REVISTA O MUNDO DA SAÚDE

Identification of anticoagulation quality in patients using warfarin and associated factors

Lucas de Faria Martins Braga*
Josiane Moreira da Costa*
Carla Jorge Machado*
Maria Auxiliadora Parreiras Martins *

Abstract

Warfarin is an oral anticoagulant widely used in the prevention of thromboembolic events and is made available by the Brazilian Unified Health System. However, maintaining the quality of oral anticoagulation is a challenge in clinical practice, other than the identification of factors that interfere in this important process for the clinical and scientific context. This was a cross-sectional study, conducted at a university hospital in Minas Gerais, with the objective of identifying the quality of oral anticoagulation in patients using warfarin and associated factors. The quality of anticoagulation was assessed using the time in therapeutic range (TTR), which allows the identification of the proportion of time in which the patient presented international normalized ratio (INR) values within the desired therapeutic range. TTR values were associated with clinical and demographic characteristics using univariate and multivariate logistic regression. The mean TTR was 61.8% (SD + 1.00), with 204 (46.3%) patients demonstrating inadequate anticoagulation control. The variables gender (OD: 1.82; P: 0.005; CI: 1.204335-2.761345), use of warfarin other than prescribed (OD: 2.81; P <0.005; CI: 1.700-4.632352) and bleeding occurrence (OD: 1.70; P <0.005; CI: 1.013157-4.632352) were predictors of inadequate TTR. Indications for use, thromboembolism and valvulopathy were predictors of adequate TTR. The findings contribute to a better understanding of the profile of patients with inadequate control of oral anticoagulation and the establishment of strategies that promote anticoagulation quality.

Keywords: Warfarin. Use of medicines. Anticoagulants.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice[1], with population aging and increased life expectancy contributing to the increased prevalence of this health problem[2]. AF is an isolated risk factor for the occurrence of ischemic stroke (CVA – cardiovascular accident)[3], and anticoagulant therapy is indicated as a preventive measure.

The use of vitamin K inhibitors (IVK) has been shown to be effective in reducing the risk of death in this patient profile, especially warfarin, which is a coumarin-derived drug[4]. Despite being effective in the prevention and treatment of thromboembolic events[5], the use of warfarin is associated with risks of complications due to its narrow therapeutic range, great variability in response, and considerable interaction with medications and foods rich in vitamin K[6]. To reduce these

DOI: 10.15343/0104-7809.202145003009

* Universidade Federal de Minas Gerais – UFMG. Belo Horizonte / MG, Brasil.
E-mail: josycostta2@yahoo.com.br

risks, warfarin treatment is monitored using the international normalized ratio (INR)[7], calculated from prothrombin activity.

The evaluation of the quality of control of oral anticoagulation with warfarin can be performed by calculating the time in therapeutic range (TTR), which allows identifying the proportion of time the patient has presented INR values within the desired therapeutic range. The TTR is calculated by the linear interpolation of a historical series of results from the INR[8]. Low TTR values are associated with a higher incidence of thromboembolic and hemorrhagic complications, such as hemorrhagic stroke[9] and suggest the need to implement strategies related to promoting the proper use of warfarin[10].

Anticoagulation clinics (AC), in general with multidisciplinary composition, carry out, among their main activities, the follow-up of patients using warfarin, INR dosage, and medication dose adjustment. Despite research pointing out the contributions of these clinics to the quality of anticoagulation[11], a study carried out in Brazil identified groups of patients followed up in AC who presented TTR below the desired average (<60.0%) exposing them to a greater risk of undesirable events[12]. The authors suggest that mean TTR values below 60% deserve investigation and can contribute to the implementation of strategies that promote better quality of oral anticoagulation[12]. This may be even more important in developing countries, where the use of oral anticoagulants has increased in recent decades[13], in addition to the fact that most patients in these countries have sociocultural specificities that influence the use of warfarin.

The present study aims to identify the quality of oral anticoagulation in patients seen in an AC as well as factors associated with low TTR.

MATERIALS AND METHODS

This is a cross-sectional study, conducted in an AC located in a university hospital in Minas Gerais.

Study location

The clinic under study provides assistance to cardiac patients through specialized monitoring, with a team composed of three doctors (a cardiologist, a clinician, and a hematologist), six pharmacists, a pharmaceutical resident, two pharmacy students, and a nurse. During consultations, the results of the INR exam - performed 48 hours in advance - are evaluated and data on life habits, food and medications in use are collected. If necessary, the warfarin dose is adjusted, followed by rescheduling the appointment. The frequency of carrying out the INR exams and the adjustment of the anticoagulant dose follows the institutional protocol. The consultation is registered in a computerized medical record.

