

Pharmacotherapy evaluation of patients on anticoagulant therapy in the internal medicine department at Hospital Universidad del Norte through pharmaceutical care practice using the Dader method

Abstract

Objective: To evaluate the pharmacotherapy of patients on anticoagulant therapy in the internal medicine department at Hospital Universidad del Norte through pharmaceutical care practice using the Dader method. **Materials and methods:** This study employed a quasi-experimental and ambispective descriptive methodology, which included a retrospective analysis of a study population called the reference group. This group consisted of 78 patients who were receiving anticoagulant therapy and were hospitalized for a period of three months in 2022. The patients in this group underwent a socio-demographic, clinical and pharmacological characterization, and analysis of medication-related problems (DRP) and negative results associated with medication (NOM), to determine the approach of the patient under pharmaceutical care practice who were hospitalized for a period of three months in the 2023, corresponding to the attended group with 66 patients. The activities were conducted in accordance with the Dader method, and the statistical analysis of the data was performed with the STATGRAPHICS Centurion XVI version 16.1.03 program, for both quantitative and qualitative data.

Results: The DRP and NOMs most frequent reported in the attended group was drug-drug interactions, and quantitative insecurity respectively, while in the reference group was reported inadequate dose, regime and/or duration as DPR and followed by the NOM quantitative ineffectiveness. The drug associated with the occurrence of NOMs was Warfarin with 57.15% in the reference group, and a 62.5% in the attended group. Finally, through the application of statistical tests (chi-squared), it was demonstrated that patients with atrial fibrillation (AF) exhibited a 4.65 probability of presenting a DRP.

Conclusion: The pharmacotherapeutic evaluation revealed potential opportunities for improvement in the management of anticoagulation in hospitalized patients. In particular, the use of warfarin was identified as a concern due to the variability in the international normalized ratio (INR), with 100% of the attended group falling outside the therapeutic window. Additionally, patients with atrial fibrillation were identified as a population that could benefit from pharmaceutical care service.

Keywords: drug therapy management, anticoagulant drug, pharmaceutical care practice, drug-drug interactions.

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Introduction

In 2019, the World Health Organization (WHO) documented that there were 55.4 million deaths globally, of which 55% were attributed to communicable and non-communicable diseases. Ischemic heart disease was identified as the leading cause of death, representing the 16% of the global total, with 8.9 million deaths.¹ Similarly, in the United States, by 2019, ischemic heart disease was the leading cause of death, responsible for 153.4 deaths per 100,000 inhabitants.² In the Colombian context, according to the National Administrative Department of Statistics (NADS), by 2022, ischemic heart disease was the leading cause of death, with 41,783 deaths registered.³ Regarding the effective reduction of the risk of stroke and systemic embolism, anticoagulant drugs are indicated. However, these drugs have a variety of limitations, including unpredictable pharmacodynamics

and pharmacokinetic responses,⁴ narrow therapeutic margin, whereby variations in plasma concentration can affect coagulation and result in either hemorrhagic or thrombotic processes, and a high frequency of interactions with drugs and food.⁵ Consequently, it is imperative to monitor the anticoagulant effect of these drugs, for which the prothrombin time is employed using a standardization formula called International Normalized Ratio (INR).⁶ Pharmacists are integral members of the health team, assuming responsibility for promoting pharmacological adherence, identifying, assessing, and preventing drug-related problems, including interactions with drugs or food, and referring patients to physicians in cases where there is a risk of adverse effects. Currently, serious drug-related problems are identified at the hospital level, making the need to address them, and by implementing the pharmaceutical care service, is possible to detect drug-related problems (DPR), in order to prevent and resolve negative

outcomes associated with medication NOMs.⁷ Therefore this practice was implemented in this study, which was focused on evaluating the pharmacotherapy of patients on anticoagulant therapy, through the sociodemographic, clinical and pharmacological characterization, DRP and NOM analysis, and the determination of this population as a target for pharmaceutical care.

