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ORIGINAL ARTICLE

Health Literacy, Patient Knowledge and Adherence to Oral Anticoagulation in Primary Care

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Abstract

Background: Warfarin is the only oral anticoagulant available in the Brazilian public health system. Health knowledge and treatment are essential to achieving the desirable therapeutic effect. However, data on these aspects among primary care patients are still lacking.

Objective: To assess health literacy, patient knowledge, and adherence to oral anticoagulation with warfarin, as well as the medication regimen complexity in primary health units in the municipality of Divinópolis, Minas Gerais, Brazil.

Methods: This cross-sectional study included patients using warfarin from primary care settings. Sociodemographic and clinical data were collected from medical records. Short Assessment of Health Literacy for Portuguese-Speaking Adults (SAHLPA-18), Oral Anticoagulation Knowledge (OAK), adaptation of the Measure of Adherence to Treatment (MAT-adapted) to oral anticoagulation, and Medication Regimen Complexity Index (MRCI) were applied, and the time in therapeutic range (TTR) was calculated. Patients were stratified in two groups (TTR < 60% and TTR ≥ 60%) and compared using Fisher's exact test at a significance level of $p < 0.050$.

Results: Analysis included 162 patients (64.8 ± 12.7 years old, 55.6% women). Nonvalvular atrial fibrillation (26.5%) and venous thromboembolism (24.1%) were the main indications for warfarin, and 67.9%, 88.3%, and 16.7% of the patients had inadequate health literacy, insufficient knowledge regarding anticoagulant therapy, and non-adherence to warfarin therapy, respectively. There was no significant association of these parameters in relation to TTR. MRCI showed high pharmacotherapy complexity between the drug prescriptions.

Conclusion: This study showed alarming insufficient knowledge about warfarin therapy and low health literacy in primary care patients.

Keywords: Anticoagulants; Warfarin; Primary Health Care; Cardiovascular Diseases; Health Literacy.

Introduction

For more than half a century, oral anticoagulants have been used for the treatment and primary and secondary prevention of venous and arterial thromboembolic events in patients with atrial fibrillation, mechanical heart valves prosthesis, after acute myocardial infarction, treatment of antiphospholipid antibody, among others.[1] Warfarin is one of the most prescribed anticoagulants in history, and, despite the advent of direct oral anticoagulants (DOACs), it is still frequently used in clinical practice.[2,3] In Brazil, it is the most used oral anticoagulant in the public health system.[4] This scenario is due to the high direct costs of the DOACs, despite the fact that a previous study has shown that, in the Brazilian context, the cumulative costs per patient using warfarin with follow-up in anticoagulation

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clinics is currently higher than the strategy of prescribing the new oral anticoagulants.[5] Furthermore, there is a lack of proven efficacy and safety of DOACs for patients with Chagas disease and mechanical heart valves prosthesis.[6]

Anticoagulation with warfarin is quite challenging due to the narrow therapeutic index, high half-life value, various food and drug interactions, genetic variations, body mass index, age, adherence, and patient knowledge about oral anticoagulation that can affect its efficacy and safety, requiring rigorous therapeutic monitoring through the International Normalized Ratio (INR) to guide dose adjustment and avoid adverse effects.[7-11] The non-adherence or the lack of knowledge about warfarin treatment is a contributor to poor quality of treatment, which increases the risk of bleeding and thromboembolic events,[11] elevating the costs associated with hospitalizations due to the warfarin adverse events.[12] Additionally, it is highlighted that medication adherence and other health outcomes, such as hospitalization, hospital readmission, and emergency room visit may be influenced by medication regimen complexity, assessed by the Medication Regimen Complexity Index (MRCI).[13]

In this context, health literacy, patient knowledge, and adherence to oral anticoagulation are essential to achieve the desirable therapeutic effect with reduced incidence of adverse drug events.[14-16] Costa et al. (2019) observed that educational interventions can contribute to the effectiveness and safety of oral anticoagulation therapy and improve the understanding and adherence of patients on warfarin treatment, favoring the achievement of better therapeutic results and the prevention of adverse events related to pharmacotherapy.[17] Moreover, the literature has emphasized the need to characterize the factors that influence medication regimen complexity through validated instruments.[6] Thus, the assessment of the mentioned aspects is the initial step towards improving the quality of anticoagulant therapy. However, information about these parameters in clinical practice, especially outside clinical trials, is still scarce. Therefore, our aim was to assess health literacy, patient knowledge, and adherence to oral anticoagulation with warfarin, as well as the medication regimen complexity in primary health units in the municipality of Divinópolis, Minas Gerais.

