Thromboembolism in Arthroplasty: Compliance to Prophylaxis*

*Tromboembolismo na artroplastia: Adesão à profilaxia**

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Abstract

Objective The present paper aims to identify the profile of compliance to thromboembolism drug prophylaxis in patients undergoing knee or hip arthroplasty at a public hospital.

Methods This is a prospective cohort study, carried out from August 2017 to September 2018, with adult patients who were followed-up from admission until the postoperative period. The Morisky Medication Adherence Scale, consisting of eight items, was applied. Compliance was quantified according to the sum of all correct answers as high (8 points), medium (6 to < 8 points), and low compliance (< 6 points). For the present study, subjects with high compliance were referred as highly compliant, whereas those with medium to low compliance were referred as partially compliant.

Results The compliance analysis showed that 73.0% of the patients were highly compliant and 27.0% were partially compliant to thromboprophylaxis. The anticoagulant prescribed at hospital discharge was rivaroxaban, a direct factor Xa inhibitor. Compliance was greater in patients who did not require reinforcement in prophylaxis guidance during follow-up; these subjects reported good and excellent acceptance of prophylaxis, although they were on multiple medications at discharge.

Conclusion The data analysis allowed us to conclude that the factors that most influenced compliance were the levels of understanding and acceptance of prophylaxis by the patients, the amount of medication used per day by the subject, the cost of the anticoagulant agent, and its potential to cause adverse reactions.

Keywords
- treatment adherence
- anticoagulants
- arthroplasty
- prophylaxis
- thromboembolism

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Resumo

Objetivo Identificar o perfil de adesão à profilaxia medicamentosa de tromboembolismo em pacientes submetidos a cirurgias ortopédicas de artroplastia de joelho ou de quadril em hospital público.

Métodos Estudo de coorte prospectivo, realizado no período de agosto de 2017 a setembro de 2018, com pacientes adultos que foram acompanhados desde a internação até o pós-operatório. Para medir a adesão, aplicou-se a Escala de Adesão Terapêutica de Morisky de oito itens. A quantificação do grau de adesão foi determinada segundo o resultado da soma de todas as respostas corretas: alta adesão (8 pontos), média adesão (6 a $<$ 8 pontos), e baixa adesão ($<$ 6 pontos). No presente estudo, foram divididos em altamente aderentes aqueles que tiveram alta adesão e parcialmente aderentes os pacientes que tiveram média ou baixa adesão.

Resultados A análise da adesão mostrou que 73,0% dos pacientes foram altamente aderentes, enquanto 27,0% foram parcialmente aderentes à tromboprofilaxia. O anticoagulante prescrito na alta hospitalar foi o rivaroxabana, inibidor direto do fator Xa. Obtiveram maior adesão os pacientes que não necessitaram de reforço na orientação sobre a profilaxia durante o acompanhamento e, por conseguinte, relataram boa e ótima aceitação à profilaxia, embora estivessem polimedicados durante a alta hospitalar.

Conclusão A análise dos dados obtidos permitiu concluir que os fatores que mais influenciaram na adesão foram os níveis de compreensão e aceitação dos pacientes quanto à profilaxia, a quantidade de medicamentos usada por dia pelo paciente, o custo do anticoagulante e o seu potencial em desenvolver reações adversas.

Palavras-chave

- aderência ao tratamento
- anticoagulantes
- artroplastia
- profilaxia
- tromboembolismo

Introduction

Venous thromboembolism (VTE) commonly refers to deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). Both phenomena are related to the Virchow triad, that is, venous stasis, endothelial injury, and hypercoagulability.[1]

Hip or knee arthroplasty is considered a very high-risk factor for VTE development; the American College of Chest Physicians (ACCP) Evidence-Based Clinical Guidelines recommend mechanical and pharmacological methods for VTE prophylaxis.[2–4]

However, patient compliance is essential to the efficacy of thromboembolism prophylaxis. The World Health Organization (WHO) defines compliance as the degree to which a person's behavior adjusts to the recommendations agreed with a health professional.[5,6]

Factors that can influence pharmacological compliance are grouped into the following five categories: those related to the patient, to the health system, to health condition and therapy, and to socioeconomic factors. The combined influence of these factors requires different approaches to assure compliance of the patient with the treatment.[7,8]

Thus, the present study aims to identify the profile and factors related to VTE drug prophylaxis compliance in adult patients after elective hip or knee arthroplasty surgery.