Methodology

The study was descriptive, quasi-experimental and ambispective (retrospective and prospective phases), carried out in the Hospital Universidad del Norte with a duration of 16 months, in patients on anticoagulant therapy attended in the Department of Internal Medicine, over 18 years of age; were not included patients who did not agree to sign the informed consent, patients who belonged to a specialty other than internal medicine and pregnant women. In the first phase (retrospective) a sociodemographic, clinical and pharmacological characterization was performed the application of the Dader method⁷ in phases such as: State of situation, study phase and evaluation phase; the information was obtained through the review of medical records of a population of 78 anticoagulated patients of internal medicine department admitted in a period of 3 months in the year 2022, in order to identify possible DRP and NOM, and to determine the risk patterns inherent to the application of this type of medication, such as diagnosis, history, paraclinical, type of anticoagulant, therefore this group of patients was considered as a reference group. As for the second phase (prospective), a convenience sample was taken considering the size of the population (reference group), and in three months, from October to December 2023, 66 patients considered as the group attended, who entered the pharmaceutical care service in relation to their day of hospitalization, The methodology of the study was based on an adaptation of the Dader method to the hospital setting, using all phases. This group also underwent sociodemographic, clinical, and pharmacological characterization, analysis of DRPs and NOMs, with the addition of pharmaceutical interventions and care plans, data necessary to determine statistically whether this was a target population for pharmaceutical care. The statistical analysis was performed with the STATGRAPHICS Centurion XVI version

16.1.03 program, for quantitative data: mean and standard deviation, Kolmogorov-Smirnov (normality distribution), and Student's t-test (comparing means of two variables). In addition, a Chi-square and ANOVA test were performed on the qualitative data. This study was approved by the mission research committee of the Faculty of Chemistry and Pharmacy of the Universidad Del Atlántico, by the research committee of the research center of the Hospital Universidad del Norte, and by the Research Ethics Committee of the Health Sciences Division of the Universidad Del Norte.

Results

For all analyses, a confidence level of 95% and an error of 5% corresponding to a P-value of 0.05 were considered. In total, 144 patients were evaluated, in the reference group 78 were retrospectively reviewed, and according to this number the sample of patients in the prospective segment corresponding to 66 patients was estimated. In the sociodemographic characterization (Table 1), different types of variables were reviewed:

- Female gender in each group was the most predominant with a percentage greater than 50%.
- The affiliation regime presented similarities with the subsidized regime in both groups with a percentage of more than 70%.
- In relation to age, there were statistically significant differences through the Student's t-test, the demographic segment was mostly adults over 68 years of age.
- As for the occupation variable, an ANOVA test was performed, and the result was not significant.
- To compare the relationship between the occupation variable and the subsidized regime, a CHI2 test was performed for the housewife occupation in the reference group, which had a P-value of 0.000, being statistically significant, and through the odds ratio test it was indicated that there is a 10.456 probability that a patient with housewife occupation is in the subsidized regime.

Table 1 Socio demographic and clinical characterization

Variables	F Attended group	RF (%)	F Reference group	RF (%)	Test	P-Value	
Count	66	-	78	-	-	-	
Age (years ± SD)	68,90 ± 15,61	-	73,64 ± 12,45	-	t: 2,042	0,043	
Female Gender	34	51,56	49	62,82	-	-	
Male Gender	32	48,49	29	37,18	-	-	
Weight (kg ± SD)	74,27 ± 19,39	-	68,54 ± 16,63	-	t = 1,869	0,064	
Health affiliation regime	Subsidized	48	72,73	60	76,92	CHI2: 1,652	0,000
	Contributory	18	27,27	18	23,08		
	Unemployed	23	34,85	18	23,08		
Occupation	Housewife	19	28,79	36	46,15	ANOVA: 2,42	0,206
	Retired	4	6,06	12	15,38		
	Other occupations	20	30,30	12	15,38		
Glomerular filtration rate (CKD-EPI) mL/min/1.73 m2	55,50 ± 20,94	-	51,08 ± 21,58	-	t: 1,228	0,221	
INR in seconds patient with Warfarin (seconds ± SE)	3,00 ± 1,82	-	2,29 ± 1,29	-	t: 1,919	0,058	
Days to target INR (Warfarin patients) (days ± SD)	7,0 ± 7,0	-	5,66 ± 3,78	-	t: 0,290	0,786	
Bleeding risk has- bled score	Low risk	7	23,3	17	27,9	ANOVA: 0,33	0,744
	Intermediate risk	9	30,0	22	36,1		
	High risk	14	46,7	22	36,1		

Abbreviations: SD, estándar deviation; F, frecuencia; R, relative frecuencia; t, student's t test; CKD-EPI, chronic kidney disease epidemiology collaboration; other occupations, miscellaneous jobs; elementary occupation, physician, lawyer, electrician, driver, sales agent, launderes, tradesman, recycler, domiciliary, welder, industrial supervisor.

