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Association evaluation between pharmacotherapy complexity and oral anticoagulation quality in patients using warfarin

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Abstract

Objective: carry out the characterization and identification of the complexity of pharmacotherapy in patients treated in an anticoagulation clinic and associate it with the control of oral anticoagulation, through the TTR. **Methods:** Data collection was carried out through the application of questionnaires and prescription requests. The complexity analysis was based on the Medication Regimen Complexity Index (MRCI), developed by George et al. (2004) and validated in Brazilian Portuguese by Melchiors, Correr and Fernandez-Llimos (2007) with the title of Pharmacotherapy Complexity Index (ICFT). Prescriptions were classified into levels of complexity according to Pantuzza et al. (2018) who considered the total MRCI value ≤9.0 points low complexity; medium complexity as 9 <total MRCI ≤ 16.5 points; and high complexity as total MRCI > 16.5 points. The TTR was calculated according to the linear interpolation method described by Rosendaal et al. (1993) and expressed as a percentage. **Results:** The sample consisted of 203 patients aged >18 years and on chronic warfarin use (>60 days). Most patients, 66.5%, had inadequate TTR (<60%). **Conclusion:** The present study allows us to infer that there is no statistically relevant association between the complexity and quality of pharmacotherapy in this population, specifically.

Keywords: warfarin; anticoagulants; drug therapy; international normalized ratio.

Avaliação da associação entre a complexidade da farmacoterapia e qualidade da anticoagulação oral em pacientes em uso de varfarina

Resumo

Objetivo: caracterizar pacientes de dois ambulatórios de anticoagulação em relação à complexidade da farmacoterapia e TTR, bem como avaliar se há associação entre essas duas variáveis. **Métodos:** A coleta de dados foi realizada por meio de aplicação de questionários e solicitação da prescrição. A análise da complexidade foi feita com base no *Medication Regimen Complexity Index* (MRCI), desenvolvido por George *et al.* (2004) e validado no português brasileiro por Melchiors, Correr e Fernandez-Llimos (2007) com o título de Índice de Complexidade da Farmacoterapia (ICFT). As prescrições foram classificadas em níveis de complexidade de acordo com Pantuzza *et al.* (2018) que consideraram baixa complexidade o valor de MRCI total ≤9,0 pontos; média complexidade como 9 <total MRCI ≤ 16,5 pontos; e alta complexidade como MRCI total> 16,5 pontos. Calculou-se o TTR de acordo com o método de interpolação linear descrito por Rosendaal *et al.* (1993) e expressou-se em porcentagem. **Resultados:** Foram incluídos 203 pacientes com idade >18 anos e em uso crônico de varfarina (>60 dias). A maioria dos pacientes, 66,5%, apresentou TTR inadequado (<60%). **Conclusão:** O presente estudo permite inferir que não há relação estatisticamente relevante entre a complexidade e a qualidade da farmacoterapia nessa população, especificamente.

Palavras-chave: varfarina; anticoagulantes; tratamento farmacológico; coeficiente internacional normatizado.

Introduction

Oral anticoagulants (OACs) encompass both vitamin K antagonists (VKAs) such as warfarin, and direct-acting anticoagulants[1]. Warfarin, whose mechanism of action involves inhibition of reductases and synthesis of vitamin K-dependent coagulation factors, is considered the drug of choice for thromboprophylaxis in patients with atrial fibrillation (AF), particularly those with mechanical valve prostheses[2-4].

Despite the benefits of using warfarin, effectiveness of the treatment is strongly influenced by factors intrinsic to each individual, such as genetic polymorphisms, age and environmental and behavioral factors, highlighting interactions with food and other medications[4-6].

Patients aged at least 65 years old have high prevalence of chronic diseases and comorbidities, culminating in polypharmacy and, consequently, increasing the chances of complex pharmacotherapy, with a greater possibility of adherence problems as well as interactions with warfarin[7-9].

Given the interference of several factors, monitoring anticoagulant therapy is considered necessary, and is carried out through the International Normalized Ratio (INR) test[1]. Anticoagulation quality is measured using the Time in Therapeutic Range (TTR) value, which estimates the time percentage that the INR remains within the therapeutic range[10,11].

