Research Article

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The One-Year Outcome of Patients with Non-valvular Atrial Fibrillation According to the Nature and Quality of the Antithrombotic Treatment Administered on an Outpatient Basis

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ABSTRACT

Background: *Prior studies have shown a treatment gap in oral anticoagulant (OAC) use among patients with atrial fibrillation. It has been also shown that the lack of correct anticoagulation leads to greater risks of thromboembolic complications*

Methods: *Using data collected beetween 2016 and 2017 we analysed the outcome of NVAF patients according to the nature and the quality of the antithrombotic treatment preccribed on an outpatients basis.*

Results: *The mea nage of patients was 61.8 years with a male predominance of 52.7%. Dilated cardiomyopathies were the most prevalente underlying cardiopathies. The thromboembolic ris was high with a mean CHA_2DS_2VASC Score of 3. The hemorragic risk was low according to the HASBLED mean score of 0.8.*

Among 186 outpatients identified in our registry 135 received oral anticoagulant mainly VKA (132/135:97.8%), 28 received aspirin while 23 received no antithrombotic treatment. The one-year analysis revealed that patients well anticoagulated (TTR ≥65%) had the less mortality prevalence while those with TTR<65%, treated with aspirin or receving no antithrombotic treatment presented the highest mortality rate (p=0.018).

Conclusion: *Our work confirms the suboptimal use of oral anticoagualnt therapy in the management of NVAF and the necessity of a good oral anticoagulation therapy in the management of NVAF even in black patients thought to have lesser risk of thromboembolic complications.*

Keywords

Non valvular Atrial fibrillation, Oral anticoagulant therapy, Antithrombotic therapy, Stroke, Haemorrage, Mortality.

Introduction

Atrial fibrillation (AF) is a major public health problem worldwide [1]. Its prevalence and incidence are increasing with the aging of the population, particularly in developed countries [1,2]. The trend seems the same in Africa despite patchy epidemiological data [3,4].

AF is also a potent independent factor of thromboembolic risk and ischemic stroke [5] and is a source of significant mortality [1,2].

The prevention of thromboembolic events by long-term oral anticoagulation remains unavoidable and therefore constitutes a major objective in the management of AF. In this context, vitamin K antagonists (VKAs) are a major therapeutic class [6,7]. Their use has increased year by year with the positive effect of a significant reduction in the frequency of thromboembolic complications related to AF but at the cost of a significant risk of bleeding [8,9].

Despite the advent of direct oral anticoagulants (DOAs), which have comparable efficacy and which induce less hemorrhage and are easier to handle [10,11], VKAs still keep in our countries a place of choice in the therapeutic strategy because of their more accessible cost.

Despite the benefits of oral anticoagulant therapy in the prevention of thromboembolic events during atrial fibrillation, its use is still suboptimal [12] or sometimes inappropriate [13]. Several studies [12,14] showed an increase in thromboembolic complications in patients who were not or inadequately anticoagulated despite a CHA_2DS_2VASC score ≥ 2 as prescribed by the recommendations [15]. We carried out this work in a black African context in order to analyze the one-year outcome of patients with non-valvular atrial fibrillation depending on the nature and quality of the antithrombotic treatment instituted on an outpatient basis. A context where accessibility to medication and adherence to recommendations sometimes constitute an obstacle to the quality of the management of patients [16, 17].

Patients and Methods

It was a retrospective cohort study carried out at the Abidjan Heart Institute (AHI).

Study population

Were included consecutively patients aged at least 18 years followed as outpatients between 2014 and 2016 for at least one documented non-valvular atrial fibrillation episode. We then subdivided them into four groups according to the existence and / or the nature of the anti-thrombotic treatment (antiplatelet agents or VKAs), then according to the quality of anticoagulation estimated by the TTR in patients treated with VKAs (TTR < 65%, TTR ≥ 65%).

Data sources

Data were obtained:

- Either from the patient's medical record and biology records for INR results.
- Or at the interrogation of the patient or people around him in case of cognitive disorders.

Criteria for judgment:

They were represented by:

- Thromboembolic complications (Ischemic stroke, TIA, peripheral embolism) and hemorrhagic complications.
- By death from any cause.

Definitions of variables

Variables to explain the TTR

The time spent in the target therapeutic zone (TTR) of each patient on VKAs was calculated by the Rosendaal method using a computer program in Excel format [18]. Patients were subsequently divided into 2 groups according to whether their anticoagulation was adequate (TTR ≥ 65%) or not adequate (TTR <65%).

Thromboembolic risk

The thromboembolic risk of each patient was assessed using the $CHA_2D_{S2}VASc$ score [15].

The risk was low, intermediate, and high for CHA_2DS_2VASc scores of 0, 1, and ≥ 2, respectively.

