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Factors that interfere with the quality of warfarin treatment in patients with atrial fibrillation in the real-world context

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Abstract

Objective: To characterize patients with atrial fibrillation (AF) treated at an anticoagulation clinic in Brazil who use warfarin and to identify factors associated with the quality of oral anticoagulation, measured by the Time in Therapeutic Range (TTR). **Methods:** Cross-sectional study conducted between April and July 2019, involving patients with AF using warfarin under outpatient follow-up. The Mini-Mental State Examination (MMSE), the Short Assessment of Health Literacy for Portuguese-speaking Adults (SAHLPA-18), and the Oral Anticoagulation Knowledge (OAK) Test were applied. TTR was calculated based on the International Normalized Ratio (INR) and was considered adequate when ≥60%. Pharmacotherapy complexity was assessed using the Medication Regimen Complexity Index (MRCI). Data were analyzed using Student's t-test, Chi-square or Fisher's exact test, and logistic regression to calculate the odds ratio (OR). **Results:** The mean age of the 82 patients was 66.77 ± 9.54 years, with a predominance of males (52.44%). Most patients had low health literacy (75.58%) and 37.21% were using highly complex pharmacotherapies. Female sex and pharmacotherapy complexity were significantly associated with TTR < 60% ($p < 0.05$). **Conclusion:** The control of oral anticoagulation with warfarin may be influenced by factors such as sex and therapeutic complexity. Targeted interventions, including intensive pharmaceutical follow-up and educational strategies, may enhance therapeutic effectiveness in patients with AF.

Keywords: Prothrombin Time; Polypharmacy; Health Literacy; Medication Regimen Complexity; Medication Adherence.

Fatores que interferem na qualidade do tratamento com varfarina em pacientes com fibrilação atrial no contexto do mundo real

Resumo

Objetivo: Caracterizar pacientes com fibrilação atrial (FA) atendidos em uma clínica de anticoagulação no Brasil que utilizam varfarina e identificar fatores associados à qualidade da anticoagulação oral, mensurada pelo Time in Therapeutic Range (TTR). **Métodos:** Estudo transversal realizado entre abril e julho de 2019, com pacientes com FA em uso de varfarina em acompanhamento ambulatorial. Foram aplicados o Mini-Mental State Examination (MMSE), o Short Assessment of Health Literacy for Portuguese-speaking Adults (SAHLPA-18) e o Oral Anticoagulation Knowledge (OAK) Test. O TTR foi calculado a partir da Relação Normatizada Internacional (RNI), sendo considerado adequado quando ≥60. A complexidade da farmacoterapia foi avaliada pelo Medication Regimen Complexity Index (MRCI). Os dados foram analisados por meio de testes de comparação de médias (t de Student), frequência (Qui-quadrado e teste exato de Fisher) e regressão logística para cálculo do odds ratio. **Resultados:** A média de idade dos 82 pacientes foi de 66,77 ± 9,54 anos, com predominância do sexo masculino (52,44%). A maioria apresentava baixo letramento em saúde (75,58%) e 37,21% utilizavam farmacoterapias de alta complexidade. O sexo feminino e a complexidade da farmacoterapia foram significativamente associados a TTR < 60% ($p < 0,05$). **Conclusão:** O controle da anticoagulação oral com varfarina pode ser influenciado por características como sexo e complexidade terapêutica. Intervenções direcionadas, como acompanhamento farmacoterapêutico intensivo e estratégias educativas, podem favorecer a eficácia terapêutica em pacientes com FA.

Palavras-chave: Tempo de protrombina; Polifarmácia; Letramento em Saúde; Complexidade da Farmacoterapia; Adesão à Medicação.