Methods

This cross-sectional study is part of the investigation named Anticoagula Divinópolis Project, a quasi-experimental study which intends to implement a computerized decision support system to assist anticoagulation control in primary care in Divinópolis, Minas Gerais, Southeast Brazil. This city has an estimated population of 242,505 inhabitants.[18] Primary care in Divinópolis is organized in 43 primary care units. There were no protocols defined for monitoring patients on anticoagulant therapy in the city. Patients on warfarin were frequently referred for secondary care or sought service in the private system. The present study focused on baseline assessment for the Anticoagula Divinópolis Project.

Study patients and procedures

Primary care facilities which had more than 2 patients on anticoagulation control were included in this study. All patients aged 18 years or older on oral anticoagulation with warfarin being monitored at those facilities were eligible. They were recruited from May 1, 2018 to February 28, 2020 and identified through an active search in the waiting rooms at the primary care centers. Prescriptions were dispensed at the municipal district's health units, and INR results were obtained in the public system.

Data collection was performed by trained pharmacists who were members of the study team. These professionals were properly trained to apply validated tests and review the medical records. The study included patients who met the eligibility criteria, agreed to participate in the study, and signed the informed consent form.

The following validated tests were applied: (i) oral anticoagulation knowledge (OAK), to assess the knowledge of patients using warfarin regarding oral anticoagulation therapy;[19] (ii) adapted Measure of Adherence to Treatment (MAT-adapted) to oral anticoagulation, an instrument designed to measure patient adherence to oral anticoagulation therapy with warfarin;[20] (iii) Short Assessment of Health Literacy for Portuguese-Speaking Adults (SAHLPA-18), which aims to assess the ability to pronounce and understand common medical terms, thus verifying the level of health literacy;[21] and (iv) MRCI.[22] This instrument is capable of measuring the complexity of pharmacotherapy from the analysis of prescriptions, taking into consideration aspects such as the number of prescribed drugs, dosage forms, dose frequency, and instructions on necessary care during administration.[22]

Data from 6 months prior to patient recruitment up to February 2020 were collected from paper and electronic medical records. The charts were reviewed to obtain information about clinical data, medications

in use, and information on anticoagulation treatment (indication for anticoagulation, therapeutic target, INR results, and hemorrhagic risk). To obtain information on thromboembolic risk and hemorrhagic risk, we planned to collect data related to CHA_2DS_2-VASc and HAS-BLED scores.[23] However, given the absence of data on these scores, we performed the estimation of the bleeding risk based on the following risk factors present on the medical records: hypertension, abnormal renal/liver function, stroke history, age > 65 years, and alcohol use.[23]

Statistical analysis

Categorical variables were reported as counts and percentages; continuous variables were reported as mean and standard deviation (SD) or median with interquartile range (IQR), as appropriate. The Kolmogorov-Smirnov test was applied to verify data normality.

Regarding the test scales applied to the patients under study, the SAHLPA-18 score ranges from 0 to 50, and inadequate health literacy is characterized as fewer than 15 correct answers. The OAK score ranges from 0 to 20, and insufficient knowledge is considered as fewer than 15 points (75%). The MAT-adapted score ranges from 1 to 6. Values 5 and 6 are computed as 1, meaning the patient is adhering to the treatment. On the other hand, values from 1 to 4 are computed as 0, indicating non-adherent patients. The MRCI is based on the analysis of drug prescriptions, and the cut-off for high complexity pharmacotherapy is equal to or greater than 13.5.[24]

Additionally, time in therapeutic range (TTR) was calculated using the Rosendaal method,[25] based on all INRs available from each patient from January 1, 2018 to March 15, 2020. TTR was used as a parameter to investigate anticoagulation control. Follow-up time was determined by the interval between the first recorded INR value (or the date of recruitment of the patient into the study, in cases of absence of an INR value or consultation record with anticoagulation information) and the end of the collection period of INR data (March 15, 2020), except for patients who died, who were permanently suspended from warfarin, or who dropped out of the study.

