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Management and risk factors of Atrial Fibrillation

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Management and Risk Factors of Atrial Fibrillation

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Summary: Atrial fibrillation (AF) is a common arrhythmia associated with various risk factors and significant morbidity and mortality. This article presents findings from a study involving 115 patients with permanent AF. The study examined demographics, risk factors, associated pathologies, complications, and anticoagulant therapy. The results showed a slight predominance of AF in males, with the highest incidence in individuals aged 75 and above. Common risk factors included arterial hypertension, dyslipidaemia, diabetes mellitus type 2, and obesity. Comorbidities such as congestive heart failure, mitral valve regurgitation, and pulmonary disorders were prevalent among the patients. Major complications included congestive heart failure, stroke, and myocardial infarction. Thromboembolic and bleeding risk assessment using CHAD2DS2-VASc and HAS-BLED scores demonstrated a high thromboembolic risk in all patients. The majority of patients were receiving novel oral anticoagulants (NOACs) before admission, while NOACs were also the most prescribed antithrombotic therapy at discharge. The study highlights the importance of risk factor management and appropriate anticoagulant therapy in AF patients to reduce complications and improve outcomes.

Keywords: atrial fibrillation; risk factors; thromboembolic events; novel oral anticoagulants; complications; hospitalization; medication monitoring

1. Introduction

Atrial fibrillation is the most common sustained arrhythmia encountered and managed in clinical practice. [1] A supraventricular tachycardia, AF is characterized by disorganized, fast, and irregular atrial electrical activation, as well as an irregular ventricular response.[3] Affecting both cardiac patients, as well as individuals with no history of cardiovascular disease, the prevalence of AF varies from 0.5-1% in the general population, to a 10-fold greater value in those aged over 65. [2] The causes of AF are relatively well defined. Acute hyperthyroidism, vagotonic episodes or alcohol intoxication may trigger the appearance of paroxystical AF, while the critical phase of the recovery period after major vascular, abdominal, or thoracic surgery is linked to acute episodes of AF. [3] Other triggers for AF include ventricular tachycardias (i.e., atrioventricular nodal reentry tachycardia – AVNRT), the progression of structural valvular, myocardial, or coronary disease, hypoxia, electrolytes imbalance or metabolic disorders, pericarditis, myocarditis, atrial or conduction tissue degeneration associated with ageing, genetical predisposition, male sex, and so on. [4] Eliminating these risk factors may prevent AF recurrence.

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Based on the duration of progression, AF is classified as: first diagnosed – not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms; paroxysmal – terminates spontaneously or with intervention within 7 days of onset; persistent – continuously sustained beyond 7 days (including episodes terminated by cardioversion after ≥ 7 days); long-standing persistent – continuous of > 12 months; permanent – accepted by the patient and physician, no further attempts to restore/maintain sinus rhythm undertaken. [4]

AF symptoms greatly vary, ranging from completely asymptomatic or silent, to haemodynamically unstable patients. Most commonly, patients accuse mild to severe palpitations. The haemodynamic effect can be extremely pronounced, based on the atrial quiver and the ventricular response, with severe symptomatic hypotension, pulmonary oedema, or angina in some cases. [3,4] The evaluation of a patient with AF should include a detailed history, including family history of AF, and a thorough physical examination to define the clinical type of AF, as well as to identify any reversible causes of arrythmia (e.g., hyperthyroidism or anaemia). [2,6]

The clinical importance of AF is determined by the loss of atrial contraction, an inadequately increased ventricular response, and the absence of atrial auricular contraction – causing the blood flow to pool, thus increasing the risk of local clot formation and thromboembolic events. [3]

AF is an important morbidity and mortality factor, as it is linked to an increased risk of stroke, heart failure, and even death. Patients' quality of life is impaired in more than 60% of cases, due to the burden, comorbidities, as well as psychological functioning and medication, while repeated hospitalizations, ranging from 10 to 40% annual rate, and prevalent depression (16-20%) further contribute. Up to 20-30% of all ischaemic strokes, and 10% of cryptogenic strokes, are AF-related, while the risk of heart failure also rises to 20-30% due to the excessive ventricular rate and irregular ventricular contractions. All these enhanced risk factors contribute to an excessive mortality rate of 1.5-3.5-fold increase, in comparison to healthy individuals. [4]