Inclusion and exclusion criteria

Patients aged >18 years, with indication for chronic oral anticoagulation and using warfarin for >60 days, attended at the clinic between August and December 2017, and with at least two INR results recorded in the period were considered eligible. Patients who had only one INR during the analyzed period were excluded.

Data collection and analysis

Data were extracted from the ambulatory's computerized system, through the generation of a report. The variables collected were: therapeutic range targeted by INR; sex; age; municipality of residence; number of anticoagulation indications per patient; use of warfarin other than that prescribed; irregular consumption of vitamin K; irregular tea consumption; occurrence of laboratory changes; occurrence of bleeding; modification of other medications in use; reports of hospitalization.

These variables are part of the outpatient care protocol, and the electronic medical record has a specific field for filling them out during consultations. This information is mandatory for each consultation and the professional responsible for the service is unable to save the record if any field has not been filled out.

According to records of the results of an INR exam, the TTR was calculated individually, using the Rosendaal formula[14], which involves the linear interpolation of the results of INR. The TTR is expressed as a percentage, requiring a minimum of two measurements of the INR for its calculation. For participants who had consultation intervals >56 days, INR values were used to calculate the TTR for valid intervals and then each value obtained was used to calculate the final TTR. All variables were recorded in a Microsoft Excel 2007 spreadsheet, followed by statistical analysis.

Statistical analysis was performed using the Stata/SE 12.0 program for Mac. Age was expressed as mean and standard deviation and was analyzed using Student's t-test; categorical variables were analyzed using Pearson's chi-squared, and this analysis consisted of a univariate analysis. Predictive factors independently associated with inadequate TTR were determined by means of logistic regression analysis, obtaining odds ratios (OR), which represent the chance of inadequate TTR for a given category of the variable compared with the reference category.

In order to compose this logistic regression model, values that had significance less than 20% ($p<0.20$) in the univariate analysis were included in an initial model. The final model was obtained by sequential deletion of variables, where those with greater statistical significance were removed one by one until only those with a significance level of 5% or less remained in the final model. The 95% confidence interval for OR was also indicated. The level of significance considered was 5% ($p<0.05$).

This study is part of the clinical trial called "Evaluation of the implementation of educational intervention in patients with inadequate control of oral anticoagulation with a vitamin K antagonist treated at two teaching hospitals", Brazilian Registry of Clinical Trials (ReBEC): RBR- 9cy6py and UTN: U1111-1217-0151 (March, 2019), approved by the CAAE ethics committee: 65928316.3.0000.5149; opinion number: 2.018.850.

RESULTS

2,113 consultation records corresponding to 441 patients were analyzed. Of these, 204 (46.3) had inadequate anticoagulation control (overall mean TTR: 61.8 SD +1.00). The mean age was 60.8 years old (SD: +13), with a predominance of females and patients with a therapeutic range of INR between 2.0 - 3.0, as shown in Table 1.

691 records of clinical indications for the use of anticoagulants were identified, with an average of 1.57 indications per patient. Table 2 shows the specifications of the indications.

In the final model, the variables gender,

indications for thromboembolism and valvulopathy, use of warfarin other than prescribed, and bleeding were identified as predictors of low TTR.

It was identified that the variables female gender, use of warfarin other than that prescribed, and bleeding are positively associated with inadequate TTR (table 3). Thromboembolism and valvulopathy are negatively associated with inadequate TTR.

The results of the final model are shown in table 3.

Through the final logistic regression model, it was identified that the chance of inadequate TTR among female patients is 82.4% higher when compared to male patients. In addition, the chance of inadequate TTR among patients with thromboembolism is 66% lower (100% - 34%) when compared to patients without thromboembolism.

Table 1 – Characterization of patients according to TTR and univariate analysis. Belo Horizonte - MG, 2017.

	TTR* < 60.0% - n (%)	TTR* > 60.0% - n (%)	Total - n (%)	P
Target therapeutic range of INR				
2.0-3.0	144 (70.59)	170 (71.49)	314 (71.20)	0.835
2.5-3.5	60 (29.41)	67 (28.51)	127 (28.80)	
Sex				
Male	137 (67.16)	128 (54.01)	265 (60.09)	0.005
Female	67 (32.84)	109 (45.99)	176 (39.91)	
City of residence				
Belo Horizonte	123 (60.29)	132 (55.32)	255 (57.82)	0.564
Metropolitan region	67 (32.84)	88 (37.45)	155 (35.14)	
Interior of Minas Gerais	14 (6.86)	17 (7.23)	31 (7.04)	
Number of anticoagulation indications per patient				
1	108 (52.94)	120 (50.63)	228 (51.70)	0.629
2 or more	96 (47.06)	117 (49.37)	213 (48.30)	
Age				
<60 years	84 (41.18)	98 (41.35)	182 (41.27)	
60 – 69 years	54 (26.47)	64 (27.00)	118 (26.76)	0.988
70 – 79 years	45 (22.06)	53 (22.36)	98 (22.22)	
> 80 years	21 (10.29)	22 (9.28)	43 (9.75)	
Use of warfarin other than prescribed				
No	141 (69.12)	206 (86.92)	347 (78.68)	<0.001
Yes	63 (30.88)	31 (13.08)	94 (21.32)	
Irregular vitamin K consumption				
No	200 (98.04)	233 (98.31)	433 (78.68)	<0.999
Yes	4 (1.69)	4 (1.96)	8 (1.81)	
Irregular tea consumption				
No	178 (87.25)	218 (91.98)	396 (89.90)	0.102
Yes	26 (12.75)	19 (8.02)	45 (10.20)	
Occurrence of laboratory change				
No	173 (84.80)	209 (88.19)	382 (86.62)	0.298
Yes	31 (15.20)	28 (11.81)	59 (13.38)	
Occurrence of bleeding				
No	151 (74.02)	204 (86.08)	355 (80.50)	