Complexity consists in classifying all medications contained in a prescription based on the following requirements: (A) pharmaceutical form; (B) dose frequency; and (C) special instructions (break or crush, administer at a specific time)[12]. Therefore, although little explored in the context of patients using anticoagulants, it is believed that measuring the complexity of pharmacotherapy can help understand the profile of the guidelines contained in medical prescriptions and possible interferences of these factors in the quality of oral anticoagulation.

Considering that the TTR value is an important predictor of adverse events and in view of the possible interference of the complexity of pharmacotherapy in this outcome, the current study aims at characterizing patients in relation to the complexity of pharmacotherapy and quality of oral anticoagulation (TTR), as well as at identifying associations between these factors[13,14].

Methods

This is a cross-sectional study carried out at two anticoagulation (AC) clinics located in two large hospitals (hospitals 1 and 2) from Minas Gerais. The AC clinics of both hospitals use the same institutional protocol to approach the patients and are made up of multiprofessional teams (physicians, pharmacists and nurses). During the outpatient consultations, the patients are approached regarding eating habits, alcohol consumption and use of additional medications. After approaching and verifying the INR measurement results, the warfarin dose is adjusted and the return date is determined, as necessary.

The inclusion criteria were as follows: age ≥ 18 years old, warfarin use for > 60 days due to valvular or non-valvular atrial fibrillation and treatment in one of the AC clinics between August and December 2018. In general, the patients had target INR values between 2 and 3, with the exception of situations in which the target was 3.5-3.5 (as in the cases of some patients with metal prostheses). However, as long as the patient had atrial fibrillation, the target INR was not considered an exclusion factor. Patients with only one INR result during the period analyzed were excluded, as it was impossible to calculate the TTR value, as well as those whose Primary Care physician's prescription data were not possible to access.

The patients were approached by previously trained Pharmacy students and invited to participate in the project through an interview with a questionnaire. If they accepted, in addition to the questionnaire, signing of the Free and Informed Consent Form (FICF) was requested. In addition, a copy of the medical prescription written by a reference physician offering assistance in Primary Care was requested. In cases where the patients did not have the prescription, they were asked to send a copy via a messaging app or a copy to be delivered at the next appointment. In cases where it was not possible to access the prescriptions presented by the patients, the AC clinics' electronic medical records were consulted in order to identify records of reported use of medications in Primary Care. When considering that the complexity calculation is carried out based on the analysis of the prescription, medications used without a medical prescription were not included in the pharmacotherapy complexity calculation.

The complexity analysis was based on the MRCI, developed by George *et al.* and validated in Brazilian Portuguese by Melchiors and collaborators, entitled ICFT[12,15]. Each person's overall score was calculated by adding the scores from the three individual sections for each medication found in the prescription. The prescriptions were classified into complexity levels according to Pantuzza *et al.*, with the total MRCI value considered low complexity when ≤ 9.0 points; medium complexity when 9 points < total MRCI ≤ 16.5 points and high complexity when total MRCI > 16.5 points[16]. Initially, the analysis was carried out by Pharmacy students and the 47 divergent results were checked by a third reviewer, MSc in Pharmacy. In the case of situations not covered in the validated document, there certain courses of action were standardized (Table 1).

Table 1. Courses of action not covered by the MRCI.

Specification of the situations and courses of action adopted
Acutely used medications were not considered.
"Multiple doses" were considered, in case of prescriptions of 1.5 tablets per day.
In the case of two undated prescriptions with most of the medications in common, the one with the highest number of medications was considered.
If the patient presented two prescriptions for medications for chronic use, different in the last three months, both were considered.
In case of multiple prescriptions from the same physician, the most recent one was considered.
In case of multiple prescriptions from different physicians: all were considered as a single prescription during scoring, excluding common medications prescribed in the same dosage.
Medications with additional instructions with the terms "morning" and "fasting" in the same sentence scored in two different categories in section C (take/use at a specific time and relationship with food).
Medications that are prescribed only for a few days a week, or for example, every 21 days, were considered "alternate days or less frequently" in section B.

The TTR value was calculated according to the linear interpolation method described by Rosendaal *et al.*. The result, expressed as a percentage, requires the minimum number of two INR results[17]. TTR values < 60% were considered inadequate and TTR ≥ 60%, adequate. In general, TTR values < 60% are considered inefficient[18].