In order to decrease the risk of mortality, stroke and hospitalization associated with AF, anticoagulants are pivotal in the management of this dysrhythmia, due to its high occurrence of thromboembolic events. Until the past decade, the most commonly used anticoagulant therapy consisted of vitamin K antagonists (VKAs) - warfarin and acenocumarol. However, due to their large interpatient variability in slow onset and offset of action, extensive food and drug interactions, the need for coagulation monitoring and dose adjustments, as well as dose response, VKAs' use created a complicated management scheme, and thus their eventual limitation was inevitable with the appearance of Novel Oral Anticoagulants (NOACs). [7] Four NOACs are currently available for the prevention of stroke in patients with AF: apixaban, edoxaban, rivaroxaban, and dabigatran, the former being oral direct Factor Xa inhibitors, and the latter an oral direct thrombin inhibitor. [5]

We investigated the management strategies and identified modifiable risk factors associated with atrial fibrillation, with the goal of enhancing treatment outcomes, reducing complications, and improving patient care. Furthermore, special attention was given when assessing the comparative efficacy and safety of different anticoagulation therapies (e.g., NOACs vs. VKAs) for stroke prevention in patients with AF. This study aims to contribute to the existing knowledge base, guide clinical decision-making, and ultimately improve patient outcomes in the management of this common cardiac arrhythmia.

2. Materials and Method

In this paper we studied 115 symptomatic patients, diagnosed with AF, and performed a systematic analysis of different clinical and paraclinical characteristics, provided by the observational charts of the Bihor County Clinical Emergency Hospital archive. The study is retrospective, taking place over the course of one year (March 2022 – March 2023). The study was approved by the ethics committee of Bihor County Clinical Emergency Hospital.

The included patients were diagnosed with permanent AF with moderate heart rate, several of them presenting multiple hospitalizations during the years, all of them unsuccessful in re-establishing sinus rhythm. The persistence of AF creates a higher risk of thromboembolic complications, some of the patients' histories already presenting thromboembolic events.

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The exclusion criteria were: first-diagnosed, paroxysmal, or long-standing persistent AF, patients with AF reestablished to sinus rhythm, permanent AF with fast heart rate.

The diagnosis of permanent AF was established based on the general physical examination and the cardiovascular exam: palpitations, dyspnoea, vertigo, syncope, fatigue, chest pain, arrhythmic cardiac sounds, asynchronous with the pulse. The EKG confirmed the diagnosis.

The parameters we followed were age group, sex, background, number of hospitalization days, symptoms at admission, AF risk factors, associated pathologies, AF complications, anticoagulant therapy before admission, anticoagulant therapy during hospitalization, antithrombotic therapy prescribed at discharge, and medication monitoring.

Satistical analyse was perform with STATISTICA 8.0, using chi-test, z–test for 2 proportions and one way ANOVA test for comparing multiple categorical variables. A p-value ≤0.05 was considered to be statistically significant.

As risk stratification tools, we used the CHA2DS2-VASc score to estimate the risk of stroke in patients with AF, as well as the HAS-BLED score to assess the risk of bleeding complications in patients who need to receive anticoagulant therapy, or patients who are already receiving antithrombotic medications. These risk stratification scores help identify patients who may require closer monitoring, or adjustments in their management.

The CHA2DS2-VASc score considers various clinical risk factors associated with stroke, and assigns a score to each factor, summing up the points assigned to each parameter. The total score can range from 0 to 9, a higher score indicating a higher risk of stroke.