Methods

Inclusion criteria

Patients $\geq$ 18 years old who underwent hip or knee arthroplasty and who had an indication for pharmacological VTE prophylaxis.

Noninclusion criteria

Patients presenting disorientation or difficulty in understanding the goals of the study and those who did not accept to participate in the research.

Exclusion criteria

Patients who did not attend postoperative follow-up visits and those who required prolonged hospitalization resulting in an extended in-hospital prophylaxis.

Study type and sample

A prospective cohort study was carried out from August 2017 to September 2018.

The sample corresponds to the total number of patients undergoing hip or knee arthroplasty during the study period, totaling 112 subjects. However, 15.2% of the sample (17 patients) met the noninclusion criteria and 22.3% (25 patients) met the exclusion criteria; therefore, they did not participate in the study. As such, the study sample consisted of a total of 70 patients (►**Figure 1**).

Location

The study was carried out at a federal public teaching hospital. According to the 2010 census from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística [IBGE, in the Portuguese acronym]), the local population of São Luiz, state of Maranhão, Brazil, comprises $\sim$ 1,014,837 inhabitants. The per capita income of 38.8% of this population is up to half minimum wage, while the Human Development Index (HDI) of the city is 0.768.[9]

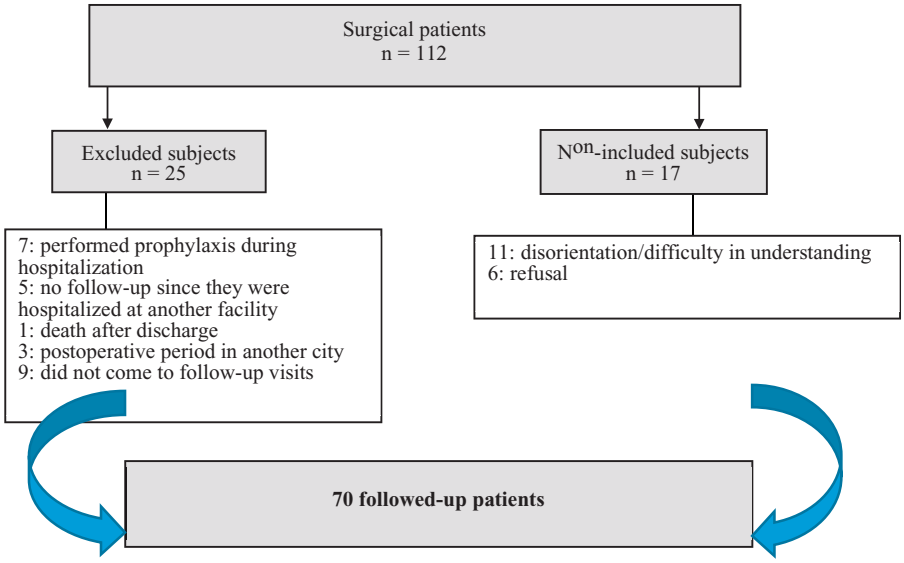

Fig. 1 Flow chart for sample determination.

Data collection

The approach to the patient started during hospitalization and continued at the orthopedics clinic until prophylaxis completion. All inpatients were screened daily for hip or knee arthroplasty using the daily surgery report.

At the first contact, the objectives of the study, the significance of VTE and its risks, and the critical role of postoperative prophylaxis were explained to the patient. At hospital discharge, the participants received guidance on medication use and on their first follow-up visit to the outpatient clinic, scheduled for 15 days after discharge. This first visit included an interview and occurred, on average, 17.9 days (standard deviation [SD], 5.8 days) after surgery.

