Int J Cardiovasc Sci. 2024; 37:e20230172

ORIGINAL ARTICLE

Factors Associated with Variation in Time in Therapeutic Range in Two Anticoagulation Clinics in Brazil

Josiane Moreira da Costa,[1] Milena S. Marcolino,[2] Carla Jorge Machado,[2] Leandro Pinheiro Cintra,[3] Izabella Fernanda Bastos Siqueira,[3] Daniel Dias Ribeiro,[2] Maria Auxiliadora Parreiras Martins[2]

Universidade Federal dos Vales do Jequitinhonha e Mucuri,[1] Diamantina, MG – Brazil
Universidade Federal de Minas Gerais,[2] Belo Horizonte, MG – Brazil
UNIFENAS,[3] Belo Horizonte, MG – Brazil

Abstract

Background: Time in therapeutic range (TTR) plays an important role in the effectiveness of anticoagulant therapy with vitamin K antagonists.

Objective: To identify factors associated with variation in TTR.

Methods: The study sites were anticoagulation clinics at two university hospitals in Minas Gerais, with a total of 1357 patients studied. TTR was calculated using the Rosendaal method. Binary logistic regressions were carried out with the study variables, followed by multiple regression with those that were significant for the model, adopting a significance level of 5%.

Results: The outpatient clinics presented different values in mean TTR; one corresponded to the expected percentage, while the other did not. Multiple regression identified the variable male sex as a protective factor in relation to TTR < 60% (odds ratio [OR]: 0.42; p = 0).

Conclusion: The identification of variables associated with inadequate TTR contributes to identifying weaknesses in the care process and implementing improvement actions in the hospitals studied.

Keywords: Anticoagulants; Warfarin; Heart Diseases

Introduction

Warfarin is the oral anticoagulant that is most widely distributed by the Unified Health System (SUS, acronym in Portuguese) in Brazil, and it is still widely used worldwide.[1] Different subgroups of patients can benefit from the use of this medication, particularly individuals with heart disease with atrial fibrillation (AF)[2] and/or mechanical valve prosthesis,[3] Chagas disease,[4] and rheumatic mitral valve diseases, as well as non-cardiac patients with indication for anticoagulation, respecting specificities and individualities.[3]

As warfarin has a narrow therapeutic range and interacts with medications and foods, its use must be monitored. This medication can cause undesirable events, such as hemorrhagic transformation associated with stroke,[5,6] which increases when patients use the medication incorrectly. It is recommended to use with caution, especially in individuals with low socioeconomic and cultural conditions.[6]

Monitoring of warfarin treatment is carried out using the international normalized ratio (INR),[3,7] a test calculated based on prothrombin activity. The therapeutic range for most indications recommends target INR between 2.00 and 3.00, and the clinical response to treatment and the assessment of coagulation stability are also influenced by drug interactions, patient genetic variability, interaction with diet, and associated comorbidities.[2,8] When the

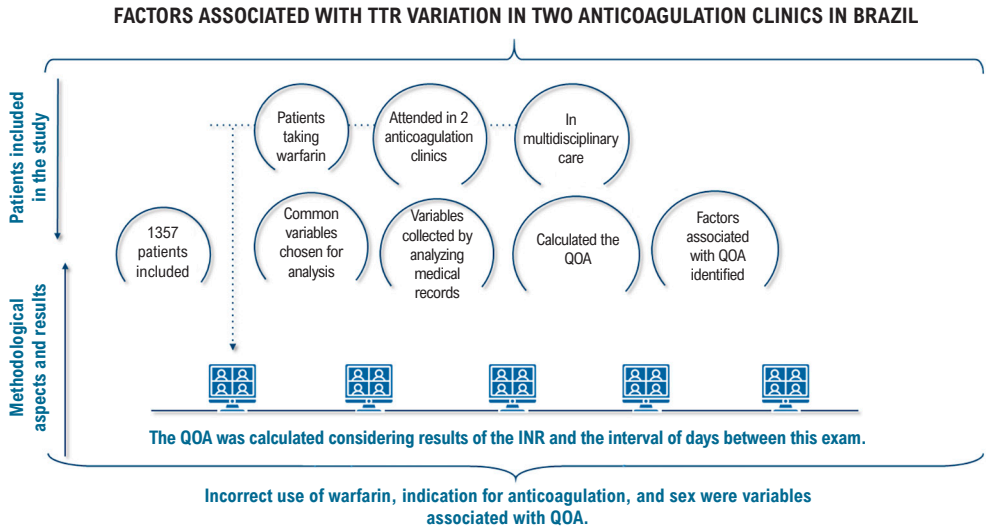
Mailing Address: Leandro Pinheiro Cintra
UNIFENAS, Campus de Belo Horizonte. Rua João Luiz, 60/601. Postal code: 31275-160. Belo Horizonte, MG – Brazil
E-mail: Lpcintra@gmail.com
Editor responsible for the review: Glaucia Maria Moraes de Oliveira