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thrombo-embolism	2
V	Vascular disease*	1
A	Age 65–74	1
S	Sex category (i.e., female sex)	1
	Maximum score	9

Congestive heart failure/LV dysfunction means LV ejection fraction ≤40%. Hypertension includes the patients with current antihypertensive medication. *Prior myocardial infarction, peripheral artery disease, aortic plaque. LV: left ventricular, TIA: transient ischemic attack

Figure 1. CHA2DS2-VASc score [8].

The calculations of the HAS-BLED score uses a similar method to the CHA2DS2-VASc score, involving different parameters. Each parameter carries a score of 1, resulting in a total score ranging from 0 to 9. A higher score indicates an increased risk of bleeding complications.

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Letter	Risk factor	Score
H	Hypertension	1
A	Abnormal renal and liver function (1 points each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g., age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2

Figure 2. HAS-BLED score.

3. Results and Discussions

According to recent studies, it is currently greatly recognized that the epidemiology of AF differs between men and women. [15] In this paper, 55% of subjects were male with 45% female, emphasizing a slight prevalence in the masculine sex. (p=0,35) . This data is similar to the ARIC (Atherosclerosis Risk in Communities) cohort findings, which notes a fairly higher lifetime risk of atrial fibrillation in white men compared to white women. [9] This small predominance can be attributed to gender-related risk factors, life and work conditions that predispose men to cardiovascular diseases, including atrial fibrillation. However, according to another study, as age increases, the gap between the genders also decreases. Over the age of 75, the prevalence of atrial fibrillation seems to be higher in women, possibly due to their increased longevity. [10][11] Thus, due to existing conflicting data between works, it is extremely difficult to affirm whether or not sex plays a role in the development of atrial fibrillation. [12] [13]

Even though the prevalence of AF varies among different ethnic populations, over the course of years, numerous epidemiological studies consistently found a gradual rise in the incidence and prevalence of AF with advancing age. [13] Most cases in this study were included in the '75 and over' age category (56 patients, 49%), and while 35% of cases were part of the 65-74 age group and 18% of the 55-64 group (p=0,001) , we can confirm that the results of this paper further enhance the preexisting data regarding the influence of age over the epidemiology of AF. We also found that the incidence of atrial fibrillation significantly increases along with age, data supported by the low number of younger patients included in the study – 2% in 15-24 y.o. group, 2% in the 35-44 and 1% in the 45-54 age group.(p=0,8) [16]

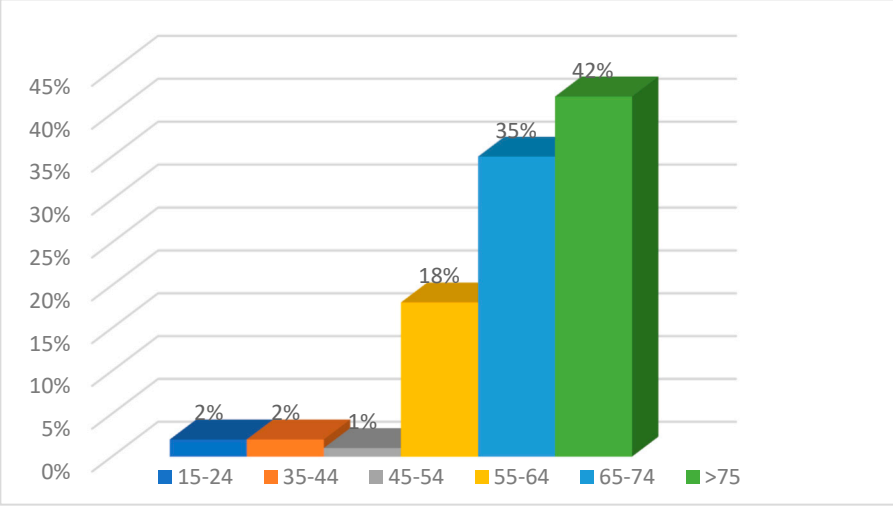

Figure 3. Age distribution.

