathologies, oral anticoagulants such as warfarin are employed either continuously or intermittently, depending on risk stratification. This is particularly pertinent in cases associated with atrial fibrillation (AF) and in patients with mechanical heart valves (3-5). Nevertheless, the use of warfarin is associated with an elevated risk of bleeding and thromboembolic events due to its Narrow Therapeutic Index (NTI). The NTI is defined as the range of drug concentrations within which there is a high probability of therapeutic efficacy with minimal toxicity. Therefore, vigilant monitoring of therapy remains essential (3-6).

In clinical practice in Colombia, patients are administered anticoagulant drugs, whether branded or generic, authorized by the National Institute for Drug and Food Surveillance (INVIMA). The selection is based on the availability of stock managed by the Pharmaceutical Manager, with whom the Health Promoting Entity has a supply contract. However, a challenge arises concerning the substitution of patients' medications. In this context, it is crucial to avoid altering the product or manufacturer of oral anticoagulants and other Medications with NTI once treatment has commenced. If a change becomes necessary, the dosage and administration regimen should be adjusted, accompanied by clinical and paraclinical monitoring (7).

Among the Medications with NTIs is warfarin, established as the most extensively utilized oral anticoagulant for treating diverse conditions. These include arterial and venous thromboembolic disease, atrial fibrillation, acute myocardial infarction, mechanical and bioprosthetic valves, pulmonary embolism, and other hypercoagulability disorders (8-11).

Despite the existence of new molecules such as Acenocoumarol, Enoxaparin, Rivaroxaban, Dabigatran, Betrixaban, Edoxaban, and Apixaban, the continued use of warfarin is

maintained due to its affordable cost and the availability of options to manage possible complications (11-15).

The characteristics associated with the use of warfarin include a slow onset and the potential for developing resistance, attributed to the wide variability in therapeutic response among individuals (16). To maintain the desired therapeutic effect, adjustment is required to achieve an International Normalized Ratio (INR) within the recommended therapeutic range. An INR target of 2.0–3.0 is indicated for most clinical conditions, while a higher therapeutic range (INR 2.5–3.5) is recommended for patients with diagnoses requiring intensified anticoagulation, particularly those with mechanical prosthetic heart valves, due to the increased risk of thromboembolic events associated with valve replacement (17,18) warfarin resistance manifests in two distinct types: incomplete resistance, characterized by the necessity of a high dosage to achieve therapeutic effects, and complete resistance, wherein patients exhibit no response to treatment irrespective of the administered dose (19,20) warfarin resistance may arise from acquired factors, including suboptimal therapeutic protocols or interactions with food and pharmaceuticals. Alternatively, it can be of hereditary nature, stemming from genetic variations in the cytochrome P450-2C9 (CYP2C9) enzymes and the vitamin K epoxide reductase complex (VKORC1) (16,19-21).

Warfarin necessitates ongoing monitoring, yet despite this diligence, unpredictable responses are evident in clinical settings, necessitating dose adjustments and regular surveillance via laboratory tests (22-24). Furthermore, it is crucial to consider frequent interactions with food and other medications, as they have the potential to influence warfarin metabolism, thereby either augmenting or diminishing its effects (17,23,24).

During the administration of warfarin, Adverse Drug Reactions (ADRs) may manifest at doses commonly employed in oral anticoagulant therapy. Therefore, continuous monitoring

of the International Normalized Ratio (INR), reflecting Prothrombin Time (PT), is imperative. The INR standardizes PT results across laboratories, ensuring consistency irrespective of the testing facility (25). This standardized value, supplied by the manufacturer, is compared to the reference thromboplastin response established by the World Health Organization (WHO). If the problematic thromboplastin closely resembles that of the WHO, the International Sensitivity Index (ISI) attains a value of 1. Reference INR values for patients not undergoing oral anticoagulant therapy typically range from 0.90 to 1.15. Conversely, in patients subjected to oral anticoagulant therapy, a targeted range of 2 to 3 is sought. It is noteworthy that these values may vary based on clinical circumstances and the specific indications for each patient (25-28).

