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Atrial fibrillation in the elderly

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in elderly population, with age being one of the most important factors involved in its pathogenesis. Conduction disturbances may be present on the surface electrocardiogram before AF onset in some patients. Once this arrhythmia is diagnosed, antithrombotic therapy is mandatory in most cases, as this is the only treatment that has demonstrated to improve survival. Age increases both the risk of thromboembolic and bleeding complications, while benefits from anticoagulant therapy outweigh that from bleeding in most scenarios, also in very elderly patients. However, elderly patients with AF are often undertreated. Non-vitamin K antagonist oral anticoagulants have emerged as an alternative to vitamin K antagonists, with significant less adverse events and better profile in terms of efficacy and safety. Other conditions related to age should be carefully evaluated in these patients (including frailty, comorbidity and polypharmacy) to ensure an individualized clinical and therapeutic approach.

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1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice.[1] Both its incidence and prevalence increase with age,[2,3] especially over 65 years,[4] affecting up to 9% of octogenarians, and even more, in developed countries.[5,6] Consequently, and due to aging population in recent years, AF has acquired an epidemic dimension.[7] In addition, a great number of patients are diagnosed of AF in routine clinical exams,[6] making it essential to perform a correct population screening.[8] There are some other factors, besides age, that have been found to be associated with AF development, such as male sex, central obesity, thyroid disease, previous heart failure or other cardiovascular diseases. Hypertension is a known condition predisposing to AF, which should also be addressed.[9]

AF is the result of some tissue changes affecting the atria (increase of size and fibrosis development) resulting in lower and worse electrical properties and conduction.[10] In this setting, the interplay of many other factors should be considered (hypocontractility and fatty infiltration, inflammation, vascular remodeling…). These changes, altogether, contribute to develop and maintain this chaotic electrical activity.[8] Some patients present changes on the surface electrocardiogram prior to developing AF, with wider P waves, as a consequence of a slowdown of electrical activation and conduction, leading to an interatrial block.[11] This clinical entity, which is known as Bayés syndrome,[12] may precede the development of AF.

2 Clinical implications

AF is not a benign clinical condition. When present, AF multiplies mortality from any cause by two, and is associated with risk of stroke approximately five times higher than that of the general population. This complication is due to the absence of mechanical activity in the left atrium, blood stasis and the subsequent formation of thrombi, particularly at the level of the left atrial appendage. Embolic strokes are particularly devastating, usually more severe and lethal than other strokes, thus entailing longer hospital stay and disability. Stroke events may be prevented by oral anticoagulant therapy, the authentic cornerstone of the treatment of patients with AF. Moreover, there is great morbidity associated with this arrhythmia, such as higher risk of hospitalizations, impaired quality of life, development of left ventricular dysfunction and heart failure, and cognitive decline,[8,13] especially in women.[14] Therefore, the different therapeutic options are aimed at improving the hemodynamics and the

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symptomatic status of these patients as well as preserving ventricular function, reducing cardiovascular risk and, above all, preventing stroke. Accordingly, the application of the available therapeutic alternatives depends on the objectives in each moment. Cardiovascular risk factors and concomitant cardiovascular diseases as well as other comorbidities (i.e., respiratory diseases) ought to be addressed in order to improve prognosis in all cases, as they are often involved in AF onset and maintenance, thus entailing worse prognosis. Elderly patients are especially vulnerable to stroke in the presence of AF,[15] thus they are more likely to benefit from oral anticoagulant therapy.[8]

According to current guidelines, AF can be classified into different patterns depending on diagnosis, duration, termination and the strategy adopted by patient and physician (rhythm or rate control). Permanent AF is the most common pattern in elderly patients.[16] It is very important to assess the symptoms derived from the arrhythmia, which vary from absent, to mild (25%–40% patients), moderate, severe and disabling (up to 15%–30% of the total). On the other hand, regarding prognosis, it is also essential to adequately address and treat the comorbidities of our patients.