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There is little consistent data regarding the influence of the patient's background on the prevalence of AF, despite the significant difference between rural versus urban environment we found, 45% versus 55%. (p=0,35) (Figure 6) We are unable to confirm the existence of predisposing factors in the urban area. However, contributing factors to cardiovascular disease in the urban environment can be notably mentioned, such as: food, sedentary lifestyle, pollution. It is important to note that background distribution also depends on the country's economic structure. A higher prevalence of AF can be observed globally in both high-income, as well as low- and middle- income countries. [17]

Due to the characteristics of patients with atrial fibrillation, e.g. older age, several associated morbidities which require thorough investigations and prolonged supervision, 70% of subjects were admitted for 6 to 10 days, a long period, which of course, implies higher hospitalization costs. On that same note, 9% of study subjects were admitted for more than 10 days, with 4% spending more than 2 weeks (15 days on average) in the hospital. The shortest admission period, seen in 17% of cases, was 3 to 5 days. (p<0,0001)(Figure 4)

These results support the findings of other works, which note that not only have the hospitalization rates for AF increase exponentially, but also the cost of hospitalization, despite the overall decline in hospital mortality. [18] This arrhythmia not only increases the risk of mortality, but also the morbidity resulting from stroke, heart failure, and impaired quality of life. Thus, the economic burden associated with AF rises considerably with each decade. [19]

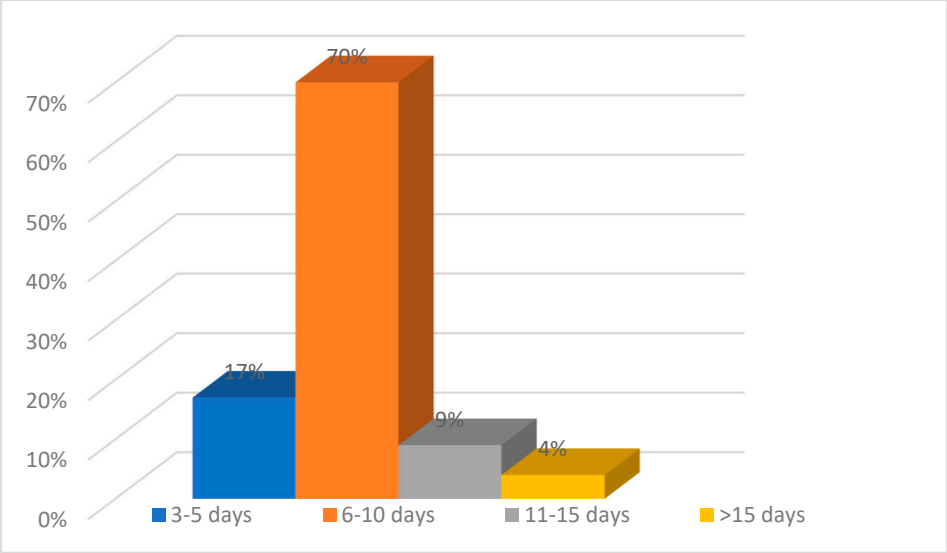

Figure 4. Hospitalization time.

Risk factors for atrial fibrillation were present in 54 of patients, out of the 115 that were included in the study. Once identified, these factors can be influenced, thus contributing to decreasing the risk of further complications and stalling the evolution of the disease, even though, this aspect of AF management is often underrecognized and underused. [20]

Most commonly identified risk factor was arterial hypertension, seen in more that 54% of cases. This fact can be explained by the haemodynamic stress caused by arterial hypertension; a surge in the intraatrial pressure causes structural changes of the heart tissue over time, as well as electrical changes in the atrial chamber, predisposing to the occurrence of atrial fibrillation. Other studies have also shown that poorly controlled blood pressure is associated with an elevated risk of AF. [21] [22] Clinical trial data also indicates a linear association between blood pressure management and adverse cardiovascular outcomes, suggesting a correlation between lower blood pressure levels and better cardiovascular results. [23] In conclusion, numerous studies agree that controlling the blood pressure is a suitable strategy for lowering the risk in patients with AF. [24–26]

Other than arterial hypertension, dyslipidaemia (21.73%), diabetes mellitus type 2 (19.13%) and obesity (15.65%) were relatively frequent as well. (p<0,0001) Even though not all studies show