While similar studies have been conducted in Colombia (29-31), specific data regarding anticoagulant therapy, particularly with warfarin, are lacking in the Santander region. Therefore, this research seeks to assess the therapeutic monitoring of warfarin in an outpatient Health Service Provider Institution (IPS) situated in eastern Colombia, focusing on a population of anticoagulated patients.

Methodology

Study design

A prospective observational analytical study was conducted over a one-year period (January 2018 to January 2019). Patients receiving warfarin therapy were followed during this period, with one or more INR measurements recorded per patient. The target population comprised outpatients under the contributory regime receiving care within the anticoagulation program of an outpatient Health Services Provider Institution in eastern Colombia. Non-probabilistic sampling was employed to select participants, encompassing individuals prescribed anticoagulation therapy for diverse pathologies, such as arterial and venous thromboembolic

disease, atrial fibrillation, acute myocardial infarction, mechanical and bioprosthetic valves, deep vein thrombosis, pulmonary embolism, and other hypercoagulability disorders.

Exclusion criteria stipulated the exclusion of patients without anticoagulant therapy and those under 18 years of age. No patients were lost to follow-up during the study period. All eligible patients with complete records and INR measurements were included.

After consultations with their attending physicians, patients received a comprehensive explanation of the study and were provided with the informed consent form for thorough review and signature. This phase extended over five months. Sociodemographic and clinical data, encompassing the diagnosis for anticoagulant therapy, weekly therapeutic doses, and International Classification of Diseases (ICD-10) codes for enrolled patients, were extracted from their respective medical records.

The information system of the clinical laboratory, where tests such as PT, INR, and ISI were conducted, was utilized for monitoring the results. In the analysis of the impact on INR concerning a change in the manufacturer, exclusive examination was limited to the group of patients receiving generic warfarin. The Health Service Provider Institution involved two pharmaceutical managers responsible for dispensing warfarin. Patients included in the sample were classified into two groups according to their diagnoses, based on ICD-10 codes, and were further categorized according to the INR therapeutic targets corresponding to each diagnostic group. The first group included individuals with an INR range between 2.0 and 3.0, identified by codes I48X, I802, I828, I679, I269, Z953, Z921, I513, D686, D689, I351, D682, D684, I749, I829, and R001. Conversely, the second group comprised patients with an INR range between 2.5 and 3.5, represented by code Z952. To assess patients' anticoagulation control, the Rosendaal method was employed to calculate the percentage of Time in Therapeutic Range (%TTR). Patients with %TTR above 60% were considered

controlled, while those with a lower %TTR were deemed at risk of hemorrhagic or thromboembolic complications (32,33).

Patients were categorized into two groups based on medication use: polymedicated, defined as individuals consuming more than six medications, and non-polymedicated, defined as those consuming six or fewer medications (34,35).

During this eight-month study phase, data were collected and recorded using Google Forms. The classification of INR was based on the percentage of tests in range (%TTR). Subsequently, %TTR for the study period was treated as a dichotomous variable (Yes ≥ 60 %TRT; No < 60 %TRT) (32,33).

Manufacturer switching was classified as 'Yes' when a patient received treatment at some point with drugs from different suppliers and as 'No' when the drug manufacturer remained constant throughout the entire treatment. This approach facilitated the evaluation of the impact of manufacturer switching on %TTR for patients receiving generic warfarin.

Adverse drug events were identified and classified through systematic review of medical records. Events were categorized based on clinical documentation by treating physicians, including pharmacological non-adherence, therapeutic failure, and suspected dietary factors affecting INR control.

Institutional review board approval was obtained from the Scientific and Ethics Committee of the Health Services Provider Institution (Resolution No. 45, December 1, 2017). Consistent with Resolution 8430 of 1993 from the Ministry of Health and Social Protection, it was determined that this research posed no significant risks to the participants (36).