The following data were collected:

a) Sociodemographic and economic data: age, gender, skin color (self-reported), family income, means of transportation (public or private), occupation, marital status, educational level, and family composition.
b) Clinical data: type of surgery (knee or hip arthroplasty), postoperative complications, presence of chronic conditions, and continuously used medications.
c) Data on medication compliance: compliance was indirectly measured using the Portuguese version of the Morisky Medication Adherence Scale (MMAS-8), consisting of 8 items, which was translated and validated in a study on compliance to antihypertensive treatment.[10]

The Morisky Scale is a self-reported questionnaire with eight closed-ended questions of a dichotomous yes/no nature; seven of these questions must be answered with a "no" and only one with a "yes". In addition, the last question is answered according to a scale of 5 options.[11] The scale was applied twice: at the first outpatient follow-up visit after discharge, and a few days before the predicted completion of prophylaxis. This last interview was conducted by telephone.

Compliance was quantified according to the sum of all correct answers as high (8 points), compliance (6 to <8 points), and low compliance (<6 points).[11] For the present study, subjects with high compliance were referred to as highly compliant, whereas those with medium to low compliance were referred to as partially compliant.

The guidelines recommend pharmacological prophylaxis for a minimum period of 10 to 14 days for total knee arthroplasty and total hip arthroplasty but suggest its continuation for up to 35 days after hip surgery.[4,12,13]

Unlike the compliance analysis in chronic conditions, in which the patient is considered compliant even when using the medication 80% of the time, studies on thromboprophylaxis compliance after hip or knee arthroplasty define a subject as noncompliant when at least 1 day of medication is missed during the prophylaxis period.[5,14]

Relationship between variables and adherence

Based on the five groups of compliance-influencing factors,[6] the present research correlated socioeconomic, health condition, and patient-related variables.

Statistical analysis

Data was analyzed using the NCSS 11 software (v. 2017, **SGM Analysis, Kaysville**, Utah, USA). Qualitative variables were presented in tables as absolute and relative frequencies, whereas quantitative variables were showed as mean and SD values. Data normality was tested according to the D'Agostinho-Pearson method. Subsequently, the nonparametric chi-squared (χ^2) test for independence determined the association of classificatory variables with both compliance levels (highly compliant and partially compliant). The

Spearman nonparametric correlation test assessed the linear correlation between numerical variables. The significance level for null hypothesis rejection was 5%, that is, a p-value < 0.05 was considered statistically significant.

Ethical aspects

The present study was approved by the institutional Research and Ethics Committee under the number 2.206.256.

Results

The sociodemographic and economic profile of the patients showed a predominance of females, > 60 years old, with an average age of 60.5 years old (SD, 16 years old), an average income of 2 to 3 minimum wages, up to 4 years of schooling, and retired individuals (►**Table 1**).

Hip arthroplasty (85.7%) and reports of some comorbidity (65.7%) were predominant. The most reported chronic condition was hypertension (52.9%), followed by diabetes and arthritis (both conditions with a 11.4% rate). Consequently, 70% of the patients took ≥ 5 pills a day at discharge (►**Table 2**).

As anticoagulant agent, all patients were prescribed rivaroxaban, a factor Xa inhibitor, at hospital discharge. This medication had to be purchased at private drugstores. During hospitalization, patients received unfractionated heparin (84.3%), rivaroxaban (10%), or low-molecular-weight heparin (LMWH) (5.7%).

Table 1 Sociodemographic and economic variables and their relationship with the compliance level

Variables	Total		Compliance				*p-value*
	n = 70		Partially compliant patients		Highly compliant patients		
	n	%	*n*	%	*n*	%	
Age range (years old)							
18 to 40	10	14.3	1	5.3	9	17.6	0.391
41 to 60	18	25.7	6	31.6	12	23.5	
> 60	42	60.0	12	63.2	30	58.8	
Gender							
Male	23	32.9	3	15.8	20	39.2	0.063
Female	47	67.1	16	84.2	31	60.8	
Schooling time (years)							
0 to 4	31	44.3	10	52.6	21	41.2	0.627
5 to 8	19	27.1	5	26.3	14	27.5	
> 8	20	28.6	4	21.1	16	31.4	
Skin color (self-reported)							
White	13	18.6	3	15.8	10	19.6	0.862
Black	8	11.4	3	15.8	5	9.8	
Brown	47	67.1	13	68.4	34	66.7	
Yellow	1	1.4	0	0.0	1	2.0	
Not informed	1	1.4	0	0.0	1	2.0	
Income (minimum wage)							
up to 1	30	42.9	8	42.1	22	43.1	0.981
2 to 3	32	45.7	9	47.4	23	45.1	
> 3	8	11.4	2	10.5	6	11.8	
Means of transportation							
Private	26	37.1	7	36.8	19	37.3	0.820
Public	38	54.3	11	57.9	27	52.9	
Other	6	8.6	1	5.3	5	9.8	
Occupation							
Retired	45	64.3	12	63.2	33	64.7	0.759
Performs paid activity	17	24.3	4	21.1	13	25.5	
Performs unpaid activity	8	11.4	3	15.8	5	9.8	