DOI: https://doi.org/10.36660/ijcs.20230172

Manuscript received November 8, 2023; revised manuscript May 6, 2024; accepted May 23, 2024.

Central Illustration: Factors Associated with Variation in Time in Therapeutic Range in Two Anticoagulation Clinics in Brazil

INTERNATIONAL JOURNAL OF Cardiovascular SCIENCES



Int J Cardiovasc Sci. 2024; 37:e20230172

INR is below 2.00, the benefits resulting from the use of the medication may be compromised, for example, preventing the occurrence of ischemic stroke, whereas INR above 3.00 is associated with hemorrhagic events.[9] These characteristics are challenges for the safety of this pharmacotherapy, making adherence to therapy a necessary condition to improve the effectiveness of the treatment.[10]

The assessment of the quality of oral anticoagulation control can be carried out by calculating the time in therapeutic range (TTR), which identifies the proportion of time in which the INR results of a given patient remained in the target therapeutic range.[9,11] The TTR is calculated from a linear interpolation of a historical series of INR results and can be used as a method for estimating the quality of anticoagulation in health systems.[12]

It is recommended that the TTR value be above 60% in order for anticoagulant therapy to be superior to isolated therapy with antiplatelet agents.[9] Mean TTR values below 60% suggest the need to implement strategies that encourage adherence, understanding, and other actions related to rational use for groups of patients who present TTR values below expectations.[9] By recognizing the importance of TTR for the effectiveness of anticoagulant therapy with warfarin, the present study aimed to identify factors associated with TTR variation.

Materials and Methods

Description of the study sites

The study sites were anticoagulation clinics at two university hospitals in Belo Horizonte, Minas Gerais, referred to in this study as hospital 1 (H1) and hospital 2 (H2). These outpatient clinics are references for the SUS in the region, providing care to outpatients who require periodic control to manage oral anticoagulation with warfarin.

Patients using warfarin, discharged from these institutions and referred by the health care network, have been regularly monitored, according to their individual needs, since 2009 in H1 and since 2010 in H2. Laboratory tests are carried out predominantly in the Functional Unit of Pathology and Laboratory Medicine at H1 and in the laboratory at H2, for patients treated at the respective institutions. Both anticoagulation clinics are made up of a multidisciplinary team, and the interval between consultations varies between 7, 14, 21, 28, or more than 28 days, depending on the results of the INR exam. Both clinics dispense warfarin in oral pharmaceutical form, with a concentration of 5 mg of the active ingredient.

Participant recruitment and data collection

Medical records of all patients monitored at the anticoagulation clinics between August and December 2017 were included in the study.

To recruit participants, a computerized report was generated at the H2 outpatient clinic, and medical records were consulted at the H1 outpatient clinic to identify all patients treated at the outpatient clinics during the study period. Data were collected from medical records of consultations carried out between August and December 2017. Data collection and standardization took place between January and April 2018.

Specification of variables

The variables that were common in the medical records of both outpatient clinics were identified, namely: age; sex; municipality of residence (considering that the anticoagulation clinics serve patients living in the metropolitan region of Belo Horizonte and in cities in the countryside of Minas Gerais; indication for anticoagulation (considering valvular or non-valvular AF, idiopathic stroke, thromboembolism, metallic prosthesis, and others); specification of the outpatient clinic (H1 or H2) INR value (considering the record of the INR test performed at each outpatient visit); record of incorrect use of warfarin; and changes in other medications in use. Data relating to the last three variables were obtained from patients' reports during consultations.