To ensure compliance with Colombian regulations governing access to and use of clinical records, this study was conducted in strict accordance with the national legal framework. Ethical principles for medical practice were observed as established in Law 23 of 1981 (37),

while the handling, custody, and use of medical records followed the provisions set out in Resolution 1995 of 1999 (38), as subsequently updated by Resolution 839 of 2017 regarding record retention periods and final disposition (39).

In addition, the processing of sensitive personal information complied with Law 1581 of 2012 on data protection (Habeas Data) (40), ensuring the confidentiality, security, and integrity of clinical data, as well as the protection of participants' rights and privacy throughout all stages of the study.

Statistical analysis

A descriptive univariate and bivariate analysis was conducted. For continuous quantitative variables, distributions, measures of central tendency, dispersion, and 95% confidence intervals were presented. Normality assessment employed the Kolmogorov-Smirnov test, and associations between variables were investigated using Pearson's Chi-square test of independence.

Multivariate analysis utilized decision trees with the Exhaustive CHAID (Chi-square Automatic Interaction Detection) method, with Adverse Drug Events (ADEs) as dependent variables. The predictive quality of the decision tree was evaluated through a classification test. A p-value of less than 0.05 was considered statistically significant. SPSS version 25 was employed for result analysis.

Missing Data

Missing data were handled through complete-case analysis. Records with incomplete information were excluded from the relevant analyses. No imputation methods were applied. No patients were lost to follow-up during the study period. All eligible patients with complete records and INR measurements were included.

Limitations

Study limitations included the lack of prospective dietary assessment using validated instruments. Dietary-related adverse events were identified through physician documentation, which may have resulted in underestimation of diet-related INR variability.

Results

Sociodemographic variables

A total of 244 patients participated in the study, with 53.7% (n=131) being female. Most participants were older adults (mean = 69 ± 5 years, median = 72, IQR = 22 - 98, Kolmogorov-Smirnov p = 0.00). Regarding educational level, 20.5% had no education, 33.3% completed primary school, 15.6% had secondary school education, and only 8.6% had a university education. In terms of socioeconomic stratum, 4.1%, 28.7%, and 57.4% belonged to socioeconomic strata 1, 2, and 3, respectively. Concerning place of origin, 59.4% resided in Floridablanca, 22.5% in Bucaramanga, 7% in Piedecuesta, 4.5% in Girón, 3.7% in other municipalities of Santander, and 2.9% in other departments.

Clinical variables

According to the ICD-10 classification, the four most prevalent pathologies diagnosed among participants were as follows: I48X (Atrial fibrillation and flutter) at 46.3% (n = 113), I802 (Phlebitis and thrombophlebitis of other deep vessels of the lower limbs) at 20.1% (n = 49), Z952 (Presence of prosthetic heart valve) at 14.75% (n = 35), and I828 (Embolism and thrombosis of other specified veins) at 6.1% (n = 15), with the remaining 13.1% (n = 32) comprising other pathologies. Table 1 presents the data by sex.

Regarding the type of oral anticoagulant (OAC) used (Table 1), it was found that 60.7% (n = 148) of the participants used generic warfarin, 22.5% (n = 55) used the drug Coumadin (commercial warfarin), and the remaining 16.8% (n = 41) were prescribed other

anticoagulants such as Dabigatran (8.2%), Apixaban (4.9%), Rivaroxaban (3.3%), and Acenocoumarol (0.4%).

Table 1 outlines adverse events occurring in 93 patients. The two most prevalent events were pharmacological non-adherence, affecting 34.4% (n = 32) of participants, and uncontrolled generic warfarin (therapeutic failure), observed in 24.7% (n = 23) of cases. Another frequent adverse event was under-targeting by diet, observed in 21.5% (n = 20) of patients, while the remaining 19.4% (n = 18) corresponded to other types of adverse events.