Table 1 (*Continued*)

Variables	Total		Compliance				*p-value*
	n = 70		Partially compliant patients		Highly compliant patients		
	n	%	*n*	%	*n*	%	
Marital status							
Lives with a partner	29	41.4	8	42.1	21	41.2	0.944
Lives without a partner	41	58.6	11	57.9	30	58.8	
Place of origin							
São Luís	40	57.1	8	42.1	32	62.7	0.272
Other location in Maranhão, Brazil	28	40.0	10	52.6	18	35.3	
Another Brazilian State	2	2.9	1	5.3	1	2.0	
Family composition							
1 to 3 people	35	50.0	6	31.6	29	56.9	0.095
4 to 5 people	25	35.7	8	42.1	17	33.3	
$>$ 5 people	10	14.3	5	26.3	5	9.8	

According to the Morisky Scale, 73% (51) of the patients were highly compliant to prophylaxis (totaling 8 points), and 27% (19) subjects were partially compliant (►**Table 3**).

The average length of stay was 5.6 days (SD, 3.7 days). The average time of extended prophylaxis was 27 days (range, 8 to 35 days) in the partially compliant group and 33 days (range, 15 to 38 days) in the highly compliant group. This difference between the groups was statistically significant ($p < 0.05$).

The most reported reasons for noncompliance were treatment abandonment or discontinuation due to suspected adverse reaction to the anticoagulant agent and lack of financial resources to buy the medication (►**Table 4**).

Only one case of VTE-related complication and one case of heparin-induced thrombocytopenia were recorded during the postoperative period. However, complications occurring in patients who were excluded from the study were not documented.

Most patients (70%) did not report rivaroxaban-related adverse reactions after hospital discharge. The most reported adverse reactions were constipation and abdominal pain (►**Figure 2**).

Table 2 Patient profile regarding clinical variables and relationship with the compliance level

Variables	Total		Compliance				*p-value*
	n = 70		Partially compliant patients		Highly compliant patients		
	n	%	*n*	%	*n*	%	
Surgery type							
Hip arthroplasty	60	85.7	17	89.5	43	84.3	0.583
Knee arthroplasty	10	14.3	2	10.5	8	15.7	
Postoperative complications							
No	62	88.6	14	82.4	46	90.2	0.385
Yes	8	11.4	3	17.6	5	9.8	
Comorbidities (self-declared)							
No	24	34.3	9	47.4	15	29.4	0.159
Yes	46	65.7	10	52.6	36	70.6	
Number of medications used per day at discharge							
1 to 4	20	28.6	9	50.0	11	21.6	0.022*
$\geq$ 5	49	70.0	9	50.0	40	78.4	

Note: † One patient could not inform how many continuous medications he took per day.
*Significant p-value < 0.05.

Table 3 Eight-item Morisky scale questions and scores

Morisky	*n*	%
Do you sometimes forget to take your medication?		
No	66	94.0
Yes	4	6.0
Thinking over the past 2 weeks, were there any days when you did not take your medication?		
No	54	77.0
Yes	16	23.0
Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?		
No	65	93.0
Yes	5	7.0
When you travel or leave home, do you sometimes forget to bring along your medication?		
No	67	96.0
Yes	3	4.0
Did you take your medication yesterday?		
No	6	9.0
Yes	64	91.0
When you feel good, do you sometimes stop taking your medication?		
No	68	97.0
Yes	2	3.0
Do you ever feel hassled about sticking to your treatment plan?		
No	68	97.0
Yes	2	3.0
How often do you have difficulty remembering to take all your medications?		
Never	59	84.0
Rarely	6	9.0
Sometimes	5	7.0
Usually	0	0
Always	0	0
Total score		
8 (high compliance)	51	73.0
6 to < 8 (medium compliance)	10	14.0
< 6 (low compliance)	9	13.0
TOTAL	70	100.0

Most subjects knew why they were taking an anticoagulant agent (82.9%), knew how to use it (92.9%), and reported good and excellent prophylaxis acceptance. As a result, there was little need for to reinforce guidelines (74.3%) regarding anticoagulant agent prophylaxis and dosage (►**Table 5**).