3 Antithrombotic therapy

As previously explained, oral anticoagulant treatment significantly reduces stroke and mortality in patients with AF. Other interventions, such as rhythm or rate control, may improve the symptoms related to AF and may preserve myocardial function, but have not been shown to reduce long-term morbidity and mortality in these patients.[8] Need for anticoagulation depends on CHA_2DS_2-VASC score (Table 1). There are some other scores validated, like the ABC stroke risk score,[17] which allows to predict events at one and three years of follow-up. Once again, age is a major factor for anticoagulant therapy prescription according to this score. Bleeding risk, on the other hand, can also be assessed by using HASBLED score (Table 2). The key is to identify those patients in whom the benefit of anticoagulation is greater than the risk of bleeding, considering that factors related to an increased thrombotic and hemorrhagic risk often coexist. Nonetheless, benefit from anticoagulation outweighs risk of bleeding in most scenarios,[18] which supports indication for anticoagulation in most patients, especially in the elderly.

Antivitamin K antagonists have played a central role in anticoagulation during the past decades. However, there are some issues physicians ought to consider when using these drugs, such as a narrow therapeutic range, variable dose-response, inter and intraindividual variability (different pharmacokinetics and pharmacodynamics, particularly in the elderly) and multiple interactions (especially in patients with comorbidities and polypharmacy), as well as the need for monitoring (international normalized ratio, INR). Moreover, they are also responsible for a great number of emergency hospitalizations for adverse drug events (most of them related to unintentional overdose) in elderly patients in the U.S. each year.[19] On the other hand, direct oral anticoagulants (NOACs, or non-vitamin K antagonist oral anticoagulant) have emerged as an alternative to antivitamin K drugs. They have demonstrated a favorable risk-benefit profile in terms of efficacy and safety, with significant reductions in stroke, intracranial hemorrhage, and mortality, though similar major bleeding and more gastrointestinal bleeding when compared with warfarin.[20–24] Recent studies confirm NOACs' good clinical profile in terms of thromboprophylaxis in very elderly patients,[25] thus being a favorable choice even in patients older than 90 years of age.[26] Of note, and irrespective of age, clinical effectiveness and safety of NOACs depend on the dose used[27,28] (Table 3). Apixaban and edoxaban showed net benefit in elderly patients versus warfarin in phase III trials, though current evidence does not support the use of one NOAC over another. These drugs do have predictable effects, with lower interactions and no need for routine monitoring.[29] However, there are some issues regarding their absorption, metabolism and excretion that need to be addressed when prescribed, especially in the elderly. Moreover, in this scenario physicians should be particularly cautious to adjust doses when neces-

Table 1. CHA_2DS_2-VASC score.

Stroke risk factors	Score
Congestive heart failure/left ventricular dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke	2
Vascular disease	1
Age 65–74 years	1
Sex (female sex)	1

Table 2. HASBLED score.

Letter	Clinical characteristic	Points
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2

INR: international normalized ratio.

Table 3. Non-vitamin K antagonist oral anticoagulant.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Dose	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily
Dose reduction in selected patients	110 mg twice daily if > 80 yrs, GFR 30-50, concomitant use of verapamil	Rivaroxaban 15 mg once daily if GFR 30-49	Apixaban 2.5 mg twice daily if at least 2 of age ≥ 80 years, body weight ≤ 60 kg or serum creatinine level ≥ 1.5 mg/dL (133 μmol/L), or if GFR 15-30.	30 mg once daily if GFR 15–49 mL/min, weight ≤ 60 kg, concomitant use of verapamil or quinidine or dronedarone

GFR: glomerular filtrate rate (mL/min per m^2).