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Introduction

With the increase in life expectancy and population growth, oral anticoagulation has been increasingly recommended for the prevention of thromboembolic events, with particular emphasis on patients with atrial fibrillation (AF)—a sustained cardiac arrhythmia considered an independent risk factor for the occurrence of stroke.[1,2]

In recent years, new oral anticoagulants, known as target-specific oral anticoagulants, have been introduced to the market.[3] However, despite requiring more intensive monitoring during use, warfarin is still considered the gold-standard anticoagulant and remains widely used in Brazil, especially within the context of the Unified Health System (Sistema Único de Saúde- SUS).[4,5]

Although widely used, warfarin is considered a potentially dangerous medication, with a narrow therapeutic range, wide dose-response variability, and susceptibility to drug interactions. Its effectiveness is also influenced by the intake of foods rich in vitamin K.[5]

Patients on warfarin therapy need to undergo frequent International Normalized Ratio (INR) tests, and it is often necessary to adjust doses during treatment to avoid undesirable adverse events such as bleeding.[6,7]

To ensure greater patient safety, it is recommended to assess the quality of oral anticoagulation using the Time in Therapeutic Range (TTR) calculation. TTR is based on a series of INR tests conducted over time and allows for linear extrapolation to evaluate the percentage of time a patient remained within the target therapeutic INR range (generally between 2 and 3).[6]

For many patients, it is advisable to assess the risk-benefit ratio of warfarin anticoagulation, considering that factors such as low health literacy, dietary habits, and degree of dependency may interfere with the quality of anticoagulation.[8] However, the literature presents conflicting evidence regarding the influence of some of these factors on the quality of oral anticoagulation, and studies based on real-world settings in developing countries like Brazil are scarce.

Therefore, this study aims to identify the variables associated with poor anticoagulation control in patients with AF, in order to provide a basis for future clinical interventions that could optimize the monitoring and therapeutic outcomes of these patients.

Methods

This was a cross-sectional study conducted between April and July 2019 at an anticoagulation clinic (AC) located in a general teaching hospital that serves as a referral center for the northern region of the municipality of Belo Horizonte, Minas Gerais, Brazil. The AC under study was established in 2012 with the purpose of providing therapeutic monitoring for patients discharged from the hospital with a recommendation for warfarin use, as well as for those referred by other healthcare services for which the hospital serves as a reference.

During the study period, the AC team was composed of a multidisciplinary staff including physicians, nurses, pharmacists, and pharmacy residents participating in a Multiprofessional Program in Elderly Health. Additionally, the service was supported by the hospital's clinical laboratory.

On the day of the appointment, a blood sample was collected from each patient to measure their International Normalized Ratio (INR). The results were analyzed, and during the multidisciplinary consultation, warfarin doses were adjusted and patients were provided with health education information.

Data Collection and Analysis

Patients aged 18 years or older, who had been receiving outpatient care for more than six months, and had an indication for warfarin use due to a diagnosis of atrial fibrillation (AF) were selected for the study.

Patients meeting the inclusion criteria were approached during the interval between blood sample collection and the start of their consultation. Those who agreed to participate signed the Informed Consent Form (ICF).

Variables for Characterization of the Study Population

After signing the ICF, each participant was invited to answer questions regarding sociodemographic, clinical, and pharmacotherapeutic information in order to supplement data not available in their medical records. The following variables were collected: age, sex, self-declared skin color, religion, city of residence, years of education, family income, number of residents in the household, literacy, indication for anticoagulation, CHA_2DS_2-VASc score, occurrence of stroke prior to hospitalization, cognitive assessment using the Mini-Mental State Examination, functional health literacy (SAHLPA), medication regimen complexity (MRCI), number of medications in use, use of 10 or more medications, assistance with administering warfarin, assistance with administering other medications, presence of a caregiver, use of alcoholic beverages, and smoking habits. The CHA_2DS_2-VASc score was calculated by the researchers based on clinical data obtained from the patients' medical records and structured interviews, using established risk criteria for assessing thromboembolism in patients with AF. Functional health literacy was assessed using the Short Assessment of Health Literacy for Portuguese-speaking Adults (SAHLPA-18), with participants classified as having inadequate health literacy if they scored below 42.[7]

Household income was expressed in minimum wage units and subsequently converted into absolute values using the minimum wage in effect in Brazil in 2019, the year of data collection. The value used was R$998.00, as established by Decree No. 9.661/2019.