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significant relation between these pathologies and AF [27], multiple large populations-based works have emphasized the development of AF in patients presenting all the aforementioned risk factors and the importance of their proper management as part of the AF treatment scheme. [28–30]

Minor risk contributors included are hypercholesterolemia (4%), hypertriglyceridemia (2,6%) and thyroid disfunction (2,6%). [20]

There is a multitude of associated pathologies patients with atrial fibrillation usually present, each comorbidity further increasing the risk of complications and mortality. Left ventricular failure was a major associate, present in more than 59% of cases, followed by arterial hypertension (54%) and congestive heart failure (35,6%) (p=0,28). However, mitral valve regurgitation represented the most frequent comorbidity, seen in 60% of cases, while 26% of patients presented tricuspid regurgitation and 19% aortic regurgitation. Mitral or aortic stenosis hold a lower position, with 6% and 11% of patients diagnosed with these pathologies. Dilated cardiomyopathy affects 32% of study subjects, while only 5% of them suffered a myocardial infarction. Approximately 5% of patients (left bundle branch block), respectively 7% (right bundle branch block) were diagnosed with arrhythmias. Heart diseases were not the only pathologies included in the study, pulmonary comorbidities being present in a relatively high proportion, with pulmonary hypertension present in 25% of cases, COPD in 11%, pleural effusion 3%, 2% for pneumonia, and 1% of patients with asthma. Metabolic diseases (diabetus mellitus) affect 15% of subjects, 4% suffer from chronic kidney disease, with also another 4% suffering from liver disease (p<0,0001).

This study supports the findings of other papers that patients with AF have a higher prevalence and incidence of a multitude of comorbidities compared to healthy individuals. [39] Mitral valvular pathology, left ventricular failure, dilated cardiomyopathy, hypertension, and heart failure, were the conditions largely associated with AF in this work, possibly explaining the origins of AF in some cases. However, when it comes to mortality, other studies argue that AF does not have an augmented impact despite the greater comorbidity burden. [39]

Our study highlights congestive heart failure as a major complication in patients with AF (32%), followed closely by stroke in almost 17% of cases. Such severe complications could be caused by an untreated or undertreated AF, in terms of both antiarrhythmic therapy, as well as antithrombotic medication. 5% of patients suffered a myocardial infarction. (Figure 5)

These results are supported by several studies which bring forth the notion that patients with heart failure have a higher risk of developing AF, while also AF is associated with an increased risk of developing heart failure, as well as a rise in hospitalization. [31–34] When it comes to myocardial infarction, which can also be an aggravating factor of AF due to the remodelling of the atria occurring after atrial ischemia, as well as a complication of AF itself [36], other works highlight the fact that coronary artery disease and AF share common risk factors [35]. It is also well-known that AF is associated with an increased risk of stroke [37], as proven by numerous studies before, while also AF-related strokes enhance the risk of long-term disability or death. [38]