Regarding the duration of oral anticoagulant use, the mean was 4 ± 5 years, (median = 2, maximum = 22, Kolmogorov-Smirnov p = 0.00). Most patients had been on anticoagulant therapy for less than 1 year, constituting 38.9% (n = 95) of the total. Additionally, 50% (n = 122) of patients had a duration of OAC consumption between 1 and 9 years. Conversely, 8.2% (n = 20) of patients had been on therapy for 10 to 18 years, and only 2.9% (n = 7) had undergone more than 20 years of OAC therapy.

The patients were categorized into two groups: polymedicated accounting for 52.9% (Mean = 4.7 ± 2.4), and non-polymedicated, comprising 47.1%. No statistically significant differences were observed between the groups (p = 0.405).

INR value during treatment

Throughout the study period, a total of 3,032 INR tests were performed among the 244 participants. In the subgroup of patients with a target therapeutic INR range of 2.0–3.0, a total of 2,381 tests were conducted (mean INR = 2.4 ± 1.2). Of these measurements, 42.2% (n = 1,004) were within the therapeutic range. In contrast, 12.0% (n = 54) showed INR values above 3.0, while 37.0% (n = 881) were below 2.0.

In the subgroup of patients with a target therapeutic INR range of 2.5–3.5, 651 tests were performed (mean INR = 2.7 ± 1.1). Therapeutic control was achieved in 39.9% (n = 259)

measurements. Supra-therapeutic values (INR >3.5) occurred in 19.2% (n = 125), indicating increased bleeding risk, whereas sub-therapeutic values (INR <2.5) were observed in 40.9% (n = 266), suggesting reduced anticoagulant effectiveness.

These findings underscore that a significant proportion of patients in both groups achieved and maintained an INR within the therapeutic range. However, the presence of INR values outside the desired ranges, both above and below the reference value, was notable. This emphasizes the crucial need for regular monitoring and appropriate adjustments in oral anticoagulant therapy to ensure optimal INR control and mitigate the risk of adverse events.

Time in therapeutic range

In this cohort, the mean time in therapeutic range (%TTR) was 149 ± 93 days (Kolmogorov-Smirnov p = 0.20). Adequate anticoagulation control (%TTR ≥ 60%) was achieved in 33% of patients (n = 56). Additionally, 39.2% of participants (n = 69) maintained %TTR above 50%, suggesting suboptimal but clinically acceptable control in a substantial proportion of the sample. The median number of INR measurements within therapeutic range per patient was 6 ± 4 (IQR = 0–18, median = 6, Kolmogorov-Smirnov p < 0.001).

Bivariate analysis

In the population of anticoagulated patients, a significant association was observed between inclusion in or exclusion from the therapeutic range (%TTR) and the alteration of weekly therapeutic dose X^2 (1, N = 144) = 15.8, p = 0.00. This implies that among patients not within the %TTR, there is a 5.7-fold increase in the likelihood of a change in the weekly therapeutic dose compared to those within the therapeutic range (OR = 0.17; 95% CI [0.07, 0.43] (Table 2).

Contrastingly, no statistically significant association was found between %TTR and the presence of comorbidities in patients using Fisher's Exact test (p = 0.76). Similarly, no

significant association was observed between %TTR and changes in the generic warfarin manufacturer using Fisher's Exact test (p = 0.06) (Table 2).

Adverse drug events in the anticoagulated patient population were significantly linked to changes in the weekly therapeutic dose of warfarin X^2 (1, N = 144) = 11.28, p = 0.00 (Table 2). This suggests that patients experiencing adverse events are 3.2 times more likely to undergo a change in the weekly therapeutic dose compared to those without adverse events (OR = 3.2, 95% CI [1.61, 6.47]. In this sample, no statistically significant association was found between adverse drug events (ADEs) and changes in the warfarin manufacturer X^2 (1, N = 134) = 0.30, p = 0.58; and no statistically significant association was found between ADEs and patient comorbidities X^2 (1, N = 148) = 0.32, p = 0.57.