Thromboembolic Complication

Was considered as thromboembolic complication related to atrial fibrillation any embolic event (ischemic stroke, TIA) occurred during the last 6 months of treatment with VKAs.

Hemorrhagic risk

The hemorrhagic risk was assessed by the HASBLED score [15]. It was low or intermediate for a score ≤ 2, high for a score ≥ 3.

Major hemorrhage

Major hemorrhage was defined according to the 2005 criteria of the International Society on Thrombosis and Haemostasis [19].

Major hemorrhage was defined as:

- Fatal hemorrhage or;
- requiring hospitalization or;
- located in a critical site, namely: intracranial, intra-spinal, retro-peritoneal, intraocular, intra-pericardial, intra-articular, intramuscular with syndrome of lodge and / or having caused a fall in hemoglobin level ≥ 2g / L or requiring a transfusion of at least 2 units of packed red blood cells or whole blood.

Explanatory variables

Explanatory variable of interest

The TTR (variable to be explained) can also explain any embolic and hemorrhagic complications in patients who have received oral anticoagulant therapy.

Definitions of terms and variables used in the survey

Basing ourselves on the different assessment scores of elderly patients' autonomy (ADL, IADL and MMS), we defined

- The total autonomy, total dependence and partial dependence of the patient.
- Total autonomy: a patient was considered autonomous when he had no physical or mental deficit and was able to follow himself his health condition and the taking of his medication.
- Total dependence: A patient was considered to be totally dependent when he had a physical and / or cognitive deficit requiring the permanent presence of a third party for his vital needs and treatment.
- Partial dependence: Was partially dependent any patient needing help for the main acts of daily life such as eating, bathing, getting up, going to bed, medication recalling.

Data processing and analysis

The collected data had been entered in an EPI info database from the software **EPI info 3.5.3**.

The software **R version 3.3.3** was used for statistical analysis of the data.

The overall features of the subjects in our study have been described. Quantitative variables were presented with their mean and standard deviation. The qualitative variables were presented according to their proportion and confidence interval.

The chi2 test or the exact Fisher tests were used for the comparison of proportions. Statistical tests were considered significant for values of $p<0.05$. When a variable was significantly associated with the TTR, the Odds Ratio (OR) was calculated with its 95% confidence interval. At the end of this univariate analysis, only the variables which, in association with the TTR classes (variable to be explained) had a value of $p<0.25$, were included in the logistic model for the multivariate analysis.

For the multivariate analysis we performed a logistic regression to characterize the relationship between the TTR classes (variable to be explained) and the explanatory variables whose p value was <0.25 during the univariate analysis. At the end of this multivariate analysis, variables with a p value <0.05 should be included in the final model.

Ethical considerations

Our study did not have any direct interference in the management of patients. We therefore obtained oral consent from patients included in the study for the use of their biomedical data.

However, the patient and/or his representatives were systematically informed about the nature and objectives of the study. The confidentiality of the biomedical data collected was ensured by anonymity on the survey sheets.

Results

Sociodemographic features

The mean age of the patients was 61.8 years (median age: 63.5 years) with a male predominance of 98 men (52.7%) (Table 1). Risk factors were dominated by hypertension (126 patients, 67.7%). A history of embolic events was found in 40 cases including 32 cases (17.2%) of strokes.

Table 1: Baseline Characteristics of the patients population

		Number	%
Heart failure		109	58,6
Diabetes		18	9,7
Hypertension		126	67,7
Stroke		32	17,2
TIA		6	3,2
Peripheral Embolism		2	1,1
Atherosclerosis		5	2,7
DVT		3	1,6
PE		2	1,1
HIV+		6	3,2
No medical history		13	7,0
DCM		60	32,3
No cardiopathy		36	19,4
Valvulopathy *		33	17,7
Hypertensive cardiopathy		15	8,1
Ischemic Cardiopathy		14	7,5
HCM		10	5,4
Thyrotoxicosis		7	3,8
Cor Pulmonale		2	1,1
Dysthyroidysm		1	0,5
Pulmonary Hypertension		1	0,5
Acute Coronary Syndrome		2	1
Péricarditis		1	0,5
CHA_2DS_2VASc	0	4	2,2
	1	75	40,3
	≥ 2	107	57,5
HASBLED	0	80	43,0
	Faible	64	34,4
	High	42	22,6

Dilated cardiomyopathy (32.3%), valvulopathies (17.7%) and hypertensive heart disease (8.1%) were the underlying heart diseases most frequently associated with AF in our study (Table 1). Heart failure predominated in 58.6% of cases. In the majority of cases the type of atrial fibrillation could not be specified (63.4%), however in 30.6% of cases it was newly diagnosed atrial fibrillation.

Thromboembolic and hemorrhagic risk scores

Thromboembolic risk was high with an average CHA_2DS_2VASc score of 3 ± 1.5 and a low bleeding risk with an average HASBLED score of 0.8.