The Mini-Mental State Examination (MMSE) was applied for cognitive screening. This test has a maximum score of 30 points. In this study, cognitive impairment was classified as a score of 17 points or less for patients with up to nine years of formal education, and 24 points or less for patients with more than nine years of education.[9,10]

To assess the complexity of pharmacotherapy, the Medication Regimen Complexity Index (MRCI) was used. This instrument, validated in Brazilian Portuguese, evaluates complexity through three sections: (A) dosage forms (32 items), (B) dosing frequency (23 items), and (C) additional instructions, such as specific times, intake requirements, or mechanical actions needed for administration (10 items). The total MRCI score varies, scores below 30 indicate low complexity, scores between 30 and 40 indicate medium complexity, and scores above 40 suggest high complexity, according to adaptations from previous studies.[11]

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The analysis of pharmacotherapy complexity was based on each patient's most recent prescription, issued by a primary care physician. To facilitate this, the return dates of all patients to the outpatient clinic were identified, and phone calls were made the day before their appointments to request that they bring their prescriptions. Each prescription was photographed and archived. If patients forgot to bring the prescription, they were asked to send a copy via the WhatsApp® application. If these attempts failed, the researchers consulted the medical record to retrieve the discharge prescription, followed by another phone call to verify the medications currently in use, allowing for a comparison between the information provided over the phone and the discharge prescription.

For patients with two or more prescriptions from specialists of different areas within a maximum interval of one month, all distinct medications were summed. In these cases, the data were consolidated into a single prescription per patient, reflecting all medications in use at the time of data collection.

Based on the International Normalized Ratio (INR) results obtained over time, the Time in Therapeutic Range (TTR) was calculated. All INR results recorded in the electronic medical records of the study participants between April and July 2019 were identified. Patients with fewer than three INR results during this period were excluded from the study. TTR was classified as follows: TTR ≥ 60% was considered indicative of good quality oral anticoagulation; TTR < 60% was considered poor quality anticoagulation[7].

Data Analysis

For the primary statistical analyses, patients were categorized into two groups based on their TTR: TTR ≥ 60%, indicating adequate anticoagulation quality, and TTR < 60%, indicating inadequate anticoagulation quality.

For comparative analysis between categories, continuous or interval variables were analyzed using Student's t-test for independent samples, as the data were considered normally distributed based on the Shapiro-Wilk test. Percentages between categories were compared using Fisher's exact test when comparisons involved expected frequencies lower than 5; otherwise, the Chi-square test was applied. A significance level of 5% ($p < 0.05$) was adopted for statistically significant findings, and 10% ($p < 0.10$) was used for findings with borderline significance. For variables that demonstrated a statistically significant association in bivariate analyses, logistic regression was conducted to calculate the odds ratio (OR), in order to estimate the strength of association between these explanatory variables and the outcome of TTR < 60%. The OR quantifies the likelihood of poor anticoagulation quality as a function of different factors, while controlling for the effect of multiple variables. No sample size calculation was performed, since the study was based on a convenience sample, comprising all patients who met the inclusion criteria during the data collection period.

Results

A total of 82 patients were included from the anticoagulation clinic (AC), with a mean age of 66.77 ± 9.54 years, predominantly male (43; 52.44%), non-White (60; 73.17%), and residing primarily in Belo Horizonte (66; 80.49%). The average educational level was 4.29 ± 2.49 years, and the mean household income was 1.76 ± 0.77 minimum wages. Among these, 68 patients (82.93%) reported being literate, and the indication for warfarin use was non-valvular atrial fibrillation (AF) in 54 patients (65.85%) and valvular AF in 28 patients (34.15%). Table 1 presents additional sociodemographic, clinical, and pharmacotherapeutic data of the study population.

Table 1. Sociodemographic, clinical, and pharmacotherapeutic characteristics of the patients in the study