Furthermore, this study assessed the association between therapeutic range (%TTR) and adverse drug events, revealing a statistically significant result χ^2 (1, N = 148) = 10.61, p = .00. This suggests that patients not within the %TTR are 4.16 times more likely to experience adverse drug events compared to those within the therapeutic range (OR = 0.24, 95% CI [0.97, 0.59].

Decision Tree

Figure 1 displays the decision tree with Adverse Drug Events (ADE) as the dependent variable at Node 0, bifurcating by Percentage of Time in Therapeutic Range (%TTR). Among patients failing to achieve adequate %TTR (Node 1), 73.4% experienced an ADE. Subsequent stratification by Change in Weekly Therapeutic Dose (CWTD) identified Nodes 3 and 4, representing 42.4% of participants. Within this subgroup, adverse events occurred in 61% versus 38.4% of patients.

The characteristic risk profile comprised inadequate %TTR combined with dose adjustments. Correct classification rates were 64% overall, 67% for ADE -positive cases, and 70% for ADE-negative cases.

This moderate accuracy reflects the complex aetiology of warfarin-associated adverse events. Unmeasured factors (dietary intake, adherence patterns, genetic polymorphisms, and drug interactions) are known contributors. The decision tree prioritized clinical interpretability over predictive performance, identifying actionable risk profiles for this eastern Colombian cohort.

Discussion

During the analysis of the sample of anticoagulated patients, a notable association was observed between the adjustment of weekly therapeutic doses and %TTR values outside therapeutic targets. Conversely, no statistically significant associations were found between the percentage of time in the therapeutic range (%TTR) and the presence of comorbidities, or with changes in the generic warfarin manufacturer. Additionally, there was no significant association identified between adverse events and changes in the generic warfarin manufacturer, in conjunction with patients' comorbidities. Addressing the challenge faced by treating physicians, it is notably intricate to precisely adjust the dose for achieving and maintaining the therapeutic range of the international normalized ratio (INR), especially considering the diverse age- and lifestyle-related characteristics within this patient group.

Other studies have underscored the necessity of dose adjustments based on the international normalized ratio (INR) test value. For instance, Kahlon et al. (41) identified that patients with hypercoagulability issues may require an additional 10 mg of warfarin in the total dose, along with an extension in the duration needed to achieve the therapeutic INR (41). In a Colombian study conducted by Pinzón et al. (29), adverse events associated with alterations in warfarin

dosage and inappropriate dosing schedules were reported, with an emphasis on their preventability (24).

It is crucial to recognize that patients undergoing chronic treatment with warfarin necessitate consistent monitoring of INR values resulting in subsequent dose modifications (29,40). This process incurs resource consumption and heightened follow-up costs, particularly when dealing with elderly individuals, those with polypharmacy, comorbidities, suboptimal administration practices (such as tablet splitting) (28,41-45), and pharmacological interactions (28).

In this study, a statistically significant association was observed between the therapeutic range (%TTR) and adverse events. This suggests that patients not within the therapeutic range are more prone to experiencing adverse events compared to those maintaining therapeutic levels (33,46). This underscores the importance of implementing best practices in the administration, follow-up, and adherence to warfarin treatment. It also emphasizes the necessity of educating both the patient and the caregiver on the proper management of therapy during treatment (46-47). This responsibility rests on the pharmaceutical service, the physician, and the support staff, with a particular focus on the nursing team. Active collaboration and participation of the patient are fundamental, as well as the implementation of pharmacotherapeutic follow-up by the healthcare institution. In addition to ensuring the safety and efficacy of the treatment, these practices contribute to optimizing therapeutic outcomes and minimizing the risks associated with the use of warfarin.