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Moving on to the clinical characterization, the relevant paraclinical parameters are presented:

- a) GFR had a mean greater than 50 ml/min/1.73 m² in both groups, thus patients had renal disease and/or renal injury.
- b) Regarding the INR parameter, 11% of the patients in the group treated were anticoagulated with Warfarin and in the reference group it was 28.57%.

With an average INR of 3.00 for the group attended and 2.29 for the reference group, an analysis was made by pathology and INR value (supra-therapeutic, infra-therapeutic and therapeutic), the distribution according to INR values is as follows:

- a) For the attended group there were patients with treatment for venous thrombosis with 40%, atrial fibrillation with 40% and

mechanical valve replacement with 20%, for these pathologies the INR is 2-3 except for mechanical valve replacement in mitral position which is 2.5-3.5.

- b) For the reference group, there were 46.85% of patients with mechanical valve replacement, 7.14% for patients with biological valve replacement, 35.74% in patients with treatment for venous thrombosis and 14.28% in treatment for stroke prevention due to atrial fibrillation. The INR for biological valve replacement is 2-3 but there is scientific evidence that approves the use of other oral anticoagulants.
- c) The INR (Table 2) was determined according to the value of the patients whether it was therapeutic, infra-therapeutic or supra-therapeutic.

Table 2 INR characterization according to range and pathology

Sub therapeutic INR AG	Pathology	Therapeutic INR range (8-9)	Patient value	Remarks
60%	Atrial fibrillation	2-3.	1,0	Extension of hospital stay
	Intra-cavitary thrombus	2-3.	1,16	
	Mechanical valve replacement	2,5-3,5	1,14	No INR monitoring
Sub therapeutic INR RG	Pathology	Therapeutic INR range (8-9)	Patient value	Remarks
64,30%	Mechanical valve replacement	2,5-3,5	1,45	Lack of knowledge in therapeutic range
	Atrial fibrillation	2-3.	1,70	Patients with GRF less than 15
	Deep vein thrombosis	2-3.	1,44	
Therapeutic INR RG	Pathology	Therapeutic INR range (8-9)	Patient value	Remarks
21,43%	Mechanical valve replacement	2,5-3,5	2,5	Abrupt increase in INR due dose adjustment
Supra-therapeutic AG	Pathology	Therapeutic INR range (8-9)	Patient value	Remarks
40%	Mechanical valve replacement	2,5-3,5	4,08-7,15	Interactions with analgesics
	Deep vein thrombosis	2-3.	3,14-3,22	
INR supra therapeutic RG	Pathology	Therapeutic INR range (8-9)	Patient value	Remarks
14,30	Mechanical valve replacement	2,5-3,5	4,98-7,05	INR sensitivity
	Atrial fibrillation	2-3.	3-75.	Posology no clear

Abbreviations: AG, group attended; GR, Reference group.

Continuing with the pharmacological characterization, it was found that the most frequent drug was enoxaparin with 53.85% in the 66 patients in the group attended. In contrast, in the reference group, the most frequent drug was Apixaban with 31.53% and rivaroxaban with 18.02% for a total of 49.55% in direct oral anticoagulants. Regarding the indication (Figure 1 and 2), in both groups, stroke prevention and systemic embolism due to atrial fibrillation stood out, with 45.45% for the group treated and 66.67% for the reference group. The correlation of the most frequent indication with anticoagulant drugs is also described:

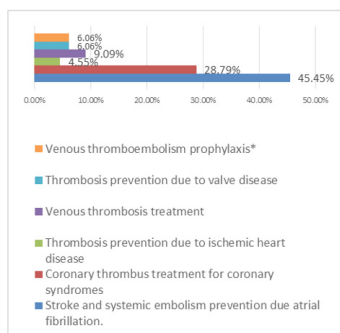


Figure 1 Anticoagulants indication in attended group.

