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Anticoagulation in atrial fibrillation: Special scenarios

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Abstract

Atrial fibrillation is the most common cardiac arrhythmia in the world, with an estimated prevalence of 2 to 4%, and represents a high burden of disease worldwide. It is defined as a supraventricular tachyarrhythmia with loss of atrial activity, diagnosed by specific electrocardiographic findings. Its classification is clearly defined, based on the form of presentation, duration and the resolution of the episodes. One of the pillars in the treatment of this pathology is anticoagulant therapy, which represents a challenge due to the heterogeneity of the patients, however there are specific situations such as chronic kidney disease, oncological diseases and liver disease, where the situation becomes even more complex, however different studies have been carried out in which the best strategies based on scientific evidence have been proposed for the approach of these patients in special situations.

Keywords: Atrial Fibrillation; Anticoagulation; Chronic Kidney Disease; Anticoagulants.

1. Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults and is associated with a high burden of morbidity. The current estimated prevalence of AF is between 2 and 4%, and it is expected to double considering the increase in life expectancy of the population, the increase in cardiovascular risk factors, and the increase in its diagnosis. This disease has been shown to be associated with functional impairment and a wide range of risks for stroke and thromboembolic diseases, with up to 30% of strokes being secondary to AF. It is estimated that between 10 and 40% of patients with AF are hospitalized each year, doubling the risk of mortality [1] [2].

AF is defined as a supraventricular tachyarrhythmia with loss of atrial electro-mechanical activity and consequently inefficient atrial contraction. Diagnosis requires an electrocardiographic recording that shows the presence of irregular R-R intervals, absence of P waves, and irregular atrial activation [3].

2. Methodology

A systematic review was carried out through the selection of original articles, available research reviews, written in English and / or Spanish, through recognized databases such as pubmed, scielo, science direct, wiley, plos one, among others. Regardless of its year of publication, using the search terms include atrial fibrillation, anticoagulation, chronic kidney disease. A search criterion was not established for a defined language, however, all the articles containing the corresponding information and of great importance for conducting our review were selected.

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3. Results

3.1. Classification of Atrial Fibrillation

Traditionally, the terms valvular and non-valvular AF were used to differentiate between patients with severe and moderate mitral stenosis or mechanical heart valves and other patients with AF, but these terms often generated confusion, which is why they are currently not recommended. Currently, a classification based on the presentation form, duration, and resolution of episodes is used, resulting in 5 groups, including first diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF, and permanent AF (See Table 1) [4].

Table 1 Classification of AF

Classification	Characteristics
First-diagnosed AF	First-diagnosed Atrial fibrillation has not been previously diagnosed, regardless of the duration of the arrhythmia
Paroxysmal AF	Paroxysmal Atrial fibrillation reverts spontaneously or with intervention within the first 7 days of onset
Persistent AF	Persistent Atrial fibrillation persists for more than 7 days, including episodes that are terminated by pharmacological or electrical cardioversion after more than 7 days
Long-standing persistent AF	Long-standing persistent Atrial fibrillation continues for more than 1 year after adopting a strategy for controlling heart rhythm
Permanent AF	Permanent AF The patient and the physician assume atrial fibrillation and no new measures are taken to restore or maintain sinus rhythm

Adapted from Hindricks G, Potpara T, Dagres N, Arbelo E, Blomstrom-lundqvist C, Castella M, et al. ESC Guidelines on AF diagnosis and management, developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Rev Esp Cardiol. 2021;74(5):437.e1-437.e116.

3.2. Clinical presentation and diagnosis

The diagnosis of AF is usually made accidentally; however, in the presence of dyspnea, chest pain, palpitations, acute neurological deficit, or syncope, AF must always be ruled out. Different risk factors for developing the disease, mainly in patients who already have underlying cardiovascular disease, should also be considered (See Table 2) [5] [6].

Table 2 Risk factors for atrial fibrillation

Male gender	**Age > 65 años**
Smoking	Alcoholism
White race	Hypertension
Metabolic syndrome	Obesity
Thyroid disease	Diabetes mellitus
Chronic kidney disease	Sleep apnea
Coronary artery disease	Structural heart disease
heart failure Valvular	Heart disease cardiac surgery

Taken from: Forero-Gómez J, Moreno J, Agudelo C, Rodríguez-Arias E, Sánchez-Moscoso P. Atrial fibrillation: approach for the non-cardiologist physician. Iatreia. 2017; 30(4):404-422.