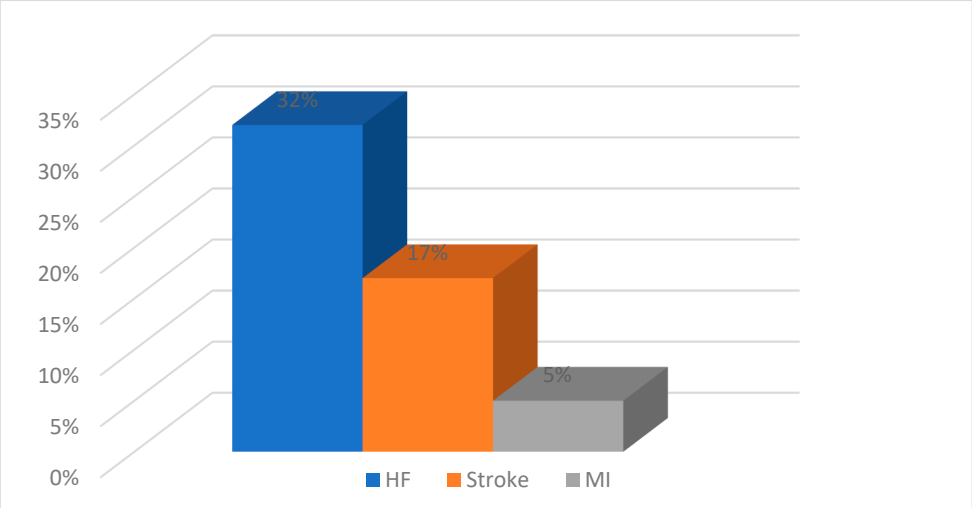

Figure 5. Complications.

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We calculated the clinical risk factor-based CHAD2DS2-VASc and HAS-BLED scores for all patients, thus appreciating the thromboembolic risk of each individual, as well as the bleeding risk when considering the appropriate anticoagulant therapy.

The European guidelines recommend the use of the CHA2DS2-VASc score since 2010, being a class I recommendation for risk stratification in patients with AF. This stroke score is closely associated with the enhanced bleeding risk as well. There is strong evidence to support the benefit of anticoagulation therapy for atrial fibrillation in patients with a higher score. [4] In this study, among the major risk factors: 16% of patients suffered a stroke, while 48% were above the age of 75 years old. Although considered minor factors, congestive heart failure (94%), arterial hypertension (54%), and diabetus mellitus (19%) were relatively common. (p=0,02). (Figure 6)

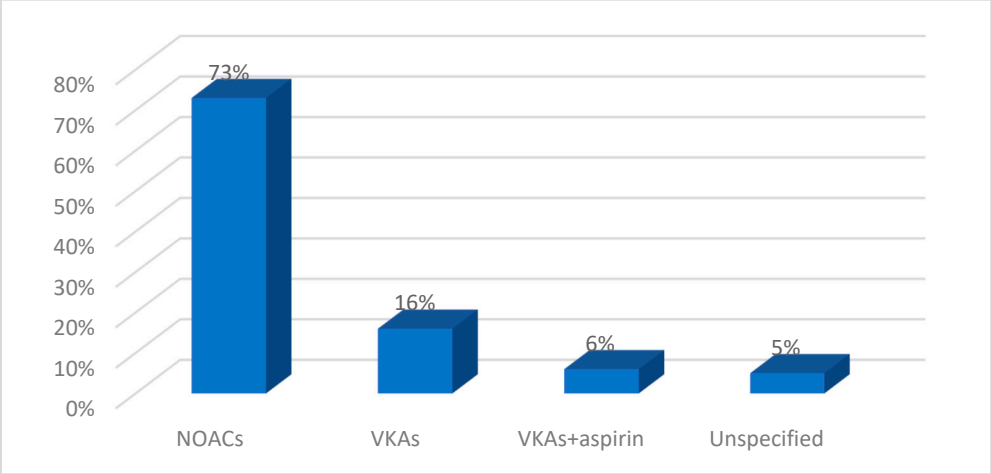

Figure 6. Antithrombotic medication before admission.

An overlap of risk factors can be found between the CHAD2DS2-VASc and the HAS-BLED score, however, there are works that prove that the HAS-BLED score performed better than the CHAD2DS2-VASc score in anticoagulated patients with AF. [41] Uncontrolled blood pressure, an element pertaining to the HAS-BLED clinical score, was seen in almost 55% of patients in this study. A labile INR was found in 30% of cases (p=0,0001) , while 8% presented abnormal renal and/or hepatic function (p<0,001), both of these factors being modifiable through medication. Among the unmodifiable risk factors, 96% of patients were 45 years old or older (p<0,001), 16% suffered a stroke (p<0,001) , while 10% experienced a hemorrhagic event (p<0,0001). (Figure 12)

According to the ESC 2020 AF guidelines, antithrombotic medication is recommended for all patients with a CHAD2DS2-VASc score >= 2 for males, and >= 3 for females. If HAS-BLED score >= 3, the modifiable bleeding risk factors should be addressed, but a high bleeding risk score should not be used as a reason to withhold anticoagulant therapy. [4] Based on the CHA2DS2-VASc score, it is recommended that no antiplatelet or anticoagulant therapy should be initiated if no risk factors are present (score 0 in males, score 1 in females). However, all the patients evaluated in this study belong to the high thromboembolic risk category, with a score value of minimum 2.