TTR calculation

With the records of the INR exams performed during the period, the adjusted TTR was calculated for all patients. TTR was calculated using the Rosendaal method, which consists of the relationship between the number of days for which the INR was in the therapeutic range in relation to the total number of days observed in the period.[13] For this purpose, a specific electronic instrument available at www.inrpro.com was used, including the INR results recorded in the services.

Data analysis

After calculating the TTR, patients were classified as adequate TTR (above 60%) and inadequate (below 60%). A description of the TTR, INR, and age variables was carried out using means, standard deviation, and 95% confidence intervals (CI). Categorical variables were described using absolute and relative frequencies. Student's t test for independent samples was used to analyze whether the means were different from each other. Secondly, for categorical, binary variables with two response categories, Pearson's chi-square tests were performed. The significance level adopted in the statistical analysis was 5%. The statistical test used to verify the normality of the data was the Shapiro-Wilk Test.

Binary logistic regressions were carried out with the study variables, followed by multiple regression with those that were significant for the model. Odds ratios (ORs) were obtained for the chance of TTR being less than 60% (inadequate), and p values and 95% CI were reported.

Ethical aspects

The study was conducted in accordance with the terms of Resolution 466/2012 of the National Health Council, and the project was submitted for consideration by the Ethics Committee of the Federal University of Minas Gerais (UFMG, acronym in Portuguese), receiving the substantiated opinion number 2,018,850, with its own financing. As data were collected from medical records of the services, which also involved the collection of data from patients who were not being monitored by the services at the time of collection, this survey did not include the signing of an informed consent form.

The present study is an excerpt from a clinical trial entitled "Evaluation of the implementation of an educational intervention for patients with ineffectiveness of oral anticoagulation with warfarin treated at a university hospital: controlled clinical trial," registered in the Brazilian Registry of Clinical Trials (REBEC, acronym in Portuguese), under codes RBR- 9cy6py and UTN U1111-1217-0151. It is noteworthy that the patients included in the clinical trial signed an informed consent form.

Results

During the study period, 889 patients from the H2 outpatient clinic were identified with a mean age of 61 years, and 482 of them were female (54%). In the H1 outpatient clinic, 468 patients were identified with a mean age of 60 years, and 270 of them were female (58%). Specification of the mean TTR and INR values in relation to the total number of monitored patients treated in the period (1,357) are displayed in Table 1, and the characterization of patients with low TTR is displayed in Table 2.

Table 1 – Characterization of patients in relation to TTR and INR.

Variable specification	H1			H2			
	Mean	Standard deviation	CI	Mean	Standard deviation	CI	P value
TTR	62.60	27.90	60.0 - 55.20	57.5	33.46	55.23 - 59.70	<0.001
INR	2.60	0.90	2.6 - 2.70	2.5	1.08	2.45 - 2.52	<0.001

H1: university hospital 1; H2: university hospital 2; INR: international normalized ratio; TTR: time in therapeutic range. Source: Prepared by the authors; CI: confidence interval.

Table 2 – Characterization of patients with inadequate TTR in the hospitals under study.

Variable specification	H1	H2	Inadequate total TTR N(%)	Percentage in relation to the total number of patients monitored (N = 1357)
	N (%)	N (%)		
Female	139 (36.58)	241 (63.42)	380 (100.00)	28.00
Male	62 (23.66)	200 (76.34)	262 (100.00)	46.13
Residents in Belo Horizonte	113 (23.54)	367 (76.46)	480 (100.00)	35.37
Residents in the countryside of Minas Gerais	10 (76.92)	3 (23.08)	13 (100.00)	0.86
Residents in the metropolitan region	67 (48.55)	71 (51.45)	138 (100.00)	10,17
Report of incorrect use of warfarin	17 (58.62)	12 (41.38)	29 (100.00)	2.14
Changes in other medications in use	26 (65.00)	14 (35.00)	40 (100.00)	2.94
Change in eating habits	14 (40.00)	21 (60.00)	35 (100.00)	2.57
Indication for anticoagulation				
Idiopathic stroke	22(48.89)	23 (51.11)	45 (100.00)	3.32
Valvular AF	36 (66.67)	18 (33.33)	54 (100.00)	3.98
Non-valvular AF/flutter	58 (18.77)	251 (81.23)	309 (100.00)	22.77
Metal prosthesis	36 (65.45)	19 (34.55)	55 (100.00)	4.05
Thromboembolism	2 (1.77)	111 (98.23)	113 (100.00)	8.32
Others	4 (18.18)	18 (81.82)	22 (100.00)	1.62

AF: atrial fibrillation; H1: university hospital 1; H2: university hospital 2; TTR: time in therapeutic range.