The findings of this study align with those of Okumura et al. (49), who investigated a population of 501 patients diagnosed with non-valvular atrial fibrillation. They identified a positive correlation between %TTR below target and dose changes, which was attributed to treating physicians adjusting doses to address bleeding risk. The %TTR in patients with

warfarin doses < 2.0, 2.0-4.9, and ≥ 5.0 mg/day was 72 ± 22%, 63 ± 25%, and 48 ± 24%, respectively (all $p < 0.001$) (48).

Unlike a study by Chou et al. (28) in Taiwan, where poor practices in warfarin administration were detected, our work did not identify such issues. In their study, they observed the splitting of warfarin tablets, especially for drugs with a narrow therapeutic range. Uneven tablet splitting could result in inadequate dosing and may lead to toxicity (28).

The main limitations of this study include the non-participation of all patients affiliated with the healthcare institution and the exclusive conduct of the study in a single anticoagulation clinic, potentially limiting the generalizability of the results. Additionally, it is crucial to note that a significant proportion of the studied patients were polymedicated, emphasizing the need for future research to identify potential pharmacological interactions and assess the impact of pharmacist intervention through Pharmacotherapeutic Follow-up (PTFS) in this population. As demonstrated by Falamic et al. (49), their study significantly improved %TTR in anticoagulated patients (93 patients with PTFS vs. 31.2% PTFS group; $p < 0.001$) (49,50).

Conclusions

Atrial fibrillation and flutter were the predominant indications for anticoagulation. Therapeutic control was poor: 42.2% of INR values fell within target for atrial fibrillation (2.0–3.0), and 39.9% for prosthetic valves (2.5–3.5). Suboptimal control appeared linked to polypharmacy, dietary non-compliance, and critically deficient patient understanding of warfarin therapy.

warfarin's narrow therapeutic index makes patient literacy essential for safety. The anticoagulation clinic should implement structured education protocols and maintain rigorous %TTR monitoring. Addressing knowledge gaps may reduce preventable adverse events in this clinically complex population.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethical responsibilities

Protection of people: This study is considered risk-free due to its nature. It was approved by the Institutional Ethics Committee.

Confidentiality of data: The authors declare they have followed their work center's protocols on the publication of patient data.

Right to privacy and informed consent: The authors have obtained the informed consent of patients and/or subjects mentioned in the article. This document is in the possession of the corresponding author referred to in the article

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Table 1. Clinical characteristics of the study population.

Variable	Gender				Total	p-value
	Male		Female			
	n	%	n	%		
Diagnosis for Oral Anticoagulation Therapy						
Atrial fibrillation and atrial flutter	54	47.8	59	52.2	113	0.03
Phlebitis and thrombophlebitis of other deep vessels of lower limbs	12	24.5	37	75.5	49	
Presence of prosthetic heart valve	21	60.0	14	40.0	35	
Embolism and thrombosis of other specified veins	8	53.3	7	46.7	15	
Other diagnoses	18	56.3	14	43.8	32	
Oral anticoagulants						
Generic warfarin	73	49.3	75	50.7	148	0.50
Coumadin (Commercial)	23	41.8	32	58.2	55	
Other oral anticoagulants	17	41.5	24	58.5	41	
Adverse events						
Pharmacological non-adherence	18	56.3	14	43.8	32	0.28
Uncontrolled by generic warfarin - therapeutic failure	14	60.9	9	39.1	23	
Suspected dietary non-adherence (vitamin K intake)†	11	55.0	9	45.0	20	
Drug-drug interaction	6	85.7	1	14.3	7	
Pharmacological interaction	2	50.0	2	50.0	4	
Overdosage	1	50.0	1	50.0	2	
Minor bleeding	1	50.0	1	50.0	2	

Change of pharmacological therapy	0	0.0	2	100.0	2	
Change of presentation of the drug	1	100.0	0	0.0	1	
Comorbidity	113	46.3	131	53.7	244	0.74
Weekly therapeutic dose changes Generic warfarin	95	47.3	106	52.7	201	0.17
Change manufacturer Generic warfarin	80	48.8	84	51.2	164	0.34
Percentage of Time in Therapeutic Range	113	46.3	131	53.7	244	0.79