sary.[30,31] An integral geriatric assessment should be considered before initiating oral anticoagulation in elderly patients. This should include careful clinical decision making regarding risks and benefits of therapy, as well as risk of stroke and bleeding, polypharmacy, renal function, cognitive status, nutritional assessment and life expectancy.[32-34] Frailty also deserves special attention in this regard.[34] Initiation and follow up of this therapy is well established, and should include a comprehensive clinical evaluation, concomitant treatment and secondary effects, and analytical monitoring with liver and renal function as well as hemoglobin values. It is recommended to monitor renal function at least annually, and every six months in patients with renal insufficiency. Dose-reduction criteria according to renal clearance is shown in Table 3. Factor Xa inhibitors can be used with caution in severe renal insufficiency (glomerular filtration rate 15–29 mL/min per 1.73 m^2), whilst dabigatran is contraindicated in this scenario.[34]

4 Rhythm *vs.* rate control

In elderly patients, neither of these two strategies has proven to be superior to the other. Long term rhythm control depends on pharmacological therapy or catheter ablation. Catheter ablation is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm, particularly in highly symptomatic cases. However, there are few studies supporting its efficacy and safety in the group of elderly patients.[8] Also, permanent AF is the most common form of presentation of AF in the elderly, thus rhythm control may be more difficult to achieve, and at the expense of drugs side effects or procedures that may involve more risks than benefits.[35]

In general, in the elderly, the best option is rate control,[36] particularly in patients with large atria. The recommended heart rate should be 80-110 beats/min at rest. Beta-blockers or calcium channel blockers (verapamil or diltiazem, in the absence of left ventricular systolic dysfunction) are the best option in this population.

5 Special situations in the elderly with AF

Elderly patients who undergo coronary artery revascularization are in higher risk of bleeding, especially those over 75 years old. In this setting, if possible, shorter antithrombotic regimens are recommended, and anticoagulation monotherapy is endorsed 6 to 12 months after an acute coronary syndrome. These patients also benefit from drug eluting stents and a short duration of dual antiplatelet therapy, as this strategy has demonstrated to be safer than bare metal stents, associating lower events (all-cause mortality, myocardial infarction, stroke, and ischaemia-driven target lesion revascularisation).[37] Two recent trials have demonstrated the efficacy of double therapy after of an acute coronary syndrome in patients in need of anticoagulation (including a NOAC and antiplatelet therapy), with lower risk of bleeding compared to triple therapy with no differences in terms of antithrombotic efficacy.[38,39] This therapeutic algorithm may also be suitable in older patients.

In patients with contraindications for long-term anticoagulant therapy (high risk of bleeding or previous fatal events under this therapy), occlusion or exclusion of the left atrial appendage may be recommended[8,40] as this approach has demonstrated to be both safe and effective, also in the long term.[41]

Baseline functional status (according to Barthel index) is strongly related to poor outcomes in hospitalized patients with AF,[42] with severe dependency entailing the worst prognosis (even worse than kidney disease and stroke). Patients with these baseline characteristics, as well as those with higher comorbidity, are also more prone to receive less antithrombotic treatments.[43-44]

Frailty is an age-associated clinical syndrome characterized by a decrease in physiological reserve in situations of stress, constituting a state of vulnerability that involves a higher risk of adverse events. Its prevalence is high, especially in elderly individuals with comorbidity and chronic diseases. When present, frailty is associated worse clinical outcomes and higher morbidity and mortality in patients with cardiovascular diseases.[45] Frail patients receive less

antithrombotic therapy,[46] especially when conditions such as malnutrition, delirium of high comorbidity are present, and irrespective of CHADS score.[47–49]

In conclusion**,** elderly patients with AF are often underrepresented in clinical studies and trials. Elderly patients, even those very elderly, benefit from anticoagulation, as risk of thromboembolism outweighs that from potentially serious bleeding in most cases. However, less than two thirds of octogenarian patients with AF are anticoagulated, often with poor INR control. NOACs should be considered in this setting, taking into account their safety and efficacy profile. Also, conditions like comorbidity, frailty and polypharmacy, common in the elderly, should be considered altogether in this vulnerable population to ensure an individualized optimal approach.

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