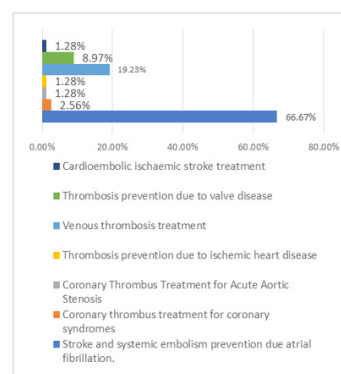


Figure 2 Anticoagulants indications in reference group.

- a) Group attended in stroke prevention and systemic embolism due to atrial fibrillation: apixaban with 17.95%, followed by rivaroxaban with 14.10%, and finally enoxaparin with 12.92%.
- b) Reference group for stroke and systemic embolism prevention due to atrial fibrillation: Apixaban with 27.93%, followed by enoxaparin with 17.11%.

It should be noted that there was an indication for thromboprophylaxis in the attended group, but the dose used was higher than 40 mg/24h, so this indication was included because it used anticoagulant doses. On the other hand, a total of 67 Drug Related Problems (DRP) were identified in the group attended, the most frequent being Drug interactions with 28.35% followed by prescription errors with 25.37%, while in the reference group there were 83 DRP, with inadequate dose, regimen and/or duration as the most frequent DRP with 24.10% followed by probability of adverse effects with 20.48% and in third place interactions with 15.66%. According to the Dader method, the

DRP situation was characterized as risk of occurrence with 40.30% for the group receiving care and 33.73% for the reference group, as well as the problems manifested (defined as NOM) with 11.94% for the group receiving care and 25.30% for the reference group. An analysis of variance was performed on all the variables through the ANOVA test: 3.22 P-value: 0.012, so there are statistically significant differences between the means of the variables. To determine which means are significantly different from others, the Levene's variance test was used in Table 3.

Table 3 Variance verification test of all variables associated with drug-related problems

Comparison	Sigma-1	Sigma-2	F-ratio	P-value
Number of DRP attended/Manifested health problems attended	7,751	1,103	49,328	0,000
Number of DRP attended/ Health problem manifested referral	7,751	3,176	5,954	0,009
Number of DRP attended/ Risk of occurrence reference	7,751	3,697	4,394	0,028
Number of DRP referral/ Reported health problem addressed	7,146	1,103	41,925	0,000
Number of DRP referral/ Health problem reported referral	7,146	3,176	5,061	0,017
Number of DRP reference/ Risk of occurrence reference	7,146	3,697	3,735	0,049
Reported health problem addressed/Reported health problem referral	1,104	3,562	0,096	0,002
Manifested health problem treated/Risk of occurrence treated	1,104	4,156	0,070	0,000
Manifested health problem addressed/ Risk of occurrence referral	1,104	3,698	0,089	0,000

There were 21 NOMs in the reference group (Table 4) and they are distributed in: ineffectiveness with 57.14% (quantitative ineffectiveness 47.61% and 9.52% non-quantitative ineffectiveness), safety with 33.33% (all are quantitative insecurities) and necessity with 9.52% (untreated health problem). The drug with the highest association was Warfarin with 57.15 %, and the NOM most frequently presented as the main cause of NOM was inadequate dose, regimen and/or duration with 52.38 %. Table 5 shows the NOMs of the group attended, where 8 NOMs were presented with the same frequency,

with 50% for safety NOMs and 50% for effectiveness (37.5% quantitative effectiveness and 12.5% non-quantitative effectiveness), as for the drug with the greatest association of NOMs was Warfarin with 62.5%, followed by the most frequent NOM dose and duration of the treatment, with a rate of 62.38%, and the most frequent NOM dose and duration of the treatment, with a rate of 12.38%. In total there were 5 pharmaceutical interventions corresponding to 38.46% of 13 interventions carried out, and 4 interventions were accepted because most of them were associated with patient and family education.