†Dietary non-adherence was suspected based on clinical documentation of vitamin K-rich food consumption or unexplained INR variability in the absence of other identifiable causes, as documented by treating physicians in medical records. Source: prepared by the authors

Source: prepared by authors

Table 2. Analysis of risk factors

Time in therapeutic range (%TTR)	OR	CI 95%	p-value
Change of weekly therapeutic dose	0.17	0.07 - 0.43	0.00*
Change of manufacturer	1.31	1.18 - 1.48	0.06**
Comorbidity	1.48	0.39 – 5.56	0.76**
Adverse drug event			
Weekly therapeutic dose change	3.23	1.61 – 6.47	0.00*
Time in therapeutic range	0.24	0.97 – 0.59	0.00*
Change of manufacturer	0.71	0.21 – 2.35	0.58*
Comorbidity	0.73	0.25 – 2.14	0.57*

Notice: * Pearson's Chi-square. ** Fisher's exact test.

Source: prepared by authors

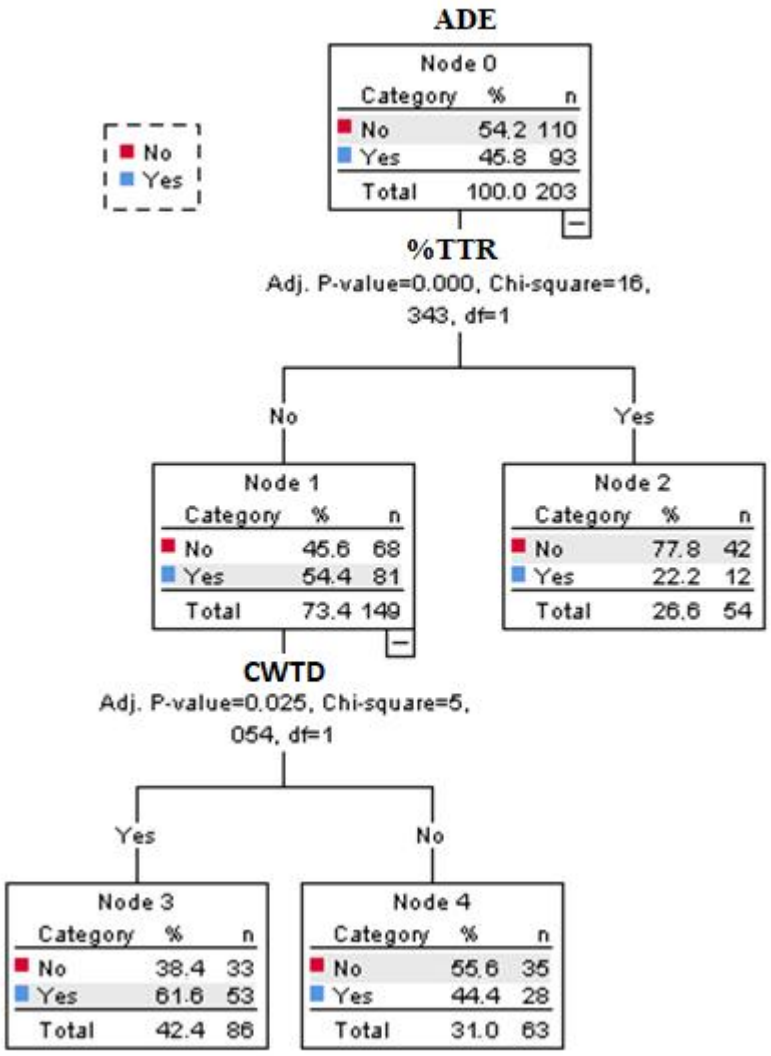

Figure 1. Decision Tree Adverse Drug Events.

Notice: ADE: Adverse Drug Events. %TTR: Percentage in Therapeutic Range. CWTD: Change in Weekly Therapeutic Dose.

Source: prepared by authors