The following variables were considered in the current study: gender, age in years old, age group, participating hospitals, place of residence, therapeutic target, number of medications, complexity of pharmacotherapy and TTR classification. Gender, age, place of residence and therapeutic target were collected by consulting the electronic medical charts in the institution's computerized system and checking the records in the physical medical charts. To calculate TTR, all values of the INR exam performed by each patient between August and December 2018 were considered and, for this purpose, a report was issued from the institution's computerized medical records system. After issuing the report, the TTR value was calculated using linear interpolation[10,11].

To analyze the association between pharmacotherapy complexity and TTR, the Analysis of Variance (ANOVA) test was performed, due to the characteristics of the variables. The p-value was calculated and, subsequently, the confidence intervals of the proportions of adequate and inadequate TTR values were determined by pharmacotherapy complexity level (Confidence level = 0.95), aiming to indicate the uncertainty margin regarding calculation of the p-value. Additionally, confidence intervals were constructed for the TTR values depending on the pharmacotherapy complexity levels. An association analysis was also carried out between categorical variables and pharmacotherapy complexity. For this purpose, we decided to use multinomial logistic regression, as the complexity classification has three categories. As the complexity calculation implies the number of medications prescribed, an association analysis between this variable and complexity was not carried out, as it was understood that this would be a bias. A 95% confidence interval was considered for all analyses performed.

This study is part of the project entitled "Implementation of an educational intervention in patients with inadequate oral anticoagulation control with vitamin K antagonist treated in two teaching hospitals", developed at the Federal University of Minas Gerais and approved by the Ethics Committee under opinion number CAAE 65928316.3.0000.5149. As the outcome of the current study differs from the main study for which the sample size was calculated (where only one patient refused to participate), the current sample (203 patients) is considered to be by convenience.

Results

A total of 217 patients were approached with the intention of participating in the study, 14 of which were excluded due to inability to access their Primary Care prescriptions. The patients' clinical and sociodemographic characteristics are described in Table 2, highlighting that the majority presented inadequate TTR values (66.5%). The median number of medications prescribed for the monitored patients was six, with 160 (78.81%) using five or more medications at the time of the analysis.

Table 2. Sociodemographic and clinical characteristics of the patients.

Variables	n (%)
Gender	
Male	84 (41.38)
Female	119 (58.62)
Age (years old) Mean ±SD	
Men	67.3 ± 10 (15.1%)
Women	62.8 ± 13 (20.3%)
Age group (years old)	
<60	65 (32.02%)
60 – 69	62 (30.54%)
≥70	76 (37.44%)
Hospital	
Hospital 1	93 (45.81)
Hospital 2	110 (54.19)
Place of Residence	
Belo Horizonte	152 (74.88)
Belo Horizonte Metropolitan Region	44 (21.67)
Inland of Minas Gerais	7 (3.45)
Therapeutic Target	
2 – 3	162 (79.80)
2.5 – 3.5	41 (20.20)
Number of Medications	
1 – 4	43 (21.18)
5 – 9	147 (72.41)
≥10	13 (6.40)
Complexity	
Low	25 (12.32)
Average	78 (38.42)
High	100 (49.26)
TTR Classification	
Inadequate	135 (66.50)
Adequate	68 (33.50)

The description of the variables depending on the TTR values is presented in Table 3, highlighting a higher percentage of patients with high complexity and inadequate TTR.

When carrying out the analysis based on the pharmacotherapy complexity values (Table 4), it was noticed that patients belonging to higher age groups had higher complexity, in most of the cases. It was also identified that males were the majority in low complexity, whereas females were preponderant in high and average complexity.

Table 3. Characterization of the patients according to the TTR values.