Antithrombotic treatment

Although 182 patients (97.8%) in our sample had high thromboembolic risk, only 135 (72.5%) received anticoagulants including 131 (97%) VKAs particularly acenocoumarol (124 that is 92%), seven (5.3%) fluindione and four patients (3%) DOAs (direct oral anticoagulants) (Figure1).

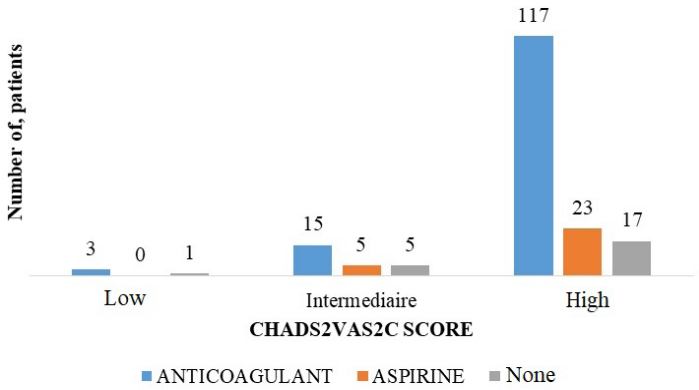

Figure 1: Antithrombotic treatment according to the $CHAS_2D_2VASC$ Score.

Among patients on VKAs, 132 (98%) had at least moderate CHA_2DS_2VASC score justifying anticoagulant therapy when three others (2%) who had a CHA_2DS_2VASC score at zero were unduly anticoagulated.

Twenty-eight patients (15%) received aspirin 23 of whom (82.1%) had a high score justifying oral anticoagulation. Twenty-three patients (12.4%) 17 of whom (74%) with a high CHA_2DS_2VASc score didn't receive any antithrombotic treatment. Among the remaining six, five had an intermediate score that could justify the prescription of antiplatelet agents. In addition to treatment with VKAs, 108 (80%) patients received more than four other drug classes.

For the surveillance of VKAs treatment, 1081 INR assays were performed in the 131 patients on VKAs during the study.
The average number of INR per patient was 8.4 and the mean duration between two INR controls was 10 days. Only 339 that

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age	70	67	68	58	85	67	78	63	77
Gender	Male	Male	Male	Male	Female	Female	Female	Male	Female
Patients medical history	Diabetes Hypertension	Hyprten-sion+Stroke	Diabetes + Hypertension +Stroke	Heart failure Diabetes+ Hypertension	Heart failure+Hy-pertension	Hyperten-sion+TIA	Hypertension	Heart failure+Di-abetes+Hyperten-sion+stroke	Heart failure +Hyperten-sion
Underlying Cardiopathy	Valvulo pathy	Ischemic Cardiopathy	Cœur Sain	Ischemic Car-diopathye	Valvulo pathy+	Hypertensive cardiopathy	Pulmonary Hypertension	DCM	Ischemic Cardiopathy
Antithrombotic treatment	Aspirin	Aspirine	VKA	VKA	VKA	VKA	VKA	VKA	VKA
CHA_2DS_2VASc	3	5	5	3	5	5	4	5	5
HASBLED	1	2	2	0	2	2	1	2	2
TTR	Unknown	Unknown	34.2	Unknown	Unknown	Unknown	23.2	36	Unknown
Thromboembol-ic complications	Stroke	Stroke	Peripheral Ischemia	Stroke	Stroke	Stroke	Stroke	Stroke	Stroke

Table 2: Characteristics of patients presenting thromboembolic complications.

	Patient 1	Patient 2	Patient 3	Patient 4
Age	55	59	78	68
Gender	Male	Male	Female	Male
Medical history	Heart failure +Hypertension	Heart failure +Hypertension +Stroke	Hypertension +Stroke	Hypertension
Underlying Cardiopathy	DCM	DCM	Pulmonary Hypertension	Valvulopathy
Antithrombotic treatment	None	VKA	VKA	VKA+ASPIRIN
CHA_2DS_2VASc	2	4	6	2
HASBLED	2	1	1	1
TTR	Unknown	Unknown	23,2	38,6
Haemorragic complications	Gastrointestinal Bleeding	Cranial Haemorrhage	Gastro-intestinal Bleeding	Gastro-intestinal bleeding

Table 3: Characteristics of patients with a major haemorragic complication.