Characteristic	Intervention (n= 82)
Sociodemographic Variables	
Age (years), mean ± standard deviation	66.77 ± 9.54
Sex, n (%)	
Female	39 (47.56)
Male	43 (52.44)
Total, n (%)	**82 (100)**
Race/Color, n (%)	
White	22 (26.83)
Non-white	60 (73.17)
Total, n (%)	**82 (100)**
Religion, n (%)	
Atheist	0
Catholic	42 (51.22)
Evangelical	37 (45.12)
Spiritist	1 (1.22)
Umbandist	0
Others	2 (2.44)
Total, n (%)	**82 (100)**
City of residence, n (%)	
Belo Horizonte	66 (80.49)
Metropolitan region	15 (18.29)
Countryside of Minas Gerais	1 (1.22)
Total, n (%)	**82 (100)**
Years of education, mean ± standard deviation	4.29 ± 2.49
Household income in minimum wages, mean ± standard deviation	1.76 ± 0.77
Number of residents in the household, mean ± standard deviation	2.46 ± 1.0
Literacy, n (%)	
Yes	68 (82.93)
No	14 (17.07)
Total, n (%)	**82 (100)**
SHALPA-18 cut-off, n (%)	
Adequate health literacy	20 (24.39)
Inadequate health literacy	62 (75.61)
Total, n (%)	**82 (100)**
Has a caregiver, n (%)	
Yes	10 (12.20)
No	72 (87.80)
Total, n (%)	**82 (100)**
Alcohol consumption, n (%)	
Yes	15 (18.29)
No	67 (81.71)
Total, n (%)	**82 (100)**
Smoking habits, n (%)	
Yes	8 (9.76)
No	74 (90.24)
Total, n (%)	**82 (100)**

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Characteristic	Intervention (n= 82)
Clinical Variables	
Indication for warfarin use, n (%)	
Valvular atrial fibrillation	28 (34.15)
Non-valvular atrial fibrillation	54 (65.85)
Total, n (%)	**82 (100)**
CHA_2DS_2-VASc score, mean ± standard deviation	3.28 ± 1.24
History of stroke, n (%)	
Yes	37 (45.12)
No	45 (54.88)
Total, n (%)	**82 (100)**
Mini-Mental cutoff – 17 and 24 points (based on years of schooling), n (%)	
Good cognition	66 (80.49)
Cognitive impairment	16 (19.51)
Total, n (%)	**82 (100)**
Pharmacotherapeutic Variables	
Pharmacotherapy complexity (<30 / 30–40 / >40 points), mean ± standard deviation	15.64 ± 5.93
Pharmacotherapy complexity cutoff, n (%)	
Low	14 (17.07)
Medium	37 (45.12)
High	31 (37.80)
Total, n (%)	**82 (100)**
Number of medications in use, mean ± standard deviation	6.07 ± 2.09
Polypharmacy, n (%)	
Yes	58 (70.73)
No	24 (29.27)
Total, n (%)	**82 (100)**
Use of 10 or more medications, n (%)	
Yes	6 (7.32)
No	76 (92.68)
Total, n (%)	**82 (100)**
Assistance with warfarin administration, n (%)	
Yes	15 (18.29)
No	67 (81.71)
Total, n (%)	**82 (100)**
Assistance with administration of other medications in use, n (%)	
Yes	13 (15.85)
No	69 (84.15)
Total, n (%)	**82 (100)**

Notes: AF, Atrial fibrillation; Stroke, Cerebrovascular Accident. Mini-Mental: cutoff 17 (illiterate), 24 (literate); SAHLPA-18: < 42 inadequate health literacy; Pharmacotherapy complexity (MRCI): low < 30, moderate 30-40, high > 40. Source: authors (2025).

Table 2 presents the analysis of the association between sociodemographic, clinical, and pharmacotherapeutic variables collected over time and the quality of oral anticoagulation.

It was identified that female sex and pharmacotherapy complexity were statistically associated with a lower Time in Therapeutic Range (TTR). Among female patients, 30 (61.2%) had TTR < 60%, compared to 9 (28.1%) with TTR ≥ 60%, both with p-values < 0.05, indicating a statistically significant difference.

In addition, pharmacotherapy complexity was also a predictive variable for lower Time in Therapeutic Range (TTR). Patients with TTR < 60% had a mean Medication Regimen Complexity Index (MRCI) of 17.1 ± 9.0 (indicating high complexity), compared to a mean of 14.0 ± 5.5 among those with TTR ≥ 60%, with a statistically significant difference ($p < 0.05$). Further details are presented in the table below.