Considering that the presentation of AF can range from asymptomatic to the presence of debilitating symptoms that affect quality of life, it is necessary to determine the symptom burden since this influences therapeutic decision-making. It is recommended to stratify symptoms according to the European Heart Rhythm Association (EHRA) symptom scale, which evaluates the following symptoms during AF episodes: palpitations, fatigue, dizziness, dyspnea, chest pain, and anxiety (see Table 3) [7].

Table 3 EHRA scale

Class	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	daily activities are not affected by AF-related symptoms
2b	Moderate	Normal daily activities are not affected by AF-related symptoms, but the patient
3	Severe	Normal daily activities are affected by AF-related symptoms
4	Incapacitating	Symptoms related to AF lead to a disruption of normal daily activities

Taken from: Steffel J, Verhamme P, Potpara T, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330-1393.

3.3. Treatment

Table 4 CHA2DS2VASc score

C	Congestive heart failure	1 point
H	Hypertension	1 point
A2	≥75 years old	2 points
D	Diabetes mellitus	1 points
S2	Previous stroke, TIA, or systemic embolism	2 Points
V	Vascular disease	1 Point
A	Age 65-74 years	1 point
Sc	Female gender	1 Point

Taken from: Hindricks G, Potpara T, Dagres N, Arbelo E, Blomstrom-lundqvist C, Castella M, et al. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42(5):373-498.

Table 5 Score HAS-BLED

H	**Uncontrolled hypertension** **PAS >160 mmHg**	**1 Point**
A	Dialysis, transplantation, serum creatinine >200 umol/L, cirrhosis, bilirubin >2 times the upper limit of normal, AST/ALT/ALP >3 times the upper limit of normal	1 Point
S	Prior stroke	1 Point
B	Prior bleeding, anemia, or thrombocytopenia	1 Point
L	INR Lábil TRT <60% in patients on VKA treatment	1 Point
E	Age > 65 years old or extreme fragility	1 Point
D	The concomitant use of antiplatelets or NSAIDs and/or excessive alcohol consumption per week	1 Point

Taken from: Fauchier L, Chaize G, Gaudin A, Vainchtock A, Rushton-Smith SK, Cotté F. Predictive ability of HAS-BLED, HEMORR2HAGES, and ATRIA bleeding risk scores in patients with atrial fibrillation. A French nationwide cross-sectional study. Int J Cardiol. 2016;217:85-91.

The cornerstone of treatment for patients with atrial fibrillation, in addition to the control of comorbidities and risk factors, is focused on stroke prevention and symptom control. For this purpose, the ABC of AF has been created: A, anticoagulation/stroke prevention; B, good symptom control; C, control of cardiovascular risk factors and comorbidities. Therefore, one of the first measures is to establish the risk of stroke, for which the CHA2DS2-VASc score is recommended (see Table 4). In addition, the bleeding risk should be established when making therapeutic decisions regarding anticoagulation, for which the HAS-BLED score is recommended (see Table 5) [4] [8].

3.4. Anticoagulant treatment

Anticoagulants should be part of the treatment for all patients with atrial fibrillation, except those with low risk or absolute contraindications for their use. Treatment with oral anticoagulants (OAC) can prevent most ischemic strokes in patients with atrial fibrillation and prolong their life. It has been shown that this treatment is superior to no treatment or treatment with acetylsalicylic acid. Patients who do not have clinical risk factors for stroke usually do not need antithrombotic treatment, however, those who have risk factors (CHA2DS2-VASc 1 point for men and 2 points for women) can benefit from OAC [9] [10].

Anticoagulant treatment presents a clinical challenge in different scenarios or special situations, in which comorbidities and the physiological changes they generate can interfere or limit the effect of the different anticoagulants available. For this reason, in this article we will mention some of these clinical situations and the updated recommendations for anticoagulant management [11].

3.5. Atrial fibrillation in chronic kidney disease

AF is the most prevalent arrhythmia in patients with CKD, representing 16 to 21% of patients without dialysis, and between 15% to 40% in patients on dialysis. Both are independent risk factors for the development of stroke by mechanisms not yet fully established. The risk scales used to establish the risk of stroke are similar to those applied in the general population, with greater evidence recommending the use of the CHA2DS2-VASc score. It is recommended to start oral anticoagulant for patients with CKD when the score is ≥2 [12].

Defining the start of anticoagulation in patients with CKD is complex, due to the concurrence of procoagulant phenomena determined by vascular alterations, the increase in proinflammatory mediators, and the presence of endothelial dysfunction, as well as the presence of prohemorrhagic conditions derived from platelet dysfunction and difficulties in adhering to the subendothelium [13].