		Patients under VKA		Patients without VKA		Total	P-value
		TTR≥65%	TTR<65%	patients under Aspirin	patients without any antithrombotic treatment		
		N (%)	N (%)	N (%)	N (%)	%	
Evolution	All cause mortality*	01 (11,1)	45 (35,7)	14 (50,0)	14 (60,9)	39,8	0,018***
	Lost in follow-up**	00 (0,00)	16 (12,7)	01 (3,6)	00 (0,00)	9,1	
	Alive***	08 (88,9)	65 (51,6)	13 (46,4)	09 (39,1)	51,1	
Complication	Thromboembolic complications	00 (0,00)	07 (5,55) * 05 *** 02	02*** (7,14)	00 (0,00)	4,84	-
	Haemorragic complications	00 (0,00)	03 (2,4) 02* 01**	00 (0,00)	01* (4,3)	2,2	

Table 4: Outcome of patients according to their antithrombotic treatment status

is 31.3% of the INR results were in the required therapeutic area between 2 and 3. Figure 2 illustrates the distribution of INR assay results by group.

As for the TTR analysis, the average time spent in the therapeutic zone was 54.5 days ± 6.3 with extremes of zero day and 249 days. Mean TTR (mTTR) was 22.6% ± 2.41 with only 7% of patients with TTR ≥ 65% (Table 4).

Evolutionary features

Nine patients (5%) whose features are summarized in table had a thromboembolic complication including eight ischemic strokes and one peripheral arterial embolism. These were high thromboembolic risk patients with a mean CHA_2DS_2VASC score of 4.4. However, they had poor anticoagulation. Seven patients received VKAs and two received aspirin. The treatment with VKAs was of poor quality since the TTR could only be calculated in four patients and was <65%, while the other three had no INR assay.

Hemorrhagic complications

They were observed in 4 patients (2.2%), including three major

hemorrhages. Among them, two received VKAs and another patient a combination VKAs and Aspirin. The fourth patient received no antithrombotic treatment. They all had a low risk of hemorrhage estimated by HAS-BLED (Table 3). None of the patients on VKAs had anticoagulation of good quality.

Deaths

At the end of one year of follow-up, 95 patients (51.1%) were alive, 74 died (39.8%) and 17 (9.1%) were lost to follow-up. The outcome of patients according to the type and quality of antithrombotic treatment is shown in table 4.

Among the 131 patients on VKAs treatment, 43 (35.2%) died, 42 of whom (97.7%) had poor quality anticoagulation (TTR <65%). Fourteen (50%) of the patients on aspirin died, as well as 14 (60.9%) who had not received antithrombotic therapy. One (25%) of the four patients who received a DOA also died.

In comparative analysis, it appeared that patients who did not receive anticoagulant treatment (those treated with aspirin or those who had no antithrombotic treatment) or those who had a poor anticoagulation quality (patients on VKA with a TTR<65%).

Discussion

In this original work in our context, we have noted that the prescription of antithrombotic therapy in the prevention of thromboembolic events of non-valvular atrial fibrillation is not optimal. It does not always respect the recommendations [15]. Several studies have already revealed this under prescription both in hospital [20] and outpatient basis [12,16,17,21] even if this prescription seems universally bad, some countries in particular Scandinavia seem to present the best rates [22].

This seems to reflect a certain efficiency of the health system in these countries. In our African countries where health systems are characterized by scarcity of resources and impoverishment of populations, it is however possible to obtain better results when setting up dedicated structures such as anticoagulation clinics [23].

The prescription of anticoagulation must also meet another objective which is that of quality. It depends closely on the monitoring. Indeed Active A study [24,] and Active W study [25] revealed that platelet anti-aggregation with aspirin (Active A) and double platelet anti-aggregation (aspirin and clopidogrel) provided very little protection against thromboembolic events during FANV and that treatment with VKAs with a TTR <65% did not do better than double platelet anti-aggregation in terms of prevention of thromboembolic events and mortality. A TTR ≥ 65% appeared as the level of anticoagulation with VKAs that provides the best protection against thromboembolic events in the management of non-valvular atrial fibrillation. In our series, patients who had thromboembolic complications received aspirin or had poor anticoagulation with VKAs (TTR < 65%) even though a low TTR or unstable INR is not currently a formal risk factor of onset of ischemic stroke [15].

Hemorrhagic complications have occurred in patients with low risk of bleeding. Patients on anticoagulants, however, had a poor TTR that can very well reflect INR >3; level of anticoagulation at which the risk of bleeding is very high [26-30].

These patients also had a history of ischemic stroke that is recognized as a predisposing factor for bleeding complications [31,32].

The ideal would be to have the level of INR at the time of the bleeding accident. In addition, the quality of anticoagulation was assessed using the TTR, which is not a constant value but varies over time. However, the retrospective nature of our work did not allow us to analyze their level of anticoagulation at the time of the bleeding accident.

Furthermore, the application of the SAMeT2TR2 score [33], which makes it possible to identify patients at risk of poor anticoagulation with VKAs, could be useful in the choice of the anticoagulant in the prevention of thromboembolic events during non-valvular atrial fibrillation by focusing on DOAs in those who will present the highest risk of poor anticoagulation.

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