Table 4 Reported reasons for noncompliance

Reasons for noncompliance	*n*	%
Treatment abandonment or termination due to suspected adverse reaction to anticoagulant agent	6	8.6
Treatment abandonment or termination due to financial reason	6	8.6
Treatment termination due to forgetfulness	4	5.7
Clinical complication with readmission	1	1.4
Communication issues	1	1.4
Treatment abandonment by own accord	1	1.4
TOTAL	19	27.1

Sociodemographic and economic factors versus compliance

►**Table 1** shows that compliance is not related to social and economic variables.

Health condition-related factors versus compliance

►**Table 2** correlates clinical variables with the compliance level and shows that the number of drugs used per day at the time of discharge was associated with compliance.

Patient-related factors versus compliance

►**Table 5** shows that the degree of prophylaxis acceptance and the patient's need for guidance were related to compliance. Therefore, patients who reported excellent and good acceptance of treatment and those who did not need guidance during follow-up were most likely to be highly compliant to prophylaxis.

Discussion

The present study demonstrated the lack of a high level of compliance to outpatient thromboprophylaxis after hip or knee arthroplasty, with 27% of partially compliant subjects (medium to low compliance). This finding is consistent with a meta-analysis that showed a thromboprophylaxis compliance rate ranging from 13 to 37%.[14]

Extended prophylaxis length was inadequate, and partially compliant subjects reported interruptions in the use of the anticoagulant agent. These findings are similar to those from a study showing a thromboprophylaxis duration range from 10 to 21 days.[14]

The rate of thromboembolic and hemorrhagic events observed is consistent with the literature, which shows that a preventive anticoagulant regimen of 35 to 40 days reduces the risk of thrombosis from 3.3 to 1.3%. The risk of a major hemorrhagic accident ranges from 0.7 to 0.9%.[15]

Antithrombotic agents include antiplatelet and anticoagulant drugs. These medications are available in a wide variety in the pharmaceutical market. They may act in one or more stages of the coagulation cascade, and their mechanisms of

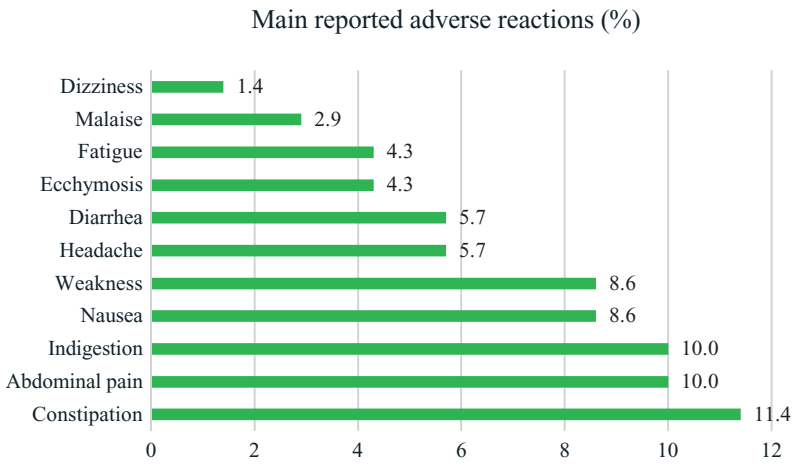

Fig. 2 Main reported adverse reactions to the anticoagulant agent.

action include direct enzyme inhibition, indirect inhibition by antithrombin binding, and antagonism of vitamin K-dependent factors.[16]

Direct factor Xa inhibitors represent the most recently introduced anticoagulants, and they are being increasingly used by clinicians. In addition to a more favorable pharmacokinetic profile, studies suggest that their safety and efficacy for VTE prevention are similar to those of the standard LMWH therapy.[11,17] Rivaroxaban is a representative from this group.