Variables	TTR* < 60.0% - n (%) Inadequate	TTR* > 60.0% - n (%) Adequate	Total - n (%)
Complexity			
High	65 (32.02)	35 (17.24)	100 (49.26)
Average	51 (25.12)	27 (13.30)	78 (38.42)
Low	19 (9.36)	6 (2.96)	25 (12.32)
Gender			
Male	58 (28.57)	26 (12.81)	84 (41.38)
Female	77 (37.93)	42 (20.69)	119 (58.62)
Age group			
<60	47 (23.15)	18 (8.87)	65 (32.02)
<70 and ≥60	40 (24.14)	22 (10.84)	62 (30.54)
≥70	48 (23.65)	28 (13.79)	76 (37.44)
Hospital			
Hospital 1	66 (32.51)	27 (13.30)	93 (45.81)
Hospital 2	69 (33.99)	41 (20.20)	110 (54.19)
Place of Residence			
Belo Horizonte	102 (50.25)	50 (24.63)	152 (74.88)
Belo Horizonte Metropolitan Region	30 (14.78)	14 (6.90)	44 (21.67)
Inland of Minas Gerais	3 (1.48)	4 (1.97)	7 (3.45)
Therapeutic Target			
2.0 – 3.0	105 (51.72)	57 (28.08)	162 (79.80)
2.5 – 3.5	30 (14.78)	11 (5.42)	41 (20.20)
Number of Medications			
1 – 4	31 (15.27)	12 (5.91)	43 (21.18)
5 – 9	96 (47.29)	51 (25.12)	147 (72.41)
≥10	8 (3.94)	5 (2.46)	13 (6.40)

Table 4. Characterization of the patients according to the *Índice de Complexidade da Farmacoterapia* (ICFT) values. as well as the analysis of the association with pharmacotherapy complexity.

Variables	Pharmacotherapy Complexity n (%)		
	Low	Average	High
Gender			
Male	15 (7.4)	34 (16.7)	35 (17.2)
Female	10 (4.9)	44 (21.7)	65 (32.0)
Age Group (years old)			
<60	7 (3.4)	33 (16.3)	25 (12.3)
≥60 age <70	7 (3.4)	21 (10.3)	34 (16.7)
≥ 70	11 (5.4)	24 (11.8)	41 (20.2)
Hospital			
Hospital 1	7 (3.4)	28 (13.8)	58 (28.6)
Hospital 2	18 (8.9)	50 (24.6)	42 (20.7)
Place of Residence			
Belo Horizonte	22 (10.8)	61 (30.0)	69 (34.0)
Metropolitan Region	3 (1.5)	16 (7.9)	25 (12.3)
Inland	0 (0.0)	1 (0.5)	6 (3.0)
Therapeutic Target			
2 – 3	23 (11.3)	57 (28.1)	82 (40.4)
2.5 – 3.5	2 (1.0)	21 (10.3)	18 (8.9)
Number of Medications			
1 – 4	31 (15.27)	12 (5.91)	43 (21.18)
5 – 9	96 (47.29)	51 (25.12)	147 (72.41)
≥10	8 (3.94)	5 (2.46)	13 (6.40)

NA: Not Applicable

When calculating F in the ANOVA test, statistical significance was identified between the associations having a target RNI between 2.5 and 3.5 and presenting average complexity (p=0.01); as well as between living in the inland of Minas Gerais and presenting average pharmacotherapy complexity (p=0-00).

No statistical significance was identified when evaluating the association between the different pharmacotherapy complexity levels and TTR (p=0.84).

Discussion

In the current study, no statistically relevant association (p=0.842) was identified between pharmacotherapy complexity, measured by ICFT, and anticoagulation quality, measured by TTR. Additionally, no association was identified between the pharmacotherapy complexity level and TTR. Despite the lack of studies evaluating the association between these variables, other authors observed that polypharmacy did not deteriorate the warfarin therapy quality in patients with AF[19]. Although the number of medications is only one of the items that can lead to high pharmacotherapy complexity, it should be considered that 160 patients (78.81%) were using 5 or more medications at the time of the analysis.

The mean TTR value was 50.6±26.2%. The literature also showed inadequate TTR mean values (42.02% and 56.6%, respectively) among patients with AF[20,21]. This fact reinforces the need to better

identify factors that interfere with anticoagulation quality with a view to implementing actions that promote improvements in this parameter. As the TTR results in the sample evaluated were mostly inadequate (approximately doubling the adequate results), the reflection of this condition is observed in the complexity ranges. There was predominance of patients with inadequate TTR values in all complexity ranges. It was also identified that the TTR ratio (inadequate/adequate) tends to increase as complexity decreases, indicating that, in the low complexity range, there are more patients classified as inadequate TTR when compared to those classified as adequate.