The most frequently used antithrombotic medications before admission to the hospital were NOACs (apixaban, edoxaban, rivaroxaban, dabigatran) with 73% of patients using these drugs in monotherapy. 16% of patients were on VKAs (acenocumarol or warfarin), while 6% had VKAs and aspirin together in their scheme. (Figure 13)

During hospitalization, when urgent treatment was needed, low molecular weight heparin (LMWH) was used in monotherapy in 9% of cases. LMWH and VKAs were used together in 27% of patients, with a loading dose of Acenocumarol for 2 to 3 days, double the maintenance dose (4-6 mg), followed by maintenance treatment of 2 mg/day. LMWH was interrupted when the INR reached a therapeutic value for 2 consecutive days. Concomitant with the interruption of LMWH, the value of the INR can decrease, without changing the VKAs dose. 6% of patients were given a combination of LMWH, VKAs and aspirin, and another 6% used Acenocumarol and aspirin together (p<001). Up to 52% of patients were given a NOAC during admission (P=0,70). (Figure 7)

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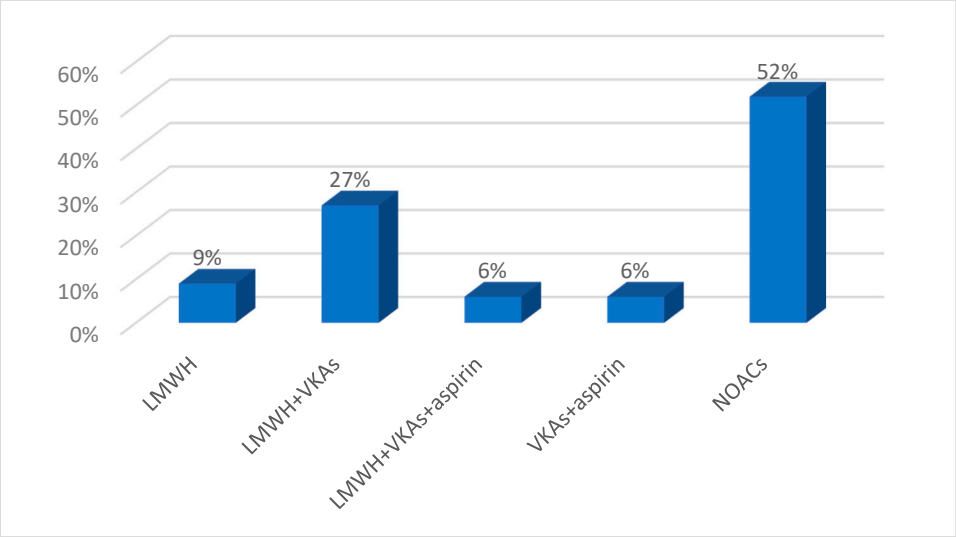

Figure 7. Antithrombotic medication during hospitalization.

At discharge, 61% of patients were prescribed a NOAC in monotherapy, with 33% receiving VKAs (acenocumarol) and aspirin together.(p=0,002) INR monitoring is required once every two weeks. Acenocumarol as single drug was only prescribed for 6% of cases. (Figure 8)