Patients were stratified according to TTR (TTR < 60% and TTR ≥ 60%), and proportions were compared using Fisher's exact test. Results were considered statistically significant at a significance level of $p < 0.050$. IBM SPSS statistics software for Windows, version 20.0 (2011 release; IBM Corporation, Armonk, NY, USA) was used for statistical analyses.

Ethics approval

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE 86822518.0.0000.5149), and it was conducted in accordance with the Helsinki Declaration. All participants provided written informed consent for their participation in the study.

Results

Overall, 188 patients were eligible for the study. Of these, 26 died before recruitment, and 162 were included in the analysis (mean age 64.8 ± 12.7 years old, 55.6% women) (Table 1).

The median time of warfarin use by study patients was 4.2 (IQR 2.2 to 8.7) years. The main indications for oral anticoagulation with warfarin were nonvalvular atrial fibrillation (26.5%) and venous thromboembolism (24.1%). In 13.6% of the patients, the reason for anticoagulation was not registered. Most patients showed moderate hemorrhagic risk (68.5%). The median of INR values was 4.0 (IQR 1.0 to 8.0) per patient. The mean TTR was 44.0% (SD 28.7%), determined with data from 117 patients. Table 2 shows the other clinical characteristics.

SAHLPA-18 results indicated that 67.9% of patients had fewer than 15 correct answers. Analysis of OAK demonstrated that 88.3% had less than 75% of correct answers. The MAT-adapted indicated that 16.7% presented non-adherence to warfarin therapy. There was no significant association when comparing the variables of interest between groups with different TTR ranges (Table 3). Additionally, it was possible to evaluate the MRCI of 151 patients, obtaining a median of 15.0 (IQR 10.0 to 19.0) points, which denotes high complexity in the medication.

The median follow-up time of the 162 patients was 16.5 (IQR 10.9 to 21.0) months. After recruitment up to March 2020, there were 16 (9.8%) deaths due to non-traumatic causes, 4 of them possibly related to anticoagulation (2 with hemorrhage and 2 with thromboembolism), and 10 patients withdrew from participating (1.9%) or had anticoagulation permanently suspended (4.3%).

Discussion

This study provides the profile of patients on oral anticoagulation with warfarin in primary health units in Minas Gerais. As expected, atrial fibrillation and venous

Table 1 – Sociodemographic characteristics of included patients (n = 162)

Characteristics	N (%)
Age (years, on recruitment), (mean ± SD)	64.8 ± 12.7
≥ 65 years	87 (53.7)
Female	90 (55.6)
Family income	
Up to 1 minimum wage*	88 (54.3)
1 to 2 minimum wages*	26 (16)
2 to 4 minimum wages*	9 (5.6)
4 to 10 minimum wages*	1 (0.6)
No income	19 (11.7)
No information	19 (11.7)
Education	
Illiterate	18 (11.1)
Complete elementary school (8 years)	12 (7.4)
Incomplete elementary school (1-8 years)	85 (52.5)
Complete high school	15 (9.3)
Incomplete high school	7 (4.3)
Complete higher education	5 (3.1)
Incomplete higher education	5 (3.1)
No information	15 (9.3)

*SD: standard deviation. Values shown are n (%) unless otherwise noted. *Minimum wage: BRL 998.00 (2019), which corresponded at that time to USD 257.88.*[48,49]

thromboembolism were the most frequent indications for anticoagulation. Lack of essential clinical information was identified in the medical records, such as indication for anticoagulation, therapeutic target, or even INR results and patient care plan. SAHLPA-18 indicated inadequate health literacy in 67.9% of the patients; OAK results suggested that 88.3% showed insufficient knowledge regarding anticoagulant therapy, and MAT-adapted indicated that 16.7% presented non-adherence to warfarin therapy. There was no significant association of these parameters in relation to TTR. MRCI showed high pharmacotherapy complexity between the drug prescriptions.