In binary logistic regression, incorrect use of warfarin, indication for anticoagulation, and changes in eating habits were associated with inadequate TTR, as seen in Table 3.

In the multiple regression, as shown in Table 4, male sex was presented as a protective factor against inadequate TTR, while incorrect use of warfarin was associated with a 3.5 times greater chance of inadequate TTR; and indication for anticoagulation (higher chance of TTR unsuitable for patients with idiopathic stroke and anticoagulation indication due to other reasons). The Central Illustration represents the article's main results.

Discussion

Anticoagulation clinics, which are generally multidisciplinary, monitor patients using warfarin, measure the INR, and adjust the dose of the medication.

Table 3 – Binary logistic regression considering the total number of patients treated.

Variable specification	Reference variable	OR	CI	P value
Male	Female	0.89	0.71 - 1.11	0.30
Age over 60	Less than 60	1.05	0.71 - 1.53	0.82
Incorrect use of warfarin	Correct use	2.81	1.42 - 5.56	0.03
Change in other medications being used	No changes	0.89	0.56 - 1.40	0.61
H2 anticoagulation site	H1	6.4	0.23 - 175.44	0.27
Indication for anticoagulation due to valvular AF + non-valvular AF/flutter	Stroke	1.70	1.12 - 2.54	0.01
Indication for anticoagulation due to metallic prosthesis	Stroke	1.44	0.84 - 2.45	0.19
Indication for anticoagulation due to thromboembolism	Stroke	1.27	0.81 - 2.01	0.30
Indication for anticoagulation - others	Stroke	0.98	0.51 - 1.89	0.95
Change in eating habits	No change	1.85	1.06 - 3.25	0.03

AF: atrial fibrillation; H1: university hospital 1; H2: university hospital 2; OR: odds ratio; TTR: time in therapeutic range. Source: Prepared by the authors; CI: confidence interval.

Table 4 – Multiple logistic regression considering the total number of patients treated.

Variable specification	Reference variable	OR	CI	P value
Male	Women	0.42	0.26 - 0.68	0.00
Age over 60 years	Less than 60	1.08	0.67 - 1.76	0.74
Resident in the metropolitan region of Belo Horizonte	Resident in BH	0.89	0.55 - 1.46	0.66
Resident in the countryside of Minas Gerais	Resident in BH	0.64	0.24 - 1.75	0.39
Incorrect use of warfarin	Correct use	3.55	1.31 - 9.63	0.01
Change in other medications being used	No changes	0.67	0.35 - 1.29	0.23
Change in eating habits	No change	1.45	0.57 - 3.71	0.44
Indication for anticoagulation due to idiopathic stroke	AF	0.65	0.34 - 1.25	0.19
Indication for anticoagulation using a metal prosthesis	AF	1.01	0.55 - 1.88	0.97
Indication for anticoagulation due to thromboembolism	Stroke	0.38	0.08 - 1.86	0.23
Indication for anticoagulation - others	Stroke	0.28	0.10 - 0.86	0.03
Change in eating habits	No change	1.45	0.57 - 3.71	0.44

AF: atrial fibrillation; BH: Belo Horizonte; OR: odds ratio. Source: Prepared by the authors; CI: confidence interval.

The mean TTR identified at the H2 clinic was below the minimum percentage recommended, which indicates the need to implement strategies that improve the care process. A multicenter study with outpatients undergoing oral anticoagulation control identified that the implementation of anticoagulation clinics contributed to better care for patients using this medication.[14,15] Another study identified that patients treated at anticoagulation reference centers tend to present better treatment results.[16]

Therefore, the identification of a mean TTR value that was lower than expected at the H2 outpatient clinic suggests an underutilization of this clinic's potential. Furthermore, this value encourages the identification of the mean TTR of patients monitored in medical clinics and basic health units, where professionals are considered less prepared to manage warfarin pharmacotherapy, with less infrastructure for the monitoring this patient profile.