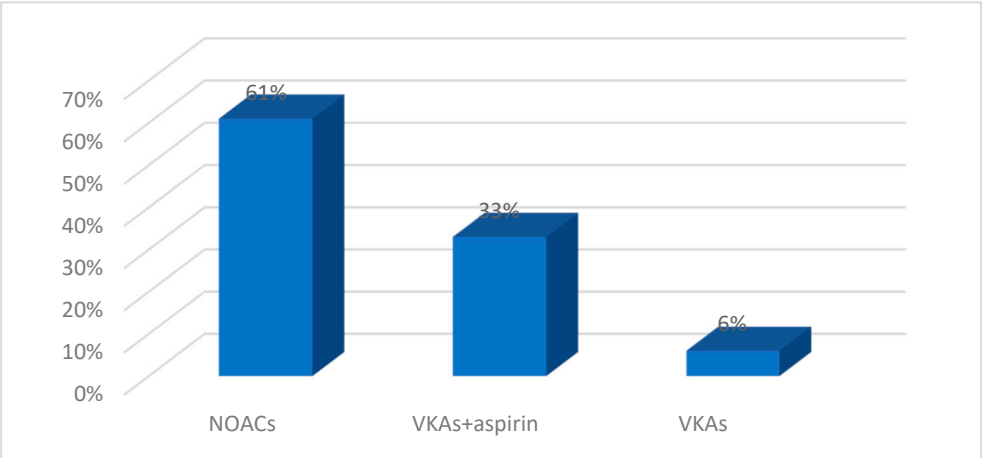

Figure 8. Antithrombotic therapy prescribed at discharge.

The clearly preferential use of NOACs outside the hospital, before, during, and after hospitalization, has risen exponentially since their discovery, multiple studies and clinical trials proving they are superior to warfarin for the prevention of stroke and systemic embolism in patients with AF, the significant reduction of intracranial haemorrhage resulting in a significant lower mortality. [42] However, the correlation between NOACs and gastrointestinal bleeding continues to remain controversial, with some trials (ARISTOTLE, J-ROCKET AF, ENGAGE TIMI AF 48, RE-LY) inclining towards significant heterogeneity and non-significant bleeding with certain NOACs (lower dose edoxaban, lower dose dabigatran), while others (ROCKET AF) clearly indicate more gastrointestinal bleeding in a higher dose of dabigatran. [43–47] Whether or not to prescribe NOACs depends on each clinician, as well as the particularities of each patient, but the evidence suggesting a favourable long-term outcome of NOACs, compared to warfarin, in patients with AF, cannot be completely disregarded.

4. Conclusions

1. This study provides valuable insights into the management and risk factors associated with atrial fibrillation (AF). The findings underscore the importance of identifying and addressing

risk factors to prevent complications and improve patient outcomes. Anticoagulant therapy, including VKAs and NOACs, play a vital role in stroke prevention in patients with AF. The selection of anticoagulant therapy should be tailored to individual patient factors, considering the benefits and risks associated with each option.

2. The study confirmed that AF is more prevalent in males, particularly in older age groups. Arterial hypertension was the most common risk factor, followed by dyslipidaemia, diabetes mellitus type 2, and obesity. These modifiable risk factors should be targeted through lifestyle modifications and appropriate medical interventions to reduce the incidence and progression of AF.
3. The presence of comorbidities, such as congestive heart failure and valvular regurgitation, further increases the risk of complications in AF patients. Therefore, comprehensive management of these associated pathologies is crucial in the overall care of AF patients.
4. The study highlights the significant complications associated with untreated or undertreated AF, including heart failure, stroke, and myocardial infarction. This emphasizes the need for timely and effective treatment strategies to control AF and minimize its impact on patient health.
5. Thromboembolic risk assessment using the CHAD2DS2-VASc score demonstrated a high thromboembolic risk in all patients, reinforcing the importance of anticoagulant therapy. After determining the HAS-BLED score, novel oral anticoagulants (NOACs) emerged as the preferred choice due to their ease of use, predictable pharmacokinetics, and reduced risk of interactions compared to traditional vitamin K antagonists.
6. In conclusion, this study emphasizes the significance of risk factor management and appropriate anticoagulant therapy in AF patients. By addressing modifiable risk factors, optimizing comorbidity management, and implementing appropriate antithrombotic strategies, healthcare professionals can reduce complications, improve patient outcomes, and enhance the quality of life for individuals living with AF.

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