to be continued...

continuation table 1...

	TTR* < 60.0% -	n (%)	TTR* > 60.0% - n (%)	Total - n (%)	P
Yes	53 (25.98)		33 (13.92)	86 (19.50)	
Modification of other medications in use					
No	112 (54.90)		149 (62.87)	261 (59.18)	0.090
Yes	92 (45.1)		88 (3713)	180 (40.82)	
Hospitalization Event					
No	183 (89.71)		226 (95.36)	409 (92.74)	0.023
Yes	21 (10.29)		11 (4.64)	32 (7.26)	
TOTAL BY CATEGORY	**204 (100.00)**		**237 (100.00)**	**441 (100.00)**	

*TTR- Time in therapeutic range

Table 2 – Specification of anticoagulation indications according to the TTR. Belo Horizonte - MG, 2017.

Anticoagulation indication	TTR* < 60.0% - n (%)	TTR > 60.0% - n (%)	Total - n (%)	P
Atrial fibrillation/flutter	135 (47.36)	150 (52.64)	285 (100)	0.527
Cardiac prosthesis	94 (48.95)	98 (51.04)	192 (100)	0.318
Stroke	42 (47.20)	47 (52.80)	89 (100)	0.843
Cardiomyopathy	27 (46.55)	31 (53.45)	58 (100)	0.962
Thromboembolism	11(25.58)	32 (74.42)	43 (100)	0.004
Valvulopathy	7 (29.20)	17 (70.80)	24 (100)	0.084

*TTR, Time in therapeutic range

Table 3 – Final model of logistic regression. Belo Horizonte - MG, 2017.

Inadequate TTR	*Odds Ratio*	p>z	95% CI	
Female sex	1.82	0.005	1.204335	2.761345
Thromboembolism	0.34	0.005	0.161002	0.717477
Valvulopathy	0.36	0.034	0.137317	0.927559
Use of warfarin other than prescribed	2.81	0	1.700653	4.632352
Occurrence of bleeding	1.70	0.045	1.013157	4.632352

DISCUSSION

It was observed that the main indications for anticoagulation are non-valve and valve AF, mechanical valve prosthesis, and stroke. Thromboembolism and valvulopathy were also identified as variables negatively associated with low TTR and this association is not identified in the literature.

The variable for adherence problems, interpreted as a report in the medical record of warfarin use other than that prescribed, was a variable identified among the study subjects. This was also a variable identified as a predictor of low TTR, as already pointed out in the literature, and remains a topic of concern[15,16]. It is noteworthy that it has a multifactorial character and reflects issues related to understanding and adherence to treatment. For this measurement, self-reported adherence is a strategy that has relevance in scientific research and is of good quality when compared to scales and other instruments[17].

Bleeding was positively associated with low TTR. When it comes to the safety of warfarin treatment, attention should be paid to the group of patients who are unable to remain in the target therapeutic range for anticoagulation and are more susceptible to hemorrhagic and/or thromboembolic events[17,18]. In the medical records analyzed, only hemorrhagic events were reported, however, more in-depth studies should be conducted to establish the main factors associated with the risk of hemorrhagic and thromboembolic events. Throughout the treatment with warfarin, other comorbidities may arise, and with them, other medications may be included in pharmacotherapy, which increases the risk of drug interactions. The literature describes that the concomitant use of medications and comorbidities may be associated with an increased risk of bleeding. INR becomes unstable with the introduction, change in dose, or suspension of many common medications, such as antibiotics[19]. However, the association between changes in the other drugs in use and low TTR was not statistically significant in the present study. This may be associated with the fact that adherence to other medications in use was not measured and only the reports of changes or no changes in pharmacotherapy. Some of these changes may be associated with changes in medications that do not interact with warfarin, which would not pose a risk of INR compromise.