Although mean TTR values lower than the desired percentages have been identified in developing countries, as a consequence of different access to health services and cultural and educational disparities that influence treatment,[2,17] the mean TTR at the H1 outpatient clinic was above this value. This indicates that mean TTR at percentages considered desirable is achievable in these countries. A large variation in INR control, measured by TTR, has been identified between different countries, with a population mean model predicting that a TTR of 60% would be necessary for patients to benefit from anticoagulant therapy.[9]

However, despite the benefits of specialized clinics in the control of oral anticoagulation, complicating factors, such as limited time for care, language barriers, advanced age, low educational level, and cognitive difficulties presented by some patients,[2,6] suggest the need for additional educational strategies that consider the specificities and individualities of patients.[18,19] Better understanding the specificities of clinical patients could contribute to a better quality of care offered.

A study involving a multiple logistic regression model showed that a 10% increase in the time outside the INR range was associated with an increased risk of mortality (OR: 1.29; $p = 0.001$), occurrence of stroke (OR: 1.10; $p = 0.006$), and other thromboembolic events (OR: 1.12; $p < 0.001$). The hospitalization rate in the study population was also higher when the INR was outside the target range. This emphasizes the association between suboptimal anticoagulation and undesirable clinical outcomes.[9]

Although the difference between the mean TTR of the clinics showed a statistically significant difference in the descriptive calculations, the anticoagulation clinic was not associated with inadequate TTR in the binary and multiple regressions. It is noteworthy that the present study is based on a real-world context, and although the mean TTR values in the two groups are close to lower TTR threshold, the mean value of 33.46% at H2 in relation to 62.60% at H1 suggests the potential benefits for H1 patients in maintaining the INR within the target therapeutic range for a longer period of time. Furthermore, it suggests that other factors were greater determinants of inadequate TTR than the clinic itself; that is, patient characteristics were more important.

Multiple regression identified that the variable male sex was a protective factor in relation to TTR < 60% (OR: 0.42; 95% CI: 0.26 to 0.68). A multicenter study that considered the global impact of geographic regions on TTR also identified a lower mean TTR value for women when compared to men (women: 53.3 ± 21.3; men: 56.4 ± 21.2; $p < 0.001$).[20] This result points to a greater need to identify possible differences and understand how to carry out treatment between male and female patients, in addition to the implementation of measures that contribute to pharmacotherapeutic success in female patients. It is noteworthy that, even with a higher percentage of female patients (58%), the H1 outpatient clinic had a higher mean TTR than that of H2.

The association between incorrect use of warfarin and inadequate TTR was already expected, considering that adherence is a fundamental factor for treatment success. This finding reinforces the need to invest in educational actions that contribute to better knowledge, empowerment, and adherence of patients who use this medication.[21-24]

Regarding the indication for anticoagulation, a greater chance of presenting TTR at lower levels was identified in patients with valvular or non-valvular AF in the binary logistic regression, as well as indication due to other reasons in the multiple regression. No studies were identified that associate variations in TTR with indications for anticoagulation, and additional studies with this focus are recommended.

Although some studies use the measurement of mean INR value to evaluate the quality of anticoagulation, the literature points to the benefits of calculating the TTR for a better projection of achieving the target INR over time.[25]

The present study has the limitation of having collected data from medical records, which restricted the choice of variables analyzed to those common to the outpatient clinics under study. Furthermore, although the results contribute to a better understanding of factors associated with low quality of anticoagulation, the design and sample used do not allow extrapolation of the data.

Conclusion

The present study aimed to identify the factors associated with TTR variation, considering the importance of TTR for the effectiveness of anticoagulant therapy with a vitamin K antagonist. The outpatient clinics presented different values in the mean TTR; one met the expected percentage, while the other did not. The identification of variables associated with inadequate TTR contributes to identifying weaknesses in the care process and implementing improvement actions.

Acknowledgements

National Council for Scientific and Technological Development (CNPq) and Graduate Program in Medications and Pharmaceutical Assistance (PPGMAF) at the Federal University of Minas Gerais (UFMG).