When determining the best anticoagulant treatment in patients with CKD and AF, it is necessary to individualize by groups taking into account the stage of CKD, the non-valvular origin of AF, and the thromboembolic risk. (5) Randomized clinical trials have shown that direct oral anticoagulants (DOACs) are not inferior to warfarin in patients with a creatinine clearance of 30 to 50 ml/min, and a superior safety profile to warfarin has been demonstrated. In trials comparing DOACs vs warfarin, the former were associated with a 50% reduction in the risk of intracranial hemorrhage [14] [15].

Currently, there is not enough evidence on the effect of vitamin K antagonists or direct-acting anticoagulants in patients with CKD with creatinine clearance of 15-29 ml/min, as this population has been excluded from the randomized clinical trials with the greatest impact. In this group of patients, based on the results of some observational studies, the use of DOACs is recommended over warfarin, considering that fewer hemorrhagic complications were observed, without a difference in stroke or thromboembolism. It is also important to consider that, according to certain comorbidities and risk factors, the dosage of DOACs should be adjusted (see table 6) [16] [17].

Table 6 Dose adjustment in patients with chronic kidney disease

Rivaroxabán	15 mg/day if creatinine clearenace is 30-49 ml/min
Apixabán	2,5 mg every 12 hours if serum creatinine: ≥ 1.5 mg/dl + Age ≥ 80 or Weight ≤ 60 kg
Edoxabán	30 or 15 mg/day if creatinine clearance < 50 ml/min

Taken from: Turakhia M, Blankestijn P, Carrero J, Herzog C, Reinecke H, Cheung M, Zareba W, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. European Heart Journal.2018;39(24), 2314–2325.

Evidence of the use of anticoagulants in advanced renal disease with creatinine clearance less than 15 ml/min is still scarce, taking into account the limited number of studies, and those that have included this specific population question the use of anticoagulants. In this group of patients, treatment with oral anticoagulants may be considered. There is limited evidence of advantages with the use of apixaban and rivaroxaban compared to warfarin in case the time in the therapeutic range is low or there are vascular calcifications [18].

3.6. Atrial fibrillation in the elderly patient

It is well known that the risk of developing AF increases with age, currently reporting a prevalence of 9% in patients between 76-85 years, and over 10% in patients over 85 years. The high prevalence in this age group is associated with the presence of a greater number of comorbidities such as diabetes mellitus, arterial hypertension, and ischemic heart disease. However, none of these contraindicates anticoagulation [19].

Elderly patients with non-valvular atrial fibrillation with a CHA2DS2-VASc score greater than 2 in men and 3 in women should receive oral anticoagulation. Therefore, all patients aged ≥ 75 years with AF should be anticoagulated. However, it has been found that a high percentage of this population do not receive anticoagulation due to fear of bleeding. However, studies have established that the risk of fatal bleeding associated with oral anticoagulation is low, mainly when using DOACs vs. Warfarin [20].

It has been demonstrated that up to 20% of patients with AF and a high thromboembolic risk receive antiplatelet therapy instead of anticoagulation. However, this practice has been dismissed, taking into account that platelet antiaggregation is associated with a higher risk of thromboembolic events without achieving a reduction in bleeding risk [21].

Regarding treatment in this group of patients, DOACs have proven to be more effective in reducing cerebrovascular accidents. They have also been associated to a lesser extent with the appearance of severe bleeding, intracranial hemorrhage, and mortality when compared to warfarin. A meta-analysis that included 4 clinical trials with patients over 75 years old showed that DOACs are associated with a significant reduction of 30% in the risk of stroke and systemic embolism and a 9% reduction in the risk of severe bleeding when compared to warfarin. The 2018 EHRA consensus recommended for patients over 75 years of age to use direct oral anticoagulants (DOACs) instead of vitamin K antagonists, given their lower association with adverse events [22].

3.7. Atrial fibrillation in cancer patients

Different studies have shown that patients with cancer have up to 47% higher risk of developing atrial fibrillation (AF), as well as double the risk of developing pulmonary thromboembolism and six times the risk of heart failure. Hematologic malignancies have been most strongly associated with the development of AF, with multiple myeloma being the most frequent [23].

In cancer patients, as in the general population, it is necessary to determine the risk of thromboembolic and hemorrhagic events in order to determine the best anticoagulation strategy, taking into account the inherent risks. The higher presence of procoagulant agents, fibrinolytics, and proinflammatory cytokines increases arterial and venous thromboembolic complications in this patient group [24].