Table 4 Manifested health problems related to negative outcomes associated with medication in reference group

Manifested health problems	NOM classification			Anticoagulant	Drug related problem
	E	N	S		
Supra-therapeutic INR			1	Warfarin	Inadequate dosage pattern and/ or duration
			1	Warfarin	Interactions: Warfarin-Clopidogrel Warfarin-Omeprazole
			1	Warfarin	Prescription error
Sub therapeutic INR	8			Warfarin	Inadequate dosage pattern and/ or duration
	1			Warfarin	Insufficient treated health problem
Thrombocytopenia			1	Apixaban	Inadequate dosage pattern and/ or duration
			1	Enoxaparin	Probability of adverse effects
Thrombocytosis			1	Enoxaparin	Probability of adverse effects
Bleeding			1	Enoxaparin	Administration error (Dose not adjusted based drug presentation)
Stroke of cardioembolic origin		2		Patient was not anticoagulated	Insufficient treated health problem
	1			Apixaban	Other health problems affecting treatment
Deep venous thrombosis in lower limb	1			Rivaroxaban	Inadequate dosage pattern and/ or duration
	1			Rivaroxaban	Other health problems affecting treatment
Total	12	2	7	57,15% Warfarin	52,38% Inadequate dosage pattern and/ or duration

Abbreviations: E, effectiveness; N, need; S, safety.

Table 5 Manifested health problems related to negative outcomes associated with medication in attended group

Manifested health problems	NOM Classification			Anticoagulant	Drug related problem	Pharmaceutical intervention
	E	N	S			
Supra-therapeutic INR			I	Warfarin	Interaction:Warfarin + Acetaminophen/Tramadol.	Patient education For self-medication
			I	Warfarin	Interaction:Warfarin + tramadol	Drug substitution (Not accepted)
Sub therapeutic INR	I			Warfarin	Other health problems affecting treatment	Patient education: INR levels, green vegetable and fruits
	I			Warfarin	Inadequate dosage pattern and/ or duration	Not performed
Thrombocytopenia			I	Warfarin	Inadequate dosage pattern and/ or duration	Add anticoagulant
			I	Enoxaparin	Probability of adverse effects	Not performed
Thrombocytosis			I	Enoxaparin	Probability of adverse effects	Not performed due active bleeding
Stroke of cardio embolic origin	I			Apixaban	Sub therapeutic dose (2.5 mg/12h)	Patient education (the dose adjustment was out of the hospital)
Total	4	0	4	62,5% Warfarin	37,5% Inadequate dosage pattern and/ or duration	62,5% Pharmaceutical interventions performed.

Abbreviations: E, effectiveness; N, need; S, safety.

To finalize the results, CHI2 independence tests were performed, p-value 0.012 on diagnostic variables (atrial fibrillation) and DRP, demonstrating that patients with atrial fibrillation have a high probability of presenting a DRP, with an odds ratio (OR) that showed that they are 4.65 times more likely to present a DRP, demonstrating that they are a target population to be attended in pharmaceutical care. The same analysis was performed on DRP and interventions with the CHI2 test p-value 0.004. As for the OR, patients with DRP have 8.83 times the probability of being intervened, which shows that it is necessary for the pharmacist to intervene so that they do not progress to NOM.

Discussion

Our study revealed some similarities with previous research, particularly regarding the prevention of stroke associated with atrial fibrillation in both groups. This finding aligns with the observations reported by Garcia and Mendez.⁸ Additionally, our DRP analysis indicated that interactions and the probability of adverse effects were the most prevalent, consistent with the findings in the group attended and the reference group, respectively. Conversely, a more comprehensive examination was conducted on the NOM, categorized according to necessity, efficacy, and safety. In relation to the NOM of necessity, the study by Cortez LJ⁹ revealed it was caused by medication not indicated for the current health problem. This finding is analogous to the insufficiently treated health problem observed in the reference group. In terms of effectiveness, there was quantitative ineffectiveness associated with dose, regimen and/or duration, with frequencies higher than 60% in both groups. In the study conducted by Cortez LJ,¹⁰ similar causes were presented with 52% of cases classified as inadequate dose for the current health problems. In terms of dosage, 10% of cases involved under dosing. In contrast, in the non-quantitative infectivity, the DRPs were associated with other health issues that could potentially impact the treatment, such as the patient's idiosyncrasies or underlying health conditions like obesity. The NOM of safety in the two groups was quantitative and in the study of Cortez JL the NOM of association was frequency or inadequate mode of administration with 32%, unlike in our study, the most frequent NOM were dose, regimen and/or duration not adequate

and probability of adverse effects, with cases of clinical significance such as interactions with acetaminophen.¹¹