Author Contributions

Conception and design of the research: Costa JM, Marcolino MS, Ribeiro DD, Martins MAP; acquisition of data: Costa JM, Machado CJ; analysis and interpretation of the data: Cintra LP, Costa JM, Machado CJ, Siqueira IFB; statistical analysis: Cintra LP, Costa JM, Machado CJ; writing of the manuscript: Cintra LP, Costa JM, Marcolino MS, Riberio DD, Machado CJ, Siqueira IFB, Martins MAP; critical revision of the manuscript for intellectual content: Cintra LP, Costa JM, Marcolino MS, Ribeiro DD, Siqueira IFB, Martins MAP.

Potential Conflict of Interest

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

Sources of Funding

The project was funded by CAPES with a doctoral scholarship.

Study Association

This article is part of the thesis of Doctoral submitted by Josiane Moreira da Costa, from Programa de Pós-graduação em Medicamentos e Assistência Farmacêutica (PPGMAF) da UFMG.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the UFMG under the protocol number 2.018.850. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study

References

1. Vinereanu D, Lopes RD, Bahit MC, Xavier D, Jiang J, Al-Khalidi HR, et al. A Multifaceted Intervention to Improve Treatment with Oral Anticoagulants in Atrial Fibrillation (IMPACT-AF): An International, Cluster-randomised Trial. Lancet. 2017;390(10104):1737-46. doi: 10.1016/S0140-6736(17)32165-7.
2. Helin TA, Joutsi-Korhonen L, Asmundela H, Niemi M, Orpana A, Lassila R. Warfarin Dose Requirement in Patients Having Severe Thrombosis or Thrombophilia. Br J Clin Pharmacol. 2019;85(8):1684-91. doi: 10.1111/bcp.13948.
3. Paixão LC, Ribeiro ALP, Valacio RA, Teixeira AL. Chagas Disease: Independent Risk Factor for Stroke. Stroke. 2009;40(12):3691-4. doi: 10.1161/STROKEAHA.109.560854.
4. Friberg L, Rosenqvist M. Less Dementia with Oral Anticoagulation in Atrial Fibrillation. Eur Heart J. 2018;39(6):453-60. doi: 10.1093/eurheartj/ehx579.
5. Heinrich K, Sanchez K, Hui C, Talabi K, Perry M, Qin H, et al. Impact of an Electronic Medium Delivery of Warfarin Education in a Low Income, Minority Outpatient Population: A Pilot Intervention Study. BMC Public Health. 2019;19(1):1050. doi: 10.1186/s12889-019-7370-4.
6. Gateman D, Trojnar ME, Agarwal G. Time in Therapeutic Range: Warfarin Anticoagulation for Atrial Fibrillation in a Community-based Practice. Can Fam Physician. 2017;63(10):425-31.
7. Rolls CA, Obamiro KO, Chalmers L, Bereznicki LRE. The Relationship between Knowledge, Health Literacy, and Adherence Among Patients Taking oral Anticoagulants for Stroke Thromboprophylaxis in Atrial Fibrillation. Cardiovasc Ther. 2017;35(6). doi: 10.1111/1755-5922.12304.
8. Silva PGMBE, Sznejder H, Vasconcellos R, Charles GM, Mendonca-Filho HTF, Mardekian J, et al. Anticoagulation Therapy in Patients with Non-valvular Atrial Fibrillation in a Private Setting in Brazil: A Real-World Study. Arq Bras Cardiol. 2020;114(3):457-66. doi: 10.36660/abc.20180076.
9. Zhu X, Xiao X, Wang S, Chen X, Lu G, Li X. Rosendaal Linear Interpolation Method Appraising of Time in Therapeutic Range in Patients with 12-Week Follow-up Interval after Mechanical Heart Valve Replacement. Front Cardiovasc Med. 2022;9:925571. doi: 10.3389/fcvm.2022.925571.
10. Viana CC. Avaliação da qualidade do controle da anticoagulação oral de acordo com o sexo: revisão sistemática e meta-análise. repositorioufmgbr [dissertation]. Belo Horizonte: Faculdade de Farmácia, Universidade Federal de Minas Gerais; 2020.
11. Razouki Z, Ozonoff A, Zhao S, Jasuja GK, Rose AJ. Improving Quality Measurement for Anticoagulation: Adding International Normalized Ratio Variability to Percent Time in Therapeutic Range. Circ Cardiovasc Qual Outcomes. 2014;7(5):664-9. doi: 10.1161/CIRCOUTCOMES.114.000804.
12. Magon A, Arrigoni C, Moia M, Mancini M, Dellafiore F, Manara DF, et al. Determinants of Health-related Quality of Life: A Cross-sectional Investigation in Physician-managed Anticoagulated Patients Using Vitamin K Antagonists. Health Qual Life Outcomes. 2020;18(1):73. doi: 10.1186/s12955-020-01326-y.
13. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A Method to Determine the Optimal Intensity of Oral Anticoagulant Therapy. Thromb Haemost. 1993;69(3):236-9. doi: 10.1055/s-0038-1651587.

14. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of Study Setting on Anticoagulation Control: A Systematic Review and Metaregression. Chest. 2006;129(5):1155-66. doi: 10.1378/chest.129.5.1155.

15. Prochaska JH, Göbel S, Keller K, Coldewey M, Ullmann A, Lamparter H, et al. e-Health-Based Management of Patients Receiving Oral Anticoagulation Therapy: Results from the Observational thrombEVAL Study. J Thromb Haemost. 2017;15(7):1375-85. doi: 10.1111/jth.13727.

16. Dantas RTSOM. Instrumentos para mensurar a adesão à farmacoterapia - uma revisão integrativa [completion of course work]. Campina Grande: Curso de Bacharelado em Farmácia; 2020.

17. Lane DA, Barker RV, Lip GY. Best Practice for Atrial Fibrillation Patient Education. Curr Pharm Des. 2015;21(5):533-43. doi: 10.2174/1381612820666140825125715.

18. Mavri A, Fernandez NO, Kramaric A, Kosmelj K. New Educational Approach for Patients on Warfarin Improves Knowledge and Therapy Control. Wien Klin Wochenschr. 2015;127(11-12):472-6. doi: 10.1007/s00508-015-0713-y.

19. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, et al. Impact of Global Geographic Region on Time in Therapeutic Range on Warfarin Anticoagulant Therapy: Data from the ROCKET AF Clinical Trial. J Am Heart Assoc. 2013;2(1):e000067. doi: 10.1161/JAHA.112.000067.

20. Colet CDF, Amador TA, Heineck I. Acompanhamento farmacoterapêutico de pacientes em uso de varfarina: uma revisão da literatura. Rev Contexto & Saúde. 2017;17(32):134-143.

21. Clarkesmith DE, Pattison HM, Khaing PH, Lane DA. Educational and Behavioural Interventions for Anticoagulant Therapy in Patients with Atrial Fibrillation. Cochrane Database Syst Rev. 2017;4(4):CD008600. doi: 10.1002/14651858.CD008600.pub3.

22. Ferreira TTD, Rabelo JGD, Borges MCF, Cruz LRV, Carvalho AFS, Leite JAC. Cuidados farmacêuticos em uma unidade de terapia intensiva pediátrica: uma revisão integrativa. Reva Cient Saúde. 2021;3(1):9-22.

23. Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, et al. Patient Satisfaction with Direct Oral Anticoagulants and Warfarin. Int Heart J. 2018;59(6):1266-74. doi: 10.1536/ihj.17-649.

24. Oliveira SHDS, Sousa MM, Bezerra SMMDS, Silva T, Gomes KKS, Silva GCCE. Beliefs Related to Diet Adherence of Patients Treated with Oral Anticoagulants. Rev Gaucha Enferm. 2019;40:e20190083. doi: 10.1590/1983-1447.2019.20190083.

25. Nguyen VN, Stevens CA, Brambatti M, Smith M, Braun OO, Mariski M Jr, et al. Improved Time in Therapeutic Range with International Normalized Ratio Remote Monitoring for Patients with Left Ventricular Assist Devices. ASAIO J. 2022;68(3):363-8. doi: 10.1097/MAT.0000000000001489.

This is an open-access article distributed under the terms of the Creative Commons Attribution License