Evidence demonstrates that health literacy is essential for improving health outcomes. Inadequate health literacy is clearly associated with an increased number of emergency visits, hospitalizations, and mortality.[26] Thus, as proper conditions for health literacy are ensured, patients become able to manage their own health status.[27] Observational studies carried out in Spain and the United States indicate that a higher level of health literacy results in better anticoagulation control.[28,29] Martins et al. (2017) and Bartolazzi et al. (2021) demonstrated high prevalence of inadequate health literacy in Brazilian patients on warfarin therapy after application of SAHLPA-18 (72.3% and 79.0%, respectively), corroborating our findings.[30,31]

Another determining factor for anticoagulation control is the patient's knowledge of warfarin therapy. More than 88.0% of the patients enrolled in the study had insufficient OAK. This is not an uncommon finding in the literature, since other investigations related to oral anticoagulation showed that 68.1% to 85.1% of patients had insufficient knowledge about the therapy.[32,33] In this regard, it is notable that the lack of understanding of the treatment may compromise the safe and effective use of warfarin, mainly due to its narrow therapeutic index.[23]

It should be noted that low health literacy was a decisive factor for our results of insufficient knowledge about oral anticoagulation. Fang et al. (2006), Oramasionwu et al. (2014), and Rolls et al. (2017) demonstrated that patients with inadequate health literacy were less likely to correctly answer warfarin-related knowledge questions.[29,34,35] In addition, 52.5% of study patients reported fewer than 8 years of schooling, and 11.1% were illiterate, which also contributed to the results obtained in the OAK. In general, patients are unaware of the reason for warfarin indication, the management of missed doses, food and drug interactions, and the possible consequences related to hypo- or hypercoagulation.[36] Therefore, the implementation of health education programs is fundamental to optimize the therapeutic results of oral anticoagulation with warfarin, especially in places with lower levels of education.

It is essential to understand the reasons for treatment, since a well-informed patient, who is included in medical decisions, responds better to treatment.[37,38] Based on the experience obtained during the development of the study in the primary health units of Divinópolis, it is possible to affirm that education strategies aimed at training patients and the health team would be able to improve the doctor-patient relationship through shared decision-making processes and, thus, optimize anticoagulation control.[39] In the Brazilian Unified Health System (SUS), primary care

Table 2 – Clinical characteristics of included patients (n = 162)

Characteristics	N (%)
Comorbidities	
Systemic arterial hypertension	118 (72.8)
Dyslipidemia	65 (40.1)
Diabetes mellitus	40 (24.7)
Hypothyroidism	29 (17.9)
Systolic heart failure	28 (17.3)
Hematological disease	5 (3.1)
Hyperthyroidism	3 (1.9)
Coronary artery disease	2 (1.2)
Liver disease	2 (1.2)
Neurological disease	2 (1.2)
Kidney disease	2 (1.2)
Peripheral arterial disease	1 (0.6)
Active neoplasm	1 (0.6)
Main indication for anticoagulation	
Non-valvular atrial fibrillation/flutter	43 (26.5)
Venous thromboembolism	39 (24.1)
Mechanical valve prosthesis	30 (18.5)
Valvular atrial fibrillation/flutter	14 (8.6)
Acute myocardial infarction	4 (2.5)
Ischemic stroke	3 (1.9)
Pulmonary hypertension	3 (1.9)
Valvulopathy	2 (1.2)
Biological valve prosthesis	1 (0.6)
Antiphospholipid antibody syndrome	1 (0.6)
Unidentified	22 (13.6)
INR therapeutic target	
2.0 to 3.0	132 (81.5)
2.5 to 3.5	20 (12.3)
Others†	5 (3.1)
Not registered	5 (3.1)
Bleeding risk‡	
High	15 (9.3)
Moderate	111 (68.5)
Low	36 (22.2)