The CHA2DS2-VASc and HAS-BLED scales are recommended for stratifying the risk of stroke and bleeding. However, in some complex cases, other scales can be used to stratify risk, such as the ABC scale (A: age, B: high-sensitivity troponin T and NT-proBNP, C: prior stroke) and the HEMORR2AGES scale (H: liver or kidney disease, E: excessive alcohol consumption, M: malignancy, R: reduced platelet count, R: prior bleeding, H: hypertension, A: anemia, G: genetics, E: elderly, S: prior stroke) [25].

In this patient group, direct oral anticoagulants are the treatment of choice due to their demonstrated benefits in terms of efficacy, tolerance, and safety when compared to vitamin K antagonists. Clinical characteristics defining their use (age, weight, renal function, bleeding risk, need for concomitant antiplatelet therapy) should be considered, as well as possible drug interactions with chemotherapy agents [26].

The use of vitamin K antagonists in patients with active AF and cancer is difficult due to their narrow therapeutic margin and high risk of drug interactions. Currently, they are reserved for patients with valvular AF and those undergoing onco-hematologic treatment. On the other hand, low molecular weight heparins may be considered in patients with serious interactions with oral anticoagulation therapy or in the presence of intolerance [27].

Currently, clinical practice guidelines recommend percutaneous closure of the left atrial appendage as an alternative in patients with contraindication for prolonged anticoagulation and high embolic risk [28] [29].

3.8. Atrial Fibrillation in a Patient with Liver Disease

In patients with liver disease and AF, it is difficult to determine anticoagulant treatment due to the high risk of bleeding that this population presents due to alterations in protein synthesis, thrombocytopenia, and gastrointestinal varices [30].

Currently, there is a lack of evidence regarding anticoagulant management in patients with liver disease, as this group of patients has been largely excluded from studies due to the high risk of bleeding. However, a recent study showed that patients with AF and hepatic fibrosis did not have an increased risk of bleeding when using direct oral anticoagulants compared to warfarin Furthermore, it was demonstrated that in patients with cirrhosis, the reduction in stroke risk is greater than the risk of bleeding when using DOACs [31].

In all patients with liver disease, liver function tests, platelet count, and coagulation times should be determined before initiating treatment with oral anticoagulants. Additionally, anticoagulation should be avoided in the presence of thrombocytopenia less than 50,000. [32].

Traditionally, warfarin has been recommended for the majority of patients with liver disease, but recent studies have shown the usefulness and safety of using DOACs in patients with mild hepatic dysfunction (Child-Pugh A). In patients with moderate hepatic dysfunction (Child-Pugh B), the use of apixaban, dabigatran, or edoxaban may be considered with caution if there are contraindications to warfarin. To date, warfarin remains the only oral anticoagulant indicated for patients with severe hepatic dysfunction (Child-Pug C) [32] [33].

3.9. Atrial Fibrillation During Pregnancy

AF is one of the most prevalent arrhythmias during pregnancy, especially if it is associated with the presence of congenital heart disease. Atrioventricular conduction disorders have significant hemodynamic implications for the mother-fetus pair, leading to an increase in mortality. The physiological changes of pregnancy involve a state of hypercoagulability with the consequent increase in thromboembolic risk, and the scales used in non-pregnant women are used to predict this risk [34].

Currently, recommendations for anticoagulant management in pregnant patients are determined by the trimester and the CHA2DS2-VASc score, indicating the use of heparin in the first trimester and the last month of pregnancy. During the second trimester and the initial phase of the third trimester, vitamin K antagonists may be used, and timely switching to unfractionated heparin or low molecular weight heparin prior to delivery is recommended. In patients on anticoagulation with vitamin K antagonists, vaginal delivery is not recommended due to the risk of intracerebral hemorrhage for the fetus. In this group of patients, new oral anticoagulants have not been studied, which is why their use is not recommended [35].

4. Conclusions

Atrial fibrillation is one of the most prevalent arrhythmias, and it is common to find multiple patients with different comorbidities or special clinical conditions such as those described in this text that make therapeutic decisions about anticoagulant management difficult. Therefore, all intervening factors must be taken into account to make the best decision about my patient and obtain the best results based on current scientific evidence.

The management of anticoagulation for atrial fibrillation in patients with special clinical conditions such as pregnancy, liver disease, chronic kidney disease, cancer patients, and elderly patients poses a challenge for the treating healthcare professional. In these cases, alternatives with better evidence and greater scientific support should be sought in order to avoid or reduce the multiple and frequent adverse events, with the aim of achieving better adherence to treatment and thus achieving better control of comorbidities and improving the quality of life of patients.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors do not declare conflicts of interest

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