At hospital discharge, all patients were prescribed rivaroxaban 10 mg. This is an anticoagulant agent with a simple dosing schedule (one tablet per day), but it has a high cost for our patients according to their socioeconomic profile, and it is not provided by the hospital.

Therefore, a relevant issue for treatment compliance is the cost of the medication, which was cited by patients as a reason for prophylaxis termination (8.6%) in the present research. The authors believe that this fact could predict poor compliance.[18]

In countries like Brazil, accessibility to medications is crucial when analyzing treatment compliance, especially in states with low HDI, such as the one where the present study was carried out.[9] Patient access to medication would be the first condition required for treatment compliance.[19]

Table 5 Profile regarding the patient-related variables and relationship with the compliance level

Variables	Total		Compliance				*p-value*
	n = 70		Partially compliant patients		Highly compliant patients		
	n	%	*n*	%	*n*	%	
Knowledge on the purpose of the treatment							
Yes	58	82.9	15	78.9	43	84.3	0.596
No	12	17.1	4	21.1	8	15.7	
Knowledge on how to use ATC							
Total lack of knowledge	3	4.3	1	5.3	2	3.9	0.059
Little knowledge	2	2.9	2	10.5	0	0	
Good knowledge	65	92.9	16	84.2	49	96.1	
Reported treatment acceptance							
Excellent	27	38.6	4	21.1	23	45.1	0.010*
Good	38	54.3	11	57.9	27	52.9	
Bad	5	7.1	4	21.1	1	2	
Guidance requirement							
Yes	18	25.7	11	57.9	7	13.7	0.000*
No	52	74.3	8	42.1	44	86.3	

Abbreviation: ATC, anticoagulant agent.
*Significant p-value < 0.05.

Considering the groups of factors potentially affecting compliance, according to Sabaté,[6] our findings showed that sociodemographic and economic data were not related to compliance levels, as previously demonstrated by other authors.[7,18]

However, it is believed that social and economic factors in countries such as Brazil may influence compliance since they may impose on the patient the need to choose between priorities.[20]

We observed a predominance of elderly patients with comorbidities and receiving multiple drugs. This last condition, defined as the simultaneous use of ≥ 5 active compounds,[21] was related to compliance ($p < 0.05$).

This finding differs from that of another study that reported multiple medications as a factor that reduces compliance or has no influence over it.[7] However, evidence suggests that patients under a higher number of continuous medications are more likely to follow the required measures to maintain or regain their health.[22]

Our study also revealed that patients who did not need reinforcement in prophylaxis guidance during follow-up had a higher percentage of high compliance, showing that the understanding of the information influenced compliance, in contrast with the level of education of the patient.

Similar data were found by a systematic review demonstrating that the greater degree of knowledge about a disease and a higher perception of its risk suggested a greater relationship with compliance. The same review also showed that the level of education of the patient plays an important role in compliance; however, understanding the instructions and the significance of treatment are probably more important than the level of education of the patient.[7]

Another compliance-related variable ($p < 0.05$) was the degree of prophylaxis acceptance. This is consistent with a study that showed that a patient who is satisfied and believes in the treatment is more likely to comply with it.[7]

Most patients did not report suspected adverse reactions during the use of anticoagulants. However, among those who reported such reactions, 8.6% (6) subjects discontinued or abandoned treatment. This data reinforces the theory that adverse events influence compliance to medication.[6]

A limitation of our study was the use of an indirect self-reported method to measure compliance to medication, which does not assure a reliable correspondence between real and verbalized behavior, potentially leading to inaccuracies in the determination of highly compliant/partially compliant subjects. In addition, the study used a single indicator to measure compliance, the Morisky Scale. It is believed that further studies should be multicentric and use more than one compliance indicator to better detail the predictive factors of non-compliance described by our research.

Conclusion

Data analysis allowed us to conclude that there was no high compliance to extended thromboprophylaxis after hip or knee arthroplasty. The factors that most influenced the lack of compliance were the levels of understanding of the prophylaxis and its acceptance by patients, the number of medications used per day by the patient, the cost of the anticoagulant agent, and its potential to cause adverse reactions.

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Conflicts of Interests
The authors declare no conflicts of interests.

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