Table 2. Analysis of the association between sociodemographic, clinical, and pharmacotherapeutic variables and the quality of oral anticoagulation

Variables, categories, and statistics	TTR < 60 (n=49)	TTR >=60 (n=32)
Sociodemographic Variables		
Female sex, n (%)	30 (61.2) **	9 (28.1) **
Age (years), mean ± standard deviation	67.0 (11.4)	68.5 (12.1)
Non-white skin color, n (%)	35 (71.4)	25 (78.1)
Religion, n (%)		
Catholic	24 (49.0)	18 (56.3)
Evangelical	23 (46.9)	13 (40.6)
All other religions / No religion	2 (4.1)	1 (3.1)
Patient reports being able to read, n (%)	41 (83.7)	27 (84.4)
Years of education, mean ± standard deviation	4.8 (3.5)	3.7 (2.7)
Smoking habits, n (%)	4 (8.2)	4 (12.5)
Alcohol consumption, n (%)	10 (20.4)	5 (15.6)
Income in minimum wages, mean ± standard deviation	1.8 (1.2)	1.8 (0.8)
Number of household residents, mean ± standard deviation	2.6 (1.3)	2.3 (1.2)
City of residence, n (%)		
Belo Horizonte	41 (83.7)	25 (78.1)
Metropolitan Region	8 (16.4)	6 (18.8)
Countryside of Minas Gerais	0 (0.0)	1 (3.1)
Presence of a caregiver, n (%)	8 (16.4)	2 (6.3)
Shalpa: adequate health literacy, n (%)	12 (24.5)	8 (25.0)
Pharmacotherapeutic variables		
Polypharmacy, n (%)	37 (75.5)	21 (65.6)
Pharmacotherapy complexity level, n (%)		
Low	6 (12.2)	7 (21.9)
Medium	23 (46.9)	15 (46.9)
High	20 (40.8)	10 (31.3)
Pharmacotherapy complexity, mean ± standard deviation	17.1 (9.0) *	14.0 (5.5) *
Assistance with warfarin administration, n (%)	11 (22.4)	4 (12.5)
Assistance with administration of other medications, n (%)	9 (18.4)	4 (12.5)
Number of medications in use, mean ± standard deviation	6.5 (2.8)	5.6 (2.3)
Use of more than 10 medications, n (%)	5 (10.2)	1 (3.1)
Clinical variables		
Mini-Mental (17 and 24 points): good cognition, n (%)	38 (77.6)	28 (87.5)
CHA_2DS_2-VASc score, mean ± standard deviation	3.4 (1.6)	3.1 (1.5)
History of stroke prior to intervention, n (%)	22 (45.0)	15 (46.9)

Notes: TTR, Time in Therapeutic Range; Stroke, Cerebrovascular Accident; *comparisons with significance below 10% ($p < 0.10$); **comparisons with significance below 5% ($p < 0.05$); Source: Authors (2025)

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In the multivariate analysis, it was found that the likelihood of achieving adequate anticoagulation control (TTR ≥ 60%) among female patients was 75% lower compared to the likelihood of inadequate control among males (OR = 0.25). At the same time, it was also identified that the likelihood of achieving adequate anticoagulation control decreased by 6% with each unit increase in pharmacotherapy complexity (OR = 0.94). This finding showed a trend toward statistical significance (p < 0.10), as presented in Table 3.

Table 3. Odds Ratio Calculation

		TTR, Time 1
Variables, Categories, and Statistics	< 60 (ref)	>=60
Female sex (ref: male sex)		0.25 (IC95% 0.09; 0.65) p=0.004
Pharmacotherapy complexity (continuous)		0.94 (IC95% 0.88; 1.01) p=0.092

Note: TTR1, Time in Therapeutic Range at time point 1; CI95%, 95% Confidence Interval. Source: Authors (2025)

Discussion

The sociodemographic, clinical, and pharmacotherapeutic characteristics of the patients in this study reveal important risk factors for poor anticoagulation quality. The literature indicates that low health literacy is directly associated with errors and poor adherence to anticoagulant therapy[12,13], as well as higher hospitalization rates and healthcare costs[14].

A study conducted among patients with cardiovascular problems demonstrated that health literacy significantly influenced anticoagulation therapy. Patients with higher scores in the health literacy dimensions showed better anticoagulation control and, consequently, more regular follow-up visits, greater information management, self-care, and empowerment[15]. Another study using the SAHLPA scale identified an association between inadequate health literacy and greater cognitive impairment, as well as increased need for assistance in treatment management. However, it did not find a correlation between inadequate health literacy and Time in Therapeutic Range (TTR) levels[16].