The study highlights representative findings in each NOM presented, in the need NOM in the reference group two patients with a history of atrial fibrillation were identified who presented stroke of cardio embolic origin, who were not anti-coagulated, taking into account that ischemic stroke is the main risk of AF, according to the Framingham study, stroke events due to AF can be fatal, and it was even determined that mortality increased by 1.84 in the presence of AF.^{12,13} In the case of quantitative ineffectivities a patient in the group attended, aged 70 years with 80 kg and normal renal function presented a stroke of cardio embolic origin, as she had a history of atrial fibrillation and was anti coagulated with Apixaban 2.5 mg/12h, this dose according to the FDA is defined as a reduced dose according to compliance with 2 of the following 3 criteria: Age > 80 years, body weight ≤ 60 kg, or serum creatinine > 1.5 mg/dL (133 micromoles/L),¹⁴ which the patient did not meet at that time, thus it could have been a possible ineffectiveness associated with under-dosing. In contrast, in the non-quantitative ineffectiveness, in the group attended there was a case of a patient anticoagulated with Warfarin at a dose considered adequate, with a history of morbid obesity and a BMI > 40 kg/m², who reached his target INR after one week, according to the literature, Warfarin does not have enough clinical studies to prove efficacy in patients with obesity this idea is supported by Moll S, Crona DJ, Martin K¹⁴ in their opinion-type article, who share that there is a lack of solid clinical data to support the prescription of oral anticoagulants in patients with BMI > 40kg/m².

Finally, the NOM of safety in the two groups was quantitative, the study by Cortez JL,¹⁰ the NOM of association was frequency or inadequate mode of administration with 32%, unlike in our study the NOM of greater frequency were dose, regimen and/or duration not adequate and probability of adverse effects, with cases of clinical significance as interactions with acetaminophen, which according to a study by Parra D, Becky NP, Stevens¹⁴ to determine if there is interaction between acetaminophen and Warfarin that alters INR which was prospective, randomized, double blind and placebo controlled, and it was determined that this interaction is clinically significant and

patients had supra-therapeutic INR at 2g/24h dose after the second week because they presented a significantly higher mean INR than the placebo group ($p=0.01$). Due to these findings, the medical team of the hospital will give more importance to patients with anticoagulant therapy through the management of clinical practice protocols in the institution including the participation of the pharmacist, likewise it was determined that the patient with Warfarin and the patient with atrial fibrillation should immediately enter the pharmaceutical care service. To conclude, the pharmacotherapy evaluation was carried out, and some opportunities for improvement in the management of anticoagulation in hospitalized patients were identified. Therefore, future studies should focus on the implementation of more personalized pharmaceutical interventions, for example, using health technologies to monitor and analyze the behavior of the INR on platforms such as applications or web pages, investigate the impact of education programs on adherence to treatment, food interactions and risks of self-medication on the optimization of this therapy, as well as explore the safety and effectiveness between direct oral anticoagulants (DOACs) and Warfarin in different populations in order to offer a safe, effective and efficient therapy to the entire population.

Limitations

This study faced limitations associated with the lack of recognition by the health team of the figure of the pharmacist with the capacity to evaluate the pharmacological treatment of the patient, as for the Dader method, which is defined for the community pharmacy in Europe, in our study it was applied to the hospital pharmacy, which limited the execution of all the phases, Finally, the ambulatory health system in Colombia limits the dose adjustment of patients with Warfarin, because the laboratory tests are analyzed days after taking the sample and the dose adjustment is not done with a real INR measurement.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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