INR: international normalized ratio. † Other therapeutic targets for INR were: 2.0 to 3.5 (n = 2), 2.5 to 3.0 (n = 2), and 3.0 to 4.0 (n = 1). ‡ The risk may be underestimated due to the lack of information about the presence/absence of risk factors for the HAS-BLED score in the medical records of the included patients.

is responsible for the management of chronic conditions, non-complex acute cases, prevention, and health promotion. That said, primary care is fully capable of managing patients using oral anticoagulants, but it is necessary to establish communication with an explicit system responsible for both care and individualized knowledge of the case, along with continuing education. The present study points to the urgent need for continuing education of physicians, nurses, and pharmacists to avoid worse results in clinical practice than those observed in clinical trials of oral anticoagulants.

Although the study patients scored low on the SAHLPA-18 and the OAK, the results of the MAT-adapted surprisingly suggest a high percentage of treatment adherence (83.3%). Adherence to warfarin treatment is a very important factor for anticoagulation control; however, this has not been demonstrated by comparing different TTR ranges. As such high adherence is not usually related to low levels of education and health literacy as well as poor socioeconomic conditions, it is possible that the accuracy of the test to detect actual adherence to warfarin treatment has significant limitations. In this sense, the self-reported questionnaire may have overestimated adherence, since a single positive answer from the patient qualifies as adherence to the treatment.[40] A possible explanation for these results is the social desirability, which leads patients to provide desirable answers, even if they are not true, to avoid a critical response from the health professional. It is also plausible that the results were affected by the Hawthorne effect, a phenomenon in which patients aware of their participation in a study actively change their behavior towards positive results.[41] Therefore, future studies may use at least two measures of adherence, such as pill count and self-reported adherence questionnaire to ensure a more realistic result.[42]

Regarding anticoagulation control, a highly reliable method for estimating the stability of warfarin therapy

Table 3 – Health literacy, patient knowledge, and adherence to warfarin therapy stratified by TTR range

Variables	Total (n = 162)	TTR < 60% (n = 82)*	TTR ≥ 60% (n = 35)*	p-value†
SAHLPA-18 (< 15, inadequate)	110 (67.9)	59 (72.0)	23 (65.7)	0.515
OAK (< 75%, inadequate knowledge)	143 (88.3%)	72 (87.8%)	32 (91.4%)	0.752
MAT (1 to 4, non-adherence)	27 (16.7%)	17 (20.7%)	6 (17.1%)	0.789

*MAT: Measure of Adherence to Treatment; OAK: Oral Anticoagulation Knowledge; SAHLPA-18: Short Assessment of Health Literacy for Portuguese-Speaking Adults; TTR: time in therapeutic range. † Comparison of groups stratified by TTR using Fisher's exact test. * As TTR requires at least 2 INR measures to be calculated, it was only possible to be obtained in 117 patients.*

over time is the TTR. The TTR is a measure of the quality of anticoagulation with warfarin that represents the time (in percentage) in which the INR remains within the desirable range.[43] We observed that the TTR value was 16.0% below the recommended minimum, resulting in increased risk of thromboembolic and bleeding events. However, given the precariousness of anticoagulation management in the city, we believe the actual results may be even worse than the data presented in this study. Due to the low frequency of patients in consultations, the number of INR measurements was reduced and the interval between these measurements was greater than recommended. Therefore, these factors may have led to an overestimation of the TTR. In addition, the TTR results were not determined based on the total sample (n = 162), as 28 patients had no recorded INR values, and 17 had only one recorded INR value. Therefore, it was not possible to perform TTR calculation for these 45 patients. Although our results showed no significant association when comparing different TTR ranges with inadequate health literacy and insufficient knowledge about oral anticoagulation, we believe these parameters had an influence on the low TTR value observed.