In the present study, a high prevalence of patients with low functional health literacy was identified (65; 75.58%). However, this variable did not show an association with low TTR. Some studies suggest that in populations where low health literacy is highly prevalent, the influence of this factor may become attenuated, making it difficult to detect a clear impact on TTR[17]. Moreover, other variables—such as sex and pharmacotherapy complexity—may have exerted a stronger influence on TTR, potentially minimizing the impact of health literacy. In studies involving multiple variables, it is common for dominant variables to overshadow the effects of others, particularly when these variables are correlated[18]. Notably, the variable "sex" may reflect specific sociocultural factors, such as caregiving burdens, less time for self-care, and barriers to accessing healthcare services—issues more frequently experienced by older women. These factors, combined with a higher prevalence of multimorbidity and polypharmacy among women, may help explain the stronger association between female sex and poor anticoagulation quality[14].

Furthermore, the substantial number of patients with low health literacy identified in this study may further hinder the understanding of complex treatment instructions, leading to medication errors and dangerous drug interactions[19,20].

Pharmacotherapy complexity was also a variable associated with low Time in Therapeutic Range (TTR). The calculation of this variable involves identifying the number of prescribed medications, dosages, daily administration frequency, pharmaceutical forms, dosing regimens, and additional administration instructions[21,22]. Thus, it is understood that receiving a complex medication regimen—that is, one requiring a range of skills to ensure correct and consistent use—may lead to medication errors. Such errors can affect the bioavailability of warfarin and consequently result in variations in TTR. Studies conducted in Africa and Italy have also reported associations between pharmacotherapy complexity and low TTR[23,24].

Regarding the sex variable, being female was statistically associated with a lower TTR (TTR < 60%), indicating poor anticoagulation quality. This difference in oral anticoagulation control based on sex has been documented in various studies, though some findings remain conflicting[25,26].

The calculation of the odds ratio (OR) helps quantify the influence of each variable on TTR variation. The fact that the likelihood of adequate anticoagulation control (TTR > 60%) among female patients is 75% lower compared to the chance of inadequate control among males (OR = 0.25) highlights the need for targeted approaches for female patients at the study site.

Regarding pharmacotherapy complexity, the likelihood of maintaining adequate anticoagulation control decreases by 6% for each incremental increase in pharmacotherapy complexity (OR = 0.94). This information is especially relevant for patients with borderline TTR values, frequent fluctuations in TTR, high sensitivity to warfarin, and limited family support.

It is important to emphasize that female patients with high pharmacotherapy complexity may accumulate multiple risk factors contributing to low TTR, thus deserving even greater attention.

These findings may also inform clinical decision-making regarding anticoagulant switching, taking into account the risks, benefits, and individual characteristics of each patient.

This study acknowledges the possibility of methodological biases, such as selection bias due to the use of a convenience sample consisting of patients available during the data collection period. In addition, the use of self-reported data and information extracted from electronic medical records may have introduced recall bias and documentation bias. These limitations were mitigated through the use of previously validated instruments and standardized data collection procedures conducted by a trained research team. Although this study does not allow for broad generalization of its findings, it is hoped that the results will contribute to the design of larger-scale studies.

Conclusion

This study concluded that, when assessing the factors influencing the quality of oral anticoagulation in patients with atrial fibrillation (AF) using warfarin, the variables female sex and pharmacotherapy complexity were identified as predictors of low Time in Therapeutic Range (TTR), indicating poor anticoagulation quality. These findings highlight the need for targeted interventions, such as specific educational programs and simplification of pharmacotherapy, especially for female patients and those on complex therapeutic regimens. Moreover, the results reinforce the importance of an individualized approach, weighing the risks and benefits of continuing oral anticoagulation with warfarin versus switching to alternative therapies. Future studies with larger samples and analyses of additional factors—such as treatment adherence and family support—are essential to deepen our understanding of strategies that can improve the quality of anticoagulation.

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Conflict of Interest Statement

The authors declare no conflicts of interest related to this article.

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