The present study has as a limitation the use of tertiary sources of information, and the record in the medical record is performed by health professionals, based on the patients' reports. As the clinic works in a municipality located in Minas Gerais, the results do not allow extrapolation of data.

CONCLUSION

The findings contribute to a better understanding of the profile of patients with inadequate control. Since the existence of variables that predict the quality of oral anticoagulation have been demonstrated, it is understood that the results may guide the establishment of strategies that promote higher quality in anticoagulant treatment.

REFERENCES

1. Westerman S, Wenger N. gender differences in atrial ibrillation: A review of epidemiology, management, and outcomes. Curr Cardiol Rev. 2019; 15(2):136–44. doi: 10.2174/1573403X15666181205110624.
2. Zimerman LI, Fenelon G, Martinelli Filho M, Grupi C, Atié J, Lorga Filho A, et al. Sociedade Brasileira de Cardiologia. II Diretrizes brasileiras de fibrilação atrial. Arq Bras Cardiol. 2016; 106 (4 supl.2):1-22. doi:: 10.5935/abc.20160055.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the framingham study. Stroke. 1991; (8):983-88. doi: 10.1161/01.str.22.8.983.
4. Gregory YHL, Amitava B, Giuseppe B, Chern C, et al. Antithrombotic therapy for atrial fibrilation. Chest. 2018 ;154(5):531-75. doi 10.1016/j.chest.2018.07.040.
5. Katzung B G et al. Farmacologia Básica e Clinica. 10. ed. São Paulo: Mc Graw Hill, 2014.
6. Gateman D, Trojnar ME, Agarwal G. Time in therapeutic range: warfarin anticoagulation for atrial fibrillation in a community-based practice. Can Fan Physician 2017;63:425-31. Disponível em: doi: 10.1111/j.1538-7836.2008.03075.x.
7. Witt DM, Niewlaat R, Clark NP, Ansell J, Holbrook A, Skov J, et. Al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018 27;2(22):3257–91. doi: 10.1182/bloodadvances.2018024893.
8. Marsh EB, Llinas RH, Schneider ALC, Hillis AE, Lawrence E, Dziedzic P, et al. Predicting hemorrhagic transformation of acuteischemic stroke prospective validation of the hers score. Medicine (Baltimore). 2016;95(2):1-8. doi: 10.1097/MD.0000000000002430.
9. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR, et al. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation results of the veterans affairs study to improve anticoagulation. Circ Cardiovasc Qual Outcomes. 2011; 4:22-29. doi: 10.1161/CIRCOUTCOMES. 110957738.
10. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008;118(20):2029-37. doi: 10.1161/CIRCULATIONAHA.107.750000.
11. Prochaska JH, Gobel S, Keller K, Coldewey M, Ullmann A, Lamparter H, et al. 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.
12. Martins MAP, Costa JM, Mambrini JVM, Ribeiro ALP, Benjamin EJ, Brant LCC, Paasche-Orlow MK, Magnani, JW. Health literacy and warfarin therapy at two anticoagulation clinics in Brazil. Heart. 2017;103(14):1089-95. doi: 10.1136/heartjnl-2016-310699.
13. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, Halperin JL, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF. J Am Heart Assoc. 2(1) 2013. doi: 10.1161/JAHA.112.000067.
14. Rosendaal FR, Cannegieter SC, Van Der Meer FJM, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb. Haemost. 1993;69(3):236-39. doi: 10.1055/s-0038-1651587.
15. Limdi NA, Brown TM, Shendre A, Liu N, Hill CE, Beasley TM. Quality of anticoagulation control and hemorrhage risk among African American and European American warfarin users. Pharmacogenet Genomics. 2017;27(10):347–55.doi: 10.1097/FPC.0000000000000298.
16. Zdyb EG, Courtney M, Malik S, Schmidt MJ, Lyden AE. Impact of discharge anticoagulation education by emergency department pharmacists at a tertiary academic medical center. J Emerg Med. 2017;53(6):896–903. doi: 10.1016/j.jemermed.2017.06.008.
17. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni J, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med. 2015;5:470–82. doi: 10.1007/s13142-015-0315-2.
18. Gellad WF, Thorpe CT, Steiner JF, Voils CI. The myths of medication adherence. Pharmacoepidemiol Drug Saf.2017;26(12):1437-41. doi: 10.1002/pds.4334.
19. Saito M, Hatakeyama S, Hashimoto H, Suzuki T, Jubishi D, Kaneko M, et al. Dose-dependent artificial prolongation of prothrombin time by interaction between daptomycin and test reagents in patients receiving warfarin: a prospective in vivo clinical study. Ann Clin Microbiol Antimicro. 2017;16-27.doi: 10.1186/s12941-017-0203-3.

Received in may 2020.
Accepted in january 2021.