The Brazilian Older Adults' Statute defines a person aged 60 or over as aged[22]. The group participating in the study was predominantly aged (67.98%), with a mean of 67.29±10 (CV 15%) and 62.81±13 years old (CV 20.3%) for females and males, respectively. The patients aged at least 60 years old were mostly in the group with average and high ICTF values, as well as in the group with inadequate TTR values. These data are in line with other studies, which observed that polypharmacy and high complexity were common factors in aged people treated in Primary Care[7]. However, when evaluating the group in the adequate TTR category, it is perceived that the majority were patients aged ≥ 70 years old, in agreement with some studies which suggested that increasing age influenced TTR positively, possibly due to strategies to enhance adherence in this group[23].

It was observed that frequency of doses and additional instructions were the components that most favored the increase in complexity[7]. The fact that there are more prescribed medications and/or greater pharmacotherapy complexity was not necessarily linked to more interactions with warfarin. As an example, we can mention patients with diabetes, as simultaneous use of oral antidiabetics with warfarin is associated with an increased risk of hypoglycemia episodes, despite not interfering with warfarin concentrations[24,25].

Regarding the gender difference, males were prevalent in the high and average complexity levels, whereas females were prevalent in low complexity. Even so, the majority were in the high complexity group, for both genders. In parallel, 77 (67.5%) women out of 119 had inadequate TTR values, whereas 58 (69.1%) out of 84 men also had low anticoagulation quality. These data are in agreement with a retrospective and observational study, which identified that women had lower TTR values than men[26].

The limitations of this study include the fact that, if the patients did not present a physical or digital copy of the medical prescription and it was necessary to consult the electronic medical record, medications prescribed by physicians outside the AC clinics were not included in the pharmacotherapy complexity calculation. The instrument used to classify the patients into complexity levels was validated in Portuguese through a cross-sectional study with patients with type 2[12] diabetes, differently from the study sample in question. In parallel, situations not covered by the ICFT were observed, as well as disparities between the cutoff values for this classification, which may lead to deviations in the results of the correlation between pharmacotherapy complexity and quality[27]. Dividing the sample into groups by comorbidities might perhaps assist in understanding the profile of patients with high pharmacotherapy complexity, as identified in another study[28].

Regarding the identification of statistical significance between the associations of variables, having target INT values between 2.5 and 3.5 and presenting average complexity (p=0.01); as well as between living in the inland of Minas Gerais and presenting average pharmacotherapy complexity (p=0.00), they may be related to the fact that patients with target INR values between 2.5 and 3.5 are clinically more complex, which can generate greater caution on the part of physicians when prescribing medications, in addition to monitoring by a single medical professional. It is also noted that the patients living in the inland are referred to the CCH due to their clinical complexity profile, which can also contribute to greater caution on the part of the physician responsible for the care when prescribing medications. It is also important to emphasize that this is an exploratory analysis. that the study does not allow identifying the patients' comorbidity profile, for example, and the "target INR" and "living in the inland" variables may be confounding factors for comorbidity. Therefore, it is recommended that larger studies be carried out in order to better explore the association found.

Although it was not possible to associate complexity with anticoagulation quality, the harms that increased complexity of the pharmacotherapy regime can cause in adherence to the treatment are well established, as previously pointed out in the literature[29,30]. Therefore, it is important to study how it is associated with increased complexity in order to guide health professionals in providing care, making it individualized and satisfactory. It is understood that there is a need to carry out new studies that evaluate comorbidities, medications or associations that most contributed to the increase in pharmacotherapy complexity and its relationship with TTR.

Conclusion

There was predominance of patients with high pharmacotherapy complexity, as well as of patients with inadequate TTR values. However, it was not possible to establish a statistically relevant association between the measurements in this study. Subsequent analyses are required to test associations inferred from the literature, such as studies that suggest worse clinical outcomes with high complexity and low TTR values. Studies aimed at better correlational understanding can support Public Health policies that contribute to the treatment of patients using warfarin.

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Collaborators

SCC, JMC, CMB and MAM were responsible for data conception, analysis and interpretation; and MOO, SCC, JMC, TRC, CMB and MAM were responsible for writing the article and critical review relevant to the intellectual content.

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Declaration of conflict of interests

The authors declare that there are no conflicts of interests in relation to this article.

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