Another significant point to be considered is the high complexity of the pharmacotherapy observed through the MRCI. Warfarin is known for its high dose-response rate variability, especially when given in combination with certain medications. In their meta-analysis, Wang et al. (2021) demonstrated a clinically relevant increase in the risk of bleeding with the concomitant administration of warfarin with drugs belonging to the most diverse therapeutic classes, such as non-steroidal anti-inflammatory drugs (OR = 1.83; 95% CI 1.29 to 2 .59), antimicrobials (OR = 1.63; 95% CI 1.45 to 1.83), selective serotonin reuptake inhibitors (OR = 1.62; 95% CI 1.42 to 1.85), antiplatelet drugs (OR = 1.74; 95% CI 1.56 to 1.94), loop diuretics (OR = 1.92; 95% CI 1.29 to 2.86), among others.[44] Additionally, we can infer that a high complexity of pharmacotherapy combined with low health literacy contributes to a decrease in adherence, although this parameter was not adequately detected in the study due to the low accuracy of the MAT questionnaire. According to Alves-Conceição et al. (2018), the high complexity of pharmacotherapy can result in outcomes such as hospitalization and even hospital readmission. Therefore, the high complexity of pharmacotherapy generates great concern, since its consequences may be related to at least 4 deaths observed during the study period.[13]

Regarding limitations of the present study, we could not access the causes of death to verify which ones were related to anticoagulation. Another important limitation refers to the lack of relevant information in the medical records. For a considerable percentage of patients (13.6%), the reason for anticoagulation and the planned duration of anticoagulation required were not recorded, and the patients were not aware of them. As for some indications that anticoagulation may be discontinued, the possibility that a number of these patients will not need to continue taking anticoagulants is a cause for concern. The absence of CHA_2DS_2-VASc and HAS-BLED scores in medical records was also alarming. This is definitely a point for improvement, which may be related to weaknesses linked to the organization of the health system. We tried to raise some hypotheses about the lack of adequate follow-up of patients using warfarin: high turnover of professionals and lack of basic training in anticoagulation control, deficit of knowledge and organization of the work process, lack of local oral anticoagulation protocol in the municipality, and lack of opportunities for continuing education.

We believe that the reality observed in Divinópolis applies to other Brazilian cities, as well as other low- and middle-income countries. The present study highlights a social problem that can be addressed by future intervention studies and competent authorities. Despite the decreasing popularity of warfarin with evidence of non-inferiority or superiority of efficacy compared to DOACs, with decreased bleeding rates,[45] it is important to highlight that our findings are also important for DOACs in clinical practice. Although this study focused on patients using warfarin, we believe that a similar scenario can also be observed in primary care patients using DOACs, mainly in low- and middle-income countries. Taking into consideration that there is no method to monitor the anticoagulant effect of DOACs[46] and the lack of monitoring is, in fact, a great advantage of these drugs, the detection of drug non-adherence can be impaired. In addition, the impact of missing doses is greater than that of warfarin, due to the shorter half-life of these drugs.[47] Therefore, knowledge of the patient's profile is also extremely important for successful treatment with these drugs.

Conclusion

This study demonstrated remarkably low health literacy and insufficient knowledge about warfarin therapy in a vulnerable population assisted by primary care. The lack of essential information in medical records related to indication of anticoagulation, time required, and thromboembolic and hemorrhagic risk is alarming. These data have great importance to the decision-making process and are essential for developing strategies regarding improvement of the management of patients who are taking anticoagulants. To summarize, since warfarin presents complex drug and food interactions, its use requires special attention from both patients and the health care system.

Disclosures

None.

Role of the funder/sponsor

The sponsors had no role in study design; data collection, management, analysis, and interpretation; writing the manuscript; and decision to submit it for publication. MSM had full access to all the data in the study and had responsibility for the decision to submit for publication.

Transparency declaration

The lead authors (MSM and ALR) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Author Contributions

Conception and design of the research: Marcolino MS, Oliveira JAQ, Martins MAP, Ribeiro ALP; acquisition of data: Marcolino MS, Oliveira JAQ, Martins MAP, Sales TLS; analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Marcolino MS, Oliveira JAQ, Rios DRA, Pedroso TM, De Sá LC, Martins MAP, Sales TLS, Ribeiro ALP; statistical analysis: Marcolino MS, Sales TLS; obtaining financing: Marcolino MS; writing of the manuscript: Marcolino MS, Rios DRA, Pedroso TM, De Sá LC, Sales TLS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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